Universidade do Estado do Rio de Janeiro
Centro Biomédico
Faculdade de Ciências Médicas

Bruno Vítor Martins Santiago

Prevalência de dor crônica no Brasil, fatores associados e o papel da resposta inflamatória aguda na cronificação da dor articular após a Febre de Chikungunya

Rio de Janeiro
2023

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Tese apresentada, como requisito parcial para obtenção do título de Doutor, ao Programa de Pós-Graduação em Ciências Médicas, da Universidade do Estado do Rio de Janeiro.

Orientador: Prof. Dr.Nivaldo Ribeiro Villela

Coorientadora: Prof.ª Dra. Maud Parise

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Prevalência de dor crônica no Brasil, fatores associados e o papel da resposta inflamatória aguda na cronificação da dor articular em pacientes após a Febre de Chikungunya

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Aprovada em 22 de junho de 2023

Coorientadora: Prof.ª Dra. Maud Parise
Faculdade de Ciências Médicas – UERJ

Banca Examinadora: _____
Prof. Dr. Nivaldo Ribeiro Villela (Orientador)
Faculdade de Ciências Médicas - UERJ

_____
Prof. Dr. Elington Lannes Simões
Faculdade de Ciências Médicas – UERJ

_____
Prof.ª Dra. Fabrícia Lima Fontes-Dantas
Instituto de Biologia Roberto Alcântara Gomes – UERJ

_____
Prof. Dr. Marco Antônio Cardoso de Resende
Universidade Federal Fluminense

_____
Prof. Dr. Luis Antonio dos Santos Diego
Universidade Federal Fluminense

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DEDICATÓRIA

A Deus, que me proporcione refúgio e fortaleza para seguir em frente, mesmo diante dos momentos mais difíceis, sendo lâmpada para os pés e luz para os meus caminhos.

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Aos meus amigos, por confiarem em mim e compreenderem os períodos de ausência.

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Sedare dolorem opus divinum est.

Hipócrates de Cos (460 l.c. - 370a.C.)

RESUMO

SANTIAGO, Bruno Vítor Martins. *Prevalência de dor crônica no Brasil, fatores associados e o papel da resposta inflamatória aguda na cronificação da dor articular após a Febre de Chikungunya.* 2023. 85 f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2023.

Introdução: O Brasil é um país continental, com significativa variabilidade populacional regional, e os dados de prevalência de dor crônica (DC) são escassos. Portanto, no primeiro artigo serão abordadas a prevalência de dor crônica benigna em diferentes regiões do Brasil e seus fatores de risco associados. Ainda dentro do contexto da DC, uma importante causa de dor articular em nosso país decorre da Febre de Chikungunya (CHIKF). Enquanto alguns indivíduos evoluem com sintomas limitados, após à exposição ao vírus Chikungunya (CHIKV), outros mantêm dor articular crônica, sendo esses mecanismos pouco elucidados. Assim, o segundo artigo abordará o papel da resposta inflamatória durante a fase aguda da CHIKF na cronificação da dor articular. Métodos: No primeiro artigo foi realizada uma busca nas bases de dados Ovid Medline, Embase, Web of Science e BVS Regional/Lilacs, para identificar estudos transversais de base populacional de 2005 a 2020, que relataram a prevalência de dor crônica benigna no Brasil (mais de três meses). O risco de viés foi avaliado usando desenho, determinação do tamanho da amostra e seleção aleatória de questões essenciais. A estimativa de prevalência agrupada foi calculada para dor crônica nas populações geral e idosa. No segundo artigo, foi analisada uma coorte retrospectiva de indivíduos expostos ao vírus Chikungunya durante o período epidêmico no Rio de Janeiro (2018-2019). Oitenta e um indivíduos de ambos os sexos, com idade entre 18-65 anos, diagnosticados com CHIKF, usando ensaio imunoenzimático IgM ou Rt-PCR, foram incluídos no estudo. A pesquisa de acompanhamento foi realizada para verificar se a dor articular persistia por 3 meses ou mais. Biomarcadores inflamatórios séricos foram avaliados nas amostras de sangue coletadas no momento do diagnóstico. Resultados: No primeiro artigo, a prevalência de dor crônica na população adulta em geral variou de 23,02% a 42,3% (estimativa combinada de 35,70%, 95% IC 30,42 a 41,17) e foi descrita como moderada a intensa. Associou-se ao sexo feminino, idade avançada, baixa escolaridade, atividade profissional intensa, consumo excessivo de álcool, tabagismo, obesidade central, transtorno de humor e sedentarismo. As regiões Sudeste e Sul apresentaram maior prevalência. A prevalência na população idosa variou de 29,3- 76,2% (estimativa agrupada 47,32%, 95% IC 33,73 a 61,11). Dos 81 pacientes incluídos no segundo artigo, 27 (33,3%) desenvolveram dor articular crônica. A maior incidência de dor articular crônica foi em mulheres entre a 4ª e 6ª década de vida, obesas e com baixo nível de escolaridade. A artrite (p=0,008) e os níveis séricos de Interleucina 1-beta - IL-1β (p=0,0135) na fase aguda foram significativamente maiores no grupo de pacientes com dor articular crônica. Observou-se correlação entre níveis elevados de Proteína 10kDa induzível por Interferon-gama - IP-10 (p=0,041) e IL-1β (p=0,015) e o desenvolvimento de dor articular crônica. O nível sérico elevado de IL-10 foi fator protetor para o desenvolvimento de dor articular crônica (p=0,038). Conclusão: A dor crônica é altamente prevalente no Brasil e está associada a sofrimento significativo, incapacidade e controle inadequado. O perfil inflamatório dos pacientes na fase aguda da CHIKF pode estar associado ao desenvolvimento de dor articular crônica.

Palavras-chave: Dor crônica. Prevalência. Fatores de Risco. Febre de Chikungunya. Artrite.

ABSTRACT

SANTIAGO, Bruno Vítor Martins. *Prevalence of chronic pain in Brazil, associated factors and the role of the acute inflammatory response in the chronicity of joint pain after Chikungunya Fever*. 2023. 85 f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2023.

Introduction: Brazil is a continental country, with significant regional population variability, and chronic pain (CP) prevalence data are scarce. Therefore, the first article will address the prevalence of benign chronic pain in different regions of Brazil and its associated risk factors. Still within the context of CP, an important cause of joint pain in our country is Chikungunya Fever (CHIKF). While some individuals evolve with limited symptoms after exposure to the chikungunya virus (CHIKV), others maintain chronic joint pain, these mechanisms being little known. Thus, the second article will address the role of the inflammatory response in the acute phase of CHIKF in the chronicity of joint pain. Methods: The first article searched the Ovid Medline, Embase, Web of Science and BVS Regional/Lilacs databases to identify population-based cross-sectional studies from 2005 to 2020 that reported the prevalence of benign chronic pain in Brazil (three months or longer). Risk of bias was assessed using design, sample size determination, and random selection of key questions. Pooled prevalence estimates were calculated for chronic pain in general and elderly populations. In the second article, a retrospective cohort of individuals exposed to the Chikungunya virus during the epidemic period in Rio de Janeiro (2018-2019) was analyzed. Eighty-one male and female individuals, aged 18-65 years, diagnosed with CHIKF using IgM enzyme immunoassay or Rt-PCR were included in the study. Follow-up survey was performed to see if joint pain persisted for 3 months or longer. Serum inflammatory biomarkers were evaluated in blood samples collected at the time of diagnosis. Results: In the first article, the prevalence of chronic pain in the general adult population ranged from 23.02% to 42.3% (combined estimate 35.70%, 95% Cis 30.42 to 41.17) and was described as moderate to intense. It was associated with female gender, advanced age, low education, intense professional activity, excessive alcohol consumption, smoking, central obesity, mood disorder and sedentary lifestyle. The Southeast and South regions had the highest prevalence. Prevalence in the elderly population ranged from 29.3-76.2% (pooled estimate 47.32%, 95% Cis 33.73 to 61.11). Of the 81 patients included in the second article, 27 (33.3%) developed chronic joint pain. The highest incidence of chronic joint pain was in women between the 4th and 6th decade of life, who were obese and had a low level of education. Arthritis ($p=0.008$) and serum levels of Interleukin 1-beta - IL-1β ($p=0.0135$) in the acute phase were significantly higher in the group of patients with chronic joint pain. There was a correlation between high levels of Interferon-gamma-inducible Protein 10kDa - IP-10 ($p=0.041$) and IL-1β ($p=0.015$) and the development of chronic joint pain. The high serum level of IL-10 was a protective factor for the development of chronic joint pain ($p=0.038$). Conclusion: Chronic pain is highly prevalent in Brazil and is associated with significant distress, disability and inadequate control. The inflammatory profile of patients in the acute phase of CHIKF may be associated with the development of chronic joint pain.

Keywords: Chronic pain. Prevalence. Risk factors. Chikungunya fever. Arthritis.

LISTA DE ABREVIATURAS E SIGLAS

CI	*Confidence interval*
CID	Classificação Internacional de Doenças
CHIKF	Febre de Chikungunya
CHIKV	Vírus Chikungunya
DC	Dor crônica
DN4	Questionário para Dor Neuropática
IASP	*International Association for the Study of Pain*
IL-1β	Interleucina 1-beta
IL-6	Interleucina - 6
IL-10	Interleucina - 10
IP-10	Proteína 10kDa induzível por Interferon-gama
PCR	Proteína C Reativa
Rt-PCR	*Reverse Transcription Polymerase Chain Reaction*
TNF-α	*Tumor Necrosis Factor*- α

LISTA DE SÍMBOLOS

%	Porcentagem
>	Maior
×	Multiplicação
α	Alfa
β	Beta

SUMÁRIO

INTRODUÇÃO

A definição de dor revisada pela *International Association for the Study of Pain* (IASP) apresenta a dor como "uma experiência sensitiva e emocional desagradável associada, ou semelhante àquela associada, a uma lesão tecidual real ou potencial" [1]. Quanto à subclassificação temporal, ela pode ser aguda e crônica, sendo a dor crônica (DC) aquela que persiste por três meses ou mais do tempo habitual de cura de uma lesão, ou que está associada a processos patológicos crônicos, que causam dor contínua ou recorrente [2]. Para dores musculoesqueléticas não oncológicas, três meses é o ponto de divisão mais conveniente entre dor aguda e crônica, mas, para fins de pesquisa, seis meses também são frequentemente utilizados [3].

Um ponto importante reside no fato de que a DC, diferentemente da dor aguda, é caracterizada como uma doença pela CID 11 (Classificação Internacional de Doenças – 11), denominada DC primária, pois existem também as dores crônicas secundárias (visceral, neuropática, musculoesquelética, relacionada ao câncer, pós-cirúrgica/pós-traumática ou cefaleia/orofacial) [4]. Quanto aos mecanismos biológicos aceitos pela IASP, a DC pode ser classificada em nociceptiva, nociplástica e neuropática [5].

A dor crônica é uma das principais causas de anos vividos com incapacidade em países desenvolvidos e em desenvolvimento [6] , o que a torna um relevante problema de saúde pública, uma vez que impacta negativamente os indivíduos e toda a sociedade [7] . Uma análise combinada de pesquisas da Europa, Américas, Austrália e Ásia mostrou que a dor crônica teve um impacto significativo fisicamente (51%), emocionalmente (40%) e na qualidade de vida (59%). Ao mesmo tempo, o tratamento precoce foi essencial para reduzir esse impacto; quanto mais tempo esperar pelo alívio de sua dor, mais grave será o impacto e o grau de cronicidade e maior será o custo para o sistema de saúde [8].

Embora a DC já tenha sido reconhecida como um problema mundial, ainda existem diversas lacunas a serem preenchidas sobre esse assunto e seus impactos na população, tais como: a falta de conscientização sobre a gravidade das implicações relacionadas à dor crônica; educação e conhecimento limitado sobre a dor crônica por parte do profissional de saúde e pacientes; dificuldade de acesso ao serviço especializado com equipe multidisciplinar, assim como o baixo investimento em pesquisas na área da dor. Por essas e outras razões, a dor crônica não aliviada é uma realidade triste e frequente [7].

No Brasil, um estudo recente conduzido por Santiago et al., [9] revelou uma elevada prevalência de dor crônica, cerca de 35 %. Portanto, pode-se considerar um problema de saúde pública e, desta forma, a sua investigação deve ser constantemente necessária [10-11]. Aproximadamente 60 milhões de pessoas sofrem de DC, correspondendo a cerca de 10% da população mundial [12]. Existem poucos estudos que buscam quantificar a prevalência da DC respeitando as diferenças entre as regiões geográficas, além das suas diversas particularidades étnicas e culturais. Sendo assim, são necessários estudos que possibilitem uma visão mais detalhada da DC, sobretudo quanto à etiologia, seus diferentes mecanismos fisiopatológicos e fatores associados predominantes, direcionando futuras ações estratégicas para as referidas condições.

Dentre as causas de dor crônica no Brasil, destaca-se aquela relacionada à Febre de Chikungunya (CHIKF), tanto pelo desconhecimento dos seus mecanismos fisiopatológicos, como pelo crescente número de casos documentados [13]. A CHIKF é uma doença viral, causada por um arbovírus – vírus Chikungunya (CHIKV) - pertencente ao gênero Alphavirus da família *Togaviridae,* e surtos recentes têm sido relatados em todo território brasileiro. Devido às características relacionadas ao tipo de clima tropical, além de questões sanitárias, o ambiente brasileiro tem propiciado a introdução do CHIKV [13].

A transmissão do CHIKV pode ocorrer através da picada de mosquitos infectados, *Aedes aegypti ou Aedes albopictus,* da mãe para o feto no período intrauterino perinatal, por transfusão sanguínea e por relações sexuais [13]. Principalmente transmitido em áreas urbanas, a CHIKF tem se tornado um grande problema de saúde pública em muitos países, incluindo a região Nordeste do Brasil. O surto da CHIKF na América Latina foi especialmente severo no Brasil, com 170.000 casos na primeira metade de 2016, correspondendo a 94% dos casos confirmados nas Américas [14].

Conforme os dados do boletim epidemiológico das semanas 1 a 16, do ano de 2022, o número de casos da CHIKF foi de 47.281 casos prováveis (22,2 casos por 100 mil hab.) no Brasil. Comparado ao ano de 2021, apresenta um aumento de 40% de casos. O aumento do número de casos tem como consequência uma maior demanda por serviços de saúde, além de uma crescente necessidade de recursos humanos e monetário [15].

A CHIKF é uma doença associada a um quadro clínico variável e tem se revelado como uma entidade clínica complexa e de manejo clínico desafiador [16]. Cronologicamente, pode ser caracterizada pela existência de três fases: aguda (5-14 dias), subaguda (até 3 meses) e crônica (>3 meses). Embora a recuperação completa desses sintomas ocorra dentro de 4-6

semanas, até 43% dos indivíduos infectados podem desenvolver sintomas persistentes marcados por dor articular, prejuízo funcional e da qualidade de vida [17].

Levando em conta o crescimento da epidemia por CHIKV e a prevalência de sintomas persistentes no primeiro ano após a fase aguda, o número cumulativo de indivíduos infectados pelo vírus Chikungunya sofrendo de dor debilitante e de longa duração é estimado em 1 a 2 milhões, sendo este um número crescente [18].

Alguns modelos experimentais de artrite induzida por alfavírus sugerem que a progressão para o estágio crônico da doença também possa resultar de uma combinação de dano celular e tecidual direto causado pela replicação viral e indiretamente pela ativação da resposta imune em tecidos-alvo [19].

Em nítido contraste com o considerável corpo de conhecimento - agora disponível sobre as vias imunes e a liberação de citocinas pró-inflamatórias - após a infecção por CHIKV, os fatores associados à dor articular crônica nestes indivíduos ainda não estão totalmente elucidados [20].

1. **JUSTIFICATIVA**

Notavelmente, é preciso levar em consideração que o Brasil é um país de dimensões continentais, com uma população heterogênea e grande desigualdade social. Consequentemente, a distribuição por gênero, localização do domicílio (rural ou urbana) [21], o acesso aos cuidados de saúde [21] e expectativa média de vida (mais baixa no norte e mais alta no sul) [22] variam de região para região ou mesmo em bairros distintos da mesma cidade [23]. Assim, determinar a prevalência de dor crônica no Brasil é um grande desafio, em primeiro lugar, pela escassez de trabalhos representativos de todas as regiões – trata-se do primeiro estudo de revisão sistemática com metanálise do país sobre o tema – em segundo lugar, pelo fato de a dor crônica estar associada a diversos fatores, tais como: idade, gênero, doença crônica e condições sociais. Entender todas essas peculiaridades regionais, bem como o seu impacto sobre a saúde é essencial para orientar as políticas de saúde pública.

Já em relação aos casos de dor articular crônica em pacientes acometidos pelo CHIKV, trata-se de um tema extremamente contemporâneo e de grande impacto na saúde pública [13], tendo em vista o crescente número de infectados e das formas persistentes da doença, ocasionando prejuízo funcional e piora da qualidade de vida [24] . Os mecanismos relacionados à cronificação da dor nestes indivíduos, também não são totalmente elucidados [25-26].

Dessa forma, faz-se necessária a condução de estudos para a avaliação de determinados fenômenos, os quais ocorrem ainda na fase aguda da CHIKF, tais como o papel da resposta inflamatória na dor articular a longo prazo [27], visando ao desenvolvimento de estratégias prognósticas e terapêuticas mais assertivas.

2. OBJETIVOS

2.1 Objetivos Gerais

Discutir dois artigos que versam, respectivamente, sobre a prevalência de dor crônica no Brasil, em suas 5 regiões, bem como os seus fatores associados, através de uma revisão sistemática com metanálise, além da análise de alguns fatores associados à cronificação da dor articular, após a infecção por CHIKV, em uma coorte retrospectiva no período de 2018-2019.

2.2 Objetivos específicos

a) Do 1º artigo:

- Sintetizar os dados existentes sobre a prevalência de dor crônica na população adulta brasileira, por meio de estudos representativos das 5 regiões do país, no período compreendido entre 2005-2020, com a finalidade de produzir estimativas nacionais mais precisas e guiar estratégias de saúde pública futuras;
- Explorar o tipo, a intensidade, localização e características da dor da população avaliada pelos estudos;
- Avaliar se as características sociodemográficas, geográficas, psicossociais estão relacionadas com as estimativas de prevalência.

b) Do 2º artigo:

- Avaliar a incidência de pacientes com dor articular crônica (3 meses ou mais), após a infecção por CHIKV, no período epidêmico compreendido entre 2018-2019, em usuários do sistema de saúde naval no Rio de Janeiro;
- Explorar os dados sociodemográficos de ambos os grupos (com e sem dor crônica articular), após a infecção por CHIKV;

- Avaliar o papel de alguns marcadores inflamatórios, através de amostras do soro de pacientes infectados durante a fase aguda da CHIKF, na cronificação da dor articular.

3 ARTIGOS

3.1 Artigo 1: Prevalence of chronic pain in Brazil: A systematic review and meta-analysis (Artigo publicado)

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Review articles

Prevalence of chronic pain in Brazil: A systematic review and meta-analysis☆

Bruno Vitor Martins Santiago[a,*], Ana Beatriz Garcez de Oliveira[a], Gabriel Machado Romão da Silva[b], Maxuel de Freitas da Silva[a], Pedro Ernandes Bergamo[a], Maud Parise[c], Nivaldo Ribeiro Villela[c]

[a] Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ, Brazil
[b] Faculdade de Medicina, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil
[c] Departamento de Especialidades Cirúrgicas, Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ, Brazil

HIGHLIGHTS

- The prevalence of chronic pain in the adult population (35.70%) and older adults (47.32%).
- Differs from region to region and is associated with heterogeneous risk factors.
- Manifested mainly with moderate or severe intensity and with an elevated rate of disability.

ARTICLE INFO

Keywords:
Chronic pain
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ABSTRACT

Objective: This review synthesized existing studies on the prevalence of chronic pain in Brazil and its associated factors to produce a recent estimation to guide public health politics.
Methods: A search was carried out in the Ovid Medline, Embase, Web of Science, and BVS Regional/Lilacs databases to identify population-based cross-sectional studies from 2005 to 2020, which reported the prevalence of benign chronic pain in Brazil (more than three months). The risk of bias was assessed using design, sample size determination, and random selection as essential issues. Pooled prevalence estimates were calculated for chronic pain in the general and elderly populations. The protocol was registered on Prospero (CRD42021249678).
Results: Of the 682 identified, 15 macheted the authors' inclusion criteria. Chronic pain prevalence in the general adult population ranged from 23.02% to 41.4% (pooled estimate 35.70%, 95% CIs 30.42 to 41.17) and was described as moderate to intense. It was associated with female sex, old age, lower education, intense professional activity, excessive alcohol consumption, smoking, central obesity, mood disorder, and sedentarism. The Southeastern and Southern regions presented a higher prevalence. The prevalence in the elderly population ranged from 29.3% to 76.2% (pooled estimate 47.32%, 95% CIs 33.73 to 61.11). In addition, this population visited doctors more frequently, had more sleep disorders, and was more dependent on daily living activities. Almost fifty percent of both populations with chronic pain reported pain-induced disability.
Conclusion: Chronic Pain is highly prevalent in Brazil and associated with significant distress, disability, and poorly controlled.

Introduction

Chronic Pain (CP) is a common, complex, and distressing disorder. According to the International Association for the Study of Pain (IASP), CP is "pain which has persisted beyond normal tissue healing time", which, in the absence of other factors, is generally taken to be 3 to 6 months or longer.[1] Although commonly present due to an injury or a disease, chronic pain is no longer considered just a symptom but rather a disease. It is a multidimensional phenomenon that involves physical, psychological, and sociocultural aspects and impacts the individual's health and well-being, health care services, and society.

CP is an underestimated healthcare problem, impacting the quality of life.[2] It has been highlighted as one of the most prominent causes of disability worldwide by the Global Burden of Disease reviews. The

*Corresponding author.
E-mail address: Santiago.bruno@posgraduacao.uerj.br (B.V.M. Santiago).
☆ The protocol for the review was planned following PRISMA guidelines and registered on Prospero (CRD42021249678).

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systematic analysis considered global, regional, and national incidence, prevalence, and Year Lived with Disability (YLD) for 354 acute and chronic diseases and injuries in 195 countries between 1990 and 2017. Over the 28 years studied, low back pain, headache disorders, and depressive disorders have prevailed as three of the top four leading diseases/conditions that caused people to live with a disability. The persistence of depressive disorders and low back pain is significant given the former's relation with self-harm and the latter with a potential loss of functional status in the workforce.[3]

Many countries recognize that chronic pain represents a major priority and challenge for their public health and healthcare systems. In this sense, it is essential to know the prevalence of chronic pain in each population to define appropriate strategies.

Worldwide, one in five adults suffers from pain, and 1 in 10 adults is diagnosed with chronic pain each year, according to IASP data.[1] While pain affects all populations, regardless of age, sex, income, race/ethnicity, or geography, it is not equally distributed globally since its prevalence is associated with social and economic conditions. Factors such as Pain coping, and racial/ethnic, occupational, or cultural differences could partially explain this difference.[4]

Brazil is a continental country with significant regional population variability. Data on the prevalence of chronic pain in the country are poor, especially when analyzing neglected subgroups (such as the elderly population, for example) and records from the 5 regions of the country. Therefore, determining chronic pain prevalence in different regions in Brazil and its associated risk factors is essential to guide public health policies.

The primary aim of this review was to synthesize existing data on the prevalence of chronic pain in the adult Brazilian population, through representative studies of the 5 regions of the country, to produce more accurate national estimates. The secondary aim is to explore the type, intensity, location and characteristics of the pain of the population evaluated by the studies and whether sociodemographic, geographic, and psychosocial characteristics are related to prevalence estimates.

Material and methods

This systematic review and meta-analysis are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis PRISMA. The study protocol was submitted to the International Prospective Register of Systematic Reviews PROSPERO (registration number CRD42021249678).

Search strategy and study selection

The authors searched Ovid MEDLINE, EMBASE, Web of Science, and BVS Regional/Lilacs from 2005 to 09/2020 (confirmed after six months: March 2021). The following medical subject heading (MeSh) and text terms were used (Supplemental Table 1) and run with Endnote software.

Eligibility criteria

The authors included all full-text articles published since 2005 that determined the prevalence of benign chronic pain, lasting three months or longer, in Brazil. The inclusion criteria used were cross-sectional population-based surveys with an adult population aged over 18 years, with self-report diagnoses, written in English, Portuguese, or Spanish.

Reasons for exclusion included the following: (1) Not report the prevalence of benign chronic pain; (2) Conference papers; (3) Reviews; (4) Data from medical record reviews; (5) Studies from which more than one publication has arisen or (6) Abstracts without full text.

Study outcome

Prevalence of chronic pain

The primary outcome was the prevalence of benign chronic pain in adults. Although the specific interpretation of chronic pain may differ across studies, the authors applied the following definition of chronic pain as the basis for inclusion: pain lasting 3 months or longer.[1] Studies meeting inclusion criteria were classified according to the type of pain investigated, specifically by organ system and anatomic structure per criteria established by the ACTTION[5] – American Pain Society Pain Taxonomy: These categories included the following: (1) Widespread musculoskeletal pain, (2) Localized musculoskeletal pain, (3) Low back/spinal pain, (4) Neuropathic pain (eg, neuralgia) and (5) Headache.

Sociodemographic, geographic, and psychosocial factors related to chronic pain

The authors explored variation in chronic pain prevalence by demographic, geographic, and psychosocial factors known to be related to risk for chronic conditions. Depending on the available data, these factors included but were not limited to (1) Sociodemographic variables (eg, sex, ethnicity/race, occupation, and education), (2) Geographic region, and (3) Psychological and behavioral health variables (eg, depression, anxiety, obesity, and disability).

Data extraction and risk of bias

After removing the duplicated articles, five researchers (B.V.M.S.; A. B.G.A.; GMRS, M.F.S.; and P.E.B.) trained by the first and third authors (M.P.; N.R.V) extracted data from each article meeting the inclusion criteria using a data extraction form, which was double coded by either the primary or third author; discrepancies were resolved by consensus.

The authors made a standardized form – with an Excel sheet – to extract meaningful information: study locations, year of article publication and data collection, study designs, number and age of the individuals in each study, the period of chronic pain considered in the studies, the prevalence of benign chronic pain (Table 1).

The factors associated with chronic pain were also extracted from the studies: sex; educational level; occupational activity, alcohol consumption; smoker status; central obesity; mental disorder; time activity; self-perception of health; marital status, and region of the country) and will be discussed in this review.

In addition, two researchers assessed the risk of bias for each study using a score of nine items, adapted from Hoy et al.,[6] to evaluate the articles and, depending on the score, classified as low risk (score 0–3), moderate risk (score 4–6), and high risk (score 7–9) (Supplemental Table 2). Finally, one other researcher helped in the decision process in case of disagreements between reviewers' judgments.

Missing data

If authors reported incomplete information (eg, providing the prevalence rate in a figure only), they were contacted by the first author (B.V.M.S) with a request to submit this information. Specifically, the authors asked the authors to provide missing descriptive data (i.e., frequencies) to determine prevalence rates in the adult age group (eg, the total number of adults in the sample, number of adults with pain condition and breakout by sex, when possible). Those without a working email were contacted through Research Gate. A reminder was sent 2 weeks after the first contact in case the authors had not responded. If a response was not obtained, the study was excluded.

Data analysis and syntheses

The authors used a descriptive statistic (percentage) to summarize the prevalence rate from individual studies. Data analyses were

Table 1
Details of selected studies.

First author and publication year	N (Gender, Male/ Female%)	City/ State/ Region	Method	Study period	Age	Period of chronic pain considered	Prevalence of chronic pain (%)	Risk of bias (score)[6]
Sá et al.[17] (2006)	2.297 (44.6/55.4)	Salvador/ Bahia NE	Domiciliary interview	1999–2000	40.91±14.73	> 6 months	41.4	Low (1)
Cordeiro et al.[8] (2008)	2.341 (35.41/64.59)	Buriticupu/Maranhão/ NE	Domiciliary interview	2001	30 (from 16 to 98)	> 3 months	23,02	Low (3)
Moraes Vieira et al.[14] (2012)	1.597 (33.6/66.4)	São Luís/ Maranhão/ NE	Domiciliary interview	2009–2010	39.5 ± 16.6	> 6 months	42.33	Low (1)
Cabral et al.[12] (2014)	826 (31/69)	São Paulo City/ São Paulo/ SE	Domiciliary interview	2011–2012	51.4 ± 19.3	> 6 months	42.01	Low (1)
Ferreira et al.[13] (2016)	2.446 (38.1/61.9)	São Paulo City/ São Paulo/ SE	Telephone interview		≈39.8 ± 18.2	> 3 months	28.09	Low (1)
Pereira et al.[15] (2017)	5.037 (47–53)	São Paulo City/ São Paulo/ SE	Domiciliary interview	2005–2007	≈39.0 ± 13.5	> 6 months	30.99	Low (2)
Souza et al.[25] (2017)	723 (48/52)	Several/ Several/ N, NE, SE, S	Cell phone interview	2015–2016	≈37.6 ± 0.81	> 6 months	38.45	Low (1)
Souza et al.[18] (2019)	560 (27.6/72.4)	Pelotas/ Rio Grande do Sul/ S	interview at primary care office	2018	48.0 ± 17.2	> 3 months	41.48	Low (2)
Blay et al.[7] (2007)	6.963 (34/66)	Several/ Rio Grande do Sul/ S	Domiciliary interview	1995–1996	≈69.9 ± 28.1	> 6 months	76.20	Low (3)
Dellaroza et al.[9] (2013)	1.271 (40.4/59.6)	São Paulo City/ São Paulo/ SE	Domiciliary interview	2006	69.5 ± 17.7	> 6 months	29.66	Low (2)
Pereira et al.[16] (2014)	872 (37.7/62.3)	Goiania/ Goiás/ M	Domiciliary interview	2010	≈70.4 ± 6.2	> 6 months	52.75	Low (1)
Santos et al.[18] (2015)	1.656 (37.5/62.5)	Florianópolis/ Santa Catarina/ S	Domiciliary interview	2009–2010	≈70,0 ± 5.9	> 6 months	30.01	Low (1)
Lini et al.[12] (2016)	416 (56.7/43.3)	Passo Fundo/ Rio Grande do Sul/S	Domiciliary interview	2011	69.0 ± 7.6	> 3 months	54.57	Low (1)
Torres et al.[23] (2018)	383 (29/71)	Belo Horizonte/ Minas Gerais/ SE	Domiciliary interview	2008–2009	75.6 ± 6.1	> 6 months	30.03	Low (1)
Perrelli et al.[19] (2019)	385 (32.7/67.3)	Chapecó, Santa Catarina/ S	Domiciliary interview	2016	≈71.3 ± 6.7	> 3 months	58.18	Low (1)

N, Northern; NE, Northeastern; M, Midwest; SE, Southeastern; S, Southern. Age is presented as mean ± SD or means (range).

performed using RStudio (version 2.1.4). For all tests, $p < 0.05$ was deemed significant.

Random-effects meta-analyses were used to calculate prevalence estimates owing to the high expected heterogeneity between studies. Prevalence statistics were depicted using the event rate. Ninety-five percent Confidence Intervals (CIs) were calculated using the sample size (n) and standard error. The authors calculated an overall prevalence rate across all pain conditions and prevalence rates stratified by pain condition.

The authors assessed the heterogeneity of prevalence estimates among studies using both the Begg's Test and I^2 statistics. For the I^2 index, values of 75% or higher represented high degrees of heterogeneity.

Subgroup analyses

The summaries were described into two groups: the prevalence of benign chronic pain in the general adult population and the elderly population. In addition, the risk/associated factors related to chronic pain were described.

Results

Search results

The authors selected 682 articles for screening, being that 128 were duplicates. Then, after additional screening by title and abstract from the 554 that remained, the researchers excluded 475 articles. Finally, the authors (N.R.V.; and B.V.M.S.;) read the full text of the 79 remaining papers. 64 articles excluded: 54 = did not report the prevalence of chronic pain; 2 = data from medical records reviews; 2 = studies in which more than one publication has arisen; 4 = abstract without full text (authors did not respond) and 2 = selection bias. 15 studies were eligible for final analysis (Table 1).[7–21] The full process and reasons for exclusion can be found in the PRISMA flow diagram (Fig. 1).

Characteristics of the included studies

Supplemental Table 2 displays the overall characteristics of the studies included in the meta-analysis. The 15 included studies were published between 2005 and 2020. Sample sizes ranged from 383 to 6.963, including a total of 27.773 participants.

The studies showed wide variations in chronic pain prevalence; therefore, the authors reported the prevalence of the adult and elderly populations.

Study quality and risk of bias

Supplemental Table 2 displays the score of risk of study bias, showing how many of the 9 criteria adapted from the Hoy et al.[6] Quality ratings ranged from 0 to 1. All articles had a low score of bias.

The 15 final studies selected applied different surveys methods: twelve studies performed domiciliar interviews (80%);[7–10,12–18,21] one study used a computer-assisted telephone interview;[11] another accessed the responders by their cell phone using a private database to random the sample,[20] and one interviewed the users of 38 units of primary care offices.[19] Ten articles determined the sample size for the chronic pain prevalence study,[10–14,16–20] and twelve selected the responders in a random approach.[9–16,20,21]

Different periods for chronic pain were established by studies. As listed in Table 1, pain duration of > 6 months was the most used definition of chronic pain (n = 9; 60% of studies), followed by pain lasting > 3 months (n = 6; 40% of studies).

Regarding geographic factors related to the prevalence of chronic pain, it should be noted that of the 15 articles that were included in this review, six had participants from the Southern region and eight from the Southeastern region (Table 1).

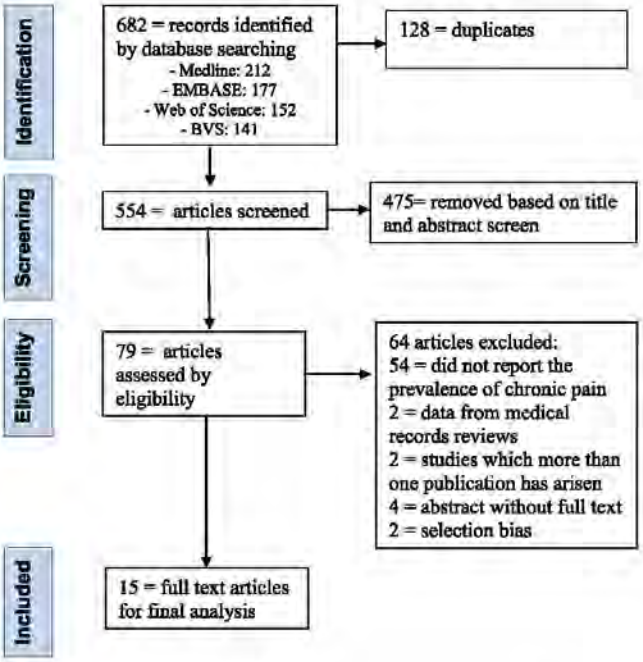

Fig. 1. Flow diagram of researched articles.

Stratified prevalence of chronic pain in adults and elderly population

Prevalence of chronic pain in the adult population

Eight studies presented prevalence data of chronic pain in the adult population.[8,11,13–15,17,19,20] In addition, five studies evaluated the respondents by a domiciliary interview,[8,13–15,17] one by consultation of primary care users,[19] one by telephone interview,[11] and one by cell phone interview. The reported prevalence of chronic pain in the adult population ranged from 23.02% to 42.33%, and the overall median prevalence was 35.70% (95% Cis 30.42 to 41.17) I_2 = 98% / p = 0.01 (Fig. 2).

In addition, the articles reported data on the population from different regions of Brazil, and male participants comprised between 27.6% and 48%.

Heterogenicity of the studies of the adult population

The studies showed a difference in sex and age distribution that could justify different categories. The difference was also apparent regarding geography (Fig. 3): three studies described the prevalence in São Paulo City,[11,13,15] the biggest city in Brazil; one from diverse regions (Northern, Northeastern, Midwest, Southeastern, and Southern);[20] three from Northeastern (Maranhão and Bahia),[8,14,17] a more impoverished area;[22] and one from Southern[19] (Pelotas) a region with a higher number of elderly[23] (Table 1).

Factors associated with chronic pain in the adult population

The studies found an association between chronic pain and gender (female),[8,11,13–15,17,19,21] older age,[8,11,13–15,17,19] lower educational level,[11,13,15] intense or heavy occupational activity,[13] excessive alcohol consumption for women,[17] smoking in men and ex-smoker status in both men and women,[17] presence of central obesity,[17] anxiety, mood, and mental disorder,[13,15] lower laze time activity, and negative self-perception of health.[19] The Southeastern and Southern regions presented a higher prevalence,[21] and when respondents indicated their marital status as separated, widowed, divorced, or single, they reported less pain.

Pain intensity and site in the adult population

The more frequent pain sites were the lumbar region,[8,13,17,19] cephalic region,[14] joints,[15] legs and feet,[11] and upper limbs.[20] The most frequent location for the responders with chronic pain with neuropathic characteristics was the lower limbs.[14] One study found a prevalence of 15% of widespread pain.[20] In addition, one study reported a prevalence of neuropathic pain of 10%, evaluated by the Douleur Neuropathic 4 Questions (DN4) tools.[14] Four articles presented the responders' mean average pain as moderate.[11,13–15] Another described that 92.4% classified their pain as moderate, intense, strong, or unsupported,[19] and one study reported pain-induced disability in 52.7% of the responders.[20]

Chronic pain prevalence in the elderly

Seven articles presented the prevalence of chronic pain, through domiciliary interviews, in the elderly population.[7,9,11,12,16,18,21] In addition, they assessed the people from different regions in Brazil: one from São Paulo city,[9] four from the Southern region,[7,9,12,18] one from Belo Horizonte (Southeastern),[21] and another from Goiania (Midwest).[16] The prevalence of chronic pain ranged from 29.66% to 76.20%, and the overall median prevalence was 47.32% (95% Cis 33.73 to 61.11) I^2 = 100% / p = 0.034 (Fig. 2). Male participants comprised between 29% and 56.7% (Table 1).

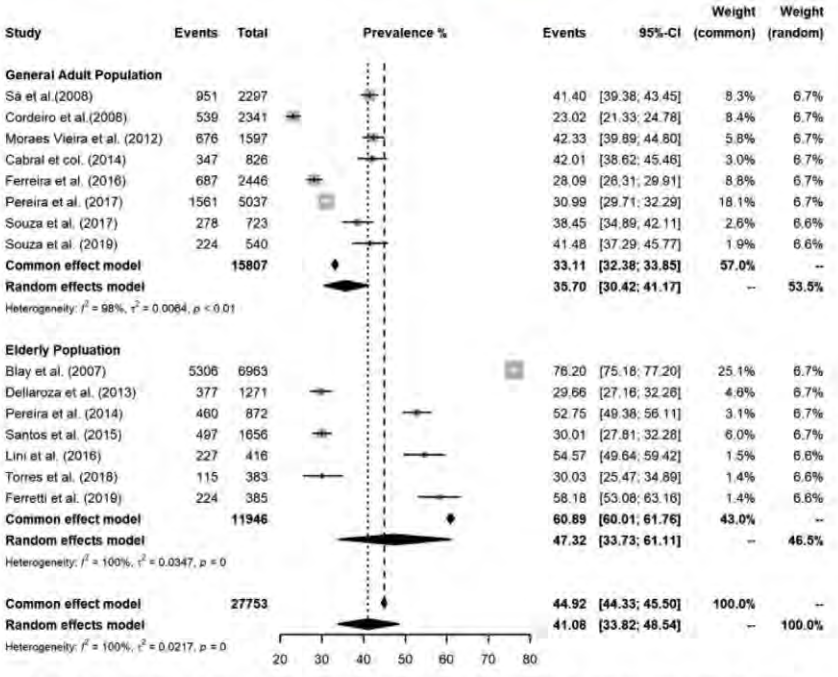

Fig. 2. Pooled estimates for chronic pain prevalence in the general adult population by publication date and by subgroups.

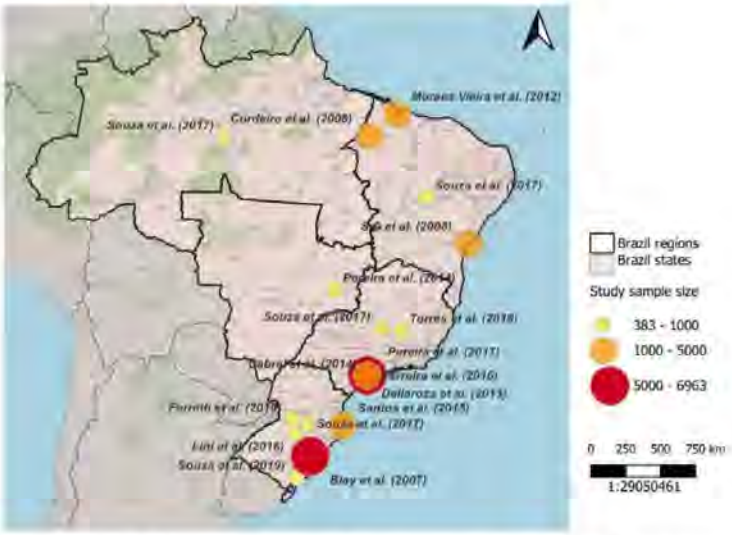

Fig. 3. The figure shows the map of Brazil with the identification of the regions where the surveys were carried out and the representation of the sample sizes (author and year of publication).

Factors associated with chronic pain in the elderly population

The studies found an association between chronic pain in the elderly and gender (female),[7,10,12,16,18] lower years of education,[16] the economic situation,[12,18] lower laze time activity, [18] sedentarism,[10,12] and presence of chronic disease.[10,16] In addition, responders with chronic pain visited doctors more frequently in the last 12 months,[21] had more sleep disorders,[7] and were more dependent on daily living.[12]

Pain intensity and pain site in the elderly population

The more frequent pain sites in the elderly responders were lower limbs,[12,16] joints,[7] and the lumbar region.[9] One study found that 15.1% of the responders reported feeling pain in more than three locations.[16] In addition, the majority of the individuals with chronic pain described their pain intensity as moderate or severe,[9,10,16,18] and 48.2% had pain-related disabilities.[21]

Discussion

This systematic review revealed that the prevalence of benign chronic pain in Brazil is high, worst in the elderly population, differs from region to region and is associated with heterogeneous risk factors. Besides, chronic pain is manifested mainly with moderate or severe intensity and with an elevated rate of disability.

The articles presented variability in the methods and groups studied; therefore, the authors summarized the data from studies that evaluated the prevalence of benign chronic pain in the adult population and the elderly population. Thus, the estimated prevalence of chronic pain in the adult population and older adults is 35.70% and 47.32%, respectively.

Brazil is a continental country with a heterogeneous population and great social inequality. Consequently, gender distribution, domicile location (rural or urban),[24] access to health care,[25] and average life expectancy (lower in the north and higher in the south)[26] vary from region to region or even in the city's distinct neighborhoods.[27] Thus, determining chronic pain prevalence in Brazil is a great challenge since chronic pain is associated with age, gender, chronic disease, and social condition. Understanding all these regional peculiarities and their impact on health is essential to guide the politics of public health.

Sá et al.,[28] in a meta-analysis, described a prevalence of chronic pain of 18% in developing countries. However, the presence of a young population, a more significant number of telephone interviews,[29] a possible regional influence, and other questions related to the methods of the selected articles would justify this low prevalence. On the other hand, Jackson et al.[30] described wide variability and high prevalence of chronic pain without clear etiology in low and middle-income countries (26%–42% in the general population and 41%–81% in the older people), where the elderly and workers had the higher prevalence, which is similar to the findings of the present research.

In a study in the United Kington (UK), Fayaz et al.[31] described that the prevalence of chronic pain in the general population is 43%. Furthermore, those over 75 years old would be 62% affected. Since the life expectancy is higher in the UK and has an older population, the authors can assume a higher prevalence than in Brazil.

Concerning the pain characteristics, one article found that fifteen percent of the responders had widespread pain,[20] and in another study, 15.1% of the elderly had pain in more than three locations.[16] Assuming that central sensitization occurs between five to fifteen percent of the general population,[32] these data suggest nociplastic pain as a possible diagnostic in these groups. In addition, one article found a prevalence of chronic neuropathic pain of 10%, and the site more affected in this group was lower limbs.[14]

Regarding pain intensity, the responders referred to moderate intense. Additionally, in one study, fifty percent reported pain-related disabilities, and 48.7% referred to their pain treatment as "no effect" or "minor effect".[20]

Concerning mental health, one article found that responders with pain had 2.3 times more anxiety disorders, 3.3 times more mood disorders, and 2.7 times more mental disorders.[15] Stubbs et al.[33] described depression and chronic pain are elevated comorbidities present in low and middle-income countries, independent of anxiety and chronic medical conditions. Furthermore, depression was associated with a higher risk for severe pain.

The articles showed an association between lower economic conditions or lower education, suggesting a relationship between socioeconomic disadvantage and chronic pain.[11–14] Besides, central obesity[17] and sedentarism[10,12,18,19] were associated with chronic pain. Previous studies support the association of socioeconomic status and chronic pain.[34] Issues such as inappropriate use of pain coping strategies, race, ethnicity, occupational reasons, exposition to violence, and absence of familiar or social support are some of the involved factors.[3]

The studies with the largest sample representation of participants who responded to the surveys came from the Southern and Southeastern regions. They demonstrated an overall prevalence of chronic pain in adult subjects ranging from 29.66% to 76.20%. These results can be expected, since there is a higher prevalence of elderly people in the population, in addition to a greater number of studies including these regions. In contrast, the smaller sample representation of participants in the Northern and Midwest regions. This can be explained by the smaller number of local studies including; lower human development index and schooling, which could influence access to diagnosis (mainly in the Northern region), corroborating with the findings of Souza et al.[20]

The present review has the merit of getting together the primary studies about Brazil's prevalence of chronic pain and its associated factors. Almost all selected studies performed face-to-face interviews and had a representative number of responders. However, the authors found some limitations. For example, there was wide variability in the study's method; several studies did not describe the prevalence of the general population, being not eligible. Besides, five eligible studies did not calculate the sample size, and the authors did not perform search references from gray literature. Also, interpretation regarding factors associated with chronic pain should be taken into account with caution since the selected articles were transversal studies. The authors decided to summarize studies performed in the last fifteen years since Brazil's population has changed with progressive aging.[23] Older studies could not reproduce the actual situation of chronic pain prevalence.

Conclusion

In conclusion, the authors have used the best available articles to demonstrate that benign chronic pain is highly prevalent in Brazil and associated with significant distress, disability, and poorly controlled. Such data suggests the necessity of prioritizing this population's access to qualified and experienced professionals in dealing with chronic pain, improving patient education about its chronic condition, and strengthening the biopsychosocial model, especially in primary care.

Authors' contributions

(1) Elaboration of the research question and (2) Literature search: B.V.M.S; M.P and N.R.V; (3) Selection of articles, (4) Data extraction (5) Assessment of methodological quality and (6) Assessment of the quality of evidence: B.V.M.S.; A.B.G.A.; G.M.R.S, M.F.S.; P.E.B.; M.P and N.R.V); (7) Data synthesis (meta-analysis): B.V.M.S and N.R.V; (8) Writing and publishing the results: B.V.M.S; M.P and N.R.V.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinsp.2023.100209.

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3.2 **Artigo 2: High serum levels of IL-1β and IP-10 markers in the acute phase of Chikungunya fever correlate with chronic joint pain (Artigo Submetido)**

Medical Microbiology and Immunology

High serum levels of IL-1β and IP-10 markers in the acute phase of Chikungunya fever correlate with chronic joint pain

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Corresponding Author:	Bruno Vítor Martins Santiago, M.D; M.S.c Rio de Janeiro State University: Universidade do Estado do Rio de Janeiro Rio de Janeiro, RJ BRAZIL
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Rio de Janeiro State University: Universidade do Estado do Rio de Janeiro
Corresponding Author's Secondary Institution:	
First Author:	Bruno Vítor Martins Santiago, M.D; M.S.c
First Author Secondary Information:	
Order of Authors:	Bruno Vítor Martins Santiago, M.D; M.S.c
	Thaís Crispim de Souza Giangiarulo, Medical Student
	Shana Priscila Coutinho Barroso, MD., M.Sc., PhD
	André Costa Ferreira, MD., M.Sc., PhD
	Maud Parise, MD., M.Sc., PhD
	Nivaldo Ribeiro Villela, MD., M.Sc., PhD
Order of Authors Secondary Information:	
Funding Information:	
Abstract:	Background and objectives: Chikungunya fever (CHIKF) is a viral disease and sporadic outbreaks have been reported in tropical regions. Many infected people develop chronic symptoms marked by persistent pain, impairing patients' quality of life. In this study, we evaluated the role of the inflammatory response during the acute phase of CHIKF and long-term pain. Methods: A retrospective cohort of individuals exposed to the Chikungunya virus during the epidemic period in Rio de Janeiro (2018-2019) was analyzed. Eighty-one individuals of both sexes, aged between 18-65 years diagnosed with CHIKF using IgM enzyme-linked immunosorbent assay or reverse transcriptase polymerase chain reaction, were included in the study. Follow-up survey was performed to ascertain disease progression (joint pain lasting 3 months or longer). In addition, inflammatory biomarkers were measured using a multiplex bead assay in the blood samples collected at the time of diagnosis. Results: Of the 81 patients, 27 (33.3 %) developed chronic joint pain and 54 (66. 6 %) were diagnosed with CHIKF without criteria for chronic joint pain. The majority incidence of chronic joint pain in the sample was the in women between the 4th and 6th decade of life, who were obese with a low level of education. Arthritis (p=0.008) and serum levels of Interleukin 1- beta - IL-1β (p=0.0135) in the acute phase were significantly higher in the group of patients with chronic joint pain. A correlation was observed between high levels of Interferon-gamma inducible Protein 10kDa - IP-10 (p=0.041) and IL-1β (p=0.015) and the development of chronic joint pain. Elevated serum level of IL-10 was a protective factor against the development of chronic joint pain (p=0.038). Conclusion: The inflammatory profile of patients in the acute phase of CHIKF may be associated with the development of chronic joint pain.

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Manuscript

Title: High serum levels of IL-1β and IP-10 markers in the acute phase of Chikungunya fever correlate with chronic joint pain

Run Title: High serum levels of IL-1β and IP-10 and chronic joint pain in Chikungunya Fever

Bruno Vitor Martins Santiago[a], Shana Priscila Coutinho Barroso[b],Thais Chrispim de Souza Carvalho Giangiarulo[c], André Costa Ferreira[d], Maud Parise[e], Nivaldo Ribeiro Villela[f]

[a] Faculdade de Ciências Médicas. Universidade do Estado do Rio de Janeiro (UERJ) e Hospital Naval Marcílio Dias (HNMD), RJ, Brazil

Email: Santiago.bruno@posgraduacao.uerj.br; http://lattes.cnpq.br/8774794011627816
Orcid: 0000-0002-2712-6311

[b] Departamento de Biologia Molecular, Instituto de Pesquisas Biomédicas, Hospital Naval Marcílio Dias (HNMD), Marinha do Brasil, RJ, Brazil.

Email: shanapriscila@gmail.com; http://lattes.cnpq.br/1566731961212840
Orcid: 0000-0001-7890-9255

[c] Departamento de Biologia Molecular, Instituto de Pesquisas Biomédicas, Hospital Naval Marcílio Dias (HNMD), Marinha do Brasil, RJ, Brazil.

Email: thaisgiangiarulo@gmail.com; http://lattes.cnpq.br/9344588451993149
Orcid: 0000-0001-6811-1557

[d] Laboratório de Imunofarmacologia, Instituto Oswaldo Cruz, (FIOCRUZ), RJ, Brazil.
Email: andre.bio2009@gmail.com; http://lattes.cnpq.br/8727053528841040

Orcid: 0000-0002-9064-2351

[e] Departamento de Especialidades Cirúrgicas, Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ, Brazil

Email: parise@infolink.com.br; http://lattes.cnpq.br/7421211262987888;

Orcid: 0000-0002-4639-0011

[f] Departamento de Especialidades Cirúrgicas, Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ, Brazil

Email: nivaldovillela@terra.com.br; http://lattes.cnpq.br/9217040898313692
Orcid:0000-0002-5947-9189

Correspondence author: Bruno Vítor Martins Santiago
Email: Santiago.bruno@posgraduacao.uerj.br

Address: Boulevard 28 de setembro, nº 77, Vila Isabel – Rio de Janeiro, Brazil.

Postcode: 20550-900 / Contact: +5521998124018

[1] Abbreviations

[1] CHIKF, Chikungunya fever; CHIKV, Chikungunya virus; IFN-α, interferon-alfa; interleukin-6, IL-6; , IL-1β ,Interleukin 1- beta; IL-1Ra, Interleukin-1 receptor antagonist; IL-18, interleukin-18; IL-12, interleukin-12; IL-15, interleukin-15; IP-10, Interferon-gamma inducible Protein 10kDa; MCP-1, Monocyte chemoattractant protein-1; RT-PCR, Real-time polymerase chain reaction.

ABSTRACT

Background and objectives: Chikungunya fever (CHIKF) is a viral disease and sporadic outbreaks have been reported in tropical regions. Many infected people develop chronic symptoms marked by persistent pain, impairing patients' quality of life. In this study, we evaluated the role of the inflammatory response during the acute phase of CHIKF and long-term pain. **Methods:** A retrospective cohort of individuals exposed to the Chikungunya virus during the epidemic period in Rio de Janeiro (2018-2019) was analyzed. Eighty-one individuals of both sexes, aged between 18-65 years diagnosed with CHIKF using IgM enzyme-linked immunosorbent assay or reverse transcriptase polymerase chain reaction, were included in the study. Follow-up survey was performed to ascertain disease progression (joint pain lasting 3 months or longer). In addition, inflammatory biomarkers were measured using a multiplex bead assay in the blood samples collected at the time of diagnosis. **Results:** Of the 81 patients, 27 (33.3 %) developed chronic joint pain and 54 (66. 6 %) were diagnosed with CHIKF without criteria for chronic joint pain. The majority incidence of chronic joint pain in the sample was the in women between the 4th and 6th decade of life, who were obese with a low level of education. Arthritis (p=0.008) and serum levels of Interleukin 1- beta - IL-1β (p=0.0135) in the acute phase were significantly higher in the group of patients with chronic joint pain. A correlation was observed between high levels of Interferon-gamma inducible Protein 10kDa - IP-10 (p=0.041) and IL-1β (p=0.015) and the development of chronic joint pain. Elevated serum level of IL-10 was a protective factor against the development of chronic joint pain (p=0.038). **Conclusion:** The inflammatory profile of patients in the acute phase of CHIKF may be associated with the development of chronic joint pain.

Keywords

Chikungunya fever, chronic pain, inflammation, joint, cytokines,

- **Question:** Could the elevation of cytokines, chemokines and inflammatory markers in the acute phase of CHIKF infection be associated with the development of chronic joint pain in patients infected with CHIKV?

- **Findings:** Elevated levels of IL-1β were significantly higher in patients with chronic pain. Elevated IL-1β and IP-10 levels were positively correlated with the development of chronic pain after CHIKF. IL-10 was negatively correlated with chronic pain outcome.

- **Significance:** The inflammatory profile of patients in the acute phase of CHIKF may be associated with the development of chronic joint pain.

INTRODUCTION

CHIKF was first discovered in 1953 during an epidemic in Tanzania, and its transmission can occur through the bite of infected mosquitoes, *Aedes aegypti* or *Aedes albopictu* [1]. The CHIKF outbreak in Latin America was especially severe in Brazil, with 170,000 cases in the first half of 2016, corresponding to 94% of confirmed cases in the Americas [2], and is still a significant public health problem [3,4].

The acute phase seems to be associated with viremia and the onset of innate immunity is related to high levels of pro-inflammatory cytokines and chemokines, such as IFN-α, IL-6, IL-1Ra, IL-18, IL-12, IL-15, MCP-1 [5-6].

The immune response against Chikungunya virus (CHIKV) during the early acute phase has not been fully elucidated [7]. Some data suggest that the robust cytokine response is necessary for viral clearance, and cytokines that are related to immune tolerance during acute infection may be protective against chronic arthritis pathogenesis [8]. Jacob-Nascimento [9] demonstrated that chemokines may play an important role in the immunopathogenesis of chronic arthralgia related to chikungunya.

Some experimental models of alphavirus-induced arthritis suggest that progression to the chronic stage of the disease may also result from a combination of direct cellular and tissue damage caused by viral replication and indirectly by activation of the immune response in target tissues [10].

In sharp contrast to the considerable body of knowledge now available regarding immune pathways and pro-inflammatory cytokine release following CHIKV infection, the factors associated with long-term joint pain in these individuals remain unclear. The impact of CHIKV on public health is often underestimated. Generally considered a mild condition of short duration; however, recent outbreaks have reported a higher incidence of severe illness, fatality, and long-term disability [11].

Thus, this article presents findings from the follow-up of a Brazilian cohort of patients with pain after CHIKV infection, as well as the role of some inflammatory markers during the acute phase of CHIKF. Our hypothesis is that CHIKV cases with greater inflammatory response during acute infection are more likely to develop chronic joint pain.

MATERIALS AND METHODS

Design

We conducted a descriptive and retrospective cohort of patients exposed to CHIKV during the 2018-2019 Brazilian epidemic period. The research was conducted at the Hospital Naval Marcílio Dias, in partnership with the State University of Rio de Janeiro and the Oswaldo Cruz Foundation.

The **STROBE** checklist was used to systematize the recommendations about the study.

Ethical Considerations

The institucional review board approved the research protocol **(Protocol Number: 42340920.7.0000.5259)**, and written informed consent was obtained from all patients.

Participants

This study was conducted as part of an enhanced surveillance investigation designed to monitor arboviral infections among acute febrile patients at an emergency health center in Rio de Janeiro during the epidemic period of 2018-2019. We collected blood samples and interviewed the patients to obtain demographic, epidemiological, and clinical data.

Setting

Blood samples were collected and centrifuged during the acute phase (≤ 14 days after symptom onset), and sera were frozen at -80°C and -20°C until molecular and serological analyses, respectively. A total of 250 blood samples were collected from suspected CHIKF patients. Of these, 100 met the inclusion criteria for the study **(Figure 1)**.

A cohort of 100 individuals exposed to CHIKV, either military or dependent on the Naval Health System, was analyzed. Individuals of both sexes, aged 18-65 years, with a confirmed diagnosis of CHIKF, either through serological or molecular biology tests (real-time polymerase chain reaction [RT-PCR]), were included in this study. Briefly, viral RNA was obtained using the serum Maxwell Total RNA Purification kit (Promega ™, Madison, WI, USA), according to the manufacturer's instructions. The product obtained was amplified by RT-PCR (Promega™ Madison, WI, USA) using previously designed primers targeting CHIKV, DENV, and ZIKV [12]. Acute-phase samples were tested by enzyme-linked immunosorbent assay for the presence of immunoglobulin M against CHIKV (Euroimmun™, Lübeck, Germany) using serum samples, in accordance with the manufacturer's specifications.

Cohort follow-up

Between November 2020 and March 2021, telephone follow-up was performed for all patients with laboratory evidence of CHIKV infection to obtain self-reported data on disease resolution or progression and duration of symptoms. The definitions recommended by the Brazilian Society of Rheumatology were used as diagnostic criteria for arthralgia and arthritis after CHIKF [13,14]. A standardized questionnaire was used to collect data on the evolution of clinical manifestations, particularly on the persistence or resolution of chronic joint pain. Patients with previous chronic pain were excluded from the study (n=19).

The 81 participants were asked about the evolution of the pain condition and were allocated into two groups: Group 1 (Chronic Pain), patients diagnosed with CHIKF who developed joint pain lasting 3 months or longer (n=27), according to the *International Association for the Study of Pain* [15]; and Group 2 (No Chronic Pain), patients diagnosed with CHIKF without criteria for chronic pain (n=54).

Inflammatory markers measurements in serum

Measurement of serum inflammatory markers in blood samples collected from a peripheral vein in the non-dominant arm, using a topical anesthetic technique (EMLA®), was used to detect inflammatory mediators using panels of six analytes (TNF-α, IL-6, IL-10, IP-10, IL-1β, and IL-8). Analysis was performed with a MilliplexR MAP Kit High-Sensitivity Magnetic Bead Panel on a MAGPIXR powered by LuminexR XMAP technology (Merck ™, Germany). The samples were processed and measured according to the manufacturer's instructions as described by Chang et al. [8]. The samples were diluted to fit the dynamic range of the assay. Bio-Plex Manager software was used to calculate the concentrations of inflammatory modulators using a five-parametric logistic standard curve derived from the recombinant standards provided in the kit.

Statistical analysis

Digitized data were stored in Microsoft Excel 2010. The Shapiro-Wilk test was used to assess data normality. Two-sample t-tests or the Mann–Whitney U test were used to compare the data between the two groups. The chi-square test (X^2) was used to study categorical variables. The point-biserial correlation was used to measure the correlation between serum inflammatory marker levels and the development of chronic pain. Statistical analyses were performed using the Stata version 17 software (StataCorp LLC, College Station, USA). Graphics were prepared using GraphPad Prism (version 5.0; GraphPad Software Inc., San Diego, CA, USA). A significance level of 5% ($p<0.05$) was used to reject the null hypothesis.

RESULTS

Of the 250 patients with acute disease enrolled in this study, 100 (40.0%) had laboratory confirmed CHIKV infection **(Figure 1)**.

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Figure 1: Study squeamatic design

After the exclusion criteria, 27 patients developed chronic joint pain lasting 3 months or more (33.3%) after exposure to CHIKV, 24 women (89%) and three men (11%). The median [1st-3rd quartiles] of age and body mass index were significantly higher in the long-term pain group when compared to the group of patients without chronic pain, with p= 0.0193/ <0.001, respectively. The number of years of education was significantly lower in the persistent pain group (p=0.02). There were no statistical differences between the groups in terms of ethnicity and salary income. Sociodemographic data of the participants are presented in **Table 1**.

Table 1 - Sociodemographic data of the sample

The number of days since symptom onset was significantly longer in the chronic pain group (p=0.043). Arthritis (p=0.008) and arthralgia (p=0.023), in acute phase, were significantly higher in the chronic pain group **Table 2.**

No deaths or serious systemic events (cardiovascular or neurological symptoms) occurred in the study sample.

Table 2. Main signs and symptoms of the sample studied

The results of the laboratory tests collected during the acute phase of the disease were also recorded. Table **3** presents the main laboratory findings of this study. Elevated CRP level and the presence of lymphocytosis were the most frequent laboratory findings in both the groups, with no statistically significant differences between them.

Table 3 Main laboratory findings of the sample

In the analysis of immune markers (TNF-α, IL-6, IL-10, IP-10, IL-1β, and IL-8), we observed higher serum levels of IL-1β in the acute phase of CHIKF in the chronic pain group (p=0.0135). The results are shown in **Figure 2**. However, significant differences in TNF-α, IL-6, IL-10, IP-10, and IL-8 levels were not observed in the studied

groups.

Figure 2: Comparison of cytokines, chemokines and inflammatory factors in patients with CHIKF in the acute phase.

Legend: CP: Chronic pain group; NCP: No chronic pain group

Note: Graphs displayed in Median Boxplot [1st quartile and 3rd quartile], Minimum and Maximum Values. * $p < 0.05$.

In addition, there was a positive correlation between serum elevations of IP-10 (coefficient=0.227; p=0.041) and IL-1β (coefficient=0.419; p=0.015) with persistent pain, and a negative correlation (-0.270) with the elevation of IL-10 (p=0.038).

DISCUSSION

In recent decades, the idea of a virus playing a role in the development of arthritis and/or arthralgia has been reinforced in several studies [16,17]. Furthermore, it is important to highlight that although CHIKF induces self-limiting symptoms in adults [18,19], the occurrence of long-term pain syndromes remains unclear. Here, we found a 33.3% incidence of chronic joint pain in individuals exposed to CHIKV, during 2018-2019 epidemic period. Recent studies indicate that 43% (95% CI, 35–52%) of these patients may have persistent painful symptoms for more than 3 months [20].

In our sample, patients affected by chronic joint pain were mostly obese women, between the 4th and 5th decade of life, and with low level of education. Previous studies have found similar findings [21–24]. However, studies carried out in the Brazilian population have reported that chronic pain is associated with female sex, old age, lower education, intense professional activity, excessive alcohol consumption, smoking, central obesity, mood disorder, and sedentarism. In other words, the profile of patients affected by chronic joint pain after CHIKF is the same as those prone to developing chronic pain [25].

The role of obesity and its relationship with the severity and persistence of painful symptoms in patients with CHIKF still does not seem to be fully elucidated, but the hypothesis is that certain metabolic conditions, such as obesity, may exacerbate CHIKV-induced arthritis or increase the susceptibility to the development of chronic polyarthritis by CHIKV, possibly because obesity is a low-grade inflammatory condition [26-29]. Pro-inflammatory immune cells and adipocytes secrete pro-inflammatory cytokines (e.g TNF-α, IL-6, IL-1β and leptin) [30].

Regarding symptom days, our findings were corroborated by research conducted by Chang et al [31], in which 4 or more days of initial symptoms was a predictor of persistent chronic joint pain.

The most prevalent symptoms were fever, arthralgia, and myalgia. Our results are in agreement with the literature, in which the presence of arthritis and arthralgia in the acute phase was significantly higher in the chronic pain group [20,32]. Ramachandran et al. [32] demonstrated that the overall incidence of persistent arthralgia is 80%. According to research carried out by Tanabe et al. [7] and Aesong et al., [33] persistent manifestations of joint changes could be explained by an increase in certain pro-inflammatory markers in the acute phase of CHIKV infection.

Concerning laboratory findings, we found higher CRP levels and leukopenia in both the groups. However, there were no significant differences between the groups. These findings were also supported by a study conducted by Genaro et al. [34] in which C-reactive protein and ferritin levels were not correlated with chronic joint disease.

Our findings showed a higher serum concentration of IL-1β in patients in the chronic pain group. Lin et al. [35] demonstrated a relationship between elevated IL-1β levels and persistent pain. It begins mainly by the activity of microglia in the nervous system, initiating the occurrence of a complex inflammatory cascade through the release of TNF- α and IL- 1β, culminating in the phosphorylation of the GluN1 subunits and the increase in the activity of N-methyl-aspartate receptors in lamina II of the spinal cord (a key point in the process of central sensitization of the nociceptive stimulus).

Furthermore, high levels of IP-10 and IL-1β were positively correlated with the development of persistent joint pain, whereas high levels of IL-10 in this phase were shown to have a negative correlation with the outcome of long-lasting pain (protective factor). These findings may raise the possibility of prognostic and therapeutic strategies for the proper management of CHIKV-infected patients in the acute phase.

A study conducted by Ng et al. [36] established a correlation between the severity of CHIKF symptoms and elevation of serum levels of certain inflammatory biomarkers, such as IL-6, IL1-β, and RANTES (CCL5), a chemoattractant for monocytes. Elevated levels of IL1-β and IL-6 along with decreased regulated on activation of T cell expressed and secreted correlate with more severe disease, whereas increased IL-1 and IL-8 coincide with more destructive arthritis demonstrating the complex, concerted interaction of multiple proinflammatory factors [37,38].

According to Ferreira et al. [39], serum elevations of IL-1β and IP-10 seem to play an important role in the gravity of symptoms presented by these patients, but not in the chronicity. In contrast, elevation of IL-10 seems to be associated with a reduction in the development of painful manifestations. The latter may be because it inhibits

macrophages, dendritic cells, IL-12 production, and class II histocompatibility complex molecules, which are involved in the control of the innate response, resulting in a decrease in the recruitment of T cells to the regions affected by the virus [40]. Consistently with cytokine and chemokine downregulation, IL-10 clearly suppresses experimental arthritis [41]. A preliminary study conducted by Kulkarni et. al [42] suggesting an association of peripheral regulatory T cells and IL-10 with recovery from chikungunya, may provide insight into chikungunya disease prognosis.

Guo et al. [43], reported the role of "Toll-Like receptors" and the innate immunity of the central nervous system, with persistent painful states. The increased expression of TNF-α, IL-6, and IL-1β can affect the processing of nociceptive pathways, enabling the activation of facilitatory pathways and inhibition of inhibitory pathways. These findings point to possible central mechanisms involved in pain persistence after CHIKF [44]. This is supported by research involving transcranial direct current stimulation and the improvement of pain symptoms in patients with chronic pain states after CHIKF [45].

Our study has some limitations. No analysis of the different strains of the virus was performed. Teo et al. [46] suggested that the Asian lineage may be less virulent. Attention should also be paid to the different viremia phases of patients within the evolution of CHIKF [47]. Possible genetic and epigenetic factors related to the development of chronic pain states after CHIKF deserve further study [48,49]. This was a unicentric study with a small sample size and clinical information was obtained from the medical records, limiting the control of possible biases between those related to acute infection by the virus and symptoms associated with the chronic phase.

CONCLUSION

The inflammatory profile of patients in the acute phase of CHIKF may be associated with the development of chronic joint pain. Even though these mechanisms are not completely understood, immune response and inflammation apparently diverge between patients who recover and those who chronify. Thus, the search for these biomarkers can reveal the prognostic factors and important therapeutic targets for disease treatment. More prospective studies are needed to identify the existence of possible painful phenotypes (central and peripheral mechanisms) in patients with CHIKF, directing more specific treatments in an attempt to reduce the progression to persistent painful states.

Competing interest

No Conflict

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Contributors

BVMS, SPCB, TCSCG and ACF were involved in the study design, data collection, analysis, and writing. NRV and MP contributed to the design of the study, writing, and revision of the article.

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Figure 1

45

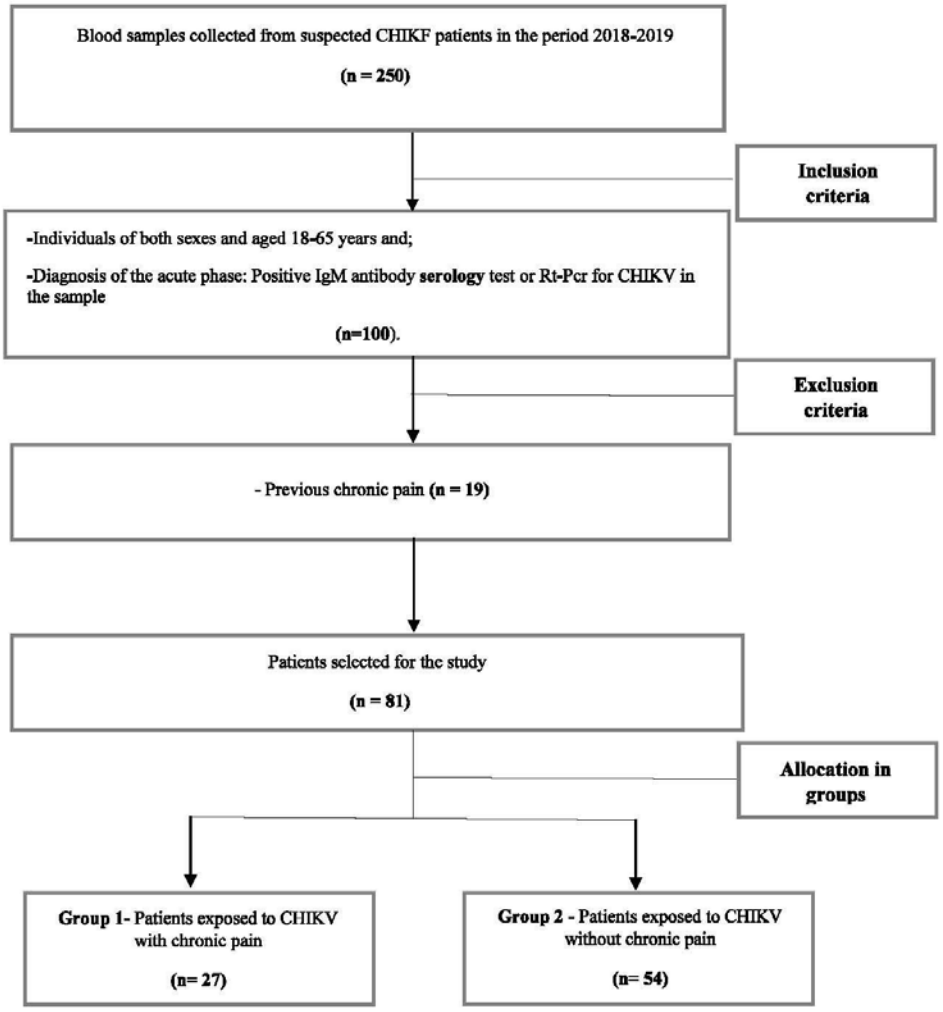

Figure 1: Study squeamatic design

Figure 2

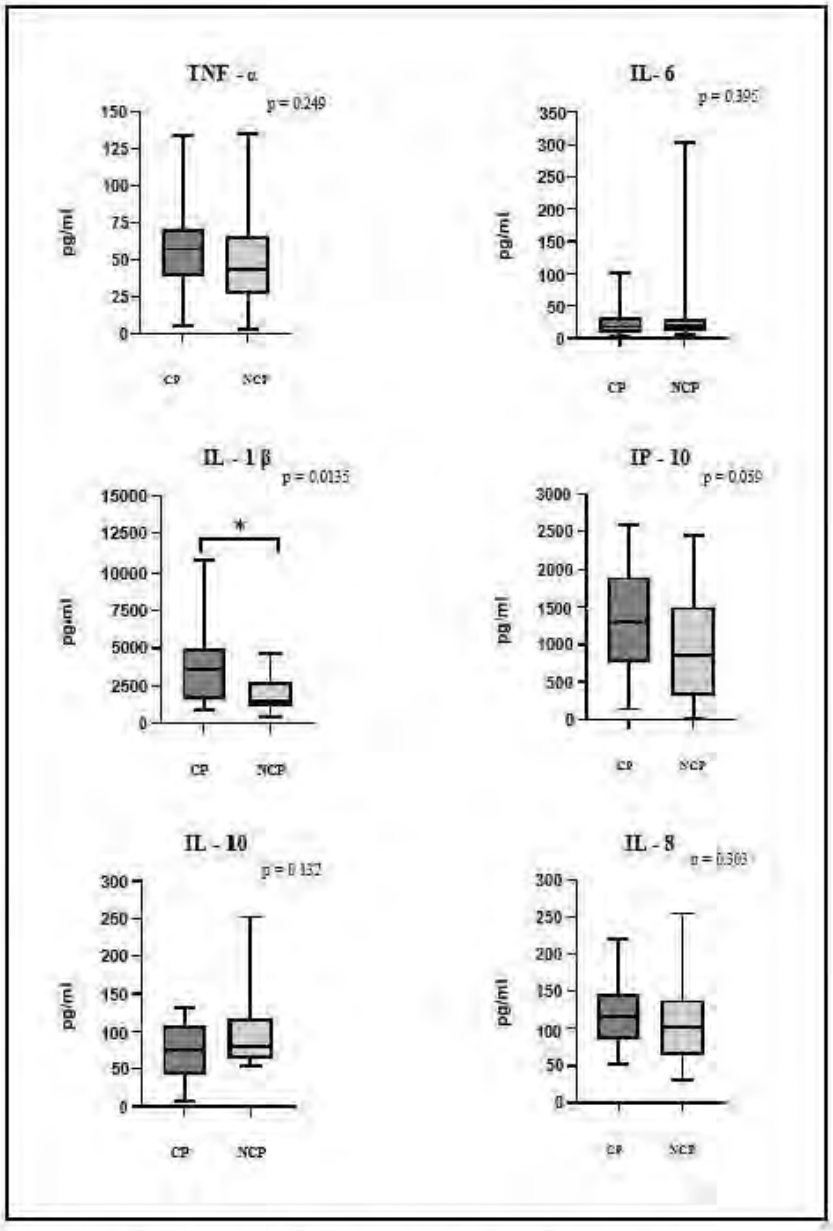

Figure 2: Comparison of cytokines, chemokines and inflammatory factors in patients with CHIKF in the acute phase.

Legend: CP: Chronic pain group; NCP: No chronic pain group

Note: Graphs displayed in Median Boxplot [1st quartile and 3rd quartile], Minimum and Maximum Values. * p <0.05.

Table 1

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Table 1 - Sociodemographic data of the sample

Analyzed Variables	Group 1 - Chronic Pain N = 27				Group 2 – No Chronic Pain N = 54				p value
	(n)	(%)	Median	[1st-3rd quartiles]	(n)	(%)	Median	[1st-3rd quartiles]	
Gender									
M:	3	11%			28	52%			<0.001*
F:	24	89%			26	48%			
Age (years)	27		56	[42 - 65]	54		39,5	[23-60,5]	0.0193*
BMI (kg/m²)	26		39,5	[23-60,5]	49		23	[21-25]	<0.001*
Ethnicity									
W:	17	73%			26	48%			0.538
NW:	10	27%			28	52%			
Education-years of study (y)									
≤ 8:	6	22%			11	20%			0.02*
9-12:	16	59%			42	77,80%			
>12:	5	19%			1	2,20%			
Estimated Income (number of Salaries)									
1-4:	3	11%			5	9,30%			0.77
5-8:	15	56%			25	46,30%			
>9:	9	33%			24	44,40%			

Legend: Data presented as median [1st quartile-3rd quartile] or n (%). N= Total number of patients in the group; n = Number of patients analyzed for a variable; W= White; NW = Non-White; M= Male; F= Female; BMI: Body mass index
1 salary = R$ 1.212,00
* p < 0,05

Table 2

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Table 2. Main signs and symptoms of the sample studied

Variables Analyzed	Group 1 - Chronic Pain N = 27				Group 2 - No Chronic Pain N = 54				p value
	n	(%)	Median	[1st-3rd quartiles]	n	(%)	Median	[1st-3rd quartiles]	
Days of onset of Symptoms	26		7	[4 - 10]	52		5	[2 - 7]	0.043*
Fever									
≥ 38°C:	27	4 (14.8%)			54	13(24%)			0.271
< 38%:	27	11 (40.8 %)			54	26 (48.1%)			0.335
Headache	27	6 (22.2%)			54	18 (33.3%)			0.302
Arthralgia	27	25 (92.6%)			54	36 (66.6%)			0.023*
Myalgia	27	15 (55.6%)			54	30 (55.5%)			1
Arthritis	27	7 (25.9%)			54	4 (7.4%)			0.008*
Rash	27	6 (22.2%)			54	20 (37%)			0.178

Legend: Data presented as median [1st quartile-3°quartile] or n (%). N= Total number of patients in the group; n = Number of patients analyzed for a variable. * $p < 0.05$

Table 3

Table 3 - Main laboratory findings found in the sample

Analyzed Variables	Group 1 - Chronic Pain N = 27				Group 2 - No Chronic Pain N = 54				p value
	n	(%)	Median	[1st-3rd quartiles]	n	(%)	Median	[1st-3rd quartiles]	
Leukopenia	25	5 (18.5%)			54	12 (22.2%)			0.859
CRP	25		2,3	[0.8 – 5.9]	43		2	[1,15 – 4.6]	0.9871
ANF (+)	13	1 (7.7%)			9	0%			0.394
RF (+)	8	1 (12.5%)			9	0%			0.274

Legend: ANF: Antinucleus Factor; RF: Rheumatoid Factor; CRP: C-Reactive Protein; (+): Reagents
Data presented as median [1st quartile-3rd quartile] or n (%). N= Total number of patients in the group; n = Number of patients analyzed for a variable.
* $p < 0.05$

4 **RESULTADOS**

Os principais achados de ambos os artigos estão sumarizados nos quadros 1 e 2.

Quadro 1 - Principais achados do 1º artigo

A prevalência de dor crônica na população geral adulta variou de 23% - 42,3%
Dor crônica foi associada ao sexo feminino, senilidade, baixo nível de escolaridade, tabagismo, elevado consumo de álcool, obesidade central, transtornos de humor e sedentarismo
As regiões Sul e Sudeste apresentaram elevadas prevalências de dor crônica nos estudos analisados
A prevalência de dor crônica na população idosa variou de 29,3% - 76,2%
Mais de 50 % de ambas as populações com dor crônica reportaram prejuízo funcional relacionado à dor
Os locais de dor mais frequentes foram as regiões lombar; cefálica; articulações; pernas e pés e membros inferiores
Na maioria dos estudos analisados os pacientes descreveram a intensidade da dor como moderada à intensa

Fonte: O autor, 2023.

Quadro 2 - Principais achados do 2º artigo

A incidência de dor crônica articular na amostra estudada foi de 33,3% (n = 27)
Dor articular crônica foi associada ao sexo feminino, obesidade, baixo grau de escolaridade e idade (entre a 4ª e 6ª década de vida)
Artrite e níveis séricos de IL-1 β e foram significativamente maiores no grupo de pacientes com dor articular crônica
Houve correlação positiva entre os níveis séricos de IL-1 β e IP-10 durante a fase aguda da CHIKF e dor articular crônica
Houve correlação negativa entre IL-10 na fase aguda e o desenvolvimento de dor articular crônica (fator protetor)
O perfil de citocinas séricas elevadas na fase aguda da CHIKF pode estar associado ao desenvolvimento de dor articular crônica

Fonte: O autor, 2023.

5 **DISCUSSÃO**

Em relação ao primeiro artigo abordado nesta tese, constata-se que a prevalência de dor crônica benigna no Brasil é alta, pior na população idosa, difere de região para região e está associada a fatores de risco heterogêneos. Além disso, a dor crônica se manifesta principalmente como moderada ou intensa e com elevada taxa de incapacidade.

Foram analisados 15 artigos, os quais preenchiam os critérios de elegibilidade para o estudo em questão, e os mesmos apresentaram variabilidade nos métodos e grupos estudados. Após a avaliação criteriosa, os autores determinaram a prevalência de dor crônica benigna na população adulta e idosa. Assim, a prevalência estimada de dor crônica na população adulta e idosa, no período avaliado, foi de 35,70% e 47,32%, respectivamente.

Sa et al., [28] em sua meta-análise, descreveram a prevalência de dor crônica (cerca de 18%), nos países em desenvolvimento. No entanto, a presença de uma população jovem, um número mais significativo de entrevistas telefônicas [29], uma possível influência regional e outras questões relacionadas aos métodos dos artigos selecionados, poderiam justificar essa baixa prevalência. Por outro lado, Jackson et al., [30] descreveram uma ampla variabilidade e alta prevalência de dor crônica sem etiologia clara, em países de baixa e média renda (26%–42% na população adulta e 41%–81% em idosos). Já nos países desenvolvidos, ao exemplo do Reino Unido, um estudo demonstrou elevadas prevalências, em torno de 43 % em adultos e 62% nos pacientes com mais de 75 anos, possivelmente em função da maior expectativa de vida da população, quando comparada à brasileira [31].

Quanto às características da dor, um artigo constatou que quinze por cento dos respondedores tinham dor generalizada [32] e, em outro estudo, 15,1% dos idosos tinham dor em mais de três locais [33]. Supondo que a sensibilização central ocorra entre cinco e quinze por cento da população em geral [34], esses dados sugerem a dor nociplástica como um possível diagnóstico nestes grupos. Esses dados foram corroborados por uma pesquisa recente conduzida por Aguiar et al., [35] na qual a prevalência de dor nociplástica no Brasil foi de 12,5%. Em relação aos nossos achados, um artigo encontrou uma prevalência de dor neuropática crônica de 10%, através da aplicação de um questionário validado para dor neuropática (DN4), sendo que o local mais acometido neste grupo foram os membros inferiores. Esses locais possivelmente estão associados a doenças como diabetes e compressão radicular, entre outras [36].

Em relação à intensidade da dor, os respondedores referiram-se como moderada a intensa. Além disso, em um estudo, cinquenta por cento relataram incapacidades relacionadas à dor e 48,7% referiram-se ao tratamento da dor como "sem efeito" ou "efeito mínimo" [32]. Esses dados reforçam o fato de que a dor crônica, em função da sua complexidade e dos inúmeros aspectos biopsicossociais que a cercam, deve ser abordada por uma equipe multidisciplinar, por meio da qual todas as dimensões da dor possam ser adequadamente avaliadas e devidamente enfrentadas [37]. Infelizmente, o tratamento precoce e eficaz da dor crônica é mais desafiador nos países em desenvolvimento, em que uma abordagem multidisciplinar é escassa na atenção primária - o primeiro atendimento acessível a esses pacientes [38].

Alguns aspectos como a falta de treinamento dos profissionais de saúde e de estratégias pouco inclusivas dos pacientes dentro do seu plano terapêutico, podem contribuir para o surgimento de certas lacunas no tratamento [39]. Além disso, alguns efeitos colaterais dos medicamentos para tratamento da dor; a crise crescente relacionada à prescrição de opioides e o fato de que um remédio raramente trata todos os aspectos biopsicossociais da dor crônica, tornam necessário o desenvolvimento de modelos terapêuticos mais eficazes, nos quais estratégias farmacológicas e não farmacológicas possam ser oferecidas a essa população, com ênfase no autogerenciamento da dor e na reabilitação funcional [40].

Com relação à saúde mental, um artigo descobriu que os respondentes com dor tinham 2,3 vezes mais transtornos de ansiedade, 3,3 vezes mais transtornos de humor e 2,7 vezes mais transtornos mentais [41]. Stubbsetal.[42] descreveu a depressão e dor crônica como comorbidades presentes em pacientes de países de baixa e média renda, independente de ansiedade e condições médicas crônicas. Além disso, a depressão foi associada a um maior risco de dor intensa. Esses dados também foram corroborados por uma pesquisa conduzida por Pinheiro et al.,[43] demonstrando a importância de incluir a saúde mental na linha de cuidado desses pacientes portadores de dor crônica.

Os artigos mostraram associação entre menores condições econômicas ou menor escolaridade, sugerindo uma relação entre desvantagem socioeconômica e dor crônica [36;44-46.] Além disso, a obesidade central [47] e o sedentarismo [45; 48-50] foram associados à dor crônica. Estudos anteriores corroboram a associação de nível socioeconômico e dor crônica [51]. Questões como uso inadequado de estratégias de enfrentamento da dor, raça, etnia, razões ocupacionais, exposição à violência e ausência de apoio familiar ou social são alguns dos fatores envolvidos [52].

Os estudos com maior representatividade amostral de participantes que responderam aos questionários são provenientes das regiões Sul e Sudeste. Eles demonstraram uma prevalência geral de dor crônica benigna em adultos variando de 29,66% a 76,20%. Esses resultados podem ser esperados, visto que há maior prevalência de idosos na população, além de maior número de estudos abrangendo as regiões. Em contrapartida, a menor representatividade amostral de participantes nas regiões Norte e Centro-Oeste. Isso pode ser explicado pelo menor número de estudos locais incluídos; menor índice de desenvolvimento humano e escolaridade, o que poderia influenciar no acesso ao diagnóstico (principalmente na região Norte), corroborando com os achados de Souza et al.[32].

A presente revisão tem o mérito de trazer os principais estudos sobre a prevalência de dor crônica benigna no Brasil e seus fatores associados, devido ao seu grande impacto social, levando ao prejuízo funcional e absenteísmo, além dos gastos por afastamentos. Quase todos os estudos selecionados realizaram entrevistas face a face e tiveram um número representativo de respondentes. No entanto, existem algumas limitações, dentre elas, destacam-se: a grande variabilidade nos métodos dos estudos; o fato de diversos estudos não descreverem a prevalência da população em geral, não sendo elegíveis; além disso, cinco estudos elegíveis não calcularam o tamanho da amostra e os autores não realizaram a pesquisa de referências da literatura cinzenta. Um outro ponto importante consiste na interpretação dos fatores associados à dor crônica, a qual deve ser considerada com cautela, pois os artigos selecionados são estudos transversais. Por fim, os autores decidiram resumir os estudos realizados nos últimos quinze anos, uma vez que a população brasileira mudou com o envelhecimento progressivo [53]. Estudos mais antigos não poderiam reproduzir a situação real de prevalência de dor crônica.

No segundo artigo desta tese, foi avaliada uma coorte retrospectiva de indivíduos expostos ao CHIKV, no período epidêmico de 2018-2019, no estado do Rio de Janeiro. A ideia de um vírus desempenhando um papel no desenvolvimento de artrite e/ou artralgia foi reforçada em vários estudos [54-55]. Além disso, é importante destacar que, embora a CHIKF induza sintomas autolimitados em adultos [56-57], a ocorrência de síndromes dolorosas persistentes permanece obscura. Neste estudo, encontramos uma incidência de 33,3% de dor articular crônica em indivíduos expostos ao CHIKV. Alguns estudos revelam que até 43% (95% CI, 35-52%) desses pacientes podem ter sintomas dolorosos persistentes por mais de 3 meses [17].

Em nossa amostra, os pacientes acometidos por dor articular crônica eram em sua maioria mulheres obesas, entre a 4ª e 5ª década de vida e com baixo nível de escolaridade.

Estudos anteriores encontraram resultados semelhantes [58-61]. No entanto, pesquisas realizadas na população brasileira relataram que a dor crônica está associada ao sexo feminino, idade avançada, menor escolaridade, atividade profissional intensa, consumo excessivo de álcool, tabagismo, obesidade central, transtorno de humor e sedentarismo. Em outras palavras, o perfil dos pacientes acometidos por dor articular crônica após CHIKF é o mesmo daqueles propensos a desenvolver dor crônica [9].

O papel da obesidade e sua relação com a gravidade e persistência dos sintomas dolorosos em pacientes com CHIKF ainda não parece totalmente elucidado, mas a hipótese é de que certas condições metabólicas, como a obesidade, podem exacerbar a artrite induzida por CHIKV ou aumentar a suscetibilidade ao desenvolvimento de poliartrite crônica por CHIKV, possivelmente porque a obesidade é uma condição inflamatória de baixo grau [62-65.] Células imunes pró-inflamatórias e adipócitos secretam citocinas pró-inflamatórias (por exemplo, TNF-α, IL-6, IL-1β e leptina) [66].

Em relação aos dias de sintomas, nossos achados foram corroborados pela pesquisa realizada por Chang et al [67], em que 4 ou mais dias do início dos sintomas foi um preditor de dor articular crônica persistente.

Os sintomas mais prevalentes foram febre, artralgia e mialgia. Nossos resultados estão de acordo com a literatura, em que a presença de artrite e artralgia na fase aguda foi significativamente maior no grupo de dor crônica [17;68]. Ramachandran et al. [68] demonstraram que a incidência geral de artralgia persistente é de 80%. Segundo pesquisa realizada por Tanabe et al. [69] e Aesong et al., [70] as manifestações persistentes de alterações articulares podem ser explicadas por um aumento de certos marcadores pró-inflamatórios na fase aguda da infecção por CHIKV.

Quanto aos achados laboratoriais, encontramos níveis mais elevados de proteína C-reativa (PCR) e leucopenia em ambos os grupos. No entanto, não houve diferenças significativas entre os grupos. Esses achados também foram corroborados por um estudo conduzido por Genaro et al. [71] em que os níveis de proteína C-reativa e ferritina não foram correlacionados com doença articular crônica.

Nossos achados mostraram maior concentração sérica de IL-1β nos pacientes do grupo de dor crônica. Lin et al. [72] demonstraram uma relação entre níveis elevados de IL-1β e dor persistente. Inicia-se principalmente pela atividade da micróglia no sistema nervoso, permitindo a ocorrência de uma complexa cascata inflamatória através da liberação de TNF-α e IL-1β, culminando na fosforilação das subunidades GluN1 e no aumento da atividade de N-

receptores de metil-aspartato na lâmina II da medula espinhal (ponto-chave no processo de sensibilização central).

Além disso, altos níveis de IP-10 e IL-1β foram positivamente correlacionados com o desenvolvimento de dor articular persistente, enquanto altos níveis de IL-10 nesta fase mostraram correlação negativa com o desfecho de dor de longa duração (fator protetor). Esses achados podem levantar a possibilidade de estratégias prognósticas e terapêuticas para o manejo adequado de pacientes infectados pelo CHIKV na fase aguda.

Um estudo conduzido por Ng et al., [73] estabeleceram uma correlação entre a gravidade dos sintomas da CHIKF e a elevação dos níveis séricos de certos biomarcadores inflamatórios, como IL-6, IL1-β e RANTES (CCL5), um quimioatraente para monócitos. Níveis elevados de IL1-β e IL-6, juntamente com diminuição na ativação de células T reguladoras expressas e secretadas, correlacionam-se com doença mais grave, enquanto IL-1 e IL-8 aumentados coincidem com artrite mais destrutiva, demonstrando a interação complexa e orquestrada de múltiplos fatores pró-inflamatórios [74-75].

Segundo Ferreira e et al.,[76], elevações séricas de IL-1β e IP-10 parecem ter papel importante na gravidade dos sintomas apresentados por esses pacientes, mas não na cronicidade. Em contraste, a elevação de IL-10 parece estar associada a uma redução no desenvolvimento de manifestações dolorosas. Esta última pode ser por inibir macrófagos, células dendríticas, produção de IL-12 e moléculas do complexo de histocompatibilidade classe II, que estão envolvidas no controle da resposta inata, resultando em diminuição do recrutamento de células T para as regiões afetadas por o vírus [77]. Consistentemente com a regulação negativa de citocinas e quimiocinas, a IL-10 suprime claramente a artrite experimental [78]. Um estudo preliminar conduzido por Kulkarni et. al [79] sugeriu uma associação de células T reguladoras periféricas e IL-10 com a recuperação da CHIKF, podendo fornecer informações sobre o prognóstico da doença articular.

Guo et al., [80], relataram o papel dos “receptores Toll-Like” e a imunidade inata do sistema nervoso central, com estados dolorosos persistentes. A expressão aumentada de TNF-α, IL-6 e IL-1β pode afetar o processamento de vias nociceptivas, possibilitando a ativação de vias facilitadoras e inibição de vias inibitórias. Esses achados apontam para possíveis mecanismos centrais envolvidos na persistência da dor após CHIKF [81]. Isso é apoiado por pesquisas envolvendo estimulação transcraniana por corrente contínua com melhora dos sintomas de dor em pacientes com estados de dor crônica após CHIKF [82].

A pesquisa apresenta algumas limitações. Nenhuma análise das diferentes cepas do vírus foi realizada. Teo et al., [83] sugeriram que a linhagem asiática pode ser menos virulenta.

Atenção também deve ser dada às diferentes fases de viremia dos pacientes na evolução da CHIKF [84]. Possíveis fatores genéticos e epigenéticos relacionados ao desenvolvimento de estados de dor crônica após CHIKF merecem um estudo mais aprofundado [85-86]. Este foi um estudo unicêntrico com tamanho amostral modesto e as informações clínicas foram obtidas dos prontuários, limitando o controle de possíveis vieses entre aqueles relacionados à infecção aguda pelo vírus e sintomas associados à fase crônica.

CONCLUSÃO

Após a análise da evidência disponível, demonstrou-se que a dor crônica benigna é altamente prevalente no Brasil e associada a sofrimento significativo, incapacidade e controle inadequado. Esses dados sugerem a necessidade de priorizar o acesso dessa população a profissionais qualificados e experientes no tratamento da dor crônica, melhorar a educação do paciente sobre sua condição crônica e fortalecer o modelo biopsicossocial, especialmente na atenção primária.

Em relação aos pacientes avaliados, após a infecção por CHIKV, o perfil inflamatório desses pacientes na fase aguda da CHIKF pode estar associado ao desenvolvimento de dor articular crônica. Embora esses mecanismos não sejam completamente compreendidos, a resposta imune e a inflamação aparentemente divergem entre os pacientes que se recuperam e os que cronificam. Assim, a busca por esses biomarcadores pode revelar os fatores prognósticos e alvos terapêuticos importantes para o tratamento da doença. Mais estudos prospectivos são necessários para identificar a existência de possíveis fenótipos dolorosos (mecanismos centrais e periféricos) em pacientes com CHIKF, direcionando tratamentos mais específicos na tentativa de reduzir a progressão para estados dolorosos persistentes.

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APÊNDICE A – **Table 2.** Search strategy from different databases (Material Suplementar do 1º artigo)

Database	Search Strategy
Ovid MEDLINE (2005 to 09/2020)	(((Prevalence[mh] OR Prevalence*[tw] OR Prevalent[tw] OR Epidemiology[mh] OR Epidemi*[tw] OR Risk Factors[mh] OR Risk Factor*[tw] OR Associated Factor*[tw] OR Related Factor*[tw] OR Cross-Sectional Studies[mh] OR Cross-Sectional Stud*[tw] OR Cohort Studies[mh] OR Cohort[tw] OR Demography[mh] OR Demograph*[tiab] OR Demographic[tiab] OR Geographic[tiab] OR Sociodemographic[tiab] OR Sociological Factors[mh] OR Sociological*[tiab] OR Social*[tiab] OR Rural[tiab] OR Cities[tiab] OR City[tiab] OR Region*[tiab]) AND (Chronic Pain[mh] OR Chronic Pain*[tw] OR "Chronic Low Back Pain"[tw] OR Widespread Chronic Pain*[tw] OR Persistent Pain*[tw] OR Neuralgia[mh] OR Neuralgia*[tiab] OR Neuropathic Pain*[tiab])) AND (Brazil[mh] OR Brazil*[tw] OR Brasil*[tw])) AND (English[lang] OR Portuguese[lang] OR Spanish[lang]) AND ("2005/01/01"[PDat] : "2020/09/10"[PDat])
EMBASE (2005 to 09/2020)	('prevalence'/exp OR 'prevalence':ti,ab OR 'prevalence study':ti,ab OR 'epidemiology'/exp OR 'clinical epidemiology':ti,ab OR 'epidemiologic factors':ti,ab OR 'epidemiologic methods':ti,ab OR 'epidemiologic research':ti,ab OR 'epidemiologic research design':ti,ab OR 'epidemiologic studies':ti,ab OR 'epidemiologic study characteristics':ti,ab OR 'epidemiologic study characteristics as topic':ti,ab OR 'epidemiologic survey':ti,ab OR 'epidemiological research':ti,ab OR 'epidemiology':ti,ab OR 'epidemiology model':ti,ab OR epidemi* OR 'risk factor'/exp OR 'relative risk' OR 'risk factor' OR 'risk factors' OR 'related factor*':ti,ab OR 'associated factor*':ti,ab OR 'cross-sectional study'/exp OR 'Cross-Sectional Stud*':ti,ab OR 'cohort analysis'/exp OR 'cohort':ti,ab OR 'demography'/mj OR 'demograph*':ti,ab OR 'geographic':ti,ab OR 'sociodemographic':ti,ab OR 'sociological factors'/mj OR 'sociological*':ti,ab OR 'social*':ti,ab OR 'rural':ti,ab OR 'cities':ti,ab OR 'city':ti,ab OR 'region*':ti,ab) AND ('chronic pain'/exp OR 'chronic intractable pain':ti,ab OR 'pain, chronic':ti,ab OR 'chronic low back pain':ti,ab OR 'widespread chronic pain':ti,ab OR 'persistent pain':ti,ab OR 'chronic pain':ti,ab OR 'neuralgia'/exp OR 'neuralgia' OR 'neuralgia, rheumatic' OR 'neuralgic pain' OR 'neuralgy' OR 'rheumatic neuralgia' OR 'neuropathic pain'/exp OR 'neuropathic pain':ti,ab OR 'pain, neuropathic':ti,ab) AND ('brazil'/exp OR 'brazil':ti,ab OR 'federative republic of brazil':ti,ab OR 'united states of brazil':ti,ab OR 'brazilian'/exp OR 'brazilian':ti,ab OR 'brazilians':ti,ab OR brasil*) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND ([english]/lim OR [portuguese]/lim OR [spanish]/lim) AND [2005-2020]/py
Web of Science (2005 to 09/2020)	TS=(Prevalence* OR Prevalent OR Epidemiology OR Epidemi* OR "Risk Factors" OR "Associated Factors" OR "Related Factors" OR "Cross-Sectional Studies" OR "Cross-Sectional Study" OR "Cohort Studies" OR Cohort OR Demography OR Demograph* OR Geographic OR Sociodemographic OR "Sociological Factors" OR Sociological* OR Social* OR Rural OR Cities OR City OR Region*) AND TS=("Chronic Pain" OR "Chronic Pains" OR "Chronic Low Back Pain" OR "Widespread Chronic Pain" OR "Persistent Pain" OR Neuralgia OR Neuralgia* OR "Neuropathic Pain" OR "Neuropathic Pains") AND TS=(Brazil OR Brazil* OR Brasil*) AND PY=(2005 OR 2006 OR 2007 OR 2008 OR 2009 OR 2010 OR 2011 OR 2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020) AND CU=(Brazil)
BVS Regional/Lilacs (2005 to 09/2020)	(tw:(Prevalence* OR Prevalent OR Epidemiology OR Epidemi* OR "Risk Factors" OR "Associated Factors" OR "Related Factors" OR "Cross-Sectional Studies" OR "Cross-Sectional Study" OR "Cohort Studies" OR Cohort OR Demography OR Demograph* OR Geographic OR Sociodemographic OR "Sociological Factors" OR Sociological* OR Social* OR Rural OR Cities OR City OR Region* OR Prevalencia* OR Prevalente OR Epidemiologia OR Epidemi* OR "Fatores de risco" OR "Fatores

associados" OR "Fatores relacionados" OR "Estudos transversais" OR "Estudo transversal" OR "Estudos de coorte" OR Coorte OR Demografia OU Demografi* OR Geografic* OR Sociodemografic* OR "Fatores Sociologicos" OR Sociologico* OR Social OR Sociais OR Rural OR Cidade* OR Regiao* OR Regioes OR "Factores de riesgo" OR "Factores asociados" OR "Factores relacionados" OR "Estudios transversales" OR "Estudio transversal" OR "Estudios de cohortes" OR Cohorte OR "factores sociologicos" OR sociologicos* OR sociales OR rurales OR Ciudad* OR Region* OR Regiones)) AND (ti:("Chronic Pain" OR "Chronic Pains" OR "Chronic Low Back Pain" OR "Widespread Chronic Pain" OR "Persistent Pain" OR Neuralgia OR Neuralgia* OR "Neuropathic Pain" OR "Neuropathic Pains" OR "Dor cronica" OR "Dores cronicas" OR "Dor lombar cronica" OR "Dor cronica generalizada" OR "Dor persistente" OR Neuralgia* OR "Dor neuropatica" OR "Dores neuropaticas" OR "Dolor cronico" OR "Dolor lumbar cronico" OR "Dolor cronico generalizado" OR "Dolor persistente" OR "Dolor neuropatico")) AND "Brazil" OR "Brasil" AND (db:("LILACS")) AND (year_cluster:[2005 TO 2020]) AND NOT (ti:(treatment OR tratamento OR tratamiento))

APÊNDICE B – Table 3. Search strategy from different databases (Material Suplementar do 1º artigo)

Table 3. The score of risk of study bias

1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	**Yes (LOW RISK):** The study's target population was a close representation of the national population	0
	No (HIGH RISK): The study's target population was clearly NOT representative of the national population	1
2. Was the sampling frame a true or close representation of the target population?	**Yes (LOW RISK):** The sampling frame was a true or close representation of the target population	0
	No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.	1
3. Was some form of random selection used to select the sample, OR, was a census undertaken?	**Yes (LOW RISK):** A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling).	0
	No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	1
4. Was the likelihood of non-response bias minimal?	**Yes (LOW RISK):** The response rate for the study was ≥75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non- responders	0
	No (HIGH RISK): The response rate was <75%, and if any alalusis comparing responders and non-responderes was done, it showed a significant diference in relevant demographic characyeristics between respinders and non-responders	1
5. Were data collected directly from the subjects (as opposed to a proxy)?	**Yes (LOW RISK):** All data were collected directly from the subjects.	0
	No (HIGH RISK): In some instances, data were collected from a proxy.	1
6. Was an acceptable case definition used in the study	**Yes (LOW RISK):** An acceptable case definition was used.	0
	No (HIGH RISK): An acceptable case definition was NOT used	1
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	**Yes (LOW RISK):** The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc.	0
	No (HIGH RISK): The study instrument had NOT been shown to have reliability or validity (if this was necessary).	1
8. Was the same mode of data collection used for all subjects?	**Yes (LOW RISK):** The same mode of data collection was used for all subjects.	0
	No (HIGH RISK): The same mode of data collection was NOT used for all subjects.	1
9. Were the numerator(s) and denominato r(s) for the parameter of interest appropriate	**Yes (LOW RISK):** The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain).	0
	No (HIGH RISK): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	1
10. Summary on the overall risk of study bias	**LOW RISK**	**0-3**
	MODERATE RISK	**4-6**
	HIGH RISK	**7-9**

APÊNDICE C – STROBE guidelines (Material Suplementar do 2º artigo)

STROBE guidelines

Section/topic	Item number	Recommendation
Title and abstract		**High serum levels of IL-1β and IP-10 markers in the acute phase of Chikungunya fever correlate with chronic joint pain**
		- Question: Could the elevation of cytokines, chemokines and inflammatory markers in the acute phase of CHIKF infection be associated with the development of chronic joint pain in patients infected with CHIKV? **- Findings:** Elevated levels of IL-1β were significantly higher in patients with chronic pain. Elevated IL-1β and IP-10 levels were positively correlated with the development of chronic pain after CHIKF. IL-10 was negatively correlated with chronic pain outcome. **-Significance:** The inflammatory profile of patients in the acute phase of CHIKF may be associated with the development of chronic joint pain.
Introduction		
Background/ Hypothesis	2	Chikungunya fever emerges as a public health problem in several countries around the world. Although the infection has a self-limited course in some patients, some studies point to a prevalence of chronic pain after Chikungunya virus (CHIKV) infection around 43%. The mechanisms of pain chronicity in CHIKV-infected patients are not fully elucidated. Our hypothesis was that CHIKV cases with a greater inflammatory response during acute infection would be more likely to develop chronic joint pain.
Objectives	3	In sharp contrast with a considerable body of knowledge now available regarding immune pathways and release of proinflammatory cytokines after CHIKV infection, the risk factors for long-term pain in these individuals are still unclear. Thus, this article presents findings from the follow-up of a Brazilian cohort of patients with pain after CHIKV infection, as well as the role of the profile of some inflammatory markers during the acute phase of CHIKF.
Methods		
Study design	4	We conducted a descriptive and retrospective cohort of patients exposed to CHIKV in the 2018-2019 Brazilian epidemic period.
Setting	5	The research took place at Hospital Naval Marcílio Dias, in partnership with the State University of Rio de Janeiro and the Oswaldo Cruz Foundation. This study was carried out as part of an enhanced surveillance investigation designed to monitor arboviral infections among acute febrile patients at an emergency health center, in Rio de Janeiro, during the epidemic period of 2018-2019.

STROBE guidelines

Section/topic	Item number	Recommendation
Participants	6	- During acute-phase (≤14 days after symptoms onset) blood samples were collected, centrifuged and sera were frozen at -80°C and -20°C until molecular and serological analyses, respectively. 250 blood samples were collected from suspected cases of CHIKF. Of these patients, 100 met the inclusion criteria for the study **(Figure 1)**. - A cohort of 100 individuals exposed to CHIKV was analyzed, either military or dependent on the Naval Health System. - Individuals of both sexes, aged 18-65 years, with a confirmed diagnosis of CHIKF, either through serological tests or molecular biology tests (real-time polymerase chain reaction - Rt-PCR) were included in this study - Patients with previous chronic pain were excluded from the research (n=19). **- Follow up survey:** Between November 2020 and March 2021, telephone follow-up was performed for all patients who had laboratory evidence of CHIKV infection to obtain self-reported data on disease resolution or progression and on the duration of symptoms (Survey). - The 81 participants were asked about the evolution of the pain condition, being allocated into 2 groups: **Group 1** (Chronic Pain) – Patients diagnosed with CHIKF that developed chronic joint pain at lasting 3 months or more (n=27), according to the *International Association for the Study of Pain - IASP* **Group 2** (No Chronic Pain) – Patients diagnosed with CHIKF without criteria for chronic joint pain (n=54).
Variables	7	We performed blood collection and interviewed the patients to obtain demographic, epidemiological, and clinical data.
Data sources/measurement	8	**- Demographic data:** A standardized questionnaire was used to collect data (telephone follow-up) on the evolution of clinical manifestations, especially on the persistence or resolution of chronic joint pain (survey). The definitions recommended by the Brazilian Society of Rheumatology were used for the diagnostic criteria for arthralgia and arthritis in after CHIKF. **- Virus RNA** was obtained from serum Maxwell Total RNA Purification kit (Promega ™, Madison, WI, USA), according to the manufacturer's instructions. The product obtained was amplified by RT-PCR (Promega™) and previously designed primers targeting CHIKV, DENV, and ZIKV. Acute-phase samples were tested by enzyme-linked immunosorbent assay (ELISA) for the presence of IgM against CHIKV (Euroimmun™, Lübeck, Germany) using serum samples in accordance with the manufacturers' specifications. **- Inflammatory markers measurements in serum:** Measurement of serum inflammatory markers blood samples collected from a peripheral vein, in the non-dominant arm, using a topical anesthetic technique (EMLA®), were used to detect inflammatory mediators, using panels of 6 analytes (TNF-α,IL-6, IL-10, IP-10, IL-1β

STROBE guidelines

Section/topic	Item number	Recommendation
		and IL-8). Analysis was performed with MilliplexR MAP Kit High Sensitivity Magnetic Bead Panel on a MAGPIXR powered by LuminexR XMAP technology. The samples were processed and measured according to the manufacturer's instructions, as described previously in Chang et al., research. Samples were diluted to fit within the dynamic range of the assay. The inflammatory modulators concentrations were calculated by the Bio-Plex Manager software using a five-parametric logistic standard curve derived from the recombinant standards provided in the kit.
Bias	9	Possible biases between those related to the acute infection by the virus and symptoms associated with the chronic phase (retrospective cohort).
Study size	10	**Figure 1**
Quantitative variables	11	Item number 12
Statistical methods	12	Digitalized data were stored in Microsoft Excel 2010. The Shapiro-Wilk test was used to assess data normality. Two sample t-tests, or Mann–Witney U-test, were used to compare the data between the two groups. The Chi-squared test (X^2) was used for the study of categorical variables. The point-biserial correlation was used to measure the correlation between the serum inflammatory markers levels and the development of chronic pain. Statistical analyses were performed using the Stata version 17 software (Stata Corporation LLC, College Station, USA). Graphics were prepared using GraphPad Prism version 5.0 (GraphPad Software Inc., San Diego, CA). A significance level of 5% ($p<0.05$) was adopted to reject the null hypothesis.
Results		
Participants	13	Of 250 patients with acute disease enrolled in this study, 100 (40.0%) had laboratory confirmation of CHIKV infection **(Figure 1)**.
Descriptive data	14	Of them, after exclusion criteria, **twenty-seven** patients developed chronic joint pain **(33.3%)** after exposure to CHIKV (lasting 3 months or longer), 24 female (89%) and 3 male (11%). The median [1st-3rd quartiles] of age and body mass index (BMI) were significantly higher in the long-term pain group when compared to the group of patients without chronic pain, with p= 0.0193/ <0,001, respectively. Years of study were significantly lower in the persistent pain group (p= 0.02). There was no statistical difference between the groups in relation to ethnicity and salary income. The sociodemographic data of the sample are shown in **Table 1**.
Outcome data	15	Days of symptom onset were significantly longer in the chronic pain group (p =0.043). Arthritis (p=0.008) and arthralgia (p=0.023), in acute phase, were significantly higher

STROBE guidelines

Section/topic	Item number	Recommendation
		in the chronic pain group **Table 2**. There were no deaths or serious systemic events (cardiovascular or neurological symptoms) in the studied sample. The results of laboratory tests collected in the acute phase of the disease were also recorded. The **table 3** shows the main laboratory findings. Elevated CRP as well as the presence of lymphocytosis were the most frequent laboratory findings in both groups, with no statistically significant differences between them.
Main results	16	In the analysis of immune markers (TNF-α,IL-6, IL-10, IP-10, IL-1β and IL-8) we observed a higher serum levels of IL-1β in the acute phase of CHIKF, in patients in the chronic pain group (p=0.0135). The results are shown in **figure 2**. However, significant differences in TNF-α, IL-6, IL-10, IP-10 and IL-8 were not observed in the studied groups. In addition, there was a positive correlation (0.227 and 0.419), respectively, between serum elevations of IP-10 (p=0.041) and IL-1β (p=0.015) with persistent pain and a negative correlation (-0.270) with the elevation of IL-10 (p=0.038).
Other analyses	17	None
Discussion		
Key results	18	Women with higher serum levels of IL-1β after CHIKF had a higher prevalence of chronic joint pain. The inflammatory profile of patients in the acute phase of CHIKF may be associated with the development of chronic joint pain. Thus, the search for these biomarkers can reveal prognostic factors and important therapeutic targets for the treatment of the disease. More prospective studies are needed to identify the existence of possible painful phenotypes (peripheral and central mechanisms) in patients with CHIKF, directing more specific treatments, in an attempt to reduce the progression to persistent painful states.
Limitations	19	No analysis of different strains of the virus was performed; Different viremia phases of the patients within the evolution of CHIKF; Possible genetic and epigenetic factors related to the development of chronic pain states after CHIKF also deserve further elucidative studies; It was a unicentric study, with a small sample and clinical information obtained from the medical records, limiting the control of possible biases between those related to the acute infection by the virus and symptoms associated with the chronic phase.

STROBE guidelines

Section/topic	Item number	Recommendation
Interpretation	20	In addition to the severity of the inflammatory response in the acute phase of patients infected with CHIKV, the type of cytokine predominant in this period can to determine the persistent character of the painful symptoms after CHIKF. Thus, these cytokines may have a prognostic function, in addition to serving as something therapeutic, mitigating the evolution of these patients to persistent painful conditions.
Generalizability	21	External validity (Considerations) - Strong points: Representative sample of the Brazilian population; validated inclusion and exclusion criteria; allocation in groups and methodological analysis. - Weak points: Observational and unicentric study with number of 100 participants.
Other information		
Funding	22	No have a funding

APÊNDICE D – Questionário da Pesquisa

Universidade do Estado do Rio de Janeiro

Centro Biomédico

Faculdade de Ciências Médicas

Questionário da Pesquisa

- Dados Sociodemográficos

1. Nome: NIP:
2. Gênero:
3. Idade: Altura: IMC:
4. Etnia: Branco ( ) Não Branco ( )
5. Militar: Sim ( ) Não ( )
6. Anos de estudo: 0-5 ( ) 6-10 ( ) 10-15 ( ) >15 ( )
7. Logradouro:_____
8. TEL:_____
9. Email:_____
10. Data da coleta:

- Perguntas sobre a dor:

- Apresenta alguma dor crônica (3 meses ou maus) anterior ao quadro de Chikungunya
Sim ( ) Não ( )

- Dor articular por 3 meses ou mais após ter tido Chikungunya?
Sim ( ) Não ( )

- Duração da dor:

( ) 3-6 meses;
( ) > 6 – 12 meses;
( ) >1 -3 anos;
( ) > 3 anos;

- Intensidade da dor nas últimas 24 h – Escala de 0-10 (sem dor – a pior dor)

- Descrição da dor – DN4 modificado:

( ) Queimante;

( ) Frio doloroso;
( ) Choque;
( ) Formigamento;
( ) Alfinetada ou agulhas;
( ) Coceira;
( ) Dormência;

- Data do início dos sintomas:
- Febre > 39: Sim ( ) Não ( )
- Febre < 39: Sim ( ) Não ( )
- Cefaleia: Sim ( ) Não ( )
- Mialgia: Sim ( ) Não ( )
- Artralgia: Sim ( ) Não ( )
- Artrite: Sim ( ) Não ( )
- Rush cutâneo: Sim ( ) Não ( )
- Acometimento Neurológico: Sim ( ) Não ( )
- Manifestações gastrintestinais: Sim ( ) Não ( )
-Gestante: Sim ( ) Não ( )
-Comorbidades:_____

- Resultado de exames:

- Sorologia para IgM (+): Sim ( ) Não ( )
-Sorologia para IgG (+):Sim ( ) Não ( )
- Rt – Pcr (+): Sim ( ) Não ( )
- FAN (+): Sim ( ) Não ( )
- FR (+): Sim ( ) Não ( )
- Valor Vitamina D:
- Valor PCR:
- Valor VHS:
- Exames de imagem: _____

- Tratamentos Realizados:

- AINES: Sim ( ) Não ( )
- Corticoides: Sim ( ) Não ( )
- Opioides Fracos: Sim ( ) Não ( )
- Opioides Fortes: Sim ( ) Não ( )
- Gabapentinoides: Sim ( ) Não ( )
- Antidepressivos: Sim ( ) Não ( )
-DARMD: Sim ( ) Não ( )
-Terapias Intervencionistas: Sim ( ) Não ( )

Protocolo para a realização do contato telefônico com os pacientes

- Identificação dos membros da pesquisa/ Explicação da pesquisa;
- Envio do TCLE por e-mail;
- Ligar em 2 dias diferentes em 2 turnos diferentes;
- Estabelecer como estratégia: 3 tentativas em cada ocasião

ANEXO A – Aprovação no Comitê de Ética em Pesquisa

UERJ - HOSPITAL UNIVERSITÁRIO PEDRO ERNESTO/ UNIVERSIDADE DO ESTADO DO RIO DE JANEIRO

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação da modulação condicionada e do perfil fenotípico da dor em pacientes portadores de dor crônica após a Febre de Chikungunya

Pesquisador: Bruno V¿tor Martins Santiago

Área Temática:

Versão: 1

CAAE: 42340920.7.0000.5259

Instituição Proponente: Faculdade de Ciências Médicas

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.626.838

Apresentação do Projeto:

Transcrição editada do conteúdo registrado do protocolo "Nome do Arquivo: PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO__1581169" e dos arquivos anexados à Plataforma Brasil.

A modulação endógena da dor é um termo abrangente que descreve a sucessão de eventos que o sistema nervoso central pode usar para reduzir e,

em alguns casos, aumentar a sensibilidade à dor. Uma forma conhecida de modulação da dor é o fenômeno de inibição por um estímulo doloroso

prévio. O termo controle inibitório nociceptivo difuso (DNIC, da sigla em inglês) foi usado para descrever o evento no qual um estímulo doloroso

intenso, em uma parte do corpo, inibe a dor em partes remotas por ativar as vias inibitórias da dor. O termo modulação condicionada da dor (CPM -

"conditioned pain modulation") foi empregado para descrever este fenômeno em humanos. Alguns estudos demonstraram uma relação entre CPM

ineficiente e quadros dolorosos crônicos, como fibromialgia, cólon irritável e dor pós-operatória persistente.

A febre de Chikungunya tem se revelado

como uma entidade clínica complexa. Apesar de sua grande relevância e impacto na qualidade de vida, sua fisiopatologia ainda é pouco

compreendida, sobretudo, devido a sua pluralidade de apresentações, variando desde indivíduos

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Bairro: Vila Isabel **CEP:** 20.551-030
UF: RJ **Município:** RIO DE JANEIRO
Telefone: (21)2868-8253 **E-mail:** cep@hupe.uerj.br

assintomáticos até aqueles com dores crônicas de
origem musculoesqueléticas e, inclusive, neuropáticas. Desta forma, o objetivo deste projeto é avaliar a modulação condicionada e o perfil
fenotípico da dor em pacientes portadores de dor crônica após a febre de Chikungunya, investigando possíveis papéis centrais e periféricos na
perpetuação da dor. Para isso, será realizado um levantamento dos prontuários, visando identificar os pacientes que tiveram seu diagnóstico
confirmado, seja através de testes sorológicos ou biologia molecular (reação em cadeia da polimerase em tempo real – rT-PcR). Em seguida, os
pacientes serão alocados em 2 grupos: Grupo 1 – Pacientes com diagnóstico de febre de chikungunya e que evoluíram com quadro assintomático,
após 3 meses. Grupo 2 – Pacientes com diagnóstico da febre de chikungunya e que evoluíram com quadro álgico persistente, após 3 meses. Serão
entregues questionários a esses pacientes (Escala graduada de dor crônica Brasil, DN 4, Qualidade de vida (WHOQOL), ansiedade e depressão
(HADS), catastrofização e sensibilização central. Todos serão submetidos aos testes de sensibilidade quantitativa – QST e da CPM, com o objetivo
de avaliar os limiares de detecção e dor térmicos e mecânicos. Também serão avaliados biomarcadores inflamatórios oriundos das amostras de
sangue coletadas dos participantes. A hipótese é que uma mesma doença tenha fenótipos distintos em seres humanos afetados, e que além dos
mecanismos periféricos relacionados a atuação do vírus nos tecidos, alguns pacientes possam ter contribuição do sistema nervoso central para a
cronificação dos sintomas. A melhor compreensão desses fenótipos poderá permitir a instituição de tratamentos individualizados, minimizar custos,
efeitos adversos e melhorar desfechos.

Objetivo da Pesquisa:

Objetivo Primário:

• Analisar a prevalência de dor crônica em uma população com diagnóstico prévio da Febre de Chikungunya e a sensibilidade à dor térmica,
mecânica e a modulação condicionada da dor, além de marcadores inflamatórios nos pacientes

que evoluíram com e sem dor crônica.
Objetivo Secundário:
• Avaliar o impacto da dor crônica na funcionalidade e qualidade de vida;
• Verificar a correlação do quadro álgico com os transtornos de humor;
• Comparar a variabilidade dos métodos empregados (QST e modulação condicionada à dor), em ambos os grupos;
• Avaliar a contribuição dos mecanismos fisiopatológicos (centrais e periféricos), na perpetuação da dor;
• Avaliar a influência das características da amostra (idade, imc e gênero) nos achados obtidos.

Avaliação dos Riscos e Benefícios:
Riscos:
Todos os voluntários serão informados dos riscos, sendo esses mínimos, principalmente, relacionados: aos limiares de desconfortos térmicos e
mecânicos, inerentes aos testes empregados, tendo em vista as variabilidades interindividuais à dor. Entretanto, os parâmetros do aparelho são
calibrados antes da realização dos testes, com o intuito de trabalhar dentro de faixas seguras; e à coleta do material biológico (amostra de sangue),
estando a mesma inserida dentro dos cuidados habituais do acompanhamento clínico dos participantes, sendo procedida através de técnica
anestésica tópica (EMLA®).
Todos os cuidados éticos serão tomados para evitar a manutenção do sigilo das informações obtidas.
Benefícios:
Ajudar a compreender os mecanismos fisiopatológicos implicados na gênese da dor crônica, em pacientes com diagnóstico da Febre de
Chikungunya, visando estudar os circuitos modulatórios endógenos e o seu papel na perpetuação da dor, verificando a contribuição da periferia e do
sistema nervoso central nestes circuitos, bem como o perfil inflamatório desses pacientes. Essas respostas irão enriquecer a literatura médica, no
que diz respeito à variação interindividual na percepção à dor, modulação condicionada da dor e predisposição à dor crônica, importantes fatores
para a determinação de grupos fenotípicos distintos.

Comentários e Considerações sobre a Pesquisa:

Estudo observacional, analítico, transversal e controlado. A pesquisa está bem estruturada e o referencial teórico e metodológico estão explicitados, demonstrando aprofundamento e conhecimento necessários para sua realização. As referências estão adequadas e a pesquisa é exequível. Foram avaliadas as informações contidas na Plataforma Brasil e as mesmas se encontram dentro das normas vigentes e sem riscos iminentes aos participantes envolvidos na pesquisa.

Considerações sobre os Termos de apresentação obrigatória:

Foram analisados os seguintes documentos de apresentação obrigatória:

1) Folha de Rosto para pesquisa envolvendo seres humanos: Documento devidamente preenchido, datado e assinado

2) Projeto de Pesquisa: Adequado

3) Orçamento financeiro e fontes de financiamento: adequado/apresentado

4) Termo de Consentimento Livre e Esclarecido: Adequado

5) Cronograma: Adequado

6) Documentos pertinentes à inclusão do HUPE: Adequado

7) Currículo do pesquisador principal e demais colaboradores: anexados e conforme as normas.

Os documentos de apresentação obrigatória foram enviados a este Comitê, estando dentro das boas práticas e apresentando todos dados necessários para apreciação ética e tendo sido avaliadas as informações contidas na Plataforma Brasil e as mesmas se encontram dentro das normas vigentes e sem riscos iminentes aos participantes envolvidos na pesquisa.

Conclusões ou Pendências e Lista de Inadequações:

O projeto pode ser realizado da forma como está apresentado. Diante do exposto e à luz da Resolução CNS nº466/2012, o projeto pode ser enquadrado na categoria – APROVADO.

Considerações Finais a critério do CEP:

Em consonância com a resolução CNS 466/12 e a Norma Operacional CNS 001/13, o CEP recomenda ao O projeto pode ser realizado da forma como está apresentado. Pesquisador: Comunicar toda e qualquer alteração do projeto e no termo de consentimento livre e esclarecido, para análise das mudanças; Informar imediatamente qualquer evento adverso ocorrido durante o

desenvolvimento da pesquisa; O Comitê de Ética solicita a V. Sª., que encaminhe relatórios parciais de andamento a cada 06 (seis) Meses da pesquisa e ao término, encaminhe a esta comissão um sumário dos resultados do projeto; Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 anos para possível auditoria dos órgãos competentes.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1581169.pdf	11/10/2020 16:34:00		Aceito
Cronograma	Cronograma.docx	11/10/2020 16:31:31	Bruno V¿tor Martins Santiago	Aceito
Orçamento	Orcamento.docx	11/10/2020 16:31:21	Bruno V¿tor Martins Santiago	Aceito
Outros	Carta_Anuencia.pdf	11/10/2020 16:27:20	Bruno V¿tor Martins Santiago	Aceito
Outros	Parecer_Final_CAPPq.pdf	11/10/2020 16:26:34	Bruno V¿tor Martins Santiago	Aceito
Outros	Termo_Compromisso.pdf	11/10/2020 16:24:52	Bruno V¿tor Martins Santiago	Aceito
Outros	Termo_Sigilo_Confidencialidade.pdf	11/10/2020 16:23:30	Bruno V¿tor Martins Santiago	Aceito
Declaração de concordância	Termos_Consentimento_Setores.pdf	11/10/2020 16:22:05	Bruno V¿tor Martins Santiago	Aceito
Declaração de Pesquisadores	Vinculo_Pesquisador.pdf	11/10/2020 16:19:52	Bruno V¿tor Martins Santiago	Aceito
Folha de Rosto	Folha_de_Rosto.pdf	11/10/2020 16:18:59	Bruno V¿tor Martins Santiago	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEmodCapq.docx	11/10/2020 16:12:17	Bruno V¿tor Martins Santiago	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_Doutorado_Bruno_Santiago.docx	11/10/2020 16:10:24	Bruno V¿tor Martins Santiago	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:

Não

RIO DE JANEIRO, 02 de Abril de 2021

Assinado por:
WILLE OIGMAN
(Coordenador(a))

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ANEXO B - Registro Internacional de Revisões Sistemáticas - **PROSPERO**

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Prevalence of chronic pain in adults in Brazil: a systematic review

Citation

Nivaldo Villela, Bruno Santiago, Ana Beatriz Oliveira, Gabriel Silva, Maxuel Silva, Pedro Bergamo. Prevalence of chronic pain in adults in Brazil: a systematic review. PROSPERO 2021 CRD42021249678 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021249678

Review question

Prevalence of chronic pain in adults in Brazil

Searches [1 change]

Ovid MEDLINE, EMBASE, Web of Science, and BVS Regional/LILACS from 2005 to 2020. We will include articles written in English, Portuguese, or Spanish. Only cross-sectional population-based studies will be selected.

Types of study to be included

We will include cross-sectional population-based studies. We will exclude those that did not report the prevalence of chronic pain, conference papers, reviews, data from medical record reviews, studies from which more than one publication has arisen, or abstract without full text.

Condition or domain being studied

Chronic pain (more than three months)

Participants/population

Adults in Brazil

Intervention(s), exposure(s)

chronic pain – lasting more than three months

Comparator(s)/control

non-chronic pain

Main outcome(s)

Prevalence of chronic pain in adults in Brazil in population-based studies. We will select studies performed by domiciliar, telephone, or internet interview

Measures of effect

Confidence Interval

Additional outcome(s)

None

Data extraction (selection and coding)

We will search Ovid MEDLINE, EMBASE, Web of Science, and BVS Regional/LILACS. After removing the duplicates articles, four researchers (ABGA, GMRS, MFS, and PEB) will select the studies independently, using article title and abstract. Two experienced researchers will perform the final selection after reading the full text from the selected articles (BVMS and NRV). We will make a standardized form -with an Excel sheet- to extract meaningful information: study locations, year of article publication and data collection, study designs, number and age of the individuals in each study, the period of chronic pain considered in the studies, the prevalence of chronic pain, and the confidence interval of the data.

Risk of bias (quality) assessment [1 change]

Two experienced researchers will assess the risk of bias for included articles (BVMS and NRV). In case of disagreements between reviewers' judgments, one other researcher will decide (MS). Only cross-sectional population-based studies will be included. It will avoid the multiple inclusion of studies from which more than one publication has arisen. Studies should use a descriptive statistic (percentage) to summarize the prevalence rate of chronic pain. It will be assessed study design (cross-sectional population-based studies), sampling technique (random selection), the sample size (determined or not), the time of chronic pain considered (more than three or six months), and the statistic method used to determine the risk/associated factors to chronic pain.

Strategy for data synthesis [1 change]

Two researchers will synthesize the data and use a descriptive statistic (percentage) to summarize the prevalence rate from individual studies and describe the confidence interval (BVMS and NRV). The summaries will describe the chronic pain prevalence in two groups: lower and higher than 60 years. Studies performed in big or small cities (rural areas) will be described. The risk/associated factors to chronic pain will be grouped and into main themes and described accordingly. In case of disagreements between reviewers' judgments, one other researcher will decide (MS).

Analysis of subgroups or subsets

We will analyze studies with an old and young population

Contact details for further information

Nivaldo Villela

nivaldovillela@terra.com.br

Organisational affiliation of the review

State University of Rio de Janeiro

Review team members and their organisational affiliations

Professor Nivaldo Villela. State University of Rio de Janeiro

Dr Bruno Santiago. State University of Rio de Janeiro

Ms Ana Beatriz Oliveira. State University of Rio de Janeiro

Mr Gabriel Silva. State University of Rio de Janeiro
Mr Maxuel Silva. State University of Rio de Janeiro
Pedro Bergamo. State University of Rio de Janeiro

Type and method of review

Epidemiologic, Systematic review

Anticipated or actual start date

17 April 2021

Anticipated completion date

01 September 2021

Funding sources/sponsors

State University of Rio de Janeiro

Conflicts of interest

Language

English

Country

Brazil

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Adult; Brazil; Chronic Pain; Humans; Prevalence

Date of registration in PROSPERO

18 May 2021

Date of first submission

17 April 2021

Stage of review at time of this submission

The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

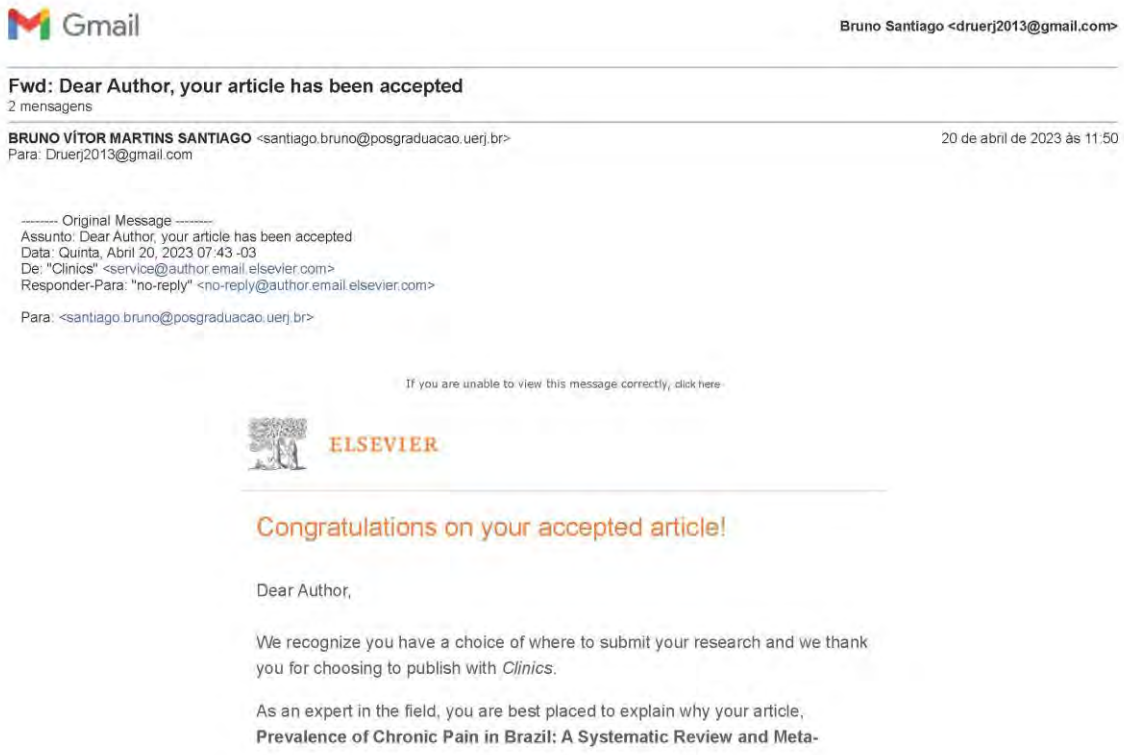
The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

18 May 2021

ANEXO C - Comprovação de aceite do 1º artigo científico



Gmail

Bruno Santiago <druerj2013@gmail.com>

Fwd: Dear Author, your article has been accepted
2 mensagens

BRUNO VÍTOR MARTINS SANTIAGO <santiago.bruno@posgraduacao.uerj.br>
Para: Druerj2013@gmail.com

20 de abril de 2023 às 11:50

-------- Original Message --------
Assunto: Dear Author, your article has been accepted
Data: Quinta, Abril 20, 2023 07:43 -03
De: "Clinics" <service@author.email.elsevier.com>
Responder-Para: "no-reply" <no-reply@author.email.elsevier.com>

Para: <santiago.bruno@posgraduacao.uerj.br>

If you are unable to view this message correctly, click here

ELSEVIER

Congratulations on your accepted article!

Dear Author,

We recognize you have a choice of where to submit your research and we thank you for choosing to publish with *Clinics*.

As an expert in the field, you are best placed to explain why your article, **Prevalence of Chronic Pain in Brazil: A Systematic Review and Meta-**

ANEXO D – Confirmação de submissão do 2º artigo

MMIM-D-23-00089 - Submission Confirmation

Sábado, Junho 03, 2023 12:28 -03

Medical Microbiology and Immunology (MMIM)
em@editorialmanager.com

Para
Bruno Vitor Martins Santiago

Dear Mr Santiago,

Thank you for submitting your manuscript, High serum levels of IL-1β and IP-10 markers in the acute phase of Chikungunya fever correlate with chronic joint pain, to Medical Microbiology and Immunology.

The submission id is: MMIM-D-23-00089
Please refer to this number in any future correspondence.

During the review process, you can keep track of the status of your manuscript by accessing the journal's website.

Your username is: bruno santiago
If you forgot your password, you can click the 'Send Login Details' link on the EM Login page at
https://www.editorialmanager.com/mmim/

Should you require any further assistance please feel free to e-mail the Editorial Office by clicking on "Contact Us" in the menu bar at the top of the screen.

With kind regards,
Springer Journals Editorial Office
Medical Microbiology and Immunology

Now that your article will undergo the editorial and peer review process, it is the right time to think about publishing your article as open access. With open access your article will become freely available to anyone worldwide and you will easily comply with open access mandates. Springer's open access offering for this journal is called Open Choice (find more information on www.springer.com/openchoice). Once your article is accepted, you will be offered the option to publish through open access. So you might want to talk to your institution and funder now to see how payment could be organized; for an overview of available open access funding please go to www.springer.com/oafunding.
Although for now you don't have to do anything, we would like to let you know about your upcoming options.

ANEXO E – Parecer do Revisor

Universidade do Estado do Rio de Janeiro - UERJ.
Programa de Pós-Graduação em Ciências Médicas - PGCM
Av. Professor Manoel de Abreu - 444 - 1º andar
Vila Isabel - Rio de Janeiro - RJ - 20550-170
Telefone 55(21)2868-8488
Email pgcm.uerj@gmail.com

FORMULÁRIO: PARECER DE TESE

Título: Prevalência de dor crônica no Brasil, fatores associados e o papel da resposta inflamatória aguda na cronificação da dor articular após a Febre de Chikungunya.

Nome do aluno: BRUNO VITOR MARTINS SANTIAGO

Orientadores: NIVALDO RIBEIRO VILLELA

MAUD PARISE

Por ocasião da emissão do parecer, deverão ser observados os seguintes aspectos:

a) Importância da tese e sua contribuição à área de conhecimento;
b) Avaliação do texto apresentado;
b.1) Atualização do problema abordado;
b.2) Metodologia empregada;
b.3) Importância dos resultados obtidos;
b.4) Pertinência da discussão realizada;
b.5) Bibliografia utilizada;
b.6) Adequação do resumo;
b.7) Sugestões (quando couber);
c) Recomendação final da tese;:

[X] Pode ser a mesma apresentada e defendida sem modificações;

[ ] Apresentação e defesa devem ser antecedidas de pequenas modificações no texto, não havendo necessidade de nova avaliação;

[ ] Modificações substanciais e/ou experimentos adicionais s&lde;o necessários, após o que uma nova avaliação deverá ser feita;

[ ] Deve ser rejeitada.

Revisor : MAUD PARISE

Data: 10.06.23

Assinatura: Maud Parise