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Disease activity Score 28 in patients with Chikungunya virus infection

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ABSTRACT:

— ***Objective:*** This study aims to evaluate different parameters for determining the inflammatory activity in patients with Chikungunya.

— ***Patients and methods:*** An observational, cross-sectional, descriptive, and analytical study was conducted with 56 patients from May 2018 to June 2020. Seven independent variables were evaluated [pain in 28 joints, oedema in 28 joints, erythrocyte sedimentation rate, global health assessment, Disease Activity Score 28 (DAS28), pain in 64 joints and oedema in 64 joints] and analysed with a regression model to determine their influence on patient satisfaction (dependent variable).

— ***Results:*** All studied variables had a significant influence on patient satisfaction, especially the DAS28. However, the agreement between patient satisfaction and the DAS28 was poor (kappa = 0.2). Thus, new cut-off points were established for the DAS28. Compared to the traditional cut-off points used in rheumatoid arthritis, the new cut-off points increased the accuracy of the DAS28 from 37.5% to 51.8%.

— ***Conclusions:*** This study contributes to the literature by presenting the DAS28 as a potentially useful instrument in patients with Chikungunya and using cut-off points adjusted for this population. The results can serve as a reference for future studies with larger sample sizes, which would allow more definitive conclusions.

— ***Keywords:*** Chikungunya fever, Arbovirus infections, Arthritis, Arthralgia, Disease activity.

INTRODUCTION

Chikungunya virus (CHIKV) is a single-stranded RNA arbovirus belonging to the *Togaviridae* family; it is transmitted by mosquitoes of the genus Aedes and causes acute febrile disease in infected humans[1]. However, some signs and symptoms of diseases in some people infected with CHIKV, such as arthralgia, joint oedema and stiffness, can last for months to years and are often recurrent[2].

Pain, which is the most frequent clinical manifestation of CHIKV, commonly becomes difficult to control, compromising the quality of life of affected patients and, consequently, constituting a serious public health problem[3]. The great challenge for physicians in endemic areas is to identify and diagnose chronic rheumatic manifestations and provide the ideal treatment to prevent the disease's progression to a potentially debilitating course[4].

In addition, there are few guidelines on the management of pain and inflammation in patients with CHIKV, and the existing guidelines are not homogeneous and use several methods to decide whether to adjust treatment.

To help define the best management approach for patients with post-CHIKV chronic arthritis, different authors have used different instruments to measure disease activity, and there is no established and/or rec-

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ommended standardization. Pereira and Schoen[1] recommend the use of the Disease Activity Score 28 (DAS28) or other instruments that have been validated to measure disease activity in rheumatoid arthritis (RA) in an extrapolated way, while de Brito et al[3] used the visual analogue pain scale along with a physical examination to define the best treatment.

It is common to use several instruments for medical decision-making in rheumatology, including the DAS28 for RA and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for ankylosing spondylitis (AS). Currently, these instruments are standardized and enable the establishment of protocols, thus facilitating clinical practice; however, this is not yet available for CHIKV[5-8].

Therefore, the objective of this study was to evaluate the best way to monitor patients with CHIKV and to determine who has active disease at the time of consultation, with the aim of establishing the best instrument for monitoring these patients.

PATIENTS AND METHODS

An observational, cross-sectional, descriptive and analytical study was conducted from May 2018 to June 2020 at the Infection and Autoimmunity outpatient clinic of the Centre for Tropical Medicine at the Federal University of Pará (UFPA), located in the city of Belém, Pará state, Brazilian Amazon region.

Patients diagnosed with CHIKV fever who were treated at the outpatient clinic and met the inclusion criteria were invited to participate in the study. The inclusion criteria included the following: laboratory confirmation of CHIKV fever; articular manifestations; 18 years of age or older; and consent provided through an informed consent form (ICF). Patients with incomplete investigation forms were excluded.

After the patients received guidance about the research objectives, risks, and benefits of the study and signed the ICF, patient data were collected using an investigation form prepared by the authors, which contained data such as sex, age, duration of disease and medications in use. In addition, the DAS28 of the patients was determined by counting the relevant painful and swollen joints and determining the erythrocyte sedimentation rate (ESR) and the response to the global patient health assessment (GA). In addition, other painful and swollen joints in the lower and upper limbs were counted. Thus, the independent variables used were pain count in 28 joints, oedema count in 28 joints, ESR, global health assessment, DAS28, pain count in 64 joints, and oedema count in 64 joints. The joint counts and DAS28 determination followed the recommendations provided in the literature[5,6].

To verify whether there was a correlation between these variables and patient satisfaction with their health status, the values of these variables were compared to the patient's response to the following question: "Considering all the ways in which the disease (CHIKV) affects you at this time, how do you feel?"

The responses were recorded using a Likert scale with the following values and meanings:

0 - Totally dissatisfied
1 - Slightly dissatisfied
2 - Slightly satisfied
3 - Completely satisfied

The data from the sample characterization were entered into a database prepared in Microsoft® Office Excel® 2021 software. To prepare a CHIKV estimator model, the seven predictor variables were presented as measurements of central tendency and variation. The normality of the variables was assessed with the D'Agostino-Pearson test. The CHIKV estimation model was constructed from seven geometric regressions with satisfaction as the dependent variable. The values that established the limits of separation between the degrees of disease activity (remission, low, moderate, severe) were calculated using the BioEstat 5.3 Cut-off Point application[9]. To assess the accuracy of the DAS28 as a marker of disease activity, the agreement between DAS28 and patient satisfaction was determined using the kappa test[9]; the classification of the agreement between DAS28 and satisfaction according to the kappa statistic was based on the values established by Landis et al[10]. The estimation of the new DAS28 cut-off points and their predictive values was performed using the cut-off point application of the BioEstat package. An alpha error of 5% ($\alpha = 0.05$) was previously established for rejection of the null hypothesis. All statistical processing was performed using BioEstat software version 5.3.

Ethics

The study was conducted according to the principles of the Declaration of Helsinki after receiving approval from the Research Ethics Committee of the Health Sciences Institute of UFPA under number 2.625.005 (CAAE 83615418.6.0000.0018).

RESULTS

The sample included a total of 56 patients with a mean age of 52.1 ± 10.3 years, most of whom were female (91.1%). Regarding the time of symptom onset, there was a predominance of the chronic phase of the disease (3 months or more), with a mean duration of symptoms of 7.9 ± 4.8 months, and there were no patients in the acute phase of infection (Table 1).

To assess patient satisfaction at the time of evaluation, the patients' response to the question "Considering all the ways in which the disease (Chikungunya) affects you at this time, how do you feel?" was used. The responses showed that there was a predominance of satisfied patients, while 37.5% indicated that they were less satisfied with their health status, and 37.5% reported being totally satisfied (Table 2).

Table 3 shows the characteristics of the independent variables that were compared with the dependent variable (patient satisfaction) in this study. Nonparametric tests were used to evaluate the interdependencies among the variables.

Table 1. Sex, age, and disease duration of patients with Chikungunya treated from May 2018 to June 2020.

	Frequency	Percentage (%)	*p*
Sex			*p<0.0001¥
Female*	51	91.1%	
Male	5	8.9%	
Total	56	100%	
Age			p=0.1520€
<40	8	14.3%	
40 to 49	13	23.2%	
50 to 59	20	35.7%	
≥60	15	26.8%	
Total	56	100.0%	
Time since first symptoms (months)			*p=0.0423€
01 to 02	6	10.7%	
03 to 04	9	16.1%	
05 to 06	9	16.1%	
07 to 08*	15	26.8%	
09 or more	6	10.7%	
12 or more	11	19.6%	
Total	56	100.0%	

SD: Standard deviation; ¥: G-adherence test; €: Chi-square homogeneity test

The seven independent variables were evaluated individually in a geometric regression model, with satisfaction as the dependent variable. The multivariate model showed that all of the variables statistically influenced patient satisfaction: pain in 64 joints (r = -0.0773; p = 0.0012); oedema in 64 joints (r = -0.1729; p = 0.0006); ESR (r = -0.1030; p = 0.0322); DAS28 (r = -0.2832; p < 0.00001); GA (r = -0.1180; p = 0.0009); pain in 28 joints (r = -0.0892; p = 0.0008); and oedema in 28 joints (r = -0.1563; p = 0.0136).

Considering that all the studied variables had a significant influence and considering the practicality of the DAS28 and its widespread use in clinical practice, proposing a new instrument for evaluating disease activity was not of interest. Thus, we decided to verify the agreement between patient satisfaction and the DAS28 categories and determine whether the cut-off points traditionally used for RA (remission ≤ 2.6; low activity > 2.6 to 3.2; moderate activity > 3.2 to 5.1; high activity > 5.1) would be adequate for decision-making in patients with CHIKV.

Table 2. Satisfaction with health status in patients with Chikungunya treated from May 2018 to June 2020.

Level of satisfaction	Frequency	Percentage
Totally dissatisfied	7	12.5%
Slightly dissatisfied	7	12.5%
Slightly satisfied*	21	37.5%
Totally satisfied*	21	37.5%
Total	56	100.0%

*p<0.0001-Chi-square test

The agreement between DAS28 and patient satisfaction was evaluated using the kappa statistic (kappa = 0.2 and p = 0.0116*). The results indicated a weak level of correspondence between the two scales. The observed agreement was only 37.5%.

From these results, receiver operating characteristic (ROC) curves were developed to estimate new DAS28 cut-off points that could be better related to the satisfaction of patients with CHIKV (Table 4).

The new cut-off points were compared to the traditional cut-off points and were found to increase the accuracy of the DAS28 from 37.5% to 51.8% (Table 5).

DISCUSSION

This is the first study to analyse the accuracy of the DAS28 for monitoring and evaluating inflammatory activity in patients with CHIKV. This evaluation may be of great value to support future studies, such as those undertaken to evaluate the best therapy for these patients.

Although the DAS28 is a widely used instrument that is established in the literature, especially for RA, and guidelines recommend its use to evaluate patients with CHIKV[1], it was hypothesized that the DAS28 may underestimate disease activity in people infected with CHIKV since it does not consider the involvement of the ankles and feet in its analysis, and these joints are commonly affected in CHIKV patients.

Peters et al[11] showed that in patients who developed chronic arthralgia, the joints with persistent pain were mainly the knees, hands, and feet, and 54% of patients studied had ankle arthralgia during the acute phase. In

Table 3. Independent variables used to formulate the Chikungunya disease impact estimate model for patients treated from May 2018 to June 2020.

	Pain in 64 joints	Oedema in 64 joints	ESR	DAS28	GA	Pain in 28 joints	Oedema in 28 joints
Minimum	0.00	0.00	4.00	1.13	0.00	0.00	0.00
Maximum	58.00	16.00	85.00	7.52	10.00	28.00	12.00
Median	3.00	0.00	25.50	3.61	4.00	2.00	0.00
Mean	7.95	1.27	28.39	3.80	4.04	5.11	0.70
SD	11.42	2.50	16.30	1.51	3.10	7.23	1.93
p-value	<0.0001	<0.0001	<0.0001	0.2465	0.2829	<0.0001	<0.0001

SD = standard deviation; ESR = erythrocyte sedimentation rate; DAS28 = Disease Activity Score 28; GA = global assessment. *p*-value: D'Agostino-Pearson normality test.

Table 4. Sensitivity and specificity of the new cut-off points proposed for DAS28.

	Remission to low activity	Low to moderate activity	Moderate to high activity
Calculated cut-off point	3.2	4.3	5.2
Sensitivity	81%	85%	42%
Specificity	71%	61%	71%

Table 5. Comparison of the accuracy of the prediction of Chikungunya activity between the original and new cut-off points of the DAS28.

Satisfaction	DAS28 Categories	DAS28 (ORIGINAL) Accuracy	DAS28 (NEW CUT-OFF POINTS) Accuracy
Totally dissatisfied	High	42.9%	23.1%
Slightly dissatisfied	Moderate	57.1%	37.5%
Slightly satisfied	Low	9.5%	61.5%
Totally satisfied	Remission	57.1%	68.2%
Total		37.5%	51.8%

DAS28 = Disease Activity Score 28

another study with 63 patients, Pereira et al[12] observed a high frequency of polyarticular and symmetrical arthralgia, commonly involving the ankles and knees. In the present study, both the 28-joint and 64-joint counts were significantly correlated with the dependent variable (patient satisfaction) and considering that the 28-joint count is much faster and more practical, it does not make sense to suggest a change in this parameter.

Sepúlveda-Delgado et al[13] used the WHO Disability Assessment Schedule II (WHODAS-II) instrument to assess the health and disability of patients with CHIKV. The results of this instrument were compared with the DAS28 results in patients who obtained a DAS28 > 5.1, indicating high disease activity, and a strong association between the two scores was observed. These results corroborate the use of the DAS28 to evaluate patient health status, although the study sample was small.

The study conducted by Sepúlveda-Delgado et al[13] also showed that evidence of inflammatory activity, such as the ESR, seems to be related to the progression of the disease to a chronic stage, and they stated that both the DAS28 and ESR were higher in patients who progressed to subacute and chronic phases of CHIKV. However, there are no studies that relate such inflammatory evidence with patients' satisfaction with their health status. In the present study, the ESR levels were inversely related to patient satisfaction, although the ESR was the variable with the lowest significance among those used to obtain the DAS28.

Although significant, the association between the DAS28 and patient satisfaction was poor (kappa = 0.2), which indicates that the DAS28 is not adequate for evaluating disease activity in patients with CHIKV, at least using the cut-off levels recommended in the literature. As it would not be practical to propose a new instrument, we decided to search for new DAS28 cut-offs for patients with CHIKV infection.

With the new cut-off points (remission ≤ 3.2; low activity > 3.2 to 4.3; moderate activity > 4.3 to 5.2; high activity > 5.2), there was an increase in accuracy of 14.3% (37.5% to 51.8%), which suggests that these new cut-off points may be more useful for monitoring inflammatory activity in patients with CHIKV. The increase in accuracy seems promising, although it is still not ideal; in RA, for example, the accuracy of the DAS28 reaches 93.3%[14].

It is important to emphasize that the establishment of a practical evaluation instrument is essential to providing quality care and treatment for patients with CHIKV. According to Franses et al[15], such instruments allow the interpretation of several aspects of a disease using a single index; such interpretation would otherwise be difficult to perform simultaneously given the number of variables. Additionally, such instruments are beneficial for statistical analyses. Van Riel and Renskers[16] state that in RA, disease activity cannot be measured in all individuals using a single variable. In clinical practice, it is important to have a way to quantify the impression generated from clinical and laboratory information to enable comparisons of treatment efficacy and improve patient progress. Instruments such as the DAS28 have emerged to address this need and help rheumatologists decide whether to initiate or terminate treatments with disease-modifying antirheumatic drugs (DMARDs) based on the patient's category.

This study has limitations that should be considered. The size of the analysed sample does not allow generalization of the results obtained; however, the results of this study offer a new perspective for studies aimed at identifying ways to monitor patients infected with CHIKV and for studies that envisage the adoption of more homogeneous and evidence-based approaches for these patients. In addition, it was not possible to study the influence of C-reactive protein (CRP) in this study due to difficulties at the local laboratory; however, ESR levels are traditionally accepted for the DAS28, and when it is calculated using CRP, the correlation when the ESR is used is strong[17-19].

CONCLUSIONS

This study contributes to the literature by presenting the DAS28 as a potentially useful instrument for patients with CHIKV and using cut-off points adjusted for this population. It is expected that the DAS28 can serve as a reference for future studies with larger sample sizes that will allow more definitive conclusions.

Informed Consent:
Obtained.

Conflict of Interest:
The authors declare that they have no conflict of interest.

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