Impact of Chronic Kidney Disease on Chikungunya Virus Infection Clinical Manifestations and Outcome: Highlights during an Outbreak in Northeastern Brazil

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Abstract. The northeastern region of Brazil has faced in the last 2 years the largest outbreak of chikungunya virus (CHIKV) infection in its history. There are still few studies on kidney involvement in CHIKV. The aim of this study is to describe the impact of chronic kidney disease (CKD) on CHIKV clinical manifestations and outcome. This is a cross-sectional study conducted in the State of Ceará, northeastern Brazil, including all registered cases of CHIKV infection in the period from January 2016 to December 2017. Clinical manifestations were collected from the notification reports from official data bank from the State Secretary of Health of Ceará: National System of Diseases Notification and Laboratory Manager. A total of 182,731 cases were notified. Patients' mean age was 32.4 ± 14.6 years, and 62.2% were female. The most common clinical manifestations were fever (88.6%), headache (72.9%), intense arthralgia (69.5%), and myalgia (65.6%). Hospital admission was required for 3,080 cases (3.3%), and death occurred in 383 cases (0.2%). Chronic kidney disease was reported in 691 cases (0.3%). Patients with CKD had a higher frequency of almost all clinical manifestations, including fever, myalgia, exanthema, vomiting, nausea, back pain, conjunctivitis, arthritis, severe arthralgia, petechiae, and retro-orbital pain. They also had a significantly higher frequency of diabetes, hematological disorders, liver diseases, hypertension, peptic ulcer disease, and autoimmune diseases. Mortality was significantly higher among CKD patients than patients without CKD (3.0% versus 0.2%, $P < 0.0001$).

INTRODUCTION

Chikungunya fever is a viral disease transmitted by mosquitoes of the *Aedes* genus, which is currently endemic in Brazil, and included in the World Health Organization's list of the neglected tropical diseases.¹ Chikungunya virus (CHIKV) (family *Togaviridae*, genus *Alphavirus*) has its origins in Africa, and its first isolation was in 1952 in Tanzania.² After this, outbreaks of CHIKV infection were reported, and in 2013, the virus was reintroduced in the Americas, in the Caribbean region.³ The northeast region of Brazil has faced the largest outbreak of CHIKV infection of its history, causing a huge social and economic burden,⁴ and uncommon complications have been described.

There are very few studies describing kidney involvement in chikungunya infection.^{5,6} In a study of autopsies of patients who had kidney injury due to CHIKV infection, there were glomerular changes, with predominance of nephrosclerosis and membranoproliferative lesion, and tubular injury, mainly acute tubular necrosis.^{5,6} Other investigations evidence that CHIKV can lead to albuminuria, hematuria, nephritis, acute kidney injury, and other renal function abnormalities.⁷ Among kidney-transplanted patients, the course of CHIKV infection was observed to be less severe, with milder arthralgia, a fact that could be attributed to the effects of the immunosuppressant drugs routinely used in the post-transplantation period.⁸ It is possible that a direct kidney damage can be caused by CHIKV (cytopathic effect of viral proteins on glomerular and tubular cells), associated with immune complex deposition on glomeruli, as has been described for other arbovirus infections such as dengue and Zika.^{9–12}

The aim of this study is to describe the impact of chronic kidney disease (CKD) on CHIKV infection clinical manifestations and outcome during a large outbreak in the state of Ceará in northeastern Brazil.

METHODS

This is a cross-sectional study conducted in the state of Ceará in northeastern Brazil, including all registered cases of CHIKV infection during the period from January 2016 to December 2017, a period in which a large outbreak occurred in this region (the largest ever observed). The current estimated population of Ceará state is 9,020,460 inhabitants and the population of Fortaleza city is 2,627,482 inhabitants.

Clinical manifestations were collected from the notification reports, from official data bank from the State Secretary of Health of Ceará: National System of Diseases Notification and Laboratory Manager. Diagnosis of CHIKV infection followed the Brazilian Ministry of Health Guidelines¹³ and was based on detection of serum immunoglobulin M (IgM) antibodies through enzyme-linked immunosorbent assay (ELISA) or virus detection through reverse-transcriptase-polymerase-chain reaction (RT-PCR).

Chronic kidney disease was based on “*Kidney Disease Improving Global Outcomes*”¹⁴ criteria, and it was considered as “abnormalities of kidney structure or function, present for more than 3 months,” and these abnormalities are expressed through the presence of albuminuria (≥ 30 mg/24 hour or albumin/creatinine ratio ≥ 30 mg/g) or glomerular filtration rate < 60 mL/minute/1.73 m². Chronic kidney disease was considered based on the information from the patients' official notification reports, as well as clinical manifestations and outcome. We have compared patients with and without kidney disease, and factors associated with kidney disease were investigated.

Statistical analysis was performed with the program SPSS for Windows version 23.0 (IBM, New York, NY). The

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Kolmogorov–Smirnov test was used to assess variable distribution. Variables with normal distribution were expressed through mean $\pm$ standard deviation (SD). The Pearson's χ^2 test was used to compare categorical variables, whereas the Student's *t*-test to compare numerical variables (for variables with normal distribution) or Mann–Whitney test (for variables with non-normal distribution). A logistic regression model was constructed to investigate the factors independently associated with kidney disease (multivariate analysis). Adjusted odds ratios and 95% confidence intervals were calculated. All outcomes which presented statistical significance ($P \leq 0.05$) in the univariate analysis were included in the logistic regression. Statistical significance was set on 5% (" P values" < 0.05).

The study protocol was reviewed and approved by the Ethics Committee of the involved institutions (protocol numbers 2.272.452/UNIFOR and 2.365.958/UFC).

RESULTS

During the study period, a total of 182,731 cases of CHIKV infection were reported to the Ceara State Secretary of Health. Patients' mean age was 32.4 ± 14.6 years, and 113,504 were female (62.2%). Regarding clinical manifestations, the most common were fever (88.6%), headache (72.9%), intense arthralgia (69.5%), and myalgia (65.6%). Hospital admission was required for 3,080 cases (3.3%), and death occurred in 383 cases (0.2%).

Chronic kidney disease was reported in 691 cases (0.3%). Clinical characteristics of patients, according to the presence of CKD are summarized in Table 1. Patients with CKD had a significantly higher mean age, and there were more elderly patients among this group. Regarding symptoms and signs, patients with CKD had a higher frequency of almost all clinical manifestations, including fever, myalgia, exanthema, vomiting, nausea, back pain, conjunctivitis, arthritis, severe arthralgia, petechiae, and retro-orbital pain (Table 1). Unfortunately, we had no information regarding patients' CKD stage nor about specific treatment (how many patients were

receiving renal replacement therapy). Among the 691 patients with CKD, 176 cases had diagnosis confirmed through RT-PCR and positive IgM serology, whereas the remaining 515 had diagnosis through positive IgM confirmed in two occasions.

Regarding comorbidities, patients with CKD has a significantly higher frequency of diabetes, hematological disorders, liver diseases, hypertension, peptic ulcer disease, and autoimmune diseases (Table 2). Mortality was significantly higher among CKD patients comparing with patients without CKD (3.0% versus 0.2%, $P < 0.0001$).

Independent factors associated with CKD were hospital admission, advanced age, clinical manifestations (positive tourniquet test, petechiae, vomiting, nausea, and back pain), and comorbidities (hematological disorders, peptic ulcer disease, liver diseases, autoimmune diseases, hypertension, and diabetes mellitus), as summarized in Table 3.

DISCUSSION

This is the first study to investigate the influence of CKD on CHIKV infection. We have faced the first and largest epidemic of this arbovirus in Brazil in the period from 2016 to 2017, and it had brought out the occurrence of a myriad of uncommon manifestations, including kidney injury, which has been reported for the first time recently,⁶ and an increase of mortality in this period has also been registered.¹⁵ In this large cohort, we have found CKD in less than 1% of patients with CHIKV infection, and this could be an underestimated number because we have data based on official reports from the health authority, but we have found important associations between CKD and the CHIKV infection manifestations and outcome.

Chronic kidney disease patients were older, had more comorbidities, and seemed to have more severe infection, requiring hospital admission more frequently in our cohort. Severe CHIKV infection has been described in immunocompromised patients, evolving with secondary bacterial infections and neurologic manifestations, such as encephalitis.¹⁶ Almost all clinical manifestations were more frequent among patients with CKD in our cohort, and this could be explained by the fact that immune function is severely compromised in CKD, mainly in its end stages.¹⁷ This relatively immune function decrease of CKD could predispose to the occurrence of more exuberant clinical manifestations of CHIKV infection, as observed in the present study. There are recent evidences that cellular immunity suffers important impairment in end-stage renal disease, with reduction in the number and function of lymphocytes, so that patients become more susceptible to

TABLE 1

Clinical characteristics of patients with CHIKV infection according to the occurrence of kidney disease. Fortaleza, Ceara, Brazil, 2016–2017

	CKD* (N = 691)	No-CKD (N = 177,240)	P
Age (years)	46.5 $\pm$ 20.1	38.3 $\pm$ 19.3	< 0.0001
Age $\geq$ 60 years	191 (28.3%)	27,605 (15.8%)	< 0.0001
Gender			
Male	259 (37.5%)	66,985 (37.8%)	0.87
Female	432 (62.5%)	110,166 (62.2%)	
Fever	632 (91.5%)	156,968 (88.6%)	0.01
Myalgia	527 (76.3%)	116,276 (65.6%)	< 0.0001
Headache	527 (76.3%)	129,173 (72.9%)	0.05
Exanthema	281 (40.7%)	482,249 (27.2%)	< 0.0001
Vomiting	212 (30.7%)	32,046 (18.1%)	< 0.0001
Nausea	334 (48.3%)	53,231 (30.0%)	< 0.0001
Back pain	394 (57.0%)	60,907 (34.4%)	< 0.0001
Conjunctivitis	100 (14.5%)	9,435 (5.3%)	< 0.0001
Arthritis	267 (38.6%)	38,510 (21.7%)	< 0.0001
Severe arthralgia	480 (69.5%)	123,223 (69.5%)	0.96
Petechiae	158 (22.9%)	14,035 (7.9%)	< 0.0001
Leukopenia	88 (12.7%)	2,785 (1.6%)	< 0.0001
Tourniquet test	95 (13.7%)	2,301 (1.3%)	< 0.0001
Retro-orbital pain	215 (31.1%)	25,018 (14.1%)	< 0.0001

CHIKV = chikungunya virus; CKD = chronic kidney disease.

* Missing data: 88,065 (without information about CKD in the notification report).

TABLE 2

Comorbidities and mortality among patients with CHIKV infection according to the occurrence of kidney disease. Fortaleza, Ceara, Brazil, 2016–2017

	CKD* (N = 691)	No-CKD (N = 177,240)	P
Diabetes mellitus	287 (41.5%)	4,890 (2.8%)	< 0.0001
Hematological disorders	243 (35.2%)	465 (0.3%)	< 0.0001
Liver diseases	247 (35.7%)	516 (0.3%)	< 0.0001
Hypertension	394 (57.0%)	11,821 (6.7%)	< 0.0001
Peptic ulcer disease	241 (34.9%)	648 (0.4%)	< 0.0001
Autoimmune diseases	230 (33.3%)	468 (0.3%)	< 0.0001
Death	19 (3.0%)	364 (0.2%)	< 0.0001

CHIKV = chikungunya virus; CKD = chronic kidney disease.

* Missing data: 88,065 (without information about CKD in the notification report).

TABLE 3

Independent factors associated with kidney disease among patients with CHIKV infection. Fortaleza, Ceara, Brazil, 2016–2017 (multivariate analysis)

	OR	95% CI	P
Hospital admission	5.60	4.16–7.54	< 0.0001
Advanced age	1.01	1.00–1.01	0.001
Clinical manifestations			
Positive tourniquet test	2.24	1.25–4.01	0.006
Petechiae	1.45	1.06–2.00	0.02
Vomiting	1.36	1.04–1.77	0.02
Nausea	1.36	1.05–1.75	0.01
Back pain	1.32	1.03–1.68	0.02
Comorbidities			
Hematological disorders	9.15	5.51–15.20	< 0.0001
Peptic ulcer disease	6.47	3.97–10.53	< 0.0001
Liver diseases	6.39	3.78–10.79	< 0.0001
Autoimmune diseases	5.14	2.95–8.97	< 0.001
Hypertension	4.22	3.17–5.61	< 0.0001
Diabetes mellitus	1.58	1.13–2.21	0.006

CHIKV = chikungunya virus; CI = confidence interval; CKD = chronic kidney disease; OR = odds ratio.

*Missing data: 88,065 (without information about CKD in the notification report)

infections, mainly viral infections.^{1,7} Another factor related to immunity is age. It is described that older adults are more susceptible to CHIKV infection because of decreased immunity, and it is also associated with more severe diseases.¹⁸ One aspect in the epidemiology of CKD is that it is increasing among elderly people.¹⁹ These two factors together (advanced age and CKD) made a proper combination for the establishment of severe CHIKV infection.

The factors identified as having independent association with CKD included hospital admission and advanced age, illustrating that CKD patients are older and have a more complicated infection and requires a more careful approach. Clinical manifestations associated with CKD were most related to vascular fragility (positive tourniquet test and petechiae), unspecific symptoms (nausea/vomiting), which could also be related to uremia or hydroelectrolyte disturbances, and back pain. As observed in other arbovirus, such as dengue and Zika virus, capillary fragility can occur and is a hallmark of severity, associated with hemorrhagic events.^{20,21}

The comorbidities were also associated with CKD, which illustrates that these patients have multiple associated diseases that contributes to complicate the course of chikungunya infection and increases its severity and mortality. A recent systematic review and meta-analysis found the following as the most prevalent comorbidities associated with CHIKV infection: hypertension (31.3%), diabetes (20.5%), heart diseases (14.8%), and asthma (7.9%), and this prevalence increased with age.²² It is described that patients with CHIKV infection who are older have cardiovascular, neurologic, and respiratory disorders or with diabetes tend to present complications.² A recent study in our region found association between increasing number of deaths attributed to type 2 diabetes mellitus and CHIKV infection in Brazil in the same period, and this could be explained by the fact that the presence of comorbidities increases the severity of the infection.²³ Diabetes was also associated with chikungunya severity in another study.²²

Previous studies show that CHIKV cause osteoarticular disturbances, which are very frequent. Cardiovascular disease is also considered common, and infrequent manifestations

of CHIKV infection include neurologic complications, skin lesions, kidney involvement, and gastrointestinal, hepatic, and hematologic disturbances.⁷

Another recent study, with patients admitted in an intensive care unit because of CHIKV infection in India, evidenced that disease severity was mainly associated with advanced age and the presence of underlying comorbidities, and risk factors for death were high acute physiology and chronic health evaluation (APACHE) II score at admission and dialysis requirement,²⁴ which also evidences that kidney injury increases mortality. Cardiovascular disorders, respiratory secondary infections, sensorimotor deficit, absence of musculoskeletal pain, history of alcoholism, digestive symptoms, and presence of confusion/delirium were factors independently associated with death among elderly patients admitted with CHIKV infection in a university hospital in Martinique²⁵ and reinforce the fact that comorbidities increase the infection severity and the risk of death.

In the present study, mortality was significantly higher among CKD patients with CHIKV infection (15 times higher than that of patients without CKD), which calls our attention to the severity of the course of the infection among patients with kidney disease. Chikungunya virus is known to cause a mild disease, with predominance of fever and arthralgia in most cases, tend to complicate, and lead to death among patients with advanced age and underlying comorbidities,^{2,25} as we have observed in the present study.

In summary, older patients with CKD present more severe clinical manifestations of CHIKV virus infection have significantly more frequent symptoms and signs, higher number of comorbidities, requires hospital admission more frequently, and have significantly higher mortality than patients without kidney disease. The global tendency for increasing number of elderly people and CKD, associated with the constant threat of arbovirus epidemics, is a matter of great concern in Public Health, and the combination of these factors brings a high probability of severe disease and high risk of death. Physicians must keep in mind that patients with CHIKV infection and kidney dysfunction are at high risk of complicating and should receive a careful intensive treatment and follow-up.

STUDY LIMITATIONS

The main limitation of our study is its retrospective nature and the collection of information from notification reports. Some information was not available, such as patients' CKD stage and information about specific treatment (e.g., how many patients were receiving renal replacement therapy). We have also not evaluated the patients individually nor performed clinical evaluation of all the cases, so we do not have the complete clinical description of these cases. With this purpose, we are currently conducting other studies, with patients with confirmed diagnosis of chikungunya fever to better comprehend its clinical picture, the complications, and the renal abnormalities associated with this infection.

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