

## Authors Reply

# Letters to the Editor: Indeterminate form of Chagas Disease: some immunological insights

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We appreciate the letter to the editor of Matos et al.. The authors present their experience in evaluating the role of CD14+/HLA-DRlow/- monocytes and CD4+ and CD8+ T lymphocytes in various clinical forms of chronic Chagas disease<sup>1</sup>.

First, I would like to emphasize that patients with asymptomatic Chagas disease do not necessarily have the indeterminate form, as there are asymptomatic patients among those in the initial stages of the cardiac form. Therefore, we prefer to use the term clinical progression to identify the transition from indeterminate form to cardiac form<sup>2</sup>.

When evaluating the clinical progression of patients in the indeterminate form, it is important to consider whether they were previously treated with trypanocidal drugs. There is a significant difference in progression rates from indeterminate form to cardiac form between treated and untreated patients<sup>3</sup>. All patients included in the data presented by Matos et al. had a history of previous treatment with benznidazole, which can improve the functional capacity of CD8+ and CD4+ T cells<sup>4</sup> and influence their results of similar quantification of CD4+/CD8+ T lymphocytes across different forms of Chagas disease.

Another relevant aspect of this discussion is the fact that only through prospective studies, where long-term follow-up of individuals is carried out, it is possible to correlate the findings with the clinical forms of the disease<sup>5,6</sup>. Cross-sectional studies do not allow us to infer cause-effect relationships, but plausible hypotheses may be raised. Few studies have evaluated the prognostic value of biomarkers over time, including but not limited to BNP, transforming growth factor  $\beta$ 1, and metalloproteinase<sup>7-9</sup>. To the best of our knowledge, no study has evaluated the long-term prognostic value of the quantification of CD4+/CD8+ T lymphocytes. With only long-term follow-up studies, we will be able to infer a role for innate

immunity, represented by macrophages and neutrophils, dendritic cells, and natural killer lymphocytes; and for adaptive immunity by B lymphocytes and T lymphocytes<sup>10</sup> in the clinical progression of the cardiac form of the disease.

### REFERENCES

1. Viana CEM, Matos DM, Oliveira M de F, da Costa AC, Filho TP de A, Filho PAM, et al. Immunosuppressive CD14+/HLA-DRlow/- monocytes in patients with Chagas Disease. *Acta Tropica*. 2021;224:106154.
2. Hasslocher-Moreno AM, Salles Xavier S, Magalhães Saraiva R, Conde Sangenis LH, Teixeira de Holanda M, Horta Veloso H, et al. Progression Rate from the Indeterminate Form to the Cardiac Form in Patients with Chronic Chagas Disease: Twenty-Two-Year Follow-Up in a Brazilian Urban Cohort. *Trop Med Infect Dis*. 2020;5(2):1-5.
3. Hasslocher-Moreno AM, Saraiva RM, Sangenis LHC, Xavier SS, de Sousa AS, Costa AR, et al. Benznidazole decreases the risk of chronic Chagas disease progression and cardiovascular events: A long-term follow up study. *EClinicalMedicine*. 2021;31:100694.
4. Pérez-Antón E, Egui A, Thomas MC, Carrilero B, Simón M, López-Ruz MÁ, et al. A proportion of CD4+ T cells from patients with chronic Chagas disease undergo a dysfunctional process, which is partially reversed by benznidazole treatment. *Santiago H da C, editor. PLoS Negl Trop Dis*. 2021;15(2):e0009059.
5. Nielebock MAP, de Freitas Campos Miranda L, Americano do Brasil PEA, de Jesus S, Pereira TO, da Silva AF, Hasslocher-Moreno AM, et al. Blood culture positivity rate for *Trypanosoma cruzi* in patients with chronic Chagas disease differs among different clinical forms. *Trans R Soc Trop Med Hyg*. 2021;115(6):720-5.
6. Nielebock MAP, Moreira OC, Xavier SC das C, Miranda L de FC, Lima ACB de, Pereira TO de JS, et al. Association between *Trypanosoma cruzi* DTU TcII and chronic Chagas disease clinical presentation and outcome in an urban cohort in Brazil. *Herrera CP, editor. PLoS ONE*. 2020;15(12):e0243008.

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7. Heringer-Walther S. Brain natriuretic peptide predicts survival in Chagas' disease more effectively than atrial natriuretic peptide. *Heart*. 2005;91(3):385-7.
8. Saraiva RM, Waghbi MC, Vilela MF, Madeira FS, da Silva GMS, Xavier SS, et al. Predictive value of transforming growth factor- $\beta$ 1 in Chagas disease: towards a biomarker surrogate of clinical outcome. *Trans R Soc Trop Med Hyg*. 2013;107(8):518-25.
9. Sherbuk JE, Okamoto EE, Marks MA, Fortuny E, Clark EH, Galdos-Cardenas G, et al. Biomarkers and Mortality in Severe Chagas Cardiomyopathy. *Glob Heart*. 2015;10(3):173-80.
10. Acevedo GR, Girard MC, Gómez KA. The Unsolved Jigsaw Puzzle of the Immune Response in Chagas Disease. *Front Immunol*. 2018;9:1929.

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