

## Major Article

# *Trypanosoma cruzi* seroprevalence among solid organ donors in Ceará State, Brazil

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### Abstract

**Introduction:** The transmission of Chagas disease (CD) through blood transfusion, organ transplantation, and oral transmission has gained greater visibility as a result of intensified vector control activities in endemic regions and to control CD in non-endemic regions. In Brazil, Ceará is one of the states that perform the most organ transplants. Therefore, the objective of this study was to assess the prevalence of *Trypanosoma cruzi* infection in organ donor candidates. **Methods:** A retrospective analysis was performed on data from potential organ donors at the Center of Transplantation of the State of Ceará from 2010 - 2015. **Results:** Data from a total of 2,822 potential donors were obtained, of which 1,038 were effective donors and 1,784 were excluded, likely due to lack of family authorization or medical contraindication. The prevalence of *T. cruzi* infection among these potential donors was 1.3% (n = 29). The majority of infected donors were males aged 41 - 60 years, residing in the interior of the state. Interestingly, 72.4% (n = 21) had positive or inconclusive serology for additional infections, such as cytomegalovirus, hepatitis B and C, and toxoplasmosis. Probability analysis revealed that stroke was the most common cause of death among potential donors with CD. **Conclusions:** There was a high prevalence of CD and other coinfections among potential solid organ donors in Ceará, and statistical tests have shown that these individuals are at increased risk of stroke when compared to potential non-reactive donors. This work highlights the importance of screening DC infection in potential donors.

**Keywords:** Organ transplantation. *Trypanosoma cruzi*. Prevalence. Brazil. Chagas disease. Stroke.

### INTRODUCTION

Brazil has the largest public organ transplantation system worldwide, and 95% of these procedures are carried out with public resources<sup>1</sup>. Ceará is one of the states that perform the most organ transplants, and 1,510 transplants were performed in 2017<sup>1</sup>. The activities performed by the transplant center occur 24 hours a day, seven days a week. The main ones are: regulating the list of organ and tissue receptors, receiving notifications from potential donors diagnosed with brain death, and coordinating the necessary supervision for transplant surgery. There is a growing need for solid organs for transplantation, and

serological profile of potential donors is an important measure used to evaluate the suitable donor candidates<sup>2</sup>.

Organ transplantation from donors who are infected with *Trypanosoma cruzi* is most often avoided due to the risk of disease transmission<sup>3</sup>. Studies have reported amastigote forms in several organs, including those for which the parasite does not have a natural tropism. Organ transplantation represents an alternative transmission route for Chagas disease (CD) that is facilitated by immunosuppressive therapy required for transplant recipients. Rates of transmission from an infected donor to recipient range from 10% to 20%<sup>3,4</sup>, with the risk of *T. cruzi* transmission being more significant in heart transplantation compared to liver or kidney transplantation.

Chagas disease is prevalent in both endemic and several nonendemic countries, including the United States and Spain<sup>5</sup>. It is endemic in Latin America where an estimated six to eight million people are infected, although the exact prevalence is

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difficult to determine as only 2% of cases are diagnosed. In Brazil, an estimated two to three million people are infected<sup>6-8</sup>. According to the Mortality Information System, 68,206 CD-related deaths were recorded in Brazil from 2000 to 2013, an average of 4,872 deaths per year<sup>9</sup>.

The northeastern region of Brazil, especially the State of Ceará, is at high risk for CD transmission for many reasons. This socioeconomically challenged region contains high rates of suboptimal housing with living conditions that are conducive to the triatomine bug, a vector for CD. In addition, Ceará is the epicenter of the *Triatoma brasiliensis* and *Triatoma pseudomaculata* species, which are difficult to control by traditional means recommended by the National Health Foundation [Fundação Nacional de Saúde (FNS)]<sup>10,11</sup>. Finally, demands for the control of emerging and reemerging diseases, such as dengue, has led to a worrying and progressive reduction of the entomological vigilance activities used to control CD<sup>11</sup>.

Therefore, the present study sought to determine the seroprevalence of *T. cruzi* in potential organ donors in the State of Ceará, and to examine the epidemiological profile of these individuals.

## METHODS

### Study design and sampling

The medical record at the Transplantation Center of the State of Ceará in Fortaleza, Brazil includes a form used by medical to collect structured data from the patient, and data were used for analysis. These data included information on sex, age, place of origin, and serological screening results for Human Immunodeficiency Virus (HIV), syphilis, Human T-cell Lymphotropic Virus (HTLV), Cytomegalovirus (CMV), hepatitis B and C, toxoplasmosis, and CD. All potential donors from 2010 to 2015 were included in this study. Only donors with incomplete information regarding serology for CD were excluded.

### Ethical considerations

This project complied with Brazil's National Health Council regulations (Directive CNS 466/12) governing human research and it was approved by the Federal University of Ceará's Research Ethics Committee (COMEPE-UFC), under protocol number 53833816.5.0000.5054 in December 2015.

## Data analysis

Data were recorded in Excel (Microsoft Corp., Redmond, WA, USA) and analyzed using GraphPad Prism version 5.0 (GraphPad, San Diego, CA, USA). The frequency of positive CD cases was calculated using the proportion of positive serological results and the total number of donors over the study period. Fisher's exact test was used to establish associations between categorical variables and groups. Simple linear regression was used to determine trends between the variables, with the year serving as the independent variable. For all tests, results were considered significant at  $p$ -value  $< 0.05$ .

## RESULTS

In total, 2,822 potential organ donors were identified from January 2010 to December 2015. Of these, 1,038 became actual donors, and 1,784 were excluded for a variety of reasons (e.g., lack of family authorization, medical contraindication). Effective donors were mostly male ( $n = 699$ ; 67.3%) aged 41 - 60 years ( $n = 436$ ; 42%). A total of 566 (54.5%) donors died due to head trauma, 407 (39.2%) due to stroke, and 65 (6.3%) due to other causes (e.g., central nervous system tumor, encephalopathy anoxic).

**Table 1** displays the prevalence of CD in potential organ donors. The number of CD serological tests performed each year increased during the 6-year period. A total of 27 (1.2%) potential donors with positive CD serology and two (0.1%) had inconclusive results. The prevalence of CD among potential donors varied between 0.9 and 1.6%. Overall, 2014 saw the highest number of positive cases ( $n = 8$ ; 1.5%) and 2010 the lowest ( $n = 1$ ; 1.0%). Organs from these individuals were rejected due to their reactive serology for this disease.

As shown in **Table 2**, 79.3% ( $n = 23$ ) of potential donors with positive or inconclusive CD serology were male, 51.8% were aged 41- 60 years ( $n = 15$ ), and 65.5% resided in the state's countryside ( $n = 19$ ). The primary cause of death of deceased donors was stroke ( $n = 11$ ; 37.9%). There were 21 potential donors with positive or inconclusive results for at least one other infection (e.g., CMV, toxoplasmosis, hepatitis B and C). As detailed in **Table 3**, potential organ donors with positive or inconclusive serology for CD were more likely to have died from a stroke than from traumatic brain injury (TBI) (relative risk = 2.472;  $p = 0.0195$ ) and were more likely to be aged over 60 years (relative risk = 2.535;  $p = 0.0346$ ).

**TABLE 1:** Prevalence of Chagas disease in potential organ donors in the state of Ceará from 2010 to 2015.

Year	Serology tests	Positive	Indeterminate	Prevalence (%)
2010	104	1	0	1.0
2011	349	5	0	1.4
2012	393	4	0	1.0
2013	466	3	1	0.9
2014	523	8	0	1.5
2015	451	6	1	1.6
<b>Total</b>	<b>2,286</b>	<b>27</b>	<b>2</b>	<b>1.3</b>

**TABLE 2:** Profile of potential organ donors presenting reactive serology (positive/indeterminate) for Chagas disease from 2010 to 2015.

Variable	Group	Number	Percentage
Sex	female	6	20.7
	male	23	79.3
	<b>Total</b>	<b>29</b>	
Age (years)	18 - 40	7	24.1
	41- 60	15	51.8
	≥ 60	7	24.1
	<b>Total</b>	<b>29</b>	
Origin	Country side	19	65.5
	Fortaleza	10	34.5
	<b>Total</b>	<b>29</b>	
Cause of death	CVA- Hemorrhagic	11	37.9
	CVA - Ischemic	7	24.1
	TBI – Physical aggression	1	3.4
	TBI – Traffic accident	7	24.1
	TBI – other causes	3	10.3
	<b>Total</b>	<b>29</b>	
Blood group	A+	7	24.1
	A-	1	3.4
	B+	6	20.7
	AB+	1	3.4
	O+	13	44.8
	O-	1	3.4
	<b>Total</b>	<b>29</b>	
Coinfection*	cytomegalovirus IgG	21	72.4
	hepatitis B	6	20.7
	hepatitis C	5	17.2
	toxoplasmosis IgG	17	58.6
	<b>Total</b>	<b>49</b>	

**CVA:** cerebrovascular accident; **TBI:** traumatic brain injury; **IgG:** immunoglobulin G. \*Each patient may have more than one coinfection.

## DISCUSSION

In the present report, no organs or tissues from individuals with reactive serology for CD were used for transplantation, according to the discretion of the medical teams from the transplant centers included in this study.

Despite the possible risk of infection, the Brazilian Intensive Medicine Association (AMIB) Committee of Organ Donation and Transplantation has stated that individuals with positive or inconclusive CD serology can donate organs including kidneys, pancreas, liver, and lungs at the discretion of the patient and the transplant center staff. The 2015 Second Brazilian Consensus on CD prohibits the transplantation of the heart and intestines from individuals infected with CD and recommends against transplanting other organs from these donors<sup>13,14</sup>.

According to Clemente *et al.*<sup>3</sup>, donation should be postponed in donors with symptomatic disease. Transplantation should

be avoided in donors who have died of CD, as the risk of transmission from the donor organs and blood is 10% to 20%, and 75% for heart transplantation<sup>3</sup>.

The 2015 Second Brazilian Consensus<sup>4</sup> does not recommend the prophylactic treatment with benznidazole (BNZ) of transplanted individuals, but rather the accomplishment of sequential monitoring with clinical evaluations, indirect parasitological examinations, and serological tests, because systematic data on the efficacy of BNZ prophylaxis (defined when the drug was administered in the absence of an acute scenario) for recipients after transplantation do not exist. Prophylaxis has not been shown to prevent the transmission of *T. cruzi* from positive donors to negative recipients<sup>4</sup>.

Clinical and serological and parasitological tests should be performed every 2 months up to 1 year after transplant, and subsequently every 6 months, as long as immunosuppression

**TABLE 3:** Profiles of donors with negative serology and potential donors with reactive serology (positive/indeterminate) for Chagas disease from 2010 to 2015, by sex, age, cause of death, and blood group.

Profiles of donors	Chagas disease				p**
	positive*		negative		
	N	%	N	%	
<b>Sex</b>					
female	6	20.7	339	32.6	0.2275
male	23	79.3	699	67.4	
<b>Total</b>	<b>29</b>	<b>100.0</b>	<b>1038</b>	<b>100.0</b>	
<b>Age (years)</b>					
<5	0	0.0	10	0.9	1.0000
06 a 11	0	0.0	21	2.0	1.0000
12 a 17	0	0.0	86	8.3	0.6140
18-40	7	24.1	373	36.0	0.2394
41-60	15	51.8	436	42.0	0.3422
>60	7	24.1	112	10.8	0.0346
<b>Total</b>	<b>29</b>	<b>100.0</b>	<b>1038</b>	<b>100.0</b>	
<b>Cause of death</b>					
TBI	11	38.0	566	54.5	0.0897
CVA	18	62.0	407	39.2	0.0195
Other	0	0.0	65	6.3	0.2570
<b>Total</b>	<b>29</b>	<b>100.0</b>	<b>1038</b>	<b>100.0</b>	
<b>Blood group</b>					
A	8	27.6	369	35.6	0.6972
AB	1	3.4	31	3.0	0.5914
B	6	20.7	98	9.4	0.0550
O	14	48.3	540	52.0	0.7105
<b>Total</b>	<b>29</b>	<b>100.0</b>	<b>1038</b>	<b>100.0</b>	

**TBI:** traumatic brain injury; **CVA:** cerebrovascular accident; \*Positive: positive/indeterminate serology. \*\*p = Fisher's Test p-value. Fisher's Test included positive/inconclusive potential donors and actual donors (negative serology).

persists. If an acute infection is detected by parasitological or serological tests at any time, conventional antiparasitic treatment should be instituted<sup>14</sup>.

Most potential donors with positive or inconclusive CD serology were from municipalities located in the countryside (Table 2). Many municipalities in this area have a high risk of CD transmission, including Limoeiro do Norte, Jaguaruana, Russas, Quixeré, Tauá, Independência, and Crateús. Although many potential donors were from Fortaleza, the state capital, it is likely that many were born in these high-risk areas and later migrated to this large capital city<sup>15-18</sup>.

The prevalence of CD in the present study is relatively high (1.3%), which confirms that Ceará is endemic to this disease. This is likely due to an abundance of disease vectors and living conditions that are conducive to its transmission. It is difficult to

compare the present results with other regions of the country, as studies that document CD infection in organ donation candidates are rare. There are few studies involving solid organ transplants and CD, and this is one of the first studies to assess the incidence of CD among organ donors in Brazil. A similar study in the State of Santa Catarina reported a 0.3% prevalence of CD among potential organ donors from 2001 to 2007<sup>12,19-21</sup>.

Studies from other countries have found similar rates of CD, however, the diversity in population and environment obscures these comparisons. A study carried out in Mexico among organ donors found a 2% prevalence of *T. cruzi* infection from 2009 to 2010. In Argentina, the prevalence was 4.6% in 2009. In Southern California, a 0.3% prevalence was reported from 2002 to 2004. In the Los Angeles County blood bank, confirmed seroreactivity for *T. cruzi* was found to be 0.1%<sup>21-24</sup>.

In most Brazilian states, death from TBI is decreasing while death from stroke is increasing among deceased donors<sup>25</sup>. This is likely due to Law No. 11,705 (Dry Law), which has resulted in fewer fatal traffic accidents<sup>25,26</sup>. Despite a 6.2% reduction in automobile accidents, Fusco *et al.*<sup>27</sup> found that TBI continues to be the leading cause of death among deceased donors in Ceará<sup>27</sup>.

In the present study, cerebrovascular events were the primary cause of death for deceased donors with positive or inconclusive CD serology. Stroke is a well-described complication of CD, and the immunopathogenic mechanisms of the disease have been linked to stroke and death. Aortic aneurysms are associated with higher incidences of embolism, although further studies are needed to understand this connection<sup>28-30</sup>.

Similarly, mural thromboses may be present in areas without symptomatic manifestations, and the resulting embolic event is then the first, and sometimes only, presentation of the disease. A recent meta-analysis has shown that CD doubles the risk of stroke. Due to the retrospective nature of this study, whether the stroke was caused by CD in these individuals cannot be determined<sup>28-30</sup>.

In the present study, many individuals had other infections in addition to CD (n = 7; 25%), including cytomegalovirus, toxoplasmosis hepatitis B and C. The likelihood of *T. cruzi* infection depends on the recipient's immune system; therefore, the use of immunosuppressants in potentially infected recipients is a matter of concern. *T. cruzi*/HIV coinfection has been widely discussed. The lower survival rate of individuals with coinfection is related to the presence of reactivation of CD and the natural complications of both diseases<sup>31</sup>. The role of antiretroviral treatment in the evolution of the patient with coinfection has not yet been defined. Quantification of the parasite burden from other infections in both the donor and recipient can help prevent or at least detect the infection, thereby allowing for early treatment that improves patient outcome. This would be beneficial in both endemic and non-endemic countries<sup>32,33</sup>.

In 2009, Decree No. 2,600 approved the Technical Regulation of the National Transplantation System and required mandatory screening for *T. cruzi* infection in Brazil using a high-sensitivity test<sup>34</sup>. For this study, an enzyme-linked immunosorbent assay (ELISA) was used for the serological screening for CD. All organs from potential donors with reactive or inconclusive serology for CD were considered unfit for donation and discarded. It was not possible to obtain data on the prevalence of *T. cruzi* infection in organ recipient candidates and their serological profiles, which represents a limitation of this study.

More studies are needed to address the post-transplant follow-up of non-CD-infected individuals who received organs from CD-infected donors and of CD-infected recipients who received organs from non-CD-infected donors towards evaluating the process of disease reactivation and patient outcome.

In summary, there was a high prevalence of CD and other coinfections among potential solid organ donors in the State of Ceará and the primary cause of death of deceased donors reactive for *T. cruzi* was stroke. This work highlights the importance of screening potential donors for CD.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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