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Short Communication

Clinical profile and factors associated with hospitalization during a Chikungunya epidemic in Ceará, Brazil

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Abstract

Introduction: The aim of this study was to characterize the clinical-epidemiological profile of Chikungunya virus infection and the factors associated with hospitalization during the peak of the most recent epidemic period in Brazil (2016-2017). **Methods**: Two official databases of the State Health Secretariat of Ceará were used, and a total of 182,731 notifications were analyzed. **Results**: Independent factors associated with hospital admission were chronic kidney disease (OR 4.56, 95% CI 3.36-6.17), hypertension (OR 1.90, 95% CI 1.69-2.14), leukopenia (OR 1.89, 95% CI 1.56-2.30) and diabetes mellitus (OR 1.70, 95% CI 1.44-1.99). **Conclusions**: The pre-existing comorbidities have shown the potential to destabilize the patients' clinical status.

Keywords: Chikungunya. Arboviruses. Comorbidities. Hospitalization. Epidemics.

The American continents have been the scene of a major arbovirus epidemic since 2014, with the highest peaks occurring in 2016 and 2017[1]. The Chikungunya virus (CHIKV) spread to 45 countries and territories in North, Central, and South America, including outbreaks in the Antilles, with approximately 2.9 million reported autochthonous cases through July 2016[1,2].

The flow of people between countries was associated with the spread of the virus in the southern region of the United States due to the entrance of contaminated travelers coming from Mexico[3,4]. The infection spread to countries in South America, according to the Pan-American Health Organization (PAHO) reports, and by March 2015, 74 cases of the disease had been recorded in Bolivia, 149 in Brazil, 1,317 in Colombia, 213 in Ecuador, 130 in Paraguay, 208 in Peru and 2,303 in Venezuela[5,6,7]. In Argentina, the transmitting mosquito *Aedes albopictus* was restricted to the northeastern province of Misiones, while the *A. aegypti* was present from the northern border to the Patagonian city of Neuquén[5]. In this same period, in Colombia, CHIKV infection was an important complication observed in pregnant women, leading to admission to intensive care due to sepsis[8].

In 2016, during Epidemiological Weeks (EW) 1 to 52 (01/03/2016 to 12/31/2016), 277,882 probable cases of CHIKV were recorded, and in 2015, 38,499 cases were recorded throughout Brazil. In 2017, 184,694 probable cases of CHIKV were recorded in the country, with an incidence of 88.6 cases/100,000 inhabitants. Of these, 151,101 (81.4%) were confirmed. The northeastern region of Brazil had the highest number of reported cases, comprising more than 76% of total notifications and an incidence rate of 250.1 cases/100,000 inhabitants[9].

Among the Federation Units (FU), the state of Ceará, located in the northeastern region of Brazil, had the highest number of

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reported cases (113,958) and the highest incidence of arbovirus infection cases (1,255.6 cases / 100,000 inhabitants) in Brazil[10].

The aim of this study is to characterize the clinical-epidemiological profile of CHIKV infection and the factors associated with hospitalization during the peak of the most recent epidemic period in Brazil (2016-2017).

This is a cross-sectional study, carried out in the state of Ceará, in northeastern Brazil, based on information from reports of suspected and confirmed cases of CHIKV infection that occurred in 2016 and 2017, when the first and highest CHIKV epidemic was observed in this region. This Brazilian state has 184 cities, with an estimated population of 9,020,460 inhabitants. The population of its capital city, Fortaleza, is of 2,627,482 inhabitants.

Information on the epidemiological-clinical aspects and case evolution were extracted from notification reports obtained from two official health system information databases of the State Health Secretariat of Ceará, the Notifiable Diseases Information System (SINAN) and the Laboratory Management System (LMS).

Laboratory data were collected from the LMS of the National Networks of Epidemiological Surveillance and Environmental Health Surveillance Laboratories which allowed epidemiological/analytical production reports of the tests performed on persons who were notified to have CHIKV to be obtained.

The files that contained all fields filled out correctly and did not show any divergence regarding the information were included in the analysis. A total of 182,731 notifications were analyzed, and files with unfilled or empty fields were excluded. The excluded fields that generated missing data cases were depicted in the analysis of the tables.

The CHIKV infection diagnosis followed the guidelines of the Ministry of Health and was based on the detection of IgM serum antibodies through ELISA or virus detection through reverse-transcriptase polymerase chain reaction (RT-PCR) assay. There were 34,510 cases with reagent exams.

Chronic kidney disease was defined based on the Kidney Disease Improving Global Outcomes (KDIGO) criteria, and was considered as "abnormalities of kidney structure or function, present for more than 3 months." These abnormalities are expressed through the presence of albuminuria $\geq$ 30 mg/24 h, albumin/creatinine ratio $\geq$ 30 mg/g, or glomerular filtration rate < 60 ml/min/1.73 m^2. The definition of other comorbidities was based on the guidelines of the World Health Organization (WHO) [11].

Statistical analysis was carried out using the software SPSS for Windows, version 23.0 (IBM, USA). Data were analyzed using the D'Agostino-Pearson, Shapiro-Wilk, or Kolmogorov tests. Data with normal distribution were expressed as mean ± standard deviation, while data with non-normal distribution were expressed as median and range. Pearson's chi-square test was used to compare categorical variables (clinical manifestations, serological results, sociodemographic characteristics, comorbidities), whereas the Student's *t*-test (for variables with normal distribution), or the Mann-Whitney test (for variables with non-normal distribution) were used to compare numerical variables for the association with hospital admission. A significance level of $p \leq 0.05$ was used in the analysis.

The study was approved by the ethics committee of all institutions involved in the study (Protocol numbers 2.272.452 /UNIFOR and 2.365.958 / UFC).

Regarding the notified cases, the mean age of the patients was 32.4 ± 14.6 years, and 113,504 were women (62.2%). As for the level of schooling, 34.4% had incomplete elementary school (ES) education (up to the 4th year of ES) or were illiterate; 45.6% had incomplete elementary school education (up to the 8th year of ES); 50.5% had complete elementary school or incomplete high school (HS) education; 52% had complete HS education and 17.6% had complete or incomplete College/ University education. The most commonly observed clinical manifestations in the reported cases were fever (88.6%), headache (72.9%), severe arthralgia (69.5%), and myalgia (65.6%). Sociodemographic characteristics, such as age, sex, level of schooling, showed a statistically significant association with the occurrence of hospital admission (**Table 1**).

Headache, exanthema, vomiting, arthritis, petechiae, severe arthralgia and leukopenia were the clinical manifestations that showed a strong association ($p < 0.0001$) with hospital admission for CHIKV infection (**Table 2**).

All comorbidities were associated with need for hospital stay, with exception of hematological disorders. Systemic arterial hypertension (6.9%) and diabetes mellitus (2.9%) were the most frequent diseases among the notified cases. When the need for hospital admission was evaluated among these patients, 3,080 cases (3.3%) required hospitalization, 269 (10.2%) died due to CHIKV infection and 68 (0.1%) died of other causes not directly associated with CHIKV infection (**Table 3**).

Factors independently associated with hospital admission were chronic kidney disease (OR: 4.56, 95% CI: 3.36-6.17, $p<0.0001$), hypertension (OR: 1.90, 95% CI: 1.69-2.14, $p<0.0001$), leukopenia (OR: 1.89, 95% CI: 1.56-2.30, $p<0.0001$) and diabetes mellitus (OR: 1.70, 95% CI: 1.44-1.99, $p<0.0001$).

When analyzing the CHIKV epidemic that occurred in the state of Ceará, Brazil, in 2016 and 2017, it was observed that the epidemiological and sociodemographic profiles of individuals with CHIKV infections were similar to those observed in other epidemics in South American countries since 2013, when the virus started circulating on this continent. CHIKV infections in Ceará mainly affected young adult women with incomplete ES education. In a similar study carried out in Bolivia, the distribution of seropositivity rates for the three arboviruses (ZIKV, DENV and CHIKV) by sex and age was observed, but, did not disclose any significant differences, showing these two variables did not significantly affect the exposure to these diseases in the susceptible population[6]. However, a statistically significant association was found between the sociodemographic

TABLE 1: Sociodemographic characteristics of patients with reported cases of Chikungunya, according to the occurrence of hospital admission, Ceará, Brazil, 2016-2017.

Sociodemographic variable	Hospital admission* (n=3,080)	Non-Hospital admission (n=91,586)	p
Age			
≥60 years	726 (25.6%)	14,316 (15.8%)	<0.0001
< 60 years	2,105 (74.4%)	76,056 (84.2%)	
Sex			
Male	1,240 (40.3%)	34,366 (37.5%)	0.002
Female	1,838 (59.7%)	57,193 (62.5%)	
Level of schooling			
1st to 4th year of Elementary School	249 (21.4%)	5,260 (17.0%)	<0.0001
5th to 8th year of Elementary School	273 (23.5%)	6,743 (21.8%)	
Complete Elementary School	257 (22.1%)	8,114 (26.2%)	
Complete High School	284 (24.4%)	7,884 (25.5%)	
College/University	101 (8.7%)	2,969 (9.6%)	

*Missing data: 88065 (no information about hospital admission in the patient's file). Fisher's exact test and Chi-square test. Significance level p <0.05.

characteristics and the cases that required hospital admission, especially among older adult women and those with incomplete ES educations.

The population with a higher level of schooling was also exposed to the *A. aegypti* vector, demonstrating that the disease is disseminated across sociocultural levels. It is possible that the high number of cases identified in the present study is because most of the notified cases originated from patients treated by the Brazilian Public Health Care System.

Another issue is related to the flow of case notification. The Individual Notification Form (*Ficha Individual de Notificação* - FIN) is filled out by health professionals in the care units for each patient, when they suspect the occurrence of a compulsory notification health problem. Most notifications are entered into of the public health system's Municipal Health Secretariat SINAN[10].

Headache, exanthema, vomiting, arthritis, severe arthralgia, petechiae, and leukopenia were clinical manifestations that were strongly associated with hospital admission in the reported cases. Regarding the laboratory findings, leukopenia showed a strong association with hospital admission due to CHIKV infection. A study carried out on a Caribbean island showed that none of the patients infected with CHIKV were hospitalized and no infection-related mortality was recorded[12]. This confirms that the disease has low lethality providing the patients do not have comorbidities and factors associated with death[11]. The infection cases are usually referred by family physicians for laboratory confirmation of suspected acute infection, and most cases are treated in primary care facilities[12].

Arterial hypertension and diabetes mellitus were the main comorbidities reported in the present study and were accompanied by other comorbidities, including gastrointestinal, hepatic, hematologic and renal diseases. A study carried out to assess risk factors associated with disease severity in atypical cases of CHIKV infection in adults showed that hypertension and underlying respiratory or cardiac conditions were independent risk factors for disease severity and identified risk factors associated with the chronic phase of the disease. Severe clinical forms of CHIKV infection are associated with the presence of several pre-existing, underlying medical conditions in approximately 90% of cases[12].

When evaluating hospitalization frequency during the two-year epidemic period in this region of Brazil, pre-existing comorbidities such as diabetes mellitus, chronic kidney disease, systemic arterial hypertension, autoimmune and liver diseases were associated with hospital admission in the reported cases of CHIKV infection.

TABLE 2: Clinical manifestations in patients with reported cases of Chikungunya, according to the occurrence of hospital admission, Ceará, Brazil, 2016-2017.

Clinical manifestation	Hospital admission* (n=3,080)	Non-Hospital admission (n=91,586)	p value
Fever	2,802 (91.0%)	84,187 (91.9%)	0.05
Myalgia	2,056 (66.8%)	63,355 (69.2%)	0.004
Headache	1,975 (64.1%)	68,393 (74.7%)	<0.0001
Exanthema	1,133 (36.8%)	28,712 (31.3%)	<0.0001
Vomiting	897 (29.1%)	17,246 (18.8%)	<0.0001
Nausea	1,081 (35.1%)	29,925 (32.7%)	0.005
Back pain	1,124 (36.5%)	34,421 (37.6%)	0.22
Conjunctivitis	192 (6.2%)	5,157 (5,6%)	0.15
Arthritis	849 (27.6%)	21,448 (23.4%)	<0.0001
Severe artralgia	1,885 (61.2%)	65,859 (71.9%)	<0.0001
Petechiae	422 (13.7%)	7,546 (8.2%)	<0.0001
Leukopenia	126 (4.1%)	1,548 (1.7%)	<0.0001
Positive tourniquet test	50 (1.6%)	1,113 (1.2%)	0.04
Retro-orbital pain	542 (17.6%)	14,351 (15.7%)	0.004

*Missing data: 88065 (no information about hospital admission in the patient's file). Fisher's exact test and Chi-square test. Significance level p <0.05.

Diabetes mellitus was the second most common comorbidity after arterial hypertension and was associated with increased length of hospital stay in patients with comorbidities. Common causes of hospital admission were the presence of unstable vital signs, such as tachycardia; presence of abnormal laboratory results, such as leukocytosis and an increase in liver enzyme levels; and acute kidney injury[13,14].

Previous studies have shown that diabetic patients with CHIKV infection have an unstable clinical picture, develop a more severe clinical picture with glycemic level oscillations, and require constant drug dose adjustments in approximately 40% of cases, even in those treated with insulin. The clinical instability observed in these patients increases systemic complications, such as vascular, renal, hepatic, and neurological lesions[14].

Another relevant issue, which is a challenge for the Brazilian health system, is the laboratory confirmation of suspected cases. Although the serological tests were available in the public health system laboratories in Ceará, only 26.3% of the cases had laboratory results included in the reports. In addition to errors when feeding data to the laboratory information system and SINAN, it is possible that there is a need for adjustments to the management of blood samples sent to the laboratory. The laboratory is located in the state capital, thus making it difficult for municipalities located in the rural parts of the state to have access to it.

Because this is a potentially epidemic event, when cases first start to appear, all efforts must be made to reach a laboratory diagnosis. However, the Brazilian Ministry of Health

TABLE 3: Association between observed comorbidities and deaths in patients with reported cases of Chikungunya, according to the occurrence of hospital admission, Fortaleza, Ceará, Brazil, 2016-2017.

Comorbidity	Hospital admission* (n=3,080)	Non-Hospital admission (n=91,586)	p
Diabetes mellitus	238 (7.7%)	2,783 (3.0%)	<0.0001
Hematological diseases	21 (0.7%)	402 (0.4%)	0.05
Liver diseases	25 (0.8%)	428 (0.5%)	0.01
Chronic kidney disease	67 (2.2%)	364 (0.4%)	<0.0001
Systemic arterial hypertension	477 (15.5%)	6,619 (7.2%)	<0.0001
Peptic ulcer disease	29 (0.9%)	515 (0.6%)	0.007
Autoimmune diseases	27 (0.9%)	393 (0.4%)	0.001
Death	269 (10.2%)	68 (0.1%)	<0.0001

*Missing data: 88065 (no information about hospital admission in the patient's file). Fisher's exact test and Chi-square test. Significance level p <0.05.

stipulates that, once the sustained transmission is established, not all patients will need laboratory confirmation. In this context, laboratory confirmation must be reserved for severe cases or those with atypical manifestations, individuals with comorbidities, and pregnant women at the end of the gestation (due to the risk of transmission to the baby). In addition to these cases, in the subacute and chronic phases, the specific diagnosis may help the clinician in the differential diagnosis with other diseases[15].

This study has some limitations, including its retrospective design which was based on official notification reports; hence, some information, such as more details about the patients' clinical history, other comorbidities not included in the notification forms, and other variables that could influence patient outcomes, was not available. However, due to the very large number of observed cases we consider the information provided by this study a significant evidence of the clinical course of CHIKV infection during an epidemic period, which is the first and the largest reported in our region at this point.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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