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Carrying *APOL1* G1 allele is associated with cardiovascular complications during COVID–19 in an admixed population

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Abstract

Background The *APOL1* G1 and G2 alleles were selected in the Sub-Saharan African population by conferring resistance to trypanosome infection. However, these alleles are associated with kidney diseases, and their role in cardiovascular complications remains uncertain. A second hit mediated by an inflammatory state is necessary for *APOL1*-mediated phenotypes. Thus, this cross-sectional study investigates the association of *APOL1* alleles with COVID-19 outcomes such as cardiovascular complications and kidney injury in an admixed population. Whole-genome sequencing was performed for 485 patients with different outcomes from a Biobank in Southern Brazil.

Results COVID-19 individuals presented median age of 51 years, 281 were hospitalized, and 10.9% had CKD previous to the infection. Global ancestry inference revealed 12.8% of African ancestry. The G1 allele frequency was 2.7% and G2 allele was 1.2%. Local ancestry inference evidenced African ancestry in the locus of *APOL1* alleles. The G1 allele frequency was higher among patients with severe outcomes. The presence of this allele was associated with kidney injury (OR = 2.78; 95% CI = 1.04-7.42; p = 0.041) using a minimally adjusted model and cardiovascular complications with a minimally (OR = 4.61; 95% CI = 1.61-13.19; p = 0.004) and fully adjusted model (OR = 4.59; 95% CI = 1.41-14.96; p = 0.011). Four individuals carried two alleles (three G1/G1 and one G1/G2) and three of them progressed to severe COVID-19 developing kidney injury.

Conclusion *APOL1* risk alleles are present in the Brazilian population due to genetic admixture and the G1 allele was associated with COVID-19 outcomes.

Keywords SARS-CoV-2 infection, Clinical outcomes, Human genetics, Risk alleles, Chronic kidney disease, Admixed population, Brazilian population

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Background

The apolipoproteins L 1 *(APOL1)*, encoded by the *APOL1* gene, is an innate immune effector responsible for combating infectious diseases caused by trypanosoma parasites [1]. Two alleles of *APOL1*, referred to as G1 and G2, defined by variants in the serum resistance-associated protein (SRA)-interacting domain, have been selected in sub-Saharan African populations likely due to increased resistance to *Trypanosoma brucei* subspecies infections with the highest frequencies observed in Ghana and Nigeria for alleles G1 (>40%) and G2 (6–24%) [2]. Currently, these alleles are strongly associated with kidney disease risk among individuals of sub-Saharan African ancestry [3]. The impact of carrying two *APOL1* risk alleles (classified as high-risk genotypes) is well established, and recent findings suggest that even a single allele may increase susceptibility to chronic kidney disease (CKD) [4]. These risk alleles were identified as the major determinant of HIV-associated nephropathy in the African-descendent population, in which high-risk genotype individuals had 89-fold higher odds for CKD [5, 6]. The activation of different innate immune pathways and type 1 interferon (IFN) signaling have been shown to upregulate *APOL1* and drive *APOL1*-mediated kidney diseases [7–9]. These findings and the high *APOL1* association with nephropathies, especially in the context of infection, led to the postulation of a 'second hit' necessity to the effect of the risk allele on the kidney damage [10]. Likely, an environmental trigger that led to IFN signaling is important to the *APOL1* risk alleles in kidney injury [10, 11]. Then, it is substantial to understand the association between *APOL1*-mediated phenotypes under an enhanced inflammatory response. Importantly, the association of *APOL1* risk alleles with other phenotypes, such as cardiac disease, is still controversial [12–15].

Severe COVID-19 is a systemic disorder caused by exacerbated inflammatory activation and physiological imbalance, which may trigger a cytokine storm, acute respiratory distress syndrome (ARDS), and multiple organ failure [16, 17]. Cohort studies have identified risk factors predisposing to severe COVID-19 such as advanced age, hypertension, and diabetes [18, 19]. Moreover, human genetic variability has been reported as an important biological aspect of COVID-19 outcomes [20, 21]. During hospitalization, COVID-19 patients may present a cytokine storm characterized by intense systemic release of inflammatory molecules due to the infection that promotes vascular permeability, disseminated intravascular coagulation, and immune infiltration [22]. These events result in tissue damage and organ dysfunction, such as acute kidney injury (AKI) and cardiovascular complications, especially myocardial injury [23–27]. Notably, two risk alleles were identified to confer a higher predisposition to AKI during COVID-19 hospitalization in Black Americans [28], which conveys the idea of SARS-CoV-2 as a second hit of *APOL1*-mediated kidney injury. However, no study identified other complications associated with *APOL1* risk alleles.

Few studies have been conducted to describe the effect of *APOL1* risk alleles in overall admixed populations [29]. A recent genomic study conducted in Brazil showed that among 70 children and adults with idiopathic collapsing glomerulopathy, 33 had high-risk genotypes [30]. Another study with Brazilian individuals with self-reported African ancestry identified high-risk genotypes associated with a 10 times higher risk of end-stage kidney disease and the initiation of dialysis 12 years earlier [31]. Again, this studies focused on kidney phenotypes only. Thus, given their public health impact, investigating the prevalence and clinical associations of G1 and G2 alleles in admixed populations is essential for advancing precision medicine and informing public healthcare policies [32]. Here, we investigated the prevalence of *APOL1* G1 and G2 risk alleles and the association between these alleles with COVID-19 complications in 485 individuals in a southern Brazilian population. Although a high European ancestry was observed, the G1 and G2 alleles remained prevalent in this population. Finally, we identified the association of one risk allele with cardiovascular complications during COVID-19 independently of CKD.

Methods

COVID-19 cohort: samples and data collection

Participants aged 18 years or older with a positive PCR test for COVID-19 at the Hospital de Clínicas de Porto Alegre were included. DNA samples were obtained from the Biobank of the Hospital de Clínicas de Porto Alegre (doi:https://doi.org/10.22491/hcpa-biobanco-amostras). DNA was extracted from whole blood using FlexiGene DNA Kit (QIAGEN), quantified by Qubit™ fluorometric quantification (Thermo Fisher Scientific), and purity accessed by NanoDrop™ One Microvolume UV-Vis Spectrophotometer (Thermo Fisher Scientific). This was a convenience sample based on the availability of recruitment from the hospital's Biobank. The cohort was prospected aiming to reach 200 individuals who had mild COVID-19 and 300 hospitalized individuals, of which 100 died due to COVID-19. All were Brazilians living in Southern Brazil. The demographic, clinical, and Brazilian Institute of Geography and Statistics' (IBGE) ethno-racial categories information was obtained from individuals' medical records and questionnaires. Patients undergoing neoplasia treatment, HIV carriers, and organ transplant recipients were classified as immunodeficient. Patients who required oxygen support > 6 L/min or invasive ventilation were classified as severe COVID-19 [33, 34]. AKI was considered when doctor-diagnosed acute kidney injury (AKI), highest creatinine greater than 1.5 times the

upper limit of normal (ULN), or ICD-10 codes for AKI (N17*). Cardiovascular complications were defined by at least one of the following: doctor-diagnosed acute myocardial infarction (AMI) or stroke, highest troponin T or troponin I greater than ULN, or ICD-10 codes for AMI or stroke (I21*, I61, I62, I63, I64, I65, I66*).

Whole-genome sequencing and data processing

The samples are part of the DNA do Brasil consortium [35]. Whole-genome sequencing was performed on the NovaSeq Illumina® platform. All samples were sequenced at high-coverage (on average 35X). Data was processed according to the guidelines of the American Association for Medical Informatics and the Association for Molecular Pathology [36]. The sequencing data was demultiplexed to obtain .fastq files for individual samples. After removing the adapters, the quality score of the.fastq files was verified. The reads were mapped with the reference human genome GRCh38 (hg38) to obtain the binary BAM file. A pre-processing of variants was carried out, obtaining the processed BAM file, which also underwent quality control. The variants were called, obtaining the. vcf file, which was used for filtering and prioritization of variants. The .vcf file was used to verify the presence of the G1 and G2 alleles in *APOL1* on chromosome 22. The workflow was developed using the GATK [37], BCFtools [38], and VCFtools [39] tools.

Ancestry analysis

The inference of the haplotypic phase from genomic data was obtained with ShapeIT4 (Segmented HAPlotype Estimation and Imputation Tools version 4) [40], using the 1000 Genomes Project data [41] as a reference panel, including African, European, and Native American continental populations. Principal Component Analysis was performed with *SNPrelate* R package, including all continental populations with a set of SNPs from the Axiom™ Genome-Wide Human Origins (Thermo Fisher Scientific) SNPs panel after an LD-pruning (variants with a pairwise correlation above 20% in a genomic window of 500Kb were removed). We then inferred local ancestry using GNOMIX [42]. GNOMIX uses a data-driven machine learning approach to directly model the correlation structure among populations and the distribution of recombination sites. The global ancestry of each individual was obtained by considering the average local ancestry of the whole genome.

Statistical analyses

The comparisons between groups were performed using Pearson's $\chi 2$ test and Fisher's exact tests for categorical variables or linear model test for continuous variables. The outcomes were compared with the presence of G1 and G2 alleles and clinical characteristics. The risk effect of the G1 allele (using 0 for allele absence and 1 for allele presence) on the COVID-19 clinical outcomes and comorbidities, odds ratios (OR), and 95% confidence interval (95% CI) were calculated with logistic regression analysis. Three models were considered for analysis: (1) a minimally adjusted model considering demographic variables (age, gender, and obesity) and CKD; (2) the minimally adjusted model including the first two principal components (PCs); (3) a fully adjusted model including age, gender, obesity, diabetes, hypertension, immunodeficiency, CKD, PC1, and PC2. No clinical or demographic data were considered missing, as all information was collected from medical records and questionnaires administered. All analyses were performed using the Statistical Package for the Social Sciences software, version 20.0 (SPSS Inc., Chicago, USA) and R software (R core team).

Results

COVID-19 hospitalization includes multi-systemic manifestations

A total of 485 COVID-19-positive individuals were included and presented a median age of 51 years, 258 (81.1%) were categorized as white, and 59 (12.2%) as black, according to IBGE classifications. Among these individuals, 281 (57.9%) were hospitalized due to COVID-19 and 167 were classified as severe COVID-19, comprising 34.4% of the whole cohort. Hospitalized patients showed a wide spectrum of clinical manifestations. Of the 281 hospitalized patients, 55.2% presented co-infections, 35.9% AKI, 19.6% venous thromboembolism (VTE), and 13.5% cardiovascular complications during hospitalization (Table 1).

APOL1 G1 and G2 risk alleles are frequent in the admixed population of Southern Brazil

Ancestry proportion was estimated for all individuals to investigate the composition of the genetic ancestry of the cohort composed by the population from Southern Brazil. The cohort was composed mainly of European ancestry (76.8%), followed by African (12.8%), and Native American (10.4%). Even though the cohort presented a high European ancestry contribution, there were heterogeneous admixture profiles considering the ancestry percentages among individuals (Fig. 1A). African ancestry was higher among hospitalized (16.3%), compared to non-hospitalized individuals (7.77%; $p < 0.001$). Among COVID–19 hospitalized patients, African ancestry was slightly higher but not significant among patients with AKI (18.2%) compared to those who did not present the damage (15.21%; $p = 0.517$). However, the African ancestry proportion was similar among patients who did not develop cardiovascular complications (16.2%) compared to those who developed (16.8%; $p = 0.616$).

Table 1 Clinical and demographic characterization of the COVID−19 cohort

	Non-hospitalized (*n* = 204)	Hospitalized (*n* = 281)	COVID-19 cohort (*n* = 485)	*p*-value
Age, median [IQR]	41 [31, 50]	60 [48, 71.5]	51 [38, 64]	< 0.001
White, *n* (%)	168 (82.4)	226 (80.4)	394 (81.2)	0.592
Black, *n* (%)	13 (6.4)	46 (16.4)	59 (12.2)	0.001
Men, *n* (%)	55 (27.0)	141 (50.2)	195 (40.2)	< 0.001
Obesity, *n* (%)	54 (26.5)	119 (42.3)	173 (35.7)	< 0.001
Diabetes, *n* (%)	8 (3.9)	122 (43.4)	130 (26.8)	< 0.001
Hypertension, *n* (%)	40 (19.6)	171 (60.9)	211 (31.8)	< 0.001
Chronic Diseases[A], *n* (%)	77 (37.7)	124 (44.1)	201 (41.4)	0.159
Chronic Kidney Disease, *n* (%)	2 (1.0)	51 (18.1)	53 (10.9)	< 0.001
Immunodeficiencies[B], *n* (%)	1 (0.5)	35 (12.5)	36 (7.4)	< 0.001
Severe COVID-19, *n* (%)	-	167 (59.4)	167 (34.4)	
ICU, *n* (%)	-	127 (45.2)	127 (26.2)	
ARDS, *n* (%)	-	163 (58.0)	163 (33.6)	
Co-infections, *n* (%)	-	154 (54.8)	155 (32.0)	
AKI, *n* (%)	-	101 (35.9)	101 (20.8)	
VTE, *n* (%)	-	54 (19.2)	54 (11.1)	
Cardiovascular complications, *n* (%)	-	38 (13.5)	38 (7.8)	
Hepatic injury, *n* (%)	-	11 (3.9)	11 (2.3)	
Deceased, *n* (%)	-	96 (34.2)	96 (19.8)	

IQR: interquartile range; ICU: intensive care unit; ARDS: acute respiratory distress syndrome; AKI: acute kidney injury; VTE: venous thromboembolism; [A]Cardiac, pulmonary, neurological, and rheumatic; [B]Ongoing neoplasia treatment, HIV carriers, transplanted patients

Global ancestry proportions of patients carrying two risk alleles are shown in Fig. 1B. Local ancestry of the 22q chromosome was carefully surveyed to determine the genetic ancestry of the G1 and G2 alleles in the Brazilian cohort. Among the risk allele carriers, the African local ancestry of the 22q chromosome was higher along the genomic region than in the whole genome. The mean local African ancestry was 54.5%, while the genomic mean was 39.8%, indicating an increase of 14.7% in local ancestry compared to the genomic mean. Also, the analysis for the individuals carrying two risk alleles confirmed the African ancestry for loci encompassing the alleles (Fig. 1C).

APOL1 risk allele G1 is associated with worse COVID−19 outcomes

The influence of *APOL1* risk alleles on clinical outcomes and severity of COVID-19 was investigated. A total of 451 individuals did not carry any risk alleles (referred as G0), while 19 individuals were G1/G0, 11 G2/G0, three G1/G1, and one individual G1/G2. *APOL1* p.N264K variant was found heterozygous in only one G0/G0 individual. Notably, all four individuals carrying two risk alleles (G1/G1 or G1/G2) were hospitalized due to COVID-19. The G1 allele frequency was 2.7% and G2 was 1.2%. In the cohort, the low number of G2 alleles hindered statistical comparisons considering the different groups of COVID-19 outcomes. Therefore, the presence of only one risk allele (G1) was considered to conduct the following analyses. The allele frequencies of G1 were compared between COVID-19 severity and clinical outcomes (Table 2 and Supplementary Table 1).

APOL1 G1 allele is associated with cardiovascular complications during COVID-19 hospitalization

First, the effect of *APOL1* G1 was investigated on COVID-19 comorbidities. The G1 allele was associated with hypertension (OR = 2.55; 95% CI = 1.06–6.12; $p = 0.037$) and CKD (OR = 3.12; 95% CI = 1.17–8.29; $p = 0.023$) prior to SARS-CoV-2 infection. The associations with hypertension (OR = 1.59; 95% CI = 0.62–4.04; $p = 0.334$) and CKD (OR = 2.09; 95% CI = 0.72–6.06; $p = 0.177$) do not remain significant after adjusting by PCs.

Second, the influence of *APOL1* G1 was investigated regarding the COVID-19 complications (Table 3). The allele G1 was associated with AKI (OR = 2.78; 95% CI = 1.04–7.42; $p = 0.041$) when considering a minimally adjusted model by gender, age, obesity, and CKD. When PCs were added to the model, AKI did not statistically correlate with *APOL1* G1 allele (OR = 2.19; 95% CI = 0.76–6.31; $p = 0.145$). Also, a fully adjusted model by age, gender, obesity, PCs, diabetes, hypertension, immunodeficiency, and CKD did not show an association between kidney injury and the *APOL1* G1 allele (OR = 2.10; 95% CI = 0.72–6.18; $p = 0.176$).

Cardiovascular complication during COVID-19 hospitalization was also associated with the *APOL1* G1 allele (OR = 4.61; 95% CI = 1.61–13.19; $p = 0.004$), considering the minimally adjusted model. After the adjustment with PCs, the minimally adjusted model maintains the statistical significance (OR = 4.78; 95% CI = 1.49–15.36; $p = 0.009$). Moreover, the fully adjusted model shows a higher predisposition to cardiovascular complications among individuals carrying one *APOL1* G1 allele (OR = 4.59; 95% CI = 1.41–14.96; $p = 0.011$).

Furthermore, in order to provide a better understanding of the role of risk alleles in the clinical outcomes of COVID-19, patients carrying two risk alleles were assessed individually, and the cases are described in Table 4. Two individuals were described as white in medical records IBGE categories, including Patient 2, who had CKD and a history of kidney transplantation before COVID-19. Patients 1, 3, and 4 presented severe COVID-19 (requiring ventilation support) and developed both AKI and cardiovascular complications during hospitalization. It is important to highlight that patient 3 did not

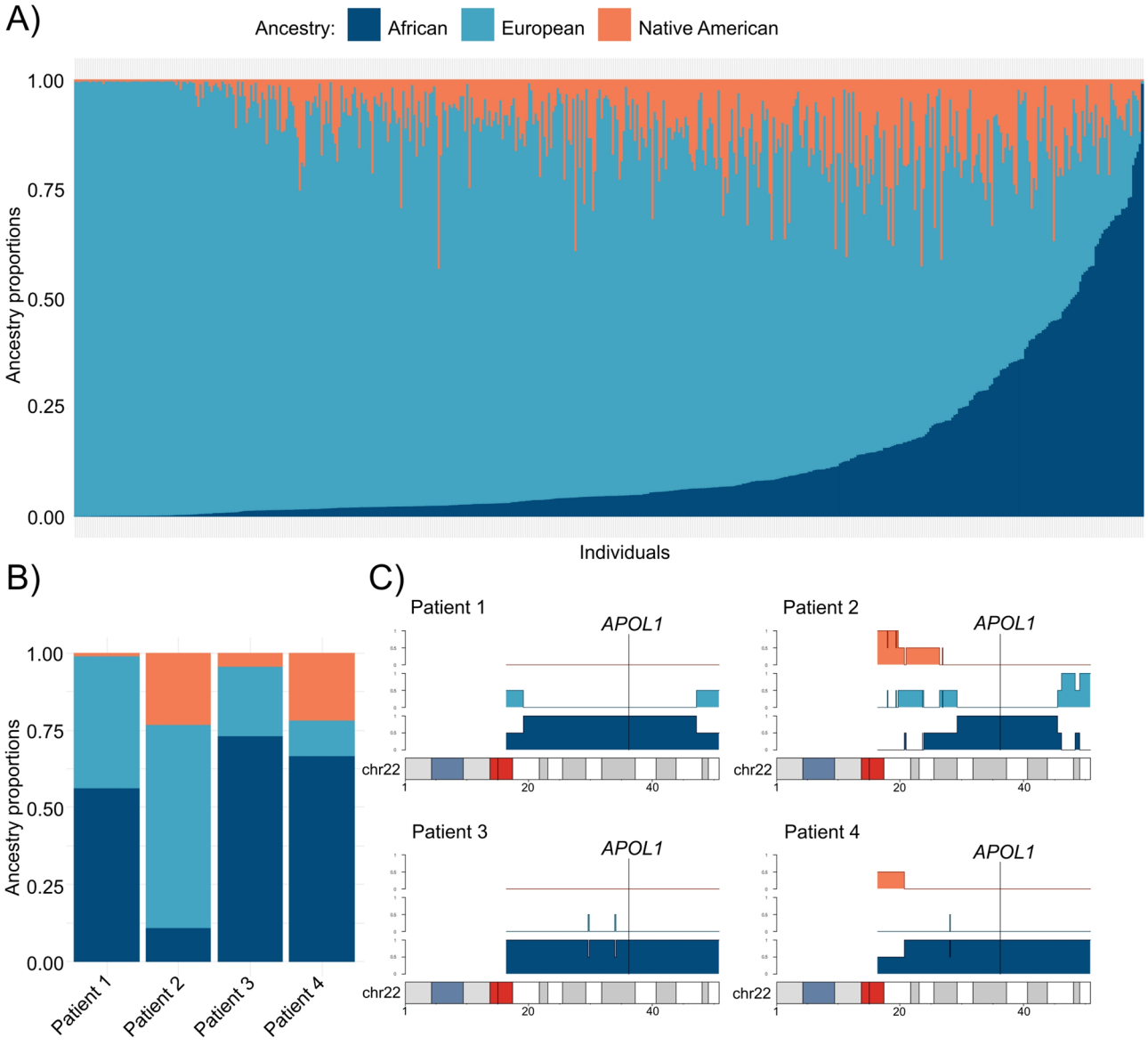

Fig. 1 Ancestry inferences of the COVID-19 cohort. **A**) Global ancestry proportions for all COVID-19 cohort individuals. We phased the dataset with SHAPEIT4 and inferred local ancestry using GNOMIX. The plot represents the averages per individual. **B**) Global ancestry analysis in individuals carrying high-risk genotypes (G1/G1 or G1/G2). **C**) Local ancestry analysis of the q arm of chromosome 22 for the individuals carrying G1/G1 or G1/G2 genotypes. The x-axis represents the genomic positions in Mb, the red indicates the centromeres, and other colors represent the chromosome banding

have pre-existing renal disease before COVID-19; however, she required hemodialysis during COVID-19 hospitalization. Only patient 1 died due to the infection.

Discussion

Here, we described the frequencies of *APOL1* risk alleles G1 and G2 in a southern Brazilian population and found an association of the G1 allele with cardiovascular complications during COVID-19 hospitalization. Studies have shown the impact of the *APOL1* risk alleles in COVID-19 clinical outcomes, especially AKI [28, 43, 44]. However, the studies have evaluated risk alleles mainly among black individuals, and little is known about the *APOL1* risk alleles in an admixed population, including different ethnicities. Also, despite the advancements in kidney genomics, Latin America is among the underrepresented regions regarding genomic studies, which implies global health inequities and hampers accurate variant interpretation [45]. In addition, the effect of only one *APOL1* risk allele (a dominant model) and the relation with cardiovascular diseases still need to be elucidated.

The genetic ancestry inference showed a higher proportion of European, followed by African, and Native American ancestral components, which are consistent with previous studies, especially in the inferences with south Brazilian groups. The Brazilian genetic admixture

Table 2 Comparisons of *APOL1* risk allele G1 frequencies

	One G1 carriers	Two G1 carriers	Allele frequency	*p*-value
Hospitalization				
Yes ($n=281$)	14 (5.0%)	3 (1.1%)	3.6%	0.047
No ($n=204$)	6 (2.9%)	0 (0.0%)	1.5%	
Pneumonia				
Yes ($n=195$)	10 (5.1%)	2 (1.0%)	3.6%	0.150
No ($n=290$)	10 (3.4%)	1 (0.3%)	2.1%	
Severe COVID-19				
Yes ($n=167$)	10 (6.0%)	2 (1.2%)	4.2%	0.035
No ($n=318$)	10 (3.1%)	1 (0.3%)	1.9%	
ICU				
Yes ($n=127$)	9 (7.1%)	0 (0.0%)	3.5%	0.322
No ($n=358$)	11 (3.1%)	3 (0.8%)	2.4%	
ARDS				
Yes ($n=163$)	11 (6.7%)	1 (0.6%)	4.0%	0.073
No ($n=322$)	9 (2.8%)	2 (0.6%)	2.0%	
Deceased				
Yes ($n=96$)	6 (6.3%)	1 (1.0%)	4.2%	0.155
No ($n=389$)	14 (3.6%)	2 (0.5%)	2.3%	
Hepatic Injury				
Yes ($n=11$)	0 (0.0%)	0 (0.0%)	0.0%	0.999
No ($n=474$)	20 (4.2%)	3 (0.6%)	2.7%	
VTE				
Yes ($n=54$)	3 (5.6%)	1 (1.9%)	4.6%	0.183
No ($n=431$)	17 (3.9%)	2 (0.5)	2.4%	
AKI				
Yes ($n=101$)	7 (6.9%)	2 (2.0%)	5.4%	0.006
No ($n=384$)	13 (3.4%)	1 (0.3%)	2.0%	
Cardiovascular complications				
Yes ($n=38$)	4 (10.5%)	2 (5.3%)	10.5%	<0.001
No ($n=447$)	16 (3.6%)	1 (0.2%)	2.0%	

ICU: intensive care unit; ARDS: acute respiratory distress syndrome; AKI: acute kidney injury; VTE: venous thromboembolism.

Table 3 Association of *APOL1* G1 allele with COVID-19 outcomes

Variables	Odds ratio (95% CI)	*p*-value
AKI - minimally adjusted[A]	2.78 (1.04–7.42)	0.041
AKI - minimally adjusted[A] with PCs	2.19 (0.76–6.31)	0.145
AKI - fully adjusted[B]	2.10 (0.72–6.18)	0.176
Cardiovascular complications - minimally adjusted[A]	4.61 (1.61–13.19)	0.004
Cardiovascular complications - minimally adjusted[A] with PCs	4.78 (1.49–15.36)	0.009
Cardiovascular complications - fully adjusted[B]	4.59 (1.41–14.96)	0.011

CKD: chronic kidney disease; [A]model adjusted for age, biological sex, obesity, and CKD; [B]age, gender, obesity, diabetes, hypertension, immunodeficiency, CKD, PC1, and PC2

is heterogeneous due to differences in migration patterns among regions of the country [35, 46]. Importantly, the studied population includes only individuals affected by COVID-19, which limits the generalization of allele frequencies and genetic ancestry to the general population. In the COVID-19 cohort, 12.8% of ancestry composition was African. The proportion of African ancestry was higher in hospitalized patients (16.3%) compared to non-hospitalized individuals (7.77%; $p<0.001$). Still, it is important to highlight that Brazil has higher rates of social and racial inequality, which were reflected in the healthcare access during the pandemic [47] and COVID-19 patients were recruited in a public hospital. Moreover, the global ancestry proportion of these patients highlights Brazilians' complex genetic admixed structure, particularly presented in Patient 2, who carried two risk alleles and only 11% of African ancestry. However, 22q chromosome genomic regions of all four patients carrying two risk alleles (G1/G1 or G1/G2) showed the genomic region of the *APOL1* composed of African ancestry, as supported by the literature [48].

The association analysis using a minimally adjusted model showed that individuals carrying at least one G1 *APOL1* allele had 2.8-fold higher odds of developing AKI during COVID-19 hospitalization. However, this association lost statistical significance after adjusting for PCs or when using the fully adjusted model. Adjustment for PCs accounts for population structure by incorporating variables that reflect the individuals' genetic ancestry. The loss of significance suggests that other genetics or population substructure may contribute to the outcome. Considering the low number of individuals carrying the risk allele is important, given the sample size and the admixed population, where the allele frequency is lower. Further investigation with a larger cohort of admixed individuals will allow us to understand the role of ancestry and the high-risk allele in kidney damage under COVID-19 hospitalization.

The effect of risk alleles on AKI and CKD development has been widely investigated among African descendants. CKD is a term used to describe heterogeneous disorders such as focal segmental glomerulosclerosis (FSGS), which is known to affect younger age and more severe histological diseases among black patients compared to white individuals [49]. The higher incidence of CKD in black individuals [50] may be explained in part by *APOL1* risk alleles within African descendants. Recently, the role of risk alleles in admixed populations has been highlighted due to their high incidence and impact on public health [30]. CKD and hypertension before COVID-19 infection were associated with the G1 allele, but did not remain significant after PCs adjustment. There is a racial disparity in the early onset and prevalence of hypertension, especially affecting black individuals [51], which may be explained by social, environmental, and genetic factors [51, 52]. Yet, the *APOL1* risk alleles were described as associated with systolic blood pressure, considering both recessive and additive models [53]. As observed in AKI, the loss of association between the G1 allele and

Table 4 Clinical description of patients who carried two risk alleles

	Patient 1	Patient 2	Patient 3	Patient 4
Age at the infection, IBGE ethno-race category, and gender	48, black, male	38, white, female	56, black, female	84, white, female
APOL1 genotype	G1/G1	G1/G1	G1/G2	G1/G1
Comorbidities	Type I diabetes, stage 5 CKD	Stage 5 CKD transplanted, thrombophilia	Obesity, diabetes, systemic arterial hypertension	Hypothyroidism, Thyroid nodules, breast neoplasia, systemic arterial hypertension, obesity, stroke, and warfarin use
Presenting symptoms	Chest and abdominal pain, hyperglycemia, hyperkalemia (K 7.4), and peaked T waves (electrocardiogram)	Diarrhea, vomiting, abdominal pain, and mild flu-like symptoms with cough and coryza	Severe ventilatory failure, with refractory hypoxemia	Flu-like symptoms and prostration
COVID-19 severity	Severe	Moderate	Severe	Severe
Interval between symptom onset and diagnosis (days)	3	5	2	3
Proteinuria	No	No	No	No
Oliguria	Yes	No	Yes	No
Previous creatinine (mg/dL)	12.73	1.1	0.78	2.56
Initial creatinine (mg/dL)	16.99	1.29	1.24	3.2
Creatinine maximum/ minimum (mg/dL)	16.99	0.98	4.33	3.2
Final creatinine (mg/dL)	3.11	1.29	0.83	1.79
Hemodialysis	Yes. Femoral permcath access	No	Yes. Shilley access during COVID-19	No
Days of hospitalization	33	3	48	3
Days in ICU	33	-	34	NA
Requirement of ventilation	Yes	No	Yes	Yes
Cardiovascular complication	Yes	No	Yes	Yes
Outcome	Deceased	Discharged	Discharged	Discharged

IBGE: Brazilian Institute of Geography and Statistics'; CDK: Chronic kidney disease; ICU: intensive care unit

both hypertension and CKD may be influenced by other genetic factors.

Cardiovascular complications were found to be associated with the presence of at least one G1 allele. The fully adjusted model inferred 4.6-fold higher chances of developing cardiovascular events. Also, considering the three models applied, the cardiovascular manifestations were shown to be independent of CKD. The comprehension of the effect of the risk alleles on cardiovascular complications is not consolidated. Indeed, a study identified among 1,959 African Americans an association between carrying two risk alleles and cardiovascular diseases. However, individuals carrying two risk alleles had lower coronary artery calcification [12]. Another study evaluated 30,903 black individuals, including 3,941 who carried two *APOL1* risk alleles, and identified a modest effect of risk alleles on cardiovascular disease likely mediated by *APOL1* association with chronic kidney disease [13]. Yet, the presence of one or two risk alleles was associated with earlier age deaths due to coronary artery disease and cardiomyopathy, and this association was independent of nephrosclerosis only among high-risk genotypes [14]. Nevertheless, a meta-analysis conducted to investigate cardiovascular events among *APOL1* risk allele carriers showed no association of the alleles with incident cardiovascular disease or death independent of kidney measures [15]. Despite different evidence regarding the effect of risk alleles on cardiovascular events, the studies revealed the impact of carrying two *APOL1* risk alleles among black individuals. Here, the association of only one risk allele with cardiovascular complications under a complex inflammatory response brings attention to the possible promotion of kidney injury mediated by one single allele known as the low-risk genotype, which is still an important question to be addressed [29].

Four patients carried high-risk genotypes, and all of them had at least two comorbidities. Notably, Patients 1, 3, and 4 required ventilatory support and developed acute kidney injury (AKI) and cardiovascular complications during hospitalization. It is important to highlight that Patients 1 and 3 were under 60 years of age. Patients 3 and 4 had no prior history of chronic kidney disease, but developed AKI and cardiovascular complications during COVID-19, supporting the hypothesis that COVID-19 may act as a second hit for *APOL1* phenotypes. Patient 3, in particular, required hemodialysis.

During SARS-CoV-2 infection and disease progression, the dynamics of type I IFN production may determine

the course of the disease [54, 55]. The hyperinflammation is systemic, which is associated with multi-organ injury, including the kidney [56]. Moreover, SARS-CoV-2 can migrate through the circulatory system and reach renal cells, where it possesses replicative capability [57, 58]. Worth mentioning, the angiotensin-converting enzyme 2 (ACE2) receptor is highly expressed in cardiovascular tissues, including cardiac myocytes, endothelial cells, fibroblasts, and smooth muscle cells [59–62]. This local or systemic inflammatory response has led to the hypothesis of COVID-19 being considered a second hit for renal dysfunction associated with *APOL1* risk alleles. The involvement of a second hit of inflammation in nephropathy associated with risk alleles has been postulated from observational and functional studies [6, 63]. The induction of *APOL1* expression during COVID-19 inflammatory response was proposed to be mediated by cytokine response and JAK/STAT/APOL1 signaling activation [64]. Thus, we investigated the effect of *APOL1* risk alleles in the context of COVID-19 outcomes. The association of COVID-19 clinical outcomes during hospitalization with the allele G1 supports the evidence of COVID-19 as a second hit for complications driven by *APOL1* risk alleles. Moreover, given the hypothesis that the effects of *APOL1* risk alleles are inflammation-dependent, it is important to highlight the potential interaction between inflammation levels and disease severity status in modulating the effect of these alleles.

The aforementioned infections and increased interferon levels are examples of effect modifiers that promote *APOL1*-mediated nephropathy. Each viral infection leads to the activation of specific antiviral response pathways, which have different impacts on the expression of *APOL1* variants [65]. Furthermore, genetic features have been proposed as modifiers of *APOL1* genotype-phenotype associations [10, 66]. These effect modifiers are determinants for the heterogeneity of *APOL1*-mediated phenotypes related to genotypes. Thus, here, we demonstrate the effect of one risk allele under a highly inflammatory context, COVID-19 hospitalization. These findings corroborate the hypothesis of a dominant toxic gain-of-function role of the *APOL1* variants, which may have a dose-dependent effect [67].

The study presents limitations that must be considered when interpreting the results. The allele frequencies of the G1 and G2 variants in the *APOL1* gene are very low in the population under study. Another significant limitation of the study is the relatively small sample size, which can significantly impact the statistical power of the genetic association analysis. This study was based on a convenience sample, with a primary aim of exploration, focusing on describing the distribution and potential associations of the G1 and G2 variants in our population. Small sample sizes can also result in wider confidence intervals, making it harder to draw reliable conclusions about the genetic variants under investigation. However, it is important to note that the study is conducted in an admixed population, which introduces additional complexity. Admixture can influence allele frequencies, genetic structure, and the potential for differential effects of genetic variants across ancestral groups.

Finally, this study contributes significant evidence to the effect of a single risk allele on COVID-19 clinical outcomes. Furthermore, *APOL1* risk alleles represent a public health concern. Herein, we demonstrate the frequency and impact of these alleles in an admixed population, underscoring the importance of further investigation among individuals with diverse ancestry compositions.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40246-025-00790-1.

Supplementary Material 1

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Author contributions

Conceptualization: N.A.C., B.S.O.F., G.C.G., T.W.K., F.S.L.V.; Data curation: N.A.C., B.S.O.F, G.C.G., T.W.K., R.C.S., M.A.C.S., M.F.F., D.R.S., R.B.L, M.R.R, K.N; Formal Analysis: N.A.C., G.C.G., M.A.C.S., F.S.L.V.; Funding acquisition: A.C.P., L.V.P., T.H., F.S.L.V.; Investigation: N.A.C., B.S.O.F, G.C.G., T.W.K., R.C.S., M.F.F., C.M.B.S., D.R.S.;O.A.P.A.; T.H., F.S.L.V.; Methodology: N.A.C., B.S.O.F, G.C.G., T.W.K., M.A.C.S., F.S.L.V.; Resources: A.C.P., L.V.P., T.H., F.S.L.V.; Supervision: F.S.L.V.; Writing – original draft: N.A.C., B.S.O.F, G.C.G., M.A.C.S.; Writing – review & editing: T.W.K., R.C.S., M.F.F., C.M.B.S., D.R.S., O.A.P.A., R.B.L, M.R.R, K.N, A.C.P., L.V.P., T.H., F.S.L.V.

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Data availability

The data of whole- genome sequencing supporting this finding are a part of the DNA do Brasil consortium, which are freely accessed at "DNA do Brasil Variant Browser" the hyperlink http://www.dnabr.science/.

Declarations

Ethics approval and consent to participate

The project was approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre (CAAE: 36974620.3.0000.5327). The participants provided informed consent through the consent form approved by the ethics committee.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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