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HLA-A homozygosis is associated with susceptibility to COVID-19

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The purpose of this single center retrospective study was to investigate the relationship between HLA and ABO polymorphisms and COVID-19 susceptibility and severity in kidney transplant recipients. It included 720 recipients who had COVID-19 and 1680 controls composed by recipients in follow-up who did not contact the transplantation center for COVID-19 symptoms, up to the moment of their inclusion in the study. HLA-A, -B, and -DRB1 allele groups and ABO frequencies were compared between recipients with COVID-19 (all cases, or separately mild/moderate and severe disease) and controls. The HLA association study was conducted in two case–control series and only associations that showed a p-value <0.05 in both series were considered. No HLA association regarding COVID-19 occurrence or severity met this criterion. Homozygosity at HLA-A locus was associated with COVID-19 susceptibility (odds ratio 1.4) but not severity. Blood groups A and O were associated with susceptibility and resistance to COVID-19, respectively. COVID-19 severity was associated only with older age and cardiac disease, in a multivariate analysis. We conclude that an influence of HLA on COVID-19 susceptibility is supported by the association with homozygosity at HLA-A locus but that there is no evidence for a role of any particular HLA-A, -B, or -DRB1 polymorphism. Thus, we suggest that what matters is the overall capability of an individual's HLA molecules to present SARS-CoV-2 peptides to T cells, a factor that might have a great influence on the breadth of the immune response.

KEYWORDS
ABO blood groups, COVID-19, HLA, HLA homozygosis

1 | INTRODUCTION

The coronavirus disease 19 (COVID-19) is a highly infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in Wuhan, China, in December, 2019, and was declared as a pandemic by the World Health Organization (WHO) in March 2020.[1–4] The first case in Brazil was diagnosed in February 2020.[5]

The main independent risk factor for COVID-19 severity and death is older age, besides other factors including diabetes, hypertension, obesity, chronic respiratory and cardiovascular diseases, smoking and chronic immunosuppression, male gender and black race.[2,6–11]

Because COVID-19 susceptibility and severity varies among individuals with apparently similar environmental risk factors, it is conceivable that viral and host genetic variants may both influence outcomes. Several genetic factors have been suggested to be involved in susceptibility to COVID-19 and its outcomes including HLA and ABO polymorphisms as the most frequently investigated ones.[12–17]

The extensive polymorphism of HLA genes and the influence of HLA alleles on the adaptive immune response, at the level of selection of peptides for presentation to T cells, make HLA genes attractive candidates with impact on susceptibility to viral infections. Actually, there is evidence that the extensive HLA polymorphism results from pathogen-driven balancing selection or, in other words, from the necessity for a species to be immunologically diverse in order to maximize the probability that at least some individuals within the general population would survive an epidemic. The advantage of HLA heterozygosis over homozygosis in terms of fitness to survive infections is a mechanism that contributes to maintenance of HLA polymorphism.[18–21]

The demonstration, by in silico analysis, that HLA molecules vary on their binding affinities for SARS-CoV-2 peptides, have strengthened the interest in the investigation of the relationship between HLA and COVID-19 and there is preliminary evidence that the peptide binding capacity of HLA class molecules may influence the outcome of COVID-19.[22–30]

Several associations between HLA polymorphisms and COVID-19 have been described in investigations that compared HLA frequencies between geographical regions with different COVID-19 prevalences,[31–33] or in case–control studies within the same population.[34–39] However, confidence in these associations is limited, not only because the majority loose significance when the p-value is corrected for multiple comparisons, but also because there is no consistency of the associated polymorphisms among the different studies, not even in those conducted in populations with similar genetic backgrounds.

ABO blood groups have been investigated in several studies and the great majority reported association of group A with susceptibility and of group O with resistance.[40–50] It has been suggested that the resistance of group O individuals is due to the presence of anti-A and anti-B isoagglutinins and, conversely, that the susceptibility conferred by group A is caused by the absence of anti-A isoagglutinins. This hypothesis is based on the fact that SARS-CoV-2 S proteins express A and/or B glycan antigens of the host and on the observation that in an experimental SARS cell model monoclonal or human polyclonal anti-A antibodies inhibited the interaction between viral S proteins carrying A antigens and cellular ACE2 proteins.[41,51,52]

The purpose of the present study was to investigate the relationship between HLA and ABO polymorphisms and COVID-19 susceptibility and severity in kidney transplantation recipients (KTR), a population that is at increased risk for COVID-19 due to chronic immunosuppression and high prevalence of comorbidities.[53,54]

2 | METHODS AND MATERIALS

2.1 | Cases and controls

This single-center, retrospective observational case–control study included 720 KTR that had COVID-19, between March and December, 2020, and 1680 KTR transplanted in the years of 2018 and 2019 who did not seek medical assistance at the transplant center, up to the moment of their inclusion in the present study. The transplants were from living or deceased donors and were performed and followed-up in Hospital do Rim, São Paulo, Brazil. For the diagnosis of COVID-19 it was required at least one positive test for SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR) from nasopharyngeal swabs or bronchoalveolar lavage. All COVID-19 cases were diagnosed after transplantation, but the onset of the disease was considered the day of the first symptoms. COVID-19 was classified as mild/moderate ($N = 501$) when there was no need for hospitalization or, when hospitalization was required, there was no need for mechanical ventilation. COVID-19 was classified as severe ($N = 219$) in cases with intubation or death.

Demographics, ABO blood type, comorbidities, and clinical data related to COVID-19 were collected from medical records of the hospital. Data on comorbidities were not collected from the control group. Concerning race, KTR were classified as white or non-white. Non-white comprised black and admixed (white/black/indigenous) individuals.

HLA typing at allele group level (low resolution) and pre-transplant calculated panel reactive antibodies (cPRA) were retrieved from the database of our laboratory, where all the pre-transplant tests were performed.

The study was approved by the local ethics committee and informed consent was obtained from all recipients diagnosed with COVID-19. Informed consent was waived for KTR without COVID-19 because the analyses used only anonymous data.

2.2 | ABO association study

ABO phenotypic frequencies were assessed by direct counting. The reference group consisted of all ABO groups,

except the one that was being considered in the comparison.

2.3 | HLA association study

The study included the analysis of 21 HLA-A, 35 HLA-B, and 13 HLA-DRB1 allelic groups. HLA-A, -B, -DRB1 phenotypic frequencies were assessed by direct counting. The 720 KTR with and the 1680 KTR controls without COVID-19 were randomly subsampled in order to construct two case–control series. HLA allele groups frequencies were compared between KTR with COVID-19 (all cases, or separately, mild/moderate and severe disease) and controls in each of the two case-controls series and only the associations that showed a p-value <0.05 in both series were considered.

An individual carrying only one HLA-A, -B, or -DRB1 allelic group was considered homozygous. The percentages of homozygous individuals were compared between the 720 KTR with COVID-19 (all cases, or separately, mild/moderate and severe disease) and the 1680 controls.

2.4 | PRA association study

Pre-transplant cPRA levels (0%–10%, 11%–49%, 50%–79%, and ≥ 80%) were compared between KTR with or without COVID-19 and between mild/moderate and severe cases.

2.5 | Statistical analyses

Categorical variables were compared with chi-square or Fisher's exact test, as appropriate. Continuous variables were analyzed with Mann–Whitney test. Logistic regression was used to test the independence of variables, which presented p-value < 0.05 in the univariate analyses. Values of $p < 0.05$ were reported as statistically significant. The analyses were performed with IBM SPSS Statistics for Windows Version 21.0 (IBM Corp, Armonk, NY).

3 | RESULTS

3.1 | Characteristics of kidney transplant recipients regarding occurrence and severity of COVID-19

The median time from transplant to the first symptoms of COVID-19 was 5.6 (−0.01–21.2) years. In one KTR the symptoms began 3 days before transplantation. Among the severe cases, 83% died. The comparison between KTR with ($N = 720$) and without ($N = 1680$) COVID-19

TABLE 1 Characteristics of the kidney transplant recipients according to COVID-19 occurrence and severity

	COVID-19			COVID-19 severity		
Variables	**No** ***N*** **= 1680**	**Yes** ***N*** **= 720**	***p*-value**	**Mild/moderate[a]** ***N*** **= 501**	**Severe[b]** ***N*** **= 219**	***p*-value**
Gender, male, *N* (%)	1006 (59.9)	437 (60.7)	0.71	290 (57.9)	147 (67.1)	0.02
Age, years, median (range)	47.0 (7–78)	51.1 (8–83)	<0.001	47.6 (8–74)	58.6 (26–83)	<0.001
Age ≥ 60 years, *N* (%)	343 (20.4)	189 (26.3)	0.002	82 (16.4)	107 (48.9)	<0.001
Race, non-white, *N* (%)[c]	493 (30.3)	218 (32.3)	0.34	160 (34.2)	58 (28.2)	0.12
Time post-transplantation, years, median (range)	Not analyzed		—	5.3 (−0.01–21.2)	6.3 (0.0– 17.7)	0.75
Hypertension, *N* (%)	Not analyzed		—	337 (67.3)	166 (75.8)	0.02
Diabetes, *N* (%)	Not analyzed		—	136 (27.1)	93 (42.5)	<0.001
Heart disease, *N* (%)	Not analyzed		—	24 (4.8)	30 (13.7)	<0.001
Other comorbidities[d], *N* (%)	Not analyzed		—	28 (5.6)	24 (11.0)	0.01

Abbreviation: *N*, number of subjects.

[a]Mild/Moderate: no intubation or death.

[b]Severe: intubation or death.

[c]Non-white comprised black and admixed (white/black/indigenous) individuals; Missing data for race: 54, in COVID-19 NO; 19, in Covid-19 YES; 33, in Mild/Moderate; 13, in Severe COVID-19.

[d]Other comorbidities include chronic lung disease, chronic liver disease and neoplasia.

TABLE 2 HLA-A,-B, and -DRB1 phenotypic frequencies that differed, considering an uncorrected p-value <0.05, between kidney transplant recipients without and with COVID-19 (all cases and cases stratified by severity) in the analyses performed in any one of the two case–control series

HLA-	Case–control series 1				Case–control series 2			
	KTR without COVID-19	KTR with COVID-19			KTR without COVID-19	KTR with COVID-19		
		All cases	Mild/moderate[a]	Severe[b]		All cases	Mild/moderate[a]	Severe[b]
	N = 840	*N* = 357	*N* = 245	*N* = 112	*N* = 840	*N* = 363	*N* = 256	*N* = 107
A*26	4.3%	**8.4%** **p = 0.004**	**9.4%** p = **0.002**	6.3% p = 0.35	6.7%	6.3% p = 0.83	7.8% p = 0.53	2.8% p = 0.14
A*30	11.9%	16.0% **p** = 0.06	13.9% p = 0.41	**20.5%** p = **0.011**	11.1%	12.4% p = 0.51	10.9% p = 0.95	15.9% p = 0.14
B*07	10.1%	**14.6%** **p = 0.02**	**15.1%** p = **0.03**	13.4% p = 0.29	13.3%	14.3% p = 0.64	15.2% p = 0.44	12.1% p = 0.73
B*14	10.2%	12.9% p = 0.18	11.8% p = 0.47	15.2% p = 0.11	8.2%	**12.4%** p = **0.02**	12.1% p = 0.06	13.1% p = 0.09
B*15	21.0%	16.8% p = 0.10	17.1% p = 0.19	16.1% p = 0.23	20.5%	16.3% p = 0.09	**12.1%** p = **0.003**	26.2% p = 0.17
B*27	2.9%	3.9% p = 0.34	3.7% p = 0.51	4.5% p = 0.37	3.9%	**1.7%** p = **0.04**	1.6% p = 0.07	1.9% p = 0.42
B*45	4.3%	4.5% p = 0.88	4.9% p = 0.68	3.6% p = 1	3.0%	5.0% p = 0.09	3.9% p = 0.46	**7.5%** p = **0.02**
B*48	1.9%	**0.3%** p = **0.03**	0.4% p = 0.14	0.0% p = 0.28	1.5%	**3.6%** p = **0.03**	3.1% p = 0.12	**4.7%** p = **0.04**
B*50	5.7%	**2.5%** **P = 0.02**	**2.4%** p = **0.04**	2.7% p = 0.26	4.9%	4.4% p = 0.72	5.1% p = 0.89	2.8% p = 0.47
B*55	1.5%	**3.9%** p = **0.01**	3.7% p = 0.07	4.5% p = 0.05	2.0%	1.7% p = 0.67	1.6% p = 0.80	1.9% p = 1
DRB1*10	5.2%	**2.5%** p = **0.04**	3.3% p = 0.20	0.9% p = 0.05	4.8%	4.1% p = 0.63	3.9% p = 0.57	4.7% p = 0.97
DRB1*13	24.8%	22.1% p = 0.33	21.2% p = 0.25	24.1% p = 0.88	24.5%	26.4% p = 0.48	22.7% p = 0.54	**35.5%** p = **0.02**

Note: No p-value remained <0.05 after correction for the number of comparisons, even considering only the number of investigated HLA-A, B, and –DR polymorphisms (*N* = 69).

Abbreviations: KTR, kidney transplant recipients; N, number of subjects.

[a]Mild/moderate: no intubation or death.

[b]Severe: intubation or death.

TABLE 3 Frequency of HLA-A, -B, and -DRB1 homozygosity in kidney transplant recipients, according to COVID-19 occurrence and severity

Homozygosity at	COVID-19			COVID-19 severity		
	No *N* = 1680	Yes *N* = 720	p-value	Mild/moderate[a] *N* = 501	Severe[b] *N* = 219	p-value
HLA-A locus, *N* (%)	143 (8.5)	83 (11.5)	0.02	58 (11.6)	25 (11.4)	0.95
HLA-B locus, *N* (%)	101 (6.0)	48 (6.7)	0.54	33 (6.6)	15 (6.8)	0.90
HLA-DRB1 locus, *N* (%)	98 (5.8)	56 (7.8)	0.07	42 (8.4)	14 (6.4)	0.36

Abbreviation: N, number of subjects.

[a]Mild/moderate: no intubation or death.

[b]Severe: intubation or death.

TABLE 4 Frequency of ABO blood groups in kidney transplant recipients, according to COVID-19 occurrence and severity

	COVID-19			COVID-19 severity		
Blood groups	No $N = 1674$	Yes $N = 720$	p-value	Mild/moderate[a] $N = 501$	Severe[b] $N = 219$	p-value
A, *N* (%)	623 (37.2)	307 (42.6)	0.01	211 (42.1)	96 (43.8)	0.67
B, *N* (%)	186 (11.1)	86 (11.9)	0.56	62 (12.4)	24 (11.0)	0.59
AB, *N* (%)	87 (5.2)	28 (3.9)	0.17	20 (4.0)	8 (3.7)	0.83
O, *N* (%)	778 (46.5)	299 (41.5)	0.02	208 (41.5)	91 (41.6)	0.99

Abbreviation: N, number of subjects.
[a]Mild/moderate: no intubation or death.
[b]Severe: intubation or death.

TABLE 5 Distribution of % PRA levels in kidney transplant recipients, according to COVID-19 occurrence and severity

	COVID-19			COVID-19 severity		
% PRA	No $N = 1680$	Yes $N = 711$	p-value	Mild/moderate[a] $N = 493$	Severe[b] $N = 218$	p-value
0–10, *N* (%)	1283 (76.4)	520 (73.1)	0.25	365 (74.0)	155 (71.1)	0.70
11–49, *N* (%)	194 (11.5)	85 (12.0)		56 (11.4)	29 (13.3)	
50–79, *N* (%)	96 (5.7)	47 (6.6)		30 (6.1)	17 (7.8)	
≥80, *N* (%)	107 (6.4)	59 (8.3)		42 (8.5)	17 (7.8)	

Abbreviations: *N*, number of subjects; PRA, panel reactive antibodies.
[a]Mild/moderate: no intubation or death.
[b]Severe: intubation or death.

regarding gender, age, and race, as well the comparison between cases with mild/moderate ($N = 501$) and severe ($N = 219$) COVID-19 regarding gender, age, race, and comorbidities, are presented in Table 1. Occurrence of COVID-19 was associated with age ≥ 60 years ($p = 0.002$), but not with gender or race. Severe disease was associated with male gender ($p = 0.02$), age ≥ 60 years ($p < 0.0001$), hypertension ($p = 0.022$), diabetes ($p < 0.0001$), heart disease ($p < 0.0001$), and other co-morbidities that included chronic lung and liver diseases and neoplasia ($p = 0.01$). White and non-white patients did not differ regarding the prevalence of severe disease.

3.2 | Association between HLA-A, -B, -DRB1, and susceptibility and severity of COVID-19

KTR with COVID-19 did not differ between case–control series 1 and 2, in respect to gender, age, race, time post-transplant to first COVID-19 symptoms, and the comorbidities considered in this study (Table S1).

Frequencies of HLA-A ($N = 21$), -B ($N = 35$), and -DRB1 ($N = 13$) allele group in KTR with any type of COVID-19, in mild/moderate cases and in severe cases were compared to those in KTR without COVID-19, in each of the two case–control series. The 12 HLA allele groups that showed significant differences in frequencies, considering a $p < 0.05$, in any of these comparisons are presented in Table 2. No p-value remained < 0.05 after correction for the number of comparisons, even considering only the number of investigated HLA-A, -B and -DR polymorphisms ($N = 69$) and not all comparisons between the groups. Moreover, no association was present in both studies. The association with HLA-B*48, although statistically significant ($p < 0.05$) in both series, was negatively associated in series 1 and positively associated with COVID-19 in series 2.

3.3 | Association between HLA-A, -B, -DRB1 homozygosity and COVID-19

The comparison of HLA-A, -B, or -DRB1 homozygosity between all KTR with and without COVID-19 showed

TABLE 6 Multivariate logistic regression analysis including the factors significantly associated with risk for COVID-19 occurrence in the univariate analysis

	COVID-19			
	No	Yes		
Variables	***N* = 1674**	***N* = 720**	**p-value**	**OR (95% CI)**
Age, ≥60 years, *N* (%)	343 (20.4)	189 (26.3)	0.004	1.4 (1.1–1.7)
Blood group A, *N* (%)	623 (37.2)	307 (42.6)	0.019	1.2 (1.0–1.5)
Homozygosity at HLA-A locus, *N* (%)	143 (8.5)	83 (11.5)	0.027	1.4 (1.0–1.8)

Abbreviations: *N*, number of subjects; OR, odds ratio; 95% CI, 95% confidence interval.

higher frequency of homozygosity at HLA-A locus (11.5% vs. 8.5%, p = 0.020), a tendency for higher frequency at HLA-DR locus (7.8% vs. 5.8%, p = 0.075), and no significant difference at HLA-B locus (6.7% vs. 6.0%, p = 0.54) (Table 3). No association was observed between HLA-A, -B, or -DRB1 homozygosity and severity of the disease.

3.4 | Association between ABO blood groups and susceptibility and severity of COVID-19

Table 4 shows the comparisons of ABO blood group frequencies in KTR with and without COVID-19 and in cases with mild/moderate and severe disease. Blood group A was positively (42.6% vs. 37.2%, p = 0.013) and group O was negatively (41.5% vs. 46.5%, p = 0.026) associated with COVID-19. No differences were observed concerning frequencies of B and AB blood groups. No association was observed between any blood group and severity of the disease.

3.5 | Association between pre-transplant cPRA and susceptibility and severity of COVID-19

Pre-transplant cPRA levels (0%–10%, 11%–49%, 50%–79% and ≥ 80%) did not show any statistically significant differences between KTR with or without COVID-19 or between mild/moderate and severe cases (Table 5).

3.6 | Multivariate logistic regression analysis for susceptibility and severity of COVID-19

All factors that showed association in the univariate analyses were considered in the multivariate analysis.

Regarding COVID-19 susceptibility, the multivariate logistic regression analysis included age ≥ 60 years, blood group A and homozygosity at HLA-A locus and these three variables remained significantly associated with odds ratios and 95% CI of 1.4 (1.1–1.7), 1.2 (1.0–1.5), and 1.4 (1.0–1.8), respectively (Table 6). Also when blood group O instead of group A was analyzed, the three variables remained significantly associated with odds ratios and 95% CI of 1.4 (1.1–1.7), 0.8 (0.7–1.0), and 1.4 (1.0–1.8), respectively (data not shown).

Regarding COVID-19 severity, however, only advanced age ≥ 60 years (OR 4.2; 95% CI 2.9–6.1; p < 0.0001) and heart disease (OR 2.1; 95% CI 1.1–3.9; p = 0.022) were independently associated with severe disease, whereas blood groups, male gender, hypertension, diabetes and other comorbidities were not.

4 | DISCUSSION

The main purpose of this study was to evaluate association of HLA and ABO polymorphisms with susceptibility to COVID-19 in KTR.

The investigation included 720 KTR with COVID-19 and 1680 KTR who did not report COVID-19 symptoms. Univariate analyses showed that older age, but not gender or race, was associated with susceptibility to COVID, while older age, male gender and co-morbidities were found to be associated with severe disease, defined as intubation or death. These findings are in agreement with previous reports.[2,6–9] On the other hand, we did not observe a higher prevalence of severe disease in non-whites, as reported in UK and in the United States,[9–11] possibly because all KTR were from the same transplantation center, with equitable access to COVID-19 treatment. This interpretation is in line with authors of UK and United States that believe that environmental factors, such as poverty and limited health care, rather than genetic factors, are responsible for the higher SARS-CoV-2 infection morbidity and mortality in racial minority populations.[9–11]

The main findings of our investigation were the association between homozygosity at HLA-A locus and susceptibility to COVID-19 and the lack of association

between any HLA-A, -B, or -DRB1 polymorphism and COVID-19.

A study of class I HLA polymorphism and COVID-19 in the Spanish population[22] found higher proportion of homozygosity at HLA-A and -C loci in moderate and severe as compared to mild COVID-19. Interestingly, as in our study, there was no association with HLA-B homozygosis. Furthermore, the study in the Spanish population showed that patients with moderate and severe disease presented an overall lower theoretical capacity of their HLA class I molecules to bind SARS-CoV-2 peptides. We therefore suggest that susceptibility to COVID-19 is not affected by any particular HLA-A, -B, or -DRB1 polymorphism, but rather by the overall limitation of the possibilities of HLA molecules to present SARS-CoV-2 peptides to T cells.

There are several examples of infectious, especially viral, diseases in animals that are influenced by homozygosity at genes of the major histocompatibility complex (MHC).[18,55–60] The clearest example in humans is AIDS, where HIV-positive individuals who are homozygous at one or more HLA class I loci progress to AIDS faster than the heterozygous patients.[58–60]

The lack of association between any particular HLA-A, -B, or -DRB1 polymorphism and COVID-19 susceptibility or severity observed in our study was not surprising, considering that it was designed with the idea of avoiding false-positive discoveries. The inconsistencies of associations across different reports concerning COVID-19,[28,31–39] as well as in studies with diseases caused by other Coronavirus, namely Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS) (MERS-CoV)[61–66] suggest that the majority, if not all, of the reported associations are false-positive. False-positive results, in fact, are a common statistical pitfall in HLA and disease association studies where cases and controls are subjected to multiple comparisons.[67]

Concerning false-negative associations, the size of the samples reduced very much this possibility. A sensitivity power analysis[68] was conducted to define the detectable differences in proportions between KTR without COVID-19 and KTR with COVID-19, in each one of the case–control series. Considering a statistical power of 80%, the observed sample sizes and the observed proportions as references, the results (not shown) indicated that for HLA allelic groups with frequencies <10% and ≥10%, the detectable percentage points differences ranged from 0.04 to 5.52, and from 3.86 to 8.84, respectively.

Our study confirmed the association of blood group A with susceptibility and of blood group O with resistance to COVID-19. These results are in accordance with findings of several previous studies.[28,39–49] On the other hand, we did not find any association between ABO blood groups and severity of COVID-19, which is agreement with some studies,[28,48–50] and at variance with other ones.[42,46,47]

Multivariate analyses of variables associated with COVID-19 susceptibility in univariate analyses showed that advanced age ≥ 60 years, blood group A and HLA-A homozygosity were independently associated with higher susceptibility, while blood group O was associated with resistance. Concerning severity of COVID-19, only age ≥ 60 years and cardiac disease were independently associated with the more severe form of disease.

As a high cPRA is sometimes considered to reflect an individual's "high responder" immune status not only to HLA but also to other antigens, we tested whether there was a relationship between the level of cPRA and susceptibility or severity of COVID-19. No associations were disclosed, in accordance with an observation in another study of KTR.[28]

This study has strengths as well as limitations. Among the strengths are the high number of KTR with (720) and without (1680) COVID-19 from the same transplantation center, and the design of the study of association between HLA and COVID-19 that aimed to avoid false-positive discoveries. The limitations include those inherent to a single center retrospective study and the impossibility to rule out the presence of KTR with symptomatic SARS-CoV-2 infection in the control group, since mild to moderate symptoms may not always have been reported to the hospital.

In summary the association with homozygosity at HLA-A locus supports an influence of HLA on COVID-19 susceptibility but, on the other hand, our study does not indicate an influence of any particular HLA-A, -B, or -DRB1 polymorphism on COVID-susceptibility or severity. Thus, we suggest that what matters is the overall capability of an individual's HLA molecules to present SARS-CoV-2 peptides to T cells, a factor that might have a great influence on the breadth of the immune response.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Renato De Marco designed the study, performed research, analyzed the data and revised the manuscript; Tathyane C Faria performed research, analyzed the data and revised the manuscript; Karina L Mine designed the

study, analyzed the data and revised the manuscript; Marina Cristelli designed the study, performed research and revised the manuscript; José O Medina-Pestana revised the manuscript; Hélio Tedesco-Silva designed the study and revised the manuscript, Maria Gerbase-DeLima designed the study, analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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