The association between different predictive biomarkers and mortality of COVID-19

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Abstract

Background: Immunocompromised individuals are expected to be more prone to severe diseases and, subsequently, death. Genetic disorders and polymorphisms in genes involved in the immune system, such as human leukocyte antigen (HLA), inflammatory cytokines, and killer-cell immunoglobulin-like receptors, can be involved in the immune system's response to various pathogens. In the current survey, the data were received from the world health organization, collected around the world.

Results: Spearman’s coefficient correlation test for evaluating the relationship between the Daily Death Rates (DDR) and immunological variables showed a statistically significant correlation between the DDR and all immunological variables except TNFa857T, TNFa863A IL2330G, and IL2166T (P < 0.001). Also, there was a statistically significant correlation between the DDR and some HLA markers.

Conclusion: This meta-analysis study shows that predictive biomarkers and mortality of COVID-19 are associated with HLA markers. However, these results should be confirmed in a more structured agreement. It is worth noting that the design of new studies should consider potential diseases with poor prognoses because they are related to these immune genetic markers.

Keywords: COVID-19, Biomarker, HLA, Polymorphism

Background

The outbreak of new coronavirus (Novel Coronavirus-2019) or SARS-CoV-2 started in Wuhan, Hubei Province, China, in December 2019 and has spread rapidly to other parts of China the world (Zhu et al. 2020). Infection with the SARS-CoV-2 leading to COVID-19 disease usually occurs through saliva droplets released by coughing and sneezing in symptomatic patients, asymptomatic carriers, and before the onset of clinical symptoms (Singhal 2020). The current outbreak of COVID-19 disease has created a state of emergency and danger to public health internationally; therefore, governments have made new decisions to control and manage this crisis to cause minor damage to communities (Allain-Dupré et al. 2020).

COVID-19 related mortality is usually measured by two parameters, including Case Fatality Rate (CFR) and Daily Death Rates (DDR) (Kim et al. 2021).

CFR is obtained by dividing the number of deaths by the number of confirmed cases of COVID-19, and DDR is calculated by dividing the number of deaths by the country’s population (Onder et al. 2020; Eikenberry et al. 2020). Mortality rates vary widely from country to country, ranging from 0 to 31 percent and from 0 to 48 daily deaths per 10 million people. Mortality rates in Asia (lower than 1.3%) were lower than in Europe (1.8%) but reached 2.2% in the Americas, where Europeans are high (Ritchie et al. 2021).

Many factors can alter mortality rates in COVID-19 patients, resulting in changes in DDR and CFR levels (Cao et al. 2020). Patients with weakened immune systems are expected to be more prone to severe disease and death. Genetic disorders and the occurrence of polymorphisms in genes involved in the immune system,
such as human leukocyte antigen (HLA), inflammatory cytokines, and killer-cell immunoglobulin-like receptors (KIR), can be involved in the immune system’s response to various pathogens (Nguyen et al. 2020; Fara et al. 2020; Bernal et al. 2021).

This systematic review retrieved worldwide allele frequencies of WHO data and correlated the HLA, inflammatory cytokines, and KIR polymorphisms with DDR and CFR. Due to the extensive missing data, statistical analysis was performed in two ways: imputation and without imputation.

**Methods**

**COVID-19 epidemiological statistics**

In the present survey, we used a method that our research team recently published to retrieve data and estimate CFR and DDR. The data about total cases, total deaths, and total recovered cases, alongside total screening tests used to diagnose COVID-19, were collected since the beginnings of the COVID-19 pandemic for all countries from the world’s most acceptable and accurate data repositories. World Health Organization (https://covid19.who.int/), Worldometer (Abdollahi et al. 2020), the Centers for Disease Control and Prevention, and the Morbidity and Mortality Weekly Report series (provided from Centers for Disease Control and Prevention) (Khafaie and Rahim 2020), consistent with the user’s guide of data sources for patient registries.

The (i) CFR, which is obtained by dividing the number of deaths by the number of confirmed cases of COVID-19, (ii) Daily Death Rate (DDR), represented as the average number of deaths per day (since the first confirmed case) per ten million inhabitants were evaluated for each country.

**Statistical analysis**

Descriptive statistics such as mean, standard deviation, median and interquartile range were computed for quantitative variables. The normality of data was evaluated using the Shapiro–Wilk test. Paired samples t-test was used to compare the CFR and DDR in May 2020-Nov 2020, 2020 and Nov 2020-May 2021.

In addition, Spearman’s coefficient correlation test was used to assess the association between quantitative variables and outcome variables (CFR and DDR). Cut-off values for interpretation of coefficient correlation are shown in Table 1 (Mukaka 2012). Data were measured and analyzed for each country, and CFR and DDR for countries with ≥ 1,000 cases (n = 90) are presented in Table 1.

Due to missing values in all quantitative variables (immunological and genetic variables and HLA markers) except CFR and DDR. Data analysis was done using Med-Calc software and free statistical software R version 4.1.0. Package miss Forest was used to impute missing values. $P < 0.05$ was regarded as a significant statistical difference. NAM = North America; EUR = Europe; SAM = South and Central America; WAS = West Asia; CAS = Central Asia; OCE = Oceania; NAF = North Africa; SAS = South Asia; NEA = North-East Asia; SSA = Sub-Saharan Africa; SEA = South-East Asia.

**Results**

Collected data from 98 countries, which WHO reported, were analyzed. Descriptive statistics of DDR, CFR, and immunological and genetic variables are shown in Tables 1 and 2. In addition, HLA markers are shown in Additional file 1: Table S1. The frequency (%) of paises was equal to 1 (1%), and the region’s frequency is shown in Fig. 1.

The results show a statistically significant difference between the mean DDR in May 2020-Nov 2020 and Nov 2020-May 2021, and the mean DDR in Nov 2020-May 2021 is significantly higher than the mean DDR in May 2020-Nov 2020 ($t (89) = −2.98, P = 0.004$). The percentage of DDR changes between these two time periods equals 28.32% (Table 3).

Paired t-test also showed that there is no statistically significant difference between the mean CFR in May 2020-Nov 2020 and Nov 2020-May 2021 and the mean CFR in Nov 2020-May 2021 is higher than the mean CFR in May 2020-Nov 2020, and the percentage of CFR changes between these. The two-time intervals are equal to 7.69% (Table 3).

The results in Table 2 showed that there was a significantly high positive correlation between DDR in May 2020-Nov 2020 and Nov 2020-May 2021 ($r = 0.87, P < 0.001$). Spearman correlation coefficient also showed that there is a slight positive correlation between CFR in May 2020-Nov 2020 and Nov 2020-May 2021 ($r = 0.16, P = 0.14$) (Table 4).

Figure 2 shows the distribution chart between DDR in May 2020-Nov 2020 and Nov 2020-May 2021 and the distribution chart between CFR in May 2020-Nov 2020 and Nov 2020-May 2021.

Spearman’s coefficient correlation test for evaluating the relationship between the DDR and immunological variables showed a statistically significant correlation between the DDR and all immunological variables except TNFa857T, TNFa863A IL2330G, and IL2166T ($P < 0.001$). In addition, this test indicated a statistically significant correlation between DDR in all immunological variables except TNFa1031C and TNFa863A (Additional file 1: Tables S2 and S3). The findings in Table 5 showed a statistically significant correlation between the CFR and only immunological variables like TNFa1031C and TNFa863A ($P < 0.05$).
Table 1 Correlation of CFR and DDR with COVID-19 vaccination frequencies across countries

| Country                      | DDR | CFR | COVID-19 vaccination |
|------------------------------|-----|-----|----------------------|
| Peru                         | 42.55% | 28.12% | 3.78% | 4.67% | 2,261,096 | 732,493 | 2.3% |
| Belgium                      | 40.60% | 30.56% | 2.63% | 1.21% | 5,100,000 | 1,277,779 | 11.2% |
| Chile                        | 30.19% | 20.56% | 2.79% | 1.67% | 16,246,599 | 7,374,467 | 38.6% |
| Brazil                       | 29.52% | 28.76% | 2.87% | 3.18% | 50,308,106 | 16,215,378 | 7.7% |
| Argentina                    | 29.38% | 21.75% | 2.70% | 2.04% | 9,541,511 | 1,629,336 | 3.6% |
| Spain                        | 29.14% | 23.90% | 2.92% | 0.73% | 21,071,940 | 6,716,156 | 14.3% |
| Mexico                       | 28.71% | 24.33% | 9.82% | 10.21% | 21,986,456 | 9,861,173 | 7.8% |
| Panama                       | 26.41% | 20.81% | 2.01% | 1.12% | 779,000 | 258,903 | 6.1% |
| Colombia                     | 25.81% | 22.25% | 2.87% | 2.84% | 6,851,163 | 2,612,556 | 5.3% |
| The United Kingdom           | 25.46% | 26.86% | 4.06% | 0.42% | 54,797,640 | 18,890,969 | 28.4% |
| United States of America     | 24.11% | 24.95% | 2.39% | 1.59% | 257,347,205 | 112,626,771 | 34.2% |
| Italy                        | 24.06% | 29.64% | 4.35% | 2.60% | 25,948,925 | 8,079,257 | 13.4% |
| North Macedonia              | 21.42% | 35.43% | 2.87% | 12.20% | 175,000 | 25,648 | 1.2% |
| France                       | 21.34% | 23.39% | 2.29% | 1.24% | 27,800,000 | 8,690,000 | 13% |
| Sweden                       | 20.94% | 19.73% | 4.11% | 0.10% | 3,957,465 | 897,321 | 8.7% |
| Czechia                      | 18.58% | 39.89% | 1.21% | 2.94% | 4,080,000 | 1,101,570 | 10.3% |
| Netherlands                  | 18.18% | 14.29% | 1.94% | 0.32% | 6,875,100 | 1,713,859 | 9.8% |
| Iran (Islamic Republic of)   | 17.37% | 12.96% | 5.59% | 2.08% | 1,770,000 | 292,000 | 0.4% |
### Table 1 (continued)

| Country          | 2021 % | 2020 % | Δ % | 2021 % | 2020 % | Δ % | 2021 % | 2020 % | Δ % |
|------------------|--------|--------|-----|--------|--------|-----|--------|--------|-----|
| Romania          | 16.06% | 21.66% | ↑   | 2.61%  | 8.26%  | ↑   | 6,410,000 | 2,636,935 | 13.6% |
| Ireland          | 15.49% | 14.21% | ↓   | 2.97%  | 0.54%  | ↓   | 1,922,913 | 514,808 | 10.5% |
| South Africa     | 13.35% | 13.25% | ↓   | 2.69%  | 2.63%  | ↓   | 474,000  | 474,318 | 0.8%  |
| Costa Rica       | 11.60% | 9.76%  | ↓   | 1.26%  | 0.95%  | ↓   | 1,093,931 | 436,630 | 8.6%  |
| Switzerland      | 11.44% | 16.64% | ↑   | 1.13%  | 0.28%  | ↓   | 3,500,000 | 1,178,891 | 13.8% |
| Portugal         | 11.42% | 23.58% | ↑   | 1.61%  | 0.45%  | ↓   | 4,284,623 | 1,171,431 | 11.4% |
| Israel           | 11.02% | 10.52% | ↓   | 0.84%  | 2.80%  | ↑   | 10,500,000 | 5,095,555 | 56.3% |
| Iraq             | 10.87% | 5.64%  | ↓   | 2.27%  | 0.62%  | ↓   | 453,000   | ND      | ND    |
| Bulgaria         | 10.27% | 35.33% | ↑   | 2.24%  | 7.96%  | ↑   | 1,073,523 | 387,980 | 5.5%  |
| Oman             | 9.86%  | 6.01%  | ↓   | 1.11%  | 1.93%  | ↑   | 326,000   | 73,269  | 1.5%  |
| Canada           | 9.62%  | 9.37%  | ↓   | 3.98%  | 0.65%  | ↓   | 17,297,879 | 1,336,187 | 3.5%  |
| Poland           | 8.47%  | 26.84% | ↑   | 1.42%  | 7.59%  | ↑   | 15,500,000 | 4,420,000 | 11.6% |
| Albania          | 8.03%  | 12.04% | ↑   | 2.31%  | 5.26%  | ↑   | 653,000   | 205,000  | 7.2%  |
| Croatia          | 7.79%  | 26.98% | ↑   | 1.21%  | 4.18%  | ↑   | 1,270,000 | 288,000  | 7.1%  |
| Slovenia         | 7.60%  | 3.55%  | ↓   | 0.87%  | 0.37%  | ↓   | 1,900,000 | 608,000  | 11.2% |
| Russian Federation| 7.49%  | 11.27% | ↑   | 1.71%  | 4.20%  | ↑   | 23,300,000 | 9,440,000 | 6.5%  |
| Tunisia          | 6.40%  | 14.13% | ↑   | 2.68%  | 6.21%  | ↑   | 537,000   | 165,000  | 1.4%  |
| Saudi Arabia     | 6.30%  | 2.92%  | ↓   | 1.58%  | 1.27%  | ↓   | 11,300,000 | ND      | ND    |
| Libya            | 5.96%  | 6.41%  | ↑   | 1.37%  | 1.31%  | ↓   | 107,000   | ND      | ND    |
| Austria          | 5.91%  | 16.34% | ↑   | 0.87%  | 1.43%  | ↑   | 3,970,000 | 1,060,000 | 11.9% |
Table 1 (continued)

| Country           | Mean   | Improved Mean | Improved Rate |
|-------------------|--------|---------------|---------------|
| Turkey            | 5.32%  | 7.46%         | 2.76%         |
|                   |        |               | 1.77%         | 25,600,000    | 10,700,000    | 13.1%         |
| Georgia           | 5.04%  | 15.75%        | 0.82%         |
|                   |        |               | 1.77%         | ↑              | 81,076        | ND            | ND            |
| Jordan            | 5.00%  | 12.88%        | 1.13%         |
|                   |        |               | 3.92%         | ↑              | 1,090,000     | 206,000       | 2.8%          |
| Denmark           | 5.00%  | 6.13%         | 1.34%         |
|                   |        |               | 0.09%         | ↓              | 2,580,000     | 976,000       | 16.8%         |
| Germany           | 4.77%  | 14.75%        | 1.67%         |
|                   |        |               | 1.69%         | ↑              | 39,400,000    | 9,060,000     | 10.9%         |
| Morocco           | 4.65%  | 3.52%         | 1.68%         |
|                   |        |               | 2.54%         | ↑              | 10,500,000    | 4,450,000     | 12.2%         |
| Serbia            | 4.12%  | 13.67%        | 1.41%         |
|                   |        |               | 1.82%         | ↑              | 3,920,000     | 1,700,000     | 24.4%         |
| Lebanon           | 4.06%  | 15.84%        | 0.77%         |
|                   |        |               | 4.12%         | ↑              | 581,000       | 204,000       | 3%            |
| Trinidad and Tobago | 3.27% | 2.40%        | 1.90%         |
|                   |        |               | 1.99%         | ↑              | ND            | ND            | 0.1%          |
| India             | 3.22%  | 27.15%        | 1.48%         |
|                   |        |               | 3.81%         | ↑              | 180,000,000   | 39,800,000   | 2.9%          |
| Greece            | 3.05%  | 15.01%        | 1.42%         |
|                   |        |               | 2.58%         | ↑              | 4,190,000     | 1,470,000     | 13.7%         |
| Slovakia          | 2.68%  | 31.85%        | 0.48%         |
|                   |        |               | 10.37%        | ↑              | 7,110,000     | 2,630,000     | 26.9%         |
| Equatorial Guinea | 2.51%  | 1.14%         | 1.67%         |
|                   |        |               | 0.0%          | ↓              | 75,518        | 10,872        | 0.8%          |
| Philippines       | 2.45%  | 2.45%         | NC            |
|                   |        |               | 1.92%         | 1.86%         | 2,790,000     | 636,000       | 0.6%          |
| Finland           | 2.28%  | 2.40%         | 2.03%         |
|                   |        |               | 0.92%         | ↓              | 2,370,000     | 278,000       | 5%            |
| Indonesia         | 2.12%  | 2.49%         | 3.33%         |
|                   |        |               | 3.55%         | ↑              | 22,600,000    | 8,920,000     | 3.3%          |
| Gambia            | 2.11%  | 1.03%         | 3.28%         |
|                   |        |               | 0.0%          | ↓              | 24,659        | ND            | ND            |
| Latvia            | 2.11%  | 16.77%        | 1.23%         |
|                   |        |               | 1.27%         | ↑              | 482,000       | 111,000       | 5.8%          |
| Norway            | 2.03%  | 2.06%         | NC            |
|                   |        |               | 1.15%         | 0.23%         | 2,130,000     | 574,000       | 10.8%         |
| Bangladesh        | 1.49%  | 1.50%         | NC            |
|                   |        |               | 1.44%         | 2.94%         | ↑              | 9,470,000     | 3,650,000     | 2.2%          |
| Country         | Unemployment | Population Growth | Population (2021) | Population Growth (2022) | Population Growth (2023) |
|-----------------|--------------|-------------------|-------------------|---------------------------|--------------------------|
| Australia       | 1.22%        | 0.51%             | 3.28%             | 0.0%                      | 2,980,000                 | ND                        | ND                        |
| Pakistan        | 1.22%        | 1.25%             | NC                | 2.02%                     | 3.21%                     | 3,840,000                 | 964,000                   | 0.4%                      |
| Venezuela       | 1.20%        | 1.36%             | ↑                 | 0.87%                     | 1.17%                     | 250,000                   | ND                        | ND                        |
| Myanmar         | 1.14%        | 0.84%             | ↓                 | 2.32%                     | 1.98%                     | 2,200,000                 | 300,000                   | 0.6%                      |
| Gabon           | 1.06%        | 0.92%             | ↓                 | 0.63%                     | 0.56%                     | 10,678                    | 2,643                     | 0.1%                      |
| Cyprus          | 0.94%        | 5.50%             | ↑                 | 0.46%                     | 0.66%                     | 424,000                   | 104,000                   | 11.9%                     |
| Guinea-Bissau   | 0.93%        | 0.49%             | ↓                 | 1.74%                     | 0%                        | ND                        | ND                        | ND                        |
| Kenya           | 0.87%        | 0.79%             | ↓                 | 1.79%                     | 4.5%                      | 933,000                   | ND                        | ND                        |
| Senegal         | 0.77%        | 0.95%             | ↑                 | 2.07%                     | 2.83%                     | 432,000                   | ND                        | ND                        |
| Uruguay         | 0.74%        | 13.4%             | ↑                 | 1.76%                     | 1.83%                     | NC                        | 2,250,000,000             | 928,458                   | 26.8%                     |
| Uzbekistan      | 0.73%        | 0.28%             | ↓                 | 0.85%                     | 0.28%                     | ↓                         | 117,000,000               | 117,000                   | 0.3%                      |
| Zimbabwe        | 0.73%        | 1.52%             | ↑                 | 2.97%                     | 7.53%                     | ↑                         | 775,000                   | 204,000                   | 1.4%                      |
| Cayman Islands  | 0.63%        | 0.43%             | ↓                 | 0.40%                     | 0%                        | ↓                         | 73,721                    | 33,921                    | 52.2%                     |
| Central African Republic | 0.53%  | 0.28%             | ↓                 | 1.27%                     | 1.04%                     | NC                        | ND                        | ND                        | ND                        |
| Hong Kong       | 0.50%        | 2.00%             |                   |                           |                           | 189,000,000               | 750,361                   | 10%                       |
| Japan           | 0.48%        | 1.3%              | ↑                 | 1.68%                     | 1.5%                      | NC                        | 559,000,000               | 1,566,103                 | 1.2%                      |
| Cuba            | 0.47%        | 0.98%             | ↑                 | 1.77%                     | 0.98%                     | ↓                         | ND                        | ND                        | ND                        |
| Ghana           | 0.43%        | 0.36%             | ↓                 | 0.65%                     | 0%                        | ↓                         | 852,000                   | ND                        | ND                        |
| Comoros         | 0.42%        | 2.4%              | ↑                 | 1.24%                     | 0%                        | ↓                         | 43,728                    | 588                       | <0.1%                     |
| Sierra Leone    | 0.42%        | 0.14%             | ↓                 | 3.11%                     | 0%                        | ↓                         | 64966                     | 6,716                     | <0.1%                     |
Spearman’s coefficient correlation indicated a statistically significant correlation between the DDR and all genetic variables except X.2DL5, X.2DS1, X.2DS5, X.3DL1, and X.3DS1 \( (P < 0.05) \). In addition, the results of the relationship between the CFR and genetic variables showed that these variables do have not a statistically significant correlation with CFR (Additional file 1: Tables S4 and S5).

The supplementary findings showed a statistically significant correlation between the DDR and all HLA markers except markers such as B21T, B1302, B1503, B3505, B3901, B4002, B4006, B4201, B4403, B4501, B4901, and B5201. Spearman’s coefficient correlation test for evaluating the relationship between the CFR and HLA markers showed a statistically significant correlation between the CFR and HLA markers, including B1302 \( (P = 0.048) \), B3503 \( (P = 0.049) \), and B5001 \( (P = 0.033) \) (Additional file 1: Tables S6 and S7).

### Discussion

Many factors such as age, underlying disorder, gender, and genetics affect the strength of the immune response against pathogens (Zhang and Cao 2019; Viveiros et al. 2021). Genetic alterations in immune system molecules can be a central factor in the severity of COVID-19 and cause significant clinical changes and mortality (da Silva et al. 2021; Li et al. 2020). Information on the relationship between immunogenetic factors and the

| Republic of Korea | 0.32% | 0.52% | ↑ | 1.75% | 0.76% | ↓ | 4,640,000,000 | 905,000 | 1.8% |
| Malaysia | 0.31% | 0.8% | ↑ | 0.71% | 0.59% | ↓ | 1,890,000,000 | 728,000 | 2.3% |
| Mali | 0.30% | 0.35% | NC | 3.70% | 12.5% | ↓ | 49,903 | ND | ND |
| Brunei Darussalam | 0.28% | 0.09% | ↓ | 2.03% | 0% | ↓ | 15,905 | 862 | 0.2% |
| Nigeria | 0.22% | 0.14% | ↓ | 1.80% | 0.33% | ↓ | 1,770,000,000 | ND | ND |
| New Zealand | 0.20% | 0.07% | ↓ | 1.53% | 0% | ↓ | 389,000 | 120,090 | 2.4% |
| Singapore | 0.16% | 0.07% | ↓ | 0.05% | 0% | ↓ | 3,200,000 | 1,300,000 | 22.8% |
| Uganda | 0.12% | 0.1% | NC | 0.91% | 0.23% | ↓ | 423,000 | ND | ND |
| China | 0.11% | 0.04% | ↓ | 5.15% | 0% | ↓ | 381,000,000 | ND | ND |
| Papua New Guinea | 0.03% | 0.2% | ↑ | 1.17% | 0.82% | ↓ | 3000 | ND | ND |
| Thailand | 0.03% | 0.11% | ↑ | 1.56% | 1.08% | ↓ | 2,120,000,000 | 708,300 | 1.0% |
| Viet Nam | 0.01% | 0.005% | ↓ | 2.88% | 0% | ↓ | 925,000 | 37,145 | <0.1% |

### Table 2

| Size of correlation | Interpretation |
|---------------------|----------------|
| 0.90–1.00 (−0.90 to −1.00) | Very high positive (negative) correlation |
| 0.70–0.90 (−0.70 to −0.90) | High positive (negative) correlation |
| 0.50–0.70 (−0.50 to −0.70) | Moderate positive (negative) correlation |
| 0.30–0.50 (−0.30 to −0.50) | Low positive (negative) correlation |
| 0.00–0.30 (−0.00 to −0.30) | Negligible correlation |
prognosis of COVID-19 is scarce. Considering the vital role of the immune system and the importance of its changes in COVID-19 patients, in this study, we summarized the data related to genetic differences in immune factors (inflammatory cytokines, HLA, and KIR). We examined their relationship with mortality (CFR and DDR). Also, known denominators are affected by low test coverage, asymptomatic or mild cases (Rajgor et al. 2020). This study showed the CFR were 1.35 and 2.75, respectively, in 2020 and 2021. However, it is for COVID-19 lower than Severe Acute Respiratory Syndrome (SARS) (9.5%) and the Middle East respiratory syndrome (MERS) (34.4%) but higher than that of influenza (0.1%) (Rajgor et al. 2020).

Case fatality rate (CFR) and daily death rates (DDR)
The CFR is obtained by dividing the number of deaths by the number of confirmed cases of COVID-19. Asymptomatic patients (carriers) or failure to perform diagnostic tests reduces this fraction’s denominator. On the other hand, the confirmed cases in the denominator are recovered and infected people, so the number of infected patients who will die is unknown. In addition, many factors, such as economic, political, and social conditions, also affect the amount of denominator. The DDR is calculated by dividing the number of deaths by the country’s population and is used in countries with limited ability to perform tests. The data analysis shows that CAS (1%) with minimum and EUR (28%) with maximum average DDR.

Restrictions on testing in different countries have a lower impact on the number of deaths than in some cases. Therefore, DDR seems to be more suitable for COVID-19 than CFR. The studied parameters had the most significant relationship with DDR in the present study.

Cytokines
The levels of TNFa, IL-6, IL-1b, IFNg, IL-2, and IL-10 have been reported as inflammatory cytokines in COVID-19 (Pedersen and Ho 2020). The cytokine polymorphisms with the allele frequencies Spearman’s correlation with CFR and DDR estimates presents in (Additional file 1: Tables S2 and S3). However, the lack of significance after correction for multiple tests, the trend for positive correlation of inhibitory genotype AA and KIR2DL3 with DDR has been reported in the literature (Wang and Xia 2004), suggesting that low NK cell activity may be relevant in SARS. It is interesting to note that, despite the lack of significance after correction for multiple tests, the trend for positive correlation of inhibitory genotype AA and KIR2DL3 with DDR has been reported in the literature. As a result, there is no obvious pattern in HLA-B ligands. NK cells also react to and generate cytokines such as IL-12 and IL-2, as well as IFNg, TNFa, and IL-6 (Semino and Rubartelli 2010), with all these cytokines being amplified in the COVID-19 cytokine storm. Furthermore, TNFa is near to the HLA-B and HLA-C genes, as well as the HLA-B, HLA-C, and TNFA SN determination.
There was a strong relation between DDR and genetic variables. However, there was no correlation between CFR and genetic variables (Additional file 1: Tables S4 and S5).

In addition, some studies have shown that COVID-19 is related to genetic factors, mainly related to the immune response, such as HLA class I genes (Wang et al. 2020). The ongoing genome-wide association studies (GWAS) initiatives may reveal additional key

### Table 3 Descriptive statistics of DDR, CFR, immunological and genetic variables

| Variable | Minimum | Maximum | Mean | Standard. deviation | Median | Interquartile range |
|----------|---------|---------|------|---------------------|--------|---------------------|
| DDR      | 0       | 42.548  | 7.99 | 9.966               | 3.436  | 10.696              |
| CFR      | 0       | 0.098   | 0.02 | 0.014               | 0.017  | 0.015               |
| Immunological |       |         |      |                     |        |                     |
| IL6174C  | 0       | 0.5     | 0.216| 0.144               | 0.244  | 0.261               |
| IL6565A  | 0       | 0.442   | 0.231| 0.093               | 0.233  | 0.105               |
| TNFα238A | 0.008   | 0.226   | 0.072| 0.03                | 0.073  | 0.029               |
| TNFα308A | 0.018   | 0.267   | 0.117| 0.043               | 0.119  | 0.046               |
| TNFα1031C| 0.103   | 0.436   | 0.213| 0.033               | 0.3    | 0.02                |
| TNFα857T | 0.01    | 0.282   | 0.122| 0.036               | 0.124  | 0.029               |
| TNFα863A | 0.065   | 0.331   | 0.152| 0.029               | 0.15   | 0.02                |
| IFNγ874T | 0.072   | 0.579   | 0.348| 0.108               | 0.373  | 0.178               |
| IFNγ5644T| 0.225   | 0.585   | 0.446| 0.056               | 0.46   | 0.053               |
| IL101082G| 0.024   | 0.549   | 0.4  | 0.103               | 0.357  | 0.081               |
| IL10592C | 0.257   | 0.796   | 0.632| 0.116               | 0.677  | 0.147               |
| IL10819C | 0.249   | 0.8     | 0.634| 0.115               | 0.7    | 0.138               |
| IL13962T | 0.01    | 0.316   | 0.189| 0.065               | 0.203  | 0.091               |
| IL1511C  | 0.3     | 0.725   | 0.548| 0.087               | 0.542  | 0.137               |
| IL2330G  | 0       | 0.568   | 0.315| 0.111               | 0.4    | 0.1                 |
| IL2166T  | 0.053   | 0.64    | 0.283| 0.095               | 0.272  | 0.114               |
| IL121188A| 0.456   | 0.832   | 0.682| 0.077               | 0.7    | 0.088               |
| Genetic  |         |         |      |                     |        |                     |
| KirAAgenotype | 1.5 | 55.275 | 29.665| 8.93               | 28.029 | 9.235               |
| X.2DL2  | 13.45   | 71.90   | 50.761| 10.453             | 53.116 | 13.249              |
| X.2DL3  | 56.50   | 99.70   | 87.92 | 6.27               | 88.66  | 5.166               |
| X.2DL5  | 28.40   | 78     | 54.615| 8.255              | 55     | 9.086               |
| X.2DS1  | 1.4     | 64.60   | 37.253| 10.967             | 39.441 | 9.568               |
| X.2DS2  | 13.80   | 71.70   | 49.221| 10.495             | 50.95  | 12.775              |
| X.2DS3  | 10.30   | 52.20   | 29.258| 7.991              | 28.886 | 10.33               |
| X.2DS5  | 0       | 83     | 34.567| 9.484              | 33.62  | 7.963               |
| X.3DL1  | 75.50   | 100    | 93.848| 4.824              | 94.516 | 4.662               |
| X.3DS1  | 0.7     | 62     | 34.687| 12.77              | 37.548 | 12.311              |

### Table 4 Comparison of DDR/CFR at May 2020-Nov 2020 and Nov 2020-May 2021

| Variable | Time                  | Mean  | Standard deviation | Mean of difference with 95% CI | Percentage of change (%) | Statistics t (89) | P value** |
|----------|-----------------------|-------|--------------------|---------------------------------|--------------------------|-------------------|-----------|
| DDR      | May 2020-Nov 2020     | 8.37  | 10.23              | −2.37 (−3.95, −0.79)            | 28.32                    | −2.98             | 0.004     |
|          | Nov 2020-May 2021     | 10.74 | 10.99              |                                 |                          |                   |           |
| CFR      | May 2020-Nov 2020     | 2.08  | 1.35               | −0.16 (−0.73, 0.40)             | 7.69                     | −0.58             | 0.56      |
|          | Nov 2020-May 2021     | 2.24  | 2.75               |                                 |                          |                   |           |

** : Paired samples t-test
***(Mean of after-Mean of before)/Mean of before) × 100

** Genetics

There was a strong relation between DDR and genetic variables. However, there was no correlation between CFR and genetic variables (Additional file 1: Tables S4 and S5).
genetic markers (Ovsyannikova et al. 2020). Therefore, the trend related to related immune genes indirectly confirms that the immune status will result from important participants in the background of COVID-19.

HLA
The results showed that the association of different HLA markers with DDR is stronger than CFR. The Spearman's correlation coefficient shows that some HLA markers with DDR have shown a significance level. However, just B1302, B3503, and B5001 HLA markers with CFR have shown a significant level (Additional file 1: Tables S6 and S7).

HLA-B* 07:03 (Ng et al. 2004) and HLA-B* 46:01 (Lin et al. 2003) were the first predisposing alleles suggested for SARS-CoV. However, these associations cannot be confirmed later (Xiong et al. 2008; Ng et al. 2010; Leite et al. 2021).

HLA-B displays the strongest selective signal (Prugnolle et al. 2005) and associations with infectious diseases. In this context (Blackwell et al. 2009), along with evidence that the HLA-B molecule's affinity to SARS-CoV-2 epitopes plays a role in the infection.

Conclusions
This study set out to determine the value of the predictive biomarker in COVID-19 mortality. Specific HLA and cytokine polymorphism emerge as a reliable prediction of DDR. Whereas just HLA B1302, B3503, and B 5001 were associated with CFR. Definitive diagnosis of patients with COVID-19 is the main challenge. To achieve this, minimize the interfering factors, including asymptomatic patients, subjects with mild symptoms, and COVID-19 misdiagnosis. On the other hand, it is worth noting that the design of new studies should consider potential diseases with poor prognoses because they are related to these immune genetic markers.

Abbreviations
HLA: Human leukocyte antigen; KIR: Killer-cell immunoglobulin-like receptors; WHO: World health organization; DDR: Daily death rates; Novel Coronavirus-2019: New coronavirus; CFR: Case fatality rate.

Supplementary Information
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Additional file 1: Further analysis between biomarkers and CFR and DDR.

Table 5 Coefficient correlation between DDR/CFR at May 2020-Nov 2020 and Nov 2020-May 2021

| Variable | Time          | Coefficient correlation | %95 CI            | P value*          |
|----------|---------------|-------------------------|-------------------|-------------------|
| DDR      | May 2020-Nov 2020 | 0.87                    | (0.81,0.91)       | < 0.001           |
|          | Nov 2020-May 2021 |                         |                   |                   |
| CFR      | May 2020-Nov 2020 | 0.16                    | (−0.05,0.35)      | 0.14              |
|          | Nov 2020-May 2021 |                         |                   |                   |

* Spearman rank correlation coefficient
Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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