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Short Communication

Development of a concise clinical index for predicting chronic chikungunya arthritis

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ABSTRACT

Objective: To evaluate the performance of an instrument for predicting chronic chikungunya arthritis (CCA) in adult patients.
Methods: A diagnostic test study was conducted and data from 217 confirmed cases of chikungunya virus (CHIKV) illness were analyzed. Two chronic chikungunya arthralgia scales (3-item CCAS-3 and 4-item CCAS-4) were constructed.
Results: Modest performance of the CCAS-3 scale was documented at the two given cut-off points. A CCAS-4 score ≥3 showed high sensitivity and specificity for predicting the persistence of CCA at 12 months after acute disease.
Conclusions: If replicated in other populations, these results could be useful in the medical management of patients with symptomatic CHIKV infection.

Introduction

Chronic chikungunya arthralgia (CCA) is characterized by relapsing episodes of articular pain for >3 m`onths after acute disease illness (Zaid et al., 2018). CCA is a frequent event (presenting in nearly a quarter of subjects at 12 months post-infection) (Paixão et al., 2018), with a potential impact on functional status and quality of life (Marimoutou et al., 2015).

Diverse exposures have been associated with an increased risk of CCA (Paixão et al., 2018). However, to the best of our knowledge, there are no published studies that have developed and evaluated a screening index for the chronic illness.

The aim of this study was to develop and evaluate the performance of a simple and concise clinical index for predicting CCA.

Methods

A diagnostic test study, based on a cohort study, was conducted in a subtropical western state of Mexico. Data from 217 confirmed

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(quantitative reverse transcription polymerase chain reaction, RT-qPCR) cases of chikungunya virus (CHIKV) illness in adults were analyzed. A complete description of the selection criteria has been published previously (Murillo-Zamora et al., 2018).

Two chronic chikungunya arthralgia scales (3-item CCAS-3 and 4-item CCAS-4) were constructed. The following exposures were included in the 3-item scale (CCAS-3) (response no/yes, with 0/1 point respectively): female, 40 years of age or older, and eight or more arthralgia sites (including: hands, wrists, elbows, shoulders, neck, upper back, lower back, hips, knees, ankles, and feet) during the acute CHIKV illness. The variables were selected according to their association with an increased risk of CCA in the study sample (Murillo-Zamora et al., 2018; Murillo-Zamora et al., 2017). Female sex was included according to recently

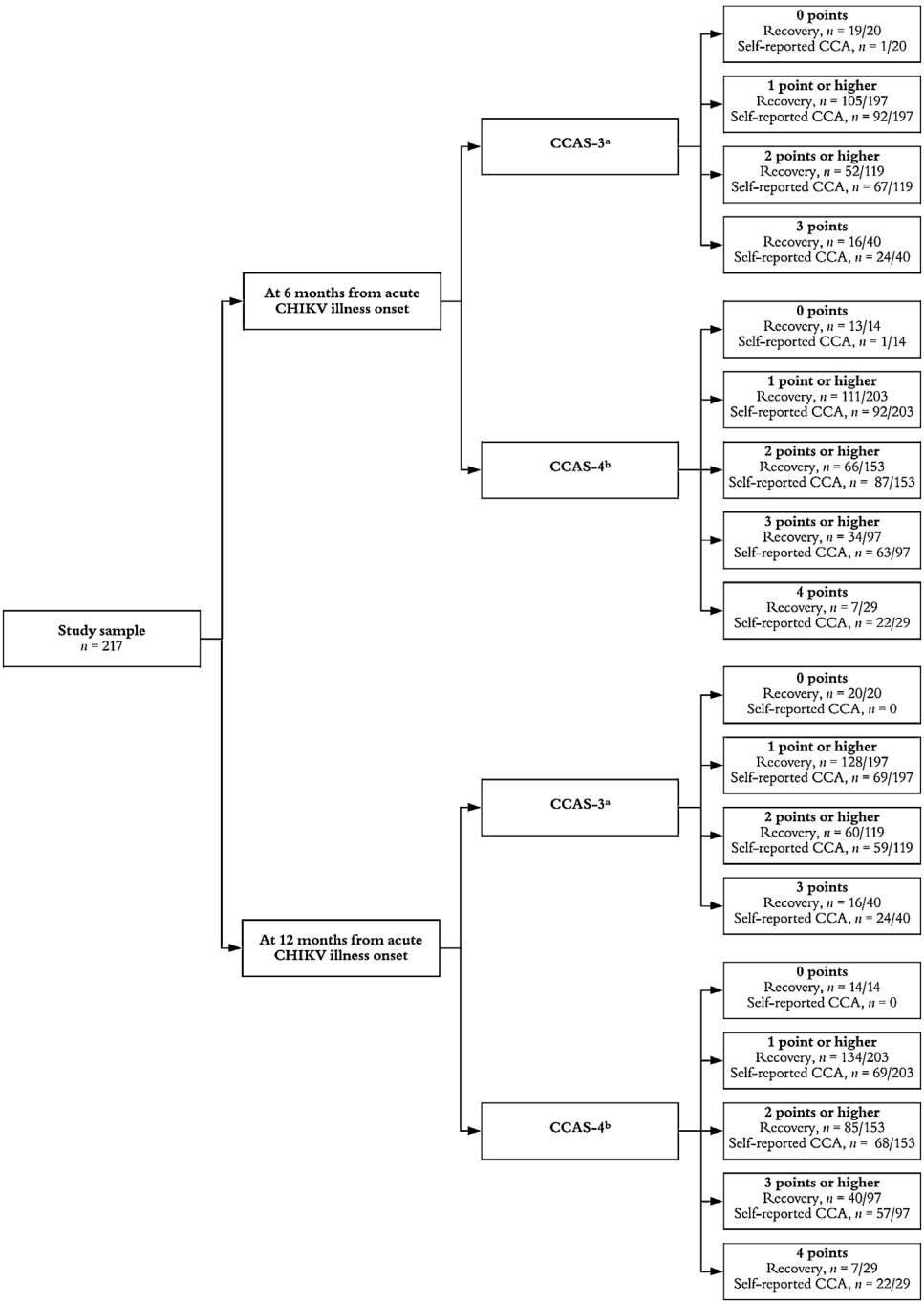

Figure 1. Study profile, Mexico 2016–2017. (Abbreviations: CHIKV, chikungunya virus; CCAS-3, 3-item Chronic Chikungunya Arthralgia Scale; CCAS-4, 4-item Chronic Chikungunya Arthralgia scale; CCA, chronic chikungunya arthralgia.)

Note: Individuals classified as CCA-positive were those who stated that they did not have a complete recovery from articular pain after disease onset and reported the recurrence of arthralgia during the 8 days prior to being interviewed.

[a]The following dichotomous variables (no/yes, with corresponding 0/1 point) were included: female, 40 years of age or older, and eight or more arthralgia sites (namely: hands, wrists, elbows, shoulders, neck, upper back, lower back, hips, knees, ankles, and feet) during the acute CHIKV illness.

[b]The following dichotomous variables (no/yes, with corresponding 0/1 point) were included: female, 40 years of age or older, eight or more arthralgia sites (namely: hands, wrists, elbows, shoulders, neck, upper back, lower back, hips, knees, ankles, and feet) during the acute CHIKV illness, and self-reported arthralgia (any site) at 3 months post-acute infection.

published findings (Heath et al., 2018). In addition to these exposures, the CCAS-4 included self-reported arthralgia (at any site) at 3 months post-infection.

The binary outcome (CCA) was evaluated with two dichotomous questions at 6 and 12 months: "Do you feel that you have made a complete recovery from articular manifestations since being diagnosed with CHIKV infection?" and "Over the past 8 days, did symptoms of CHIKV illness subside and then recur?" (Sissoko et al., 2009). Individuals who responded 'No' and 'Yes' to the first and second question, respectively, were classified as CCA-positive. Performance parameters (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, positive likelihood ratio (LR+), negative likelihood radio (LR−), Youden's index (J), and area under the receiver operating characteristics (AUROC)) and 95% confidence intervals (CI) were estimated (Stata 13.0, StataCorp.).

Results

The study profile is summarized in Figure 1. A complete description of the study population has been published previously (Murillo-Zamora et al., 2018). The AUROC of the CCAS-3 was 0.677 (95% CI 0.610–0.743) at 6 months and 0.759 (95% CI 0.698–0.820) at 12 months. Higher AUROCs were observed using the CCAS-4 (6 months: 0.769, 95% CI 0.708–0.828; 12 months: 0.834, 95% CI 0.784–0.884).

The performance parameters are presented in Table 1. The accuracy of the CCAS-3 was modest and it was higher when predicting the longer-term articular manifestations (12 months), particularly when a score of ≥2 was used (J = 0.450) as the cut-off point.

Modest estimators were obtained with the CCAS-4 scale at 6 months post-infection. A score of ≥3 was associated with the best performance of the screening tool in predicting self-reported CCA at 12 months from illness onset (sensitivity 82.6%, 95% CI 74.0–88.8%; specificity 73.0%, 95% CI 63.6–80.7%).

Discussion

The study results suggest that this concise index performs well for predicting self-reported CCA, particularly at 12 months from the acute disease. The findings, if later replicated in other populations, could be of clinical and epidemiological use as part of the integral medical attention of patients presenting at ≥3 months post-infection.

According to the results, a score of ≥3 in the CCAS-4 has a PPV of 71.2% (95% CI 61.7–79.2%) and NPV of 83.3% (95% CI 75.4–89.7%) for predicting CCA at 12 months from the acute disease. More than three out of four individuals (76.0%, 95% CI 66.8–83.3%) would be correctly classified.

Due its potential functional implications, the factors associated with the risk of chronic CHIKV-related manifestations have been studied widely, but mainly as independent exposures (Paixão et al., 2018). This study appears to be the first to provide a risk assessment tool that enables the prediction of chronic manifestations in CHIKV patients. The proposed index is simple and purely syndromic. Therefore, it could be useful in predicting the outcome of interest in health care settings, including those with limited resources.

This study had the following limitations: first, the performance of the scale increased after the inclusion of the fourth item, meaning that the evaluation would need to be made at least at 3 months post-infection and when the chronic disease is already established (criterion in CCAS-4, self-reported arthralgia (any site) at 3 months post-acute infection) (Zaid et al., 2018). However, factors involved in the persistence of CCA are poorly understood and the timely identification of patients at increased risk of persistent manifestations at 6 and 12 months post-acute disease may potentially reduce the negative and multidimensional impact of CCA on health.

Second, biomarker data were lacking, such as CHIKV genotype, and variations in the frequency of CCA have been documented according to the pathogen genotype (Paixão et al., 2018). The Asian

Table 1
Predictive accuracy of the CCAS-3 and CCAS-4 in predicting chronic chikungunya arthralgia, Mexico, 2016–2017; the estimated parameters and 95% confidence intervals (CI) are presented.

Cut-off point	Sensitivity, %		Specificity, %		Prevalence, %		PPV, %		NPV, %		Accuracy, %		LR+	LR−	J
CCA-3[a]															
At 6 months acute after illness, score															
1/higher	98.9	(94.8, 99.8)	15.3	(9.5, 23.6)	90.8	(83.5, 95.1)	92.0	(85.0, 95.9)	58.5	(48.7, 67.7)	51.2	(41.5, 60.8)	1.168	0.070	0.142
2/higher	72.0	(62.5, 79.9)	58.1	(48.3, 67.3)	54.8	(45.0, 64.2)	67.6	(57.9, 76.0)	63.1	(53.3, 71.9)	64.1	(54.3, 72.8)	1.718	0.482	0.301
3	25.8	(15.7, 31.9)	87.1	(79.1, 92.3)	18.4	(12.0, 27.1)	31.1	(22.9, 40.7)	83.9	(75.5, 89.8)	60.8	(51.0, 69.8)	2.000	0.852	0.129
At 12 months after acute illness, score															
1/higher	100	–	13.5	(8.1, 21.6)	90.8	(83.5, 95.1)	91.9	(84.9, 95.8)	100	–	41.0	(31.9, 50.8)	1.156	0.000	0.135
2/higher	85.5	(77.3, 91.1)	59.5	(49.7, 68.6)	54.8	(45.0, 64.2)	71.9	(62.4, 79.8)	77.2	(68.1, 84.3)	67.7	(58.0, 76.1)	2.109	0.244	0.450
3	34.8	(26.2, 44.5)	89.2	(81.6, 93.9)	18.4	(12.0, 27.1)	42.1	(32.9, 51.9)	85.9	(77.7, 91.4)	71.9	(62.4, 79.8)	3.217	0.731	0.240
CCA-4[b]															
At 6 months after acute illness, score															
1/higher	98.9	(94.4, 99.8)	10.5	(5.9, 18.0)	93.5	(86.9, 96.9)	94.1	(87.7, 97.3)	39.9	(30.8, 49.7)	48.4	(38.8, 58.1)	1.105	0.103	0.094
2/higher	93.6	(87.0, 97.0)	46.8	(37.3, 56.5)	70.5	(60.9, 78.5)	80.8	(72.0, 87.3)	75.4	(66.1, 82.8)	66.8	(57.1, 75.3)	1.758	0.138	0.404
3/higher	67.7	(58.0, 76.1)	72.6	(63.1, 80.4)	44.7	(35.5, 54.5)	66.6	(56.9, 75.1)	73.5	(64.1, 81.2)	70.5	(60.9, 78.5)	2.471	0.444	0.403
4	23.7	(16.4, 32.9)	94.4	(88.0, 97.5)	13.4	(8.1, 21.4)	39.6	(30.6, 49.4)	88.9	(81.3, 93.7)	64.1	(54.3, 72.8)	4.191	0.809	0.181
At 12 months after acute illness, score															
1/higher	100	–	9.5	(5.2, 16.8)	93.5	(86.9, 96.9)	94.1	(87.7, 97.3)	100	–	38.3	(29.4, 48.1)	1.105	0.000	0.095
2/higher	98.6	(93.9, 99.7)	42.6	(33.4, 52.4)	70.5	(60.9, 78.5)	80.4	(71.6, 87.0)	92.7	(85.9, 96.4)	60.4	(50.6, 69.4)	1.716	0.034	0.412
3/higher	82.6	(74.0, 88.8)	73.0	(63.6, 80.7)	44.7	(35.5, 54.5)	71.2	(61.7, 79.2)	83.8	(75.4, 89.7)	76.0	(66.8, 83.3)	3.057	0.238	0.556
4	31.9	(23.6, 41.6)	95.3	(89.2, 98.0)	13.4	(8.1, 21.4)	51.2	(41.5, 60.8)	90.0	(82.6, 94.5)	75.1	(65.8, 82.5)	6.741	0.715	0.272

Abbreviations: CCAS-3, 3-item Chronic Chikungunya Arthralgia scale, for predicting chronic chikungunya arthralgia at 6 and 12 months after acute chikungunya illness; CCAS-4, 4-item Chronic Chikungunya Arthralgia scale, for predicting chronic chikungunya arthralgia at 6 and 12 months after acute chikungunya illness; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio; J, Youden's index.

[a] The following dichotomous variables (no/yes, with corresponding 0/1 point) were included: female, 40 years of age or older, and eight or more arthralgia sites (namely: hands, wrists, elbows, shoulders, neck, upper back, lower back, hips, knees, ankles, and feet) during the acute chikungunya illness.

[b] The following dichotomous variables (no/yes, with corresponding 0/1 point) were included: female, 40 years of age or older, eight or more arthralgia sites (namely: hands, wrists, elbows, shoulders, neck, upper back, lower back, hips, knees, ankles, and feet) during the acute chikungunya illness, and self-reported arthralgia (any site) at 3 months post-acute infection.

viral genotype was isolated during the disease outbreak in Mexico, in the location where the study was conducted (Díaz-Quiñonez et al., 2015). The CCAS-3 and CCAS-4 could be perfected and the inclusion of biomarker data (i.e., specific IgG titers) (Gérardin et al., 2013) could potentially improve its accuracy.

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Ethical approval

The National Commission for Scientific Research of the Mexican Institute of Social Security approved this study.

Conflict of interest

The authors declare that they have no conflict of interest.

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