International Journal of Infectious Diseases 98 (2020) 454–459

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short Communication

Mortality in COVID-19 disease patients: Correlating the association of major histocompatibility complex (MHC) with severe acute respiratory syndrome 2 (SARS-CoV-2) variants

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ARTICLE INFO

Article history:
Received 24 May 2020
Accepted 15 July 2020

Keywords:
SARS-CoV-2
COVID-19
SARS
T-cells
MHC
HLA
Cytokines
Peptides
Epitope
Disease association
Viral variants
MHC binding
Cross-reactivity
Autoimmunity

ABSTRACT

Genetic factors such as the HLA type of patients may play a role in regard to disease severity and clinical outcome of patients with COVID-19. Taking the data deposited in the GISAID database, we made predictions using the IEDB analysis resource (TepiTool) to gauge how variants in the SARS-CoV-2 genome may change peptide binding to the most frequent MHC-class I and -II alleles in Africa, Asia and Europe. We caracterized how a single mutation in the wildtype sequence of of SARS-CoV-2 could influence the peptide binding of SARS-CoV-2 variants to MHC class II, but not to MHC class I alleles. Assuming the ORF8 (L84S) mutation is biologically significant, selective pressure from MHC class II alleles may select for viral varients and subsequently shape the quality and quantity of cellular immune responses aginast SARS-CoV-2. MHC 4-digit typing along with viral sequence analysis should be considered in studies examining clinical outcomes in patients with COVID-19.

Introduction

As the 2019 (COVID-19) pandemic caused by the novel coronavirus, SARS-CoV-2 spreads globally, differences in adverse clinical management outcomes have been associated with age >65 years, male gender, and comorbidities such as smoking, diabetes, hypertension, cardiovascular comorbidity, and immunosuppression. Ethnicity has been the focus of attention after data from the United Kingdom showed a disproportionate number of deaths among healthcare workers from Black, Asian, and other ethnic minority backgrounds (Khunti et al., 2020). In addition to ethnicity, socioeconomic factors, prior vaccinations, exposure to other

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https://doi.org/10.1016/j.ijid.2020.07.016

coronaviruses, and other factors need to be considered to explain the geographical and regional variations in susceptibility and severity of the clinical expression of COVID-19 disease and outcomes. In the United States, there have been disproportionate COVID-19 death rates among African Americans at around 2.6 times higher than that of other groups. Although these data could be due to multiple cultural and socioeconomic factors an underlying genetic susceptibility to SARS-CoV-2 infection may be a factor.

Genetic factors were thought to play a causative role in the SARS outbreak's pathogenesis in 2003 in a group of Taiwanese patients, where the HLA-B*4601 haplotype was associated with the severity of the SARS infection (Lin et al., 2003). In Hong Kong Chinese patients, a strong association was shown between HLAB*0703 and HLA-DRB1*0301 alleles and increased susceptibility to SARS infection (Ng et al., 2004). In contrast, L-SIGN homozygote individuals seemed to have a significantly lower risk of SARS infection (Chan et al., 2006).

Covid-19, HLA, and ethnicity

Generally, peripheral blood lymphocytes counts of Black Americans show lower neutrophil counts and a proportionally higher frequency of lymphocytes compared to the rest of the population (Freedman et al., 1997). HLA-association studies of SARS-CoV-1 with HLA-ligands for SARS-CoV-2 have been compiled (Sanchez-Mazas, 2020a). The biological and clinical relevance of immune responses to SARS-CoV-2 requires further discussion:

Autoimmune associations with COVID-19

Some individuals with COVID-19 experienced neurological symptoms, e.g., Guillain Barre Syndrome (Zhao et al., 2020), suggesting an autoimmune background, which has been associated with MHC alleles (Hasan et al., 2014). The role of MHC variants in increased susceptibility to infections or, *vice versa*, immune protection, is well known for a number of viral diseases, e.g., the role of MHC alleles in HIV-control, or increased risk for chronic hepatitis B (Matzaraki et al., 2017).

MHC variants impact the quality of cellular immune responses and the potential for increased inflammation

For instance, *DRB1**15:01-*DQA1**01:02-*DQB1**06:02 (abbreviated 'DR2') dampens autoimmune responses and confers protection from type I Diabetes (Noble and Valdes, 2011; Siebold et al., 2004) associated with strong IFN-γ production. HLA-DQB1*06:02 has been selected for increased resistance to *Yersinia pestis* in immigrants from Africa to Europe; the engagement of CD4+ T-cells to HLA-DQB1*06:02 leads to increased, pro-inflammatory IL-17 production, independent of MHC class II presented peptides (Mangalam et al., 2013) and confers increased risk to the development of anti-myelin directed autoimmune responses (Kaushansky and Ben-Nun, 2014). The haplotypes HLA-DR2-DQ6, DR4-DQ8, and DR3-DQ2 accommodate peptides from infectious pathogens to CD4+ T-cells from Europeans who survived the bottleneck of different, life-threatening infections prevalent in Europe (Matzaraki et al., 2017). These alleles have also shown to be associated with increased risk for autoimmune diseases, for instance, to dietary antigens (celiac disease) (Cecilio and Bonatto, 2015) in part due to their intrinsic capacity to stimulate more robust IL-17 production, that facilitates Central Nervous System (CNS) associated disease manifestations (Pierson et al., 2012). Perhaps the most prominent example for MHC association with infection is the development of HLA-DQ*06:02 associated narcolepsy following H1N1 infection and H1N1-vaccination efforts in 2009/2010 (Mahlios et al., 2013). Such aspects should be considered while examining neurological symptoms in patients after COVID-19 recovery, and also in SARS-CoV-2 vaccination efforts. Thus, certain MHC class II alleles are associated, in part independent of their antigenic peptides, with stronger inflammatory responses that are manifested as increased risks to the development of autoimmune diseases.

Binding of (variant) antigenic peptides to certain MHC class I or class II alleles are the prerequisite for the quality of anti-virus directed cellular immune responses

A prime example is the oncogene E6 from HPV 16, the causative agent of cervical cancer. European HPV-16 E6 variants, such as the E6 variant L83V (at the nucleotide position 350) is associated with increased risk of HPV infection and progression to malignant transformation (de Araujo Souza et al., 2009). HPV E6 variability and clinical outcome are associated with different DRB1*04-DQB1*03 MHC haplotypes in the Swedish compared to other, e.g., Italian, populations: the association is between a viral variant and MHC haplotypes (de Araujo Souza et al., 2009; Zehbe et al., 2003). Such associations ought to be explored in SARS-CoV-2 variants as well. The tremendous impact of single amino acid substitutions in viral pathogens and MHC-restricted T-cell recognition has been described for over 30 years (Rothbard et al., 1989). Single mutations in HIV (Klenerman et al., 1994) and Hepatitis B (Bertoletti et al., 1994) annul cytolytic activities of epitope-specific T-cells. The mutant epitope still binds to the MHC molecule, yet serves as a T-cell antagonist. A similar phenomenon is called a partial agonist, where a mutation in the nominal T-cell epitope leads to the dissociation of IL-4 production and T-cell proliferation (Evavold and Allen, 1991).

Not only do peptide variants from the identical viral pathogen lead to abrogation or dissociation of immune functions in T-cells, but also in very similar peptides (regarding their amino acid composition), that stem from different, unrelated pathogens.This has been previously described for T-cell responses for cross-reactive T-cell responses to *M. tuberculosis* and HIV (Hohn et al., 2003) associated with differential cytokine production. A different example is the cross-reactivity of HPV-specific T-cells to SARS-CoV-1 (Nilges et al., 2003). Thus, not only differential MHC-binding and T-cell responses should be considered in examining SARS-CoV-2 variants, but also potential similar 'cross-reactive' epitopes from other pathogens or 'self'-proteins should be studied.

The question arises, would single mutations in the wildtype of SARS-CoV-2 (or the so-called B strain (Forster et al., 2020) or L strain (Tang et al., 2020)) have an impact on potential MHC presentation?

In order to test this possibility, we analyzed the most frequent MHC class I and II alleles in Europe, Asia, and Africa for binding to the mutations in ORF8 (L84S) and ORF3a (G251V) (see supplementary data sets). The MHC class I binding predictions were made with the IEDB analysis resource (TepiTool; Paul et al., 2016) using a consensus method (Wang et al., 2010) which employs a Stabilized Matrix, Artificial Neural Networks and combinatorial library methods; the MHC Class II binding predictions were done with the IEDB analysis resource (TepiTool; Paul et al., 2016) using the NetMHCIIpan method (Karosiene et al., 2013; Nielsen et al., 2008). These resources have been shown to produce satisfactory results for MHC binding predictions for SARS-CoV-1 and *bona fide* T-cell recognition and MHC class I-predictions of SARS-CoV-2 epitopes (Sanchez-Mazas, 2020b). For MHC class I, starting with a peptide with the mutation site in the middle (flanked by seven amino acid residues to the left and right, resulting in a 15mer peptide) for ORF8 (L84S) (GNYTVSC**L**PFTINCQ and GNYTVSC**S**PFTINCQ) and for

Table 1
ORF8 variants and differential peptide binding.

Protein	Peptide	Rank **wt**	Rank **mut**	Allele
HA	PKYVKQN**T**(K)LKLATGM	1.50	41.00	HLA-DRB1*04:01
HA	CPKYVKQN**T**(K)LKLATG	1.60	41.00	HLA-DRB1*04:01
HA	ACPKYVKQN**T**(K)LKLAT	1.70	41.00	HLA-DRB1*04:01
HA	GACPKYVKQN**T**(K)LKLA	1.80	41.00	HLA-DRB1*04:01
HA	YGACPKYVKQN**T**(K)LKL	2.00	41.00	HLA-DRB1*04:01
HA	YVKQN**T**(K)LKLATGMRN	7.80	32.00	HLA-DRB1*04:01
HA	KYVKQN**T**(K)LKLATGMR	8.50	51.00	HLA-DRB1*04:01
ORF8	*DIGNYTVSC**L**(S)PFTIN*	*9.60*	*19.00*	*HLA-DPA1*01:03/DPB1*02:01*
ORF8	*IDIGNYTVSC**L**(S)PFTI*	*9.60*	*22.00*	*HLA-DPA1*01:03/DPB1*02:01*
ORF8	*IGNYTVSC**L**(S)PFTINC*	*9.60*	*19.00*	*HLA-DPA1*01:03/DPB1*02:01*
ORF8	*PIQYIDIGNYTVSC**L**(S)*	*9.60*	*16.00*	*HLA-DRB1*15:01*
ORF8	DIGNYTVSC**L**(S)PFTIN	17.00	4.40	HLA-DRB3*02:02
ORF8	IGNYTVSC**L**(S)PFTINC	18.00	4.50	HLA-DRB3*02:02
ORF8	IDIGNYTVSC**L**(S)PFTI	19.00	5.30	HLA-DRB3*02:02
ORF8	GNYTVSC**L**(S)PFTINCQ	21.00	6.20	HLA-DRB3*02:02
ORF8	YIDIGNYTVSC**L**(S)PFT	24.00	6.70	HLA-DRB1*04:01
ORF8	IDIGNYTVSC**L**(S)PFTI	28.00	4.90	HLA-DRB1*09:01
ORF8	DIGNYTVSC**L**(S)PFTIN	29.00	5.60	HLA-DRB1*09:01
ORF8	YIDIGNYTVSC**L**(S)PFT	30.00	5.80	HLA-DRB1*09:01
ORF8	IGNYTVSC**L**(S)PFTINC	30.00	7.10	HLA-DRB1*09:01
ORF8	GNYTVSC**L**(S)PFTINCQ	30.00	8.20	HLA-DRB1*09:01
ORF8	IDIGNYTVSC**L**(S)PFTI	39.00	7.90	HLA-DRB1*04:01
ORF8	GNYTVSC**L**(S)PFTINCQ	43.00	9.30	HLA-DRB1*04:01
ORF8	DIGNYTVSC**L**(S)PFTIN	44.00	8.30	HLA-DRB1*04:01
ORF8	IGNYTVSC**L**(S)PFTINC	45.00	8.60	HLA-DRB1*04:01

A lower ranking value designates better MHC class II binding; we used the default recommended rank <10 as the cutoff value for binding. Two MHC class II alleles accommodate the ORF8 wildtype, yet not the variant (L84S). Three MHC class II alleles predict binding to the SARS-CoV-2 ORF8 mut (L84S) variant. For comparison (top of the tablepa), a well-characterized Flu A hemagglutinin epitope showing strong binding of the wildtype, but not the mutant variant to HLA-DRB1*04:01; this epitope is also recognized by T-cells. In bold and underlined, the amino acid in the wildtype sequence, and in parentheses, the amino acid in the mutant variant.

ORF3a (G251V) (VQIHTID**G**SSGVVNP and VQIHTID**V**SSGVVNP), we tested all possible combinations of length from 8 to 14 residues for MHC class I binding, For MHC class II, starting with a peptide with 33 residues with the mutation site in the middle for ORF8 (L84S) (KSPIQYIDIGNYTVSC**L/S**PFTINCQEPKLGSLVV) and for ORF3a (G251V) (KIVDEPEEHVQIHTID**G/V**SSGVVNPVMEPIYDEP), we tested all possible combinations to bind to MHC class II alleles listed in the supplementary data set since MHC class II molecules can accommodate longer peptides, and nominal epitopes may 'glide' within the MHC class II peptide binding cleft (Rammensee, 1995).

We could not identify differences in MHC class I or class II binding characteristics (see Appendix- supplementary data sets Tables S1, S2 and S3) except for three MHC class II alleles, i.e., DRB3*02:02, DRB1*09:01, and DRB1*04:01, that do not allow binding of the wildtype, but accommodate the SARS-CoV-2 ORF8 (L84S) variant (Table 1) and also two MHC class II alleles HLA-DPA1*01:03/DPB1*02:01 that do the opposite: they accommodate the wildtype but not the SARS-CoV-2 ORF8 (L84S) variant (Table 1).

In order to show the validity of the peptide prediction methodology, we examined the literature for viral variants that

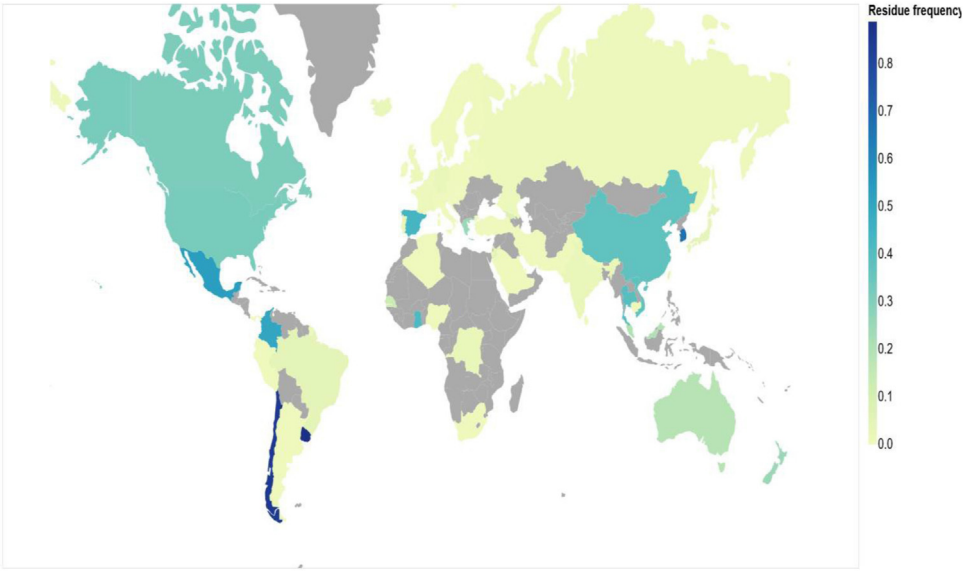

Figure 1. Distribution of the SARS-CoV-2 ORF8 S residue at position 84. 11970 SARS-CoV-2 sequences deposited in the GISAID database by April 27th, 2020. 87% have the Leucine amino acid at position 84 and 13% exhibit Serine. In the countries that submitted more than 100 sequences where the proportion is different: in China, 38% SARS-CoV-2 sequences account for ORF8 (S84L), in Spain 43%, in the USA 32% and in Canada 31%.

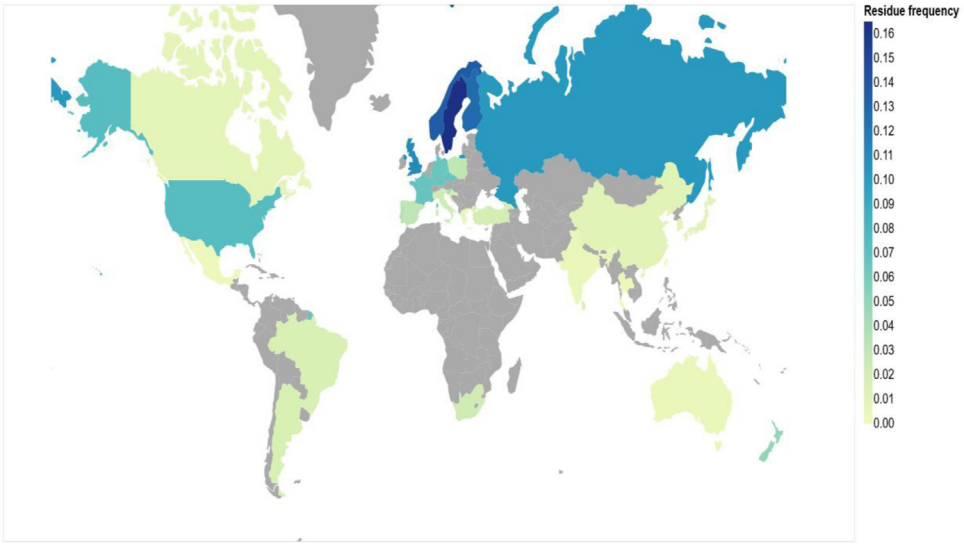

Figure 2. Frequency of HLA-DRB1*04:01 that allows binding of the ORF8 variant epitope. Based on previous studies (Solberg et al., 2008), the allele frequency of HLA-DRB1*04:01 is around 0.03 in Spain, around 0.1 in Caucasians in the USA, but around 0.02 in other ethnicities in the USA, around 0.01 in China, and 0.008 in Canada.

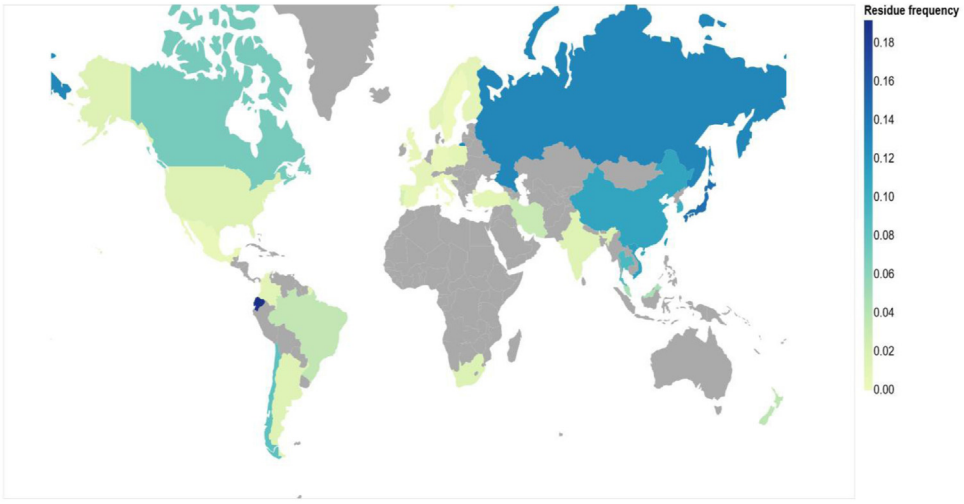

Figure 3. Frequency of HLA-DRB1*09:01. Based on previous studies (Solberg et al., 2008) for HLA-DRB1*09:01, the allele frequency is around 0.008 in Spain, approximately 0.1 in Asians in the USA, but around 0.01 in other ethnicities in the USA, and approximately 0.07 in Canada.

bind differently to one of these alleles and identified the epitope PKYVKQNTLKLATGM, representing the wildtype hemagglutinin sequence from Influenza A virus subtype H3N2 that is recognized by a well-characterized T clone (Hennecke and Wiley, 2002). For this prediction we used a 33 residue peptide with the mutation site in the middle (VNKITYGACPKYVKQN**T**LKLATGMRNVPEKQTR) and the best fitting peptide with 15 residues that were predicted to bind to HLA-DRB1*04:01, is exactly the peptide reported earlier (Hennecke and Wiley, 2002) recognized by a Flu epitope-specific T-cell clone. In contrast, one of the Flu variant (T314K) peptides does not bind to to HLA-DRB1*04:01 (Table 1).

Of the 11,970 SARS-CoV-2 sequences deposited in the GISAID database by April 27th, 2020, 85% exhibit the amino acid Leucine at the position 84 and 15% exhibit Serine. From the countries that have submitted more than 100 sequences, there are four where the distribution of ORF8 (L84S) is different from the worldwide trend: in China, 38% SARS-CoV-2 sequences account for ORF8 (L84S), in Spain 43%, in the USA 32% and in Canada 31% (Figure 1). Based on the information from previous studies (Solberg et al., 2008), the allele frequency of HLA-DRB1*04:01 is around 0.03 in Spain, around 0.1 in Caucasians in the USA but around 0.02 in other ethnicities in the USA, around 0.01 in China and around 0.008 in Canada (Figure 2); for HLA-DRB1*09:01 the allele frequency is around 0.008 in Spain, around 0.1 in Asians in the USA but around 0.01 in other ethnicities in the USA, and around 0.07 in Canada (Figure 3); there is insufficient information available regarding HLA-DRB3*02:02. Thus, ORF8 L84S variant in SARS-CoV-2, but not the wildtype, can be accommodated by DRB1*0401, which has been reported to be associated with susceptibility to HPV infections (de Araujo Souza et al., 2009; Zhao et al., 2018; Chambuso et al., 2018; Chen et al., 1999, 2017), Multiple Sclerosis (Laroni et al., 2006), Rheumatoid Arthritis (Angelini et al., 1992),

type 1 diabetes (Fernandez-Vina et al., 1993; Undlien et al., 1997), and Lyme disease-induced arthritis (Gross et al., 1998). DRB1*09:01 is associated with early childhood myasthenia gravis (Shinomiya et al., 2004). DRB3*02:02 is linked to Grave's disease (Shinomiya et al., 2004), serum IgG antibodies to Chlamydia pneumoniae with essential hypertension (Zabay et al., 2005), and acute necrotizing encephalopathy (Oh et al., 2004). In contrast, the ORF8 L84S variant annuls binding to two MHC class II alleles that the wildtype virus allows: HLA-DPA1*01:03/DPB1*02:01 and DRB1*15:01. DPA1 and DPB1 encode different amino acid residues in the peptide-binding groove of MHC class II alleles that determine which peptides can be presented to CD4+ T-cells. HLA-DPA1*01:03-DPB1*04:02 (but not DPB1*02:01) was associated with an increased risk of developing narcolepsy (Ollila et al., 2015). We have not been able to identify reports of associations of the HLA-DPA1*01:03/DPB1*02:01 heterodimers with increased or decreased risk for disease. DRB1*15:01 represents a significant risk factor for multiple sclerosis and is strongly expressed, due to hypomethylation, in monocytes from DRB1*15:01-positive individuals (Kular et al., 2018). It remains to be demonstrated whether these MHC class II alleles can present the nominal ORF8 epitope – and whether there are MHC class II-peptide specific T-cells in the TCR repertoire that would recognize the MHC II-peptide complex. Peptide binding to specific MHC alleles has been shown to be associated with increased risk for autoimmune diseases. Conceptually, this may argue that more robust cellular immune responses may help in viral clearance, yet also present potential increased risks for subsequent autoimmune diseases affecting the CNS.

In conclusion, there appears to be no selective pressure from MHC class I alleles for the tested SARS-CoV-2 variants. Most likely, there is selective pressure from MHC class II alleles regarding the binding of the ORF8 (L84S) variants, assuming that this mutation may be biologically relevant (Forster et al., 2020; Tang et al., 2020). These data underlines the need to examine SARS-CoV-2 variants and MHC-associations along with clinical outcomes, a detailed longtime observation with a specific focus on CNS-associated symptoms, chiefly in individuals with an increased risk to develop autoimmune responses. Functional analysis applying 'real-world' T-cell recognition assays in association with MHC 4-digit typing is required to determine and gauge SARS-CoV-2 directed cellular immune responses associated with the clinical expression of severity of disease and relevant management endpoints including deaths.

Ethical approval

No ethical approval was required; we used publicly available data and performed predictive in silico analyses

Conflict of interest

All authors declare no conflicts of interest.

Acknowledgments

Professor Ippolito, Sir Zumla, and Prof Mohamed Osman are co-investigators of the Pan-African Network on Emerging and Re-emerging Infections (PANDORA-ID-NET) funded by the European and Developing Countries Clinical Trials Partnership the EU Horizon 2020 Framework Programme for Research and Innovation. Sir Zumla is in receipt of a UK-NIHR Senior Investigatorship. Professor Maeurer is a member of the Gates Foundation's innate immunity advisory group, and the Champalimaud Foundation funds his work. All authors are members of the Global Cancer and Infectious Diseases consortium for Host-directed therapies: Web link: https://fchampalimaud.org/covid19/aci.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2020.07.016.

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