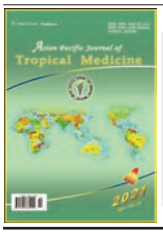

Short Communication

Asian Pacific Journal of Tropical Medicine

apjtm.org

doi: 10.4103/1995-7645.312519

Impact Factor: 1.94

Clinical outcomes of hospitalized patients with chikungunya fever: A retrospective analysis

Lucas Lobo Mesquita[1]✉, Ênio Simas Macedo[1], Sérgio Luiz Arruda Parente Filho[1], Francisca Lillyan Christyan Nunes Beserra[1], Evelyne Santana Girão[2], Juliana Mandato Ferragut[3], Roberto da Justa Pires Neto[4], Geraldo Bezerra da Silva Júnior[5], Elizabeth De Francesco Daher[6]

[1]*School of Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil*

[2]*Hospital Regional da Unimed, Fortaleza, Ceará, Brazil*

[3]*Intensive Care Unit, Hospital São Carlos, Fortaleza, Ceará, Brazil*

[4]*Department of Public Health, School of Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil*

[5]*Public Health and Medical Sciences Post-Graduation Programs, School of Medicine, Health Sciences Center, University of Fortaleza. Fortaleza, Ceará, Brazil*

[6]*Medical Sciences Post Graduate Program, Department of Internal Medicine, School of Medicine, Federal University of Ceará. Fortaleza, Ceará, Brazil*

ABSTRACT

Objective: To describe the prognostic and clinical profile of hospitalized patients with chikungunya virus (CHIKV) infection focusing on renal outcomes.

Methods: This is a cross-sectional study including all patients with confirmed chikungunya fever (CHIKF) admitted to 3 different high-complexity hospitals in Fortaleza, Brazil between January 2016 and June 2017. Data analysis was carried out to evaluate correlation between clinical profile and outcomes.

Results: Fifty-five patients were included, with a median age of 77 (IQR=21) years, and 23 (41.82%) were male. Twenty-five patients (45.45%, 25/55) developed acute kidney injury (AKI), and 15 (60.00%, 15/25) were classified as KDIGO 1, 1 (4.00%) as KDIGO 2, and 9 (36.00%) as KDIGO 3. The overall mortality was 34.54% whilst AKI-related mortality was 64.00% (16/25). Both AKI and encephalitis were associated with higher mortality. Patients who died were significantly older [82 (IQR=12) years *vs.* 70 (IQR= 28.75) years, $P<0.001$)]. In the multivariate analysis, abdominal pain was associated with an increased risk of severe AKI (*OR*=5.33, 95% *CI*=1.11–25.64, $P=0.037$) and AKI was an independent risk factor of death (*OR*=12.06, 95% *CI*=2.55–57.15, $P=0.002$). Recovery of renal function was similar among the different age groups.

Conclusions: AKI is present in half of the study population and is an independent risk factor of death. Thus, renal function should be carefully monitored in hospitalized patients with CHIKV infection.

KEYWORDS: Arbovirus infections; Chikungunya fever; Acute kidney injury; Elderly; Mortality

1. Introduction

Chikungunya fever (CHIKF) is a disease caused by chikungunya virus (CHIKV), which is transmitted by *Aedes* spp. mosquitoes[1]. In 2016 and 2017, 185 792 cases were reported in Ceara, a northeastern Brazilian federative state, where this study took place. Among all cases notified in the state, 70% (130 108 cases) were confirmed by serology[2]. Nevertheless, it is believed that the actual burden of the disease is several times greater than the number of notified cases. This infection is characterized by flu-like symptoms and intense arthralgia, especially in the knees, which are the most commonly affected joints. Neuropathic pain, arthritis and tenosynovitis may also be present. Approximately half of patients persist with arthralgia for at least one year. Risk factors for chronicity include female sex, age above 45 years, pre-existing joint disease and intense manifestations during the acute phase[1].

Severe manifestations of the disease may occur in different phases and may be life-threatening. The heart is the most frequently affected organ, often resulting in cardiac failure, myocarditis,

✉To whom correspondence may be addressed. E-mail: lobolucasm@gmail.com

How to cite this article: Mesquita LL, Macedo ÊS, Filho SLAP, Beserra FLCN, Girão ES, Ferragut JM, et al. Clinical outcomes of hospitalized patients with chikungunya fever: A retrospective analysis. Asian Pac J Trop Med 2021; 14(4): 183-186.

Article history: Received 12 November 2020 Revision 2 March 2021
Accepted 20 March 2021 Available online 12 April 2021

arrhythmias and pericarditis. The nervous system is the second most common site of complications (such as meningoencephalitis, encephalitis and Guillain-Barré syndrome), followed by the kidney. Risk factors for severe disease include comorbidities, extremes of age and use of certain medications (aspirin, NSAIDs and acetaminophen in high doses). Severe disease and extremes of age are also considered risk factors for death[3,4]. Despite the relevance of kidney dysfunction in both morbidity and mortality of CHIKV infection, there are still very few studies addressing this issue.

2. Subjects and methods

2.1. Study population

This is a cross-sectional study including all patients with confirmed CHIKF admitted to São José Infectious Diseases Hospital (public institution), Unimed Regional Hospital (private institution) and São Carlos Hospital (private institution), all located in Fortaleza, Ceara, Brazil, between January 2016 and June 2017. Inclusion criteria were age above 18 years old and positive ELISA IgM serology for CHIKV. Data collection was performed using a standard form. The present study was approved by the Research Ethics Committee of São José Infectious Diseases Hospital, Unimed Regional Hospital and São Carlos Hospital (Protocol No. 2.405.527).

2.2. Clinical and laboratory parameters evaluated

Clinical parameters, such as age, sex, hospital stay, intensive care unit (ICU) stay, clinical manifestations (including symptoms, signs, and physical examination findings) and outcomes were assessed. The analyzed laboratory data were serum urea, creatinine, hemoglobin, hematocrit, liver enzymes, sodium and potassium. Renal biopsy was not performed.

2.3. Definitions

Acute kidney injury (AKI) was defined according to *Kidney disease: Improving global outcomes (KDIGO) 2012 criteria*[5]. Severe AKI was defined as KDIGO 3 category. Glomerular filtration rate (GFR) was calculated using the CKD-EPI formula[6].

2.4. Statistical analysis

Statistical analysis was carried out using SPSS program for Windows version 20.0 (IBM, USA). Numerical variables underwent Shapiro-Wilk test in order to assess distribution. Comparison of categorical variables was performed using Pearson's *Chi*-square or Fisher's exact test, while numerical variables were compared using Student's *t* test (for variables with normal distribution) or Mann-Whitney *U* test (for variables with non-normal distribution). Comparison of GFR variation within age and between age groups were evaluated by Wilcoxon Signed-Rank test and Split-Plot ANOVA tests. *P* values < 0.05 were considered statistically significant. In order to evaluate risk factors for death and renal outcomes, a logistic regression model was used for categorical variables. Variables with statistical significance in univariate analysis were included in multivariate analysis. Adjusted odds ratios (*OR*s) and 95% confidence intervals (*CI*s) were calculated. Data was expressed as mean ± standard deviation (mean±SD) for parametrical variables or median (Interquartile range, IQR) for non-parametrical variables.

3. Results

A total of 55 patients were included in the study, among whom 23 (41.82%) were male. Age ranged from 20 to 96 years with a median of 77 (IQR=21) years. The most common symptom was fever (81.82%), followed by arthralgia (80.00%), myalgia (43.64%), and vomiting (30.91%). Regarding the outcomes, 19 patients (34.55%) died and 34 (61.82%) required admission to the ICU, with median ICU stay of 10 (IQR=25) days. Patients who died were significantly older [82 (IQR=12) years *vs.* 70 (IQR=28.75) years, *P*<0.001)].

Out of the 25 patients (45.45%) who developed AKI, 16 (64%) died. Fifteen (60.00%) were classified as KDIGO 1, 1 (4.00%) as KDIGO 2 and 9 (36.00%) as KDIGO 3. Significant higher percentage of non-AkI patients developed skin rash (43.33% *vs.* 12.00%, *P*=0.011) and arthritis (23.33% *vs.* 0%, *P*=0.012), whereas more patients with encephalitis had AKI (32% *vs.* 10%, *P*=0.042). Patients who developed AKI had higher serum potassium levels [(4.33±0.77) mEq/L *vs.* (3.97±0.43) mEq/L, *P*=0.041]. Both AKI (84.21% *vs.* 25%%, *P*<0.001) and encephalitis (42.11% *vs.* 8.33%, *P*=0.005) were associated with higher mortality, whilst patients with skin rash had lower mortality (10.53% *vs.* 38.89%, *P*=0.028). The presence of abdominal pain was associated with severe AKI (44.44% *vs.* 13.04%, *P*=0.047) (Table 1). In the multivariate analysis, AKI was an independent risk factor for death (*OR*=12.06, 95% *CI*=2.55–57.15, *P*=0.002) and abdominal pain increased the risk of severe AKI (*OR*=5.33, 95% *CI*=1.11–25.64, *P*=0.037), compared to patients without AKI and abdominal pain, respectively (Table 2). Patients were stratified by age in 5 groups: <60 years; 60-70 years; 71-80 years; 81-90 years, and > 90 years. Table 3 displays the analysis of GFR variation from admission to discharge or death according to age. Patients younger than 60 years presented higher GFR on admission compared to other age groups but there was no statistically significant difference within or between groups.

Table 1. Comparison of clinical and laboratory parameters on admission and length of ICU stay between survivors *vs.* non-survivors, AKI *vs.* non-AKI and KDIGO 3 *vs.* non-KDIGO 3.

Variables	General (*n*= 55)	Survivors (*n*=36)	Non-survivors (*n*=19)	*P*-value	AKI (*n*=25)	Non-AKI (*n*=30)	*P*-value	KDIGO 3 (*n*=9)	Non-KDIGO 3 (*n*=46)	*P*-value
Median age (years)	77.00 (21.00)	70.00 (28.75)	82.00 (12.00)	<0.001*	79.00 (19.00)	72.50 (28.75)	0.103	80.00 (17.50)	74.50 (25.00)	0.109
GFR (mL/min/1.73m^2)	67.68±33.64	80.51±30.68	43.37±24.76	<0.001#	43.48±26.19	87.84±24.79	<0.001#	31.24±21.25	74.81±30.99	<0.001#
Creatinine (mg/dL)	0.93 (0.80)	0.79 (0.34)	1.40 (1.21)	<0.001*	1.40 (1.23)	0.75 (0.26)	<0.001*	2.15 (2.01)	0.83 (0.46)	0.001*
Urea (mg/dL)	35.00 (53.50)	25.00 (20.25)	73.00 (46.00)	<0.001*	71.00 (64.00)	23.00 (16.50)	<0.001*	98.00 (76.50)	32.00 (36.00)	<0.001*
Hemoglobin (g/dL)	12.21±2.33	12.01±2.44	12.57±2.10	0.399	12.25±2.14	12.17±2.51	0.894	12.74±1.78	12.10±2.42	0.452
Hematocrit (%)	36.12±5.96	35.78±6.20	36.73±5.64	0.591	35.69±5.79	36.52±6.21	0.627	35.79±4.58	36.19±6.27	0.856
Sodium (mEq/L)	133.60±7.60	132.58±7.50	135.53±7.61	0.174	133.92±7.49	133.33±7.81	0.779	135.78±4.89	133.17±7.99	0.352
Potassium (mEq/L)	4.13±0.63	4.07±0.55	4.24±0.75	0.344	4.33±0.77	3.97±0.43	0.041#	4.12±0.81	4.13±0.59	0.936
AST (U/L)	63.00 (60.50)	35.50 (53.25)	81.00 (36.00)	0.051	81.00 (45.50)	35.50 (37.25)	0.057	78.00(144.50)	50.00 (61.00)	0.293
ALT (U/L)	41.00 (43.50)	35.50 (52.00)	42.00 (37.00)	1.000	53.00 (44.00)	34.50 (42.00)	0.218	46.00 (132.00)	41.00 (41.00)	0.926
ICU stay (days)	10.0 (25.0)	8.0 (13.0)	17.0 (33.5)	0.438	17.5 (37.5)	8 .0 (10.0)	0.132	16.0 (63.0)	9.0 (18.0)	0.636
Rash[*n* (%)]	16.00 (29.09)	14.00 (38.89)	2.00 (10.53)	0.028[a]	3.00 (12.00)	13.00 (43.33)	0.011[a]	2.00 (22.22)	14.00 (30.43)	1.000
Arthritis[*n* (%)]	7.00 (12.73)	7.00 (19.44)	0.00 (0.00)	0.082	0.00 (0.00)	7 (23.33)	0.012[b]	0.00 (0.00)	7.00 (15.22)	0.585
Encephalitis[*n* (%)]	11.00 (20.00)	3.00 (8.33)	8.00 (42.11)	0.005[b]	8.00 (32.00)	3.00 (10.00)	0.042[a]	4.00 (44.44)	7.00 (15.22)	0.067
Abdominal pain[*n* (%)]	10.00 (18.18)	6.00 (16.67)	4.00 (21.05)	0.723	6.00 (24.00)	4.00 (13.33)	0.484	4 (44.44)	6 (13.04)	0.047[b]
AKI[*n* (%)]	25.00 (45.45)	9.00 (25.00)	16.00 (84.21)	<0.001[a]	-	-	-	-	-	-

GFR–glomerular filtration rate; AST–aspartate aminotransferase; ALT–alanine aminotransferase; ICU–intensive care unit; IQR–interquartile range. *Mann-Whitney *U* test. #Student's *t* test. [a]*Chi*-squared test. [b]Fisher's exact test. *P*-values <0.05 were considered statistically significant.

Table 2. Analysis of risk factors for death and severe AKI.

Factors	*OR*	95% *CI*	*P*-value
Outcome: death			
AKI	12.06	2.55 – 57.15	0.002
Encephalitis	5.69	0.93 – 34.75	0.060
Skin rash	0.51	0.08 – 3.21	0.469
Outcome: severe AKI			
Abdominal pain	5.33	1.11 – 25.64	0.037

Table 3. Comparison of mean glomerular filtration rate variation between admission and last measurement before hospital discharge or death, according to age groups.

Age (years)	GFR on admission	Last GFR	*P*-value*	*P*-value#
< 60	99.75±31.82	103.28±22.78	0.721	
60–70	44.67±32.17	54.43±35.71	0.917	
71–80	60.36±30.82	53.67±30.60	0.124	0.429
81–90	64.34±23.21	62.29±26.68	0.917	
> 90	45.36±22.11	58.52±34.44	0.500	

*Wilcoxon Signed-Rank test. #Split-Plot analysis of variance (ANOVA). Variables were expressed as mean±standard deviation. *Comparision within groups; #comparisionbetween groups.

4. Discussion

Almost half of the studied patients developed AKI, with predominance of extremes of KDIGO classification. Previous studies have investigated the pattern of AKI in CHIKV infection. Economopoulou *et al.* studied patients presenting atypical manifestations of CHIKF. They identified 120 cases of pre-renal AKI and found high rates of pre-existent renal dysfunction and NSAID use prior to hospitalization[4]. More recently, a case report by Hamid *et al.* suggested rhabdomyolysis as another mechanism of kidney injury in CHIKV infection[7]. A study by Mercado *et al.* assessed renal biopsies of fatal CHIKF cases and found that kidney impairment was related mainly to acute interstitial nephritis[8]. These findings indicate that CHIKV, like other viruses, may cause primary kidney injury, since the presence of nephrotoxins has not been documented to date. AKI may also occur in dengue fever, especially in severe cases, as observed in CHIKF. Multiple mechanisms are probably involved in dengue fever kidney damage, such as hypotension, immune complex deposition and rhabdomyolysis, which may play a role in CHIKF renal damage as well[9].

As expected, due to the decline in GFR with aging, patients above 60 years old presented lower GFR on admission, reinforcing that this population is especially vulnerable and should be managed more carefully. We did not have access to creatinine measurements prior to hospital admission, which limits our ability to assess renal sequellae. Although an upward trend in GFR was observed from the first to the last measurements in most age groups, which would point to a recovery of renal function, there was no statistically significant GFR increase within age groups. Split-Plot ANOVA demonstrated that there was no significant difference in GFR variation between age groups during hospitalization, although patients younger than 60 years presented higher mean GFR on admission. Such findings suggest that older age did not interfere in renal recovery until hospital discharge. However, prospective studies with long-term follow-up are necessary to fully elucidate differences in renal recovery in CHIKF and how it is influenced by age.

Although patients may consider cutaneous rash and arthritis among the most frightening or incapacitating CHIKF symptoms, they were associated with better renal outcome and higher survival rate in the univariate analysis. Prospective studies should better define this association. Meanwhile, patients may be reassured about the lack of reasons to think such symptoms could bring worse survival prognosis. On the other hand, abdominal pain was associated with increased risk of severe AKI. This symptom is considered a warning sign in dengue fever, emphasizing the possible similarity between severe presentations of both diseases[10], hence its presence should also be investigated in CHIKF.

In conclusion, AKI was very common in the studied patients and independently increased the risk of death. Abdominal pain was a risk factor for severe AKI. Further studies are needed to elucidate the mechanisms of kidney injury and recovery of renal function.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Authors' contributions

EDFD, GBSJ and RJPN designed the study and guided data collection. LLM, ESM, FLCNB and JMF contributed to literature research. ESG, JMF, FLCNB and LLM performed data acquisition. SLAPF executed data analysis. ESM, LLM and SLAPF prepared the manuscript. EDFD, GBSJ and RJPM helped in data interpretation. LLM and SLAPF revised the manuscript thoroughly.

References

[1] Hua C, Combe B. Chikungunya virus-associated disease. *Curr Rheumatol Rep* 2017; **19**(11): 69.

[2] Ceara State Government, Secretariat of Health. *Epidemiological report–dengue, Zika, chikungunya*. 2017.[Online]. Available from: http://www.saude.ce.gov.br/index.php/boletins?download=3411%3Aboletim-epidemiologico-arboviroses--10-de-novembro-de-2017 [Accessed on 7 April 2018].

[3] Brazil Ministry of Health, Health Surveillance Secretariat. *Primary care secretariat chikungunya: Clinical management*. Brasilia: Ministry of Health; 2017. [Online]. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/chikungunya_manejo_clinico.pdf [Accessed on 2 July 2020].

[4] Economopoulou A, Dominguez M, Helynck B, Sissoko D, Winchmann O, Quenel P, et al. Atypical chikungunya virus infections: Clinical manifestations, mortality and risk factors for severe disease during the 2005-2006 outbreak on Réunion. *Epidemiol Infect* 2009; **137**: 534-541.

[5] Acute Kidney Injury Work Group. Kidney disease: Improving global outcomes (KDIGO). KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; **2**: 1-138.

[6] Levey AS, Stevens LA, Schmid CH, Zang YL, Castro AF 3rd, Feldman HI, et al. CKD-EPI (Chronic kidney disease epidemiology collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604-612.

[7] Hamid A, Dhrolia MF, Qureshi R, Imtiaz S, Ahmad A. Acute kidney injury secondary to rhabdomyolysis: A rare presentation of chikungunya fever. *J Coll Physicians Surg Pak* 2018; **28**: S94-S96.

[8] Mercado M, Acosta-Reyes J, Parra E, Guzmán L, Beltrán M, Gasque P, et al. Renal involvement in fatal cases of chikungunya virus infection. *J Clin Virol* 2018; **103**: 16-18.

[9] Gurugama P, Jayarajah U, Wanigasuriya K, Wijewickrama A, Perera J, Seneviratne SK. Renal manifestations of dengue virus infections. *J Clin Virol* 2018; **101**:1-6.

[10]McFee RB. Selected mosquito borne illnesses–Dengue. *Dis Mon* 2018; **64**: 246-274.