Amerindian genetic ancestry is associated with higher survival rates compared to African and European ancestry in Brazilian patients with heart failure ☆

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To the Editor:

Heart failure (HF) is a chronic limiting disease associated with high morbidity and mortality [1–2]. Several clinical and laboratory variables have been recognized as associated with the prognosis, morbidity and mortality of patients with heart failure, including patients' ethnicity [3–4].

The evaluation of the association between self-declared skin color with complex diseases, such as HF, may be challenging because of the heterogeneity within ethnic groups, especially in countries like Brazil where there is a large admixture. Thus, the estimated genomic ancestry of a population or individual, with the use of autosomal ancestry informative markers (AIMs) and mitochondrial haplogroups (mt-haplogroups), may provide a more accurate prediction of the ethnic-associated genetic risk factors that influence health and disease [5–7].

The aim of the present study was to examine the association between genetic ancestry, estimated by autosomal ancestry informative markers and mitochondrial DNA (mtDNA), with the survival rate of 503 patients with heart failure.

A cross-sectional study was performed in 503 patients with heart failure from the Public Health System (SUS), belonging to the healthcare program developed by the Heart Institute of the Medical School, University of São Paulo. The patients were clinically followed up for four years or until death or heart transplantation. The research protocol was approved by the Ethics Committee of the Clinical Hospital of the Medical School, University of São Paulo, and all participants signed an informed consent.

The mtDNA analysis for the composition of haplotypes (sequences) and mt-haplogroup classification was realized in the control region of mtDNA [8].

The mtDNA sequence data reported in this paper has been deposited in the NCBI GenBank database under accession numbers: KC676330–KC676585 and KC688421–KC688674.

The evaluation of genomic ancestry was conducted using 48 biallelic ancestry informative markers (AIMs) (16 markers of African ancestry, 16 of European ancestry, and 16 of Amerindian ancestry) type insertion–deletion (INDEL) from autosomal chromosomes [8–9].

For establishing the association between mitochondrial haplogroups and survival, Kaplan–Meier curves were constructed and compared through the log rank test. Cox's proportional hazards regression model, Gehan–Breslow test and Tarone–Ware test were used to evaluate the effect of independent predictors of patient survival.

For genomic ancestry, association with survival was determined using univariate and multivariate analysis, with the Cox proportional hazards regression model. All statistical analyses were carried out using SPSS software (version 16.0, IBM, New York, NY), with the level of significance set at $p \leq 0.05$.

Of the 503 patients with heart failure evaluated in this study, the mean age was 58 years (SD = ±14.4 years) and the majority were male (59.6%, n = 300). The majority of patients self-declared as white (73.4%, n = 369), followed by brown (13.5%, n = 68) and black (10.5%, n = 53).

The analysis of mtDNA showed that the African mt-haplogroups were the most prevalent (n = 234, 46.4%) followed by Amerindian (n = 142, 28.2%), and European mt-haplogroups (n = 127, 25.4%). From the analysis of 48 INDELs, the major contribution of autosomal genomic ancestry was the European, 57.4% (±22.2%), followed by the African, 28.4% (±21.7%) and fewer from the Amerindian, 14.1% (±10%).

At the end of four years of evaluation, 50.3% (n = 253) of the patients had died. Duration of follow-up of the patients from the time of enrollment until death or last contact was 3.8 years (mean 1401 days, ±207 days).

The probability of survival of patients relative to autosomal genomic ancestries showed higher survival for patients with a higher contribution of Amerindian genomic ancestry (p = 0.004 [OR 0.13 {0.03–0.52}]), (Table 1). These data remained statistically significant after adjusting for age, sex, left ventricular ejection fraction, self-declared ethnicity, cause of heart failure, and mt-haplogroups (Table 2).

This finding is particularly relevant since the information about the Amerindian genetic background is not usually retrieved by the

Table 1
Prognosis of patients with heart failure relative to autosomal genomic ancestry.

Genomic ancestry	p-Value	Odds ratio (95% confidence interval)
Amerindian	**0.004**	**0.13 (0.03–0.52)**
European	0.653	1.15 (0.63–2.10)
African	0.313	1.36 (0.75–2.48)

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Table 2
Variables associated with prognosis in patients with heart failure in relation to Amerindian autosomal genomic ancestry.

Variables	p-Value	Odds ratio
Amerindian ancestry	**0.003**	**0.09 (0.02–0.44)**
Age	0.001	1.02 (1.01–1.77)
Sex	0.782	0.96 (0.71–1.29)
Ejection fraction	0.001	0.98 (0.97–0.99)
Self-declared ethnicity		
White	0.195	1.15 (0.93–1.44)
Brown	0.540	1.07 (0.87–1.32)
Black	0.524	1.21 (0.67–2.20)
Etiology		
Chagas' heart disease	0.099	0.22 (0.03–2.25)
Idiopathic	0.204	1.55 (0.79–3.07)
Hypertensive	0.655	0.84 (0.40–1.78)
Ischemic	0.308	0.71 (0.37–1.37)
Valvular	0.473	1.27 (0.66–2.41)
Other	0.311	1.41 (0.72–2.76)
mt-haplogroups		
African	0.521	1.06 (0.89–1.27)
Amerindian	0.481	0.89 (0.63–1.24)
European	0.745	0.86 (0.34–2.17)

The bold data indicates the parameter with statistical significancy.

standard self-referred questions about ethnicity [8]. In fact, for a mixed population, such as the Brazilian, genetic determination of autosomal ancestry may be the best technique to unveil this characteristic associated with better prognosis.

Some recent studies, which also used AIMs, demonstrated/suggested that the genomic Amerindian ancestry may be protective against hypertension in women from the United States [10], protective against metabolic syndrome in the population of Costa Rica [11] and protective against Alzheimer's disease in Brazilian population [12]. Furthermore, recent studies in the Brazilian population showed that Amerindian individuals had lesser arterial stiffness and hypertension [13–14]. These studies suggest that lower risk of diseases studied in individuals with Amerindian ancestry may be due to the existence of protective genetic factors associated with this ancestry.

In conclusion, our study found that individuals with a higher contribution of Amerindian ancestry had higher survival rates in Brazilian patients with heart failure. We were not able to find previous reports of the main findings of our study. If such findings are confirmed, operative mechanisms deserve further research. We added data to substantiate the hypothesis that differences in ethnic backgrounds may be a significant issue in epidemiological studies and may help to better understand complex diseases like heart failure.

There is no conflict of interest.

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