Republic of Iraq

Ministry of Higher Education and Scientific Research

University of Diyala

College of Medicine

The Impact Of Tonsillectomy On COVID19

2022

Presented By

Mustafa Rafea Mohammed

SUPERVISED BY :

Dr. Anfal shakir Motib

بسم الله الرحمن الرحيم

(يَرْفَعِ اللَّهُ الَّذِينَ آمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ)

[المجادلة: ١١]

Contents

Acknowledgement

I owe to great many thanks to a great many people who helped and supported me to complete this research.

My deepest thanks to (Dr. **Anfal shakir Motib**) the guide of the project for guiding and correcting various documents of mine with attention and care. She has taken pain to go through the project and make necessary correction as and when needed.

I would also thank my patients and member of isolation unit of Al-Baquba teaching hospital and my faculty members without whom this project would have been a distant reality. I also extend my heartfelt thanks to my family and well wishes.

Abstract

Patients with Coronavirus Disease 2019 (COVID-19) can present with a broad spectrum of symptomatology. However, the impact of surgical history on the course of this disease has not been extensively investigated. Due to many different reasons such as coronavirus colonization in tonsillar tissue, decreased enzymatic antiviral activity, decreased cytokine activity from palatine tonsil tissue and reduced humoral and cellular immune response, tonsillectomy may alter the incidence of Covid–19. This study aimed to interrogate the effect of tonsillectomy in the symptomatology and other clinical parameters of the patients with COVID-19.

1. Introduction

1.1. Covid 19

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or Coronavirus disease 2019 (COVID-19) was identified for the first time in the Hubei province of China and spread around the world. The first COVID-19 case was diagnosed on the 11th of March 2020 in Turkey and spread across the country.

Coronavirus disease 2019 (COVID-19) , caused by the severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2), has shown a wide variety or manifestations, ranging from asymptomatic infection to critical respiratory failure . Fever, cough, shortness of breath and sudden onset of smell and taste deficiency are frequently reported, alongside gastrointestinal disturbances and non-specific complaints such as myalgia

and malaise. Various risk fac- tors have been debated to influence symptom severity and prognosis, such as sex, coexisting chronic disorders and tobacco use; however, the interindividual variability and susceptibility are not fully understood .

Coronaviruses are enveloped RNA viruses with crown-like spikes ranging from 60 nm to 140 nm in length on their surface under the electron microscope. Most coronaviruses cause mild respiratory tract infections in human beings.

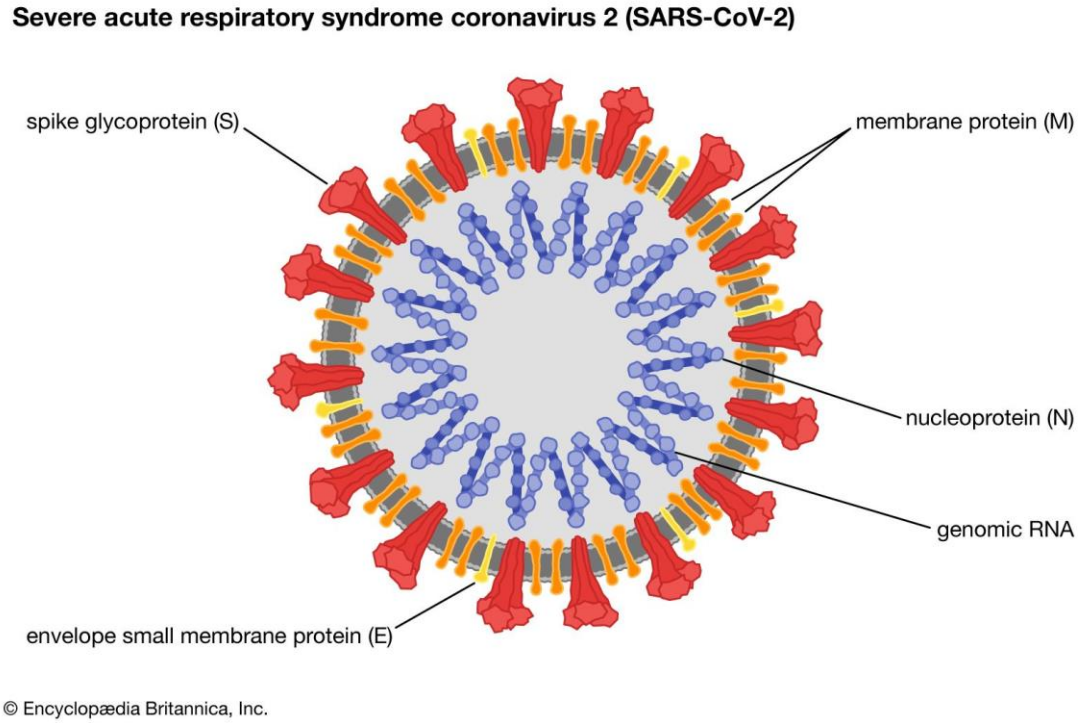

Figure 1: Covid 19 structure.

This study aimed to investigate the incidence of tonsillectomy in patients with COVID-19 and the progress of this disease in patients with tonsillectomy history.

1.2 Epidemiology

The epidemiological dynamics of COVID-19 has changed dramatically over the course of months. At the beginning of the outbreak, the most affected continent was Asia, with China being the most affected country worldwide. However, nowadays, the Americas, driven mainly by the USA and Brazil, have converted the region in the most affected on the planet.

The mortality rate is variable, ranging from 2% to 5% variability amongst different studies. It is probably due to different patient features and/or infection prevalence rates and is affected by the relative number of diagnostic tests performed in symptomatic individuals.

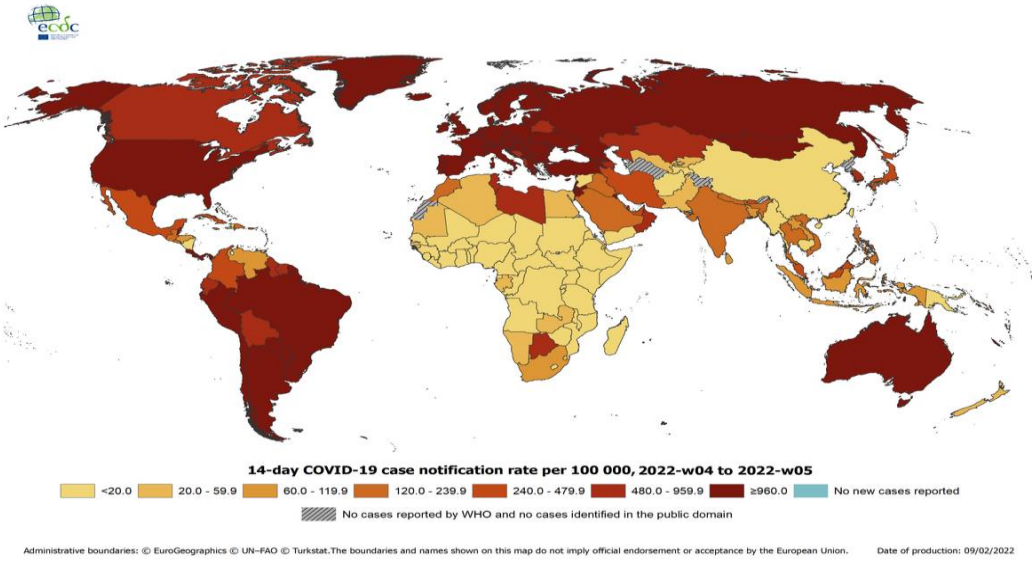

Figure 2: COVID19 situation update worldwide

1.3. Transmission

Currently available evidence indicates that COVID-19 transmitted from person to person through several different routes such as respiratory

droplets generated by breathing, sneezing, coughing, etc., as well as direct contact with an infected subject or indirect contact, through hand-mediated transfer of the virus from contaminated fomites to the mouth, nose, or eyes.

Severe acute respiratory syndrome coronavirus-2 RNA has been found in stool samples and RNA shedding often persists for longer than in respiratory samples.

Although common clinical manifestations of novel coronavirus infection do not include eye symptoms. The analysis of conjunctival samples from confirmed and suspected cases of COVID-19 suggests that the transmission of COVID-19 is not limited to the respiratory tract and that eye exposure may provide an effective way for the virus to enter the body.

Human breast milk for the search on existence of COVID-19 traced the presence of viral RNA.

Silent transmission of disease during the pre-symptomatic and asymptomatic stages is responsible for more than 50% of the overall attack rate in severe acute respiratory syndrome COVID-19 outbreaks.

1.4. Risk Factor

1.4.1. Age

Advancing age is increasingly recognized as one of the strongest predictors for severe COVID-19. Older adults (aged above 60 years) are at increasing risk of contracting severe COVID-19 with higher complication and case fatality rates.

Patients with COVID-19 infection have shown that people with underlying diseases not only have a higher risk of developing the disease

but also are more likely to die from the virus infection. Although age has emerged as the most important risk factor for adverse health outcomes related to the development of the cytokine storm and mortality, some younger individuals also fall gravely ill and develop a similar cytokine storm pathology with COVID-19.

1.4.2. Gender

Accumulating data also show the existence of a gender-associated predisposition to COVID-19 , with men being more prone to develop severe disease than women. Possible explanations of male predominance among COVID-19 patients may be differences in exposure, smoking behavior, other lifestyle factors, differences in chromosomal ACE2 expression, ACE2 expression in testicular tissue, sex hormone-driven immune system regulation, or gender differences in renin-angiotensin aldosterone (RAAS) regulation. Other biological factors may influence the sex-bias observed in this study, expression of angiotensin converting enzyme 2 receptors which facilitate COVID-19 viral entry and human to human transmission. Also, the difference between the sexes, Oestradiol may influence ACE2 expression, and the gene for ACE2 is located in the X chromosome, which may render it susceptible to escaping X-inactivation in women. The observation that women with COVID-19 show higher risk of severe COVID-19 is consistent with the possibility that estrogens could protect females from severe COVID-19. High testosterone levels could upregulate transmembrane serine protease 2 facilitating the entry of severe acute respiratory syndrome coronavirus 2 into host cells via angiotensin-converting enzyme 2.

1.4.3. Other Disease

Interestingly, in two independent cohorts of patients with heart failure, plasma concentrations of ACE2 were higher in men than in women. Patients with cardiovascular disease and over the age of 60, with a history of high blood pressure, obesity with a BMI above 25, and a history of smoking are at a higher risk of COVID-19 infection. Researchers at the Wuhan University of China found that of 416 patients admitted to the hospital, about 20% had severe muscle heart damage due to a severe COVID-19 infection, of whom more than half died. Older adults are far more likely than younger adults to have the chronic conditions type 2 diabetes mellitus, hypertension, cardiovascular disease, renal failure, and chronic obstructive pulmonary disease. These chronic conditions greatly increase the likelihood that those infected with COVID-19 experience more severe illness adverse outcomes, including acute respiratory distress syndrome and respiratory failure, sepsis, acute cardiac injury, and hypercoagulability.

1.4.4 Obese

Obese patients with COVID-19 may have an increased risk of intensive care unit (ICU) admission and mortality. Although obese patients frequently present with mechanical hypoventilation (leading to hypercapnic respiratory failure), those with COVID-19 present with hypoxic respiratory failure. This led to discussions about a potential role of fat tissue in COVID-19 pathogenesis in relation to ACE2 expression, granting that obesity predisposes to developing chronic disease, obesity could also be an independent risk factor for COVID-19.

2-Materials and Methods

Patients diagnosed with COVID-19 and admitted to Baquba Hospitals. Data including age, gender, symptom status (i.e., asymptomatic patients who were tested after close contact with another patient with COVID-19 or symptomatic patients who presented due to COVID-19 related complaints), chief complaint, and physical examination findings were all recorded.

Also, patients were interrogated regarding comorbidities such as hypertension, cardiac diseases, thromboembolic events, diabetes mellitus, asthma, chronic obstructive pulmonary disease, and past surgical history. Patients were divided into two groups based on their past surgical history of tonsillectomy. During the study period, all COVID-19 PCR test positive patients were admitted regardless of the symptom status.

Study Design

Case control study included 50 patients with COVID-19 who were admitted to Epidemiological Monitoring Unit at Emergency Department in Baqubah Teaching Hospital during period from 1 of febriuary to the 10 of febriuary 2022. Their ages range between 15-90 years old, 34 were males and 16 were females. The diagnosis of each case was established using clinical diagnosis and confirmed by reverse transcriptase polymerase chain reaction. A careful case history was taken from each patient using formula sheet.

3-Results

3.1. Distribution of study population according to Gender

The total number of the patients who were positive COVID-19 was 50, 34 (68%) of them were males and 16 (32 %) were females, the result of statistical analysis shown in, Table 1-1.

Table 1 : Distribution of study population according to Gender.

Gender	Patients NO (%)
Male	34 (68 %)
Female	16 (32 %)
Total	50 (100%)

3.2. Distribution of study population according to Age

Patients were divided into four categories; minimum age group was 15 years old and maximum age group was 90 years old. The highest number of patients 18 were in age group 15-35 years old, followed by 16 cases in age group 36-50 years old, while low frequency 7 cases was noticed within age group 71-90 years old. The statistical analysis revealed highly significant differences among them as shown in, Table 1.2.

Table 2: Distribution of study population according to Age

Age group years	Patients No (%)
15-35	18 (36%)
36-50	16 (32%)
51-70	9 (18 %)
71-90	7 (14%)
Total	50 (100%)

3.3. Distribution of study population according to presence of Chronic Disease

Out of 50 patients with COVID-19, 11 were diabetic, 7 were hypertensive and 5 have cardiac disease as shown in table 1.3.

Table 3: Distribution of study population according to the presence of chronic disease .

chronic disease	Patients No (%)
Diabetes Mellitus	11 (22%)
Hypertension	7 (14%)
Cardiac Disease	5 (10%)
Asthma	3(6%)
No Chronic Disease	24 (48%)

3.4. Distribution of study population according to smoking habit

The highest incidence rate was noticed among non-smoking patients (38 cases), in compare to smokers (12 cases) as shown in table 1.4. and the distribution of study according to the presence of tonsillectomy history.

Table 1.4: Distribution of study population according to smoking habit

Smokers	12 (24%)
Non-Smokers	38 (76%)
Total	50 (100%)

Table 1.5: Distribution of study population according to presence of Tonsillectomy History

Tonsillectomy History (+)	3 (6%)
Tonsillectomy History (-)	47 (94%)
Total	50 (100%)

Table 1.6: Distribution of study population according to presence of signs and symptoms among tonsillectomy

signs and symptoms	Patients No (%)	Tonsillectomy (+) **n=3**	Tonsillectomy (-) **n=47**
Asymptomatic	3 (6%)	0 (0%)	3 (6.4%)
fever	37 (74%)	3 (100 %)	34 (72 %)
cough	26 (52 %)	3 (100%)	23 (49%)
Shortness of breath	18 (36%)	1 (33.33%)	17 (36%)
chills	17 (34%)	1 (33.33%)	16 (34%)
malaise	29 (58%)	1 (33.33%)	28 (60%)
Sore throat	12 (24%)	2 (66.66%)	10 (21%)
headache	20 (40%)	2 (66.66%)	18 (38 %)
diarrhea	18 (36%)	2 (66.66%)	16 (34 %)
myalgia	22 (44%)	2 (66.66%)	20 (42%)

4- Discussion

In our population, tonsillectomised patients showed an increased risk of developing fever and temperatures higher than 39°C, along with malaise and chills. It is plausible that malaise and chills were consequences of the fever and its intensity, reflecting a more intense systemic involvement. Patients with previous history of tonsillectomy were older and with more coexisting disorders than those who did not receive the operation. However, even accounting for these possible confounding factors in the multivariate logistic regression, tonsillectomised patients still showed a greater risk to express a more intense systemic response to the virus.

As mentioned above, tonsillectomy itself is probably an indicator rather than the cause of a decreased Waldeyer's ring immune function; its activity of defense and inflammatory regulation is furtherly worsened by chronic infections that eventually lead to a vicious cycle and to surgical removal '. Significant differences have been demonstrated between frequently infected palatine tonsils compared to healthy controls, such as a different composition on the antigen- presenting cell (APC) population, a reduced capability in regulating the inflammatory response and decreased IgA and IgM production.

Frequently infected tonsils show an abnormal distribution of activated dendritic cells (DCs), the most efficient APC, which appear superficially concentrated on the lympho-epithelium in addition to the interfollicular T-cell areas: this suggests an increased production of inflammatory mediators and chemotactic dysregulation. DCs also mediate B-/T-cell interaction, which results in the selection of specific activated B-cells, memory B-cells and anti- inflammatory T-cell-derived cytokines such as IL-10:

impairment of the role of DC could undermine these essential immune functions in patients with chronic tonsillitis.

Moreover, tonsils subjected to chronic inflammation show a reduced production of anti-inflammatory cytokines and a lowered tolerance to viral infections compared to isolated hyperplasia. In a study by Mikola et al., tonsillar in RNA expression of IL-37, a fundamental inhibitor of innate immunity and inflammatory cytokines, appeared to be diminished in the chronic tonsillitis group when adjusted for age. Additionally, B-regulatory cells suppress effector T-cells and other lymphocytes via production of IL-10, IL- 35 and TGF-beta, and they are involved in supporting immunological tolerance. These cells are distributed among all human lymphoid tissues, including the palatine and naso- pharyngeal tonsils.

Finally, the impaired secretion of IgM and IgA finds its molecular counterpart in a reduced cytoplasmatic expression of" the J-chain, a peptide implied in the formation of the cited polymeric immunoglobulins, among youngsters with recurrent tonsillitis. In the possibility of routine application of a rapid salivary COVID-19 screening test, it might be necessary to take into account the role of the tonsils in mediating the production of secretive antibodies and local clearance of the virus.

All these features, together with the components of the innate immunity hosted by pharyngeal MALT, are involved in the response against viruses and have a role in the inter-individual variability of the manifestation and transmission of COVID-19 ', as our findings appear to support.

For what concerns the severity and clinical course of the disease, assuming hospital admission as a surrogate indicator of severity, no significant differences emerged between tonsillectomised and non-tonsillectomised patients. This finding, representing the secondary outcome of our work, may have been partially biased by the impossibility to retrieve accurate data from those who died, as well as the lack of other surrogate indicators such as hospitalisation time, complication rate and the small percentage of asymptomatic subjects. A more inclusive cohort accounting for all the above-mentioned biases and possible indicators of severity and complications may be necessary to specifically clarify the possible role of Waldeyer's ring status on the global severity and clinical course of the disease.

Our results seem to corroborate a potentially independent role of pharyngeal-associated lymphoid organs in the host response to COVID-19 infection. The fundamental importance of these organs in patrolling the upper airways against COVID-19 and other infective agents has been widely recognised. The higher prevalence of systemic signs and symptoms in the tonsillectomised patients in our cohort can be explained hypothesising that intrinsic impairment of the pharyngeal lymphoid tissues led to both chronic tonsillitis and tonsillectomy in the past, and now the same dysfunction could be responsible for an altered response to COVID-19. An uncontrolled inflammatory reaction to the virus, mediated by a dysfunctional Waldeyer's ring, could have led to fever, higher temperatures and associated symptoms. From this perspective, previous tonsillectomy as an indicator or an impaired immunological activity of pharyngeal MALT could be regarded as a predictor of an altered host response

to COVID-19 infection. Vice-versa, people with a functional Waldeyer's ring could develop more subtle and less intense symptoms, possibly leading to lack of identification of viral carriers.

As tonsillectomy is frequently performed and has a high prevalence in general population, this anamnestic information may take on potential relevance in the context of the COVID-19 pandemic . If these findings are confirmed by further studies, investigating history of previous tonsillectomy could help physicians to characterise the clinical manifestations in patients with suspected COVID-19 infection: knowing that non-tonsillectomised patients might show less symptoms and pass unnoticed, this could be a relevant information to correctly refer for screening tests wherever these are administered on the basis of the reported symptomatology .

The main limitation of this study is represented by the absence of deceased patients in our cohort, which may have affected the analysis of disease severity according to the variables investigated. This was unavoidable because of the impossibility to retrieve complete information about previous operations, coexisting disorders and COVID- 19-related symptoms. However, it was deemed acceptable at the time of the study design given the small percentage of deaths in relation to the total number of cases in Italy during the recruitment phase, probably with low effects on the outcomes .

Another limitation may be the self-reported nature of the information on coexisting disorders. We tried to limit inac- curacies by relying on objective data such as pharmacological history and diagnosis made during hospital admission. The main strength of this work is the completeness of the data analysed, prospective collection of information and lack of assumptions for missing data.

5- Conclusions

According to the results of this study, patients with COVID-19 infection and previous tonsillectomy might be more likely to develop a more intense and systemic response, with fever, higher temperatures, chills and malaise. This may reflect subtle differences in the immunological response to the virus caused by impaired pharyngeal MALT functionality. Although non-conclusive, these findings may shed new light on the pathophysiology of COVID-19 and support current evidence on the role of the pharyngeal microenvironment on the disease course. lf confirmed, these results could help discriminate suspected COVID-19 carriers, providing indications for the screening test knowing the higher risk of a subtler manifestation in non-tonsillectomised patients, and potentially delineating more precise prognostic models.

It is recommended to further study on Covid 19 by increasing the samples of patients with tonsillectomy.

References

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020;395(10223):470-3.

2. Di Natale C, La Manna S, De Benedictis I, Brandi P, Marasco D. Perspectives in peptide-based vaccination strategies for syndrome Coronavirus 2 pandemic. Front Pharmacol. 2020;11:578382.

3. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382(13):1199-207.

4. Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proc Natl Acad Sci USA. 2009;106(14):5871-6.

5. Altwairqi RG, Aljuaid SM, Alqahtani AS. Effect of tonsillectomy on humeral and cellular immunity: A systematic review of published studies from 2009 to 2019. Eur Arch Otorhinolaryngol. 2020;277(1):1-7.

6. Radman M, Ferdousi A, Khorramdelazad H, Jalali P. Long-term impacts of tonsillectomy on children's immune functions. J Family Med Prim Care. 2020;9(3):1483-7.

7. Yi Y, Lagniton PNP, Ye S, Li E, Xu RH. COVID-19: What has been learned and to be learned about the novel coronavirus disease. Int J Biol Sci. 2020;16(10):1753-66.

8. Byars SG, Stearns SC, Boomsma JJ. Association of long-term risk of respiratory, allergic, and infectious diseases with removal of adenoids and tonsils in childhood. JAMA Otolaryngol Head Neck Surg. 2018;144(7):594- 603.

9. Santos FP, Weber R, Fortes BC PS. Short and long term impact of adenotonsillectomy on the immune system. Braz J Otorhinolaryngol. 2013;79(1):28-34.

10. Holdoway A. Nutritional management of patients during and after COVID-19 illness. Br J Community Nurs. Br J Community Nurs. 2020;25(Sup8):S6-10.

11. Guo JW, Radloff CL, Wawrzynski SE, Cloyes KG. Mining twitter to explore the emergence of COVID-19 symptoms. Public Health Nurs. 2020;37(6):934-40.

12. Pascarella G, Strumia A, Piliego C, Bruno F, Del Buono R, Costa F, et al. COVID-19 diagnosis and management: A comprehensive review. J Intern Med. 2020;288(2):192-206.

13. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.

14. Baradaran A, Ebrahimzadeh MH, Baradaran A, Kachooei AR. Prevalence of comorbidities in COVID-19 patients: A systematic review and metaanalysis. Arch Bone Jt Surg. 2020;8(Suppl 1):247-55.

15. Soeroto AY, Soetedjo NN, Purwiga A, Santoso P, Kulsum ID, Suryadinata H, et al. Effect of increased BMI and obesity on the outcome of COVID-19 adult patients: A systematic review and meta-analysis. Diabetes Metab Syndr. 2020;14(6):1897-904.

16. Dong X, Yuan CY, Xia LX, Jin ZJ, Du H, Qin YY, et al. Eleven faces of coronavirus disease 2019. Allergy Eur J Allergy Clin Immunol. 2020;75(7):1699-709.

17. Paces J, Strizova Z, Smrz D, Cerny J. COVID-19 and the immune system. Physiol Res. 2020;69(3):379-88.

18. Padoan A, Sciacovelli L, Basso D, Negrini D, Zuin S, Cosma C, et al. IgA-Ab response to spike glycoprotein of SARS-CoV-2 in patients with COVID-19: A longitudinal study. Clin Chim Acta. 2020;507:164-6.

19. Polat C DK. Türkiye' nin doğusunda, Elazığ ilinde çocuklarda tonsillektomi ve adenoidektomi sıklığı Frequency of the tonsillectomy and adenoidectomy in children in Elazig. Tıp, Dicle Dicle, Derg. 2010;37(3):263-6.

20. Soh CH, Ul Hassan SW, Sacre J, Maier AB. Morbidity measures predicting mortality in inpatients: A systematic review. J Am Med Dir Assoc. 2020;21(4):462-8.e7.