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Frequency of Chronic Joint Pain Following Chikungunya Virus Infection

A Colombian Cohort Study

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Objective. **To estimate the frequency of chronic joint pain after infection with chikungunya virus in a Latin American cohort.**

Methods. **A cross-sectional follow-up of a prospective cohort of 500 patients from the Atlántico Department, Colombia who were clinically diagnosed as having chikungunya virus during the 2014–2015 epidemic was conducted. Baseline symptoms and follow-up symptoms at 20 months were evaluated in serologically confirmed cases.**

Results. **Among the 500 patients enrolled, 485 had serologically confirmed chikungunya virus and reported joint pain status. Patients were predominantly adults (mean ± SD age 49 ± 16 years) and female, had an education level of high school or less, and were of Mestizo ethnicity. The most commonly affected joints were the small joints, including the wrists, ankles, and fingers. The initial virus symptoms lasted a median of 4 days (interquartile range [IQR] 3–8 days). Sixteen percent of the participants reported missing school or work (median 4 days [IQR 2–7 days]). After 20 months, one-fourth of the participants had persistent joint pain. A multivariable analysis indicated that significant predictors of persistent joint pain included college graduate status, initial symptoms of headache or knee pain, missed work, normal activities affected, ≥4 days of initial symptoms, and ≥4 weeks of initial joint pain.**

Conclusion. **This is the first report to describe the frequency of chikungunya virus–related arthritis in the Americas after a 20-month follow-up. The high frequency of chronic disease highlights the need for the development of prevention and treatment methods.**

Chikungunya virus is a mosquito-borne illness that can lead to chronic joint pain and arthritis (1). Patients with acute infection present with fever, headache, muscle pain, rash, and joint pain. Prior outbreaks have been reported in Africa, Asia, Europe, and the Indian and Pacific Ocean islands (2). In 2013, chikungunya virus was seen for the first time in the Caribbean basin, and it has now infected >1.2 million people throughout the Americas (3). Studies conducted prior to the American epidemics showed that 30–70% of chikungunya virus–infected patients have persistent joint pain months or years after their acute illness (1,3–14). Until now there have been no large-scale observational studies of the frequency of chikungunya arthritis in the Americas. It is estimated that ~48% of Latin American patients will develop chronic chikungunya arthritis a median of 20 months after chikungunya virus infection (15).

The views expressed herein are solely the responsibility of the authors and do not necessarily represent the official views of the Rheumatology Research Foundation, the NIH, or the US Army.

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With the exception of the Andes Mountains region, most of Colombia has an elevation of less than 1,000 meters and is thus favorable for the proliferation of *Aedes aegypti*, the mosquito vector of chikungunya virus in the Americas. Thus, much of the population is vulnerable to infection with this virus. In the Americas in 2015, 693,489 cases of chikungunya virus were reported, of which Colombia bore the largest burden with 356,079 cases (16).

There has been little description of the frequency of chronic arthritis in the Americas. One study of 39 Colombian patients with chikungunya virus, ranging from 6 to 65 weeks after infection, showed that 90% had persistent polyarthralgias or arthritis at the time of evaluation (17).

The primary objective of the present study was to describe the frequency of persistent joint pain and disability in a Latin American cohort of chikungunya virus patients from Colombia. Our hypothesis was that chronic joint pain will be present in one-third of our Latin American cohort, which is similar to findings reported from other outbreaks of the Asian strain of the virus at 18 months (5,18). Defining the frequency of chronic joint pain and disability after chikungunya virus infection is important to understanding the long-term impact of the American outbreak.

PATIENTS AND METHODS

Study design. Five hundred patients with clinically confirmed chikungunya virus infection were enrolled as part of a prospective cohort in January 2015. Diagnosis of chikungunya virus was serologically confirmed via IgM and IgG antibody capture enzyme-linked immunosorbent assay (ELISA) (described below). A baseline 33-item survey was conducted to ascertain demographic characteristics, exposure history, and symptoms. A subsequent 56-item telephone survey was performed a median of 20 months after infection and included an assessment of the character and duration of persistent chikungunya arthritis symptoms, including swollen joint count, tender joint count, comorbidities, missed work or school, and a global score of pain during the last week (from the Disease Activity Score in 28 joints [DAS28] [19]), as well as therapies received.

Institutional review board (IRB) approval. This study was approved by the ethics committee of the Universidad El Bosque under a protocol entitled "Surveillance of sentinel infectious events prevalent in Colombia" with a non–human subjects determination made by The George Washington University IRB for analysis of deidentified data. Written informed consent was obtained from all participants, and all samples were collected by qualified medical personnel.

Setting. Patients were referred to the study from the Sabanalarga, Barranquilla, Juan de Acosta, Manatí, Luruaco, and Baranoa municipalities in the Atlántico Department, Colombia, which is located on the Caribbean coastal plane (20).

Participants. Primary care providers referred patients with clinically suspected chikungunya virus for enrollment. Clinical chikungunya virus was defined by the Colombian Institute of Health as a fever of >38°C, severe joint pain or arthritis, and acute onset of erythema multiforme, with symptoms not explained by other medical conditions. In addition, patients must reside in or have visited a municipality with evidence of chikungunya virus transmission or traveled within 30 km of confirmed viral transmission (21). Clinically suspected cases of chikungunya virus were confirmed serologically for the purposes of this study.

Variables. Demographic factors obtained included age, sex, ethnicity, education level, and insurance status. Outcomes were assessed at the follow-up survey. The primary outcome measure was the percentage of individuals with self-reported persistent chikungunya virus–related joint pain at follow-up ~20 months after infection. Secondary self-reported outcomes included the duration of initial joint pain since many individuals describe relapsing–remitting symptoms after initial infection, the percentage of individuals who missed work or school, the median days of missed work or school, the percentage of patients whose symptoms impacted their capacity to continue normal activity, and an estimate of disease severity. The latter included elements of the DAS28, including mean swollen joint count, mean tender joint count, and mean global pain score (19). The full DAS28 could not be calculated because this measure includes the C-reactive protein level, and no follow-up blood draw was performed. Potential effect modifiers included medical comorbidities such as chronic arthritis, gout, osteoarthritis, ischemic heart disease, kidney disease, lung disease, diabetes, hypertension, and depression. Finally, analysis included the types of therapies used for chikungunya arthritis, including aspirin, ibuprofen, acetaminophen, prednisone, methotrexate, medicinal plants, or other modalities.

Anti-chikungunya virus IgG and IgM. IgG and IgM levels were assayed using a Euroimmun anti–chikungunya virus ELISA (IgG/IgM) according to the manufacturer's instructions. These assays provide a qualitative evaluation of the presence or absence of anti-chikungunya virus IgG and IgM.

Statistical analysis. All 500 patients were contacted for the follow-up telephone survey. Excluded patients (n = 15) had no serologic confirmation of chikungunya virus or were missing data on current joint pain status. Variable distributions were examined for normality and outliers. Continuous variables were log-transformed if necessary. Univariable associations between patient variables and the presence of persistent joint pain, and between initial symptoms and sex, were tested using chi-square or Fisher's exact test for categorical variables and *t*-test or the Kruskal-Wallis test for continuous variables. A multivariable logistic regression model for persistent joint pain was tested using any baseline variable that was significantly associated with persistent joint pain as a factor. Backward selection was used, dropping predictors that had a *P* value of greater than 0.20. SAS (version 9.3) was used for data analysis. *P* values less than 0.05 were considered significant, except when Bonferroni correction was applied, as indicated in the table footnotes.

RESULTS

Five hundred participants with clinically suspected chikungunya virus infection were enrolled (Figure 1). Four

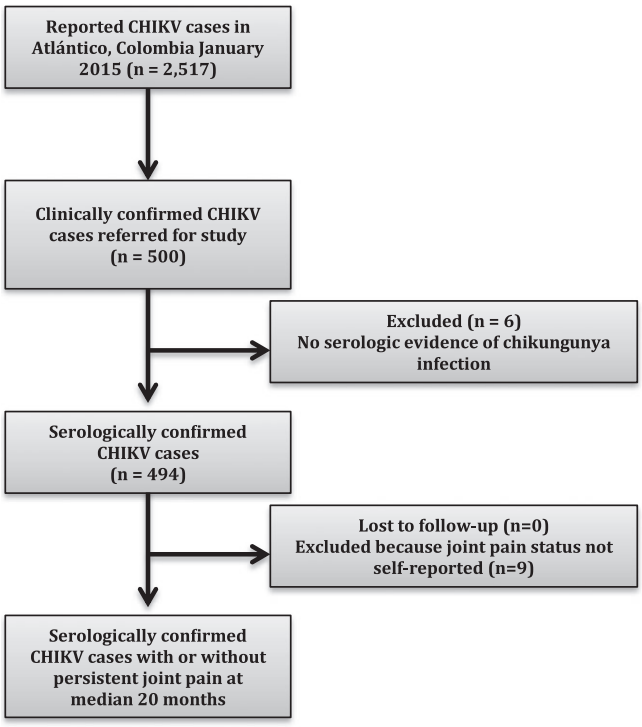

Figure 1. Study flow diagram. A chikungunya virus (CHIKV) epidemic occurred in 2014–2015 in the Atlántico Department of Colombia. At the time of study enrollment, there were 2,517 affected cases. Five hundred clinically confirmed cases were referred for the study, of which 494 were serologically confirmed. There was no attrition. All patients completed the follow-up telephone survey a median of 20 months after infection.

hundred ninety-four cases were confirmed by ELISA. Of these, 483 were acute cases (481 who were positive for both IgM and IgG and 2 who were positive for IgM and negative for IgG) and 11 were convalescent (6 who had equivocal IgM status but were positive for IgG and 5 who were negative for IgM and positive for IgG). Six cases were negative for IgM and IgG antibodies and were excluded from the analysis. All 500 participants were reached for the follow-up telephone survey. However, 9 participants did not report joint pain status and were excluded from the analysis (n = 485).

At baseline (Table 1), the confirmed cases were predominantly adults (mean age 49.1 years) and female and had an education level of high school or less. Almost all were of Mestizo ethnicity (i.e., mixed European, often Iberian, and indigenous Latin American ancestry) and had health insurance. The most common baseline comorbidity was hypertension (12%), and only 17 patients (4%) reported prior arthritis at baseline. The most commonly reported initial symptoms were muscle pain, weakness, joint pain, rash, fever, and headache (Table 2). The most commonly affected joints were the small joints, including the wrists, ankles, and fingers. The most commonly used medication to treat chikungunya virus–related joint pain was acetaminophen, which was taken by every patient. Forty-six patients took ibuprofen, prednisone, or medicinal plants. The initial joint pain during acute infection lasted a median of 4 weeks (interquartile range [IQR] 2–16 weeks), and many patients had intermittent or persistent joint pain after the initial infection. Sixteen percent of the participants reported missing school or work as a result of their chikungunya virus infection, with a median of 4 days (IQR 2–7 days) lost (Table 3). When patients were stratified by sex (Table 4), it was found that women were more likely to have chikungunya virus infection symptoms, including weakness, rash, nausea or vomiting, and elbow pain.

After 20 months, one-fourth of the participants (123 of 485) had persistent joint pain. Among these patients, most had only 1 swollen joint but had tenderness in 3 other joints. They had a mean ± SD global pain score of 47 ± 20 (Table 3). Participants with persistent joint pain were more likely to be female (Table 1) and to have had more severe initial symptoms (Table 2). These patients reported greater joint involvement, including the number of joints involved and the duration of initial joint symptoms. They were also more likely to report having

Table 1. Baseline demographic characteristics of the patients with serologically confirmed chikungunya virus classified according to joint pain status at a median follow-up of 20 months*

	All serologically confirmed cases (n = 485)	Persistent joint pain (n =123)	No persistent joint pain (n = 362)
Age at baseline, mean ± SD years	49.1 ± 16.1	49.1 ± 17.1	49.2 ± 15.8
Female	388 (80)	109 (89)	279 (77)†
Ethnicity‡			
Mestizo	451 (94)	115 (96)	336 (93)
African Colombian	4 (1)	0 (0)	4 (1)
White Colombian	26 (5)	5 (4)	21 (6)
Mean education level			
High school or less	377 (78)	96 (78)	281 (78)
Some college	98 (20)	23 (19)	75 (21)
College graduate	10 (2)	4 (3)	6 (2)
Health insurance‡	461 (97)	117 (98)	344 (97)
Prior comorbidity			
Hypertension	57 (12)	16 (13)	41 (11)
Diabetes	34 (7)	9 (7)	25 (7)
Any type of arthritis	17 (4)	7 (6)	10 (3)
Lung disease	19 (4)	5 (4)	14 (4)
Depression	21 (4)	6 (5)	15 (4)
Chronic foot pain	14 (3)	5 (4)	9 (2)
Gout	12 (2)	5 (4)	7 (2)
Osteoarthritis	13 (3)	4 (3)	9 (2)
Ischemic heart disease	13 (3)	4 (3)	9 (2)
Kidney disease	12 (2)	3 (2)	9 (2)

* Except where indicated otherwise, values are the number (%).
† $P = 0.004$ versus persistent joint pain.
‡ Data were not available for all patients.

Table 2. Initial symptoms and treatment of patients with serologically confirmed chikungunya virus classified according to joint pain status at a median follow-up of 20 months*

	All serologically confirmed cases (n = 485)	Persistent joint pain (n = 123)	No persistent joint pain (n = 362)	*P*
Initial symptoms				
Muscle pain	471 (98)	119 (98)	352 (98)	0.99
Weakness	427 (88)	114 (93)	313 (86)	0.09
Joint pain and/or inflammation	476 (98)	120 (98)	356 (98)	0.70
Rash	409 (85)	104 (85)	305 (84)	0.99
Fever	376 (79)	99 (83)	277 (78)	0.28
Headache	354 (73)	101 (82)	253 (70)	0.009
Lymphadenopathy	343 (71)	90 (73)	253 (70)	0.52
Cool extremities	257 (53)	68 (55)	189 (52)	0.57
Nausea or vomiting	178 (37)	54 (44)	125 (35)	0.16
Bruising	76 (16)	22 (18)	54 (15)	0.42
Hemorrhage	11 (2)	1 (1)	10 (3)	0.21
Nose bleed	5 (1)	1 (1)	4 (1)	0.99
Oral bleeding	6 (1)	2 (2)	4 (1)	0.65
Initial rheumatic symptoms during acute chikungunya infection				
Wrist pain	426 (90)	110 (92)	316 (89)	0.37
Ankle pain	412 (87)	113 (94)	299 (84)	0.0047
Finger pain	403 (84)	103 (86)	300 (84)	0.64
Elbow pain	395 (83)	111 (93)	284 (80)	0.0013†
Toe pain	387 (81)	109 (92)	278 (78)	0.001†
Knee pain	383 (80)	113 (94)	270 (76)	<0.0001†
Hip pain	342 (72)	106 (89)	236 (66)	<0.0001†
Initial chikungunya virus symptom duration, days				<0.0001†‡
Mean ± SD	12.9 ± 30.6	14.2 ± 22.8	12.3 ± 33.3	–
Median (IQR)	4 (3–8)	5 (4–10)	4 (3–7)	–
Range	1–365	1–90	1–365	–
Duration of initial joint pain, weeks				<0.0001†‡
Mean ± SD	18.4 ± 32.4	45.3 ± 39.5	10.5 ± 25.1	–
Median (IQR)	4 (2–16)	40 (6–92)	3 (2–8)	–
Range	0–365	0.6–104	0–365	–
Treatment				
Acetaminophen	478 (100)	122 (100)	356 (100)	–
Ibuprofen	36 (8)	11 (9)	25 (7)	0.47
Prednisone	5 (1)	2 (2)	3 (1)	0.61
Medicinal plants	5 (1)	1 (1)	4 (1)	0.99
Aspirin	0 (0)	0 (0)	0 (0)	–
Methotrexate	0 (0)	0 (0)	0 (0)	–

* Except where indicated otherwise, value are the number (%). Data were not available for all patients. IQR = interquartile range.
† Significant ($P < 0.002$) after Bonferroni adjustment.
‡ By Kruskal-Wallis nonparametric test.

missed work or school and to report that their normal activities were affected by the infection (Table 3).

In a model to examine factors that had independent associations with persistent joint pain, the area under the receiver operating characteristic curve was 0.84, indicating good discrimination. Significant factors included being a college graduate, headache, knee pain, missed work, normal activities affected, ≥4 days of initial symptoms, and ≥4 weeks of initial joint pain (Table 5).

DISCUSSION

We found the frequency of chronic joint pain after infection with chikungunya virus in a large Latin American cohort to be 25% a median of 20 months after infection. Significant predictors of persistent joint pain included being a college graduate, headache, knee pain, missed work, normal activities affected, ≥4 days of initial symptoms, and ≥4 weeks of initial joint pain.

This is the first large-scale observational study of chikungunya virus–associated arthritis in the Americas. The finding of chronic joint pain ~2 years after initial infection in one-fourth of the patients infected with chikungunya virus has important implications for the prediction of the magnitude of disability and health system costs after the Latin American epidemic. Prior predictions had overestimated the expected frequency of chikungunya virus–related joint pain in Latin America, indicating that 48% of chikungunya virus–infected patients were predicted to have chronic chikungunya arthritis 20 months

Table 3. Symptoms and disability in patients with serologically confirmed chikungunya virus classified according to joint pain status at a median follow-up of 20 months

	All serologically confirmed cases (n = 485)	Persistent joint pain (n = 123)	No persistent joint pain (n = 362)	*P*
Time since onset, months				0.017
Mean ± SD	20.0 ± 1.3	20.2 ± 0. 8	19.9 ± 1.4	–
Median (IQR)*	19.7 (19.4–20.8)	19.8 (19.4–20.9)	19.6 (19.4–20.6)	–
Range	8.9–31.4	19.2–22.9	8.9–31.4	–
No. (%) who missed work or school during initial infection	79 (16)	49 (40)	30 (8)	<0.0001†
Days of missed work/school				0.83‡
Mean ± SD	5.5 ± 5.3	6.0 ± 6.3	4.7 ± 3.0	–
Median (IQR)	4 (2–7)	4 (2–7)	3.5 (2–7)	–
Range	0–30	2–30	0–14	–
No. (%) with symptoms impacting capacity to continue normal activity	46 (9)	33 (27)	13 (4)	<0.0001†
Swollen joint count, mean ± SD	0.2 ± 0.6	0.5 ± 1.0	0.06 ± 0.3	<0.0001†‡
Tender joint count, mean ± SD	0.9 ± 1.8	2.9 ± 2.3	0.2 ± 0.8	<0.0001†‡
Global pain score in the last week, mean ± SD (range 0–100)	45.8 ± 19.6	46.7 ± 20.2	41.5 ± 16.3	0.39

* IQR = interquartile range.
† Significant ($P < 0.0017$) after Bonferroni adjustment.
‡ By Kruskal-Wallis nonparametric test.

Table 4. Initial chikungunya virus symptoms and baseline comorbidities by sex*

	Women (n = 388)	Men (n = 95)	*P*
Initial symptoms			
Muscle pain	377 (97)	93 (98)	0.99
Weakness	353 (91)	73 (77)	<0.0001†
Joint pain and/or inflammation	383 (99)	92 (97)	0.19
Rash/itch	339 (87)	69 (73)	0.0004†
Fever	304 (80)	71 (76)	0.49
Headache	291 (75)	62 (65)	0.06
Lymphadenopathy	287 (74)	55 (58)	0.002
Cool extremities	216 (56)	40 (42)	0.018
Nausea or vomiting	157 (41)	21 (22)	0.0004†
Bruising	69 (18)	7 (7)	0.012
Hemorrhage	8 (2)	3 (3)	0.46
Nose bleed	3 (1)	2 (2)	0.25
Oral bleeding	4 (1)	2 (2)	0.34
Initial rheumatic symptoms			
Wrist pain	347 (91)	78 (85)	0.10
Ankle pain	331 (86)	80 (87)	0.89
Finger pain	325 (85)	77 (83)	0.62
Elbow pain	329 (86)	65 (71)	0.0005†
Toe pain	312 (82)	74 (80)	0.78
Knee pain	306 (80)	76 (82)	0.72
Hip pain	286 (75)	55 (59)	0.0022
Prior comorbidities			
Arthritis	9 (2)	8 (9)	0.009
Chronic foot pain	8 (2)	6 (6)	0.04
Gout	7 (2)	5 (5)	0.07
Osteoarthritis	10 (3)	3 (3)	0.73
Heart disease	10 (3)	3 (3)	0.73
Kidney disease	10 (3)	2 (2)	0.99
Lung disease	17 (4)	2 (2)	0.39
Diabetes	31 (8)	3 (3)	0.10
Hypertension	47 (12)	10 (11)	0.66
Depression	15 (4)	5 (5)	0.58

* Values are the number (%). Data on sex were missing for 2 patients; data on symptoms were not available for all patients.
† Significant ($P < 0.00167$) after Bonferroni adjustment.

after acute infection (15). Our findings are consistent with findings reported from other outbreaks of the Asian strain of the virus at 18 months, showing that approximately one-third of the patients had persistent joint pain (5,18), and lower than the findings of a 15–18-month follow-up of patients affected by the East Central African strain on Réunion Island from 2005–2006, in which persistent joint pain was reported in 43–75% of chikungunya virus–infected patients (9,12,13).

Significant predictors of persistent joint pain included factors that may indicate a more severe or prolonged initial infection, such as missed work, normal activities affected, ≥4 days of initial symptoms, and ≥4 weeks of initial joint pain. Determination of the risk factors for persistent arthritis during initial infection enables early

Table 5. Multivariable logistic regression model of persistent joint pain in patients with chikungunya virus*

Baseline factor	Adjusted OR (95% Wald confidence limit)	*P*
College graduate	5.53 (1.13–27.17)	0.0353
Headache	2.17 (1.16–4.07)	0.0157
Knee pain	4.69 (1.91–11.51)	0.0007
Missed work	5.23 (2.87–9.52)	<0.0001
Normal activities affected	8.80 (3.89–19.89)	<0.0001
≥4 days of initial symptoms	2.69 (1.57–4.60)	0.0003
≥4 weeks of initial joint pain	2.39 (1.40–4.08)	0.0014

* C = 0.84. Backward selection was used, dropping predictors that had a *P* value of less than 0.20. SAS (version 9.3) was used for data analysis, with *P* values less than 0.05 considered significant, except for values where Bonferroni correction was applied. (*P* values less than 0.002 were considered significant in Table 2 and *P* values less than 0.0017 were considered significant in Table 3.) OR = odds ratio.

identification of patients who may require follow-up care. This finding is consistent with the findings of Hoarau et al (22) and Sissoko et al (9) on Réunion Island (East Central African chikungunya virus strain outbreak) that showed that increased initial chikungunya viral load (22) and severe initial joint pain (9) were predictors of persistent arthritis. However, in contrast to the findings of Hoarau et al and Sissoko et al, we did not find that older age was associated with an increased frequency of persistent chikungunya virus–related arthritis. This difference may be due to differences in the chikungunya virus strains involved in the epidemics on Réunion Island as opposed to the Americas and the significantly smaller cohort sizes, older mean age, and higher prevalence of underlying osteoarthritis comorbidity in the Réunion Island studies (26% in the study by Sissoko et al [9] versus 3% in our cohort).

A limitation of this study is the lack of a control group. It is possible that, over the course of 20 months, a few of the study participants might have developed joint symptoms and pain due to another etiology that they attributed to chikungunya virus infection. Furthermore, patients were not tested for other arboviral infections that may contribute to joint pain. While dengue and Zika are flaviviruses known to cause acute joint pain, Mayaro virus is an alphavirus, like chikungunya virus, known to cause similar chronic joint pain with known cross-reactivity between anti-Mayaro and anti-chikungunya virus antibodies (23). Both patients with chikungunya virus and those with Mayaro virus viral arthritis almost universally report morning stiffness, which is a symptom of true inflammatory arthritis, even in the chronic phase of the disease. In comparison, dengue and Zika infections most commonly cause arthralgias rather than inflammatory arthritis, which is an important distinction, since the alphaviruses preferentially invade and replicate within the synovium, whereas flaviviruses do not. During the chikungunya virus epidemic there was no known Mayaro virus circulation in the Atlántico Department. However, Mayaro virus is known to sporadically affect the Colombian Amazon region (24), so it is possible that a few of these cases could have been Mayaro virus infections. Other limitations include the fact that self-reported joint pain was the primary outcome without serologic markers of inflammation, and the lack of formal assessment of validated quality of life measures.

This study represents the largest Latin American cohort of chikungunya patients to be followed up a median of 20 months after infection. The study sample was Colombian and consisted predominantly of Mestizo women. Nevertheless, our findings have important implications for future planning as this outbreak spreads.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Chang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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