Clinical Manifestations and Outcomes in Disease-Modifying Antirheumatic Drug-Naive Adult Patients with Chronic Chikungunya Arthritis

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Abstract. Most studies on chronic chikungunya virus (CHIKV) arthritis include patients treated with disease-modifying antirheumatic drugs (DMARDs), likely altering the expression of clinical manifestations and outcome. Therefore, we sought to evaluate the clinical features and correlates in DMARD-naive patients with chronic CHIKV arthritis. We conducted a case–control study in adult patients with serologically confirmed CHIKV infection in Puerto Rico. Demographic features, clinical manifestations, comorbidities, disease activity (per Clinical Disease Activity Index [CDAI]), functional status (per Health Assessment Questionnaire Disability Index [HAQ-DI]), and pharmacologic treatment were ascertained. Patients with and without chronic CHIKV arthritis were compared. Furthermore, a sub-analysis was performed among patients with chronic CHIKV who presented with mild disease activity versus moderate-to-high disease activity at study visit. In total, 61 patients were studied; 33 patients had chronic arthritis and 28 had resolved arthritis. Patients with chronic arthritis had significantly more diabetes mellitus, chronic back pain, and fever, tiredness, and myalgias on the acute phase. The mean (SD) HAQ score was 0.95 (0.56), and 57.6% had moderate-to-high disease activity. Patients with moderate-to-high disease activity had higher scores in overall HAQ-DI and HAQ-DI categories (dressing and grooming, arising, hygiene, reaching, and activities) than in those with mild activity. In conclusion, in this group of DMARD-naive patients with chronic CHIKV arthritis, nearly 58% had moderate-to-high disease activity and had substantial functional disability. Diabetes mellitus, chronic back pain, and some manifestations on acute infection were associated with chronic CHIKV arthritis.

INTRODUCTION

Chikungunya virus (CHIKV) is a single-stranded RNA virus from the *Alphavirus* genus transmitted to humans through the *Aedes aegypti* and *Aedes albopictus* mosquitoes.^{1,2} It was first described in 1955 by Robinson after an outbreak in East Africa in 1952.³ By 2013, it reached the Western Hemisphere, accumulating more than 3 million cases in the Americas.⁴ In Puerto Rico, the first locally acquired CHIKV infection was documented in May 2014.⁵

Acute CHIKV infection is characterized by high-grade fever, polyarthralgia, polyarthritis, maculopapular rash, fatigue, and myalgias.^{1,2} Viremia usually lasts from 5 to 10 days. Affected individuals may develop CHIKV manifestations lasting months to years after infection that vary from 25% to 80% of patients.^{6–16} Risk factors for developing chronic CHIKV manifestations include female gender, older age, comorbid conditions (arterial hypertension, osteoarthritis, and diabetes mellitus), and severe disease in the acute phase.^{2,9,13–16}

Patients with chronic CHIKV arthritis have polyarthralgia and/or polyarthritis affecting both small and large joints, on occasions mimicking autoimmune inflammatory arthritis such as rheumatoid arthritis (RA).^{1,2,17} It is associated with significant disability and loss of productivity.^{13–15,18–20} Nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose corticosteroids, and synthetic and biologic disease-modifying antirheumatic drugs (DMARDs) have been used for chronic CHIKV arthritis.^{4,21} However, recommendations have a low level of evidence due to a lack of randomized clinical trials. As climate shifts, it is expected that more individuals will become at risk of

infection.² Without effective vaccines or antiviral therapies, consequences of CHIKV infection sequelae may remain a substantial burden for public health.

Despite limited evidence for therapy, most studies describing patients with chronic CHIKV arthritis include individuals treated with DMARDs. As expected, the use of these drugs alters the expression of clinical manifestations during the chronic phase. Understanding the natural history of a disease allows refocusing research priorities for prevention, treatment, and recovery. Therefore, we sought to evaluate the clinical features and correlates in patients with chronic CHIKV arthritis who have not received therapy with DMARDs.

MATERIALS AND METHODS

Patient population. We conducted a case–control study in CHIKV-infected adults with and without chronic arthralgia and/or arthritis. Study participants included adults (≥ 21 years) who had CHIKV infection. All patients had inflammatory polyarthritis in the acute phase of infection defined as the period < 3 months from infection. Previous CHIKV infection was confirmed by viral IgG detection using ELISA. Exclusion criteria included the following: 1) minors, < 21 years of age; 2) patients having or fulfilling classification criteria for autoimmune/inflammatory rheumatic diseases such as RA, seronegative arthritis, and systemic lupus erythematosus, among others; 3) patients treated with corticosteroids 3 months after the onset of CHIKV; 4) those treated at any time with synthetic or biologic DMARDs; 5) patients who were unwilling to give informed consent; and 6) those unable to understand the informed consent form and the protocol procedure.

Chronic CHIKV arthritis was defined as arthralgias/arthritis lasting ≥ 3 months after disease onset. To have patients with chronic CHIKV arthritis with at least 3 months of follow-up, we included those who had acute CHIKV infection ≥ 6 months

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before enrollment. Controls were defined as individuals who had CHIKV infection but recovered completely in less than 3 months after infection. Matching by age and gender was used for the selection of the control participants. Participants were enrolled between February 2016 and April 2018 at the University of Puerto Rico Medical Sciences Campus (UPR-MS), San Juan, Puerto Rico, and the Ponce Health Sciences University, Ponce, Puerto Rico. At study visit, a comprehensive history and physical examination were performed to each participant by a rheumatologist certified in Internal Medicine and Rheumatology by the American Board of Internal Medicine. This study was approved by the UPR-MS Institutional Review Board (number 2460215). Research on human subjects was performed in compliance with the Helsinki Declaration. Before study participation, each subject signed an informed consent.

Variables. Sociodemographic features, lifestyle behaviors, clinical manifestations (on acute CHIKV infection and at study visit), cumulative comorbidities, pharmacologic treatment, disease activity, and functional status were ascertained. Sociodemographic features included age, gender, time period from acute infection to study visit, and years of education. Among lifestyle behaviors, cigarette smoking and exercise were determined. The following clinical manifestations were ascertained on the acute infectious phase: arthralgias, arthritis, myalgias, morning stiffness, fever, tiredness, and maculopapular rash. Distribution of joint tenderness and joint swelling at study visit were examined. Cumulative comorbidities included those that have been linked with chronic CHIKV arthritis: overweight/obesity per body mass index, arterial hypertension, diabetes mellitus (type 1 or type 2), chronic back pain, and osteoarthritis. Exposure to acetaminophen, NSAIDs, and prednisone (or equivalent) on the acute phase of infection was determined. Disease activity was measured using the Clinical Disease Activity Index (CDAI), which consists of a 28 tender and 28 swollen joint count plus patient's and evaluator's global assessments of general health using a visual analog scale.²² Clinical Disease Activity Index (CDAI) scores of 0.0–2.8, 2.9–10.0, 10.1–22.0, and 22.1–76.0 correspond to clinical remission, mild activity, moderate activity, and high activity, respectively. Functional status was determined using the Health Assessment Questionnaire Disability Index (HAQ-DI), which evaluates the functional disability in eight categories of regular daily activities. Health Assessment Questionnaire Disability Index scores of 0, 1, 2, and 3 are interpreted as no disability, moderate disability, severe disability, and complete disability, respectively.²³

Statistical analysis. Patients with and without chronic CHIKV arthritis were compared in terms of their sociodemographic features, lifestyle behaviors, clinical manifestations (on acute CHIKV infection and at study visit), cumulative comorbidities, pharmacologic treatment, disease activity, and functional status characteristics. Comparisons between groups (with and without chronic CHIKV arthritis) were performed using Pearson's chi-squared test or Fisher's exact test as appropriate for categorical variables. For continuous variables, Shapiro–Wilk and Bartlett's tests were performed to evaluate normality and homoscedasticity of the data. A Wilcoxon rank-sum test was later chosen to compare continuous variables by CHIKV groups. Similar tests (e.g., Fisher's exact test, Pearson's chi-squared test, and the Wilcoxon rank-sum test) were performed for a sub-analysis among patients with

chronic CHIKV arthritis who presented with mild disease activity (CDAI < 10) versus moderate-to-high disease activity (CDAI ≥ 10) at study visit. *P*-values ≤ 0.05 were considered statistically significant. All statistical analyses were performed using STATA SE 16 (Stata Corp., College Station, TX).

RESULTS

Seventy-eight patients who had CHIKV infection were screened. Seventeen subjects were excluded (RA = 2, psoriatic arthritis = 1, systemic lupus erythematosus = 3, fibromyalgia syndrome = 2, chronic therapy with low-dose prednisone = 5, conventional DMARD therapy = 3, and biologic DMARD therapy = 1). In total, 61 patients were studied; 41 (67.2%) were women. The mean (SD) period between onset of CHIKV infection and study visit was 23.4 (9.4) months. Thirty-three patients had chronic CHIKV arthritis, and 28 had resolved arthritis.

Table 1 shows sociodemographic features, lifestyle behaviors, cumulative comorbidities, clinical manifestations, and treatment on acute infection between patients, disease activity, and functional status with and without chronic CHIKV arthritis. Those with chronic CHIKV arthritis were less likely to exercise (21.2% versus 57.1%, *P* = 0.004) and had more diabetes mellitus (18.2% versus 0.0%, *P* = 0.027) and chronic back pain (24.2% versus 0.0%, *P* = 0.006) than those with resolved arthritis. Patients who presented with myalgias (97.0% versus 75.0%, *P* = 0.019), fever (97.0% versus 78.6%, *P* = 0.041), and tiredness (100% versus 82.1%, *P* = 0.017) on acute infection were more likely to develop chronic CHIKV arthritis. Those with chronic CHIKV arthritis were treated more frequently with NSAIDs (75.8% versus 50.0%, *P* = 0.037) during the acute phase. As expected, mean (SD) CDAI (14.0 [9.3] versus 0.07 [0.3], *P* < 0.001) and HAQ-DI (0.95 [0.56] versus 0.06 [0.17], *P* < 0.001) scores were higher for patients with chronic CHIKV arthritis at study visit. No significant differences were found for age, gender, time period from acute infection to study visit, years of education, smoking, overweight/obesity, arterial hypertension, dyslipidemia, and osteoarthritis.

Table 2 shows the distribution of joint tenderness and joint swelling among patients with chronic CHIKV arthritis at study visit. Overall, joints of upper extremities were more commonly involved than those of lower extremities. Joint tenderness was most common in metacarpophalangeal (MCP) joints (54.6%), shoulders (51.5%), proximal interphalangeal (PIP) joints (45.5%), and knees (39.4%). Joint swelling was more commonly observed in PIP joints (15.2%), MCP joints (12.1%), shoulders (9.1%), wrists (6.1%), and ankles (6.1%).

Nineteen (57.6%) patients with chronic CHIKV arthritis had moderate-to-high disease activity. Table 3 shows a sub-analysis between patients with chronic CHIKV arthritis presenting with mild disease activity (CDAI ≤ 10) and moderate-to-high disease activity (CDAI > 10). Those with moderate-to-high activity had lower mean (SD) years of education (15.6 [4.5] versus 17.4 [2.7], *P* = 0.049) and a higher mean (SD) HAQ score (1.19 [0.47] versus 0.63 [0.50], *P* = 0.006) than those with mild disease activity. Among HAQ-DI categories, patients with moderate-to-high disease activity presented with more functional disability in the following categories: dressing and grooming, arising, hygiene, reaching, and usual activities. No differences were found for demographic features, lifestyle

TABLE 1

Demographic features, lifestyle behaviors, comorbidities, clinical manifestations, disease activity, and functional status in patients with and without chronic CHIKV arthritis

Features	Chronic CHIKV arthritis (n = 33)	Resolved CHIKV arthritis (n = 28)	P-value
Mean age (SD) (years)	52.5 (10.5)	48.3 (13.7)	0.205
Gender, %women	69.7	64.3	0.786
Mean period from acute infection to study visit (SD) (months)	25.3 (10.8)	21.1 (7.0)	0.651
Mean years of education (SD)	16.3 (3.9)	17.0 (3.9)	0.631
Lifestyle behaviors, %			
Smoking	12.1	14.3	> 0.999
Exercise	21.2	57.1	0.004
Cumulative comorbidities, %			
Overweight/obese (body mass index ≥ 25)	87.9	78.6	0.490
Arterial hypertension	24.2	28.6	0.775
Diabetes mellitus (type 1 or type 2)	18.2	0.0	0.027
Dyslipidemia	18.2	25.0	0.517
Chronic back pain	24.2	0.0	0.006
Osteoarthritis	15.2	14.3	> 0.999
Clinical manifestations on acute infection, %			
Arthralgias	100	96.4	0.459
Arthritis	87.9	71.4	0.107
Myalgias	97.0	75.0	0.019
Morning stiffness	97.0	82.1	0.085
Fever	97.0	78.6	0.041
Tiredness	100	82.1	0.017
Maculopapular rash	93.9	75.0	0.067
Treatment on acute infection, %			
Acetaminophen	90.9	85.7	0.693
Nonsteroidal anti-inflammatory drugs	75.8	50.0	0.037
Prednisone	33.3	14.3	0.085
Clinical Disease Activity Index mean score (SD) at study visit	14.0 (9.3)	0.07 (0.3)	< 0.001
Health Assessment Questionnaire Disability Index mean score (SD) at study visit	0.95 (0.56)	0.06 (0.17)	< 0.001

CHIKV = chikungunya virus.

behaviors, comorbidities, and clinical manifestations and treatment on acute infection.

DISCUSSION

Patients with chronic CHIKV arthritis have similar clinical manifestations, disease activity, and functional disability when compared with those with autoimmune inflammatory arthritis such as RA. Previous studies have not evaluated clinical features and correlates in DMARD-naïve patients with chronic CHIKV arthritis. This approach may allow studying the natural history of chronic CHIKV arthritis. Thus, we examined the clinical features in patients with serologically confirmed CHIKV infection who did not receive therapy with DMARDs and found that chronic arthritis was associated with diabetes mellitus, chronic back pain, and several

symptoms on the acute phase of infection. Among patients with chronic CHIKV arthritis, joints of upper extremities were more commonly involved, more than half had moderate to high disease activity, and most presented moderate functional disability.

We found an association of chronic CHIKV arthritis with diabetes mellitus. Similarly, in patients from La Réunion Island, diabetes mellitus was a risk factor for chronic CHIKV arthritis.²⁴ This association is not unexpected, as patients with diabetes mellitus exhibit inflammatory features. For example, diabetes mellitus patients have elevated IL-6 and IL-1 β , which seem to be critical in the pathogenesis of chronic CHIKV arthritis.²⁵ High levels of these cytokines are observed in patients with severe acute CHIKV infection and persistent arthralgias.^{26,27} Unlike what was reported by Sissoko et al.,²⁸ we did not find an association with osteoarthritis in patients

TABLE 2

Joint tenderness and swelling in patients with chronic chikungunya virus arthritis

Joints	Joint tenderness, n (%)	Joint swelling, n (%)	Joint tenderness or swelling, n (%)
Proximal interphalangeal joints	15 (45.5)	5 (15.2)	16 (48.5)
Metacarpophalangeal joints	18 (54.6)	4 (12.1)	18 (54.6)
Wrists	12 (36.4)	2 (6.1)	12 (36.4)
Elbows	12 (36.4)	0 (0.0)	12 (36.4)
Shoulders	17 (51.5)	3 (9.1)	17 (51.5)
Knees	13 (39.4)	0 (0.0)	13 (39.4)
Ankles	7 (21.2)	2 (6.1)	7 (21.2)
Metatarsophalangeal joints	6 (18.2)	1 (3.0)	6 (18.2)

TABLE 3

Demographic features, lifestyle behaviors, comorbidities, clinical manifestations on acute infection and at study visit, and functional status in patients with chronic CHIKV presenting with mild and moderate-to-high disease activity per Clinical Disease Activity Index

Features	All chronic CHIKV arthritis (n = 33)	Mild disease activity (n = 14)	Moderate-to-high disease activity (n = 19)	P-value
Mean age (SD) (years)	52.5 (10.5)	51.7 (11.5)	53.1 (10.0)	0.771
Gender, % women	69.7	85.7	57.9	0.131
Mean period from acute infection to study visit (SD) (months)	25.3 (10.8)	23.0 (10.7)	27.1 (10.8)	0.084
Mean years of education (SD)	16.3 (3.9)	17.4 (2.7)	15.6 (4.5)	0.049
Lifestyle behaviors, %				
Smoking	12.1	0.0	21.1	0.119
Exercise	21.2	21.4	21.1	> 0.999
Comorbidities, %				
Overweight/obese (body mass index ≥ 25)	87.9	85.7	89.5	> 0.999
Arterial hypertension	24.2	37.5	62.5	> 0.999
Diabetes mellitus	18.2	14.3	21.1	> 0.999
Dyslipidemia	18.2	28.6	10.5	0.363
Chronic back pain	24.2	28.6	21.1	0.695
Osteoarthritis	15.2	14.3	15.8	> 0.999
Clinical manifestations on acute infection, %				
Arthralgia	100	100	100	—
Arthritis	87.9	78.6	94.7	0.288
Myalgias	97.0	92.9	100	0.424
Morning stiffness	97.0	92.9	100	0.424
Fever	97.0	92.9	100	0.424
Tiredness	100	100	100	—
Maculopapular rash	93.9	100	89.5	0.496
Treatment on acute infection, %				
Acetaminophen	90.9	92.9	89.5	> 0.999
Nonsteroidal anti-inflammatory drugs	75.8	85.7	68.4	0.416
Prednisone	33.3	35.7	31.6	> 0.999
Clinical manifestations at study visit, %				
Tiredness	66.7	50.0	79.0	0.136
Joint swelling	54.6	42.9	63.2	0.247
Morning stiffness	90.9	78.6	100	0.067
HAQ-DI mean score (SD)	0.95 (0.56)	0.63 (0.50)	1.19 (0.47)	0.006
HAQ-DI categories, mean score (SD)				
Dressing and grooming	0.8 (0.7)	0.4 (0.5)	1.2 (0.6)	< 0.001
Arising	1.2 (0.7)	0.8 (0.7)	1.4 (0.5)	0.009
Eating	0.6 (0.7)	0.4 (0.6)	0.8 (0.8)	0.070
Walking	1.1 (0.7)	0.9 (0.7)	1.3 (0.7)	0.083
Hygiene	0.7 (0.6)	0.5 (0.7)	0.9 (0.5)	0.034
Reaching	1.2 (0.9)	0.9 (0.9)	1.5 (0.8)	0.025
Grip	0.8 (0.8)	0.6 (0.6)	1.0 (0.8)	0.121
Usual activities	1.1 (0.8)	0.7 (0.8)	1.4 (0.7)	0.006

CHIKV = chikungunya virus; HAQ-DI = Health Assessment Questionnaire Disability Index.

with chronic CHIKV arthritis. The disparities observed between our work and other studies could be attributed to diversity in genetic and socioeconomic factors as well as differences in CHIKV genotypes.

Some manifestations on the acute phase have been associated with the development of chronic CHIKV arthritis, but these vary among different ethnic groups. Fever, tiredness, and myalgias at the onset of CHIKV infection were associated with chronic arthritis in our patients. Similarly, Heath et al.²⁹ found that fever at initial infection was a risk factor for chronic disease, whereas Murillo-Zamora et al.¹⁶ found an association with gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain. Conversely, studies from Brazil and La Martinique did not find a relationship with fever or myalgias at the acute phase.^{13,19}

In our patients with chronic CHIK arthritis, the most commonly involved joints were MCPs, shoulders, and PIPs. This finding is in agreement with other studies in which upper extremities are the most affected.^{19,30} By contrast, Rahim et al.¹¹ reported predominant lower limb involvement (knees and

ankles) over upper limbs (elbows, wrists, and shoulders). The single consensus among all studies of patients with chronic CHIKV arthritis is the involvement of both small and large joints. Unique to our study is the unaltered clinical expression due to lack of treatment with DMARDs or corticosteroids. Also, most studies evaluated involved joints through surveys frequently administered by telephone. In our study, an expert rheumatologist performed the history and physical examination, eliminating subjective bias from respondents or variability on the assessments from multiple physicians.

As in our work, studies evaluating disease activity in patients with chronic CHIKV arthritis have consistently demonstrated a high disease burden comparable to autoimmune inflammatory arthritides. In studies using DAS28, patients with chronic CHIKV arthritis display moderate-to-high disease activity using the established threshold for RA. For example, Chang et al.³¹ measured the mean (SD) DAS28-C-reactive protein (CRP) in patients with chronic CHIKV arthritis and found a high disease activity (4.5 ± 0.8). Even after excluding patients with preexisting arthritic disorders, disease activity

remained high at 4.4 ± 0.7 . Similarly, Hyad et al.¹⁹ found a high mean DAS28 score at 4.4 ± 1.1 . A limitation in their study is that CRP levels were assumed to be normal for all patients because of a lack of laboratories, likely underestimating disease activity scores. In another study using RAPID3 to measure disease activity, 68% had moderate-to-high disease activity.⁹ As noted before, in these studies, patients treated with DMARDs or that had recent corticosteroid exposures were included. Our study group with chronic CHIKV arthritis could have excluded patients with presumably severe disease that warrant DMARDs therapy. Despite this selection bias, disease activity per CDAI was moderate-to-high in 58% of our patients.

Not only disease severity was substantial in our patients, but functional disability measured by the HAQ-DI was considerable too. The mean HAQ-DI score in our patients with chronic CHIKV arthritis was 0.95 ± 0.56 . Furthermore, in those with moderate-to-high disease activity, the mean HAQ-DI score increased to 1.19 ± 0.47 . These HAQ-DI scores are comparable to patients with RA, osteoarthritis, and fibromyalgia.^{32–35} The HAQ-DI categories in which our patients had more disability were arising, reaching, walking, and performing usual activities. Similar to our study, in patients from South India, the most affected HAQ-DI categories were (in decreasing order) arising, walking, performing usual activities, and reaching for those with a severe disability.¹¹ Amaral et al.¹⁸ reported a mean HAQ-DI score of 1.0 ± 0.4 in Brazilian patients with chronic CHIKV arthritis. In addition, they evaluated five other studies measuring functional status and found a combined HAQ-DI mean score of 1.59 ± 0.46 . Four of the five studies had a mean HAQ-DI score consistent with moderate-to-severe disability ($\text{HAQ-DI} \geq 1$).¹⁸ On the other hand, in the RHEUMATOCHIK study, the mean HAQ-DI score was lower at 0.44 ± 0.5 . The authors explained that this relatively low score was possibly due to younger age of patients as well as the heterogeneity of CHIKV strains.¹⁰ In contrast to our study, all these works included patients treated with antimalarial drugs, methotrexate, biologics, and corticosteroids, and occasionally included patients with other rheumatic inflammatory arthritides.

Our study has some limitations. First, because we matched our patients and controls for age and gender, we could not evaluate if these demographic factors were associated with chronic CHIKV. In other studies, age and female gender were found to be risk factors for chronic CHIKV arthritis.^{8,15,24,28} Second, we did not examine additional risk factors for chronic CHIKV arthritis, such as the severity or duration of symptoms during the acute phase and viremia (CHIKV RNA in serum, mean IgG/IgM levels, and/or persistence of IgM). Third, our study was conducted in Puerto Ricans for which the results may not be extrapolated to other ethnic groups. Finally, it would be important to determine further inflammatory markers relevant to establish chronicity. Also, it would be interesting to explore the role of the inflammasome in the initial phase and if HLA-DR4 patterns may orchestrate the chronicity. These two immunogenetic features might have therapeutic implications.

In summary, to the best of our knowledge, this is the first study that determines the clinical manifestations, disease activity, and functional status in patients with chronic CHIKV arthritis who are naive to synthetic or biologic DMARDs. In addition, we excluded patients who received treatment with corticosteroids during the chronic phase and those who had

other autoimmune rheumatic diseases. Thus, the findings described here are those of patients with unaltered clinical expression and solely secondary to chronic CHIKV arthritis. In our group of patients, diabetes mellitus, chronic back pain, and manifestations (fever, tiredness, and myalgias) on the acute phase of infection were associated with chronic CHIKV arthritis. Those with chronic CHIKV arthritis had substantial disease activity and functional disability.

Received December 10, 2020. Accepted for publication January 22, 2021.

Published online March 8, 2021.

Acknowledgments: We are grateful to Luisa Alvarado and Vanessa Rivera-Amill to facilitate the enrollment of CHIKV patients at the Ponce Health Sciences University, Ponce, Puerto Rico.

Financial support: This work was supported by the National Institute of General Medical Sciences (NIGMS) grant number U54GM133807 for the Hispanic Alliance for Clinical and Translational Research and the National Institute of Minority Health and Health Disparities grant number G12MD007600 for the Research Centers for Minority Institutions (RCMI) Program.

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