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Research article

Impact of HLA polymorphisms on the susceptibility to SARS-CoV-2 infection and related mortality in patients with renal replacement therapy

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ABSTRACT

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection could present in a clinical spectrum of varying severity. Human leukocyte antigen (HLA) is a crucial component of the viral antigen presentation pathway and immune response to the virus. Therefore, we aimed to assess the impact of HLA allele polymorphisms on the susceptibility to SARS-CoV-2 infection and related mortality in Turkish kidney transplant recipients and wait listed patients, along with clinical characteristics of the patients. We analysed data from 401 patients with clinical characteristics according to presence (n = 114, COVID+) or absence of SARS-CoV-2 infection (n = 287, COVID-) who had previously been HLA typed to support transplantation. The incidence of coronavirus disease-19 (COVID-19) was 28 %, and the mortality rate was 19 % in our wait listed/ transplanted patients. Multivariate logistic regression analysis showed that a significant HLA association between HLA- B*49 (OR = 2.57, 95 % CI, 1.13–5.82; p = 0.02) and HLA- DRB1*14 (OR = 2.48, 95 % CI, 1.18–5.20; p = 0.01) with SARS-CoV-2 infection. Besides, in COVID + patients, HLA-C*03 was correlated to mortality (OR = 8.31, 95 % CI, 1.26–54.82; P = 0.03). The new finding from our analysis suggests that HLA polymorphisms could be associated with the occurrence of SARS-CoV-2 infection and COVID-19 mortality in Turkish patients with renal replacement therapy. This study may provide new information for the clinician to identify and manage sub-populations at risk in the setting of the current COVID-19 pandemic.

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was seen for the first time in December 2019 in China, and the disease caused by the virus is called coronavirus disease-19 (COVID-19). Due to the COVID-19 has quickly spread worldwide, the WHO classified it as a pandemic on March 11, 2020. As of June 7, 2021, COVID-19 caused over 172 million confirmed cases and 3.7 million deaths worldwide [1].

The infection could present in a clinical spectrum of varying severity, ranging from very mild flu-like symptoms to acute respiratory distress syndrome associated with high mortality and morbidity [2]. The defined risk factors for complicated disease are older age, male sex, smoking, comorbidities including obesity, hypertension (HT), diabetes mellitus (DM), chronic kidney diseases (CKD) and, chronic pulmonary disease [3–7]. Also, some studies reported that the occurrence of SARS CoV-2 infection in patients with renal replacement therapy (RRT) was markedly higher than that of the general population, with high morbidity and mortality [8,9]. On the other hand, the genetic background that controls immune response is thought to play an essential role in different host responses to infection and disease severity.

Human leukocyte antigens (HLA) represent one of the most highly polymorphic systems in the human genome and currently include 33,490 alleles in three different gene classes (Classes I, II, and III) [10]. Molecules encoded by HLA genes are involved in antigen presentation, inflammation and the innate and adaptive immune responses [11]. HLA molecules are membrane bound glycoproteins that bind peptides derived from endogenous or exogenous proteins, including viral ones, and present to T and B lymphocytes [12]. Thus, the HLA type of the patient is likely to be an essential factor in individual variability in immune responses to foreign antigens and hence disease severity, depending on peptides binding affinity.

Studies have been demonstrated the roles of HLA gene polymorphisms in infectious agents, such as hepatitis B virus (HBV), hepatitis

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C virus (HCV), and the previous SARS-CoV [13–15]. Similarly, some HLA alleles are associated with an increased risk of various viral infections in patients who have kidney transplantation (KT) or are on dialysis [16,17]. Besides, in recently published studies found a higher rate of some HLA alleles in COVID-19 patients than the control subjects [18,19]. However, the association between HLA allele polymorphisms and COVID-19 has not been thoroughly analyzed in patients with RRT along with clinical confounders. Therefore, this study aimed to assess the impact of HLA allele polymorphisms on the presence and mortality of COVID-19, with clinical characteristics of the patients.

2. Materials and methods

2.1. Study population

This retrospective and observational study was conducted to evaluate the effect of HLA allele polymorphisms on the transmission of SARS-CoV-2 and related mortality in Turkish patients with RRT [hemodialysis (HD), peritoneal dialysis (PD) or kidney transplantation (KT)]. The inclusion criteria were as follows; age ≥ 18 years, patients with KT or waiting list for KT at our unit who previously HLA typed at least HLA-A, B, C, DRB1, and DQB1 (n = 401). As of April 1, 2021, 114 COVID-19 positive subjects (based on a positive test for SARS-CoV-2 RNA of nasopharyngeal swab specimens, and/or compatible findings on a computed tomography scan of the lungs when the first hospital application) were detected and defined as study group (COVID +). Afterward, all patients diagnosed with compatible findings on CT scan were confirmed for COVID-19 by taking a nasopharyngeal swab sample. Subjects without clinical history of the SARS-CoV-2 infection (n = 287) were defined as the control group (COVID-). The National Ministry of Health and the local ethics committee of our institution approved the study's design and procedures in agreement with the principles of the Declaration of Helsinki and ethical standards for human experimentation. In view of the retrospective nature of the study and as all the procedures performed were part of the routine care, no informed consent was required.

2.2. Data collection

Medical records were reviewed for patient data. Patient demographics were determined as age, sex, body mass index (BMI), current smoking, RRT status (HD, PD or KT), RRT vintage, and systemic disease including DM, HT, coronary artery disease (CAD), heart failure (HF) and chronic obstructive pulmonary disease (COPD).

2.3. Class I and class II HLA typing

HLA typing was routinely performed at low resolution (one-field HLA typing) to support transplantation activities using mainly DNA-based techniques in our laboratory. Genomic DNA was extracted from the peripheral blood samples by using the Bio Robot EZ1 system (Qiagen GmbH, Hilden, Germany). The HLA class I (HLA-A, B and C) and class II (HLA DRB1 and DQB1) typing was performed by polymerase chain reaction sequence specific oligonucleotide (PCR-SSO) technique developed by LIFECODES® HLA-SSO Typing (Immucor Inc, CA, USA). All tests were performed according to manufacturers' instructions.

2.4. Statistical analysis

Data distribution was determined using the Kolmogorov-Smirnov test and two-tailed *t* test or Mann-Withney *U* test were performed as appropriate. The homogeneity of variables was determined using the one-way ANOVA homogeneity of variance test. We weighted cases by the HLA frequencies and used Hardy-Weinberg chi-square test to check compliance of our data to Turkish population (p = 0.35). Continuous variables were reported as the means and standard deviation or as median and minimum–maximum according to data distribution. Categorical variables were reported by percentages. We tested the possible association between some HLA alleles and susceptibility to COVID-19 and mortality using logistic regression analysis, and Odds Ratio and its 95 % confidence intervals were calculated as measurement of the clinical impact of the predictor variables. Only variables with a p-value < 0.1 in the univariate logistic regression analysis were considered for multivariate analysis. Cox-regression survival analysis was used to determine the association between the HLA allele and mortality. A p-value < 0.05 was considered statistically significant. Analyses were performed with SPSS 21.0.0.1 (SPSS, IBM, Armonk, NY) software for Windows.

3. Results

The mean age of the participants was 48.6 ± 15.7 years, 39 % were female, and 107 (27 %) of the patients were older than 60 years. The mean BMI of the cohort was 24.6 ± 5.02 kg/m^2. The distribution of HD, PD, and KT by RRT modalities in the total cohort was 32 %, 6 %, and 62 %, respectively. We identified 114 COVID + patients: 89 waited-list patients (80 HD and 9 PD patients) and 25 KT recipients. Patients defined as COVID– were the untested or asymptomatic counterparts. HLA frequencies in 401 patients with COVID-19 previously HLA typed to support transplantation were shown in Supplementary Figure 1 and 2 in the supplemental material.

COVID + patients had a higher probability of older age than those without infection (56 ± 17 years vs. 46 ± 14 years; OR = 1.04, 95 % CI, 1.03–1.06; p < 0.001). Particularly, in patients over the age of 60, the risk of COVID-19 was increased more significantly (48 % vs. 18 %; OR = 4.21, 95 % CI, 3.01–5.89; P < 0.001). In addition, systemic diseases including DM (OR = 2.97, 95 % CI, 2.14–4.12; p < 0.001), HT (OR = 1.64, 95 % CI, 1.11–2.42; p = 0.01), CAD (OR = 6.92, 95 % CI, 4.83–9.93; p < 0.001), HF (OR = 17.0, 95 % CI, 9.32–31.02; p < 0.001) and COPD (OR = 6.78, 95 % CI, 2.94–15.63; p < 0.001) were the associated factors for COVID-19. HD and PD modalities as RRT were increased the risk of COVID-19 compared to kidney transplantation (OR = 14.87, 95 % CI, 10.10–21.88; p < 0.001 and OR = 5.02, 95 % CI, 2.63–9.58; p < 0.001, respectively).

The frequency of HLA-B*18 were higher in COVID- patients than in COVID+ (6 % vs. 3 %; OR = 0.41, 95 % CI, 0.16–1.07; p = 0.07). On the other hand, HLA-B*49 (15 % vs. 4 %; OR = 1.88, 95 % CI, 0.95–3.71; p = 0.07), HLA-DRB1*14 (8 % vs. 6 %; OR = 1.7, 95 % CI, 0.94–3.09; p = 0.08) and HLA-DQB1*06 (15 % vs. 11 %; OR = 1.62, 95 % CI, 1.03–2.56; p = 0.04) alleles showed a higher frequency in COVID + than in COVID- patients. All demographic characteristics of the patients and associated risk factors for the COVID-19 were demonstrated in Table 1.

Univariate regression analysis was performed to determine the affecting factors for the death due to COVID-19 infection. Age (OR = 1.09, 95 % CI, 1.05–1.12; p < 0.001), being over the age of 60 (OR = 9.85, 95 % CI, 3.96–24.49; <0.001), higher BMI (OR = 1.1, 95 % CI, 1.03–1.17; p = 0.003) DM (OR = 4.15, 95 % CI, 2.01–8.58; p < 0.001), and CAD (OR = 4.62, 95 % CI, 2.15–9.91; p < 0.001) were associated with higher mortality risk for COVID-19 patients. Besides, HD (OR = 6.97, 95 % CI, 1.61–30.07; p = 0.009) and PD (OR = 12.00; 95 % CI, 2.15–67.07; p = 0.005) were the risk factors for death due to COVID-19. HLA-DRB1*13 (14 % vs. 5 %; OR = 0.18, 95 % CI, 0.02–1.37; p = 0.09) was found to be more frequent in surviving patients. On the other hand, the frequency of HLA- A*26 (9 % vs. 2 %; OR = 4.17, 95 % CI, 0.88–19.67; p = 0.07), HLA- C*01 (9 % vs. 4 %; OR = 3.19, 95 % CI, 0.87–11.66; p = 0.08), HLA-C*03 (14 % vs. 5 %; OR = 3.18, 95 % CI, 0.98–10.27; p = 0.05), HLA-DRB1*04 (18 %

Table 1
Univariate analysis of the demographic characteristics of the study population.

	Total n:401	COVID (+) n:114 (28 %)	COVID (−) n:287(72 %)	Odds Ratio (95 % CI)	P value
Age	48.6 ± 15.7	56 ± 17	46 ± 14	1.04 (1.03–1.06)	<**0.001**
>60 years	107(27 %)	55(48 %)	52(18 %)	4.21 (3.01–5.89)	<**0.001**
Gender (F)	158(39 %)	45(40 %)	113(39 %)	0.99 (0.73–1.36)	0.9
BMI	24.6 ± 5.02	24.3 ± 5.2	25.08 ± 4.58	0.97 (0.93–1.02)	0.2
RRT group					
HD	128(32 %)	80(70 %)	48(17 %)	14.87 (10.10–21.88)	<**0.001**
PD	25(6 %)	9(8 %)	16(6 %)	5.02 (2.63–9.58)	<**0.001**
KT	248(62 %)	25(22 %)	223(77 %)	Reference	Ref.
RRT vintage					
HD or PD	4.26 ± 4.96	4.8 ± 5.3	4.05 ± 4.8	1.03 (0.87–1.06)	0.2
KT	9.9 ± 5.4	8.7 ± 5.4	10.1 ± 5.4	0.95 (0.91–0.99)	**0.03**
DM	115(29 %)	52(46 %)	63(22 %)	2.97 (2.10–4.12)	<**0.001**
HT	306(77 %)	94(83 %)	212(74 %)	1.64 (1.11–2.42)	**0.01**
CAD	91(23 %)	56(49 %)	35(12 %)	6.92 (4.83–9.93)	<**0.001**
HF	41(10 %)	34(30 %)	7(3 %)	17.0 (9.32–31.02)	<**0.001**
COPD	14(4 %)	10(9 %)	4(2 %)	6.78 (2.94–15.63)	<**0.001**
Smoking	106(27 %)	32(28 %)	74(26 %)	1.11 (0.79–1.57)	0.5
HLA-B					
B*18	21 (5 %)	3 (3 %)	18 (6 %)	0.41 (0.16–1.07)	0.07
B*49	19 (5 %)	7 (15 %)	12 (4 %)	1.88 (0.95–3.71)	0.07
HLA-DRB1					
DRB1*14	26 (6 %)	9 (8 %)	17 (6 %)	1.7 (0.94–3.09)	0.08
HLA-DQB1					
DQB1*06	50 (12 %)	17 (15 %)	33 (11 %)	1.62 (1.03–2.56)	**0.04**

BMI: Body mass index; **CAD:** Coronary artery disease; **COPD:** Chronic Obstructive Pulmonary Disease; **DM:** Diabetes mellitus; **HD:** Hemodialysis; **HF:** Heart Failure; **HLA:** human leukocyte antigen; **HT:** Hypertension, **KT;** Kidney Transplantation; **PD:** Peritoneal dialysis; **RRT:** Renal Replacement Therapy.

vs. 11 %; OR = 2.58, 95 % CI, 1.01–6.62; p = 0.05), and HLA-DRB1*15 (14 % vs. 5 %; OR = 3.60, 95 % CI, 1.20–10.82; p = 0.02) alleles were higher in non-surviving patients (Table 2).

The frequencies in different 11 countries of HLA class I and II alleles identified as risk factors for SARS-CoV-2 transmission and related death in the univariate regression analysis were searched by a publicly available database. Allele Frequency Net Database (https://www.allelefrequencies.net), using an HLA searching option (HLA classical allele freq search). The frequencies of the HLA alleles for each country were shown in Supplementary Table 1 in the supplemental material.

The presence of HLA- B*49 (OR = 2.57; 95 % CI, 1.13–5.82; P = 0.02) and HLA-DRB1*14 (OR = 2.48; 95 % CI, 1.18–5.20;

Table 2
Characteristics of the COVID-19 patients according to mortality.

	COVID (+)			
	Dead n: 22(19 %)	Alive n: 92(81 %)	Odds Ratio (95 % CI)	P value
Age	69 ± 12	53 ± 16	1.09 (1.05–1.12)	<**0.001**
>60 years	19(86 %)	36(39 %)	9.85 (3.96–24.49)	<**0.001**
Gender (F)	7(32 %)	38(41 %)	1.51 (0.75–3.03)	0.2
BMI	26.58 ± 6.8	23.7 ± 4.6	1.1 (1.03–1.17)	**0.003**
RRT group				
HD	18(82 %)	62(67 %)	6.97 (1.61–30.07)	**0.009**
PD	3(14 %)	6(7 %)	12.0 (2.15–67.07)	**0.005**
KT	1(4 %)	24(26 %)	Reference	Ref.
RRT vintage				
HD or PD	3.27 ± 3.1	5.15 ± 5.7	0.92 (0.85–1.03)	0.06
KT	5.7 ± 2.2	8.9 ± 5.5	0.87 (0.71–1.06)	0.2
DM	16(73 %)	36(39 %)	4.15 (2.01–8.58)	<**0.001**
HT	20(91 %)	74(80 %)	2.43 (0.82–7.24)	0.1
CAD	17(77 %)	39(42 %)	4.62 (2.15–9.91)	<**0.001**
HF	7(32 %)	27(29 %)	1.12 (0.55–2.28)	0.7
COPD	2(9 %)	8(9 %)	0.93 (0.33–3.31)	0.9
Smoking	7(32 %)	25(27 %)	1.25 (0.61–2.55)	0.5
HLA-A				
A*26	2 (9 %)	2 (2 %)	4.17 (0.88–19.67)	0.07
HLA-C				
C*01	2 (9 %)	4 (4 %)	3.19 (0.87–11.66)	0.08
C*03	3 (14 %)	5 (5 %)	3.18 (0.98–10.27)	0.053
HLA DRB1				
DRB1*04	4 (18 %)	10 (11 %)	2.58 (1.01–6.62)	**0.048**
DRB1*13	1 (5 %)	13 (14 %)	0.18 (0.02–1.37)	0.09
DRB1*15	3 (14 %)	5 (5 %)	3.6 (1.20–10.82)	**0.02**

BMI: Body mass index; **CAD:** Coronary artery disease; **COPD:** Chronic Obstructive Pulmonary Disease; **DM:** Diabetes mellitus; **HD:** Hemodialysis; **HF:** Heart Failure; **HLA:** human leukocyte antigen; **HT:** Hypertension, **KT;** Kidney Transplantation; **PD:** Peritoneal dialysis; **RRT:** Renal Replacement Therapy.

P = 0.01) were the alleles conferring the most significant risk of SARS-CoV-2 transmission, as determined by logistic regression analysis adjusted for all the variables with statistical significance in the univariate analysis. Also, HD and PD as RRT modalities (OR = 9.00; 95 % CI, 5.68–14.27; p < 0.001 and OR = 3.99; 95 % CI, 1.79–8.88; p < 0.001, respectively), DM (OR = 1.72; 95 % CI, 1.06–2.79; P = 0.03) and HF (OR = 8.19; 95 % CI, 3.54–18.94; p < 0.001) were other confirmed independent factors that significantly influence the risk of infection. More advanced age (OR = 16.12; 95 % CI, 3.38–76.91; p < 0.001) and higher BMI (OR = 1.13; 95 % CI, 1.03–1.23; P = 0.009) were the associated risk factors for the death caused by COVID-19. Finally, among HLA alleles, HLA-C*03 was significantly associated with a higher risk of death (OR = 8.31; 95 % CI, 1.26–54.82; P = 0.03). The multivariate logistic regression analysis of the associated factors for susceptibility to COVID-19 and related death is shown in Table 3. The survival of patients with COVID-19 was analyzed by the Cox proportional hazards regression analysis (Fig. 1), and the presence of HLA C*3 was shown to be a predictor of a poor outcome (HR = 3.71; 95 % CI, 1.38–9.94; P = 0.009).

4. Discussion

In this study, we investigated a possible association between HLA allele polymorphisms and susceptibility or mortality for COVID-19 in KT recipients and patients with ESRD on dialysis. We confirmed well-known risk factors for susceptibility to COVID-19 and mortality, such as older age, dialysis treatment, DM, HF, and higher BMI. In addition to these risk factors, we described the association of increased disease transmission with the HLA-B*49 and HLA-DRB1*14 alleles, as well as the possible association between increased mortality and HLA-C*03.

Patients with ESRD are at higher risk of mortality as they are generally older and have more chronic underlying conditions such as DM, HT, and cardiovascular disease [20]. Besides, the risk of susceptibility to infections of ESRD patients and developing severe symptoms may increase with the long-term immunodeficiency state of the disease, including immunosuppressive drugs [21,22]. Therefore, it requires special attention to this vulnerable group of patients who may be more seriously affected by the pandemic. Indeed, a recently published study from France shown that KT and ESRD on dialysis increased the risk of COVID-19-related hospitalization and in-hospital mortality [23].

The scientific community has spent the past few years making an unprecedented global effort to improve knowledge about SARS-CoV-2 and COVID-19. One central point is to identify the factors responsible for the spread of the disease and the variety of clinical manifestations. Some studies have reported that male sex, age, and comorbidities responsible for adverse outcomes [24]. In this study, we found that advanced age is a risk factor for death due to COVID-19, but not for the transmission of SARS-CoV-2. In addition, DM and HF are the risk factors for presence of COVID-19, while DM, HT, CAD, HF and COPD did not emerge as independent risk factors for death in kidney transplant and dialysis patients, similar to study of European Renal Association COVID-19 Database (ERACODA) collaboration [25]. Our results showed that HD and PD as RRT increased the risk of COVID-19 compared to KT recipients but did not affect the mortality. This result may occur because dialysis patients need more frequent hospital admissions and particularly HD patients in closer contact with each other. Another finding of our study was that higher BMI is associated with mortality related to COVID-19. A meta-analysis demonstrated that increased BMI and obesity were associated with the risk of composite adverse outcomes in adult COVID-19 patients [26].

HLA class I and II genes are critical components of the cell-mediated immune responses because they encode molecules involved in antigenic peptides to antigen-specific T-cell receptors [27]. The first step in initiating a host-specific immune response is binding peptides from infectious pathogens to HLA proteins. Different HLA molecules with polymorphic amino acid residues have slightly different peptide-binding clefts, potentially influencing the specificity and affinity of peptide binding [12]. Adequate immune clearance of any virus can be achieved when the individual's HLA antigens present the pathogen-derived peptide efficiently and produce a sufficient immune response to eradicate it [28]. Therefore, genetic factors that can cause

Table 3
Multivariate logistic regression analyses for the risk factors associated with susceptibility to COVID-19 and related death.

	Risk factors for COVID-19		**Risk factors for the death due to COVID-19**	
	Odds Ratio (95 % CI)	**P value**	**Odds Ratio (95 % CI)**	**P value**
Age > 60 years	0.84 (0.48–1.44)	0.5	16.12 (3.38–76.91)	**< 0.001**
BMI			1.13 (1.03–1.23)	**0.009**
RRT group				
HD	9.0 (5.68–14.27)	**< 0.001**	3.14 (0.29–33.68)	0.1
PD	3.99 (1.79–8.88)	**< 0.001**	4.31 (0.69–27.14)	0.3
KT	Reference	Ref.	Reference	Ref.
RRT vintage				
HD or PD			0.89 (0.76–1.04)	0.1
KT	0.63 (0.31–1.27)	0.08		
DM	1.72 (1.06–2.79)	**0.03**	3.29 (0.95–11.41)	0.06
HT	0.81 (0.49–1.33)	0.4		
CAD	1.77 (0.99–3.17)	0.06	3.89 (0.41–36.53)	0.2
HF	8.19 (3.54–18.94)	**< 0.001**		
COPD	1.39 (0.34–5.64)	0.6		
HLA allele				
A*26			7.53 (0.75–76.14)	0.09
C*01			1.78 (0.34–9.38)	0.5
C*03			8.31 (1.26–54.82)	**0.03**
DRB1*04			4.12 (0.82–8.29)	0.1
DRB1*13			0.12 (0.01–1.27)	0.08
DRB1*15			3.59 (0.86–14.93)	0.08
B*18	0.49 (0.14–1.65)	0.2		
B*49	2.57 (1.13–5.82)	**0.02**		
DRB1*14	2.48 (1.18–5.20)	**0.01**		
DQB1*06	1.26 (0.71–2.23)	0.4		

BMI: Body mass index; **CAD:** Coronary artery disease; **COPD:** Chronic Obstructive Pulmonary Disease; **DM:** Diabetes mellitus; **HD:** Hemodialysis; **HF:** Heart Failure; **HLA:** human leukocyte antigen; **HT:** Hypertension, **KT;** Kidney Transplantation; **PD:** Peritoneal dialysis; **RRT:** Renal Replacement Therapy.

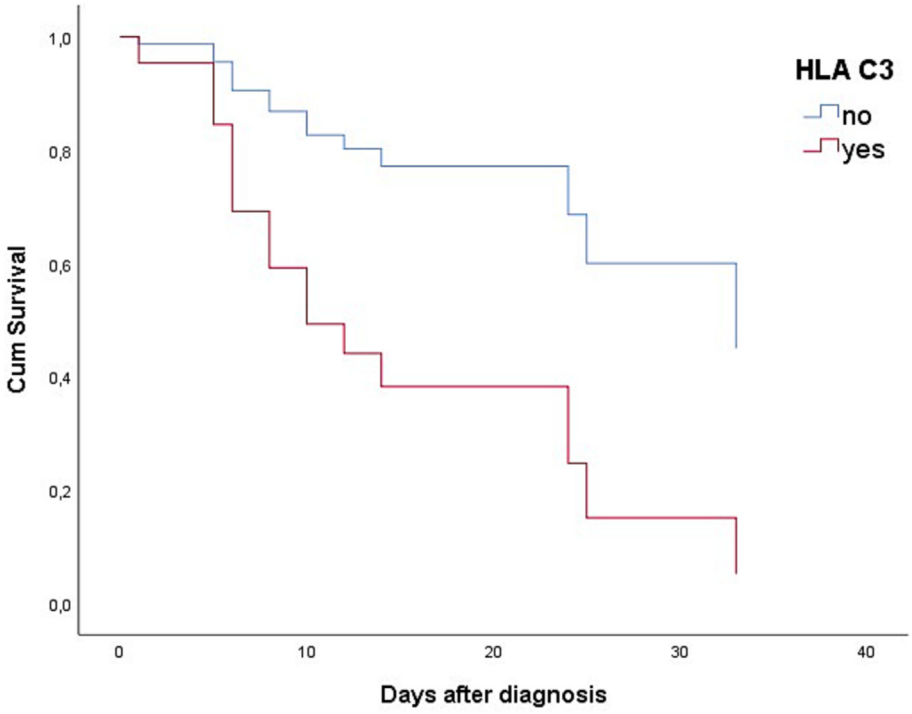

Fig. 1. Cox proportional hazard survival curve of COVID-19 patients based on HLA types.

individual heterogeneity may impact different clinical outcomes due to viral infection.

In this series of individuals, we found that possession of HLA Class I type HLA-B*49 or HLA Class II type HLA DRB1*14 is associated with an increased risk of SARS-COV-2 transmission. Thus, it is conceivable to speculate that these patients cannot present the viral peptides required to form a protective T-cell repertoire and are consequently unable to mount a fast and effective anti-viral immune response. HLA-B*49 has previously been identified as a predisposing type to symptomatic acute human parvovirus B19 and recurrent American cutaneous leishmaniasis infections [29]. In addition, a higher rate of DRB1*14 was found in patients with asthma, late-onset myasthenia gravis, and susceptibility to kidney allograft rejection in compared to controls [30–32]. The associations of these alleles with inflammatory and autoimmune diseases could highlight their ability to trigger non-proficient and often improper immunological reactions. On the other hand, some HLA class I polymorphisms (ie, HLA B*46:01, HLA-B*07:03, and HLA-Cw*08:01) have been significantly associated with susceptibility previous SARS-COV infection and/or disease severity in various populations [33–35]. Therefore, in silico analyses of previous studies designed to investigate HLA gene polymorphism and the differences in morbidity and mortality of COVID-19 indicated possible associations with HLA class I genotypes (HLA-A*02:01 and HLA-B*46:01) and an increased risk for COVID-19 due to lower capacity to present SARS-CoV-2 antigens [36,37]. Besides, in database analysis, Correale et al. reported that HLA-B*44 and C*01 prevalence correlated with spreading SARS-COV-2 in Italy. However, this paper's analytical approach is based on an epidemiological analysis instead of on the well-known history of clinical confounders in our study.

On the other hand, we found that HLA-C*03 may represent a risk factor for COVID-19 related death. Chan et al. identified that HLA-C molecules as an attachment factor for the spike protein in coronavirus HKU1 infection and facilitated the entry of the virus into the cell [38]. In addition, some evidence suggested that HLA-C*03 expression on (both human and murine) target cells confers selective protection from lysis mediated by natural killer (NK) clones [39]. It may cause the inhibition of the activity of NK cells, which represent the first line of host defense against infection, before a more specific T-cell response is elicited. HLA-C*03 has previously been with infectious diseases such as Borrelia Burgdorferi and chronic viral hepatitis [40,41]. Some studies already reported different HLA alleles (HLA-DRB1*08 and HLA-C*05) associated with COVID-19 mortality [18,42]. Besides, Norin et al. demonstrated that HLA B53 positive hospitalized COVID-19 patients with African American ancestry were at a 7.4 fold greater risk of death than those who were B53 negative [43]. On the other hand, the severe COVID-19 genome-wide association study (GWAS) group included participants from Italy and Spain. It failed to show a significant allele association of classical HLA loci with COVID-19 or disease severity [44]. However, blood donors with unknown COVID-19 status as controls might have precluded the detection of weaker associations between classical HLA loci.

This study has limitations in view of the single-center and retrospective nature. Within the limits of a single-center, the study population was localized and included a small number of patients with RRT. Therefore, this may have caused wide CI ranges in our study, and the readers should consider these circumstances when interpreting these outcomes. In addition, our results are restricted to this cohort, and our findings may not be generalizable to a nationwide population. Second, our study group contains a single ethnic group; thus, any HLA associations may only reflect results in this group and not apply to other ethnic groups. Third, we studied individuals at higher risk of SARS-CoV-2 transmission and higher risk for related death. And last, this study was not designed as an in silico analysis to examine the association of these alleles with COVID-19.

On the other hand, we think that our study has several strengths. First, we identified a cohort with well-known status for SARS-CoV-2 in the pandemic period. Second, we assessed the relative importance of HLA type compared to known risk factors that could potentially influence morbidity and mortality for COVID-19, such as age, BMI, and clinical comorbidities. Although HLA typing was mainly low resolution, it included HLA A, B, C, and also DR and DQ loci.

5. Conclusion

The new finding from our preliminary study was that HLA polymorphisms could play a role in SARS-CoV-2 infection and related mortality. Although the number of samples in the present study was small, these data may provide new insights for exploring the impact of HLA polymorphisms on susceptibility to COVID-19 and patient outcomes. Future works with prospective manner are required to confirm these results in the broad population, and to predict the peptide-binding groove of these alleles may help explain their association with SARS-CoV-2.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection were performed by EY, YU, OFA and HHY. OFA and HHY analyzed the data and prepared the manuscript. OFA wrote the manuscript; SG and UD supervised, and reviewed the manuscript. All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humimm.2023.01.008.

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