

## REVIEW

# The association of human leucocyte antigen (HLA) alleles with COVID-19 severity: A systematic review and meta-analysis

Zorana Dobrijević<sup>1</sup>  | Nikola Gligorijević<sup>1</sup> | Miloš Šunderić<sup>1</sup> | Ana Penezić<sup>1</sup> | Goran Miljuš<sup>1</sup> | Sergej Tomić<sup>2</sup> | Olgica Nedić<sup>1</sup>

<sup>1</sup>Department for Metabolism, University of Belgrade—Institute for the Application of Nuclear Energy, Belgrade, Serbia

<sup>2</sup>Department for Immunology and Immunoparasitology, University of Belgrade—Institute for the Application of Nuclear Energy, Belgrade, Serbia

## Correspondence

Zorana Dobrijević, Department for Metabolism, Institute for the Application of Nuclear Energy (INEP), University of Belgrade, Belgrade, Serbia.  
Email: [zorana.dobrijevic@inep.co.rs](mailto:zorana.dobrijevic@inep.co.rs)

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## Abstract

Due to their pivotal role in orchestrating the immune response, HLA loci were recognized as candidates for genetic association studies related to the severity of COVID-19. Since the findings on the effects of HLA alleles on the outcome of SARS-CoV-2 infection remain inconclusive, we aimed to elucidate the potential involvement of genetic variability within HLA loci in the molecular genetics of COVID-19 by classifying the articles according to different disease severity/outcomes and by conducting a systematic review with meta-analysis. Potentially eligible studies were identified by searching PubMed, Scopus and Web of Science literature databases. A total of 28 studies with 13,073 participants were included in qualitative synthesis, while the results of 19 studies with 10,551 SARS-CoV-2-positive participants were pooled in the meta-analysis. According to the results of quantitative data synthesis, association with COVID-19 severity or with the lethal outcome was determined for the following alleles and allele families: HLA-A\*01, HLA-A\*03, HLA-A\*11, HLA-A\*23, HLA-A\*31, HLA-A\*68, HLA-A\*68:02, HLA-B\*07:02, HLA-B\*14, HLA-B\*15, HLA-B\*40:02, HLA-B\*51:01, HLA-B\*53, HLA-B\*54, HLA-B\*54:01, HLA-C\*04, HLA-C\*04:01, HLA-C\*06, HLA-C\*07:02, HLA-DRB1\*11, HLA-DRB1\*15, HLA-DQB1\*03 and HLA-DQB1\*06 (assuming either allelic or dominant genetic model). We conclude that alleles of HLA-A, -B, -C, -DRB1 and -DQB1 loci may represent potential biomarkers of COVID-19 severity and/or mortality, which needs to be confirmed in a larger set of studies.

## KEYWORDS

COVID-19, HLA-A, HLA-B, HLA-C, HLA-DQB1, HLA-DRB1

**Abbreviations:** APC, Antigen-presenting cells; CI, Confidence interval; COVID-19, Coronavirus induced disease 2019; DCs, Dendritic cells; GWAS, Genome-wide association study; HLA, Human leucocyte antigen; I<sup>2</sup>, Inconsistency index 2; IL-6, Interleukin 6; IRF-8, Interferon regulatory factor 8; MENA, Middle Eastern and North African; MHC, Major histocompatibility complex; MV, Mechanical ventilation; NGS, Next-generation sequencing; NK, Natural killer (cells); NOS, Newcastle-Ottawa Scale; OR, Odds ratio; ORF, Open reading frame; PCR-SSP, Polymerase chain reaction—sequence-specific primer; PCR-rSSO, Polymerase chain reaction—reverse sequence-specific oligonucleotide; PRISMA, The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SD, Standard deviation; UAE, United Arab Emirates; WHO, World Health Organization.

## 1 | INTRODUCTION

Coronavirus induced disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection of the upper and lower respiratory tract. Besides direct pathological effects of SARS-CoV-2,<sup>1</sup> most data indicated that COVID-19 pathogenesis is underlined by the dysregulated immune response<sup>2</sup> characterised by cytokine release syndrome<sup>3</sup> and lymphocytopenia,<sup>4</sup> which have different features from that in sepsis and severe cases of influenza virus infection.<sup>5</sup> The number and anti-viral functions of T and natural killer cells were found to be critically impaired in severe COVID-19,<sup>6</sup> whereas controversial data were reported for a number and functions of B/plasma cells.<sup>7,8</sup>

Highly variable T cell response in donors with different severity of COVID-19,<sup>6</sup> together with human leucocyte antigen (HLA)-restricted mechanism of T cells activation by antigen-presenting cells (APC),<sup>9</sup> point to a critical role of HLA in the response to SARS-CoV-2. Indeed, it was shown previously that severe COVID-19 patients display a reduced expression of HLA-DR in different APC subsets in blood, including monocytes, B cells and dendritic cells compared to healthy donors or COVID-19 patients displaying mild symptoms.<sup>10</sup> Different mechanisms could explain COVID-19-induced down-regulation of HLA expression on APC, such as increased levels of interleukin 6 (IL-6),<sup>11</sup> viral open reading frame (ORF)-mediated inhibition of IFN-type I production,<sup>12</sup> down-regulation of autophagy and interferon regulatory factor 8.<sup>10</sup> However, these mechanisms could not explain why some individuals develop more severe symptoms than others.

Several genome-wide association studies (GWASs) associated regions and variants of immune regulatory genes with COVID-19 severity, including genes for cell migration, autophagy, antiviral restriction enzyme activators and immune regulators.<sup>13–17</sup> The reported associations were considered as very low (Odds ratio (OR) below 1.5) and weakly predictive genomic markers of disease severity.<sup>17</sup> On the other hand, alleles of HLA genes within the major histocompatibility complex (MHC) represent obvious candidates for association studies on COVID-19 severity, due to their pivotal role in orchestrating the immune response. Major histocompatibility complex class I molecules are expressed by many cell types, and are involved in the presentation of most SARS-CoV-2 epitopes to cytotoxic CD8+ T cells.<sup>18</sup> MHC class II are expressed exclusively by APC and activated subsets of T cells, and they are critically involved in the presentation of antigens to CD4+T cells.<sup>19</sup> Since HLA genes are among the most polymorphic genes in the human genome, such repertoire of alleles with different binding affinity for SARS-CoV-2 peptides could represent the important mechanism involved in the inter-individual differences in the clinical presentation of COVID-19.

Based on this hypothesis, a relatively large number of studies investigated the role of HLA class I and class II alleles as predictors of COVID-19 clinical course and the disease outcome.<sup>13,20–51</sup> However, their results varied significantly, possibly due to the differences in the study designs, severity-based classification criteria, ethnicity of participants, or other factors with potential confounding effects. The

observed heterogeneity between these studies makes it difficult to comprehensively assess the impact of allelic variants on disease severity. Therefore, in order to elucidate the involvement of HLA alleles in the molecular basis of the immune response to SARS-CoV-2, we classified articles according to different outcomes of SARS-CoV-2 infection and conducted the systematic review and the meta-analysis. To our knowledge, this is the first meta-analysis on the effects of HLA alleles on COVID-19 severity and outcome. Furthermore, the pooled analysis was conducted for allelic and dominant genetic model, since one of the reasons for between-study variations could be the difference in the assumed genetic model. Since we aimed to reclassify the results of the eligible studies in order to match the same criteria, whenever possible, as well as to analyse different genetic models, the present meta-analysis could even yield associations not presented in the original eligible studies and lead to the identification of additional risk alleles.

## 2 | MATERIAL AND METHODS

The present systematic review and the quantitative data synthesis were conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA).<sup>52</sup>

### 2.1 | Publication search

Potentially relevant articles were initially identified by searching the literature databases PubMed, Web of Science and Scopus using the search strategy which included the combinations of keywords: gene/protein name or identifier ('Human leucocyte antigen' or 'HLA' or 'Major histocompatibility complex' or 'MHC'); term 'polymorphism' or related terms ('variant', 'allele', 'genotype' or 'frequency'); term 'COVID-19' or 'SARS-CoV-2'. During the initial publication search, language restriction was not applied. The thorough examination of reference lists of the retrieved original articles and previously published reviews was conducted in order not to miss additional potentially relevant studies. The search was limited to publication date in 2020–2021 (database inception to 31<sup>st</sup> December 2021).

### 2.2 | Inclusion/exclusion criteria, data extraction

The following predetermined criteria were used for eligibility assessment of the retrieved studies: a) study included allele frequencies/carrier rates of HLA loci -A, -B, -C, -DRB1, -DQA1, -DQB1, -DPA1 and -DPB1 in groups of SARS-CoV-2-positive human participants which allowed estimation of associations with COVID-19 severity and/or outcome; b) original full-text articles; c) sufficient data on allele/carrier counts for the calculations of risk estimates; d) detailed information provided on the study design, recruitment of participants, diagnostic and severity assessment procedure, outcome assessment, ethnicity of participants, HLA typing and statistical

methodology, as well as on other relevant data; e) article written in English. In cases when certain data were not presented, mainly allele/carrier counts, or clarification of a specific methodological procedure and the presented results was needed, we attempted to acquire the necessary information through personal communication with corresponding authors.

Ecological studies were not considered relevant for this meta-analysis. The predetermined exclusion criteria included the retraction of articles, poor quality of study design and errors in the presentation of results. Studies analysing the severity of COVID-19 in patients with malignant diseases were excluded. Separate entries were made, based on the results of each eligible study, in order to assess as many as possible severity group comparisons, COVID-19-related fatality rates or other potential outcomes. We reclassified the groups of patients based on the COVID-19 severity in order to match the World Health Organisation (WHO) guidelines,<sup>53,54</sup> since severity categories varied substantially between studies.

The data considered relevant for the extraction included: first author's name and the year of publication, country and the ethnicity of participants, study design, the diagnostic criteria for COVID-19, severity assessment criteria, follow-up period, patient recruitment method, analysed HLA loci, typing methodology, number of SARS-CoV-2-positive participants, age and gender of participants, allele counts/frequencies or allele-carrier counts/frequencies. The data synthesis was possible in cases when: a) three or more entries corresponded to a specific comparison of allele/carrier frequency in certain groups of patients with different disease severity/outcome; b) allele/carrier frequency was  $\geq 5\%$  in at least one of the patient groups included in the same comparison. Based on the allele counts and their classification according to peptide-binding properties,<sup>55</sup> we calculated HLA-A and HLA-B supertype frequencies in different COVID-19 severity/outcome groups. Whenever possible, we calculated counts of two-digit resolution alleles, based on the data presented for 4-digit alleles.

In order to assess the methodological quality of the studies suitable for the inclusion in qualitative and quantitative data synthesis, we used the Newcastle-Ottawa Scale (NOS).<sup>56</sup> The scoring for each study in all three domains (selection of subjects, comparability and the outcome) was based on the methodology related to SARS-CoV-2-positive participants, even though some studies had case-control design, since the present data synthesis considers disease severity/outcome.

## 2.3 | Statistical analysis

The between-study heterogeneity and the quantitative data synthesis were conducted using statistical software OpenMeta-analyst (The Centre for Evidence-based Medicine, Brown University, Providence, RI, USA).<sup>57</sup> ORs and their 95% confidence intervals (CIs) were used as risk estimates. Cochran's Q test and the inconsistency index ( $I^2$ ) were used for assessing between-study heterogeneity ( $p$  value  $< 0.1$  or  $I^2 \geq 50\%$  indicated significant heterogeneity). In

cases of significant heterogeneity, we selected random-effects statistical model for pooling risk estimates by the method proposed by DerSimonian and Laird.<sup>58</sup> Otherwise, Mantel-Haenszel method was selected for pooling results under the fixed-effect model.<sup>59</sup> Separate analyses were conducted for studies that presented allele counts or frequencies and for those presenting allele-carrier counts/frequencies. Meta-analyses based on allele counts tested the allelic model of association, while the supposed genetic model in the pooled analysis relying on allele-carrier rates was dominant (treating homozygotes and heterozygotes as a single category).

We considered plausible to conduct the publication bias assessment in cases when the number of entries to a single comparison was more than 5. For such purpose, the visual inspection of funnel plots and the results of Egger's test were used.

## 3 | RESULTS

### 3.1 | Study identification

Figure 1 illustrates the study selection process for the present systematic review and meta-analysis. Out of 1041 records retrieved in the database search, 499 were initially excluded from further screening procedure as duplicate records. During the phase of screening by the title and abstract, additional 451 records not relevant for the topic were removed. The eligibility assessment led to the exclusion of 64 records, most of which had inadequate study design (35 review articles, eight ecological studies). Among the rest of the records that did not meet the inclusion criteria were 2 articles not written in English, 2 pre-prints and 8 meeting abstracts. We excluded 1 study that compared genotype distributions between patients with severe COVID-19 and healthy controls, instead of between SARS-CoV-2-positive patients stratified according to disease severity. Additional 2 studies were excluded since they provided results either for patients with severe or mild disease. Other 4 records were eliminated from data synthesis since they did not provide enough methodological data, or the study group and the methodological approach were inadequate. One study was excluded from qualitative and qualitative data synthesis as it presented results as single nucleotide polymorphism genotypes, instead of HLA alleles named according to the standardized nomenclature.<sup>60</sup> Finally, after eliminating a study that did not provide allele/carrier counts or frequencies, a total of 28 studies<sup>13,20–23,25,27–31,33–42,44,46–51</sup> with 13,073 SARS-CoV-2-positive participants were selected for qualitative data synthesis and their basic characteristics are given in Table 1.

Among the eligible studies, 17 were conducted in Caucasian or populations of the Middle Eastern - North African ancestry, while six included participants with East Asian or South Asian origin. Majority of the studies analysed HLA class I classical loci (HLA-A, -B and -C), while among the class II loci, HLA-DRB1 was the most extensively studied. The methodological quality assessment suggested that NOS score 7–9, corresponding to high quality, was assigned to the majority of the studies, while 3 studies were rated as of moderate

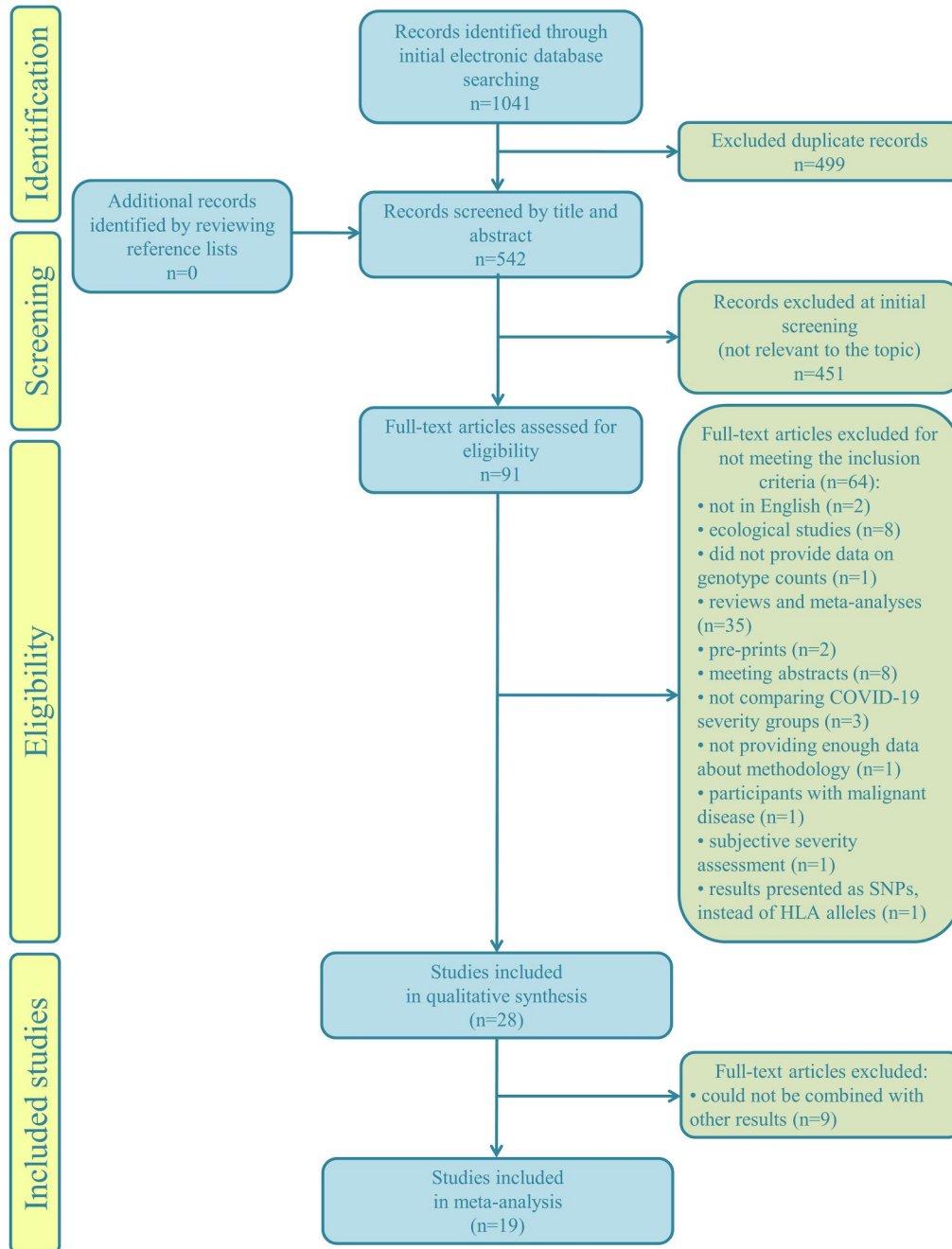


FIGURE 1 Flowchart of the study selection process

quality (score 6) (Table S1). The largest number of studies failed to score points for comparability domain, due to the lack of adjustments of results for potential confounders.

Even though we attempted to include the results of nine eligible studies in the quantitative data synthesis, the entries based on the data from these studies could not be combined with the results from other articles. The reasons for their exclusion from the meta-analysis were: significant differences in the classification of SARS-CoV-2-positive patients according to the clinical presentation of symptoms, disease severity or outcome, as well as the unmatched typing resolution.

### 3.2 | Quantitative data synthesis

The final selection of studies for quantitative data synthesis resulted in 19 articles with the overall number of 10,551 SARS-CoV-2-positive patients. The vast majority of selected articles provided data for multiple HLA loci, as well as for various groups of patients stratified according to COVID-19 severity/outcome, which were used as separate entries in the meta-analysis (Table 1, Table S2). The number of the selected studies and the corresponding entries for pooled analysis was adequate for HLA-A, -B, -C, -DRB1 and -DQB1.

TABLE 1 Characteristics of the studies included in the qualitative synthesis

Authors <sup>ref</sup>	Year	Country	Ethnicity	Genotyping method	HLA locus	Allele counts/freq.	Allele carrier counts/freq.	SARS-CoV-2+ participants (n)	Male/female (n)	Age (years)	Included in quantitative synthesis
Littera et al. <sup>20</sup>	2020	Italy	Caucasian	PCR-SSP, confirmation by NGS	-A, -B, -C, -DRB1	+	-	182	70/112	53.2 (18.1) <sup>a</sup>	+
Wang et al. <sup>21</sup>	2020	China	East Asian	NGS	-A, -B, -C, -DRB1, -DQA1, -DQB1, -DRB3/4/5, -DPB1	+	-	332 (284 unrelated)	135/149	-	+
Amoroso et al. <sup>22</sup>	2021	Italy	Caucasian	DNA-based techniques (not-specified)	-A, -B, -DRB1	-	+	265	193/72	59.8 (11.9) <sup>a</sup>	-
Anzures et al. <sup>23</sup>	2021	Japan	East Asian	PCR-rSSO	-A, -B, -C	+	+	178	106/72	57.5 (44.0–77.0) <sup>b</sup>	+
Bernal et al. <sup>25</sup>	2021	Spain	Mixed	PCR-rSSO	-A, -B, -C	-	+	201	120/81	57.6 (11.8) <sup>a</sup>	+
De Marco et al. <sup>27</sup>	2021	Brazil	Mixed	Not specified	-A, -B, -DRB1	-	+	720	437/283	51.1 (8–83) <sup>c</sup>	+
Detsika et al. <sup>28</sup>	2021	Greece	Caucasian	PCR-rSSO, PCR-SSP	-A, -B, -C, -DRB1, -DQB1	-	+	125	76/49	53.3 (20–86) <sup>c</sup>	+
Ebrahimi et al. <sup>29</sup>	2021	Iran	MENA	PCR-SSP	-DRB1, -DQB1	+	+	144	79/65	-	+
Ertosun et al. <sup>30</sup>	2021	Turkey	MENA	PCR-rSSO, serological typing for A10 and B22	-A, -B, -DRB1	+	+	100	74/26	47.41 (13.40) <sup>a</sup> 49.5 (37.5–58) <sup>b</sup>	+
Farahani et al. <sup>31</sup>	2021	Iran	MENA	PCR-SSP	-A, -B, -DRB1	+	-	48	-	-	-
Gutiérrez-Bautista et al. <sup>33</sup>	2021	Spain	Caucasian	PCR-rSSO	-A, -B, -C, -DRB1, -DQB1	+	-	450	230/220	25–98 <sup>d</sup>	+
Hajebi et al. <sup>34</sup>	2021	Iran	MENA	PCR-SSP	-A, -B, -DRB1	+	-	25	19/6	18–70 <sup>d</sup>	-
Iturrieta-Zuazo et al. <sup>35</sup>	2021	Spain	Caucasian	PCR-rSSO	-A, -B, -C	-	+	45	27/18	-	+
Khor et al. <sup>36</sup>	2021	Japan	East Asian	NGS	-A, -B, -C, -DRB1, -DQA1, -DQB1, -DRB3/4/5, -DPA1, -DPB1	+	-	190	101/89	-	-

(Continues)

TABLE 1 (Continued)

Authors <sup>ref</sup>	Year	Country	Ethnicity	Genotyping method	HLA locus	Allele counts/freq.	Allele carrier counts/freq.	SARS-CoV-2+ participants (n)	Male/female (n)	Age (years)	Included in quantitative synthesis
Kreutmair et al. <sup>37</sup>	2021	Germany and France	Mixed	NGS, PCR-rSSO	-A, -B, -C	+	+	57	34/23	62.15 (13.96) <sup>a</sup>	+
Langton et al. <sup>38</sup>	2021	UK	Caucasian	NGS	-A, -B, -C, -DRB1, -DQA1, -DQB1, -DRB3/4/5, -DPA1, -DPB1	+	+	147	59/88	51 (24-77)	-
Lorente et al. <sup>39</sup>	2021	Spain	Caucasian	PCR-rSSO	-A, -B, -C, -DRB1, -DQB1	-	+	72	31/41	-	-
Naemi et al. <sup>40</sup>	2021	Bangladesh, India, Pakistan	South Asian	PCR-rSSO	-A, -B, -C, -DRB1, -DQA1, -DQB1	+	-	95	89/6	-	+
Naemi et al. <sup>41</sup>	2021	Saudi Arabia	MENA	PCR-rSSO	-A, -B, -C, -DRB1, -DQB1	+	-	135	93/42	47.7 (15.7) <sup>a</sup>	+
Norin et al. <sup>42</sup>	2021	USA	Mixed	PCR-rSSO	-A, -B, -C, -DRB1, -DQA1, -DQB1, -DRB3/4/5, -DPA1, -DPB1	+	+	76	-	-	+
Scheteilig et al. <sup>44</sup>	2021	Germany	Caucasian	NGS	-A, -B, -C, -DRB1	-	+	6919	2282/4637	18-61 <sup>d</sup>	+
Severe Covid-19 GWAS Group <sup>13</sup>	2021	Italy	Caucasian	NGS	-A, -B, -C, -DRB1, -DQA1, -DQB1, -DPB1	+	-	835	586/249	65 (56-75) <sup>b</sup>	-
Vishnubhotla et al. <sup>46</sup>	2021	India	South Asian	NGS	-A, -B, -C, -DRB1, -DQA1, -DQB1, -DRB3/4/5, -DPA1, -DPB1	-	+	96	46/50	16-85 <sup>d</sup>	-
Warren et al. <sup>47</sup>	2021	USA	Mixed	RNA-sequencing	-A, -B, -C, -DRB1, -DQA1, -DQB1, -DPA1, -DPB1	+	+	100	62/38	61.06 (16.07) <sup>a</sup>	+
Weiner et al. <sup>48</sup>	2021	Germany	Mixed	NGS	-A, -B, -C, -DRB1, -DQA1, -DQB1, -DRB3/4/5, -DPA1, -DPB1	-	+	135	90/45	60 (48-71) <sup>b</sup>	+
		Spain and Switzerland	Not-specified	NGS	-A, -B, -C, -DRB1, -DQA1, -DQB1, -DRB3/4/5, -DPA1, -DPB1	-	+	153	71/82	57 (44-67) <sup>b</sup>	+

TABLE 1 (Continued)

Authors <sup>ef</sup>	Year	Country	Ethnicity	Genotyping method	HLA locus	Allele counts/freq.	Allele carrier counts/freq.	SARS-CoV-2+ participants (n)	Male/female (n)	Age (years)	Included in quantitative synthesis
		USA	Mixed	RNA-sequencing		-	+	147	95/52	60 (48-72) <sup>b</sup>	+
Yung et al. <sup>49</sup>	2021	China	East Asian	Sequencing	-B	+	+	190	96/94	32 (17-93) <sup>c</sup>	+
Abdelhafiz et al. <sup>50</sup>	2022	Egypt	MENA	PCR-rSSO	-B, -C	+	-	69	31/38	-	-
Alnaqbi et al. <sup>51</sup>	2022	UAE	MENA	NGS	-A, -B, -C, -DRB1, -DQB1	-	+	115	79/36	16-80 <sup>d</sup>	+

Abbreviations: MENA, Middle Eastern and North African; NGS, Next-generation sequencing; PCR-rSSO, Polymerase chain reaction - reverse sequence-specific oligonucleotide; PCR-SSP, Polymerase chain reaction - sequence-specific primer; UAE, United Arab Emirates.

<sup>a</sup>Mean (SD).

<sup>b</sup>Median (IQR).

<sup>c</sup>Median (range).

<sup>d</sup>Range.

The comparison of HLA-A allele/carrier frequencies among COVID-19 patients with severe and non-severe disease (moderate + mild, according to WHO criteria) did not yield statistically significant results (Table 2 and Tables S3 and S4). However, HLA-A\*68:02 and the allele family HLA-A\*68 were found to associate with the reduced risk of admittance to intensive care unit (ICU) among hospitalised COVID-19 patients ( $p = 0.036$ , OR = 0.219, 95% CI = 0.053-0.908 and  $p = 0.014$ , OR = 0.448, 95% CI = 0.236-0.850 for HLA-A\*68:02 and HLA-A\*68, respectively) (Table 2, Figure 2). In the same comparison, marginal significance was reached for the association of HLA-A\*31 allele with the ICU-admittance status (ICU + vs. ICU-) (Table 2, Figure 2). HLA-A supertypes were not found to associate with the disease severity in either of these two comparisons (severe vs. non-severe and ICU + vs. ICU-) (Table 2). When HLA-A allele frequencies were compared between hospitalised COVID-19 patients and those with mild disease, HLA-A\*01 was associated with lower hospitalisation risk (Table 2). Furthermore, HLA-A\*03 allele family was found to associate with an increased risk of lethal outcome in hospitalised COVID-19 patients (Table 2).

Carrier frequencies did not differ between ICU+ and ICU- patients for any HLA-A allele tested. The comparison of allele-carrier rate among hospitalised and non-hospitalised SARS-CoV-2-positive participants demonstrated the protective effect of HLA-A\*03, while the opposite direction of association under dominant genetic model was found for HLA-A\*11 and HLA-A\*23 (Table 2, Figure 3).

When HLA-B allele frequencies were compared between patients with severe and non-severe COVID-19, HLA-B\*51:01 was found to associate with an increased disease severity ( $p = 0.039$ , OR = 1.699, 95% CI = 1.027-2.809), while the opposite effect was determined for HLA-B\*54:01 ( $p = 0.025$ , OR = 0.353, 95% CI = 0.141-0.879) (Table 2, Figure 4). Furthermore, HLA-B\*53 allele family associated with significantly increased risk of COVID-19-related hospitalisation (allelic genetic model  $p < 0.001$ , OR = 6.403, 95% CI = 2.253-18.198) (Table 2, Figure 4). Among the tested HLA-B alleles, only HLA-B\*14 showed a statistically significant association with the lethal outcome, with the OR suggesting the protective effect (allelic model,  $p = 0.030$ , OR = 0.434, 95% CI = 0.203-0.924) (Table 2, Table S5).

Test of genetic association under the dominant genetic model demonstrated the association of HLA-B\*07:02 with the reduced risk of ICU-admittance in hospitalised patients (Table 2, Table S6, Figure 4). However, such association was not found in the comparison which included both hospitalised patients and those with mild symptoms (Table 2). Marginal significance was reached in the comparison of HLA-B\*40:02 carrier rate between hospitalised and non-hospitalised patients, while SARS-CoV-2 carriers of HLA-B\*15 were found to have an increased need for mechanical ventilation (Table 2, Figure 4).

In tests of association which referred to HLA-C, statistically significant differences in allele frequencies between groups of patients classified according to COVID-19 severity/outcome were found only for HLA-C\*06 family in the ICU + versus ICU- comparison



TABLE 2 Meta-analysis of association between HLA-A alleles and COVID-19 severity/outcome: allelic and dominant genetic models

Allelic model	HLA allele	Severe versus Non-severe <sup>a</sup>			Hospitalised versus Non-hospitalised <sup>b</sup>			ICU + versus ICU-			Lethal versus Non-lethal						
		n <sup>c</sup>	OR (95% CI)	p	Phet <sup>d</sup>	n	OR (95% CI)	p	Phet	n	OR (95% CI)	p	Phet				
	A*01	3	0.829 (0.327–2.099)	0.692	0.498	3	<b>0.283 (0.118–0.679)*</b>	<b>0.005</b>	0.939	4	1.233 (0.860–1.766)	0.254	0.259	3	1.116 (0.729–1.708)	0.613	0.892
	A*03	3	0.894 (0.367–2.178)	0.805	0.698	3	0.718 (0.183–2.809)	0.634	0.013	4	1.376 (0.941–2.013)	0.100	0.719	3	<b>1.810 (1.175–2.788)</b>	<b>0.007</b>	0.621
	A*31	-	-	-	-	3	1.665 (0.409–6.788)	0.477	0.472	3	<b>0.367 (0.137–0.984)</b>	<b>0.046</b>	0.980	3	0.563 (0.195–1.627)	0.289	0.888
	A*68	-	-	-	-	3	1.947 (0.871–4.352)	0.104	0.795	4	<b>0.448 (0.236–0.850)</b>	<b>0.014</b>	0.731	3	1.206 (0.652–2.233)	0.551	0.474
	A*68:02	-	-	-	-	3	<b>0.219 (0.053–0.908)</b>	<b>0.036</b>	0.511	-	-	-	-	-	-	-	-
	B*14	-	-	-	-	3	0.868 (0.481–1.567)	0.639	0.982	3	<b>0.434 (0.203–0.924)</b>	<b>0.030</b>	0.800	-	-	-	-
	B*51:01	4	<b>1.699 (1.027–2.809)</b>	<b>0.039</b>	0.863	-	-	-	-	3	0.994 (0.611–1.617)	0.982	0.311	-	-	-	-
	B*53	-	-	-	-	3	<b>6.403 (2.253–18.198)</b>	<b>&lt;0.001</b>	0.279	3	0.770 (0.286–2.075)	0.605	0.265	-	-	-	-
	B*54	3	<b>0.353 (0.141–0.879)</b>	<b>0.025</b>	0.877	-	-	-	-	-	-	-	-	-	-	-	-
	B*54:01	3	<b>0.353 (0.141–0.879)</b>	<b>0.025</b>	0.877	-	-	-	-	-	-	-	-	-	-	-	-
	C*06	3	1.480 (0.817–2.682)	0.196	0.983	-	-	-	-	4	<b>1.630 (1.102–2.412)</b>	<b>0.014</b>	0.842	3	1.520 (0.816–2.833)	0.187	0.132
Dominant model	HLA allele	n <sup>c</sup>	OR (95% CI)	p	Phet <sup>d</sup>	n	OR (95% CI)	p	Phet	n	OR (95% CI)	p	Phet	n	OR (95% CI)	p	Phet
	A*03	3	<b>0.443 (0.201–0.980)</b>	<b>0.044</b>	0.299	3	0.996 (0.475–2.090)	0.992	0.819	3	1.027 (0.482–2.192)	0.444	0.932	-	-	-	-
	A*11	4	<b>2.312 (1.216–4.399)</b>	<b>0.011</b>	0.187	3	1.089 (0.093–12.743)	0.946	0.025	3	1.046 (0.084–12.979)	0.972	0.023	-	-	-	-
	A*23	3	<b>5.594 (1.777–17.613)</b>	<b>0.003</b>	0.155	3	0.704 (0.201–2.475)	0.585	0.902	3	0.728 (0.203–2.605)	0.625	0.969	-	-	-	-
	B*07:02	-	-	-	-	5	0.752 (0.446–1.268)	0.285	0.165	3	<b>0.415 (0.183–0.939)</b>	<b>0.035</b>	0.403	4	0.634 (0.347–1.157)	0.138	0.287
	B*15	-	-	-	-	-	-	-	-	-	-	-	-	3	<b>1.487 (1.017–2.173)</b>	<b>0.041</b>	0.638
	B*40:02	3	<b>0.424 (0.183–0.979)</b>	<b>0.045</b>	0.512	3	2.996 (0.463–19.380)	0.249	0.542	3	7.600 (0.566–101.981)	0.126	0.377	-	-	-	-
	C*04	3	<b>3.165 (1.732–5.785)</b>	<b>&lt;0.001</b>	0.971	3	0.920 (0.141–6.016)	0.931	0.020	3	0.858 (0.121–6.081)	0.878	0.015	-	-	-	-
	C*04:01	3	1.119 (0.831–1.505)	0.459	0.221	5	1.324 (0.555–3.158)	0.527	0.080	3	0.842 (0.158–4.478)	0.841	0.041	4	<b>2.414 (1.415–4.119)</b>	<b>0.001</b>	0.122
	C*07:02	-	-	-	-	5	0.801 (0.514–1.247)	0.325	0.106	3	<b>0.526 (0.288–0.961)</b>	<b>0.037</b>	0.365	4	0.786 (0.458–1.350)	0.383	0.677

<sup>a</sup>Non-severe = Moderate + Mild (World Health Organisation [WHO] criteria).<sup>b</sup>Hospitalised = Severe + Moderate, Non-hospitalised = Mild (WHO criteria).<sup>c</sup>Number of studies/datasets.<sup>d</sup>p value obtained in heterogeneity test.<sup>e</sup>MV—mechanical ventilation.

\*Statistically significant results are shown in bold.

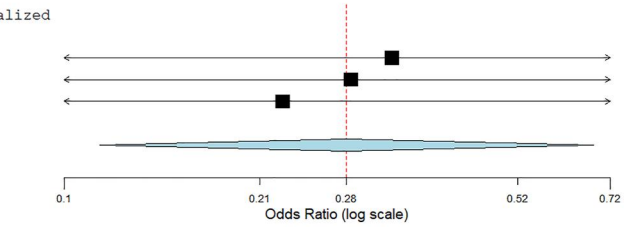


(Table 2, Table S7, Figure 5). For dominant genetic model of association, however, the protective effect against the ICU-admittance in patients hospitalised due to COVID-19 was shown for HLA-C\*07:02 (Table 2, Table S8, Figure 5). The carrier frequency for HLA-C\*04 was significantly higher in the group of hospitalised COVID-19 patients,

compared to those with mild disease. Additionally, carriers of HLA-C\*04:01, which belongs to the same allele family, were found to have an increased risk of developing severe clinical presentation of COVID-19, requiring invasive mechanical ventilation (Table 2, Figure 5).

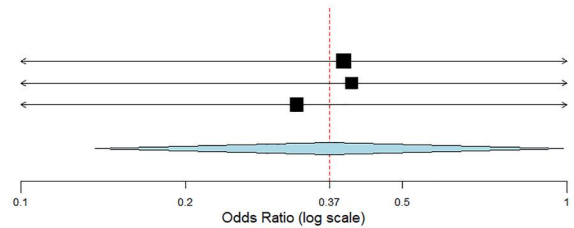
**(a)**

Studies	Estimate (95% C.I.)	Ev/Hospitalized	Ev/Non-hospitalized
Littera et al. 2020 [20]	0.332 (0.076, 1.448)	2/78	21/286
Ertosun et al. 2021 [30]	0.287 (0.064, 1.280)	2/50	19/150
Norin et al. 2021 [42]	0.225 (0.047, 1.081)	2/72	9/80
<b>Overall (I<sup>2</sup>=NA, P=0.939)</b>	<b>0.283 (0.118, 0.679)</b>	<b>6/200</b>	<b>49/516</b>



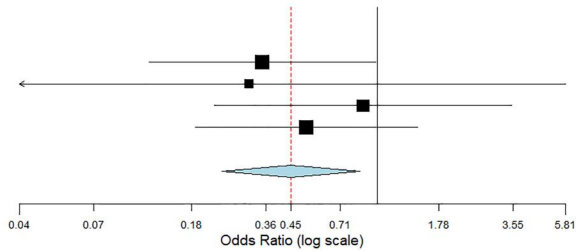
**(b)**

Studies	Estimate (95% C.I.)	Ev/ICU+	Ev/ICU-
Gutierrez-Bautista et al. 2021 [33]	0.390 (0.087, 1.739)	2/252	13/646
Naemi et al. 2021 [40]	0.403 (0.046, 3.528)	1/62	5/128
Warren et al. 2021 [47]	0.320 (0.063, 1.624)	2/100	6/100
<b>Overall (I<sup>2</sup>=NA, P=0.980)</b>	<b>0.367 (0.137, 0.984)</b>	<b>5/414</b>	<b>24/874</b>



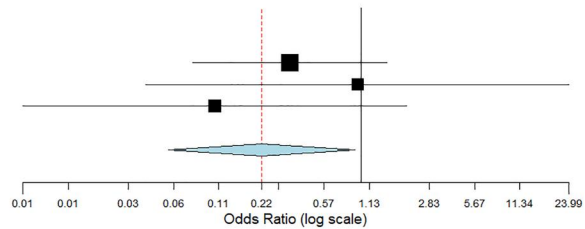
**(c)**

Studies	Estimate (95% C.I.)	Ev/ICU+	Ev/ICU-
Gutierrez-Bautista et al. 2021 [33]	0.343 (0.119, 0.986)	4/252	29/646
Kreutmair et al. 2021 [37]	0.302 (0.016, 5.810)	0/24	4/70
Naemi et al. 2021 [40]	0.879 (0.219, 3.521)	3/62	7/128
Warren et al. 2021 [47]	0.516 (0.183, 1.455)	6/100	11/100
<b>Overall (I<sup>2</sup>=NA, P=0.731)</b>	<b>0.448 (0.236, 0.850)</b>	<b>13/438</b>	<b>51/944</b>



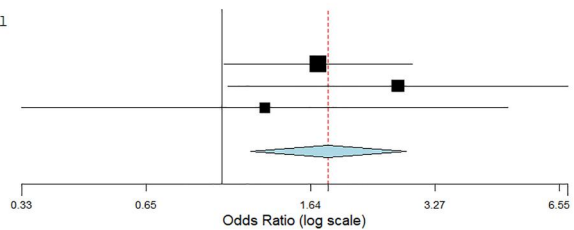
**(d)**

Studies	Estimate (95% C.I.)	Ev/ICU+	Ev/ICU-
Gutierrez-Bautista et al. 2021 [33]	0.337 (0.076, 1.482)	2/252	15/646
Kreutmair et al. 2021 [37]	0.946 (0.037, 23.989)	0/24	1/70
Warren et al. 2021 [47]	0.107 (0.006, 2.008)	0/100	4/100
<b>Overall (I<sup>2</sup>=NA, P=0.511)</b>	<b>0.219 (0.053, 0.908)</b>	<b>2/376</b>	<b>20/816</b>



**(e)**

Studies	Estimate (95% C.I.)	Ev/Lethal	Ev/Non-lethal
Gutierrez-Bautista et al. 2021 [33]	1.708 (1.011, 2.885)	21/140	71/758
Naemi et al. (Saudi Arabian) 2021 [41]	2.667 (1.035, 6.873)	8/58	12/212
Naemi et al. (South Asian) 2021 [40]	1.270 (0.327, 4.929)	3/40	9/150
<b>Overall (I<sup>2</sup>=NA, P=0.621)</b>	<b>1.810 (1.175, 2.788)</b>	<b>32/238</b>	<b>92/1120</b>



**FIGURE 2** Meta-analysis of the association between HLA-A alleles and COVID-19 severity under allelic genetic model. (a) HLA-A\*01, comparison hospitalised versus non-hospitalised; (b) HLA-A\*31, comparison intensive care unit (ICU) + versus ICU-; (c) HLA-A\*68, comparison ICU + versus ICU-; (d) HLA-A\*68:02, comparison ICU + versus ICU-; (e) HLA-A\*03, comparison lethal versus non-lethal. Each entry in the pooled analysis is presented by the first author's name and the publication year, together with a reference number in square brackets. The results of the included studies are presented as Odds ratios (ORs), with 95% confidence interval (CI), and the overall effects with 95% CIs are given in forest plots. The size of the square symbol representing the study's result is proportional to the weight assigned to the study. Presented *p* values are derived from heterogeneity tests and the overall effect is represented by diamond symbol with lateral tips corresponding to 95% CI. Hospitalised = Severe + Moderate disease, Non-hospitalised = Mild (World Health Organisation criteria); ICU+/- = ICU admittance status; Ev—events (allele/carrier count)

The meta-analyses of the association between HLA-DRB1 alleles and ICU-admittance resulted in marginal statistical significance for the effect of HLA-DRB1\*15, while HLA-DRB1\*11 allele family was found to be protective against both COVID-19-related hospitalisation and the clinical progression of disease requiring treatment in ICU (Table 3, Figure 6). In the pooled analysis related to another HLA class II locus, HLA-DQB1, allele families HLA-DQB1\*03 and HLA-DQB1\*06 exhibited the opposite effect on ICU-admittance ( $p = 0.019$ , OR = 0.748, 95% CI = 0.587–0.953 and  $p = 0.011$ , OR = 1.384, 95% CI = 1.077–1.779 for HLA-DQB1\*03 and HLA-DQB1\*06, respectively) (Table 3, Figure 6).

### 3.3 | Publication bias assessment and sensitivity analysis

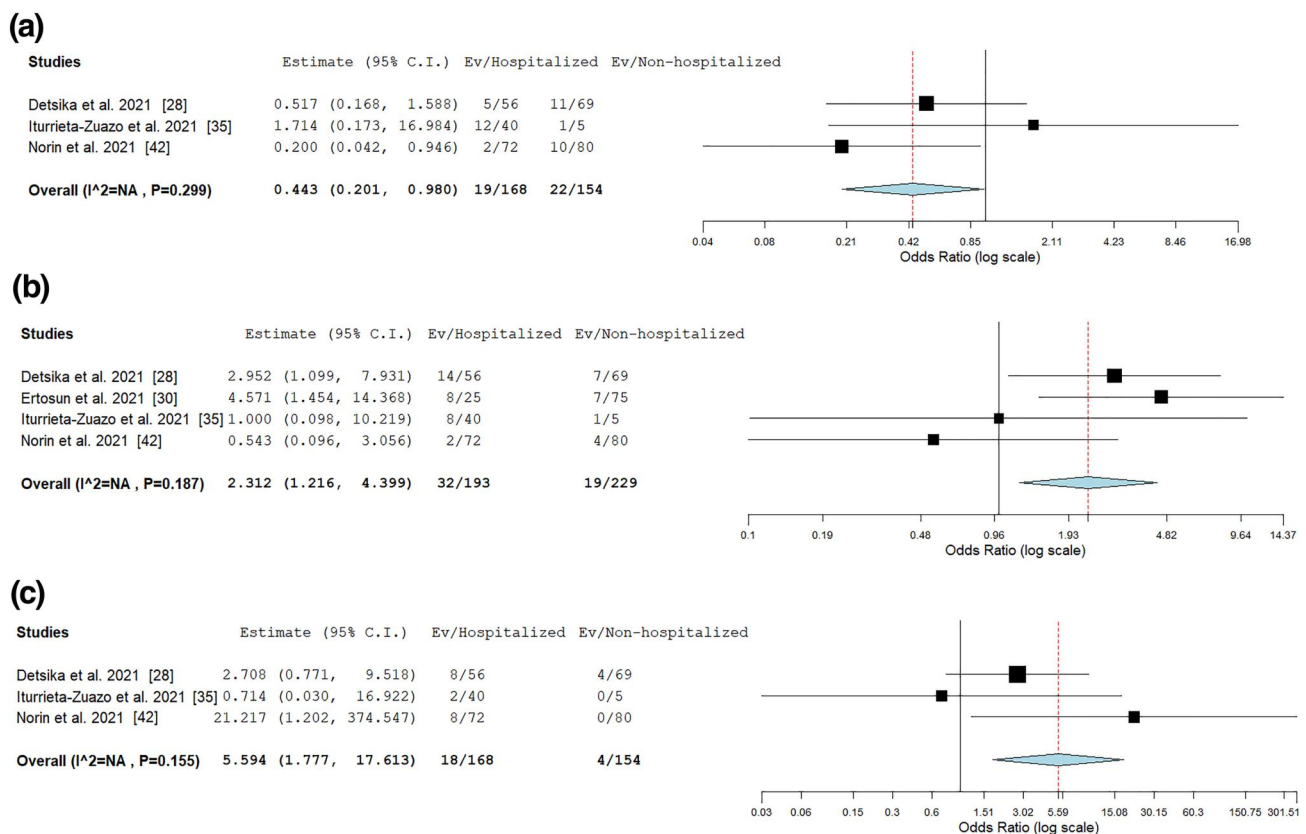
Publication bias was assessed only for studies which presented HLA-A, HLA-B and HLA-C allele-carrier counts/frequencies in patients stratified according to ICU-admittance (when five entries corresponded to a specific allele). The visual inspection of Funnel

plots and the corresponding  $p$  values from Egger's test did not suggest the presence of publication bias (results not shown).

## 4 | DISCUSSION

In the first two years of extensive research in the area of molecular genetics of COVID-19, a significant number of association studies related to the disease severity, clinical course and the outcome of SARS-CoV-2 infection focused on host polymorphisms in HLA loci.<sup>13,20–51</sup> These studies were driven by previous results suggesting the involvement of HLA system in the regulation of the immune response to other viruses, as well as by the fine regulation of peptide-binding properties by the extreme polymorphic feature of HLA loci.<sup>61,62</sup>

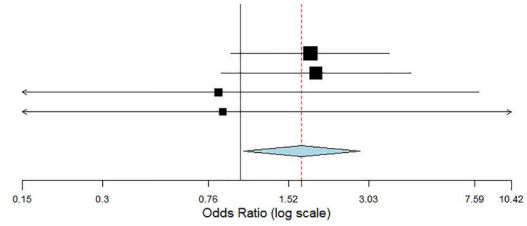
The majority of studies on COVID-19 focussed on HLA class I loci -A, -B and -C, which are expressed in most nucleated cells and thrombocytes. To date, the most reproducible results on the association between a certain HLA allele and COVID-19 clinical phenotype were obtained for HLA-A\*11. Allelic variants belonging to this HLA-A



**FIGURE 3** Meta-analysis of the association between HLA-A alleles and COVID-19 severity under dominant genetic model. (a) HLA-A\*03, comparison hospitalised versus non-hospitalised; (b) HLA-A\*11, comparison hospitalised versus non-hospitalised; (c) HLA-A\*23, comparison hospitalised versus non-hospitalised. Each entry in the pooled analysis is presented by the first author's name and the publication year, together with a reference number in square brackets. The results of the included studies are presented as Odds ratios (ORs), with 95% confidence interval (CI), and the overall effects with 95% CIs are given in forest plots. The size of the square symbol representing the study's result is proportional to the weight assigned to the study. Presented  $p$  values are derived from heterogeneity tests and the overall effect is represented by diamond symbol with lateral tips corresponding to 95% CI. Hospitalised = Severe + Moderate disease, Non-hospitalised = Mild (World Health Organisation criteria); Ev—events (allele/carrier count)

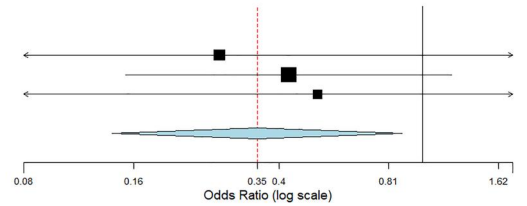
(a)

Studies	Estimate (95% C.I.)	Ev/Severe	Ev/Non-severe
Wang et al. 2020 [21]	1.829 (0.922, 3.626)	14/138	25/430
Anzures et al. 2021 [23]	1.919 (0.845, 4.355)	14/146	11/210
Kreutmair et al. 2021 [37]	0.824 (0.086, 7.872)	1/18	4/60
Yung et al. 2021 [49]	0.856 (0.048, 15.231)	0/20	9/342
<b>Overall (I<sup>2</sup>=NA, P=0.863)</b>	<b>1.699 (1.027, 2.809)</b>	<b>29/322</b>	<b>49/1042</b>



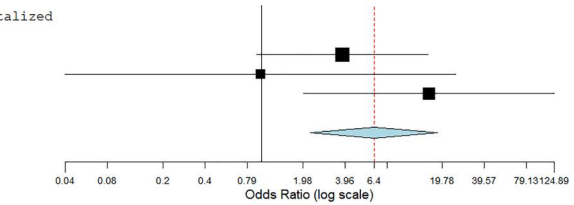
(b)

Studies	Estimate (95% C.I.)	Ev/Severe	Ev/Non-severe
Wang et al. 2020 [21]	0.278 (0.036, 2.173)	1/138	11/430
Anzures et al. 2021 [23]	0.430 (0.154, 1.201)	5/146	16/210
Yung et al. 2021 [49]	0.515 (0.030, 8.921)	0/20	15/342
<b>Overall (I<sup>2</sup>=NA, P=0.877)</b>	<b>0.353 (0.141, 0.879)</b>	<b>6/304</b>	<b>42/982</b>



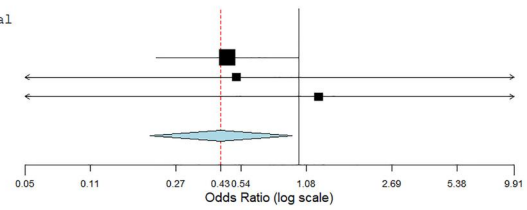
(c)

Studies	Estimate (95% C.I.)	Ev/Hospitalized	Ev/Non-hospitalized
Littera et al. 2020 [20]	3.811 (0.931, 15.599)	4/78	4/286
Ertosun et al. 2021 [30]	0.987 (0.040, 24.611)	0/50	1/150
Norin et al. 2021 [42]	15.800 (1.999, 124.890)	12/72	1/80
<b>Overall (I<sup>2</sup>=NA, P=0.279)</b>	<b>6.403 (2.253, 18.198)</b>	<b>16/200</b>	<b>6/516</b>



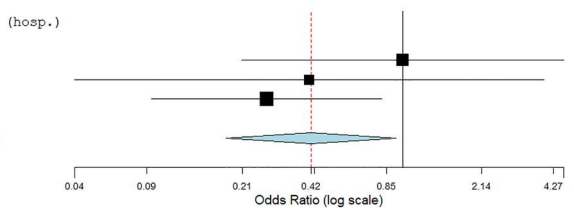
(d)

Studies	Estimate (95% C.I.)	Ev/Lethal	Ev/Non-lethal
Gutierrez-Bautista et al. 2021 [33]	0.464 (0.217, 0.993)	8/252	50/758
Naemi et al. (Saudi Arabian) 2021 [41]	0.512 (0.026, 10.045)	0/58	3/212
Naemi et al. (South Asian) 2021 [40]	1.230 (0.049, 30.777)	0/40	1/150
<b>Overall (I<sup>2</sup>=NA, P=0.800)</b>	<b>0.434 (0.203, 0.924)</b>	<b>8/350</b>	<b>54/1120</b>



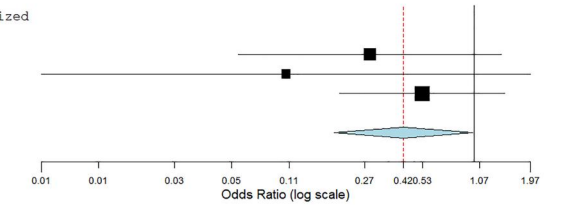
(e)

Studies	Estimate (95% C.I.)	Ev/ICU+ (hosp.)	Ev/ICU- (hosp.)
Iturrieta-Zuazo et al. 2021 [35]	1.000 (0.212, 4.709)	4/20	4/20
Kreutmair et al. 2021 [37]	0.407 (0.043, 3.883)	1/10	6/28
Weiner et al. (USA) 2021 [48]	0.270 (0.090, 0.816)	5/79	12/60
<b>Overall (I<sup>2</sup>=NA, P=0.403)</b>	<b>0.415 (0.183, 0.939)</b>	<b>10/109</b>	<b>22/108</b>



(f)

Studies	Estimate (95% C.I.)	Ev/Hospitalized	Ev/Non-hospitalized
Detsika et al. 2021 [28]	0.282 (0.057, 1.388)	2/56	8/69
Iturrieta-Zuazo et al. 2021 [35]	0.103 (0.005, 1.973)	1/40	1/5
Schetelig et al. 2021 [44]	0.533 (0.196, 1.448)	4/233	195/6148
<b>Overall (I<sup>2</sup>=NA, P=0.512)</b>	<b>0.424 (0.183, 0.979)</b>	<b>7/329</b>	<b>204/6222</b>



(g)

Studies	Estimate (95% C.I.)	Ev/MV	Ev/Non-MV
Bernal et al. 2021 [25]	1.468 (0.493, 4.372)	5/43	13/158
De Marco et al. 2021 [27]	1.559 (1.036, 2.347)	46/219	73/501
Kreutmair et al. 2021 [37]	0.359 (0.018, 7.376)	0/8	4/31
<b>Overall (I<sup>2</sup>=NA, P=0.638)</b>	<b>1.487 (1.017, 2.173)</b>	<b>51/270</b>	<b>90/690</b>

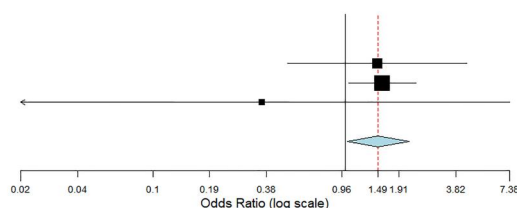
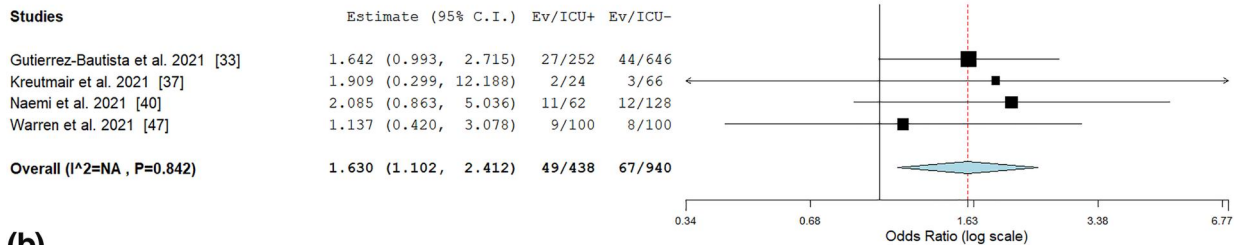
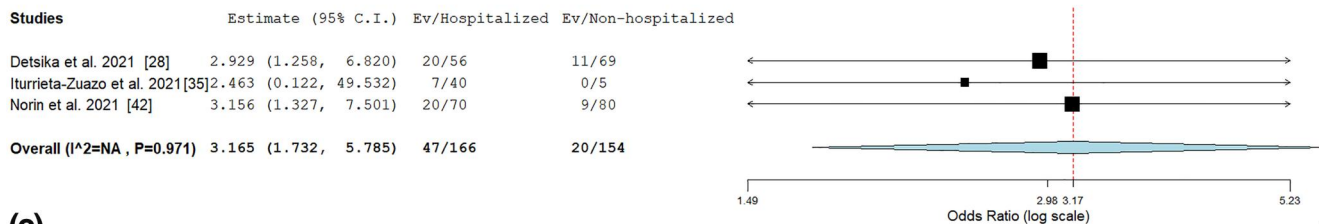


FIGURE 4 Meta-analysis of the association between HLA-B alleles and COVID-19 severity. (a) HLA-B\*51:01, comparison severe versus non-severe, allelic genetic model; (b) HLA-B\*54:01, comparison severe versus non-severe, allelic genetic model; (c) HLA-B\*53, comparison hospitalised versus non-hospitalised, allelic genetic model; (d) HLA-B\*14, comparison lethal versus non-lethal, allelic genetic model; (e) HLA-B\*07:02, comparison intensive care unit (ICU) + versus ICU- (hospitalised patients), dominant genetic model; (f) HLA-B\*40:02, comparison hospitalised versus non-hospitalised, dominant genetic model; (g) HLA-B\*15, comparison MV versus non-MV, dominant genetic model. Each entry in the pooled analysis is presented by the first author's name and the publication year, together with a reference number in square

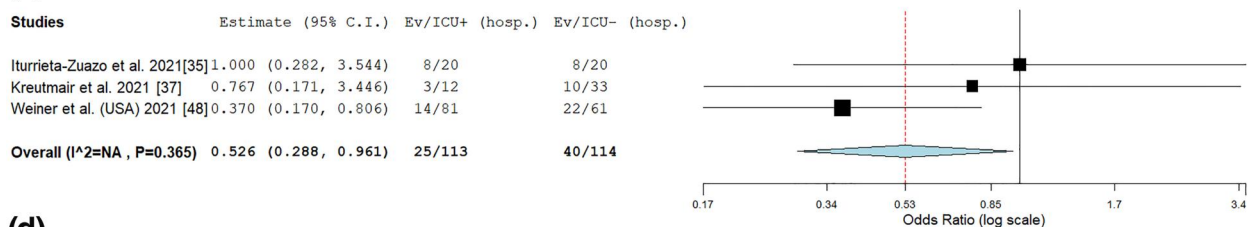
(a)



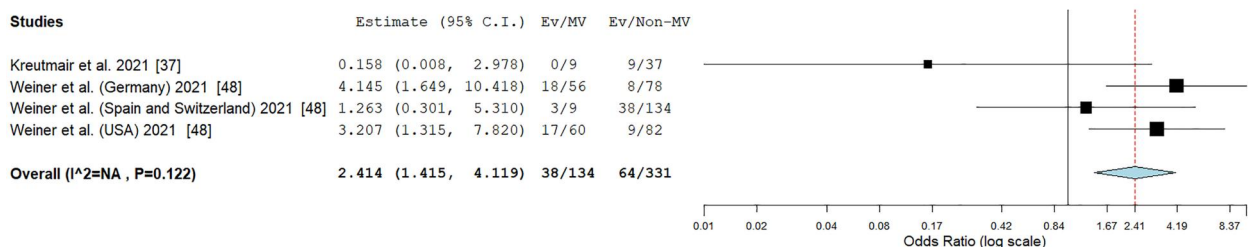
(b)



(c)



(d)



**FIGURE 5** Meta-analysis of the association between HLA-C alleles and COVID-19 severity. (a) HLA-C\*06, comparison intensive care unit (ICU) + versus ICU-, allelic genetic model; (b) HLA-C\*04, comparison hospitalised versus non-hospitalised, dominant genetic model; (c) HLA-C\*07:02, comparison ICU + versus ICU- (hospitalised patients), dominant genetic model; (d) HLA-C\*04:01, comparison MV versus non-MV, dominant genetic model. Each entry in the pooled analysis is presented by the first author's name and the publication year, together with a reference number in square brackets. The results of the included studies are presented as Odds ratios (ORs), with 95% confidence interval (CI), and the overall effects with 95% CIs are given in forest plots. The size of the square symbol representing the study's result is proportional to the weight assigned to the study. Presented  $p$  values are derived from heterogeneity tests and the overall effect is represented by diamond symbol with lateral tips corresponding to 95% CI. Hospitalised = Severe + Moderate disease, Non-hospitalised = Mild (World Health Organisation criteria); ICU+/- - ICU admittance status; MV—mechanical ventilation, Ev—events (allele/carrier count)

family were associated with disease severity, need for hospitalisation or ICU admittance, as well as with COVID-19-related mortality.<sup>21,28,30,36,39,47</sup> In their GWAS conducted in the relatively early stage of pandemics in Chinese population, Wang et al. identified HLA-A\*11:01 as a predisposing factor for severe COVID-19.<sup>21</sup> The same allele was associated with severe disease in Japanese hospitalised

COVID-19 patients.<sup>36</sup> Furthermore, in a study of Ertoşun *et al.* which involved Turkish kidney transplant recipients, HLA-A\*11 allelic family showed the association with the development of severe COVID-19 symptoms requiring hospitalisation.<sup>30</sup> These results were not confirmed in the present meta-analysis of the association under allelic genetic model, but the carrier status HLA-A\*11 was found to

brackets. The results of the included studies are presented as Odds ratios (ORs), with 95% confidence interval (CI), and the overall effects with 95% CIs are given in forest plots. The size of the square symbol representing the study's result is proportional to the weight assigned to the study. Presented  $p$  values are derived from heterogeneity tests and the overall effect is represented by diamond symbol with lateral tips corresponding to 95% CI. Hospitalised = Severe + Moderate disease, Non-hospitalised = Mild (World Health Organisation criteria); ICU+/- - ICU admittance status; MV—mechanical ventilation, Ev—events (allele/carrier count)

significantly associate with the hospitalisation related to COVID-19. This finding is consistent with the finding of Detsika et al., according to which a higher frequency of HLA-A\*11 carriers was seen in hospitalised than in non-hospitalised COVID-19 patients from Greece.<sup>28</sup> Results showing the association of HLA-A\*11 carrier state with COVID-19 mortality in Spanish patients,<sup>39</sup> as well as with ICU-admittance in COVID-19 patients from USA,<sup>47</sup> additionally supported the role of this allelic family in the genetic predisposition to the poor outcome of SARS-CoV-2 infection. Still, we could not perform the meta-analysis for potential association of HLA-A alleles with the lethal outcome of COVID-19 for dominant genetic model due to the lack of the corresponding studies. According to the findings of Warren et al., the results regarding the role of HLA-A\*11 in COVID-19 could be influenced by the gender and age distribution, as well as by patient ethnicity, which may explain the lack of association in other studies included in the present systematic data synthesis.<sup>47</sup> All together, our meta-analysis supports previous findings suggesting that HLA-A\*11 affects the clinical progression of COVID-19.

Besides HLA-A\*11, HLA-A allelic families HLA-A\*03, HLA-A\*23, HLA-A\*24 and HLA-A\*02 showed the relation with COVID-19

severity in more than one study. However, previous articles showed disagreements in the reports related to the effects of the members of HLA-A\*03 family. Results on the requirement of mechanical ventilation from different datasets included in the study of Weiner *et al.* were significantly discordant,<sup>48</sup> while the opposing effect on disease severity was shown in studies conducted in Russia and United Arab Emirates (UAE).<sup>45,51</sup> As for HLA-A\*23, the relation of this allelic group with COVID-19 severity was reported in Greek population,<sup>28</sup> while Littera *et al.* found HLA-A\*23:01 allele exclusively in hospitalised patients from their Sardinian cohort.<sup>20</sup> Other two allelic families, HLA-A\*24 and HLA-A\*02, showed opposing effects on different aspects of COVID-19 clinical manifestation,<sup>34,41,44,45</sup> which could explain the lack of significant associations of these allelic groups in the present meta-analysis. On the other hand, we confirmed the effects of HLA-A\*03 and HLA-A\*23 on COVID-19 severity through quantitative data synthesis. Namely, HLA-A\*03 was the only HLA-A allele group associated with the lethal outcome of COVID-19 in the present data synthesis. This allele family was also found to associate with the necessity for hospitalisation, assuming the dominant genetic model. Paradoxically, the direction of the

TABLE 3 Meta-analysis of association between HLA-DRB1<sup>b</sup> and HLA-DQB1 alleles and COVID-19 severity/outcome: allelic genetic model

HLA-DRB1 allele	Hospitalised versus Non-hospitalised <sup>a</sup>				ICU + versus ICU-				Lethal versus Non-lethal			
	n <sup>b</sup>	OR (95% CI)	p	Phet <sup>c</sup>	n	OR (95% CI)	p	Phet	n	OR (95% CI)	p	Phet
DRB1*01	3	1.547 (0.880–2.718)	0.130	0.921	4	1.028 (0.693–1.526)	0.892	0.917	3	1.196 (0.724–1.975)	0.485	0.806
DRB1*03	-	-	-	-	4	1.143 (0.835–1.564)	0.404	0.403	3	0.852 (0.557–1.302)	0.459	0.997
DRB1*04	3	0.992 (0.367–2.681)	0.988	0.033	4	0.977 (0.697–1.370)	0.892	0.233	3	0.998 (0.646–1.543)	0.994	0.402
DRB1*07	3	1.030 (0.549–1.934)	0.927	0.525	4	1.007 (0.740–1.370)	0.965	0.970	3	1.060 (0.730–1.539)	0.758	0.737
DRB1*08	3	2.503 (0.274–22.893)	0.417	0.094	4	0.634 (0.321–1.253)	0.190	0.802	3	0.528 (0.208–1.341)	0.179	0.704
DRB1*10	-	-	-	-	4	0.656 (0.301–1.426)	0.287	0.600	3	1.205 (0.537–2.704)	0.651	0.676
DRB1*11	3	<b>0.513 (0.300–0.878)*</b>	<b>0.015</b>	0.462	4	<b>0.638 (0.446–0.916)</b>	<b>0.015</b>	0.492	3	0.833 (0.506–1.374)	0.475	0.232
DRB1*12	3	0.208 (0.029–1.469)	0.115	0.25	4	0.427 (0.172–1.057)	0.066	0.279	3	0.436 (0.099–1.925)	0.273	0.663
DRB1*13	3	1.052 (0.549–2.013)	0.879	0.259	4	1.345 (0.983–1.840)	0.064	0.688	3	1.312 (0.659–2.610)	0.439	0.112
DRB1*14	3	0.520 (0.204–1.325)	0.171	0.567	4	1.058 (0.658–1.701)	0.816	0.802	3	1.552 (0.851–2.833)	0.152	0.865
DRB1*15	3	1.075 (0.596–1.939)	0.810	0.540	4	<b>1.393 (1.002–1.938)</b>	<b>0.049</b>	0.786	3	0.887 (0.556–1.417)	0.617	0.691
DRB1*16	-	-	-	-	4	1.068 (0.570–2.002)	0.837	0.463	3	1.238 (0.600–2.555)	0.564	0.384
HLA-DQB1 allele	Hospitalised versus Non-hospitalised <sup>a</sup>				ICU + versus ICU-				Lethal versus Non-lethal			
	n <sup>b</sup>	OR (95% CI)	p	Phet <sup>c</sup>	n	OR (95% CI)	p	Phet	n	OR (95% CI)	p	Phet
DQB1*02	-	-	-	-	4	1.078 (0.838–1.388)	0.558	0.553	3	0.858 (0.624–1.181)	0.349	0.196
DQB1*03	-	-	-	-	4	<b>0.748 (0.587–0.953)</b>	<b>0.019</b>	0.776	3	0.855 (0.618–1.183)	0.345	0.616
DQB1*04	-	-	-	-	4	0.764 (0.399–1.466)	0.419	0.721	3	1.068 (0.487–2.343)	0.870	0.221
DQB1*05	-	-	-	-	4	0.940 (0.716–1.233)	0.653	0.188	3	1.223 (0.872–1.716)	0.249	0.597
DQB1*06	-	-	-	-	4	<b>1.384 (1.077–1.779)</b>	<b>0.011</b>	0.419	3	1.114 (0.795–1.562)	0.530	0.896

<sup>a</sup>Hospitalised = Severe + Moderate, Non-hospitalised = Mild (World Health Organisation critdria).

<sup>b</sup>Number of studies/datasets.

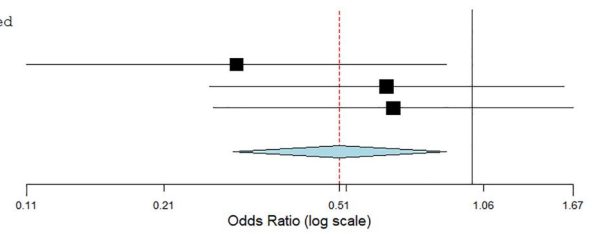
<sup>c</sup>p value obtained in heterogeneity test.

\*Statistically significant results are shown in bold.



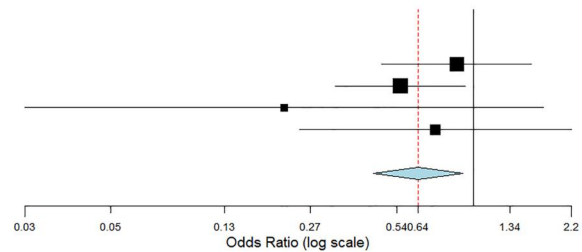
(a)

Studies	Estimate (95% C.I.)	Ev/Hospitalized	Ev/Non-hospitalized
Littera et al. 2020 [20]	0.305 (0.106, 0.879)	4/78	43/286
Ertosun et al. 2021 [30]	0.651 (0.266, 1.591)	7/50	30/150
Norin et al. 2021 [42]	0.673 (0.272, 1.666)	9/72	14/80
<b>Overall (I<sup>2</sup>=NA, P=0.462)</b>	<b>0.513 (0.300, 0.878)</b>	<b>20/200</b>	<b>87/516</b>



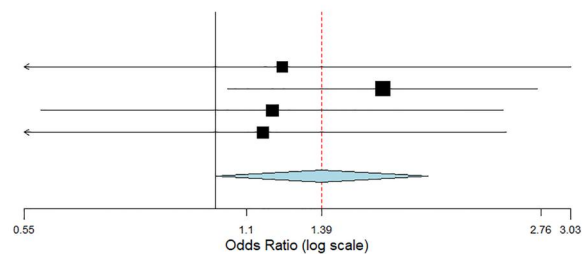
(b)

Studies	Estimate (95% C.I.)	Ev/ICU+	Ev/ICU-
Ebrahimi et al. 2021 [29]	0.872 (0.477, 1.593)	19/88	48/200
Gutierrez-Bautista et al. 2021 [33]	0.553 (0.328, 0.932)	19/252	83/646
Naemi et al. 2021 [40]	0.217 (0.027, 1.751)	1/62	9/128
Warren et al. 2021 [47]	0.734 (0.245, 2.198)	6/100	8/100
<b>Overall (I<sup>2</sup>=NA, P=0.492)</b>	<b>0.638 (0.445, 0.916)</b>	<b>45/502</b>	<b>148/1074</b>



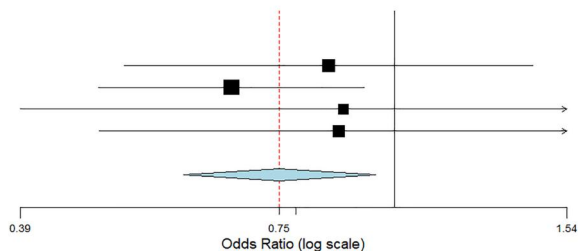
(c)

Studies	Estimate (95% C.I.)	Ev/ICU+	Ev/ICU-
Ebrahimi et al. 2021 [29]	1.233 (0.503, 3.025)	8/88	15/200
Gutierrez-Bautista et al. 2021 [33]	1.684 (1.040, 2.725)	30/252	48/646
Naemi et al. 2021 [40]	1.194 (0.581, 2.452)	15/62	27/128
Warren et al. 2021 [47]	1.161 (0.544, 2.475)	17/100	15/100
<b>Overall (I<sup>2</sup>=NA, P=0.786)</b>	<b>1.393 (1.002, 1.938)</b>	<b>70/502</b>	<b>105/1074</b>



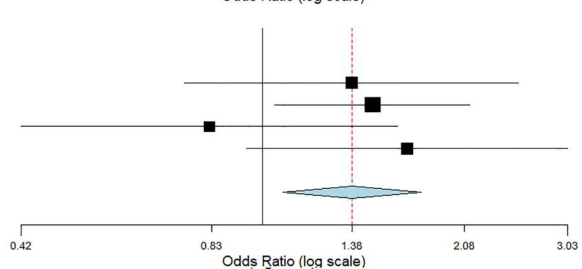
(d)

Studies	Estimate (95% C.I.)	Ev/ICU+	Ev/ICU-
Ebrahimi et al. 2021 [29]	0.846 (0.505, 1.416)	33/88	83/200
Gutierrez-Bautista et al. 2021 [33]	0.662 (0.474, 0.926)	59/252	204/646
Naemi et al. 2021 [40]	0.878 (0.389, 1.980)	10/62	23/128
Warren et al. 2021 [47]	0.868 (0.475, 1.586)	29/100	32/100
<b>Overall (I<sup>2</sup>=NA, P=0.776)</b>	<b>0.748 (0.587, 0.953)</b>	<b>131/502</b>	<b>342/1074</b>



(e)

Studies	Estimate (95% C.I.)	Ev/ICU+	Ev/ICU-
Ebrahimi et al. 2021 [29]	1.381 (0.753, 2.532)	21/88	37/200
Gutierrez-Bautista et al. 2021 [33]	1.490 (1.045, 2.123)	60/252	112/646
Naemi et al. 2021 [40]	0.824 (0.416, 1.632)	16/62	38/128
Warren et al. 2021 [47]	1.690 (0.943, 3.029)	42/100	30/100
<b>Overall (I<sup>2</sup>=NA, P=0.419)</b>	<b>1.384 (1.077, 1.779)</b>	<b>139/502</b>	<b>217/1074</b>



**FIGURE 6** Meta-analysis of the association between HLA-DRB1 and HLA-DQB1 alleles and COVID-19 severity under allelic genetic model. (a) HLA-DRB1\*11, comparison hospitalised versus non-hospitalised; (b) HLA-DRB1\*11, comparison intensive care unit (ICU) + versus ICU-; (c) HLA-DRB1\*15, comparison ICU + versus ICU-; (d) HLA-DQB1\*03, comparison ICU + versus ICU-; (e) HLA-DQB1\*06, comparison ICU + versus ICU-. Each entry in the pooled analysis is presented by the first author's name and the publication year, together with a reference number in square brackets. The results of the included studies are presented as Odds ratios (ORs), with 95% confidence interval (CI), and the overall effects with 95% CIs are given in forest plots. The size of the square symbol representing the study's result is proportional to the weight assigned to the study. Presented *p* values are derived from heterogeneity tests and the overall effect is represented by diamond symbol with lateral tips corresponding to 95% CI. Hospitalised = Severe + Moderate disease, Non-hospitalised = Mild (World Health Organisation criteria); Ev—events (allele/carrier count)

association in these two comparisons was opposite. In line with the association with lethal outcome from COVID-19, HLA-A\*03 was previously associated with a 2-fold increase in the risk of self-reported severe difficulties with daily routine following vaccination with mRNA-based vaccines.<sup>63</sup>

Besides confirming the previous findings related to the effects of HLA-A alleles on COVID-19 severity, our pooled analysis revealed the association of HLA-A\*31 and HLA-A\*68 with ICU-admittance. Results suggesting the potential involvement of these alleles in the determination of the clinical course of COVID-19 were not reported

before, possibly due to their low frequency in various populations, especially for HLA-A\*31. Additional reason for the lack of these reports could be the presentation of results on the effect of higher-resolution alleles, without considering the contribution of the allelic family. The present meta-analysis also suggests the effect of HLA-A\*01 on COVID-19 severity, as determined in the comparison of allele frequencies between patients requiring hospitalisation and those with mild symptoms. Previously, a single study reported the association of HLA-A\*01:01 with clinical presentation of SARS-CoV-2 infection, but their results were obtained through the comparison of severely ill patients and healthy controls.<sup>45</sup>

Evidence of the association between HLA-B alleles and COVID-19 severity/outcome were rarely replicated in association studies. To date, the only allelic variants of this locus identified as predisposing factors for worse clinical manifestation of SARS-CoV-2 infection in more than a single study are HLA-B\*51 and HLA-B\*35. HLA-B\*51:01 was previously reported in the GWAS from China as a predisposing allele for severe COVID-19,<sup>21</sup> while the opposite effect on COVID-19-related hospitalisation was determined in a study conducted in UAE,<sup>51</sup> which analysed the association under dominant model. Naemi et al. found higher frequency of HLA-B\*51 in fatal cases, compared to patients with mild symptoms, suggesting that the worse outcome of SARS-CoV-2 relates to this allele family.<sup>40</sup> As for HLA-B\*35, borderline significance was found for the negative association with fatal COVID-19 in Saudi Arabian population,<sup>41</sup> while HLA-B\*35:01 allele also associated with shorter duration of hospitalisation.<sup>32</sup> Still, only HLA-B\*51:01 showed a statistically significant association with the severe disease in the present pooled analysis, while we found no evidence to support the protective effect of HLA-B\*35. Additionally, the present meta-analysis confirmed the findings of Norin et al.<sup>42</sup> which related HLA-B\*53 alleles with the risk of COVID-19-related hospitalisation. Among 3 studies taken for pooled analysis, the one that included the largest number of HLA-B\*53 alleles was also the only study that involved patients with African ancestry.<sup>42</sup> This observation is in accordance with the allele frequency data showing significant ethnicity-related variations.<sup>64</sup>

The present meta-analysis also revealed the protective effect of HLA-B\*54:01 against severe disease. Surprisingly, this allele was previously identified as COVID-19 susceptibility variant and one of the weakest binders to SARS-CoV-2 among HLA-B alleles.<sup>49,62</sup> The only HLA-B allele family associated with COVID-19 mortality rate in the pooled analysis was HLA-B\*14, which displayed the protective effect and was not previously determined as relevant contributing factor for better COVID-19 outcome. Still, the frequency of these alleles in the cohorts included in the meta-analysis was low, reaching 5% only in a study conducted in Spanish population.<sup>33</sup> Other novel findings related to HLA-B alleles and the clinical features of COVID-19 in the present meta-analysis include the protective effect of HLA-B\*07:02 and HLA-B\*40:02 against more severe disease. HLA-B\*07:02 is one of the most common HLA-B alleles, and its potential protective role in SARS-CoV-2 infection is supported by the findings suggesting its association with the pre-existing immunity towards SARS-CoV-2 in unexposed individuals.<sup>65</sup> Furthermore,

immunodominant NP<sub>105-113</sub>-B\*07:02 cytotoxic T cell response was found to control viral replication and is associated with milder COVID-19.<sup>66</sup> As for HLA-B\*40:02, the results need to be taken with caution, since the number of mild COVID-19 patients in one of the included studies was only 5.<sup>35</sup> When allele carrier rates were compared between intubated and non-intubated COVID-19 patients, HLA-B\*15 allele family was identified as a risk factor. These results are hard to explain based on the SARS-CoV-2 binding properties, since this family includes numerous alleles, ranging from the strongest to the weakest binders.<sup>62</sup> A study conducted in Egypt reported on the protective role of HLA-B\*15 against COVID-19 related mortality, but we detected various discordances in the presentation of their results.<sup>50</sup>

To date, various reports suggested the involvement of HLA-C\*04 in genetic predisposition for severe COVID-19. For instance, Detsika et al.<sup>28</sup> reported the association between HLA-C\*04 and the risk of hospitalisation, while the evidence from Indian population supports the effect of HLA-C\*04:01:01:01 on the risk of developing symptomatic infection.<sup>46</sup> HLA-C\*04:01 was further associated with an increased risk of hospitalisation in ICU, as well as with the shorter ventilator-free period upon hospitalisation.<sup>47,48</sup> Therefore, the findings of the present meta-analysis, which confirmed the effects of HLA-C\*04, were expected. Namely, among HLA-C alleles, HLA-C\*04 and the common member of this family, HLA-C\*04:01, were the most significantly associated with the clinical course of COVID-19. Predictions of peptide-binding properties also supports the supposed involvement of HLA-C\*04 in the regulation of SARS-CoV-2 infection, since most of the members of this allele family were defined as weak binders.<sup>62</sup>

The association of HLA-C\*06 allele with the adverse effects on SARS-CoV-2 infection was previously shown in Saudi Arabian patients, by comparing allele frequencies between fatal cases and the entire group of infected patients, as well as between fatal COVID-19 cases and healthy controls.<sup>41</sup> Additionally, HLA-C\*06:02, the most common allele belonging to this family, was classified as one of the weakest SARS-CoV-2 peptide binders.<sup>62</sup> Our pooled analysis confirmed the association of HLA-C\*06 with COVID-19 severity, and also revealed the association between negative carrier status of HLA-C\*07:02 and ICU-admittance. Still, the later result might have been influenced by the largest study included in the pooled analysis.<sup>48</sup>

Allelic variants of class II HLA loci were less frequently analysed in terms of their association with COVID-19 severity. To date, the most replicated results are related to HLA-DRB1\*15:01 and HLA-DRB1\*04 alleles, although these findings were published in just few articles. HLA-DRB1\*15:01 was shown to increase the risk of developing severe respiratory symptoms in a study of Schetelig et al.<sup>44</sup> Furthermore, HLA-DRB1\*15:01 was more abundant in severe COVID-19 cases from Italy, compared to healthy controls,<sup>67</sup> while the carrier rate was higher in hospitalised COVID-19 patients than in the group of SARS-CoV-2 infected participants with mild or no symptoms from UAE.<sup>51</sup> Similarly, HLA-DRB1\*04 was identified as the most significant severity predictor among HLA class II alleles in Iranian population,<sup>29</sup> while its protective effect was also detected by Langton et al. in their group of participants from UK.<sup>38</sup> Naemi et al. further showed the



association of this allele group with lower risk of lethal outcome, although their findings were based on the comparison of fatal cases with healthy controls.<sup>41</sup> The present meta-analysis confirmed the effect of HLA-DRB1\*15 on COVID-19 severity, since marginal significance was reached for the association of HLA-DRB1\*15 with an increased risk of ICU-admittance. Still, we failed to confirm the protective role of HLA-DRB1\*04. The strongest evidence of the involvement of HLA class II loci in the genetic basis of SARS-CoV-2 clinical progression was obtained for HLA-DRB1\*11 in the present meta-analysis. This allele family is associated with the reduced risk of the expression of severe symptoms which require hospitalisation, as well as with the reduced necessity for ICU-admittance. Association with COVID-19 severity was previously reported only for HLA-DRB1\*11:01 in a single study which compared allele frequencies between hospitalised patients and healthy controls.<sup>33</sup>

Meta-analysis of the effects of HLA-DQB1 alleles on COVID-19 severity revealed the association of HLA-DQB1\*03 and HLA-DQB1\*06 with the ICU-admittance status. These two allele groups were found to confer the opposite effect, with the protective features associated with HLA-DQB1\*03. However, there are rare reports on the association of HLA-DQB1 with the clinical course of COVID-19 and previous findings suggesting the involvement of HLA-DQB1\*06 in the predisposition to developing severe disease were based on the comparison of HLA-DQB1\*06:02 frequency between severe cases and healthy controls.<sup>67</sup> Some of the members of this allele family, in combination with common HLA-DQA1 alleles, were described as the weakest SARS-CoV-2 binders.<sup>62</sup>

It should be noted that in several studies none of the analysed HLA alleles showed the association with the clinical presentation of COVID-19.<sup>13,24,25,27,49</sup> Among these studies is a large GWAS which included Italian and Spanish COVID-19 patients.<sup>13</sup> Still, their results could not be combined with findings of other previous studies in the quantitative pooled analysis, since all participants were diagnosed with respiratory failure and their definition of disease severity was based on the necessity of mechanical ventilation, which included both invasive and non-invasive type and, therefore, was unmatched with other eligible studies.

Our meta-analysis is the first comprehensive quantitative summary of the results on the relation of HLA genetic variations with the outcomes of SARS-CoV-2 infections. The results of the present data synthesis qualify certain alleles of HLA class I and II loci (HLA-A\*01, HLA-A\*03, HLA-A\*11, HLA-A\*23, HLA-A\*31, HLA-A\*68, HLA-A\*68:02, HLA-B\*07:02, HLA-B\*14, HLA-B\*15, HLA-B\*40:02, HLA-B\*51:01, HLA-B\*53, HLA-B\*54, HLA-B\*54:01, HLA-C\*04, HLA-C\*04:01, HLA-C\*06, HLA-C\*07:02, HLA-DRB1\*11, HLA-DRB1\*15, HLA-DQB1\*03, HLA-DQB1\*06) as variants associated with COVID-19 severity. This especially refers to alleles and allele families which were found to associate with several different features of COVID-19 clinical progression, such as HLA-C\*04 and HLA-DRB1\*11. However, the number of studies included in all the pooled analyses is relatively low, which suggests caution while interpreting the obtained results. Another limitation of this review is the lack of studies on the effects of certain alleles, preventing their inclusion in the pooled analysis.

Furthermore, the number of patients in certain severity-based groups was small, while several studies were excluded for unmatched study design or SARS-CoV-2 outcome definition. Relatively low number of entries in the pooled analysis is also a consequence of the differences in the resolution of allele typing and the inability to calculate the counts of low-resolution alleles from several studies due to the lacking genotyping results. All mentioned limitations certainly highlight the need for further studies with larger sample sizes in order to confirm the associations found in the present data-synthesis, as well as to enable the pooled analysis on the association of various excluded alleles. Additional data should also enable the assessment of the influence of ethnicity, gender and other potential confounders.

## AUTHOR CONTRIBUTIONS

**Zorana Dobrijević:** Conceptualisation, Investigation, Formal analysis, Visualisation, Writing - original draft. **Nikola Gligorjević:** Investigation, Formal analysis, Visualisation, Writing - review and editing. **Miloš Šunderić:** Investigation, Formal analysis, Validation, Writing - review and editing. **Ana Penezić:** Validation, Writing - review and editing. **Goran Miljuš:** Validation, Writing - review and editing. **Sergej Tomić:** Validation, Writing - review and editing. **Olgica Nedić:** Conceptualisation, Validation, Supervision, Project administration, Funding acquisition, Writing - review and editing.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

## DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available within the article, its supplementary materials, or from the corresponding author, upon reasonable request.

## ORCID

Zorana Dobrijević  <https://orcid.org/0000-0002-4652-7719>

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## SUPPORTING INFORMATION

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

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