Correlation Between the Rh/ABO System and Infection Due to SARS Cov2 in Morocco*
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Abstract
The association between COVID-19, ABO blood group system and Rhesus needs to be explored in order to suggest a model of the mechanism linked to SARS CoV2 infection. A retrospective case-control association study was performed on the different regions of Morocco and carried out on a population of size n = 5039 including a total of 4268 COVID-19 patients and 771 control groups. The differences in the Rh/ABO blood group distribution between COVID-19 patients and the control group were analyzed. The relationship between ABO blood type, sexes, Rhesus and COVID-19 characteristics was analyzed. The analyzes of association between the blood group and the infection related to SARS CoV2 showed a statistically significant difference in the individuals of groups B, O, AB) respectively, but not blood group A. In addition, patients with the Rh+ phenotype are less vulnerable to infection therefore the latter are considered to have a protective effect, however the Rh- categories are more vulnerable to infection so they are risk factors. Blood type was related to some clinical characteristics of patients with COVID-19. The presence of the A and B antigens increase the risk of infection with SARS COV2. While the presence of anti A and anti B antibodies makes group O protector against infection. Patients with the Rh+ phenotype are less vulnerable to infection than Rh-negative—therefore these are considered to have a protective effect which is the presence of the D antigen in red blood cells.

Keywords: ABO Blood Group System, Rhesus, COVID-19, Association Analysis, Antibodies.

I. INTRODUCTION

The ABO system has direct links with several diseases and the hemostatic balance of the individual, mentioned by authors in several articles, including viral diseases, cardiovascular diseases and in particular diseases related to infections caused by SARS CoV2 (severe acute respiratory syndrome coronavirus 2) [1].

Generally the ABO system is moderated by an enzymatic activity of fucotransferase which is harmonized and governed by well-established genetic rules: a gene which codes for fucotransferase is responsible for the production of the H antigen on the cell surface through a cascade of enzymatic reactions started by the transport of fucose according to two ways: the first way of neovo which promotes the production of GDF from mannose 4, hydratase and GTP deoxy 1,2 epimerase, the second is called the way of recovery which is glycosyletransferase, to ensure an addition of fucose to the glycans chain of the hydrate [3].

The hemolytic phenotype of individual A, B or AB is linked to the enzymatic dynamics of two enzymes: N-Acyl glycotransferase (enzyme A) which adds fucose to the N-acetyl glycosamine bond in order to give the hemolytic character. A while the addition of fucose at the terminal 1,2 galactose position by galactotransferase is the main mode responsible for the appearance of hemolytic phenotype B (enzyme B) [4].

Furthermore, the codominance expression of the two enzymes A and B provides the appearance of the AB phenotype, in addition to the absence of the enzymatic activity of these two enzymes coding for the hemolytic phenotype O. Other phenotypes are linked to the enzymatic aspect of the ABO system such as the Oh Bambay phenotype which was favored by disturbances in the enzymatic kinetics of 1,2 a fucose transferase, generated by missense mutations [3].

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Activation of the cytokine, due to SARS CoV2 is accompanied by a significant production of coagulation factors which activate von wellbrand factors [5, 6], this is associated with a significant increase in adhesion molecules with a view to ensure a turnover that involves the interaction of leukocytes with endothelial cell P-selectin and E-selectin followed by leukocyte attachment mediated by I-CAM 1 that had shown an association with the SNP polymorphism ABO 11-14 [7], this increase is mainly due to a cellular asymmetry reflected by the abnormal release of interleukin 6 (IL6) which provides upregulation of the expression of the gene encoding I-CAM (InterCellular Adhesion Molecule) [6], this is accompanied by a release of serotonin and ADP stored in the granules of activated platelets [8, 9].

However, the concentration of these is low 30 times in individuals with the O phenotype compared to other hematological groups, which makes them less vulnerable to complications due to SARS CoV2 [1].

This marked low sensitivity in the group can be interpreted by the presence of a protease called ADAMTS13 (A disintegrin and metalloprotease with thrombospondin type 1 repeats) from multiple domains, including a cysteine-rich domain containing an RGDs sequence potentially involved in the interaction with integrins, which promotes the production of coagulation factors [10].

In addition, genomic analyzes on Spike S of SARS CoV2 revealed a 34R mutation encoded for an RGD domain which contains remarkable complementarity with respect to anti-A and anti-B antibodies and marks a higher affinity for ACE2 enzyme (Angiotensine-converting enzyme 2) [11], that is similar to that of RGD-ADMAPTS1.

It is therefore suggested that the low levels of von welbrand factor in the plasma of group O patients and the low vulnerability to SARS CoV2 is due to the antigenic recognition of anti-A and anti-B antibodies with the activating domain of ADMPST13, the thing that prevents creation of activation connections between VWF and ADAMTS13 [10].

The antigenicity of anti A and anti B with ADP / P2Y2 receptors blocks the formation of thrombosis [12] and consequently reduces the intense production of coagulation factors which are expressed by the inactivation of VWF factors this confirms the implication of these antisera in reducing the vulnerability to complications of activation of coagulation factors associated with infection by SARS CoV2 in group O.

It is suggested that the Rhesus system also has impacts that act either directly or indirectly on the degree and intensity of SARS CoV2 infection.

Generally, the rhesus system is presented by antigens located on the proteins of the RH complex (RhD, Rh E, e, CC) [13, 14]. Usually, a deletion which was produced by homoyzgous crossingbreed is the main origin of the (Rh-) phenotype [13]. Individuals of this phenotype always had a reduction in ammonium excretion due to the low expression of proteins that transport NH3 and provide hemostatic regulation of physiological pH through proteins located in the basolateral membrane, which provide detoxification cellular by glutamate synthase according to bidirectional transport [15-17], and exchange of CO2 and O2. These proteins mark a regulated distribution at the level of the basolateral membrane of the collecting tube and potentially expressed in the liver [13-18].

Knowing that infection by SARS CoV2 is accompanied by a drop in extracellular pH to ensure effective attachment of the virus and therefore ensure viral entry into the host cell [19]. As part of this work, we studied the relationship between blood group and Rhesus factor, sex and viral infection in order to propose a model of the mechanism linked to SARS CoV2 infection.

II. MATERIALS AND METHODS
A. Study Design and Data Source

A retrospective case-control association study was performed during the period from 1 August 2021 to 31 December 2021, with a total of 5039 subjects (4268 cases vs. 771 controls) in an age range of between 18 and 70 years, that distributed in the different regions of Morocco. The study contains 44% of females and 56% of males. The ABO type, Rh and gender of each participant was revealed via participant statements in the questionnaire.

B. Association and Statistical Analysis

The association between different blood groups and COVID-19 has been carried out in the Moroccan population. According to gender, subgroups were stratified to assess whether there was a significant difference between blood group and incidence of COVID19. In addition, we performed a correlation analysis between blood group, Rhesus factor, gender and COVID-19 infection.

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS). The ABO blood group and Rhesus frequency in all populations and different gender subgroups was tested using chi-square tests and odds ratios (ORs) with 95% confidence intervals (CIs). Analysis of the association between the ABO blood group and the lymphocyte count was calculated p -value. A p < 0.05 was considered significant.
III. RESULTS

The Association Between Blood Group and SARS Cov2 Infection

As shown in the table 1, we performed a combined association analysis between the ABO phenotype and SARS CoV2 infection which shows a statistically significant difference in COVID19 infection in group B, O, AB individuals (p = 0.000 p < 0.05, OR = 0.416; 95% CI [0.34 - 0.50]), (p = 0.000 p < 0.05, OR = 13.51; 95% CI [10.52 - 17.35]), (p = 0.000 p < 0.05, OR = 0.10; 95% CI [0.09 - 0.13]) respectively, but not blood group A (p = 0.22 p < 0.05, OR = 1.129; 95% CI [0.92 - 1.37]).

<table>
<thead>
<tr>
<th></th>
<th>COVID19 (+)</th>
<th>COVID19 (-)</th>
<th>OR</th>
<th>IC95% inf</th>
<th>IC95% sup</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>879 (20.6%)</td>
<td>144 (18.7%)</td>
<td>1.129</td>
<td>0.929</td>
<td>1.373</td>
<td>0.223</td>
</tr>
<tr>
<td>B</td>
<td>540 (12.7%)</td>
<td>199 (25.8%)</td>
<td>0.416</td>
<td>0.346</td>
<td>0.501</td>
<td>0.000</td>
</tr>
<tr>
<td>AB</td>
<td>2484 (58.2%)</td>
<td>72 (9.3%)</td>
<td>13.51</td>
<td>10.527</td>
<td>17.359</td>
<td>0.000</td>
</tr>
<tr>
<td>O</td>
<td>365 (8.6%)</td>
<td>356 (46.2%)</td>
<td>0.109</td>
<td>0.091</td>
<td>0.130</td>
<td>0.000</td>
</tr>
</tbody>
</table>

The Association between the Rhesus System and Infection Due to SARS Cov2

Association analyzes reveal a highly significant difference for the rhesus system and infection due to SARS CoV2, patients with the Rh + phenotype are less vulnerable to infection caused by SARS CoV2 (p = 0.000 p < 0.05, OR = 0.518 95% CI [0.443 - 0.606]) (table 2).

Therefore, the Rh + factor is considered as a protective effect, however the Rh - categories are more vulnerable to infection due to SARS COV2 so its absence is a risk factor (p = 0.000 p < 0.05, OR = 1.930 95% CI [1.651 - 2.256]).

<table>
<thead>
<tr>
<th></th>
<th>COVID19 (+)</th>
<th>COVID19 (-)</th>
<th>OR</th>
<th>IC95% inf</th>
<th>IC95% sup</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh+</td>
<td>1863 (43.7%)</td>
<td>462 (59.9%)</td>
<td>0.518</td>
<td>0.443</td>
<td>0.606</td>
<td>0.000</td>
</tr>
<tr>
<td>Rh-</td>
<td>2405 (56.3%)</td>
<td>309 (40.1%)</td>
<td>1.930</td>
<td>1.651</td>
<td>2.256</td>
<td>0.000</td>
</tr>
</tbody>
</table>

The Association between Sex, ABO Group and SARS CoV2 Infection

As shown in the table 3, a statistical significance is revealed for the subpopulations A (males), B, AB and O (females + males). However, the subpopulation A (females) does not indicate any statistical significance (p = 0.466, OR = 0.911, 95% CI [0.708 - 1.171]).

Based on analyzes of the association between sex and disease it can be concluded that subpopulations of females of different blood groups A, B and O are less infected than males so there is statistical significance. For the AB group which does not mark a highly serious risk factor for both sexes with a slightly positive deviation towards the females (p = 0.000 p < 0.05, OR = 22.654 95% CI [14.15 - 36.26]), (p = 0.000 p < 0.05, OR = 10.037 95% CI [7.42 - 13.56]).

<table>
<thead>
<tr>
<th></th>
<th>COVID 19+</th>
<th>COVID19-</th>
<th>p-value</th>
<th>OR</th>
<th>IC in 95% inf</th>
<th>IC in 95% sup</th>
<th>polymorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>M</td>
<td>520 (21%)</td>
<td>46 (14.5%)</td>
<td>0.007</td>
<td>1.568</td>
<td>1.131</td>
<td>2.175</td>
</tr>
<tr>
<td></td>
<td>W</td>
<td>359 (20.1%)</td>
<td>98 (21.6%)</td>
<td>0.466</td>
<td>0.911</td>
<td>0.708</td>
<td>1.171</td>
</tr>
<tr>
<td>B</td>
<td>M</td>
<td>298 (12%)</td>
<td>86 (27%)</td>
<td>0.000</td>
<td>0.368</td>
<td>0.280</td>
<td>0.485</td>
</tr>
<tr>
<td></td>
<td>W</td>
<td>242 (13.5%)</td>
<td>113 (24.9%)</td>
<td>0.000</td>
<td>0.471</td>
<td>0.366</td>
<td>0.607</td>
</tr>
<tr>
<td>AB</td>
<td>M</td>
<td>1464 (59%)</td>
<td>19 (6%)</td>
<td>0.000</td>
<td>22.654</td>
<td>14.151</td>
<td>36.266</td>
</tr>
<tr>
<td></td>
<td>W</td>
<td>1020 (57.1%)</td>
<td>53 (11.7%)</td>
<td>0.000</td>
<td>10.037</td>
<td>7.425</td>
<td>13.567</td>
</tr>
<tr>
<td>O</td>
<td>M</td>
<td>199 (8%)</td>
<td>168 (52.8%)</td>
<td>0.000</td>
<td>0.078</td>
<td>0.060</td>
<td>0.101</td>
</tr>
<tr>
<td></td>
<td>W</td>
<td>166 (9.3%)</td>
<td>188 (41.5%)</td>
<td>0.000</td>
<td>0.144</td>
<td>0.113</td>
<td>0.185</td>
</tr>
</tbody>
</table>

- M: Man, W: Women

Analyzes of the combination of Rh system, gender and infection caused by SARS CoV2 show statistical significance for both sexes p= 0.000 p < 0.05 (table 4).

Generally, the results mentioned in the table allow us to conclude that individuals with Rh + are less vulnerable than those with Rh-, therefore the presence of Rh+ is a protective factor, but the absence Rh- is a risk factor.
Table IV

<table>
<thead>
<tr>
<th>Sex</th>
<th>COVID19+</th>
<th>p-Value</th>
<th>OR</th>
<th>IC in 95% inf</th>
<th>IC in 95% sup</th>
</tr>
</thead>
<tbody>
<tr>
<td>RH+</td>
<td>M 1099 (44.8%)</td>
<td>198 (62.3%)</td>
<td>0.000</td>
<td>0.482</td>
<td>0.379</td>
</tr>
<tr>
<td></td>
<td>W 764 (42.8%)</td>
<td>264 (58.3%)</td>
<td>0.000</td>
<td>0.535</td>
<td>0.434</td>
</tr>
<tr>
<td>RH-</td>
<td>M 1382 (55.7%)</td>
<td>121 (38.1%)</td>
<td>0.000</td>
<td>2.047</td>
<td>1.611</td>
</tr>
<tr>
<td></td>
<td>W 1023 (57.2%)</td>
<td>188 (41.5%)</td>
<td>0.000</td>
<td>1.887</td>
<td>1.531</td>
</tr>
</tbody>
</table>

Model of the Cellular Mechanism of Action as a Function of Rh During Infection with SARS Cov2

The presence of the Rh AG complex is correlated by the abundance of D proteins which mark the category of the rhesus that will interact with the extracellular environment by regulating the extracellular pH via transmembrane exchanges of CO2 and O2 as well as the NH3 to an adequate pH which ensures the establishment of unfavorable conditions for the binding of the virus with the host cell by inhibiting mechanisms of their evolution. The absence of the Rh AG complex may create a favorable environment for virus uptake which is accompanied by the increased risk of hospitalization in Rh negative patients “Fig. 1”.

![Fig. 1: Mechanism of involvement of the Rhesus system in SARS COV2 infection](image-url)

IV. DISCUSSION

Our studies in the framework of evaluating the correlation between SARS CoV2 and the ABO system reveal a variation in the level of infection due to SARS CoV2 between the phenotype A and B. This can be attributed to the variability of the affinity anti-A and anti-B antibodies to the Spike S, which had shown a high sensitivity against the anti-A antibodies, and consequently their capacity to inhibit the adhesion of the complex (ACE2 / Spike S) against low sensitivity of anti-B antibodies. This explains the statistically significant difference in infection between the phenotypes (A) and (B) [20, 21].

The individuals of group O are the least infected, characterized by the abundance of anti-A and anti-B antibodies having a more remarkable antigenicity towards the viral actors which drive the entry of SARS CoV2 into the host cell (Spike S) due to their peptide sequences which contain specific complementarities at the stereochemical and molecular scale [7].

The activation of the cytokine, due to SARS CoV2 is accompanied by a significant production of coagulation factors which activate von wellbrand factors, this is associated with a significant elevation of adhesion molecules in order to ensure a turnover that involves the interaction of leukocytes with P-selectin and E-selectin of endothelial cells and then leukocyte attachment mediated by I-CAM 1 [22], that had shown an association with the SNP polymorphism ABO 11-14 [7]. This increase is mainly due to a cellular asymmetry expressed by the abnormal release of interleukin 6 (IL6) which offers an upward regulation of the expression of the gene coding for I-CAM [22]. This is accompanied immediately by a significant release of serotonin and ADP stored in the granules of activated platelets [8] [9], in addition to the antigenicity of anti A and anti B with ADP/P2Y2 receptors, blocks the formation of trombose...
[12], and consequently reduces the intense production of coagulation factors which are expressed by the inactivation of VWF factors, this confirms the implication of these antisera in reducing susceptibility to coagulation factor activation complications associated with SARS CoV2 infection in group O [22]. It is therefore suggested that the low rates of SARS CoV2 infection in group O, which is characterized by a low level of von willebrand factor in plasma, is due to the antigenic recognition of anti-A and anti-B antisera with the activation domain of ADMPTS13 [10], the thing that prevents creation of activation links between VWF and ADAMTS13. Consequently, this explains the remarkable low values of the Odd Ratio in patients with the O phenotype (OR≤1) in our population.

The fact of inhibiting these Spike using therapeutic strategies based on Anti-A and anti-B antibodies provides better protection against SARS CoV2 preventing the adhesion of the ACE2 / Spike S complex due to their high affinity to the exact adhesion site that binds virally using an extended RBD loop that includes residues 424 in direct contact with ACE2, this is a motif unglycosylated but surrounded by a glycan site [20].

Our study provides a physiological approach explaining the involvement of the rhesus system in infection due to SARS CoV2. The proteins of the Rh system contain an anion exchanger complex (C1- / HCO3-) AE with ankrin which plays a role of a complex involved in acid / base hemostasis by excreting ammonia or urine protein [16-18]. The second composition of the Rh system is a RhAG protein macrocomplex, which functions as a CO2 / O2 exchange metabolone [15-18].

Generally the viral entry is ensured first by the fixing of the S spikes with the ACE2 receptors these spikes are functioned by two subunits, the S1 subunit which is responsible for binding to the cell receptor and which plays a role of signal peptide containing the N terminal domain with residue 14-305 and a domain with residue 319-541. The second subunit is the S2 subunit which ensures the fusion of the viral and cellular membrane and which contains the residue 788 – 806, a heptapeptide repeat, a transmembrane domain with 1213-1237 and a transmembrane domain 1237-1273 [19].

SARS COV2 S proteins are rich in positively charged amino acid residues so acidification of the extracellular environment may increase upon SARS COV2 infection due to the remarkable increase of CO2 in the extracellular environment. Which results in a combination of increased positive charges on the S-glycoprotein and enhances complex glycosylation and thus SARS-CoV-2-ACE2 receptor binding 10-20 times more than normal [19, 20].

Moreover, patients with the Rh+ phenotype may have the risk of acidification linked to SARS COV2 due to the presence of the RhAG macrocomplex which ensures gas exchange between CO2 and O2 and the establishment of the balance of the extracellular concentration of CO2 this will then promote the regulation of extracellular pH and the occupancy of residues of positively charged amino acids by the O2 emitted to the outside of the cells through the RhAG complex [15-17].

On the other hand, Rh- patients are more vulnerable to the risks associated with acidification linked to SARS COV2 due to the absence of the RhAg macrocomplex allowing the establishment of pH hemostasis and the reduction of the extracellular concentration of CO2.

The immunological aspect of RhAG proteins was expressed at the cellular scale by a diminution of basal adhesion and erythroid complex assembly with a complete loss of ICAM-4 molecules [24]. Those have the ability to interact with several types of integrin due to domains that contain a binding site for CD11a and CD18 [25] the latter conceded as a ligand for the receptors of integrin that model adhesion to other cells or to components of the extracellular matrix [26]. CD11 proteins present a SER1158, phosphorylation site showing that it is necessary for phagocytosis so the lack of ICAM-4 immediately generates an immune deficiency which promotes complications related to SARS CoV2 infection [25].

Generally ICAM-4 favored the formation of erythroblastic islands of the marrow niche composed of erythroblasts surrounding a central macrophage, via interactions with integrin α, against ICAM-4 receptor expressed on macrophages [27]. These marrow niches are the hematopoiesis environment, where strains and immunological actors are formed, therefore the sensitivity to infection due to SARS CoV2 will be greater for the Rh- phenotype than for the Rh+ phenotype due to the difference in hematopoietic stimulation.

The protective factor in women is explained by the approach on which Graziano Pinna's research is based and which confirms that the female sex hormones, estrogen and progesterone, but also allopregnanolone, resulting from the metabolism of progesterone, play an anti-inflammatory role, influence immune cells, stimulate antibody production, promote repair of certain respiratory cells and inhibit the ACE2 receptor the pathway for coronavirus to enter cells [28]. In other words, these hormones would protect women against certain symptoms.

V. CONCLUSION

Patients with blood group AB had an increased risk for infection with SARS-CoV-2, whereas blood group O was associated with a decreased risk, indicating...
that certain ABO blood groups were correlated with SARS-CoV-2 susceptibility. Blood type was related to some clinical characteristics of patients with COVID-19. The presence of the A and B antigens increase the risk of infection with SARS CoV2. While the presence of anti-A and anti-B antibodies makes group O protector against infection.

Patients with the Rh + phenotype are less vulnerable to infection caused by SARS CoV2 due to the sufficient breakdown of RhAG, which is correlated by the presence of the D antigen. RhAG is vulnerable to the risk of acidifications associated with the absence of the D antigen. These are considered to have a protective effect which is vulnerable to infection caused by SARS CoV2 therefore they are risk factors with absence of the D antigen.

Moreover, the Rh + phenotype patients are less vulnerable to the risk of acidifications associated with the entry of SARS CoV2 due to the sufficient breakdown of RhAG, which is correlated by the presence of the D antigen. The rhesus system is responsible for regulating pH through ammonium transport and CO2 /O2 exchange. This promotes the creation of an unfavorable environment for viral attachment with the host cell.

REFERENCES


