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ORIGINAL ARTICLE

Comparison of Serum Total IgA Levels in Severe and Mild COVID-19 Patients and Control Group

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Abstract

Background The present study aimed to compare serum total IgA levels between severe and mild COVID-19 patients' groups and the control group.

Methods In this cross-sectional study, 216 definite severe COVID-19 patients (as the inpatient group), 183 subjects with positive specific COVID-19 IgG with mild or no symptoms as the (outpatient group), and 203 healthy subjects with negative specific serology, as the control group were investigated. The cases' laboratory data were collected, and thereafter, statistical tests, including independent samples *t* test, ANOVA test, and post hoc test, were performed using SPSS software version 22.

Result The mean ± SD of IgA in all the included subjects was 2.23 ± 0.78 (g/L). According to the obtained results, there were statistically significant changes in IgA among the three study groups (P value < 0.05). This difference was significant between both outpatient and inpatient groups (P value < 0.05). The mean ± SD of serum IgG in all the subjects was calculated as 15.83 ± 5.73 (g/L). A strong statistically significant change was also seen in IgG among all three groups (P value < 0.001). Of note, there was a significant negative correlation between IgG and IgA total titers of the outpatient group (P value = 0.011*r = −0.188).

Conclusion It was shown that the total serum IgA and IgG levels are significantly associated with the severity of COVID-19 infection. As well, we found that total serum IgA and IgG are associated with the severity of illness. Since a low level of IgA is asymptomatic and high frequent in Iran and other countries, we suggest the evaluation of serum IgA levels in high-risk people and strengthening immune system in subjects with a low level of IgA, in order to reduce the rate of death. In this regard, oral or nasal mucosal vaccines in combination with parenteral vaccination are recommended due to increasing immunity versus COVID-19 by further secretion of the IgA antibody and preventing virus transmission.

Keywords Serum IgA level · severe COVID-19 · mild COVID-19

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Introduction

In December 2019, a cluster of acute respiratory illness caused by a novel coronavirus (SARS-CoV-2), has occurred in Wuhan, Hubei Province, China [1, 2]. Thereafter, the disease has rapidly spread from Wuhan to other regions and other countries. The World Health Organization (WHO) declared the novel coronavirus outbreak as a pandemic [3]. Up to 03 September 2021, there have been 218,946,836 confirmed cases of COVID-19 worldwide, of which, 4,539,723 death cases were reported to WHO. As well, 5,055,512 of confirmed COVID-19 cases and 108,988 deaths were reported in Iran [4]. SARS-CoV-2 is classified in the beta coronavirus 2b lineage, which is broadly distributed in both human beings and other mammals [5].

In human beings, immunoglobin A (IgA) is divided into two subclasses of IgA1 and IgA2 encoded by separate genes [6]. Unlike other Ig classes, IgA exists in multiple molecular forms. In human's serum, the predominant IgA form was found to be monomeric with a subclass distribution of about 90% of IgA1 and 10% of IgA2. In contrast, the main molecular form found at mucosal surfaces, known as secretory IgA (SIgA), is dimeric; however, some higher molecular weight species, including trimers and tetramers, are present as well. The relative proportion of the two subclasses is more closely matched, an average distribution of about 40% of IgA1 and 60% of IgA2 [7].

IgA is present in both serum, where it is the second most prevalent circulation antibody at 2–3 mg/ml following IgG and external secretions, where it is the predominant Ig. Moreover, it plays an essential protective role against bacteria and viruses [7–9] and is the most produced antibody playing an important role in infections that target mucosal tissues like influenza [10]. The development of mucosal immunity via IgA may be important in order to prevent COVID-19 infection. In addition, the secretory IgA plays a critical role in the protection of mucosal surfaces by naturalizing virus or preventing virus attachment to the mucosal epithelium [11]. Serum total IgA represents sIg, and a decrease in serum total IgA indicates a decrease in SIgA. It is noteworthy that great genetic differences exist in IgA activity between different populations [12].

Considering the important role of IgA in causing respiratory infections and the lack of any scientific reports on the association between IgA and COVID-19 in different groups of patients, in the present study, we aimed to investigate total serum IgA levels in severe and mild COVID-19 patients' groups and control group.

Material and Methods

Study Design and Participants

In this cross-sectional study, 602 subjects were included and investigated in Mashhad, the capital of Khorasan Razavi Province, Iran, from May 2020 to July 2020. The current study was conducted on three groups of participants (two cases groups and one control group). According to the WHO interim guidance, the first case group consisted of 216 definite severe COVID-19 patients (inpatient group) mostly hospitalized in both Emam Reza and Ghaem hospitals, Mashhad, Iran. Accordingly, they were diagnosed with COVID-19 infection according to the WHO interim guidance and managed in the inpatient setting [13]. Moreover, the second case group included 183 subjects with mild or no symptoms (outpatient group) who had specific positive serum IgG for COVID-19. The control group consisted of 203 healthy subjects negative for COVID-19 infection with specific IgG or IgM. These study groups were matched in terms of gender.

The following data were collected from 157 patients ($N=81$, severe COVID-19) and ($N=76$, mild COVID-19): demographic information, past medical history, history of present illness, symptoms, laboratory tests' results, and treatment measures (including antiviral therapy, corticosteroid therapy, respiratory support, and kidney replacement therapy). Where any data was missing from the cases' medical records or when clarification was needed, we contacted the patients and their family members for any additional information that we did not obtain from their medical records or providers. In this study, ARDS was defined according to the Berlin definition [14]. Acute kidney injury was diagnosed according to the Kidney Disease Improving Global Outcomes guidelines [15]. Moreover, cardiac injury was defined as serum levels of cardiac biomarkers (e.g., troponin I) above the 99th percentile upper reference limit or as new abnormalities observed in both electrocardiography and echocardiography. The time from hospital admission to hospital discharge was recorded as well. Diagnosis of 2019-nCoV was confirmed by lymphocyte count, CRP level, chest CT, clinical symptoms, and PCR performed at Mashhad University of Medical Sciences.

Blood samples of the participants of the inpatient group were collected during their hospitalization stay or by passing 2 weeks from their illness period. The outpatient's blood samples, due to the absence of specific symptoms, were randomly obtained from our recent cohort study. We collected the blood samples of the control and other groups

simultaneously to ensure that there is no seasonal or temporal interference with antibody levels and also to reduce study bias. Additionally, we obtained the blood samples of some inpatients and outpatients by passing 6 months from the manifestation of their symptoms, in order to control the total serum IgG antibody changes and compare the basic antibody to that of during illness. After sampling 5 ml peripheral blood, serum was separated, divided into several aliquots, and immediately frozen at − 80 °C.

Exclusion and Inclusion Criteria

The following inclusion criteria were considered in this investigation: (1) Patients with positive specific serum IgG or clinically confirmed COVID-19 infection based on the last updates of WHO Guideline regarding the evaluation and laboratory testing for COVID-19. (2) Healthy subjects with negative specific serology for COVID-19.

The following exclusion criteria were also considered: patients younger than 16 years old.

Serum Specific IgG Detection

In this study, (SARS-CoV-2) IgG antibody detection kit (Code: PT-SARS-CoV-2.IgG-96, PishtazTeb, Iran) was used based on the Indirect ELISA method. Accordingly, in this assay, nucleocapsid (N) antigen is used as a target. Of note, SARS-CoV-2 assay IgG was qualitative. The sensitivity and specificity of the utilized SARS-CoV-2 IgG assay were obtained as 94.1% and 98.3%, respectively.

Serum Total IgA Detection

MININEPHTM HUMAN IgA kit (Code: ZK010.R, The binding site group Ltd, Birmingham, UK) was also used for the determination of total serum IgA.

Serum Total IgG Detection

Serum total IgG was measured using MININEPHTM HUMAN IgG kit (Code: ZK004.R, The binding site group Ltd, Birmingham, UK).

Ethical Considerations

The ethics Committee of Mashhad University of Medical Sciences approved our study with the approval code IR.MUMS.REC.1399.332. Written informed consent and verbal assent were obtained from the patients before enrolment when collecting the required data.

Data Analysis

All the statistical analyses were conducted using Statistical Package for the Social Science for Windows (SPSS, version 22, 0; IBM Corp, Armonk, NY, USA). The Kolmogorov–Smirnov test was also performed to assess normal distribution of the data. The normal and abnormal quantitative data were expressed as mean ± standard deviation (SD) using one sample *T* test and as median ± interquartile range (IQR) using the Mann–Whitney *U* test, respectively. Moreover, ANOVA and Tukey tests were employed to compare the total serum IgA and IgG levels among the three groups. The chi-squared test was also performed for qualitative data, which were expressed as a number (percentage). The correlation between the variables was measured by Spearman's test. As well, paired sample *T* test was performed to compare differences between two periods of sampling. A *P* value less than 0.05 was considered as statistically significant.

Results

In the present cross-sectional study, 216 confirmed COVID-19 patients with severe symptoms, 183 positive specific COVID-19 IgG subjects with mild or no symptoms, and 203 healthy subjects with negative specific serology were enrolled.

Of the total of 602 participants, 183 (30.4%) cases were outpatients, while 216 (35.9%) cases were severe COVID-19 patients, and 203 (33.7%) cases were healthy subjects included in the control group. Approximately 53.8% of them were men and 46.2% were women. These three groups were matched in terms of gender, and there were no significant changes among the groups according to gender (*P* value = 0.544).

The mean age of 157 patients was 45.75 years old (ranged from 16 to 88 years old). The mean age in both the severe COVID-19 ($N = 81$) and outpatient ($N = 76$) groups were 53.63 ± 16.14 and 37.36 ± 7.40 years old, respectively. Correspondingly, the mean age was observed to be statistically significant between these two groups (*P* value < 0.001).

The clinical features of the inpatient and outpatient groups are shown in Table 1. Hypertension was the most common medical history in both of the inpatient and outpatient groups. The five most common symptoms in the inpatient group were the followings: dyspnea in 71 cases (87.7%), fatigue or myalgia in 58 cases (71.6%), fever in 58 cases (71.6%), cough in 52 cases (64.2%), and chills in 43 cases (53.1%). In addition, the five most common symptoms in the outpatient group were fatigue or myalgia in 48 cases

Table 1 Baseline demographic characteristics and symptoms of COVID-19 patients

Variable	Inpatients ($N=81$)	Outpatients ($N=76$)	Total	P value
Age, year	53.63 ± 16.14	37.36 ± 7.70	45.75 ± 15.12	< 0.001**
Diabetes history	26 (32.1%)	0 (0%)	26 (16.6%)	< 0.001**
Hypertension history	29 (35.8%)	3 (3.9%)	32 (20.4%)	< 0.001**
Cardiovascular disease history	19 (23.5%)	1 (1.3%)	20 (12.7%)	< 0.001**
Symptoms				
Fever	58 (71.6%)	27 (35.5%)	85 (54.1%)	< 0.001**
Chills	43 (53.1%)	29 (38.2%)	72 (45.9%)	0.061
Cough	52 (64.2%)	20 (26.3%)	72 (45.9%)	< 0.001**
Fatigue or myalgia	58 (71.6%)	48 (63.2%)	106 (67.5%)	0.259
Headache	33 (40.7%)	28 (36.8%)	61 (38.9%)	0.616
Sweeting	29 (35.8%)	23 (30.3%)	52 (33.1%)	0.461
Sputum production	9 (11.1%)	3 (3.9%)	12 (23.5%)	0.091
Nausea or vomiting	34 (42.0%)	11 (14.5%)	45 (28.7%)	< 0.001**
Diarrhea	24 (29.6%)	18 (23.7%)	42 (26.8%)	0.400
Abdominal pain	22 (27.2%)	12 (15.8%)	34 (21.7%)	0.084
Olfactory dysfunction	24 (29.6%)	21 (27.6%)	45 (28.7%)	0.782
Nasal congestion	21 (25.9%)	9 (11.8%)	30 (19.1%)	0.025*
Sneezing	10 (12.3%)	8 (10.5%)	18 (11.5%)	0.721
Rhinorrhea	11 (13.6%)	12 (15.8%)	23 (14.6%)	0.696
Eye problems	11 (13.6%)	7 (9.2%)	18 (11.5%)	0.390
Sore throat	11 (13.6%)	13 (17.1%)	24 (15.3%)	0.540
Dyspnea	71 (87.7%)	16 (21.1%)	87 (55.4%)	< 0.001**
Chest pain	27 (33.3%)	15 (19.7%)	42 (26.7%)	0.054
Reduced level of consciousness	32 (39.5%)	0 (0%)	32 (20.4%)	< 0.001**

The one-sample T-test and crosstab were performed by SPSS version 22. The significant level was intended as *P value < 0.05 and **< 0.001

(63.2%), chills in 29 cases (38.2%), headache in 28 cases (36.8%), fever in 27 cases (35.5%), and sweeting in 23 cases (30.3%).

The most common initial presenting symptoms among the severe COVID-19 patients were found to be fever in 20 cases (25.0%); dyspnea in 11 cases (13.8%); and fatigue, myalgia, and cough in 10 cases (12.5%). Furthermore, myalgia in 16 cases (21.3%), fever in 9 cases (12.0%), headache in 7 cases (9.3%), and olfactory dysfunction and cough in 6 cases (8.0%) were the most initial symptoms among the outpatients. Besides, 11 (14.7%) of the outpatients had no symptoms.

The majority of the inpatients received antibiotic therapy 74 (91.4%). As well, 21 (25.9%) of them received antiviral treatment and 20 (24.7%) received corticosteroids. High-flow oxygen was administered in 64 (79.0%) patients. In addition, invasive mechanical ventilation was needed in 22 (27.2%) inpatients. Moreover, dialysis was performed in 10 (12.3%) inpatients.

The most common complications in the inpatient group were ARDS in 64 (80.0%), shock in 18 (22.2%), death in

Table 2 The mean ± SD of total IgA between inpatient, outpatient, and control groups

Groups	IgA Mean ± SD (g/L)	P value between groups		P value
COVID-19 positive with severe symptoms (inpatient, $N=216$)	2.12 ± 0.71	Outpatient	0.009*	0.012*
		Control	0.204	
IgG positive with mild or no symptoms (outpatient, $N=183$)	2.35 ± 0.84	Inpatient	0.009*	
		Control	0.400	
IgG negative with no symptoms (control, $N=203$)	2.25 ± 0.79	Inpatient	0.204	
		Outpatient	0.400	

The ANOVA and post hoc test were performed by SPSS version 22. The significant level was intended as *P value < 0.05

17 (21.0%), acute cardiac disorder in 15 (18.5%), acute kidney disorder in 13 (16.0%), and secondary infection in 13 (16.0%) subjects.

According to the obtained results, the mean number of days from the hospitalization time up to the discharge time among the inpatients was 10.87 ± 10.35 (ranged from 1 to 67 days).

The mean ± SD of IgA in all the subjects was 2.23 ± 0.78 (g/L). Table 2 shows the mean ± SD of total IgA among the three groups. According to the ANOVA test, there were statistically significant changes in terms of IgA among the three groups (P value < 0.05). Post hoc test showed that this difference was resulted from the difference between the outpatient and inpatient groups (P value < 0.05). Figure 1 shows the mean of IgA among these three groups.

The mean ± SD of IgG in all the subjects was 15.83 ± 5.73 (g/L). The mean ± SD of the total IgG among three groups of inpatients, outpatients, and control is shown in Table 3. According to the ANOVA test, there were statistically significant changes in IgG among the three groups (P value < 0.001). Post hoc test showed that all the groups had a significant differences with each other (P value < 0.001). Figure 2 shows the mean of IgG among the three groups.

In this study, the correlation between IgG and IgA levels among the three groups was investigated by Spearman's test. There was a significant negative correlation between IgG and IgA total titers of the outpatient group (P value = 0.011*r = −0.188). A positive correlation was also observed between IgG and IgA total titers in the inpatient and control groups, but it was not statistically significant (P value = 0.787, r = 0.018; and P value = 0.145, r = −0.103, respectively).

We measured the IgG in six inpatient and five outpatient subjects by passing 6 months from their symptoms and then compared them to those of during illness. According to the paired sample T test, IgG antibody was found to be

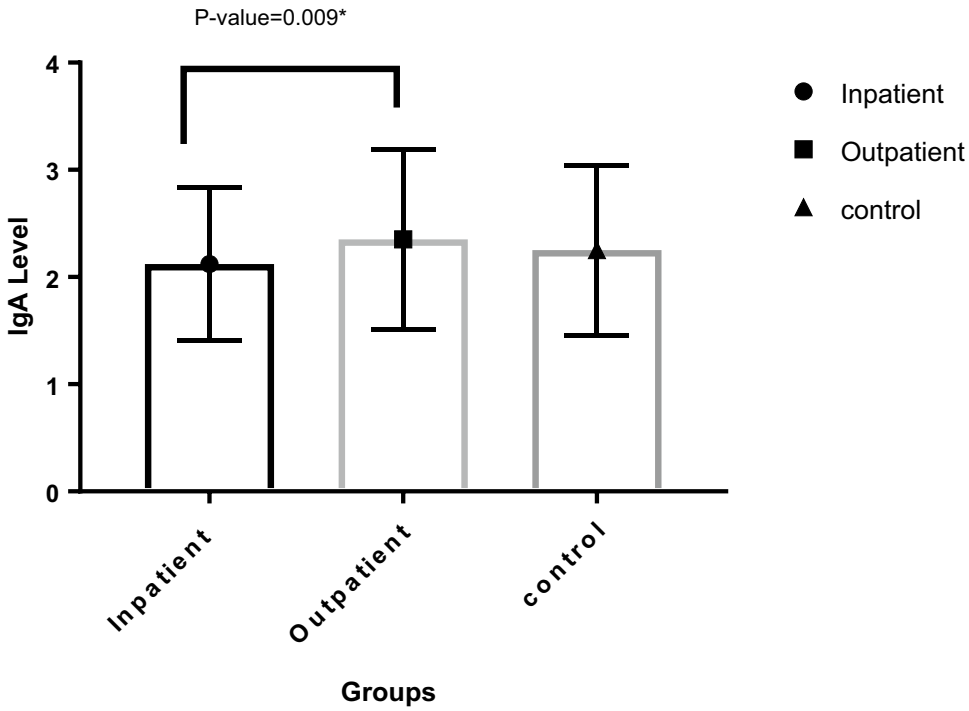

Fig. 1 Total IgA levels between inpatient, outpatient, and control groups

Table 3 The mean ± SD of total IgG between inpatient, outpatient, and control groups

Groups	IgG Mean ± SD (g/L)	P value between groups		P value
COVID-19 positive with severe symptoms (inpatient, N = 216)	10.82 ± 4.47	Outpatient	< 0.001**	< 0.001**
		Control	< 0.001**	
IgG positive with mild or no symptoms (outpatient, N = 183)	22.34 ± 2.48	Inpatient	< 0.001**	
		Control	< 0.001**	
IgG negative with no symptoms (control, N = 203)	15.59 ± 2.50	Inpatient	< 0.001**	
		Outpatient	< 0.001**	

The ANOVA and post hoc test were performed by SPSS version 22. The significant level was intended as **P value < 0.001

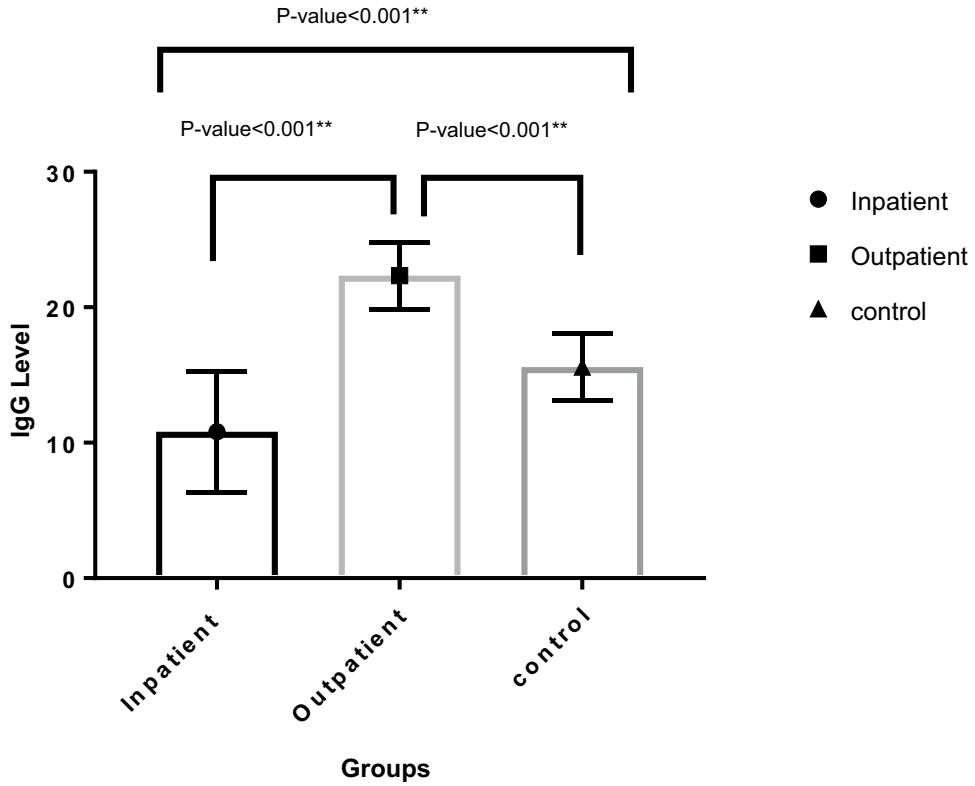

Fig. 2 Total IgG levels between inpatient, outpatient, and control groups

significantly higher during illness up to 6 months later in the inpatient group (P value = 0.003). Besides, IgG antibody titers were higher in the first blood sampling compared to 6 months later in the outpatient group, but it was not statistically significant (P value = 0.209).

Discussion

It was shown that viral infections affect the mucosal surfaces, which act as a primary barrier in innate immunity and play a key role against microorganisms, especially against viruses and coronavirus. Therefore, mucosal surface antibodies play a key and primary role as a defense barrier in innate immunity against microorganisms, especially viruses. Notably, one of the defense mechanisms in mucosal surfaces is the presence of secretory IgA (SIgA). Saliva is the most relevant one to measure SIgA. However, because it was hard to measure, especially in the inpatients, and on the other hand, because serum total IgA represents mucosal IgA, in this study, we decided to measure serum total IgA in the included patients. Serum IgG is known as an important antibody in dedicated immunity, acting after the innate immunity. Our study aimed to investigate the roles of innate immune level in the prevention and severity of infection, not secondary immune responses related to the disease. Therefore, we did not measure specific SARS-CoV-2 IgA level, and SARS-CoV-2 IgG assay was done only for COVID-19 positive confirmation.

Considering the important role of serum IgA in preventing the virus infection in the human immune system, and the lack of a valid study in this field, we aimed to investigate the serum total IgA levels in severe and mild COVID-19 patients and control group.

According to the obtained results, there were statistically significant changes in total serum IgA among the three groups, and this difference was resulted from the difference between the outpatient and inpatient groups (P value < 0.05). The total serum IgA level was not significant between the control and patient groups. Up to now, no studies were performed showing significant changes in total IgA antibody levels during the course of the disease. The lack of significant changes between the control and other COVID-19 positive groups also confirmed that the total IgA antibody does not significantly change during the disease's course. As well, this can be explained by saying that a control group is a group that has not encountered the virus yet; therefore, their antibody levels can be higher or lower than the normal level. So, no statistically significant difference was observed between the control group and other groups. However, the total IgA was lower in severe COVID-19 patients, and due to the lack of defense, their antibody levels showed a very small increase. In asymptomatic patients, due to the

powerful immune system, better responses were observed after being infected.

In this regard, only one study in Iran in 2003 has evaluated the normal ranges of IgA and IgG immunoglobines in 914 healthy subjects, and reported the reference intervals of IgA and IgG as 1.65 and 10.77, respectively. However, due to the passage of time, it cannot be considered as a reference range [16]. In another study conducted on 270 subjects in Paris in 2015, the reference intervals of both IgA and IgG were reported as 2.12 (g/l) and 10.58 (g/l), respectively [17].

In a newly performed international study, the total IgA, IgG, and aPL were measured in 64 patients with mild and severe symptoms. Surprisingly, it was shown that higher total IgA and IgA-aPL were consistently associated with severe illness in patients. So, it was suggested that a vigorous antiviral IgA response, possibly triggered in the bronchial mucosa, induces systemic autoimmunity. However, the results of our study, contrary to this study, show that the levels of total IgA and IgG were higher in people with mild symptoms, and the severity of the disease was inversely correlated with the levels of total IgA and IgG antibodies. In this international study, no significant association was found between the severity of illness and total IgG. All of these findings are surprisingly opposite to our results. This difference could possibly be due to the reason that they have evaluated a small number of patients and the control group has not been considered in their study [18].

In a study conducted in Iran between 2005 and 2006, the mean value of serum IgA in 13,002 healthy subjects was 87.7 ± 140.7 (mg/dl) [19]. They have also reported the incidence of selective IgA deficiency in Iranian blood donors (frequency; 1:651), which is considerable in this country compared to those of other countries (1:163–1:18,500) [20–22].

In a recent study, the COVID-19 information on the number of infected people and deaths in the country was compared with the national frequency of selective IgA deficiency. Accordingly, a strong positive correlation was found between the frequency of selective IgA deficiency and COVID-19 infection rate in population. The low infection rate contributed to the low death rate caused by COVID-19 infection in Japan, suggesting that the extremely low frequency of selective IgA deficiency may be considered as a contributing factor [23].

There is no study on the correlation between serum total IgG and IgA in COVID-19 patients. In a study conducted by Edward E et al. in the USA in 2004, a low positive correlation was found between nasal IgA and IgG titers in patients with respiratory syncytial virus (RCV). Surprisingly, in the current study, we found a statistically significant low negative correlation between these antibodies in the outpatient group, but there was a low insignificant positive correlation between these antibodies in both the inpatient and control groups. Accordingly, this may possibly be due to a proper safety related to IgA in the outpatients, which has eliminated the need for increasing IgG antibody [24].

According to some recently performed studies, there is a strong positive correlation between the frequencies of selective IgA deficiency and the prevalence of COVID-19 infection in population and death ratio caused by COVID-19 [12, 23].

IgA deficiency was found to be significantly higher among allergic patients [25]. As well, in similar studies, a significantly higher number of respiratory tract infections were observed among allergic patients. In other words, a low s-IgA level is an important factor for the risk of developing respiratory tract infection [25, 26]. None of our subjects was selective serum IgA deficient, but our results show that serum IgA level is significantly correlated with the severity of COVID-19 infection.

Moreover, IgA deficiency (IgA < 10 ng/dl) in those who received IVIG is important in terms of ectopic response to IVIG. Based on the high prevalence of IgA deficiency among Iranian population [19] as well as the critical role of serum IgA in the severity of COVID-19 infection and considering that serum IgA deficiency is often asymptomatic, we suggest the evaluation of serum IgA levels in high-risk people, including medical staff, cardiac, diabetic, and hypertensive patients along with performing immunotherapy among IgA-deficient subjects, in order to reduce the rate of death in countries. Since our study was performed on non-immunodeficient subjects and serum IgA antibody level was indicated to play a significant role in the severity of the disease, it is suggested that more studies be done to produce an immunotherapy drug effective on increasing mucosal immunity. The purpose of immunotherapy in these patients must be strengthening the immune system with IVIG, which is prepared specifically; and in contrary to the usual types, it contains high values of serum IgA. In other words, the purpose of the IVIG could be the replacement of IgA instead of IgG in COVID-19 patients for therapeutic purposes.

Since mucosal vaccine via oral or nasal targeting COVID-19 induces the secretion of IgA within the mucosa, and due to the reason that we demonstrated that IgA plays an important role in the severity of COVID-19 infection, this could be a better therapeutic strategy for preventing COVID-19 development compared to the parenteral vaccination [23, 27–29].

Conclusion

In conclusion, our study showed that the total serum IgA and IgG levels are significantly associated with the severity of COVID-19 infection. As well, we found that the total serum IgA and IgG levels are associated with the severity of illness, but the reason behind this correlation is not understood

yet. Therefore, we recommend performing more studies with larger sample size in this regard. Additionally, since a low level of IgA is asymptomatic and highly frequent in Iran and other countries, we suggest the evaluation of serum IgA levels in high-risk people and strengthening immune system in subjects with a low level of IgA, in order to reduce the rate of death in countries. Oral or nasal mucosal vaccines in combination with parenteral vaccination are recommended due to increasing immunity versus COVID-19 by further secretion of the IgA antibody and preventing virus transmission.

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Author Contribution Farahzad Jabbari-Azad: Conceptualization, Project administration, Supervision, Writing—Review and Editing, Validation

Maral Barzegar-Amini: Software, Formal analysis, Writing—Original Draft, Visualization

Mahmoud Mahmoudi: Investigation, Resources, Writing—Review and Editing

Maliheh Dadgarmoghaddam: Software, Methodology, Formal analysis

Faramarz Farzad: Investigation

Ali Qaraee Najafabadi: Investigation

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Data Availability 4TU.Centre for Research Data

DOI code: https://doi.org/10.4121/15086301

Declarations

Ethics Approval and Consent to Participate Ethics Committee of Mashhad University of Medical Sciences allowed us to perform our study and the approval code was as follows: IR.MUMS.REC.1399.332. Written informed consent and verbal assent were obtained from patients involved before enrolment when data were collected.

Consent for Publication All the patients give consent for information about themselves to be published.

Conflict of Interest The authors declare no competing interests.

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