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Research article

HLA B53 is associated with a poor outcome in black COVID-19 patients

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ABSTRACT

A disproportionate incidence of death has occurred in African Americans (Blacks) in the United States due to COVID-19. The reason for this disparity is likely to be multi-factorial and may involve genetic predisposition. The association of human leukocyte antigens (HLA) with severe COVID-19 was examined in a hospitalized population (89% Black, n = 36) and compared to HLA typed non-hospitalized individuals (20% Black, n = 40) who had recovered from mild disease. For additional comparison, HLA typing data was available from kidney transplant recipients and deceased donors. Hospitalized patients were followed for 45 days after admission to our medical center with death as the primary end-point. One HLA allele, B53, appeared to be more prevalent in the hospitalized COVID-19 patients (percent of positive subjects, 30.5) compared to national data in US Black populations (percent of positive subjects, 24.5). The percent B53 positive in non-hospitalized COVID-19 patients was 2.6, significantly less than the percent positive in the hospitalized COVID-19 patients ($p = 0.001$, Fisher's exact test) and less than the 8 percent positive listed in national data bases for US Caucasian populations. Significantly greater deaths (73 percent) were observed in HLA B53 positive hospitalized COVID-19 patients compared to hospitalized COVID-19 patients who were B53 negative (40 percent). Multi-variate analysis indicated that HLA B53 positive Black hospitalized COVID-19 patients were at a 7.4 fold greater risk of death than Black COVID-19 patients who were B53 negative. Consideration for accelerated vaccination and treatment should be given to HLA B53 positive Black COVID19 patients.

1. Introduction

The COVID-19 pandemic caused by the SARS-CoV-2 has posed a disproportionate burden of illness and death in racial and ethnic minorities in the United States [1,2]. The University Hospital of Brooklyn (UHB), State University of New York Health Sciences University located in Brooklyn, New York, was designated as a COVID-19 only hospital in April 2020 by the governor of New York State between March 13 and June 30, 2020. During this period, 765 COVID-19 patients were treated. UHB mostly serves a local population of ethnic minorities, of which > 80% are Caribbean Americans and African Americans (Blacks). About 19% of deaths in the US occurred in non-hispanic Blacks although they only represent about 12% of the US population [3,4]. Blacks frequently have underlying medical conditions that place them at increased risk for severe COVID-19 but other factors may play a role in poor outcomes such as genetic and socio-economic issues. [5,6].

Major histocompatibility complex genes (MHC, known as Human Leukocyte Antigens, HLA) play a critical role in immune responses to intracellular pathogens such as viruses [7-9]. Class 1 HLA bind viral peptides in the endoplasmic reticulum where they migrate to the cell surface of infected cells in membrane bound exocytic vesicles. This complex is then presented to T lymphocytes in the paracortical regions of the draining lymph nodes resulting in activation and differentiation of T cells and B cells [9]. There are many examples of autoimmune reactions stemming from viral infections including coronavirus [10,11]. Several mechanisms have been proposed for viral induced autoimmune reactions including; epitope spreading, bystander activation and molecular mimicry [10,12-15]. In the latter case it is thought that a viral peptide mim-

Abbreviations: COVID-19, coronavirus disease of 2019; CP, convalescent plasma; ELISA, enzyme-linked immunosorbent assay; HLA, human leukocyte antigen; HR, hazard ratio; MHC, major histocompatibility complex; SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SUNY, State University of New York; UHB, University Hospital of Brooklyn.

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ics a self - peptide in that both combine with the same HLA allele thus causing a pathogenic immune reaction [15-17].

We hypothesized that in Blacks, an increased risk for severe COVID-19 may be due, in part, to the prevalence of HLA allele(s) that not only binds a SARS-CoV-2 peptide but may bind a self-peptide as well. In the current investigation, we determined the HLA type of a cohort of hospitalized COVID-19 patients at UHB [18]. We compared their HLA types to a cohort that had mild COVID-19 symptoms and had volunteered to donate convalescent plasma (CP) to critically ill COVID-19 patients under the Mayo Clinic Convalescent Plasma Treatment Program [19]. The CP donors were from a wide area in New York City and suburbs whereas the hospitalized patients were predominately from the local community near UHB. We also compared the HLA types of our hospitalized COVID-19 patients to local patients who were recipients of kidney transplants at our center. The association of a genetic trait (HLA) with the outcome of COVID-19 in a middle - class Black community is a strength of the current study as this circumstance may reduce the influence of confounding socioeconomic factors and health issues. We report a significantly greater incidence of death in HLA B53 positive Black hospitalized COVID-19 patients compared to Black HLA B53 negative hospitalized COVID-19 patients.

2. Methods

2.1. Hospitalized COVID-19 patients

From April 4, 2020 to June 26, 2020, 28 hospitalized COVID-19 patients (19 males and 9 females) received CP transfusion at UHB under the Mayo Protocol. The plasma treated patients and an additional 8 hospitalized non plasma treated patients (5 males and 3 females) were HLA typed (n = 36) by reverse Sequence Specific Oligonucleotide probes (rSSO) on a Luminex platform (Immucor, Norcross, GA) as previously described [20]. The following loci were typed to at least the serologic equivalent level: HLA - A, B, C, DRB1, 3, 4, 5, DQA, DQB, DPA and DPB. The racial composition of the hospitalized COVID-19 patients was 32 Black, 4 Caucasian. The Downstate Institutional Review Board (IRB) reviewed and approved the studies in this report (IRB #1232938–3 and IRB #341403–1). Characteristics of patients given CP and those not given CP as well as CP donor characteristics were previously published [18].

2.2. Non hospitalized COVID-19 convalescent plasma donors

UHB conducted a COVID-19 Convalescent Plasma Donation and Treatment Program under the auspices of the Mayo Clinic (ClinicalTrials.gov Identifier: NCT04338360) between April 23, 2020 to June 26, 2020. One hundred and seventy-one (171) volunteers were screened for possible donation. All volunteers were first screened with a lateral flow assay that detects IgM and IgG antibodies against the receptor-binding domain (RBD) of S1 spike protein of SARS-CoV-2. Sixty-five (38.0%) tested positive for IgG and their anti-SARS-CoV-2 RBD IgG titer, determined by enzyme-linked immunosorbent assay (ELISA), was considered of sufficient strength to be a CP donor. Demographic characteristics of volunteers screened for possible CP donation are provided in our previous publication [18]. Genomic DNA was available from 40 of the 65 anti- RBD positive plasma donors for HLA typing in the CLIA certified UHB Transplant Immunology & Immunogenetics Laboratory by rSSO / Luminex technology (Immucor, Norcross, GA). All HLA loci were typed as indicated above for the hospitalized COVID-19 patients.

2.3. HLA typing of kidney transplant recipients and donors

For comparison with community residents prior to the COVID-19 pandemic de-identified HLA typing data was available from historical cohorts of kidney transplant recipients and deceased kidney donors that were transplanted at UHB (2018 to 2019). HLA typing of these patients for the A, B, C, DRB1, 3, 4, 5, DQA, DQB, DPA and DPB loci were performed by the same methodology as the COVID-19 hospitalized patients and plasma donors.

2.4. Statistical analysis

Statistical analyses were performed using IBM® SPSS Statistics Version 26 (IBM SPSS Japan, Tokyo, Japan) and GraphPad Prism 8 (GraphPad Software, La Jolla, CA). Sample size calculations were not performed. The study populations included 40 volunteers for the COVID-19 Convalescent Plasma Donation Program, 28 hospitalized COVID-19 patients who received CP and 8 hospitalized COVID-19 patients that did not receive CP. Fisher's exact test was used to determine significant differences in racial composition and in the frequency of HLA alleles in the study groups. Based on this initial analysis, subjects were grouped according to the following HLA B35 positive, B53 positive, both B35 and B53 positive and non-B35/B53. Survival in the 45 day follow after hospitalization of the above cohorts was analyzed with the Kaplan-Meier estimator and by the log-rank statistic. Cox regression analysis was performed to analyze the association of multiple variables with survival. A two-sided p value of less than 0.05 (2-tailed) was considered statistically significance. The raw data set for this study is available on a secure server hosted by SUNY Health Sciences University.

3. Results

HLA typing was performed on two consecutive cohorts of 18 hospitalized patients each who were admitted to UHB for moderate to severe COVID-19 symptoms with a 45-day follow up. Demographic characteristics of these patients are shown in Supplementary Table 1. HLA typing results for the A, B, C, DRB1, 3, 4, 5, DQA, DQB, DPA and DPB loci is shown in Supplementary Table 2. After the first group of 18 hospitalized patients were typed the results were analyzed. There were 6 patients (33%) in this group who were B53 positive. As the percent of B53 was higher in this initial group than the national average for US Blacks (24.5%) [21], we hypothesized that B53 was increased in prevalence in hospitalized Black COVID-19 patients and that this antigen may be associated with a poor outcome. Accordingly, we performed HLA typing on an additional 18 hospitalized patients. After typing of the second group of 18 patients was completed we determined that 5 patients were B53 positive. Fisher's exact test was significant for the presence of B53 in each independent cohort and in the combined group of 36 hospitalized COVID-19 patients (Table 1) when compared to the CP donors that recovered from mild COVID-19 (see below, n = 40). All 11 patients with the B53 serologic type were B*53:01.

For comparative purposes HLA typing was also performed on 40 convalescent plasma (CP) donors who had had mild COVID-19 symptoms, were never hospitalized and volunteered to donate CP. Inclusion criteria for CP donors was a previous positive RT-PCR test for SARS-CoV-2 and/or detectable antibodies to SARS-CoV-2 of either the IgM type, IgG type or both [18][18]. HLA typing of 40 CP donors for the A, B, C, DRB1, 3, 4, 5, DQA, DQB, DPA and DPB loci is shown in Supplementary Table 3. Complete HLA typing data was also available (2018–2019) for comparative purposes from kidney transplant recipients (i.e., local UHB patients similar

Table 1
Comparison of B53 in Hospitalized and Non-Hospitalized Covid-19 Subjects.. Hospitalized COVID-19 patients, n = 36, non-hospitalized COVID-19 patients, n = 40, transplant recipients n = 65 and transplant donors n = 63. Eighty nine percent of the hospitalized COVID-19 patients were Black whereas only 20 percent of the non-hospitalized COVID-19 CO donors were Black. The proportion of Blacks that are B53 in US data bases is 24.5 percent and in Caucasians B53 is 8 percent [21,22].The presence of B53 in hospitalized Covid-19 patients was significantly greater than in non-hospitalized COVID-19 subjects (Fisher's Exact Test, two tailed, p = 0.001) but not significantly greater in the transplant recipients or transplant donors, Fisher's Exact Test, two tailed, p = 0.479 and p = 0.141, respectively, The presence of B53 in non hospitalized COVID-19 CP donors was significantly lower than B53 in transplant recipients and donors (Fisher's Exact Test, two tailed, p = 0.004 and p = 0.026, respectively. The frequency of B53 in Black hospitalized COVID-19 patients was 34.4% (11/32) and in non-hospitalized Blacks who donated plasma 1/ 8 ie 12.5%.

	Covid-19 Hospitalized	Covid-19 non-Hospitalized	Transplant Recipients	Transplant Donors
B53 Present	11	1	15	11
B53 Absent	25	39	50	52
Percent B53^{+}	30.5	2.6	23.1	17.5

to the demographics of hospitalized COVID-19 patients and non-local kidney transplant donors, similar to the characteristics of CP donors) (full typing data not shown). The percent B53 positive is shown in Table 1

The hospitalized COVID-19 cohort was comprised of 32 non-Hispanic Blacks (89%), three Caucasians and one Asian of 36 total patients. The typical UHB census of Black patients is reflected in the UHB kidney transplant recipient population, 2018 – 2019 of 82%. In comparison, the CP donor group was comprised of 8 of 40 (20%) Black subjects (p = 0.0001, Fisher's Exact Test non hospitalized COVID-19 subjects compared to hospitalized COVID-19 patients. The majority of CP donors were healthcare workers that came from many different locations in the NYC region.

We compared the frequency of HLA alleles in hospitalized COVID-19 patients to the frequency of HLA alleles in non - hospitalized convalescent plasma donors. Of all the HLA loci examined in these cohorts, a B- locus antigen, B53, was more prevalent in the hospitalized COVID-19 patients then in non-hospitalized COVID-19 plasma donors (Table 1). HLA B53 is highly expressed in Black populations as compared to Caucasians [21,22]. Eleven of 36 hospitalized COVID-19 patients were B53 positive whereas only one of 40 non – hospitalized CP donors was positive for B53 (Table 1). The prevalence of B53 was also significantly lower in the non-hospitalized COVID-19 group compared to transplant recipients and transplant donors (Table 2). Interestingly, the prevalence of the related B35 antigen in hospitalized COVID-19 patients was not significantly different in non-hospitalized subjects, transplant recipients and transplant donors, Fisher's Exact Test, two tailed, p = 0.590, p = 0.315 and p = 0.117, respectively. The presence of B35 in non-hospitalized Covid-19 was not significantly different than in transplant recipients and transplant donors, Fisher's Exact Test, two tailed, p = 0.598 and 0.587, respectively. Also of note is that significantly fewer B53 positive subjects were observed in the non-hospitalized COVID-19 group (2.6%) compared to the frequency of B35 in the non-hospitalized group, 20% (Fisher's Exact Test, p = 0.049). It appears that B53 is significantly more prevalent in the hospitalized COVID-19 group and depleted in the non - hospitalized COVID-19 group relative to B35. This observation is likely due to at least two possible factors. One is the disparity in the prevalence of B53 in Blacks compared to Caucasians, 24 percent compared to 8 percent, respectively. Whereas the presence of B35 in these racial groups is similar, 10.6 percent in Blacks compared to 12.4 percent in Caucasians [21,22]. Secondly, B53 positive patients may be more likely to have severe disease that requires hospitalization.

We determined, therefore, whether the presence of HLA B53 and the closely related B35 allele was associated with mortality in hospitalized COVID-19 patients who had neither of these B locus antigens. In the first cohort of 18 hospitalized patients, 5 of 6 HLA B53 positive patients died whereas death occurred in 3 of 5 B53 positive hospitalized COVID-19 patients in the second cohort. In total, 8 of 11 (72.7%) patients that expressed B53 died in the hospital during the 45-day observation period. In contrast, 4 of 15 (26.7%) of the hospitalized COVID-19 patients who were not B53 positive died after admission to UHB (Fisher's exact test, p = 0.045). Six of 10 (60%) of the hospitalized COVID-19 patients who expressed B35, died compared to 4 of 15 (27%) deaths in patients who expressed neither B53 nor B35 (Fisher's exact test, p = 0.122, NS). When patients were considered who were either B53 or B35 then 67%, 14 of 21 were deceased compared to non - B53, non - B35 patients (Fisher's exact test p = 0.041).

Fig. 1 shows the Kaplan-Meier 45-day survival curves of COVID-19 patients based on their B35 or B53 HLA type. Patients who were HLA B53 positive had significantly shorter survival then patients who were B53 negative including B35 positive patients (log-rank p = 0.0322). The survival of patients who were B35 positive did not significantly differ from B53 positive patients, log-rank p = 0.2780. Survival of B35-positive patients did not significantly differ from patients who were B35 and B53 negative (log-rank p = 0.1060). Survival of patients who were B53 positive was significantly less when compared to patients who lacked B53 and B35 (HR 3.928, 9% CI 1.187 to 13.00; log rank p = 0.0134).

The association of multiple risk factors; including, HLA, age, gender, race and co-morbidity factors on the survival of patients (from admission to a 45 days follow up period) was analyzed by the Cox proportional hazards regression model (Fig. 2). Table 3 shows the Cox statistical analysis including; p-values, hazard ratios and 95% confidence intervals. After accounting for the above factors, the presence of HLA B53 was shown to be an independent

Table 2
Comparison of percent positive B35 patients in hospitalized and non-hospitalized Covid19 subjects. Hospitalized COVID-19 patients, n = 36, non-hospitalized COVID-19 patients, n = 40, transplant recipients n = 65 and transplant donors n = 63. Eighty nine percent of the hospitalized COVID-19 patients were Black whereas 20 percent of the non-hospitalized COVID-19 patients were Black. The proportion of Blacks that are B35 in US data bases is 10.6% and in Caucasians the proportion of B35 is 12.4% [21,22]. The presence of B35 in hospitalized Covid-19 was not significantly different than in non– hospitalized subjects, transplant recipients and transplant donors, Fisher's Exact Test, two tailed, p = 0.590, p = 0.315 and p = 0.117, respectively. The presence of B35 in non– hospitalized Covid-19 was not significantly different than in transplant recipients and transplant donors, Fisher's Exact Test, two tailed, p = 0.598 and 0.587, respectively.

	Covid-19 Hospitalized	Covid-19 non-Hospitalized	Transplant Recipients	Transplant Donors
B35 Present	10	8	10	9
B35 Absent	26	32	55	54
Percent B35^{+}	27.8	20.0	15.4	14.3

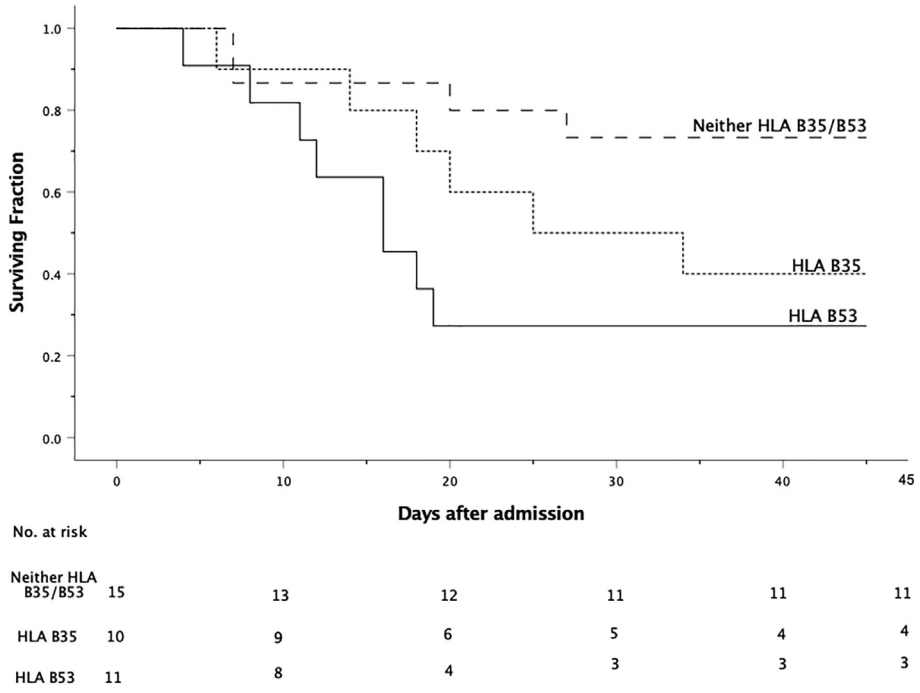

Fig. 1. Kaplan-Meier 45-day survival curve based on HLA types of hospitalized Covid-19 patients. Patients with HLA B53 had a significantly poorer outcome when compared to patients without B53 (log-rank p = 0.0322).

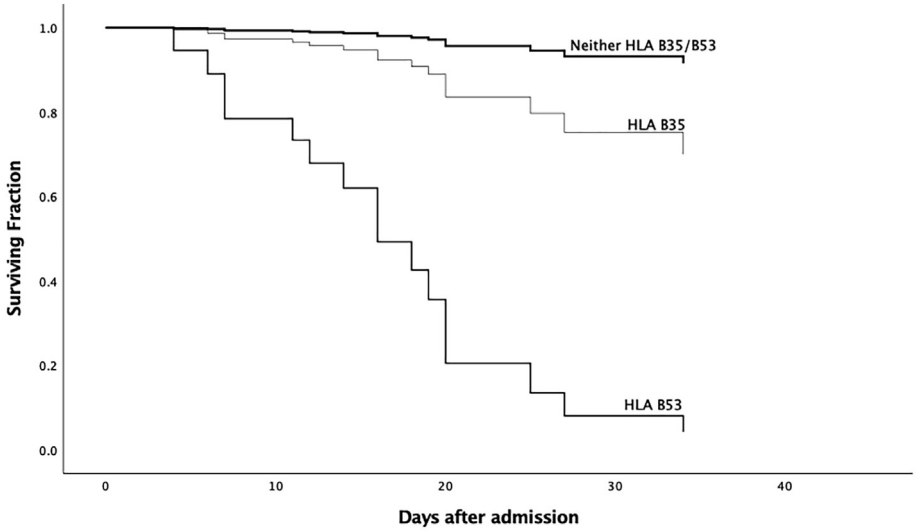

Fig. 2. Cox proportional hazard survival curve of hospitalized COVID-19 patients based on HLA types. HLA B53 was an independent predictor of a poor outcome after controlling for age, sex, race, convalescent plasma treatment and co-morbidities. See Table 3 for statistical analysis.

predictor of a poor outcome (7.4 fold likelihood of death). HLA B35 was not a significant predictor of death.

4. Discussion

It is clear that Black COVID-19 patients have a disproportionate share of morbidity and mortality than Caucasians in the US population [1–6]. However, in a number of studies that used multivariant analyses, outcomes did not differ between Black and White COVID-19 patients after adjusting for sociodemographic factors and comorbidities [3,5,6]. In the current report, we evaluated genetic loci within the MHC in hospitalized COVID-19 patients from a relatively homogeneous middle-class Black community for association with survival of COVID-19.

We found a significantly greater frequency of HLA B53 in hospitalized Black COVID-19 patients compared to COVID-19 CP donors who had mild symptoms and were therefore not hospitalized. Multivariate regression analysis indicated that B53 was the only independent predictor of death in Black COVID-19 patients admitted to our hospital. Since most of these patients were Black (89%) it is not possible to assess the presence of B53 on the outcome of COVID-19 in Caucasians, non-black Hispanics or Asian patients. B53 is highly expressed in US Blacks at a frequency of 0.1330 as it confers protection against malaria in Africa [23,24] whereas the frequency of B53 is rare in Caucasians (0.004) [21]. We note that the frequency

Table 3
Multi-variant analysis. Cox proportional hazard regression analysis was performed to assess the association between survival and a number of risk factors including: age, sex, convalescent plasma (CP) treatment, race, HLA type and the most common co-morbidities. [a]CNS disease includes history of cerebrovascular accident (stroke), seizures and dementia. [b]Pulmonary disease includes history of asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), pulmonary embolism (PE), pulmonary hypertension and obstructive sleep apnea. [c]CVS disease includes history of congestive heart failure (CHF) and arrhythmia. The analysis indicates that HLA B53 remains as an independent predictor (p = 0.026) of death among Black COVID-19 patients.

Variables	*P* value	Hazard Ratio	95.0% Confidence Interval	
			Lower	Upper
Age	0.572	1.015	0.964	1.069
Sex	0.532	1.708	0.318	9.175
Race	0.145	0.273	0.048	1.563
CP treatment	0.375	2.238	0.378	13.247
HLA B53	0.026	7.450	1.274	43.563
HLA B35	0.121	3.330	0.729	15.213
Hypertension	0.215	0.341	0.062	1.866
Diabetes mellitus	0.495	1.661	0.386	7.137
Chronic kidney disease	0.303	2.699	0.408	17.861
CNS disease[a]	0.335	0.434	0.080	2.368
Pulmonary disease[b]	0.286	3.990	0.313	50.792
Hyperlipidemia	0.147	7.555	0.492	116.099
CVS disease[c]	0.877	1.168	0.163	8.384

of HLA B53 in the hospitalized Black COVID-19 patients was 0.344, substantially higher than in US national frequencies for Blacks (0.244) and only 0.125 in Black CP donors.

HLA B53 is closely related by structure to HLA B35 [25]. They are nearly identical except for a short region at the 3′ end of exon 2. Consequently, both alleles share homology at the alpha 2 and 3 domains of the class 1 heavy chain but differ by five amino acid in the alpha 1 domain, specifically residues at 77, 80–83 [26]. One consequence of these altered residues is a change in the serologic type of B35 from Bw4 to Bw6 in B53 [27]. Importantly, the altered residues create a broader spectrum of C-terminus peptides that can bind to B53 compared to B35 [28,29]. This circumstance may permit the binding of certain SARS COVID-19 peptides to B53, which by molecular mimicry to B53 bound self- peptides may lead to pathogenic T cell responses in Black COVID-19 patients expressing this allele. Evidence for molecular mimicry due to viral infections and vaccinations have been reported [10,15,16] The HLA B53 allele may be more permissive in binding pathogenic peptides than other HLA alleles, a phenomenon that was recently described in diabetes [30]. Interestingly, a significant positive association between the HLA B22 serotype and SARS-CoV-2 infected Chinese (Hong Kong) was observed [31]. The authors speculated that poor binding of viral peptides to HLA B22 alleles could result in a diminished T cell response though $B22^{+}$ patients did not have more severe disease than patients with other HLA alleles. A significant association was found for severe COVID-19 patients (n = 99) compared to the results of a healthy reference group of 1017 Italian individuals [32]. The latter study did not compare the association of HLA alleles in the severe disease group with a control group with mild symptoms as in the current study of Black COVID-19 patients.

Accelerated /more aggressive treatment may be warranted in early symptomatic COVID-19 patients who are B53 positive, particularly in Black individuals. Black patients as well as those in other racial groups that are B53 negative may not require preemptive treatment unless they have other risk factors. We suggest that Black persons who are B53 positive, should be considered as an at- risk - group and therefore be prioritized for early the SARS – Covid-2 vaccination and treatment. In fact, Black Americans appear to be receiving SARS – Covid-2 vaccinations at lower rates than Caucasian Americans in the first weeks after the rollout according to news analyses [33,34].

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.

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Disclaimer

The views and opinions expressed in this publication are those of the authors and do not reflect the official policy or position of the SUNY, the US Department of Health and Human services and its agencies including the Biomedical Research and Development Authority and the Food and Drug Administration, as well as any agency of the U.S. government. Assumptions made within and interpretations from the analysis are not reflective of the position of any New York State or U.S. government entity.

Data availability

Data from this study is available on reasonable request from the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humimm.2021.07.003.

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