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Research Article

Effect of Measles Immunity on the Prognosis of Acute COVID-19 Infection

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Abstract

Objective: Coronaviruses and paramyxoviruses, both of which are RNA viruses, have similar structural glycoprotein characteristics. It is considered that antibodies developed against these structures may protect by cross-reaction because the glycoproteins of viruses are related to their ability to infect the cell.

Methods: In the present study, the clinical course of patients who were hospitalized with the diagnosis of COVID-19 and found to be positive for PCR, and whether they were affected by Measles immunity was evaluated.

Results: A total of 56 (34.5%) of 162 patients who had a mean age of 50 with at least one comorbid disease and 41 (25.4%) of them were followed up in the Intensive Care Unit and 15 (9.3%) patients died. Measles IgG was positive in 148 (91.3%) of the patients. No statistically significant differences were detected between the Measles IgG values of the patients hospitalized in the Intensive Care Unit and the ward (p=0.41). Similarly, no significant differences were detected between the Measles IgG values of the patients who died and those who were discharged (p=0.60). ROC analysis revealed that IgG values did not have a cut-off value to predict mortality (AUC=0.542, p=0.53). In the Logistic Regression Analysis made for independent predictors of mortality, it was found that each increase in age increased mortality by 10% (OR: 1.1, 95% CI: 0.05-1.16, p<0.001), and the presence of pneumonia was a risk factor for mortality.

Conclusion: No relationship was detected between vaccination against Measles or the presence of antibodies in the prognosis of COVID-19 infection.

Keywords: COVID-19; Immunity; Measles; Prognosis

Introduction

Coronaviruses are single-stranded, enveloped RNA viruses from the Coronaviridae family and might cause a wide variety of diseases in mammals and birds. Human coronaviruses are primarily respiratory pathogens and often cause upper respiratory tract infections. They were first detected to cause severe acute respiratory failure in the winter of 2002-2003 and the newly isolated virus was defined as SARS-CoV. A coronavirus epidemic was detected in the Middle East and this virus was defined as MERS-CoV in 2015 [1]. The new type of coronavirus, which was detected by the cluster of pneumonia cases in Wuhan in 2019, was named SARS-CoV-2 because of its similarity to SARS-CoV. The disease caused by this virus was defined as COVID-19, and the effects of the disease causing the pandemic still continue all over the world [2]. There are four subgroups of coronaviruses; α, β, ϒ, δ. It is the β subgroup [3] that is responsible for the epidemics and pandemics. Its structural glycoproteins are called S (spike), E (envelop), M (membrane), N (nucleocapsid), and HE (Hemaglutinin Esterase). S glycoproteins are located on the cell surface and allow the virus to attach to cells [4] and are effective in T-cell response and release of neutralizing antibodies. It has two subunits S1 providing attachment to the ACE-2 receptor of the host cell and S2 providing the fusion of the virus and the host cell [5]. The N protein has important effects on the replication and transcription of viruses. The HE glycoprotein exists only in β coronaviruses. In the development of the disease, IgM (Immunoglobulin M) and IgG (Immunoglobulin G) antibodies, which are detected in the serum, develop against S and N proteins [4]. Measles virus is an RNA virus of the Paramyxoviridae family of the Morbillivirus genus. It has eight structural proteins, F (fusion), C, H (hemagglutinin), L (large protein), M (matrix), N (nucleoprotein), P (phosphopolymerase protein), and V protein. Among these, the H protein plays roles in the entry of the virus into the host cell, the C and V proteins in transcription and replication, and the F glycoprotein in the transmission of the virus from one cell to another [6]. They also provide lifelong immunity with neutralizing antibodies against H and F proteins [7].

It was found in genetic studies that the glycoprotein structures of the coronaviruses and the paramyxovirus family are similar. Viral envelope glycoproteins catalyze an important step in cell entry, the fusion of the viral and cellular membrane. Coronavirus spike glycoproteins are Class I viral membrane fusion proteins and therefore share the same trimeric α-helix structure with other Class I fusion proteins, including those from ortho and paramyxoviruses [8]. Previous studies showed that the SARS-CoV-2 S2 surface glycoprotein and the 369 amino-acid part of the Measles F glycoprotein have a 20% similarity [9,10]. For these reasons, it is argued that immunity against Measles may be protective against COVID-19 [3,9-11]. In the present study, the purpose was to investigate the effect of the presence of Measles antibodies on the prognosis of patients who are followed up with the diagnosis of COVID-19.

Patients and Methods

The study was planned in a prospective design. Serum samples were collected from 234 patients hospitalized with the diagnosis of COVID-19 in our hospital. Sera were stored at -80ºC and 162 patients who met the inclusion criteria were included in the study. The demographic data, clinical characteristics, and clinical course of the patients were recorded. The Measles IgG antibody was studied with the ELISA (Vircell®) Method in the stored sera samples when the target number of patients was reached. Also, 9IU/ml and below were evaluated as negative, between 9-11 IU/ml as intermediate value, and above 11 IU/ml as positive. The patients, who were over the age of 18, hospitalized with the diagnosis of COVID-19, and who were positive for COVID-19 PCR in nasal/nasopharyngeal/tracheal samples were included in the study. Those who were under the age of 18, hospitalized for another reason, coincidentally found to be positive for COVID-19, PCR-negative despite being hospitalized with the diagnosis of COVID-19, and patients under the age of 18 were not included in the study.

Statistical Analysis

The categorical data of the study were presented by using the median and interquartile range (MWA - 25th and 75th percentile values) after the frequency and percentage values and numerical data were evaluated according to the normal distribution criteria. The Mann-Whitney U-Test was used for numerical data comparisons between independent data groups. The usability of Measles IgG values to predict mortality was examined with the ROC Analysis. The Logistic Regression Analysis was used for the evaluation of the independent determinants of mortality. All analyzes were made by using the SPSS 25 software (IBM Inc., Armonk, NY, USA) and the statistical significance limit was taken as $p<0.05$ in all analyzes.

Ethics Committee Approval Date and Number: 20.05.2020-88/08. R.T. Ministry of Health, Health Sciences University, Diskapi Yildirim Beyazit Training and Research Hospital, Clinical Research Ethics Committee. Signed informed consent forms were obtained from all the patients.

Results

The mean age of the 162 patients who were included in the study was 50 [CAA: 36-63], and the number of male patients was 86 (53.1%). There was at least one comorbidity in 56 (34.5%) of the patients, and no comorbidity was detected in 106 (65.5%) of the patients. Table 1 summarizes the comorbid diseases and

smoking status of the patients. The most common complaints were found to be cough, fever, and shortness of breath (Table 2). The number of patients with pneumonia because of COVID-19 was 97 (59.9%). Although there were 121 (74.6%) patients who were followed in the ward, 41 (25.4%) patients were followed up in the Intensive Care Unit. Mechanical ventilation was used in 23 (56.1%) patients in the Intensive Care Unit, and non-invasive mechanical ventilation was used in 11 (26.8%) patients. The Univariate Analysis of the effect of the clinical characteristics of the patients on the prognosis is discussed in Table 3. There were 147 (90.7%) patients who were discharged after healing and 15 (9.3%) patients died. Measles IgG was found to be positive in 148 (91.3%) of the patients. Quantitatively, the mean value was 20.1IU/ml [AAA: 17.8-22]. No statistically significant differences were detected between the Measles IgG values of the patients hospitalized in the Intensive Care Unit and the ward (p=0.41). Similarly, no significant differences were detected between the Measles IgG values of the patients who died and those who were discharged after healing (p=0.60). The Logistic Regression Analysis made for the independent predictors of mortality is given in Table 4.

Disease/Risk factor	n (%)
At least one disease/risk factor	56 (34.6%)
Hypertension	50 (30.9%)
Diabetes Mellitus	30 (18.5%)
Smoking	20 (14.8%)
Coronary Artery Disease	12 (7.4%)
Asthma	8 (4.9%)
Chronic Obstructive Pulmonary Disease	7 (4.3%)
Immunodeficiency	5 (3.1%)
Malignity	2 (1.2%)

Table 1: The comorbidities and risk factors of patients followed up with the diagnosis of COVID-19 infection.

Cough	86 (53.1%)
Fever	60 (37%)
Shortness of breath	49 (30.2%)
Myalgia	45 (28%)
Fatigue	42 (26.1%)
Sore throat	21 (13%)
Headache	21 (13%)
Nausea/Vomiting	7 (4.4%)
Diarrhea	8 (4.9%)
Stomach ache	5 (3.1)

Table 2: Admission complaints of patients followed up with the diagnosis of COVID-19.

	Intensive Care Hospitalization			**Discharge Status**		
	No	**Yes**	**p**	**Survival**	**Death**	**p**
Age group (65)			<0.001			<0.001
<65	106 (87.6)	21 (51.2)		124 (84.4)	3 (20)	
≥65	15 (12.4)	20 (48.8)		23 (15.6)	12 (80)	
Age group (80)			<0.001			0,003
<80	120 (99.2)	34 (82.9)		143 (97.3)	11 (73.3)	
≥80	1 (0.8)	7 (17.1)		4 (2.7)	4 (26.7)	
Gender			0.03			0,291
Male	59 (48.8)	28 (68.3)		77 (52.4)	10 (66.7)	
Female	62 (51.2)	13 (31.7)		70 (47.6)	5 (33.3)	
Diabetes			<0.001			0,008
-	108 (89.3)	24 (58.5)		124 (84.4)	8 (53.3)	
+	13 (10.7)	17 (41.5)		23 (15.6)	7 (46.7)	
Hypertension			<0.001			0,017
-	94 (77.7)	18 (43.9)		106 (72.1)	6 (40)	
+	27 (22.3)	23 (56.1)		41 (27.9)	9 (60)	
Coronary Artery Disease			0.002			0,307
-	117 (96.7)	33 (80.5)		137 (93.2)	13 (86.7)	
+	4 (3.3)	8 (19.5)		10 (6.8)	2 (13.3)	
Immunodeficiency			0.107			0,393
-	117 (98.3)	38 (92.7)		141 (97.2)	14 (93.3)	
+	2 (1.7)	3 (7.3)		4 (2.8)	1 (6.7)	

Asthma/COPD			0.048			1
-	114 (94.2)	34 (82.9)		134 (91.2)	14 (93.3)	
+	7 (5.8)	7 (17.1)		13 (8.8)	1 (6.7)	
Malignity			0.443			0,177
-	120 (99.2)	40 (97.6)		146 (99.3)	14 (93.3)	
+	1 (0.8)	1 (2.4)		1 (0.7)	1 (6.7)	
SO_2 <90%			<0.001			<0,001
-	97 (94.2)	15 (38.5)		109 (85.2)	3 (21.4)	
+	6 (5.8)	24 (61.5)		19 (14.8)	11 (78.6)	
Fever >38.2°C			0.144			0,232
-	85 (80.2)	28 (71.8)		103 (78.6)	10 (71.4)	
+	21 (19.8)	11 (28.2)		28 (21.4)	4 (28.6)	
D-dimer >1			<0.001			<0,001
-	106 (93.8)	24 (64.9)		126 (92)	4 (30.8)	
+	7 (6.2)	13 (35.1)		11 (8)	9 (69.2)	
Fibrinogen >412			<0.001			0,031
-	80 (78.4)	11 (31.4)		88 (69.3)	3 (30)	
+	22 (21.6)	24 (68.6)		39 (30.7)	7 (70)	
CRP >5			<0.001			0,016
-	52 (48.6)	1 (2.6)		52 (39.7)	1 (7.1)	
+	55 (51.4)	37 (97.4)		79 (60.3)	13 (92.9)	
Ferritin >400			<0.001			<0,001
-	82 (95.3)	9 (30)		91 (84.3)	0 (0)	
+	4 (4.7)	21 (70)		17 (15.7)	8 (100)	
WBC <3500			0.17			0,696
-	101 (84.2)	38 (92.7)		125 (85.6)	14 (93.3)	
+	19 (15.8)	3 (7.3)		21 (14.4)	1 (6.7)	
WBC >11000			0.004			0,003
-	118 (98.3)	35 (85.4)		142 (97.3)	11 (73.3)	
+	2 (1.7)	6 (14.6)		4 (2.7)	4 (26.7)	
Lymphocyte <20%			<0.001			0,001
-	99 (82.5)	11 (26.8)		106 (72.6)	4 (26.7)	
+	21 (17.5)	30 (73.2)		40 (27.4)	11 (73.3)	
Neutrophil >75%			<0.001			<0,001

-	110 (91.7)	20 (48.8)		126 (86.3)	4 (26.7)	
+	10 (8.3)	21 (51.2)		20 (13.7)	11 (73.3)	
Urea >42 and/or Creatinine>1.2			<0.001			<0,001
-	113 (94.2)	24 (58.5)		132 (90.4)	5 (33.3)	
+	7 (5.8)	17 (41.5)		14 (9.6)	10 (66.7)	
ALT >40			0.041			0,444
-	106 (88.3)	30 (75)		125 (85.6)	11 (78.6)	
+	14 (11.7)	10 (25)		21 (14.4)	3 (21.4)	
PCR group			<0.001			<0,001
Below 0.05	35 (50)	3 (8.8)		38 (41.3)	0 (0)	
Between 0.05-0.5	34 (48.6)	21 (61.8)		51 (55.4)	4 (33.3)	
Between 0.05-0.5	0 (0)	5 (14.7)		0 (0)	5 (41.7)	
2 and above	1 (1.4)	5 (14.7)		3 (3.3)	3 (25)	

Table 3: The Univariate Analysis of the effects of clinical characteristics of patients on prognosis.

	OR	**95% C.I. for OR**		**p**
		Lower	**Upper**	
Initial model				
Age	1.11	1.05	1.17	<0.001
Male gender	0.34	0.08	1.47	0.148
Diabetes Mellitus	2.13	0.41	11.2	0.373
Hypertension	0.74	0.12	4.58	0.742
Smoking Status	0.6	0.09	4.11	0.604
Presence of Pneumonia	7.14	0.55	92.5	0.133
Measles IgG Quantitative	0.96	0.77	1.21	0.733
Constant	0			0.004
Final model				
Age	1.1	1.05	1.16	<0.001
Presence of Pneumonia	7.89	0.81	77	0.076
Constant	0			0

Table 4: The Logistic Regression Analysis of independent predictors of mortality in Covid-19 infection.

The ROC analysis showed that Measles IgG values did not have a cut-off value to predict mortality (AUC=0.542, p=0.53) (Figure 1). In the Logistic Regression Analysis made for independent predictors of mortality, it was found that each increase in age increased mortality by 10% (OR: 1.1, 95% CI: 0.05-1.16, p<0.001), and the presence of pneumonia was a risk factor for mortality.

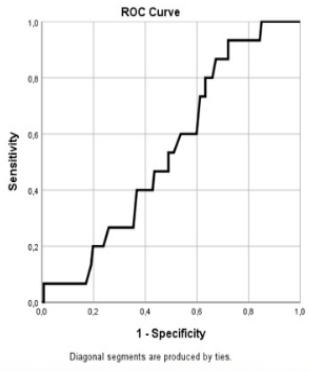

Figure 1: Evaluation of the relationship between measles IgG value and mortality.

Discussion

Paramyxoviruses are from the Paramyxoviridae family and contain enveloped virions and single-stranded, negative-stranded non-segmented RNA along with positive-ended RNA and RNA polymerase for protein synthesis. There are hemagglutinin-neuraminidase and fusion factors in the lipoprotein envelope [9]. The main receptor for the Measles virus is the Signaling Lymphocyte Activation Molecule (SLAM; CDw150), which is a surface membrane protein produced in T and B lymphocytes and antigen-presenting cells. This explains the immunosuppressive and lymphotropic effects of the disease [6]. CD8 and CD4 T-cells are responsible for virus clearance and rash development during the infection [6]. Temporary cellular immunosuppression develops during both vaccination and infection. Both neutrophil and lymphocyte counts decrease, but this lasts for approximately one week [7] and an antibody response develops afterward. The effects of innate immunity and the vaccine on the immune system are similar in Measles infection [6]. The Measles vaccine is live-attenuated. The antigenic stimulation it generates is great because it mimics natural infection and provides a strong antibody response [12]. It is one of the safest and most effective vaccines known to date. It was licensed for the first time in the USA in the 1960s [13]. The measles vaccine was started in our country in 1970. After the recommendation of the World Health Organization's Extended Immunization Program vaccination rates have increased over the years and were reported as 64%, 76%, and 98%, respectively, in the reports of 1980-1983, 2000, and 2014 [12].

There is an association between the coronavirus SP and paramyxovirus F proteins in the evolutionary development process and there are structural similarities [9]. Both are Class 1 membrane proteins sharing a similar regulatory helix [1]. For this reason, it was considered in the studies conducted before the COVID-19 pandemic that antibody development strategies against the F protein could be used in the development of vaccines against coronavirus [14].

Cross-immunity is the reaction of an antibody response to an antigen with other antigens, which are structurally similar to that specific antigen. Cross-reactivity does not mean an absolute cross-protection. For example, previous studies showed that neutralizing antibodies against the H1N1 virus may provide partial protection against H5N1 infection [9]. For this reason, there are several reports arguing that there will be a similarity in the T-cell response against Paramyxovirus and coronavirus antigens identified as similar between surface antigens, and this response will bring partial protection through effector memory T-cells [1,3,9-11,15-20]. In a prospective observational study that was conducted in Mexico, 225 people received a single dose of the Measles-Mumps-Rubella (MMR) vaccine, and only 36 people were infected with COVID-19. Mild symptoms were detected in those who had the infection. This study supports that cross-reaction provides partial protection [11]. In the study by Hassani et al. conducted with healthcare workers, Measles and Tetanus antibodies were found to be higher in workers with COVID-19 infection when compared to uninfected workers [21]. In the study of Mysore et al., it was shown that the severity of COVID-19 was reduced with cross-reactive T-cells in those who received MMR and Tetanus-Diphtheria-Pertussis (Tdap) vaccine. Also, higher T-cell activation was observed against the antigen of MMR and Tdap vaccines in people who were infected with COVID-19 in the same study. A strong correlation was detected between the activation of memory T-cells during COVID-19 infection in individuals who had previously received these two vaccines [22]. However, in an epidemiological study that was conducted using the World Health Organization (WHO) Global Health Observatory data, MMR vaccination rates of countries and the number of COVID-19 and death rates were compared, and it was found that vaccination did not have a protective effect on the disease [23]. In the study of Gold et al., no correlation was detected between Measles antibody titers and COVID-19 severity [24]. In the present study, no correlation was detected between the severity of COVID-19 infection, intensive care hospitalization, or deaths in patients with Measles antibodies. In light of this information, it can be considered that the cytokines secreted as well as the memory cells formed in the body during the COVID-19 infection are more effective in determining the prognosis.

The limitation of the present study was the presence of patients who had different risk factors that affected mortality during COVID-19 infection. Repeating the study with patients who do not have any comorbidities in the same age range and gender may increase the reliability of the results.

Conclusion

It was predicted that Measles vaccination would protect against a poor prognosis in COVID-19 infection because of the structural

similarity between the membrane proteins of paramyxoviruses and coronaviruses. However, it was found in the present study that the presence of Measles antibodies did not protect from intensive care hospitalization and mortality, and COVID-19 vaccination should be continued.

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