Archives of Current Medical Research
Arch Curr Med Res 2024;5(2):56-65

Received: 20 November 2023
Revised: 24 April 2024
Acccepted: 3 May 2024
DOI: 10.47482/acmr.1393582

ORIGINAL ARTICLE

The prevalence of immunodeficiency in a special population: intern doctors

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ABSTRACT

Background: This study analyzes the immune system parameters of intern doctors working actively during the COVID-19 pandemic. When an intern doctor failed to respond to the treatment during a severe COVID-19 condition, the immune system panel was examined and as a result, it revealed an underlying immunodeficiency. The death of the intern doctor caused several concerns among other intern doctors, and for this reason, their immune systems were also considered to be examined. This study aims to demonstrate that immunodeficiencies might be more common than is known among the general population.

Methods: In this single-center study, the demographic characteristics and European Society for Immunodeficiencies (ESID) diagnostic criteria of 92 intern doctors have been examined retrospectively. For the study, immune system parameters (complete blood count, serum immunoglobulins and subgroup levels, specific vaccine responses, isohemagglutinin titers, lymphocyte subgroups, and class-switched memory B cell (cSMB) levels have been evaluated.

Results: When the demographic characteristics have been analyzed it is seen that the median age is 23.6 (21-28) years, and 64 (70%) of the intern doctors are female. In immune system parameters, one or more are found to be low in 51.08% of the doctors. Among the immunoglobulin subgroups, low IgG4 has been the most common. Selective IgA deficiency has been detected in 2.17% and selective IgM deficiency has been detected in also 2.17% of them. Low B cells (CD19+) are detected in 10.9% and low levels of class-switched memory B cells are found in 35.7% of them.

Conclusion: This study reveals that deficient immunological parameters, especially selective Ig A, selective IgM deficiency, and low IgG4, might be more frequent than known. Depending on the data, it can be concluded that immunodeficiency might be more common than it is known among the general population; however, low immunological parameters alone do not lead to immunodeficiency.

Keywords: Intern doctor, immune system, immunodeficiency, immunoglobulins, lymphocyte subgroup

Cite this article as: Aykan F, Çölkesen F, Evcen R, Kılınç M, Yıldız E, Ergün Ü, et al. The prevalence of immunodeficiency in a special population: Intern doctors. Arch Curr Med Res. 2024;5(2):56-65

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INTRODUCTION

Immunity means the protection from diseases. The immune system consists of the cells, tissues, and molecules that provide this protection. The importance of the immune system is based on the susceptibility of individuals with immune system damage to serious and life-threatening infections. Innate immunity and adaptive immunity form the host defense mechanism (1).

Inborn errors of immunity (IEI), which are also called primary immunodeficiency (PID), are a heterogeneous group of disorders caused by damage to germline variants in single genes. In such conditions, an increased susceptibility to infections, autoimmunity, autoinflammatory diseases, allergies, bone marrow diseases, and/or malignancies has been observed. Although it is a rare group of diseases, it represents an important health burden (2). It is estimated that approximately 6 million people worldwide suffer from IEI. However, the number of reported cases is lower. Several studies suggest that the lack of awareness by physicians for IEI might delay the diagnosis and the treatment of these patients (3).

It is known that a pandemic was declared by the World Health Organization on March 11, 2020, due to Coronavirus Disease 2019 (COVID-19), which was caused by Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in 2019. During the pandemic, more than 600 million cases of COVID-19 were followed up and it was reported that the pandemic caused more than 6 million deaths (4). In addition to the physiological effects of COVID-19, there has also been a psychological impact on global society. Health crises such as the COVID-19 pandemic can have a psychological impact on both society and health workers by causing fear, anxiety, depression, or insecurity (5).

This study aims to analyze the data obtained after the evaluation of the immune system parameters of the intern doctors who had severe concerns after the death of an intern doctor during the COVID-19 pandemic.

MATERIALS AND METHODS

Study Design

This retrospective cohort study was conducted at Necmettin Erbakan University Faculty of Medicine Department of Internal Medicine Division of Allergy and Immunology clinic.. The Local Ethics Committee approved the study protocol (Decision no: 2023/4212, Date: 03.03.2023), which complied with the Declaration of Helsinki (1975) tenets. As the data in this study was scanned retrospectively, it was optional to obtain informed consent after the approval of the ethics committee. This study was approved by the Necmettin Erbakan University of Medical Faculty Ethics Committee (Dated: 03.03.2023; Approval Number: 2023/4212). Therefore, informed consent was not obtained from the patients. The study protocol included 92 intern doctors (≥18 years of age, working actively in clinics) who worked during the COVID-19 pandemic between 2020 and 2022. The study did not include those who met the exclusion criteria (Figure 1).

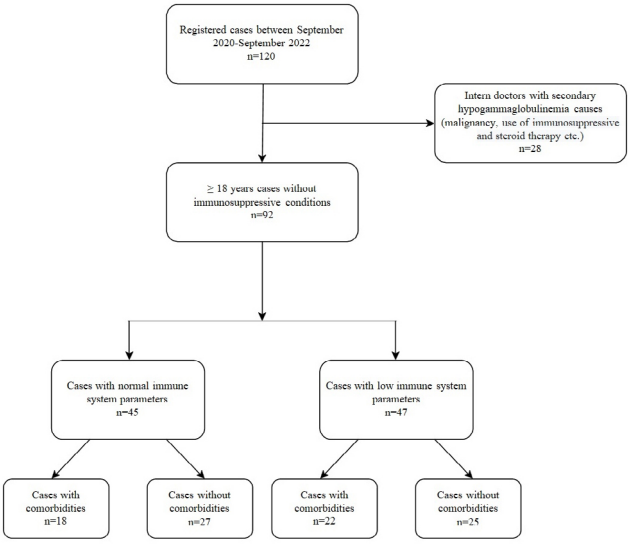

Figure 1. Flow chart of the study protocol

Data collection

The age, sex, medical history information, and laboratory values of 92 intern doctors were obtained from the electronic medical record and archive system of the hospital. Their symptoms, background information, parents' consanguinity, immunodeficiency history, European Society for Immunodeficiencies (ESID) criteria, and comorbidities

were also recorded. Besides, serum immunoglobulin (Ig) values (IgG, IgA, IgM), IgG subgroups (IgG1, IgG2, IgG3, IgG4), CD3+ T cell, CD3+CD4+ T cell (T helper), CD3+CD8+ T cell (T cytotoxic), CD4/CD8 ratio, CD19+ B cell, CD19+CD27+IgD- class-switched memory B (cSMB) cell and CD16+CD56+ Natural Killer (NK) cell counts, specific antibody responses to protein and polysaccharide vaccines (tetanus and pneumococci) and isohemagglutinin titers (Anti-A, Anti-B) were recorded.

Those with one or more of the six warning signs recommended by ESID for adult immunodeficiency were considered to be important (6):

1. Four or more infections requiring antibiotics within one year (otitis, bronchitis, sinusitis, pneumonia).

2. Recurrent infections or infections requiring prolonged antibiotic therapy.

3. Two or more serious bacterial infections (osteomyelitis, meningitis, septicemia, cellulitis).

4. Two or more radiologically proven pneumonias within 3 years.

5. Infection with unusual site or unusual pathogen.

6. PID in the family.

Serum immunoglobulin measurements

Serum immunoglobulin levels were determined by nephelometric methods (Siemens BNII System, Erlangen, Germany).

Specific antibody responses

Pneumococcal polysaccharide antibody titers were measured by using a multiplex immunoassay (Elizen, Angleur, Belgium). An impaired response to Pneumovax-23 vaccine was considered if the post-vaccination titer was <250 mU/mL or less than a twofold increase from the pre-vaccination titer. Tetanus antitoxin IgG ELISA kits (Novalisa, Vienna, Austria) were used to detect tetanus antibodies. Tetanus antitoxin IgG was recognized as an antibody at a protective level ≥ 0.1 IU/mL.

Isohemagglutinin titer

To measure isohemagglutinin titer, blood samples in ethylenediaminetetraacetic acid (EDTA) tubes were centrifuged at 5000 rpm for 1 minute. After the centrifugation, the separated plasma was diluted with saline for titration. Titers ≥ 1:8 were considered to be normal.

Flow cytometric analysis

Peripheral blood samples (2 mL) were collected in an EDTA anticoagulant tube and tested within 6 hours. Peripheral blood lymphocyte subsets were measured by multicolor flow cytometry using a key panel. Cells were analyzed on a BD FACS Canto II Flow Cytometry System (BD Biosciences).

Statistical Analysis

The statistical analysis of this study has been performed by using the SPSS statistical package program (V.22.0). Descriptive statistics have been calculated for each variable. Continuous variables with normal distribution are presented as mean ± standard deviation, continuous variables without normal distribution are presented as median with range (min-max), and categorical variables are presented as numbers and percentages in each category and applied to the whole analyses.

RESULTS

This study has included 92 intern doctors who applied to our outpatient clinic after the death of an intern doctor who was unaware of her illness and had an underlying immunodeficiency during the COVID-19 pandemic. In our study, the median age is 23.6 (21-28) years, and 64 (70%) of the intern doctors are female. When they applied to the clinic, there were no complaints in 52 (56%) of them (Table 1).

According to the analyses, the complete blood counts showed normal lymphocyte values. In addition, immune system parameters were within the normal range in 48.9% of the participants. Comorbid conditions accompanied 40.4% of them with normal values. The most common comorbid disease in this group was allergic rhinitis. It is seen that one or more immune system parameters were low in 51.08% of them. Of these, 51.06% had comorbid conditions, and the most common condition was allergic rhinitis. Although immunological parameters were low in two of the three individuals with ESID criteria, it did not lead to a diagnosis of immunodeficiency (Table 1).

Table 1. General characteristics and comorbidities of the intern doctors included in the study

Number of intern doctors	92
Gender, n (%)	
Female	64 (70)
Male	28 (30)
Age, years, mean ± sd (range)	23.6 ± 1.4 (21-28)
Consanguinity between parents, n (%)	9 (9.8)
Smoking, n (%)	10 (10.9)
Family history of immunodeficiency	0 (0)
Complaints and history at admission, n (%)	
None	52 (56.5)
Allergic rhinitis symptoms and history	32 (34.7)
History or suspicion of frequent infections*	8 (8.6)
History of itchy skin lesions	3 (3.2)
Recurrent oral aphthae	2 (2.1)
Comorbidity, n (%)	
Allergic rhinitis	21 (22.8)
Skin diseases**	8 (8.6)
Asthma	7 (7.6)
Gilbert's Disease	4 (4.3)
Anemia	4 (4.3)
Other***	18 (19.5)
ESID criteria, n (%)	3 (3.2)

**Upper respiratory tract infections that do not require hospitalization, conjunctivitis, herpes labialis, urinary tract infection, cryptic tonsillitis, etc.*

***Acne vulgaris, urticaria, atopic dermatitis, lichen planus*

****Hyperthyroidism, chronic sinusitis, peptic ulcer, Wilson's disease, familial mediterranean fever, irritable bowel syndrome, polycystic ovary syndrome, hirsutism, anxiety disorder*

Abbreviations: *ESID, European Society for Immunodeficiencies*

When serum immunoglobulin (Ig) values and IgG subgroups were examined, it was seen that while IgG2 deficiency was not detected in all intern doctors, IgG4 deficiency was the most common (7.6%). Besides, while low IgA was detected in 4.3% of them, it was observed that 2.17% of the participants met the diagnosis of selective IgA deficiency. While 6.5% of them were found to have low IgM, 2.17% were found to have selective IgM deficiency.

When peripheral lymphocyte subgroups were evaluated, low CD19+ B cells were detected in 10.9% of them. cSMB cell levels were able to be measured in 30.4% of them, and a low level was observed in 35.7% of the participants. It was observed that there was low CD3+ in 1.1% and low CD4+ in 6.5% of them. On the other hand, low CD8+ was not detected. The CD4/CD8 ratio was found to be low at 18.5% of the intern doctors. Also, low NK cells were detected in 4.3% of them (Table 2 and Table 3). Finally, deficiency in immunological parameters was found to be more frequent in those with parental consanguinity (Table 4).

Table 2. Laboratory findings of intern doctors at the time of admission

Parameter	Normal range	Value, median (range)
Lymphocyte count, 103/uL	0.8 – 5.5	2.1 (0.9 – 3.8)
Immunoglobulins, g/L		
IgA	0.07 – 4	1.5 (0.02 – 4.4)
IgM	0.46 – 3.04	1 (0.1 – 4.7)
IgG	7 – 16	11.7 (6.7 – 20)
Immunoglobulin G subgroups , g/L		
G1	4.05 – 10.1	(3.7 – 15.8)
G2	1.69 – 7.86	4.2 (2.1 – 7.9)
G3	0.11 – 0.85	0.36 (0.07 – 1.47)
G4	0.03 – 2.01	0.52 (0.008 – 4.02)
Surface markers,%		
$CD3^+$ T cells	57 – 85	75 (56 – 88)
$CD3^+CD4^+$ T cells	30 – 61	40 (25 – 58)
$CD3^+CD8^+$ T cells	12 – 42	32 (16 – 48)
$CD4^+/CD8^+$ ratio	>0.9	1.3 (0.6 – 3.2)
$CD19^+$ B cells	6 – 29	10 (2.9 – 21)
$CD19^+27^+IgD^-$	9.2-18.9	11.7 (4.5 – 21)
$CD16^+56^+$ NK cells	4 – 25	11 (3 – 31)

Abbreviations: *CD, cluster of differentiation; Ig, immunoglobulin; NK, natural killer*

Table 3. Distribution of immunological parameters according to normal limits

Parameter	Detected low, n (%)	Normal detected, n (%)
Lymphocyte count	0 (0)	92 (100)
Ig A	4 (4.3)	88 (95.6)
Ig M	6 (6.5)	86 (93.5)
Ig G	1 (1.1)	91 (98.9)
G1	2 (2.2)	90 (97.8)
G2	0 (0)	92 (100)
G3	1 (1.1)	91 (98.9)
G4	7 (7.6)	85 (92.4)
$CD3^+$ T cells	1 (1.1)	91 (98.9)
$CD3^+CD4^+$ T cells	6 (6.5)	86 (93.5)
$CD3^+$ $CD8^+$ T cells	0 (0)	92 (100)
CD4/CD8 ratio	17 (18.5)	75 (81.5)
$CD19^+$ B cells	10 (10.9)	82 (89.1)
$CD19^+27^+IgD^-$ (n:28)	10 (35.7)	18 (64.2)
$CD16^+56^+$ NK cells	4 (4.3)	88 (95.7)
Tetanus antibody response	3 (3.2)	89 (96.7)
Pneumococcal antibody response	2 (2.2)	90 (97.8)
Isohemagglutinin#	3 (3.3)	86 (93.3)

 # The blood group of 3 patients was AB.

Abbreviations: *CD, cluster of differentiation; Ig, immunoglobulin; NK, natural killer*

Table 4. Distribution of immunological parameters according to the characteristics of intern doctors

	ESID criteria (n:3)	Family history of consanguinity (n:9)	Symptom Yes (n:40)	Symptom No (n:52)	Comorbidity Yes (n:43)	Comorbidity No (n:49)
Individuals with low immune parameters n=47	2	6	22	25	24	23
IgG, n=1	0	0	0	1	1	0
IgG1, n=2	0	1	1	1	2	0
IgG2, n=0	0	0	0	0	0	0
IgG3, n=1	0	1	1	0	1	0
IgG4, n=7	0	0	5	2	1	6
IgA, n=4	0	2	2	2	3	1
IgM, n=6	1	0	3	3	4	2
$CD3^+$ T cells, n=1	0	0	1	0	1	0
$CD3^+CD4^+$ T cells, n=6	1	1	2	4	1	5
$CD3^+CD8^+$ T cells, n=0	0	0	0	0	0	0
CD4/CD8, n=17	1	2	8	9	9	8
$CD19^+$ B cells n=10	0	0	5	5	5	5
$CD19^+27^+IgD^-$, n=10	0	1	3	7	5	5
$CD16^+56^+$ NK cells, n=4	0	1	0	4	2	2
Tetanus antibody response, n=3	0	0	3	0	1	2
Pneumococcal antibody response, n=2	0	0	1	0	1	0
Isohemagglutinin, n=3	1	0	2	1	1	2

Abbreviations: *CD, cluster of differentiation; ESID, European Society for Immunodeficiencies; Ig, immunoglobulin; NK, natural killer*

DISCUSSION

This study has examined the immune systems of intern doctors who were working actively during the COVID-19 pandemic. An intern doctor who had an underlying immunodeficiency and was unaware of her condition died of severe COVID-19 disease during the pandemic which heightened the fears of other intern doctors. For this reason, those who did not even have symptoms suggesting immunodeficiency went to immunology and allergy polyclinics voluntarily or on the orders of the units where they worked. Low immune system parameters, especially selective IgA, selective IgM, and IgG4 deficiency, were higher than usual among this educated and well-informed group.

IEIs are considered to be rare diseases, affecting one in 10,000 to 50,000 births. However, 70 to 90 percent of them remain undiagnosed (7). Delayed diagnosis of adult patients with IEI remains a challenge for clinicians worldwide. This can be explained by the lack of immunologic studies required to diagnose IEI due to a lack of awareness (8). The International Union of Immunological Societies (IUIS) has increased the number of IEIs to 485 in 2022. The purpose of the IUIS-IEI Expert Committee is to increase awareness, facilitate diagnosis, promote optimal treatment, and support research in clinical immunology (9). A study showed that the awareness of IEI was limited to 32% of the physicians, and awareness was higher among pediatricians (10). The lack of awareness among physicians explains the limited number of reported cases of IEI and delayed diagnosis. The starting point of our study is this lack of awareness.

It is reported that at least 7,000 healthcare workers worldwide have died from COVID-19 (11). The emergence of new pathogens with the COVID-19 pandemic continues to pose potential health risks to the general population due to the lack of immune memory. Individuals with known and unknown IEIs might be at higher risk for a more severe illness following the infection with SARS-CoV-2 (9). In addition to the physiological effects of the disease, it also had psychological effects on the global community. A systematic meta-analysis has shown that the COVID-19 pandemic had a high psychological impact on healthcare workers and people with chronic diseases (12). Another study has also reported that there was an association between higher levels of education and increased anxiety, depression, and stress during the COVID-19 pandemic (5). The population in our study has also consisted of health care workers, which is a group with high levels of education and anxiety at the same time.

ESID suggests 6 warning signs in those with suspected PID and recommends evaluating these drawings more than their owners (6). However, a study has claimed that the ESID criteria are not sufficient to identify immunocompromised patients, and more infection-related questions are required (13). In our study, it has been observed that participants with ESID criteria did not meet any diagnosis of immunodeficiency.

As the spectrum of immunodeficiencies and diagnostic capabilities expand, it is increasingly recognized that IEI is becoming more common. The burden of this disease has been increasing in low and middle-income countries with high consanguinity rates and poor access to diagnosis and treatment (14). Family studies of blood donors have demonstrated that first-degree relatives have a prevalence of selective IgA deficiency of 7.5%, which is 38 times higher than unrelated donors (15). Several other studies have reported that the diagnosis of selective IgA deficiency is more common in families with a consanguineous history (16). In this study, it has been determined that 9.8% of the individuals had consanguinity between their parents. In addition, selective IgA deficiency was observed in 11.1% of those with a family history. It is better to highlight that the high rate of consanguineous marriages in Turkey can explain one of the reasons for the high rate of selective IgA deficiency in our study. In general, selective IgA deficiency ranges from 1:143 to 1:965 in different regions. In a study conducted in Turkey, the rate of selective IgA deficiency was found to be 1/188 (0.53%), and similar results were obtained in other European countries (17). It is considered that the high rate (2.17%) in our study might be due to the high rate of consanguineous marriages in our country and the fact that the population in the study were health professionals with a high level of education and awareness. However, it is argued that the true rate would be higher due to the lack of routine immunodeficiency screening programs and many patients with selective IgA deficiency are asymptomatic (18). The results obtained from the analyses for this study also support this hypothesis.

A method for determining the prevalence of common immunoglobulin deficiencies was the prevalence of selective IgA and IgM deficiencies of 0.097% and 0.03%, respectively. Isolated IgG deficiency was not detected

(19). In another study with adults, selective IgM deficiency was found to be more common than previously thought, with a rate of 0.26% (20). In this study, isolated low IgG was found to be 1.1%, selective IgA deficiency was detected in 2.17%, and selective IgM deficiency was seen in 2.17% of the participants. The rates are found to be higher in this study than similar studies in adults.

IgG, which is one of the most abundant proteins in human serum, is evaluated in four subgroups. Selective subgroup deficiencies are generally not harmful to the individuals and sometimes result in an increased susceptibility to certain pathogens. Generally, one or more IgG subgroup levels (usually IgG2 and/or IgG4) are low in healthy individuals (21). In our study, IgG4 deficiency was seen as the most common, while G2 deficiency was not detected. It is also believed that IgG4 deficiency is common in the general population and most of them are considered to be asymptomatic (22). The results of our study also support this statement.

Deficiencies of lymphocyte subsets are rare and their prevalence is not completely known, especially among the healthy population (23). While low CD8+ was not detected in our study, 1.1% of the participants had low CD3+ and 6.5% of them had low CD4+. However, immunodeficiency was not detected.

A low CD4/CD8 ratio is associated with aging, comorbidities, and mortality. In addition, severe infections such as HIV, chronic inflammatory diseases, diabetes mellitus, and cardiovascular disease are other conditions in which the CD4/CD8 ratio seems to be low (24). In this study, it has been observed that the CD4/CD8 ratio was low in 18.5% of the participants, and comorbid diseases other than infections were present in 9.7% of them. Despite the young age group, it is thought that the comorbidities might have been effective in the low rate.

In the literature, conflicting results have been reported regarding B lymphocyte subsets. Some previous studies have shown that the percentage and the number of cSMB cells decrease significantly with age. However, two different groups have reported an increase in the percentage of total memory B cells with age (25). A recent publication has determined that there were specific changes in B cell subpopulations and an overall age-related decrease in the percentage of CD19+ B cells. Also, a decrease in one or both of the absolute numbers and percentages of memory B cells has been observed in older individuals when compared to younger individuals (26). In this study, low CD19+ B lymphocyte levels were found in 10.9% of the participants, and comorbidity was observed in half of them. Although it has been reported that the number of B cells decreases with age, the data of our study, which consisted of a young population, were seen to be inconsistent with the current literature. In this case, comorbidities are thought to be effective at this low rate. In our study, only 28 of the cSMB cells were able to be examined. Miscarriage was found in 35.7% of those screened for cSM and comorbidity was observed in half of them. When the literature is reviewed, the data belonging to the changes in cSMB cell levels with age seem to be conflicting. However, the decrease in our study which consists of a young age group (between 21 and 28 years old) might be due to comorbidities.

Although NK cell deficiencies are rare, drugs, infections, and genetic factors can affect their number or function. A significant increase in the percentage of NK cells can be seen with age in healthy individuals. In contrast, individuals with chronic diseases have lower NK cytotoxicity (27). In this study, a low NK cell count was determined in 4.3% of the participants and comorbidity was observed in half of them.

In the literature, no significant change in the immune response specific for tetanus and pneumococcal antigens with age has been reported (28). In our study, tetanus-specific antibody deficiency was found in 3.3% of the participants and pneumococcal-specific antibody deficiency was found in 2.2% of them. However, it should be noted that a limitation of this study is that control antibodies could not be examined after vaccination. Although there are significant limitations in their usefulness, isohemagglutinins can be used as another way to assess polysaccharide response. In our study, isohemagglutinin titers were as low as 3.3% of the participants. Isohemagglutinins do not allow the assessment of IgG mediated immunity as they are both IgM and IgG antibodies. It can be recommended to be used in conditions with limited adult population resources (29).

It can be expressed that this study has several limitations. Firstly, it is a cross-sectional and retrospective study. Secondly, control measurements were not able to be made in individuals with low immunologic parameters, control responses could not be checked after vaccination in individuals with insufficient specific antibody responses, and long-term follow-up results could not be obtained. Lastly, a higher number of healthy patients might yield statistically stronger results.

In conclusion, it can be said that studies on the prevalence of immune parameters in young and healthy adults are limited. The low awareness of immunodeficiencies, especially rare diseases, was thought to be one of the obstacles to the detection of this prevalence. In our patient population with a high level of education and awareness, it has been observed that immune system parameters are lower than normal, especially selective IgA, selective IgM deficiency, and low IgG4 are observed to be more frequent. According to the data obtained from this study, more comprehensive and prospective studies are required to understand the reasons for low levels of these parameters better, how they affect the immune system in the long term, and what side effects they might cause in individuals.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by the Necmettin Erbakan University of Medical Faculty Ethics Committee (Dated: 03.03.2023; Approval Number: 2023/4212).

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