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Assessment of severity and mortality of COVID-19 with anti-A1 and anti-B IgM isohaemagglutinins, a reflection of the innate immune status

Fatih Ozcelik[1] | Alpaslan Tanoglu[2] | Bulent Barış Guven[3] | Umran Keskin[4] |
Mustafa Kaplan[5]

[1]Department of Medical Biochemistry, University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training and Research Hospital, Istanbul, Turkey

[2]Department of Gastroenterology, University of Health Sciences Turkey, Sancaktepe Şehit Prof Dr Ilhan Varank Training and Research Hospital, Istanbul, Turkey

[3]Department of Anesthesia and Reanimation, University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training and Research Hospital, Istanbul, Turkey

[4]Department of Internal Medicine, University of Health Sciences Turkey, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey

[5]Department of Internal Medicine, University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training and Research Hospital, Istanbul, Turkey

Correspondence
Fatih Ozcelik, Department of Medical Biochemistry, University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training Hospital, 34668 Istanbul, Turkey.
Email: 68ozcelik@gmail.com

Abstract

Aims: The relationship between the innate immune system that creates the polysaccharide antibody response and COVID-19 is not fully understood. In this study, it was aimed to determine the predictive values of isohaemagglutinins in COVID-19 severity/mortality.

Methods: Approximately 15 440 patients diagnosed with COVID-19 were examined, and a total of 286 patients with anti-B and anti-A1 IgM isohaemagglutinins test results were randomly enrolled in the study. These patients were stratified into two groups according to anti-A1 (n: 138 blood type B or O) and anti-B (n: 148 blood type A) IgM isohaemagglutinins. Anti-A1 or/and anti-B IgM, biochemical parameters, symptoms, chronic diseases, hospitalisation status, intubation status, admission to intensive care unit (ICU) and exitus status were recorded and evaluated for all patients.

Results: Anti-A1 IgM and anti-B IgM were significantly lower in ICU patients (7.5 ± 9.9 vs 18.0 ± 20.4 and 5.5 ± 6.3 vs 19.3 ± 33.6 titres, respectively; $P < .01$) and in exitus patients (3.8 ± 3.6 vs 16.7 ± 18.7 and 3.5 ± 4.7 vs 16.9 ± 29.6 titres respectively; $P < .01$). In the ROC analysis performed to differentiate between exitus and discharge within groups, the sensitivity of anti-B IgM and anti-A1 IgM at cut-off ≤4 was 88.9% and 79.6%, specificity 66.0% and 73.4%, and AUC 0.831 and 0.861, respectively ($P < .01$). Anti-A1 IgM decreased the mortality risk 0.811 times per unit while anti-B IgM decreased 0.717 times ($P < .01$).

Conclusion: Anti-B and anti-A1 isohaemagglutinins, which are an expression of the innate immune system, can be used to predict the severity and mortality of COVID-19 disease.

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19), which predominantly affects the lungs, has killed millions of people around the world, with dramatic health and economic effects, and has evolved into a global health crisis that emerged nearly 100 years after the 1918 influenza pandemic. Like other RNA viruses, the coronavirus evolved mutations over time to adapt to new human hosts, turning into variants that have different characteristics from its ancestral strains and were not recognised by the innate immune system.[1] Unfortunately, the pattern recognition receptors (PRRs) of innate immune cells that recognise lipopolysaccharides, glycoproteins and methylated CpG nucleotides of bacteria and various RNA structures of viruses have therefore become dysfunctional. These PRRs regulate the early host response and its

severity and duration by stimulating variable pro-inflammatory molecules and later activating the acquired immune system.[2,3] Previously, it was found that pathogenic microbes can develop complex molecular strategies that disrupt host defences by affecting inflammatory signaling.[4,5] Corona viruses also cause deadly diseases such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19 by overcoming the host antiviral defence with similar strategies.[6] This has prompted researchers to search for new biomarkers associated with disease severity and mortality to understand and counter the coronavirus invasion.[7,8]

Almost the only option for protection from animal virus pandemics, such as severe pandemic influenza A (H1N1) 2009 and COVID-19 caused by the new type of coronavirus (SARS-CoV-2), is that immune system works flawlessly in all stages of life.[4,9,10] In addition, natural antibodies, the product of the innate immune system, constitute the first barrier of organism defence. Anti-A1 and/or Anti-B IgM and IgG isohaemagglutinins are also natural antibodies of this innate immune system.[11] At this point, it is thought that immunohematology is an important guide in evaluating immune events (antigen-antibody reactions) associated with blood cells, especially natural antibodies against erythrocyte antigens.

The formation of antibodies that directly neutralise animal viruses or prevent them from binding to the cell surface receptor is insufficient in the elderly and some diseases with weak immune response such as common variable immunodeficiency (CVID) and autoimmunity or cancer. In this context, the use of convalescent immune plasma (CIP), which is thought to contain neutralising antibodies, is recommended.[12,13] Early detection of individuals who cannot create an adequate immune response against the SARS-CoV-2 virus is of vital importance in the treatment of the disease. It is thought that this can be achieved practically by detecting the titre of anti-A1 and/or Anti-B isohaemagglutinins as an expression of the innate immune system. In addition, it has recently been reported that Anti-A natural isohaemagglutinins can prevent the adhesion of viruses causing SARS to cells and accelerate complement-mediated neutralisation of viral particles. This idea was shaped by the recent reporting that anti-A natural isohaemagglutinins can inhibit the adhesion of viruses causing SARS to cells and accelerate complement-mediated neutralisation of viral particles.[14]

In this study, it was aimed to investigate the relationship between isohaemagglutinins titres and routine biochemical parameters and disease morbidity/mortality of COVID-19 patients. In addition, the relationship between isohaemagglutinins, haemogram and biochemical parameters, age, use of CIP or erythrocyte suspension (ES) and disease morbidity and mortality were investigated.

2 | MATERIALS AND METHODS

2.1 | Study population

Before the study, which was planned with a retrospective cohort, the records of approximately 15 440 patients hospitalised with diagnosis of COVID-19 according to the results of reverse transcription

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What's known

- Isohaemagglutinins can be easily measured with the reverse blood typing test.
- Isohaemagglutinins are members of the innate immune system.
- There is no information about the relationship between isohaemagglutinins and the severity of COVID-19.

What's new

- High levels of isohaemagglutinins are associated with reduced rates of COVID-19 mortality.
- In addition, isohaemagglutinins are related with intensive care unit admission.

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polymerase chain reaction (RT-PCR) test and/or thorax computed tomography between June and December 2020 were screened. Among these patients, 286 patients who had a reverse blood grouping test (anti-A1 and anti-B IgM) were randomly selected for the study. The patients were divided into two groups as 148 patients with blood type A (Rh positive or negative) with anti-B IgM isohaemagglutinins in their plasma (anti-B group) and 138 patients with blood type B or O (Rh positive or negative) with anti-A1 IgM isohaemagglutinins (anti-A1 group). Anti-A1 and anti-B IgM isohaemagglutinins are not found in the blood type AB. For this reason, cases with blood type AB were excluded from study. Since anti-A1 IgM titres tend to be higher than anti-B IgM and to reach a sufficient population number, patients with blood type O containing two isohaemagglutinins were included in the anti-A1 group.

Ethical approval for the study was obtained from the University of Health Sciences Turkey Hamidiye Scientific Research Ethics Committee (2020-071).

2.2 | RT-PCR test for COVID-19

RT-PCR test detected ORF1ab + N genes belonging to conserved regions of SARS-CoV-2 virus.

2.3 | Anti-A1 IgM and anti-B IgM isohaemagglutinins titres

Anti-A1 or Anti-B IgM titration results for all patients included innate natural polysaccharide antibodies against A or B erythrocyte antigens detected by reverse blood grouping method (microplate direct haemagglutination method for ABO/Rh D blood grouping and typing, Neo Iris, Immucor, Inc., Germany). Anti-A1 and/or Anti-B IgM titrations were measured using the fully automated blood bank instrument (Neo Iris, Immucor, Inc., Germany).

ABO isohaemagglutinins are mostly IgM class antibodies, although they are found in plasma as IgM, IgG and IgA.[15] Therefore, the results of titres for IgM class isohaemagglutinins were included in the study. The range of anti-A and/or anti-B IgM titres was designated as 1/1, 1/2, 1/4, 1/8, 1/16, 1/32, 1/64, 1/128 and 1/256. The endpoint titre was the highest dilution indicating a positive reaction score. That is, if the final titre is 1/256, this titre is expressed as the highest (expressed as 256) and if the final titre is 1/1, the titre is expressed as 1.

Since there is no similar study in the literature, post-hoc power analysis was performed using PS Power and Sample Size Calculations Version 3.0 instead of a priori power analysis. Since five independent variables were used for the binary logistic regression model, the sample size was calculated by taking at least 10 subjects for each independent variable. In the post-hoc power analysis performed according to the results of the anti-B IgM independent variable of the patients admitted and not admitted to the ICU, the power of the study was 0.867 ($\alpha = 0.05$) and the effect size was 0.57 (Cohen d). Similarly, the power of the study was 0.957 ($\alpha = 0.05$) and the effect size was 0.65 according to the anti-A1 IgM independent variable results of the patients admitted and not admitted to the ICU.

2.4 | Blood haemogram and biochemical parameters

Haemogram results (leukocyte count, neutrophil ratio, lymphocyte ratio, monocyte ratio, eosinophil ratio, basophil ratio, erythrocyte count, haemoglobin, haematocrit, mean corpuscular volume (MCV), red cell distribution width (RDW), platelet crit (PCT), mean platelet volume (MPV) and platelet distribution width (PDW) and biochemistry parameters such as glucose, urea, creatinine, estimated glomerular filtration rate [eGFR], aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], γ-glutamyl transferase [GGT], lactate dehydrogenase [LDH], creatine kinase [CK], $Na^+/K^+/Ca^{++}$, albumin, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], procalcitonin, prothrombin time, international normalised ratio [INR], fibrinogen, D-dimer) were obtained from the patient records. ARCHITECT c16000 clinical chemistry analyzer (Abbott, Illinois, USA), Mindray Auto Hematology Analyzer BC-6800 (Shenzhen, China) and STA Compact Max3 automatic coagulation device (Diagnostica Stago, Asnieres sur Seine, France) were used for all tests. The haemoglobin and biochemical data in the first 24-hour period were used for patients who were admitted to the clinic or intensive care unit (ICU) with diagnosis of COVID.

2.5 | Clinical and demographic data of patients

Age, gender and symptoms of all patients (loss of smell or taste, back or joint pain, muscle pain, cough, shortness of breath, fever, headache, weakness, sore throat, diarrhoea), chronic diseases, hospitalisation status, length of stay, oxygen support, intubation, ICU admission, ICU duration, CIP/ES treatment and discharge/exitus status records were collected. Anti-B and anti-A1 groups were

compared primarily in terms of gender and age, as differences and other limitations between groups would reduce significance.

2.6 | Statistical analysis

For the statistical analysis of all data, SPSS Statistics 25 software (IBM Corp, Chicago, USA), MedCalc version 15.8 Software and InStat3 GraphPad Statistics software were used. In the study, the unpaired t test was used to compare parametric data of independent groups with two groups, and the Mann-Whitney test was used to compare nonparametric data. To determine the effectiveness and odds ratio (OR) of independent variables such as anti-A1 IgM, anti-B IgM, neutrophil to lymphocyte ratio (NLR), D-dimer, CRP and age, which are thought to influence ICU or exitus status, binary logistic regression analysis was used. To evaluate the diagnostic power of Anti A1 and anti-B IgM, which are indicators of the innate immune system, related to ICU admission and exitus status, Receiver Operating Characteristic (ROC) analysis was used. The chi-square test was used to evaluate categorical data.

3 | RESULTS

Of the 286 patients between the ages of 18-97 included in the study, 148 of them had blood type A (94 males and 54 females), 55 blood type B (38 males and 17 females) and 83 blood type O (55 males and 28 females). There was a total of 93 male and 45 female patients in the anti-A1 group.

The demographic results of patients with COVID-19 according to their clinical or ICU treatment status are given in Table 1. The patients who received treatment in ICU had higher age, chronic disease, CT finding, hospital stay, use of ES and CIP, and respiratory distress ($P < .01$). There was no difference between the clinical and ICU treatment in terms of blood types and gender ($P > .05$). It was noteworthy that all patients who were exitus were intensive care patients.

While anti-B IgM and anti-A1 IgM titrations of the groups were statistically significantly lower in patients treated in ICU, NLR, D-dimer and CRP levels were found to be higher ($P < .01$) (Figures 1A-D and 2A-D). Similarly, anti-B IgM and anti-A1 IgM titration values of exitus patients in both anti-B group and anti-A1 group were statistically significantly lower than those who were discharged while NLR, D-dimer and CRP levels were higher ($P < .01$) (Figures 3A-D and 4A-D).

In the anti-B group, the mean anti-B IgM titration value of patients 65 years and older (n: 77) and patients under 65 years of age (n: 71) were significantly lower (mean: 6.9 ± 9.1 vs 19.2 ± 34.6, median: 4 (0.5-64) vs 8 (1-256), respectively; $P < .0001$). Similarly, anti-A1 IgM titrations of the patients 65 years and older (n:71) in the anti-A1 group were quite low compared to the others (n: 67) (mean: 8.8 ± 10.3 vs 16.7 ± 20.6, median: 4 (0.5-64) vs 8 (1-128), respectively; $P = .0008$).

Haemogram, sedimentation and biochemical test results are compared in Tables 2 and 3 according to the treatment received by patients in the clinic (n:145) and ICU (n:141) without being divided into

TABLE 1 Comparison of demographic and isohaemagglutinins results in patients with COVID-19 according to the units they receive treatment

	All patients	Patients in clinical units	Patients in ICU	P values
n	286	145	141	—
Gender, F (%)/M (%)	99 (35)/187 (65)	45 (31)/100 (69)	54 (38)/87 (62)	.2782**
Age, y	63 ± 18.2	55 ± 18.9	70 ± 14.2	<.0001*
Chronic disease, n	217	83	134	<.0001**
Loss of smell or taste, n	25	20	5	.1134**
Back or joint pain, n	44	24	20	.5806**
Muscle pain, n	42	26	16	.3167**
Cough, n	119	65	54	.3317**
Shortness of breath, n	135	52	83	.0006**
Fever, n	161	76	85	.2423**
Headache, n	39	26	13	.1848**
Weakness, n	136	71	65	.6706**
Sore throat,	14	10	4	.5302**
Diarrhoea,	23	11	12	.8873**
CT findings, n (%)	237 (83)	101 (70)	136 (96)	<.0001**
Hospital stay, d	15 ± 11	10 ± 7	20 ± 12	<.0001*
ICU stay, d	—	—	11 ± 10	—
Oxygen support, n	238	98	141	—
Intubation statement, n	—	—	93	—
ES treatment, n	105	19	86	<.0001**
CIP treatment, n	97	21	76	<.0001**
Exitus status, n (%)	—	—	89 (63)	—
Blood typing A/B/O, n	148/55/83	78/24/43	70/36/35	.4695**

While parametric data were given as mean and standard deviation, nonparametric data were given as mean, standard deviation and median (min-max). The P value is approximate (from chi-square distribution). If *P* value is less than .005, the difference is significant. Anti-A1 IgM titres belong to patients with blood types B and O. Anti-B IgM titres belong to patients only with blood type A.

Abbreviations: CIP, convalescent immune plasma; CT, computed tomography; ES, erythrocyte suspension; F/M, female/male; ICU, intensive care unit.

*Unpaired *t* test for parametric data.

**Mann-Whitney test.

study groups. Leukocyte count, neutrophils ratio, NLR, RDW, MPV and ESR values were higher in patients admitted to ICU, while lymphocyte ratio, monocyte ratio, eosinophil ratio, basophil ratio, erythrocyte count, haemoglobin, haematocrit, platelet count and PCT values were lower ($P < .05$). While glucose, urea, creatinine, AST, GGT, LDH, Na, CRP, procalcitonin, prothrombin time, INR and D-dimer levels were higher in those who admitted to ICU, eGFR, albumin and Ca levels were lower ($P < .05$). There was no difference between the groups in terms of ALT, ALP, CK, K and fibrinogen levels ($P > .05$).

In the ROC curve analysis using the anti-B IgM titres to distinguish between patients in anti-B group receiving treatment in clinic (n: 78) and ICU (n: 70), the sensitivity for anti-B IgM at cut-off ≤4 was 71.4%, specificity 67.9% and area under the curve (AUC) 0.757 ($P < .0001$) (Figure 5A). In the same group, in the analysis to distinguish between exitus (n: 45) and discharged patients (n:103), the sensitivity of anti-B IgM titres at cut-off ≤4 was found to be 88.9%, specificity 66.0% and AUC 0.831 ($P < .0001$) (Figure 5B).

In the ROC curve analysis using the anti-A1 IgM titres to distinguish between patients in anti-A1 group receiving treatment in clinic (n:67) and ICU (n:71), the sensitivity of anti-A1 IgM at cut-off ≤4 was 62.0%, specificity 76.1% and area under the curve (AUC) 0.761 ($P < .0001$) (Figure 5C). In the same group, the analysis to distinguish between exitus (n:44) and discharged patients (n: 94) found the sensitivity of anti-A1 IgM titres at cut-off ≤4 was 79.6%, specificity 73.4% and AUC 0.861 ($P < .0001$) (Figure 5D).

Binary regression analysis to determine the effect of five independent variables, consisting of Anti-A1 or anti-B IgM, NLR, D-dimer, CRP and age, on dependent variables (ICU admission and exitus status) as indicators of disease severity are given in Tables 4 and 5. Although the model with five independent variables for predicting both ICU admission and exitus status in the anti-B group seems appropriate in total (Omnibus Test, $P < .0001$ and Hosmer-Lemeshow test, $P > .05$), the effects of CRP and age in the models for both conditions were statistically insignificant ($P > .05$). Similarly, in the anti-A1 group, the model
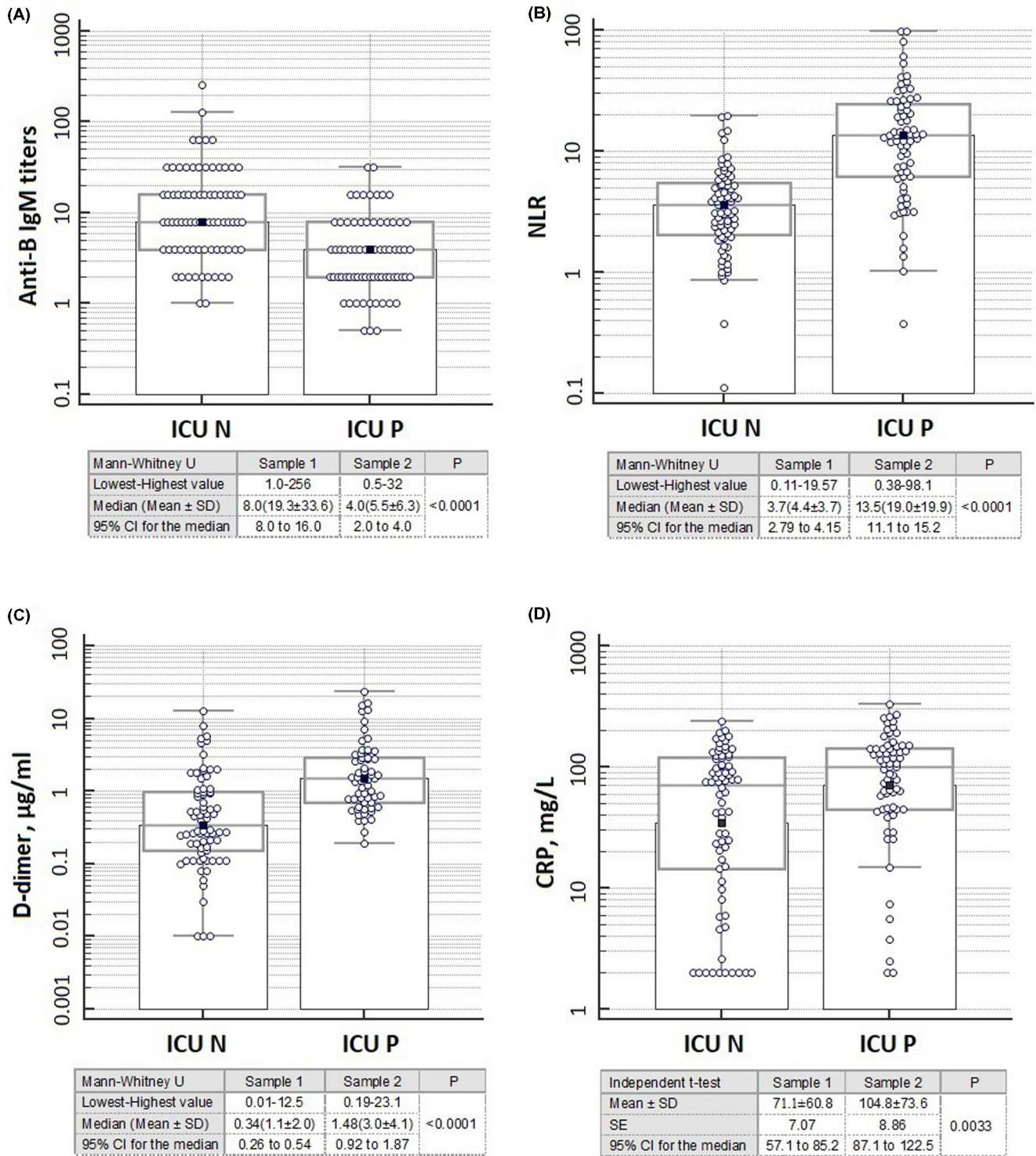
(A)

Mann-Whitney U	Sample 1	Sample 2	P
Lowest-Highest value	1.0-256	0.5-32	
Median (Mean ± SD)	8.0(19.3±33.6)	4.0(5.5±6.3)	<0.0001
95% CI for the median	8.0 to 16.0	2.0 to 4.0	

(B)

Mann-Whitney U	Sample 1	Sample 2	P
Lowest-Highest value	0.11-19.57	0.38-98.1	
Median (Mean ± SD)	3.7(4.4±3.7)	13.5(19.0±19.9)	<0.0001
95% CI for the median	2.79 to 4.15	11.1 to 15.2	

(C)

Mann-Whitney U	Sample 1	Sample 2	P
Lowest-Highest value	0.01-12.5	0.19-23.1	
Median (Mean ± SD)	0.34(1.1±2.0)	1.48(3.0±4.1)	<0.0001
95% CI for the median	0.26 to 0.54	0.92 to 1.87	

(D)

Independent t-test	Sample 1	Sample 2	P
Mean ± SD	71.1±60.8	104.8±73.6	
SE	7.07	8.86	0.0033
95% CI for the median	57.1 to 85.2	87.1 to 122.5	

FIGURE 1 A, Anti-B IgM; B, NLR; C, D-dimer and D, CRP results according to the ICU admission status of patients in the anti-B group (blood type A). NLR, D-dimer and CRP levels of the patients who were admitted to the ICU were higher while their anti-B IgM titrations were significantly lower. Statistical comparisons were made according to whether the data were parametric or not

with five independent variables for predicting both ICU admission and exitus status seemed appropriate in total (Omnibus Test, $P < .0001$ and Hosmer-Lemeshow test, $P > .05$). However, while the effects of D-dimer, CRP and age variables were statistically insignificant for the prediction of ICU admissions, D-dimer and CRP variables were found to be ineffective for predicting the exitus status ($P > .05$). Therefore,

when D-dimer, CRP and age as independent variables, which did not have sufficient effect on ICU admission and exitus status in both groups, were excluded from the model, a simpler model with two variables was achieved with anti-A1 or anti-B IgM and NLR. It was determined that this two-variable model classified with an accuracy close to the model with five independent variables (correct percentage of
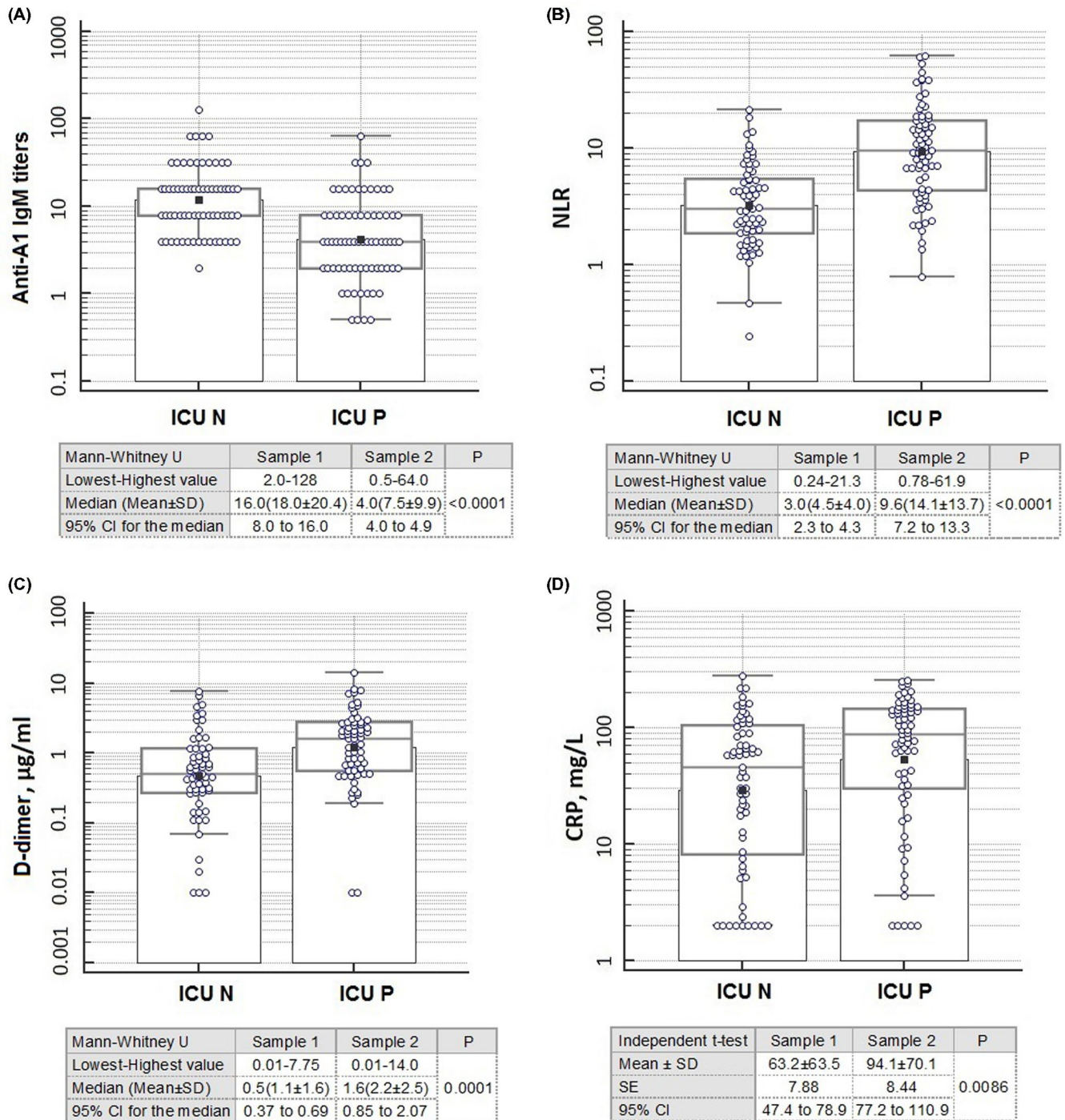
(A)

Mann-Whitney U	Sample 1	Sample 2	P
Lowest-Highest value	2.0-128	0.5-64.0	
Median (Mean±SD)	16.0(18.0±20.4)	4.0(7.5±9.9)	<0.0001
95% CI for the median	8.0 to 16.0	4.0 to 4.9	

(B)

Mann-Whitney U	Sample 1	Sample 2	P
Lowest-Highest value	0.24-21.3	0.78-61.9	
Median (Mean±SD)	3.0(4.5±4.0)	9.6(14.1±13.7)	<0.0001
95% CI for the median	2.3 to 4.3	7.2 to 13.3	

(C)

Mann-Whitney U	Sample 1	Sample 2	P
Lowest-Highest value	0.01-7.75	0.01-14.0	
Median (Mean±SD)	0.5(1.1±1.6)	1.6(2.2±2.5)	0.0001
95% CI for the median	0.37 to 0.69	0.85 to 2.07	

(D)

Independent t-test	Sample 1	Sample 2	P
Mean ± SD	63.2±63.5	94.1±70.1	
SE	7.88	8.44	0.0086
95% CI	47.4 to 78.9	77.2 to 110.9	

FIGURE 2 A, Anti-A1 IgM; B, NLR; C, D-dimer and D, CRP results according to the ICU admission status of the patients in the anti-A1 group (blood type B and O). NLR, D-dimer and CRP levels of the patients who were admitted to the ICU were higher while their anti-A1 IgM titres were significantly lower

prediction for ICU: 80.4% vs 83.3% and for exitus: 85.1% vs 87.9% in anti-B group; for ICU: 77.5% vs 76.4% and exitus: 84.1% vs 83.7% in anti-A1 group, respectively).

The fact that the Nagelkerke R2 values given in Tables 4 and 5 for both groups were 0.535 and 0.392 for ICU admission and 0.600 and 0.526 for exitus status, respectively, demonstrates that the two-variable models explained the dependent variables (ICU admission and exitus status) at a good level. In addition, the following formula

created from the B constants obtained from this simple model can be used to predict the probability of ICU admission and exitus. If the probability value is above the cut-off point 0.5, it is accepted as occurrence of the event, in other words 1.

$$P(Y) = \frac{1}{1 + e^{-9(B0 + B1 \times X1 + B2 + X2)}}$$

(A)

Mann-Whitney U	Sample 1	Sample 2	P
Lowest-Highest value	1.0-256	0.5-32.0	
Median (Mean ± SD)	8.0(16.9±29.6)	2.0(3.5±4.7)	<0.0001
95% CI for the median	8.0 to 16.0	2.0 to 4.0	

(B)

Mann-Whitney U	Sample 1	Sample 2	P
Lowest-Highest value	0.11-37.8	1.3-98.1	
Median (Mean)	4(5.9)	15.2(23.7)	<0.0001
95% CI for the median	3.2 to 4.6	13.2 to 22.7	

(C)

Mann-Whitney U	Sample 1	Sample 2	P
Lowest-Highest value	0.01-12.5	0.41-23.1	
Median (Mean ± SD)	0.49(1.2±2.0)	1.69(3.6±5.1)	<0.0001
95% CI for the median	0.29 to 0.79	1.15 to 2.72	

(D)

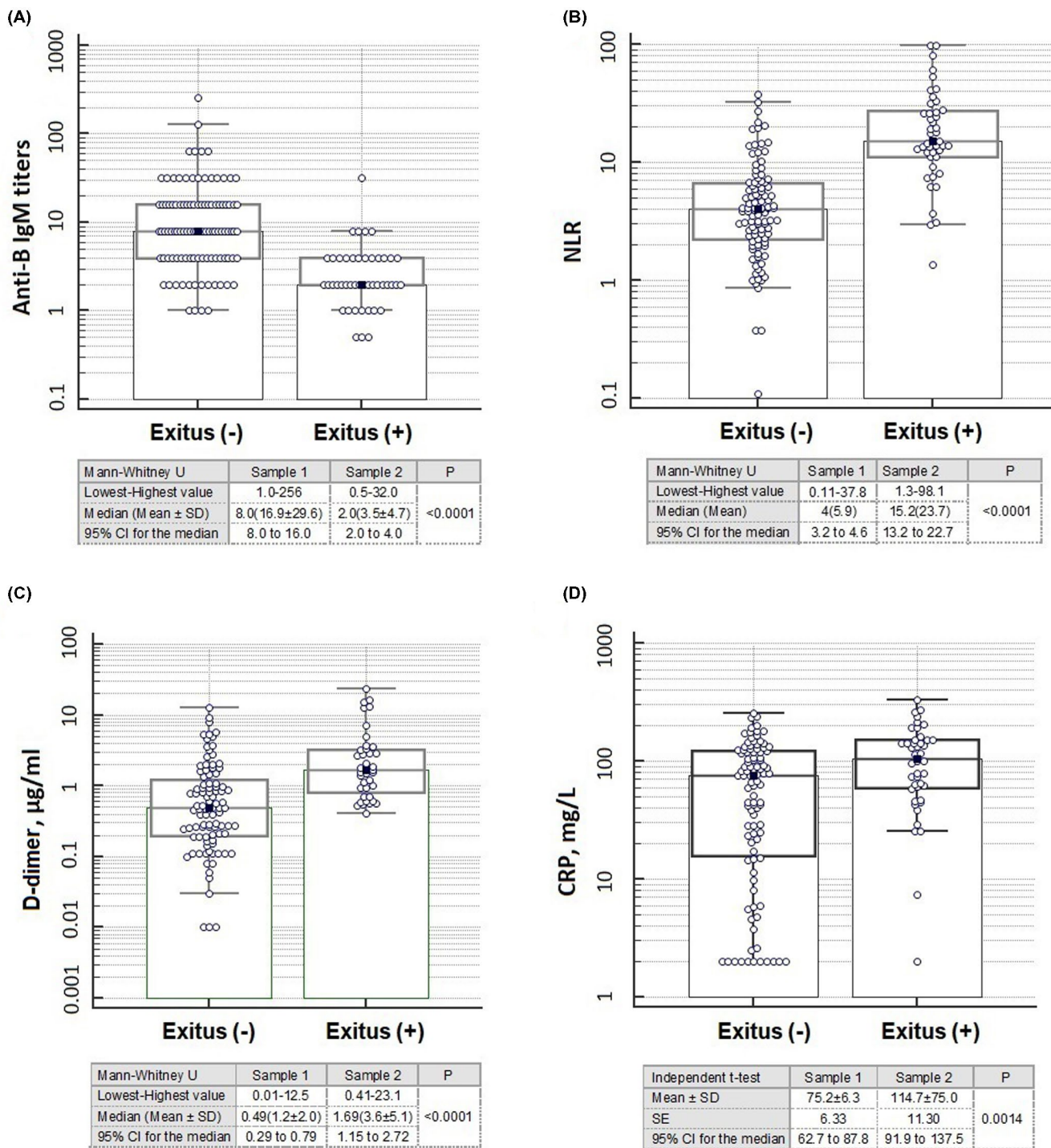| Independent t-test	Sample 1	Sample 2	P
Mean ± SD	75.2±6.3	114.7±75.0	
SE	6.33	11.30	0.0014
95% CI for the median	62.7 to 87.8	91.9 to 137.5	

FIGURE 3 A, Anti-B IgM; B, NLR; C, D-dimer and D, CRP results according to the exitus status of the patients in the anti-B group (blood type A). NLR, D-dimer and CRP levels of the exitus patients were higher while their anti-B IgM titres were significantly lower

According to the OR results identified with binary logistic regression analysis, a one-unit increase in anti-A1 titres decreased the probability of ICU admission 0.956 times and an increase in anti-B IgM titres decreased this probability 0.933 times ($P < .01$) (Tables 4 and 5). It was determined that a one-unit increase in the NLR value increased the probability of ICU admission by 1.193 in the anti-A1 group and 1.227 in the anti-B group ($P < .01$). Similarly, a one-unit increase in anti-A1 IgM and anti-B IgM titres was found to reduce the risk of mortality from COVID-19 by 0.772 and 0.759, respectively. ($P < .01$). On the other hand, a one-unit increase in NLR increased the risk of mortality by 1.087 and 1.139 times, respectively ($P < .01$).
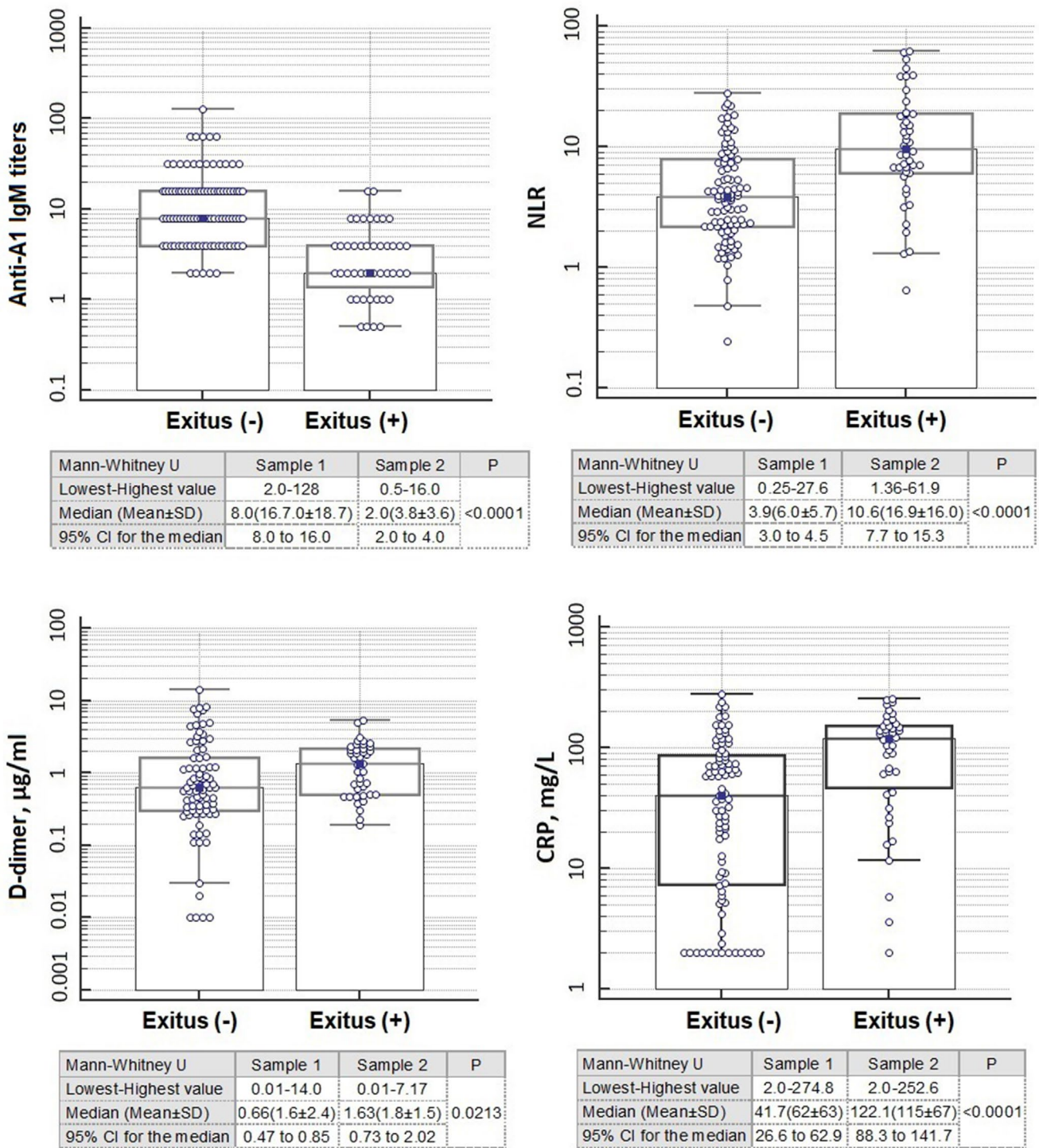
Mann-Whitney U	Sample 1	Sample 2	P
Lowest-Highest value	2.0-128	0.5-16.0	
Median (Mean±SD)	8.0(16.7.0±18.7)	2.0(3.8±3.6)	<0.0001
95% CI for the median	8.0 to 16.0	2.0 to 4.0	

Mann-Whitney U	Sample 1	Sample 2	P
Lowest-Highest value	0.25-27.6	1.36-61.9	
Median (Mean±SD)	3.9(6.0±5.7)	10.6(16.9±16.0)	<0.0001
95% CI for the median	3.0 to 4.5	7.7 to 15.3	

Mann-Whitney U	Sample 1	Sample 2	P
Lowest-Highest value	0.01-14.0	0.01-7.17	
Median (Mean±SD)	0.66(1.6±2.4)	1.63(1.8±1.5)	0.0213
95% CI for the median	0.47 to 0.85	0.73 to 2.02	

Mann-Whitney U	Sample 1	Sample 2	P
Lowest-Highest value	2.0-274.8	2.0-252.6	
Median (Mean±SD)	41.7(62±63)	122.1(115±67)	<0.0001
95% CI for the median	26.6 to 62.9	88.3 to 141.7	

FIGURE 4 A, Anti-A1 IgM; B, NLR; C, D-dimer and D, CRP results according to the exitus status of the patients in the anti-A1 group (blood type B and O). NLR, D-dimer and CRP levels of the exitus patients were higher while their anti-A1 IgM titres were significantly lower

4 | DISCUSSION

The discussions about the related COVID-19 disease are especially centred around the angiotensin-converting enzyme 2 (ACE2) receptor, senility, inappropriate immune response and the chronic disease paradigm.[16,17] In most patients, chronic diseases cause recurrent infections, by reducing resistance against viral or bacterial pathogens.

In addition, this deterioration in the immune system may cause autoimmune diseases and cancers due to impaired immunological tolerance of the body against its own cells.[12,18,19] Therefore, the immune system response should be the primary focus in combating COVID-19 disease.

The COVID-19 pandemic is characterised by an inadequate polysaccharide antibody response. Isohaemagglutinins, which are

TABLE 2 Comparison of haemogram and sedimentation test results in patients with COVID-19 according to the units they receive treatment

	All patients	Patients in clinical units	Patients in ICU	P values[*]
N	286	145	141	—
Leukocytes, ×10^6/mL	9.7 ± 8.2 7.6 (0.31-70.7)	7.6 ± 5.1 6.5 (1.4-51.9)	11.8 ± 10.1 8.8 (0.3-70.7)	<.0001[**]
%Neutrophils	75.4 ± 16.3 78.8 (9.9-98.1)	67.9 ± 15.6 69.9 (9.9-92.0)	83.0 ± 13.2 87.2 (15.2-98.1)	<.0001[**]
%Lymphocytes	17.4 ± 13.2 14.3 (1.0-89.6)	23.5 ± 13.2 20.7 (4.3-89.6)	11.1 ± 9.7 7.3 (1.0-49.0)	<.0001[**]
NLR	10.4 ± 13.8 5.4 (0.1-98.1)	4.4 ± 3.9 3.2 (0.1-21.3)	16.5 ± 17.3 12.0 (0.4-98.1)	<.0001[**]
%Monocytes	6.1 ± 7.2 5.2 (0.1-101)	6.7 ± 4.2 6.1 (0.2-44.4)	5.5 ± 9.3 4.1 (0.1-101)	<.0001[**]
%Eosinophils	1.0 ± 1.7 0.3 (0.0-14.0)	1.3 ± 1.7 0.7 (0.1-9.9)	0.8 ± 1.7 0.2 (0.0-14.0)	<.0001[**]
%Basophils	0.3 ± 0.2 0.2 (0.0-2.4)	0.3 ± 0.2 0.3 (0.1-1.1)	0.3 ± 0.3 0.2 (0.0-2.4)	.0279[**]
Erythrocytes, ×10^9/mL	4.1 ± 0.8 4.2 (1.4-6.3)	4.4 ± 0.8 4.5 (1.4-6.3)	3.8 ± 0.8 3.8 (1.8-5.6)	<.0001[**]
Haemoglobin, g/dL	11.6 ± 2.7 11.8 (4.5-17.8)	12.7 ± 2.6 13.1 (4.5-17.8)	10.5 ± 2.2 10.1 (5.3-16.1)	<.0001[**]
Haematocrit, %	35.2 ± 7.2 35.7 (13.4-51.9)	37.8 ± 6.8 38.8 (13.4-51.9)	32.5 ± 6.5 32.3 (16.0-50.0)	<.0001[**]
MCV, fL	86.3 ± 6.7 86.9 (58.0-101)	85.6 ± 6.5 86.6 (58.0-99.8)	86.9 ± 6.9 87.2 (59.3-101)	.1800[**]
RDW, %	14.5 ± 2.6 13.8 (11.4-30.2)	14.0 ± 2.7 13.3 (11.6-30.2)	14.9 ± 2.4 14.2 (11.4-26.6)	<.0001[**]
Platelets, ×10^6/mL	232 ± 114 217 (11-986)	249 ± 104 227 (60-594)	214 ± 121 209 (11-986)	.0001[**]
PCT, %	0.23 ± 0.10 0.22 (0.01-0.95)	0.24 ± 0.09 0.22 (0.06-0.59)	0.21 ± 0.11 0.21 (0.01-0.95)	.0086[**]
PDW, %	16.3 ± 0.4 16.3 (14.7-17.9)	16.3 ± 0.4 16.3 (15.0-17.9)	16.3 ± 0.5 16.3 (14.7-17.9)	.3096[**]
MPV, fL	10.1 ± 1.2 10.1 (7.4-16.2)	9.9 ± 1.1 9.9 (7.4-13.4)	10.4 ± 1.3 10.2 (7.8-16.2)	.0171[**]
ESR, mm/h	58 ± 33 56 (3-140)	50 ± 31 44 (3-140)	65 ± 33 66 (4-140)	.0015[**]

Nonparametric data are given as mean, standard deviation and median (min-max). If P value is less than .005, the difference is significant.

Abbreviations: MCV, mean corpuscular volume; RDW, red cell distribution width; PCT, plateletcrit; MPV, mean platelet volume; PDW, platelet distribution width, ESR, erythrocyte sedimentation rate; NLR, neutrophil to lymphocyte ratio; mm/h, millimetres per hour; fL, femtolitre,
**Mann-Whitney Test.

polysaccharide antibodies, are kinds of natural antibodies produced by thymus-independent B1 lymphocytes (activated naturally without the help of T cells) in response to A or B polysaccharide antigens on red blood cells. It is generally assumed that these antibodies are produced in response to polysaccharides on intestinal bacteria and cross react with AB blood group antigens.[3,12,20,21] IgM antibodies secreted by B1 cells, which play an important role in innate immunity, are the dominant antibodies during primary threat. While participating in the neutralisation and cleaning of pathogens, they also initiate inflammatory reactions against pathogens. The innate immune system also stimulates the acquired immune system, which creates the humoral immune response. Thus, the pathogen is stopped more strongly and specifically. Isohaemagglutinins and pneumococcal polysaccharide antibody titres, which are currently used as indicators of natural antibodies, are used as a measure to assess defects in this immune response.[11,20,22–24] The routine use of isohaemagglutinins for the detection of suspected immunodeficient patients is still under discussion. Based on this information, we used anti-A1 and anti-B IgM antibodies, which are indicators of the effectiveness of the innate immune system, to predict severe cases of COVID-19 disease in this study.

In this study, patients with COVID-19 who received ICU treatment had higher leukocyte, neutrophil, NLR, urea, creatinine, albumin, CRP,

	All patients	Patients in clinical units	Patients in ICU	P values
n	286	145	141	—
Glucose, mg/dL	132 ± 77 107 (25-603)	109 ± 54 90 (46-368)	155 ± 90 129 (25-603)	<.0001**
Urea, mg/dL	59 ± 50 40 (11-242)	40 ± 30 31 (11-230)	79 ± 58 59 (14-242)	<.0001**
Creatinine, mg/dL	1.6 ± 1.63 1.1 (0.42-10.8)	1.5 ± 1.6 1.1 (0.7-10.8)	1.8 ± 1.7 1.2(0.4-10.8)	.0146**
eGFR, mL/min/1.73 m²	67.2 ± 30.4 71.0 (3.6-130)	74 ± 26 77.8(3.6-126)	59 ± 34 62 (4.8-130)	.0003**
AST, U/L	42 ± 48 29 (4-411)	36 ± 42 28 (6-411)	47 ± 54 33 (4-408)	.0195**
ALT, U/L	47 ± 48 31 (5-340)	43 ± 37 30 (5-199)	51 ± 57 33 (5-340)	.4373**
ALP, U/L	90 ± 51 74 (21-350)	84 ± 47 73 (33-332)	95 ± 55 75 (21-350)	.3261**
GGT, U/L	54 ± 60 37 (2-540)	45 ± 45 34 (3-351)	64 ± 71 45 (2-540)	.0106**
LDH, U/L	589 ± 330 494 (7-1925)	509 ± 254 453 (7-1924)	672 ± 376 590 (8-1925)	<.0001**
CK, U/L	155 ± 246 80(5-1780)	128 ± 230 64 (5-1780)	194 ± 266 96 (11-1100)	.2442**
Albumin, g/L	30 ± 6 29 (17-52)	33 ± 6 33 (21-52)	27 ± 5 27 (17-39)	<.0001**
Na, mEqL	139 ± 5 139 (122-157)	138 ± 4 138 (122-149)	140 ± 6 140 (122-157)	.0048**
K, mEqL	4.2 ± 0.7	4.3 ± 0.5	4.2 ± 0.8	.1356*
Ca, mg/dL	8.4 ± 0.8 8.5 (5.5-12.8)	8.6 ± 0.7 8.6 (6.4-10.1)	8.3 ± 0.8 8.3 (5.5-12.8)	.0048**
CRP, mg/L	83 ± 69 73 (2-332)	67 ± 62 58 (2-275)	99 ± 72 92 (2-332)	<.0001**
Procalcitonin, µg/L	1.85 ± 6.16 0.15 (0.01-52)	0.8 ± 5.2 0.1 (0.01-52)	2.8 ± 6.8 0.3 (0.01-48)	<.0001**
PT, s	16.4 ± 5.1 15.2 (11.4-59.7)	15.1 ± 3.6 14.5 (11.4-46)	17.5 ± 5.9 16.1 (12.4-60)	<.0001**
INR	1.3 ± 0.45 1.17 (0.86-4.76)	1.2 ± 0.3 1.1 (0.86-3.7)	1.4 ± 0.5 1.3 (0.93-4.8)	<.0001**
Fibrinogen, mg/dL	539 ± 173	542 ± 164	535 ± 184	.9359*
D-dimer, µg/mL	1.81 ± 2.89 0.79 (0.01-23)	1.1 ± 1.8 0.5 (0.01-12.5)	2.6 ± 3.6 1.5 (0.01-23)	<.0001**

TABLE 3 Comparison of biochemistry test results in patients with COVID-19 with according to the units they receive treatment

While parametric data were given as mean and standard deviation, nonparametric data were given as mean, standard deviation and median (min-max). If *P* value is less than .005, the difference is significant.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; Ca, calcium; CK, creatine kinase; CRP, C-reactive protein; eGFR: estimated glomerular filtration rate calculated by Modification of Diet in Renal Disease (MDRD) study equation, AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, international normalised ratio; K, Potassium; LDH, lactate dehydrogenase; Na, Sodium; PT, prothrombin time.

*Unpaired *t* test for parametric data.

**Mann-Whitney Test.

procalcitonin, prothrombin time, D-dimer, AST, GGT, LDH and ESR values, and lower values for lymphocytes, platelet count, erythrocyte count, haemoglobin, and haematocrit. These findings are consistent with the results for COVID-19 patients with severe and fatal disease conducted by Henry et al.[8] Our results also coincided with the marked lymphopenia and high LDH detected in a recent study by Fan et al. on their patients with COVID-19.[25] In addition, in our study, the decrease in anti-A1 and anti-B IgM titres and the increase in NLR values
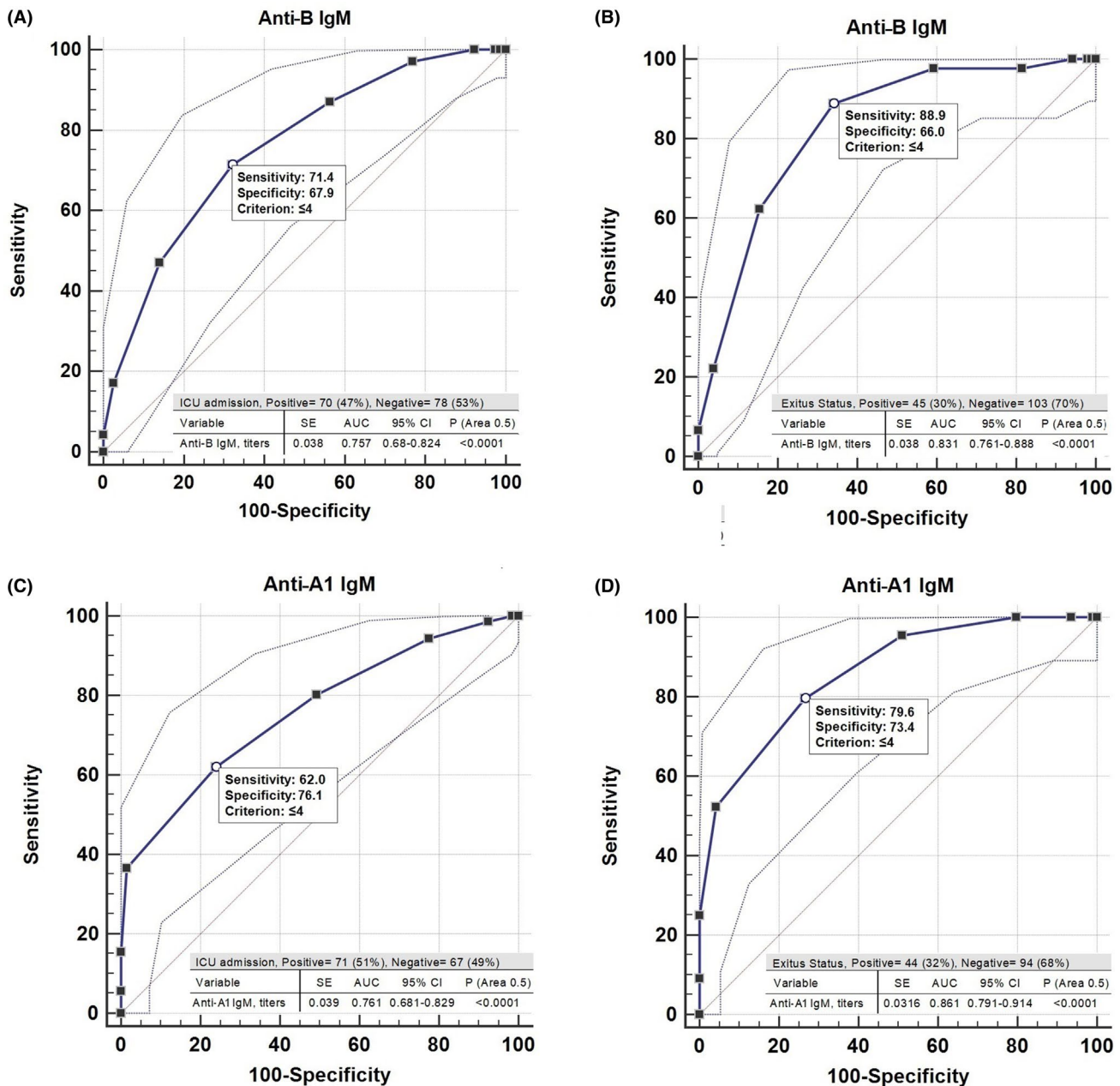
FIGURE 5 ROC analysis for A, anti-B IgM to distinguish between the ICU admission, or not. B, Anti-B IgM to distinguish between the patients with exitus, or not. C, Anti-A1 IgM to distinguish between the ICU admission, or not. D, Anti-A1 IgM to distinguish between the patients with exitus, or not. As a result of the analysis, the most suitable cut-off value was found to be ≤4. At this cut-off value, sensitivity, specificity and area under the curve (AUC) results of anti-B and anti-A1 IgM are seen. Anti-B and anti-A1 IgM had good sensitivity and specificity in diagnostic power for the severity of COVID-19

of exitus patients with COVID-19 compared to discharged patients were quite prominent. Therefore, it was understood from this finding that there was a relationship between the severity of COVID-19 and anti-A1 and anti-B IgM isohaemagglutinins. Hence, in the model with five independent variables for the prediction of ICU and exitus status, CRP and partially D-dimer and age variables were found to be ineffective (contribution insignificant), different to NLR and anti-A1 and anti-B IgM. Possible reasons for this can be explained as follows. CRP is synthesised by lymphocytes as well as hepatocytes. It is therefore

directly related to NLR. The effect of the CRP variable in the model was absorbed by the NLR variable. The population in the study generally consisted of elderly patients. This may have caused age to be partially ineffective in predicting the ICU admission and exitus status. Moreover, the effect of the age variable in the model may have been limited by the isohaemagglutinins because anti-A1 and anti-B IgM isohaemagglutinins antibodies are biomarkers that tend to decrease with age. Another variable that was found to be partially ineffective in the regression model was D-dimer. D-dimer is a small protein found in the

TABLE 4 Binary logistic regression models to evaluate the effect of five and two variables on ICU and exitus status in patients with blood type A

	ICU admission			95% CI		P	Exitus status			95% CI		P
	B	SE	OR				B	SE	OR			
Five variables												
Anti-B IgM	−0.078	0.034	0.925	0.866	0.988	.020	−0.333	0.097	0.717	0.593	0.867	0.001
NLR	0.166	0.048	1.181	1.074	1.298	.001	0.105	0.030	1.110	1.048	1.176	.000
D-dimer	0.221	0.106	1.247	1.012	1.536	.038	0.303	0.141	1.354	1.027	1.783	.031
CRP	0.002	0.004	1.002	0.995	1.010	.594	0.004	0.004	1.004	0.995	1.012	.420
Age	0.023	0.015	1.024	0.993	1.055	.130	0.035	0.020	1.035	0.995	1.077	.085
Constant	−2.839	1.186	0.058			.017	−3.659	1.587	.026			.021
	Correct percentage of prediction: 83.3%, Omnibus Test (Chi-sq. = 73.37, P < .0001), HL test (Chi-sq. = 12.67, P = .124), Nagelkerke R2 = 0.569						Correct percentage of prediction: 87.9%, Omnibus Test (Chi-sq. = 85.697, P < .0001), HL test (Chi-sq. = 1.941, P = .983), Nagelkerke R2 = 0.676					
Two variables												
Anti-B IgM	−0.070	0.027	0.933	0.885	0.982	.009	−0.276	0.069	0.759	0.664	0.868	.000
NLR	0.204	0.045	1.227	1.123	1.339	.000	0.130	0.026	1.139	1.082	1.198	.000
Constant	−1.114	0.433	0.328			.010	−0.815	0.379	0.443			.032
	Correct percentage of prediction: 80.4%, Omnibus Test (Chi-sq. = 75.72, P < .0001), HL test (Chi-sq. = 5.66, P = .686), Nagelkerke R2 = 0.535						Correct percentage of prediction: 85.1%, Omnibus Test (Chi-sq. = 81.72, P < .0001), HL (Chi-sq. = 10.79, P = .214), Nagelkerke R2 = 0.600					

P value < .05 is considered significant.

If the CI of OR does not contain 1 value, the P value is found significant.

Abbreviations: CI, confidence interval; HL test, Hosmer-Lemeshow test; OR, odds ratio.

TABLE 5 Binary logistic regression models to evaluate the effect of five and two variables on ICU and exitus status in patients with blood type B/O

	ICU admission			95% CI		P	Exitus status			95% CI		P
	B	SE	OR				B	SE	OR			
Five variables												
Anti-A1 IgM	−0.062	0.027	0.940	0.891	0.991	0.023	−0.209	0.064	0.811	0.716	0.920	0.001
NLR	0.131	0.048	1.140	1.039	1.251	0.006	0.073	0.033	1.076	1.009	1.148	.027
D-dimer	0.179	0.125	1.196	0.936	1.528	0.152	0.008	0.014	1.008	0.981	1.036	.556
CRP	−0.001	0.004	0.999	0.992	1.006	0.850	0.008	0.004	1.008	1.000	1.016	.052
Age	0.045	0.017	1.046	1.012	1.081	0.008	0.028	0.019	1.029	0.992	1.067	.131
Constant	−3.416	1.211	0.033			0.005	−2.477	1.478	0.084			.094
	Correct percentage of prediction: 76.4%, Omnibus Test (Chi-sq. = 56.30, P < .0001), HL test (Chi-sq. = 4.89, P = .769), Nagelkerke R2 = 0.490						Correct percentage of prediction: 83.7%, Omnibus Test (Chi-sq. = 56.30, P < .0001), HL test (Chi-sq. = 10.38. P = .239), Nagelkerke R2 = 0.578					
Two variables												
Anti-A1 IgM	−0.045	0.021	0.956	0.917	0.996	.030	−0.259	.066	0.772	0.678	0.879	.000
NLR	0.177	0.044	1.193	1.095	1.301	.000	0.083	.030	1.087	1.026	1.151	.005
Constant	−0.720	0.415	0.487			.083	0.202	.503	1.224			.688
	Correct percentage of prediction: 77.5%, Omnibus Test (Chi-sq. = 48.02, P < .0001), HL test (Chi-sq. = 11.77, P = .162), Nagelkerke R^2 = 0.392						Correct percentage of prediction: 84.1%, Omnibus Test (Chi-sq. = 64.98, P < .0001), HL test (Chi-sq. = 12.01, P = .151), Nagelkerke R^2 = 0.526					

P value < .05 is considered significant.

Abbreviations: CI, confidence interval; HL test, Hosmer-Lemeshow test; OR, odds ratio.

blood after blood clots are broken down by fibrinolysis. Although it was reported to be a strong predictor of mortality in COVID-19 patients, 3% of COVID-19 patients have coagulopathy.[26,27] This finding explains why we found the D-dimer variable ineffective in predicting ICU admission and exitus status in the anti-B group in our study. As a result, the most suitable independent variables for the prediction of ICU admission and exitus status were NLR and anti-A1/anti-B IgM isohaemagglutinins.

In COVID, which is used as a reference for immune system failure, and some pathologies (such as splenectomy, immunosuppression and acquired immunodeficiency, HIV, autoimmunity, or aging) with impaired immune response, reduction, or absence of anti-A and/or anti-B isohaemagglutinins and poor polysaccharide antibody response to vaccines are expected.[20,28,29] Assessment of this impaired immunological response is possible by detecting pneumococcal polysaccharide antibody response and isohaemagglutinins levels, although these are still under discussion. Of these, isohaemagglutinins were chosen in our study because they are more accessible and practical. In the study conducted considering the above information, the fact that the patients with low isohaemagglutinins levels were 65 years and older and most of them had chronic disease was interpreted in favour of low immune system response in these patients. This situation is a sign that this population will need multiple therapies such as antiviral and complex vitamins, oxygen supplementation, CIP, early Ig and interferon β and/or γ therapies support to support the immune system.[30,31] However, in our study, the mortality rate was found to be high, even though a significant portion of the elderly population with low isohaemagglutinins levels was treated in the ICU and received multiple therapies. The probable reason for this is that patients who are likely to have severe disease and who will need additional therapies cannot be identified in the early period. Moreover, the lack of expected effect from CIP treatment was not yet explained. In general, this situation may be attributed to the lack of early treatment and the lack of sufficient antibodies in CIP to provide viral neutralisation. Therefore, isohaemagglutinins, which are indicators of innate immune response, may be used for the prediction of disease severity in the early period.

Age-related insensitivity of the immune system to most of the current vaccines is attributed to newly formed neo-antigens that the immune system cannot recognise and the decrease in the number and functions of T and B cells involved in this recognition.[12,19,32,33] It has also been reported that there are significant age-related changes in the transcription levels of biomolecules related to the immune system, inflammation and oxidative stress. It may be possible to overcome this insensitivity in the immune system with mRNA-based vaccines.[34,35] However, the use of these vaccines may be considered for immune-insensitive risky groups instead of the entire population since the full understanding of the effects of these vaccines on humans may take a long time. Therefore, finding an appropriate marker to detect the insensitivity of the immune system is important for maintaining health. In this study, the finding that the increase in anti-A1 and anti-B IgM levels was inversely proportional to the risk of ICU admission and mortality, independent of NLR, showed

that these isohaemagglutinins are suitable markers. In addition, the finding that anti-A1 and Anti-B IgM levels have very good diagnostic power for the differentiation of ICU admission and exitus in ROC analysis confirms this result.

As with COVID-19, the main problem is the activation of the immune system. Anti-A and/or Anti-B type isohaemagglutinins may be one of the options that can easily demonstrate this situation in clinical laboratories. However, while there is no problem in blood types A, B and O, it does not seem possible to use this method as there is no anti-A and/or anti-B isohaemagglutinins in the serum of individuals with blood type AB. For these people, the problem can be solved by investigating the polysaccharide antibody response against the pneumococcal vaccine.[15,20,36] Therefore, individuals with AB blood group were not included in this study. Therefore, individuals with blood type AB could not be included in this study. In addition, since anti-A1 and anti-B isohaemagglutinins are separate parameters, both were not evaluated in one group. Again, since we found that anti-A1 IgM tends to be higher, we consider that it would be more appropriate to conduct the study in two different groups. Moreover, anti-A1 IgM results tended to be higher compared to anti-B IgM. The probable reason for high anti-A1 IgM is that the natural antibodies detected against A1 or B antigens in erythrocytes do not consist of only anti-A1 or anti-B IgM because anti-A and anti-B reactivity is possible in people with blood type O. This reactivity observed in sera with O blood type is due to the reaction of anti-A and anti-B immunoglobulins with a shared epitope in cells with A or B antigens.[15,37] Therefore, in the group evaluated with anti-A1 IgM, high values due to anti-A, B reactivity can be observed. However, since the study was conducted in two different groups, the effect of this negativity on the results was limited.

In a study examining the relationship between ABO blood group type and COVID-19, researchers suggested that individuals with blood type O are more resistant to the disease and that anti-A and anti-B antibodies may contribute to viral neutralisation by binding to antigens on the viral envelope.[14] Unlike these researchers, in our study, no relationship was found between the blood group type and the mortality status. In another study by Guillon et al,[38] it was reported that monoclonal or naturally occurring anti-A antibodies inhibit the interaction between the SARS-CoV S protein and ACE2R depending on the dose, which is close to our study findings. However, our findings were not intended to show that isohaemagglutinins may directly target the S protein. In short, we suggested that isohaemagglutinins levels are related with resistance to COVID-19 disease rather than the blood group types.

Few studies have been conducted about the diagnostic value of isohaemagglutinins antibody deficiency. Although there are conflicting data, it was reported that it can be used for the diagnosis of immunodeficiency such as congenital immunologic deficiency syndromes, CVID and Wiskott-Aldrich syndrome, or to check the restoration of immunological competence.[11,20,39] Basically, the results obtained from our study showed that isohaemagglutinins are satisfactory in predicting the severity of COVID-19. If this function can be combined with a second parameter that activates the acquired immune system, such as NK-cell activity which measures the innate

immune system's ability to function or NLR,[4,5] more effective results will be achieved in predicting the severity of COVID disease.

In conclusion, anti-A1 and anti-B IgM isohaemagglutinins, which are expressions of the innate immune system, can be used alone or in combination with NLR for predicting the severity and mortality of COVID-19.

AUTHORS' CONTRIBUTIONS

F Ozcelik: Designed the research study, provided the research guidance, collected the data, performed the statistical analysis and wrote the manuscript. A Tanoglu and BB Guven: Collected or analysed the data. K Umran and M Kaplan: Interpreted the data and critically revised and edited the manuscript.

ETHICS APPROVAL

This study was approved by the Ethics Committee of the University of Health Sciences Turkey Hamidiye Scientific Research (registration number: 20/324). This study was conducted with the approval (No. 2020-08-27T18-07-40) of the Republic of Turkey Ministry of Health Research Platform.

ORCID

Fatih Ozcelik https://orcid.org/0000-0003-2439-3964
Alpaslan Tanoglu https://orcid.org/0000-0002-7477-6640
Bulent Barış Guven https://orcid.org/0000-0002-3628-7408
Umran Keskin https://orcid.org/0000-0002-7494-2733
Mustafa Kaplan https://orcid.org/0000-0002-0354-4762

REFERENCES

1. Features, Evaluation, and Treatment of Coronavirus (COVID-19) - PubMed. https://pubmed.ncbi.nlm.nih.gov/32150360/. Accessed June 19, 2021.
2. Mogensen TH. Pathogen recognition and inflammatory signaling in innate immune defenses. *Clin Microbiol Rev*. 2009;22:240-273.
3. Kumar H, Kawai T, Akira S. Pathogen recognition by the innate immune system. *Int Rev Immunol*. 2011;30:16-34.
4. Schroeder HW, Cavacini L. Structure and function of immunoglobulins. *J Allergy Clin Immunol*. 2010;125:S41-S52.
5. Warren H. Target-induced natural killer cell loss as a measure of NK cell responses. *Curr Protoc Immunol*. 2013;101:1–21.
6. Kasuga Y, Zhu B, Jang K-J, Yoo J-S. Innate immune sensing of coronavirus and viral evasion strategies. *Exp Mol Med*. 2021;53:723-736.
7. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. *Crit Rev Clin Lab Sci*. 2020;57:389-399.
8. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med*. 2020;58:1021-1028.
9. Béné MC, de Carvalho BM, Eveillard M, Le Bris Y. Good IgA bad IgG in SARS-CoV-2 infection? *Clin Infect Dis*. 2020;71:897-898.
10. Hung IFN, To KKW, Lee C-K, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clin Infect Dis*. 2011;52:447-456.
11. Palma J, Tokarz-Deptuła B, Deptuła J, Deptuła W. Natural antibodies – facts known and unknown. *Cent Eur J Immunol*. 2018;43:466-475.
12. Ameratunga R, Brewerton M, Slade C, et al. Comparison of diagnostic criteria for common variable immunodeficiency disorder. *Front Immunol*. 2014;5:1-9.
13. Seghatchian J, Lanza F. Convalescent plasma, an apheresis research project targeting and motivating the fully recovered COVID 19 patients: a rousing message of clinical benefit to both donors and recipients alike. *Transfus Apher Sci*. 2020;59:102794.
14. Li J, Wang X, Chen J, Cai Y, Deng A, Yang M. Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. *Br J Haematol*. 2020;190:24-27.
15. Branch DR. Anti-A and anti-B: what are they and where do they come from? *Transfusion*. 2015;55:S74-S79.
16. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol*. 2020;146:110-118.
17. Radzikowska U, Ding M, Tan G, et al. Distribution of ACE2, CD147, CD26, and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID-19 risk factors. *Allergy Eur J Allergy Clin Immunol*. 2020;75:2829-2845.
18. Oksenhendler E, Gérard L, Fieschi C, et al. Infections in 252 patients with common variable immunodeficiency. *Clin Infect Dis*. 2008;46:1547-1554.
19. Ohmori H, Kanayama N. Mechanisms leading to autoantibody production: link between inflammation and autoimmunity. *Curr Drug Targets Inflamm Allergy*. 2003;2:232-241.
20. Schaballie H, Vermeulen F, Verbinnen B, et al. Value of allohaemagglutinins in the diagnosis of a polysaccharide antibody deficiency. *Clin Exp Immunol*. 2015;180:271-279.
21. Parker W, Yu PB, Holzknecht ZE, Lundberg K, Buckley RH, Platt JL. Specificity and function of "natural" antibodies in immunodeficient subjects: clues to B cell lineage and development. *J Clin Immunol*. 1997;17:311–321.
22. Cerutti A, Cols M, Puga I. Marginal zone B cells: virtues of innate-like antibody-producing lymphocytes. *Nat Rev Immunol*. 2013;13:118-132.
23. Wang H, Coligan JE, Morse HC. Emerging functions of natural IgM and its Fc receptor FCMR in immune homeostasis. *Front Immunol*. 2016;7:99.
24. Siber GR, Santosham M, Reid GR, et al. Impaired antibody response to Haemophilus influenzae type b polysaccharide and low IgG2 and IgG4 concentrations in apache children. *N Engl J Med*. 1990;323:1387-1392.
25. Fan BE, Chong VCL, Chan SSW, et al. Hematologic parameters in patients with COVID-19 infection. *Am J Hematol*. 2020;95:E131-E134.
26. Velavan TP, Meyer CG. Mild versus severe COVID-19: laboratory markers. *Int J Infect Dis*. 2020;95:304-307.
27. Zhou X, Cheng Z, Luo L, et al. Incidence and impact of disseminated intravascular coagulation in COVID-19 a systematic review and meta-analysis. *Thromb Res*. 2021;201:23-29.
28. Kwong PD, Wilson IA. HIV-1 and influenza antibodies: seeing antigens in new ways. *Nat Immunol*. 2009;10:573-578.
29. Bonilla FA, Bernstein IL, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol*. 2005;94:S1-S63.

30. Gerber S, Gaida A, Spiegl N, et al. Reduction of isoagglutinin in intravenous immunoglobulin (IVIG) using blood group A- and B-specific immunoaffinity chromatography: industry-scale assessment. *BioDrugs*. 2016;30:441-451.

31. Ozcelik F, Tanoglu A, Çıracı MZ, Ozcelik IK. Use of immune modulator interferon-gamma to support combating COVID-19 pandemic. *Int J Coronaviruses*. 2020;1:1-15.

32. Gavazzi G, Krause K-H. Ageing and infection. *Lancet Infect Dis*. 2002;2:659-666.

33. Scholz JL, Diaz A, Riley RL, Cancro MP, Frasca D. A comparative review of aging and B cell function in mice and humans. *Curr Opin Immunol*. 2013;25:504-510.

34. Peters MJ, Joehanes R, Pilling LC, et al. The transcriptional landscape of age in human peripheral blood. *Nat Commun*. 2015;6:8570.

35. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines — a new era in vaccinology. *Nat Rev Drug Discovery*. 2018;17:261-279.

36. Gainza P, Sverrisson F, Monti F, et al. Deciphering interaction fingerprints from protein molecular surfaces using geometric deep learning. *Nat Methods*. 2019;17:184-192.

37. Rochu D, Crespeau H, Fine A, et al. ABO-blood-group-related idiotypic network: mimicry of oligosaccharide epitope by rabbit antiidiotypic antibodies to murine monoclonal anti-A antibody. *Res Immunol*. 1990;141:373–387.

38. Guillon P, Clément M, Sébille V, et al. Inhibition of the interaction between the SARS-CoV Spike protein and its cellular receptor by anti-histo-blood group antibodies. *Glycobiology*. 2008;18:1085-1093.

39. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA. A multiinstitutional survey of the Wiskott-Aldrich syndrome. *J Pediatr*. 1994;125:876-885.