Renin-Angiotensin-Aldosterone System (RAAS) and clinical outcomes in COVID-19 patients in south Brazil

Bibiana S. O. Fam[1,3], Nathan A. Cadore[1,3], Renan Sbruzzi[1,3], Marilea F. Feira[1,3], Giovanna C. Giudicelli[4], Alexandre C. Pereira[5], Lygia V. Pereira[2,6], Tábita Hünemeier[2,7], Fernanda S. L. Vianna[1,3]

[1]Laboratory of Genomic Medicine, Center of Experimental Research, HCPA, Porto Alegre, RS, Brazil;[2]Department of Genetics and Evolutionary Biology, Institute of Biosciences, USP, São Paulo, SP, Brazil; [3]Laboratory of Immunobiology and Immunogenetics, Graduate Program in Genetics and Molecular Biology, Department of Genetics, Institute of Biosciences, UFRGS, Porto Alegre, RS, Brazil; [4]Bioinformatics Core, HCPA, Porto Alegre, RS, Brazil; [5]Heart Institute, University of São Paulo Medical School, São Paulo, SP, Brazil; [6]National Laboratory of Embryonic Stem Cells, USP, São Paulo, SP, Brazil; [7]Laboratory of Human Population Genomics, USP, São Paulo, SP, Brazil.

INTRODUCTION

The Renin-Angiotensin-Aldosterone System (RAAS) regulates cardiovascular and inflammatory homeostasis and plays a key role in COVID-19 pathophysiology, since ACE2 acts as the entry receptor for SARS-CoV-2 (Figure 1). Thus, genetic variants in RAAS genes may modulate individual susceptibility and clinical severity.

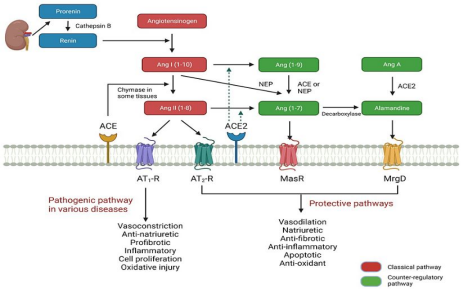
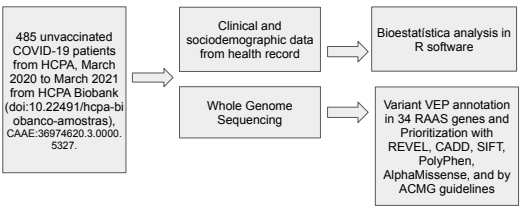


Figure 1. RAAS pathway (modified from Kanugula eta al., 2023)

OBJECTIVES

Investigate the genetic variability of RAS genes in an admixed population from southern Brazil diagnosed with COVID-19, and identify rare and/or pathogenic variants potentially associated with severe outcomes such as ICU admission, kidney or cardiovascular complications, thromboembolism, and death.

MATERIAL AND METHODS



RESULTS AND DISCUSSION

The cohort was 59% male, with a mean age of 51 years, predominantly White (81.2%). Severe outcomes were frequent (Figure 2.a) and, in age-, sex–adjusted models, hypertension (OR 4.45, 95% CI 2.75-7.36), diabetes (OR 3.54, 2.22-5.66), and CKD (OR 2.58, 1.38-4.72) were associated with higher odds of death, whereas obesity and immunodeficiencies did not reach statistical significance (Figure 2.b).

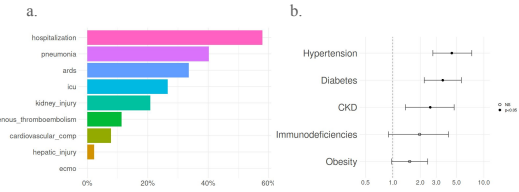


Figure 2. Clinical outcomes and mortality risk by comorbidity in the COVID-19 cohort (n=485). (a) Prevalence of clinical outcomes in the overall cohort (outcomes are not mutually exclusive). (b) Plot of age and sex adjusted odds ratios (OR) for death by baseline comorbidity, points show aOR and horizontal lines 95% CI.

WGS identified 38,684 38,684 RAAS variants, mostly intronic SNVs (86.2%, Figure 3a). Among missense variants annotated with REVEL (n=246), 22 (8.9%) were likely deleterious and 13 (5.3%) were deleterious (≥0.75) (Figure 3b). Overall, 4,343 variants (11.2%) were novel, of which 1,415 were predicted as high-impact by at least one in silico predictor (REVEL>0.5, CADD>20, AlphaMissense>0.5). Pathogenic/likely pathogenic variants in *ACE*, *AGTR1* , *HSD17B3*, or *SLC6A19*, and predicted recurred deleterious VUS in *ACE2, CYP19A1, KNG1,* and *NR3C2,* were identified among severe cases and 4.2% deceased individuals.

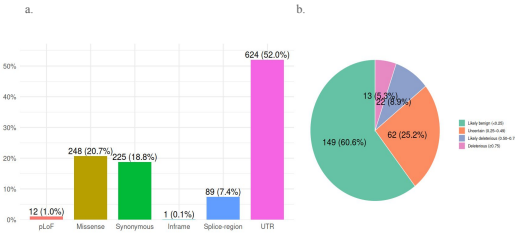


Figure 3. (a) Distribution of variant consequences in RAAS variants, bars show proportion and counts, and (b) REVEL categories for missense variants (<0.25, 0.25–0.49, 0.50–0.74, ≥0.75). Labels indicate n (%).

Rare, high-impact RAAS variants were identified in severe COVID-19, suggesting they may contribute to disease susceptibility and adverse outcomes. Highlighting the potential for risk stratification and personalized management during pandemics, especially in genetically diverse populations.

CONCLUSIONS AND PERSPECTIVES

Potentially deleterious RAAS variants were found in COVID-19 patients from southern Brazil. Ongoing analyses expanding to broader gene networks and clinical outcomes will help clarify their role in disease progression and genomic medicine.

Acknowledgment