

## RESEARCH ARTICLE

## Chikungunya Death Risk Factors in Brazil, in 2017: A case-control study

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## Abstract

### Background

In 2016/2017 we had a major epidemic of chikungunya (CHIK) in Brazil, with many deaths. We evaluated to factors associated with deaths from CHIK that occurred in the city of Fortaleza, Brazil.

### Methods

A matched case-control study was conducted (1:2), by sex, age ( $\pm 5$  years) and neighborhood. Cases were CHIK deaths that occurred between January 1 and December 31, 2017, in Fortaleza, Brazil, and which were laboratory confirmed. Controls were laboratory confirmed CHIK patients occurring in the same neighborhood and in the same period, but which did not progress to death.

### Results

82 cases of CHIK and 164 controls were included. Considering the clinical history, significant associations were found between other chronic heart diseases (OR 3.8; CI: 1.53–9.26) and chronic kidney disease (OR 12.77; CI: 2.75–59.4). In the multivariate analysis of the variables related to signs and symptoms, fever (OR: 19.23 CI: 1.73–213.78), abdominal pain (OR: 3; 74 CI: 1.06–13.16), apathy (OR: 11.62 CI: 2.95–45.82) and dyspnea (OR: 50.61; CI: 12.37–207.18) were identified with greater likelihood of death from CHIK. It also stood out that altered blood glucose was associated with cases with a worse prognosis (OR:

design, data collection and analysis, decision to publish, or preparation of the manuscript.

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13.5; CI: 1.3–135.0). Among the laboratory findings, only lymphocytes and albumin were not associated with greater likelihood of death.

## Conclusion

The factors related with deaths were chronic kidney disease and previous heart disease, presence of fever, abdominal pain, apathy, dyspnea and arthritis and laboratory findings such as leukocytosis, leukopenia, thrombocytopenia, neutropenia and lymphopenia.

## Introduction

The chikungunya virus (CHIKV) is an alphavirus, belonging to the *Togaviridae* family, which was described in 1952 in Tanzania [1]. Chikungunya (CHIK) presents a clinical picture that can vary from asymptomatic infections to severe and potentially fatal ones [2].

At the end of 2013, chikungunya transmission was confirmed in the Americas [3] and in the following year it was reported in Brazil, with more than 300,000 cases being recorded between 2016 and 2017, with approximately 300 deaths [4]. In Ceará, Northeastern Brazil, the first cases were confirmed in October 2015. In the following years, two epidemic waves occurred (2016/2017), with a large number of reported cases (>150,000) and with a record 245 deaths [5,6]. Fortaleza was the municipality that registered the highest number of chikungunya deaths in Brazil, probably due to the large number of cases and a joint action between surveillance, laboratory, death verification service and the arbovirus death investigation committee working together in collaboration [7,8].

Despite this large number of deaths recorded in Brazil, before the outbreak in Réunion, this disease had not been associated with high mortality rates [9]. However, in recent years, some studies have challenged the conventional view of the non-lethal nature of CHIKV [10–13]. There is evidence that advanced age and the presence of comorbidities increase the likelihood of cases progressing more severely [9,14], however the relative importance of each of these and other factors in progression to death is not well known.

The objective of this study was to assess potential factors associated with deaths from CHIK that occurred during the 2017 epidemic in the city of Fortaleza, Brazil.

## Methods

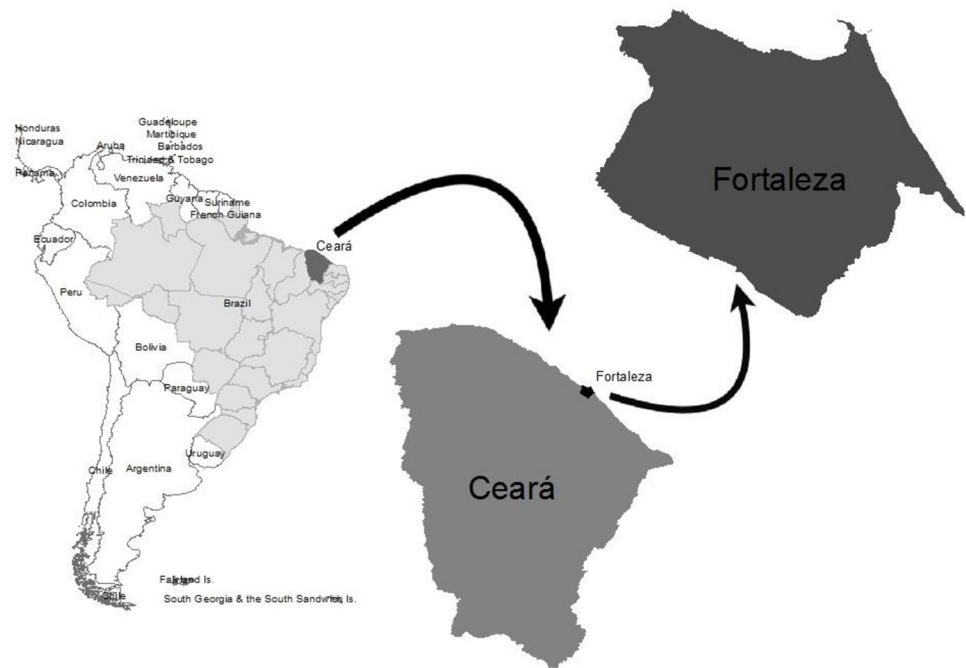
### Study area

This study was carried out in the city of Fortaleza, located in the Northeast region of Brazil (Fig 1). It is considered the 5th most populous state capital in Brazil, with almost 2.5 million inhabitants spread over 315 km<sup>2</sup>. The climatic condition is very favorable for the survival of *Aedes* mosquitoes, with dengue epidemics registered since 1986 [15].

### Study design

A matched case-control study was conducted (1:2), by sex, age ( $\pm 5$  years) and neighborhood.

Cases were chikungunya associated deaths between January 1 and December 31, 2017, which were laboratory confirmed by serology (IGM) or by RT-PCR. In the same way, controls were laboratory confirmed CHIK patients (IgM and / or RT-PCR), which occurred in the city of Fortaleza in the same period but did not progress to death. These controls were randomly



**Fig 1. City of Fortaleza, Ceará, Brazil.**

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selected among eligible cases (according to sex and age) reported in the same neighborhood as the deaths, using the Brazilian Ministry of Health disease notification system (SINAN online).

### Source and procedure for data collection

The data were collected by a trained nurse who administered a semi-structured questionnaire during home visits to the controls and to the family members of cases (deaths). The interviews took place between August 2017 and September 2018, after signing an informed consent form. The SINAN database for the city of Fortaleza / CE was used in order to identify the addresses of deaths and confirmed cases.

When necessary, information was complemented by telephone contact and secondary data sources were accessed, such as patient records in the hospital institutions where they were treated, the arbovirus death investigation forms used by the epidemiological surveillance service of the city of Fortaleza, the reports of the Ceará Arbovirus Death Investigation Committee [6], the reports of the Ceará Death Verification Service and the Brazilian Ministry of Health Mortality Information System.

### Data quality control

The procedures for systematic review of the questionnaires and verification of the collected data were carried out in 10% of the sample aiming at the quality and reliability of the collected primary data and correction of consistency and typing errors.

### Variables analyzed

The explanatory variables analyzed were demographic variables, such as sex (male and female), age, race / color (white, multiethnic black, hispanic and black), education (<1 year, 1–3, 4–7, 8–10, 11–14, 15 or more years of study), marital status (single, married, widowed or divorced);

medical history (cardiovascular diseases, diabetes, hypertension and others), household environmental characteristics (type of habitation, water storage, etc) as well such as presence of signs and symptoms during the clinical course and also musculoskeletal signs and laboratory tests including amount of platelets and leukocytes such as neutrophils and lymphocytes of those patients who had access to the exams or that were in the medical record (supplementary document). The time between symptom onset and death was categorized into acute (within 20 days), postacute (21–90 days) and late (more than 90 days) [40].

### Data analysis

Data were entered on Epi Info 7.2 software and analyzed using JAMOV 1.0 and SPSS 20.0. Absolute and relative frequencies were calculated, and the chi-squared and Fisher's exact tests were used to assess associations between risk factors and death from CHIK. The Mann-Whitney U test was used to analyze the characteristics of the participants. Crude (ORc) and adjusted (ORadj) odds ratios and respective confidence intervals were estimated using multiple logistic regression models. The stepwise forward method was performed to select the final logistic model. Explanatory variables were analyzed by groups of factors, as follows: demographic, behavioral, pre-existing diseases, symptoms, complications and were analyzed within them. After this stage, a final model was run with the variables that were significant in the analysis of each group. A significance level of 5% was adopted. In turn, the variation range explained by the model was described with Nagelkerke R<sup>2</sup> values.

### Ethical aspects

The study was approved by the Ethics Committee of the Federal University of Ceará, as per Certificate of Submission for Ethical Appraisal (CAAE) No. 69013017.8.0000.5054.

### Results

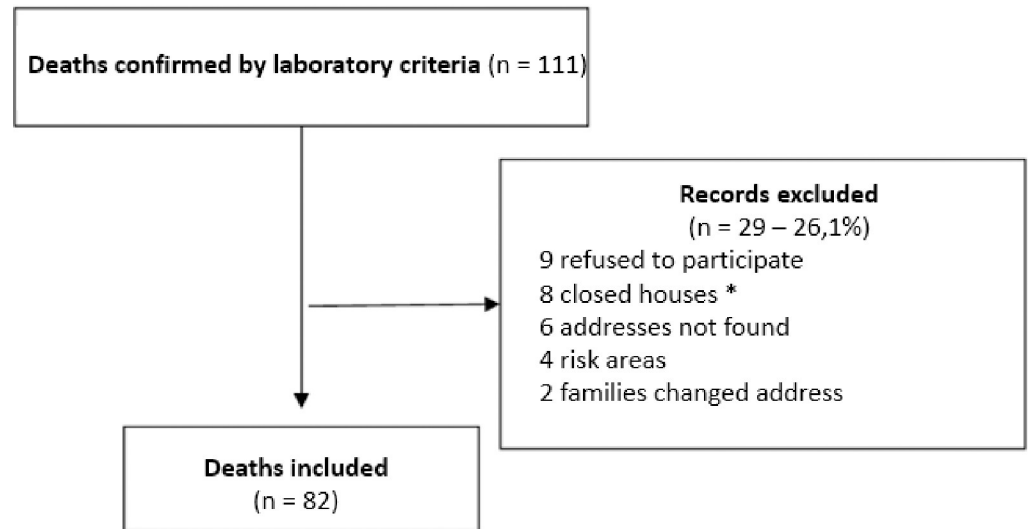
In 2017, 111 CHIK deaths were confirmed according to laboratory criteria. Of these, 82 (73.9%) were included in the study and were paired with 164 controls (Fig 2).

Among the deaths, males (56.1%), people of multiethnic black (58.5%), those who had up to 7 years of study (31.6%), were married (50.0%) and sedentary (69.5%) were all predominant (Table 1). Death occurred in the acute phase in 41 (49.4%), in the postacute phase in 38 (45.8%) cases, in the late phase in 2 (2.4%) cases. The time between symptom onset and death was ignored in 1 (1.2%) case.

Age at death ranged from 0 to 98 years and median time to death was 19 days. The peak of the onset of symptoms occurred in April 2017 (41.2%).

Considering their clinical history, people with other chronic heart diseases (OR 3.8; 95% CI: 1.53–9.26;  $p = 0.004$ ) and chronic kidney disease (OR 12.77; 95% CI: 2.75–59.4;  $p = 0.001$ ) (Nagelkerke R<sup>2</sup> = 0.819) were identified as having greater likelihood of progressing to death and remained associated after multiple logistic regression. Risk of dying was not associated with any vaccination history.

In the multivariate analysis of the variables related to signs and symptoms, the fever (OR 19.23 CI: 1.73–213.78  $p = 0.016$ ), abdominal pain (OR: 3; 74 CI: 1.06–13.16  $p = 0.04$ ), apathy (OR: 11.62 CI: 2.95–45.82  $p = 0.001$ ) and dyspnea (OR: 50.61; CI: 12.37–207.18;  $p < 0.001$ ) variables were identified with greater likelihood of death from CHIK. On the other hand, symptoms such as pruritus (OR: 0.18; CI: 0.05–0.66;  $p = 0.01$ ) and retro-orbital pain (OR: 0.15; CI: 0.04–0.55;  $p < 0.005$ ) were significantly more reported by patients who progressed to cure (Table 2).



**Fig 2. Flowchart of cases investigated during the chikungunya epidemic in the city of Fortaleza in 2017.** \* After 4 attempts at different times.

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Among musculoskeletal symptoms, people with arthritis (51.2%) were 7.75 times more likely to die from CHIK ( $p < 0.001$ ). All other symptoms analyzed in this group, such as morning stiffness, joint pain, extent of pain, location, and intensity of joint pain, were not associated with death (Table 3).

Among the laboratory findings analyzed, only two were not associated with greater likelihood of death: lymphocytes and albumin ( $p > 0.05$ ). Greater likelihood of progressing to death was observed among patients who presented thrombocytopenia (OR: 10.1; CI: 3.9–26.3;  $p < 0.001$ ), leukopenia (OR: 7.4; CI: 2.4–23.0;  $p < 0.001$ ) and leukocytosis (OR = 14; IC = 5.4–36.5;  $p < 0.001$ ). Neutropenia and lymphopenia were also associated with greater likelihood of death with odds ratios (OR) of 6.4 and 14.2, respectively ( $p = 0.001$ ). Other laboratory markers also showed an association with evolution to death, such as CRP > 3 (OR: 12.4; CI: 2.9–52.6;  $p < 0.001$ ), TGO > 40 (OR: 9.4; CI: 3, 1–28.6;  $p < 0.001$ ), TGP > 45 (OR: 3.2; CI: 1.1–9.1;  $p = 0.027$ ), urea > 45 (OR: 17.8; CI: 5, 5–57.3;  $p < 0.001$ ) and creatinine < 1.3 (OR: 17.8; CI: 5.8–54.2;  $p < 0.001$ ). It also stood out that altered blood glucose was associated with cases with a worse prognosis (OR: 13.5; CI: 1.3–135.0;  $p = 0.038$ ) (Table 4).

## Discussion

This study identified a predominance of males, people of multiethnic black, with up to 7 years formal education, married and over 65 years of age. In addition, we found that the factors most strongly associated with the deaths of people with CHIK were: chronic kidney disease and previous heart disease, presence of fever, abdominal pain, apathy, dyspnea and arthritis, as well as laboratory findings such as leukocytosis, leukopenia, thrombocytopenia, neutropenia and lymphopenia.

Having a record of fever increased likelihood of death 16 times. This symptom has been reported as being more frequent among people who died in other cities around the world [16]. In addition, having a record of high fever has also been associated with patients with severe chikungunya who required hospitalization [9,17,18]. This symptom is likely to be very intense due to the increase in pro-inflammatory cytokines such as IL-6 or IFN- $\alpha$  which are stimulated as a result of viral infection. Economopoulou et al. [9] revealed that high fever increased

**Table 1. Distribution of sociodemographic characteristics of cases (deaths) and controls (survivors).** Fortaleza (Brazil), 2017.

Variables	Groups		p-value
	Case N (%)	ControlN (%)	
Sex			
Male	46 (56.1)	92 (56.1)	
Female	36 (43.9)	72 (43.9)	
Age (years)			
0 to 19 ys	2 (1.2)	1 (1.2)	
20 to 39 ys	7 (4.3)	3 (3.6)	
40 to 59 ys	21 (12.8)	8 (9.5)	
60 more ys	134 (81.7)	70 (83.3)	
Race/color			0.010 <sup>d</sup>
White	29 (35.4)	88 (53.7)	
Black	5 (6.1)	3 (1.8)	
Hispanic	0 (0.0)	1 (0.6)	
Multiethnic black	48 (58.5)	72 (43.9)	
Years of study			0.441 <sup>c</sup>
<1 year	14 (17.1)	19 (11.6)	
1–3 years	13 (15.9)	17 (10.4)	
4–7 years	26 (31.7)	61 (37.2)	
8–10 years	16 (19.5)	36 (22.0)	
11–14 years	6 (7.3)	17 (10.4)	
15 or more	6 (7.3)	14 (8.5)	
No answer	1 (1.2)	0 (0.0)	
Marital status			0.886
Single	13 (15.9)	21 (12.8)	
Married	43 (52.4)	95 (57.9)	
Widowed	19 (23.2)	38 (23.2)	
Divorced	7 (8.5)	10 (6.1)	
Smoking			0.555
Yes in the past	42 (51.2)	73 (44.5)	
Yes and still smoking	4 (4.9)	9 (5.5)	
No	35 (42.7)	82 (50.0)	
No answer	1 (1.2)	0 (0.0)	
Drink alcohol			0.693
Yes	23 (28)	50 (30.5)	
No	59 (72)	114 (69.5)	

Data expressed as mean  $\pm$  standard deviation and median (25th percentile - 75th percentile) b: Mann-Whitney test; c: Pearson's chi-square test; d: Fisher's exact test.

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substantially in patients who used non-steroidal anti-inflammatory drugs (NSAIDs) before hospitalization which can lead to a more severe form of the disease or later hospitalization. However, the role of specific NSAIDs (aspirin or paracetamol) in the disease has not yet been clearly determined and needs to be investigated. It should be noted that fever with the presence of arthralgia is one of the most sensitive markers with regard to the identification of suspected chikungunya cases [17].

Another symptom that proved to be a manifestation related to increased mortality from chikungunya was dyspnea. This finding also appears in the study by Alvarez et al. [19]

**Table 2. Frequency of signs and symptoms of several systems and likelihood of death from Chikungunya.** Fortaleza (Brazil), 2017.

Systems	Variables	Groups		Crude analysis		Multiple logistic regression*	
		Case	Control	OR (95%CI)	p-value	OR (95%CI)	p-value
		N (%)	N (%)				
General symptoms	Fever	77 (93.9)	120 (73.2)	7.06 (2.44–20.43)	<0.001 <sup>c</sup>	19.23 (1.73–213.78)	0.016
	Hypothermia	9 (11.11)	0 (0.0)	45.63 (2.62–79.4)	<0.001 <sup>d</sup>		
	Myalgia	51 (62.2)	96 (58.5)	1.29 (0.74–2.25)	0.369 <sup>e</sup>		
	Prostration	71 (86.6)	80 (48.8)	9.32 (4.22–20.58)	<0.001 <sup>c</sup>		
	Irritability	39 (47.6)	94 (57.3)	0.74 (0.43–1.28)	0.285 <sup>e</sup>		
	Apathy	36 (44.0)	32 (19.5)	3.53 (1.96–6.37)	<0.001 <sup>c</sup>	11.62 (2.95–45.82)	<0.001
	Postural hypotension	34 (41.5)	24 (14.6)	4.41 (2.37–8.20)	<0.001 <sup>c</sup>		
	Lipothymia / fainting	34 (41.5)	47 (28.7)	1.92 (1.10–3.37)	0.021 <sup>c</sup>		
Respiratory symptoms	Dyspnea	60 (73.2)	16 (9.8)	27.75 (13.47–57.16)	<0.001 <sup>c</sup>	50.61 (12.37–207.18)	<0.001
	Cough	31 (37.8)	23 (14.0)	3.88 (2.07–7.28)	<0.001 <sup>c</sup>		
	Coryza	8 (9.8)	14 (8.5)	1.22 (0.49–3.05)	0.664 <sup>e</sup>		
	Sore throat	7 (8.5)	11 (6.7)	1.40 (0.52–3.77)	0.599 <sup>d</sup>		
	Pharyngitis	1 (1.2)	2 (1.2)	1.09 (0.10–12.19)	>0.999 <sup>d</sup>		
	Canker sores in mouth and/or throat	25 (30.5)	66 (40.2)	0.75 (0.43–1.35)	0.342 <sup>e</sup>		
Digestive symptoms	Abdominal pain	40 (48.78)	50 (30.5)	2.44 (1.40–4.27)	0.002 <sup>e</sup>	3.74 (1.06–13.16)	0.04
	Diarrhea	41 (50.0)	42 (25.6)	3.13 (1.78–5.51)	<0.001 <sup>c</sup>		
	Nausea	41 (50.0)	51 (31.1)	2.39 (1.38–4.15)	0.002 <sup>e</sup>		
	Vomiting	32 (39.0)	39 (23.8)	2.14 (1.2–3.79)	0.009 <sup>e</sup>		
	Hepatomegaly	5 (6.1)	0 (0.0)	37.14 (2.01–685)	0.001 <sup>d</sup>		
Skin	Rash	45 (54.88)	74 (45.1)	1.52 (0.89–2.60)	0.124 <sup>e</sup>		
	Itching	26 (31.7)	86 (52.4)	0.44 (0.25–0.78)	0.004 <sup>e</sup>	0.18 (0.05–0.66)	0.01
	Petechiae	13 (15.9)	38 (23.2)	0.65 (0.33–1.31)	0.229 <sup>e</sup>		
	Bruise	6 (7.3)	2 (1.2)	6.75 (1.33–34.25)	0.015 <sup>d</sup>		
	Epistaxis	2 (2.4)	0 (0.0)	10.89 (0.51–229)	0.101 <sup>d</sup>		
	Hematoma	8 (9.8)	5 (3.1)	3.63 (1.15–11.5)	0.030 <sup>d</sup>		
Central Nervous System	Headache	52 (63.4)	123 (75.0)	0.55 (0.29–1.01)	0.286 <sup>e</sup>		
	Retro-orbital pain	20 (24.4)	74 (45.1)	0.44 (0.24–0.80)	0.007 <sup>e</sup>	0.15 (0.04–0.55)	0.005
	Paresis	14 (17.1)	15 (9.2)	2.24 (1.02–4.92)	0.040 <sup>e</sup>		
	Paralysis	18 (22.0)	3 (1.8)	16.95 (4.81–59.69)	<0.001 <sup>c</sup>		
	Somnolence	73 (89.0)	116 (70.7)	4.32 (1.85–10.05)	<0.001 <sup>c</sup>		
Others	Dry conjunctivitis	10 (12.2)	24 (14.6)	0.87 (0.39–1.92)	0.732 <sup>e</sup>		
	Lymphadenopathy	1 (1.2)	2 (1.2)	1.17 (0.10–13.16)	>0.999 <sup>d</sup>		
	Splenomegaly	2 (2.4)	0 (0.0)	15.32 (0.72–324)	0.063 <sup>d</sup>		
Antecedent	Diabetes	28 (34.1)	37 (22.6)	1.8 (0.9–3.1)	0.052 <sup>e</sup>		
	HAS	64 (78.0)	101 (61.6)	2.2 (1.2–4.1)	0.010 <sup>e</sup>		
	Heart failure	8 (9.8)	3 (1.8)	5.8 (1.5–22)	<0.001 <sup>c</sup>		
	Other chronic heart disease	17 (20.7)	9 (5.5)	4.5(1.9–10.6)	<0.001 <sup>c</sup>	3.77 (1.53–9.26)	0.004
	Chronic kidney disease	13 (15.9)	2 (1.2)	15 (3.3–69)	<0.001 <sup>d</sup>	12,77 (2,75–59,4)	0.001
	Chronic lung disease	6 (7.3)	16 (9.8)	0.7 (0.2–1.9)	0.527 <sup>e</sup>		
	Other chronic disease	41 (50)	86 (52.4)	0.9 (0.5–1.5)	0.718 <sup>e</sup>		

Data expressed in n and%; c: Pearson’s chi-square test; d: Fisher’s exact test. \* Nagelkerke R<sup>2</sup> = 0.819.

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characterizing both a symptom of cardiovascular failure aggravated by arbovirus and a symptom of respiratory dysfunction which may be due to a more severe condition of the disease which involves the cardiovascular and respiratory system [12]. This fact was also evidenced in

**Table 3. Frequency of musculoskeletal signs and symptoms associated with likelihood of death from Chikungunya.** Fortaleza (Brazil), 2017.

Variables	Groups		ORc	p-value
	Case	Control		
	N (%)	N (%)		
Arthritis	42 (51.2)	22 (13.4)	7.75 (4.12–14.61)	<0.001 <sup>c</sup>
Joint pain	78 (95.12)	161 (98.2)	0.73 (0.12–4.44)	0.664 <sup>c</sup>
Joint pain extension				0.351 <sup>c</sup>
Oligoarthritis	19 (24.36)	31 (19.2)	1.36 (0.71–2.60)	
Polyarthralgia	59 (75.64)	131 (80.9)	1	
Pain intensity				0.169 <sup>c</sup>
Mild	4 (5.19)	14 (8.6)	1	
Moderate	31 (40.26)	80 (49.4)	1.35 (0.41–4.41)	
Intense	42 (54.55)	68 (42.0)	2.16 (0.67–7.00)	
Pain site				
Head Neck	1 (1.25)	4 (2.4)	0.51 (0.05–4.61)	>0.999 <sup>d</sup>
Spine Torso	3 (3.75)	2 (1.2)	3.16 (0.52–19.28)	0.334 <sup>d</sup>
Sacral spine	3 (3.75)	9 (5.5)	0.67 (0.17–2.55)	0.756 <sup>d</sup>
Shoulder	7 (8.75)	12 (7.3)	1.21 (0.46–3.21)	0.695 <sup>c</sup>
Elbow	4 (5)	9 (5.5)	0.91 (0.27–3.04)	>0.999 <sup>d</sup>
Fist	6 (7.5)	22 (13.4)	0.52 (0.20–1.35)	0.204 <sup>c</sup>
Fingers	4 (5)	17 (10.4)	0.45 (0.15–1.40)	0.161 <sup>c</sup>
Toes	1 (1.25)	7 (4.3)	0.28 (0.3–2.35)	0.279 <sup>d</sup>
Soles of the feet	10 (12.5)	28 (17.1)	0.69 (0.32–1.51)	0.355 <sup>c</sup>
Hip	2 (2.5)	5 (3.1)	0.82 (0.15–4.30)	>0.999 <sup>d</sup>
Knees	24 (30)	35 (21.3)	1.58 (0.86–2.90)	0.138 <sup>c</sup>
Ankle	13 (16.25)	32 (19.5)	0.80 (0.39–1.63)	0.537 <sup>c</sup>
All joints	36 (45)	83 (50.9)	0.79 (0.46–1.35)	0.386 <sup>c</sup>
Morning stiffness	67 (81.71)	150 (91.5)	0.58 (0.24–1.39)	0.218 <sup>c</sup>

Data expressed in n and%; c: Pearson's chi-square test; d: Fisher's exact test.

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patients with arboviruses who progressed to worse outcomes [20]. As previously mentioned, cardiovascular diseases are also a predictive factor for a worse outcome and they alone cause respiratory manifestations such as difficulty in breathing. In addition, it is known that CHIKV infection tends to exacerbate other pre-existing diseases generating decompensation [21].

Furthermore, in our study severe abdominal pain was associated with greater likelihood of death from chikungunya. This result was also found in studies by Bonifay et al. [22]. The authors defined it as an atypical and severe manifestation of the disease due to hepatitis and acute pancreatitis with a worse prognosis in patients with a history of alcoholism and older than 85 years [22].

Apathy was also significantly associated with a greater likelihood of progressing to death. Work by Cunha and Trinta [23] in Brazil pointed out that 4.6% of patients declared themselves extremely depressed and 35.5% felt unmotivated to perform daily activities, revealing great apathy. This is probably due to persistent arthralgia that usually affects multiple joints causing functional loss, reduced quality of life and symptoms of asthenia, depression, and anxiety [24].

This study detected significant association of chronic kidney disease as a factor that increased the likelihood of death in chikungunya, probably due to a central component of kidney injury. This same finding was observed in other studies, such as that by Brito [25], in which some deaths occur indirectly due to infection mainly resulting from decompensation of



Table 4. Laboratory tests of cases (deaths) and controls (survivors).

Laboratory tests	Groups		ORc (95%CI)	p
	Case N (%)	Control N (%)		
Platelets (n = 113)				<0.001
<150,000 mm <sup>3</sup>	51 (68.92)	7 (17.95)	10.1 (3.9–26.3)	
>150,000 mm <sup>3</sup>	23 (31.08)	32 (82.05)	1	
Leukocytes_min (n = 113)				<0.001
<3500 mm <sup>3</sup>	34 (45.95)	4 (10.26)	7.4 (2.4–23)	
>3500 mm <sup>3</sup>	40 (54.05)	35 (89.74)	1	
Leukocytes_max (n = 113)				<0.001
>10000 mm <sup>3</sup>	58 (78.4)	8 (100.0)	14.1(5.4–36.5)	
<10000 mm <sup>3</sup>	16 (21.6)	31 (0.0)	1	
Neutrophils_min (n = 82)				<0.001
<1500 mm <sup>3</sup>	28 (60.87)	7 (19.44)	6.4 (2.3–17.8)	
>1500 mm <sup>3</sup>	18 (39.13)	29 (80.56)	1	
Neutrophils_max (n = 82)				0.008
>7500 mm <sup>3</sup>	13 (28.26)	2 (5.56)	6.7 (1.4–32)	
<7500 mm <sup>3</sup>	33 (71.74)	34 (94.44)	1	
Lymphocytes_min (n = 99)				<0.001
<1000 mm <sup>3</sup>	52 (85.25)	11 (28.95)	14.2 (5.2–38.4)	
>1000 mm <sup>3</sup>	9 (14.75)	27 (71.05)	1	
Lymphocytes_max (n = 99)				>0.999
>3500 mm <sup>3</sup>	3 (4.92)	2 (5.26)	0.9 (0.1–5.8)	
<3500 mm <sup>3</sup>	58 (95.08)	36 (94.74)	1	
CRP_max (n = 48)				<0.001
>3 mg/dL	27 (81.82)	4 (26.67)	12.4 (2.9–52.6)	
<3 mg/dL	6 (18.18)	11 (73.33)	1	
TGO_max (n = 74)				<0.001
>40 U/L	40 (81.63)	8 (32.0)	9.4 (3.1–28.6)	
<40 U/L	9 (18.37)	17 (68.0)	1	
TGP_max (n = 72)				0.027
>45 U/L	26 (55.32)	7 (28.0)	3.2 (1.1–9.1)	
<45 U/L	21 (44.68)	18 (72.0)	1	
Urea_max (n = 91)				<0.001
>45 mg/dl	60 (90.91)	9 (36.0)	17.8 (5.5–57.3)	
<45 mg/dl	6 (9.09)	16 (64.0)	1	
Creatinine_max (n = 94)				<0.001
<1.3 mg/dL	59 (89.39)	9 (32.14)	17.8 (5.8–54.2)	
>1.3 mg/dL	7 (10.61)	19 (67.86)	1	
Albumin_max (n = 21)				0.128
<3.5 g/L	3 (16.67)	2 (66.67)	0.1 (0–1.5)	
>3.5 g/L	15 (83.33)	1 (33.33)	1	
Glucose_max (n = 25)				0.038
>125 mg/dL	3 (60.0)	2 (10.0)	13.5 (1.3–135)	
<125 mg/dL	2 (40.0)	18 (90.0)		

Data expressed in n and %; c: Pearson's chi-square test; d: Fisher's exact test. min = lowest values; max = highest values.

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previous comorbidities, which include patients with kidney, heart or lung diseases [26]. Comorbidities such as hypertension and diabetes are associated with greater chronicity as well as with worse outcomes or with increased pain severity [17]. It is known that hypertension and diabetes are predictive factors for the progression of kidney disease and that there is decompensation of underlying diseases in patients with CHIKV infection [21,27]. This can be a contributing factor to severe evolution in these patients [17], especially when these comorbidities are decompensated [28].

With regard to pre-existing cardiovascular diseases, heart failure, systemic arterial hypertension (SAH) and chronic heart disease were recognized in the study as factors associated with death from chikungunya. This observation is in line with what has been documented by Alvarez et al. [19] who identified that patients with cardiovascular comorbidities showed faster deterioration and worse prognosis. It should be added that as recorded in the work of Azevedo, Oliveira & Vasconcelos [29], chikungunya can still present cardiac alterations, especially myocarditis, pericarditis, and dilated cardiomyopathy. One of the explanations for this cardiovascular impairment is the possible cardiac tropism of CHIKV, which upon penetrating myocytes generates direct damage to muscle fibers, culminating in an inflammatory response which results in damage to cardiac tissue and necrosis [19,30].

In this study, itching and retro-orbital pain were considered protective factors against death from chikungunya. Retro-orbital pain is a symptom reported in other cases [31]. This finding is justified because both symptoms are self-limiting occurring in the acute phase of the disease and lasting approximately 1 week when IgM anti-CHIKV antibodies appear [32]. On the other hand, these are symptoms very often reported in patients with dengue or Zika [33] and may be associated with false-positive cases. In addition, according to the study by Caglioti et al. [34], most eye manifestations have a benign course with complete resolution and preservation of vision.

We demonstrated that prior presence of arthritis significantly increased the likelihood of progressing to death. Despite the persistence of musculoskeletal complaints being the main characteristic of chikungunya, there are some factors that are associated with a worse prognosis. Some studies show that prominent joint involvement in the acute phase (joint edema and stiffness, polyarthritis, tenosynovitis) can be a marker for worse disease progression [35]. Therefore, prior presence of arthritis may have contributed to patients having worse outcomes. This may be due to direct tissue damage induced by the virus; long-term persistence of CHIKV infection in tissues with concomitant inflammation; and activation of autoimmune responses [36].

We found a set of laboratory markers that can be important markers of poor prognosis and that are found in blood counts, this being an examination that is part of the routine investigation of any infectious condition. Among the markers of poor prognosis are leukocytosis and leucopenia, as well as thrombocytopenia, neutropenia, and lymphopenia. These laboratory findings have already been described as severity markers in patients with dengue fever, another arbovirus disease very common in Brazil [37]. It is well established that laboratory abnormalities are observed in CHIKV infection with a direct correlation with higher viral load [38]. It is important to highlight that patients with thrombocytopenia are often patients with worse prognosis both in the pediatric population and in adults [16,39,40]. Leukopenia has also been associated with greater severity and need for hospitalization [18]. Changes in liver enzymes, increased urea creatinine and elevated CRP were also good predictors of death and should be considered in the presence of a patient with clinical suspicion of chikungunya. There is also evidence that patients with CHIK may go on to suffer albuminuria, hematuria, nephritis, kidney damage and other kidney function abnormalities [19,28]. We report here that renal markers such as creatinine and urea showed significant alteration.

The main limitation of this study is due to the possible memory bias of the cases that survived and even more so among the relatives of the people who died. This bias has been minimized, as far as possible, by searching for information in medical records, surveillance records, laboratories and hospitals attended by each case and control. Another aspect that deserves to be highlighted is that even though all these deaths have undergone exhaustive investigation by the expert committee [6], it is always difficult to define precisely whether disease manifestation was serious due to the presence or exacerbation of existing comorbidities or, alternatively, whether comorbidities decompensate due to severe CHIK, which would suggest the potential for reverse causality bias. Additionally, it is difficult to establish whether people died with chikungunya or from chikungunya [7,13,40].

Many more prospective studies will be necessary for us to fully understand chikungunya mortality. However, in this study we found that the factors most strongly associated with death, such as chronic kidney disease and previous heart disease and some signs and symptoms, such as fever, abdominal pain, apathy, dyspnea and arthritis, should serve as a warning to professionals for closer monitoring of this type of patient. In addition, blood count findings such as leukocytosis, leucopenia, thrombocytopenia, neutropenia and lymphopenia should draw attention to the risk of severity and reinforce the importance of complete blood tests as part of investigation of all patients with suspected chikungunya.

## Supporting information

### S1 File.

(DOC)

### S2 File.

(DOC)

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