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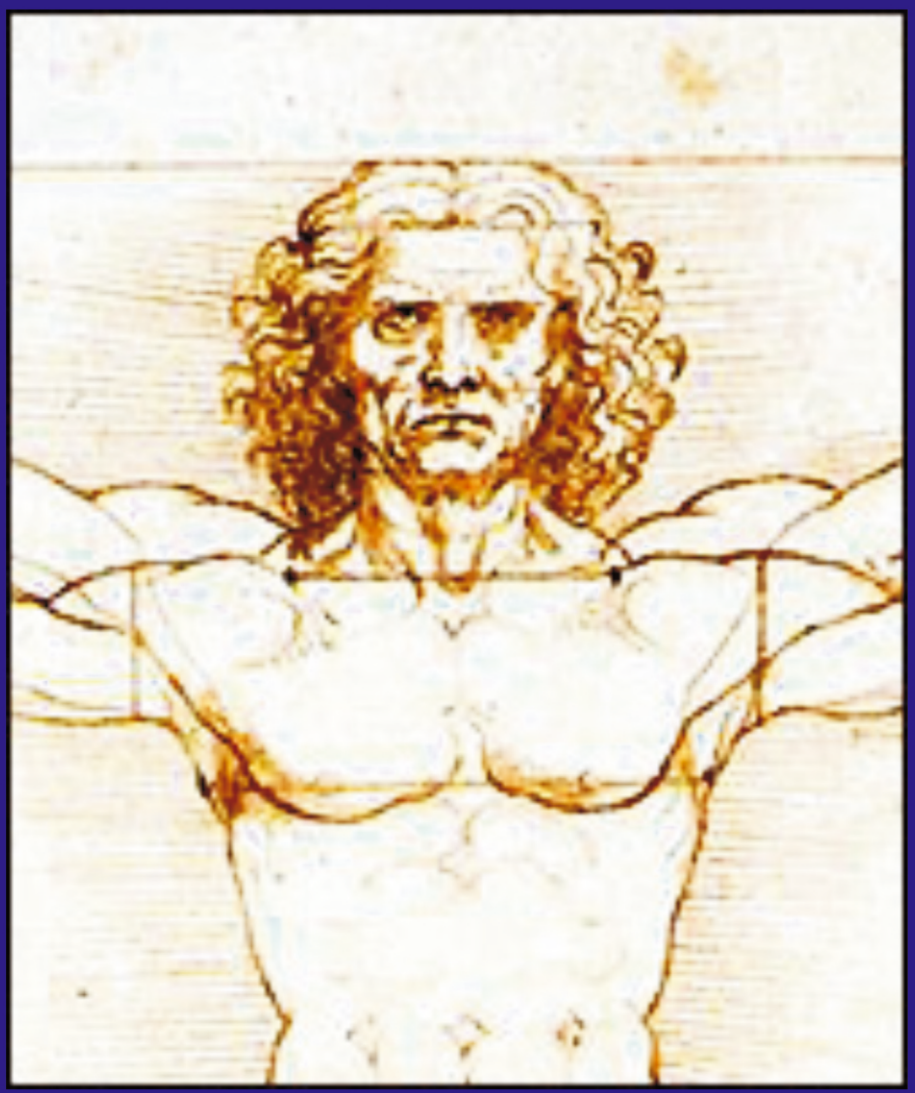

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A PREDICTIVE VALUE OF EARLY CLINICAL PARAMETERS FOR ABNORMAL BRAIN MRI SCAN IN NEONATES TREATED WITH THERAPEUTIC HYPOTHERMIA

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Abstract: **Introduction:** Brain MRI scans can predict neurodevelopmental outcomes in neonates treated with therapeutic hypothermia. It is a common clinical practice to perform brain MRI before discharge, but brain MRI scans performed at around four months of age have a better prognostic value for a long-term neurological outcome in asphyxiated neonates.

Aim: To identify which of three selected clinical parameters (oral feeding ability, muscle tone, history of seizure) evaluated 10 days after therapeutic hypothermia could predict the primary outcome of an abnormal brain MRI.

Methods: We reviewed the medical records of neonates ≥ 36 completed weeks of gestation consecutively treated with therapeutic hypothermia who underwent brain MRI. Clinical parameters on day 10 after therapeutic hypothermia were correlated with brain MRI findings in the first 7-14 days of life. Logic regression analysis was performed using all three covariates of the clinical status, with an abnormal MRI as the primary outcome.

Results: Brain MRI was abnormal in 42 (51.85 %) neonates with the following distribution of brain injury patterns: abnormal signal in the basal nuclei in 6, an abnormal signal in the cortex in 16, an abnormal signal both in the cortex and basal nuclei in 20 neonates. Out of three analyzed clinical parameters, feeding difficulty ($P < 0.001$, OR 8.3, 95% CI 2.9 - 28.9) and a history of seizures ($P < 0.001$, OR 11.95, 95% CI 3 - 44.5) were significantly associated with an abnormal MRI.

Conclusion: Neonates who were capable of full oral feeding by day 10 after therapeutic hypothermia and had no history of seizures were unlikely to have an abnormal MRI. This may be used in selective planning of pre-discharge MRI in asphyxiated neonates.

Keywords: therapeutic hypothermia, clinical parameters, feeding difficulties, seizures, brain MRI.

INTRODUCTION

The neuronal injury after perinatal asphyxia is a process that lasts, rather than being an isolated, one-time event (1). The primary cell injury is a direct consequence of hypoxia and ischemia. During the primary injury the cerebral concentrations of energy-rich compounds, adenosine triphosphate, and phosphorus creatine are decreased, which causes cytotoxic edema and neuronal injury. The next stage is the reperfusion stage, where cellular edema subsides in approximately thirty minutes. Next comes the latent phase, in which oxidative cerebral energy metabolism is very close to normal and lasts around 6 hours after acute asphyxia. After the latent phase, secondary injury develops with extracellular accumulation of excitatory amino acids, free radicals, and induction of apoptosis and inflammatory activity with a final breakdown of oxidative metabolism and neuronal death. Therapeutic hypothermia is a standard neuroprotective therapy in asphyxiated neonates (2). The therapeutic window for the implementation of hypothermia corresponds to the latent phase of hypoxic-ischemic brain injury (3).

The brain magnetic resonance imaging (MRI) findings after perinatal hypoxia have a predictive value for the neurodevelopmental outcome. The common clinical practice is to perform brain MRI before discharge, but the studies of serial MRI findings following therapeutic hypothermia showed that brain MRI findings at around four months of age have the highest

correlation with a long-term neurodevelopmental outcome (4). Thus, in some cases, it might be better to prolong brain MRI to that age.

This study aimed to analyze a correlation between the clinical findings ten days after therapeutic hypothermia and the brain MRI findings which might lead to identifying neonates who should have a brain MRI performed before discharge and neonates in whom it is better to postpone the brain MRI scan to be more informative. This selective and targeted approach to the brain MRI evaluation of asphyxiated infants might be more useful.

MATERIAL AND METHODS

The medical records of 88 neonates ≥ 36 completed weeks of gestation consecutively treated with therapeutic hypothermia between December 2017 and December 2021 at Pediatric Clinic University Medical Center Sarajevo, Bosnia and Herzegovina were reviewed. Our research was conducted by the ethical standards of the Declaration of Helsinki and the ethical standards of the University Medical Center of Sarajevo, Bosnia and Herzegovina.

Both three selected clinical parameters (oral feeding ability, muscle tone, history of seizure) and brain MRI scans were analyzed in 81 of the 88 neonates treated with therapeutic hypothermia. The medical records of the seven neonates who died were excluded. The therapeutic hypothermia for 72 h, initiated before 6 h of life was performed according to Bristol Royal Hospital's guidelines for therapeutic hypothermia in neonates. In all cases, prior to the initiation of therapeutic hypothermia parental consent was obtained.

All neonates underwent a brain MRI before discharge. The brain MRI was performed using a 1,5-T magnet with T1- and T2- weighted imaging and the scans were interpreted by neuroradiologists. We used the categorization of the brain injury similar to the categorization described by Barkovich et al (6). This categorization is based on the recognition of two basic imaging patterns of hypoxic-ischemic brain injury, one in which the primary damage is to the basal nuclei and another in which the damage is primarily to the cortex (6–9). Injuries to both basal nuclei and cortex were considered 'severely abnormal'.

The three selected clinical parameters (oral feeding ability, muscle tone, history of seizure) were evaluated 10 days after therapeutic hypothermia.

Data were analyzed by PASW Statistics 18. The clinical parameters between the groups were compared by X^2 test or t-test or Mann - Whitney test, as appropriate. The multivariate analysis was performed to determine which of the selected clinical parameters could predict an abnormal or severely abnormal MRI scan. Two-sided P-values ≤ 0.05 were regarded as significant.

RESULTS

We analyzed an MRI scan and three selected clinical parameters (oral feeding ability, muscle tone, history of seizure) in 81 neonates treated with therapeutic hypothermia. MRI scans were performed at median postnatal age of 9 days (range 6 to 24 and 50% IQR 6 to 10). Ten days after completion of treatment with therapeutic hypothermia 45 neonates (55.55%) failed to achieve full oral feeding, 24 (29.63%) had a deviation in muscle tone (hypotonia or hypertonia) and 53 (65.43%) had a history of one or more seizures which required treatment with anticonvulsants. Brain MRI was abnormal in 42 (51.85%) neonates. 35 out of 45 neonates with feeding difficulties, 20 out of 24 neonates with a deviation in muscle tone, and 38 out of 53 neonates who had clinical seizures by day 10 after completion of therapeutic hypothermia had an abnormal MRI. Table 1. shows the predictive values of these three selected clinical findings evaluated for an abnormal MRI.

The brain MRI findings for all 81 neonates were: normal scan in 35, an abnormal signal in the basal nu-

Table 1. *Predictive value of three clinical parameters (oral feeding ability, deviation in muscle tone, history of clinical seizures) for abnormal brain MRI in 81 neonates treated with TH*

Clinical parameter evaluated 10 days after TH	*Abnormal MRI scan*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*P-value (OR,95%Cl)*
Inability of oral feeding (n = 45)	35	81	72	75	72	< 0.001 (8.3, 2.9 - 28.9)
Deviation in muscle tone (hypotonia/hypertonia) (n = 24)	20	48	87	83	55	0.004 (3.9, 1.6 - 9.8)
Hystory of clinical seizure (n = 53)	38	90	55	69	80	< 0.001 (11.9, 3 - 44.5)

Abbrevations: TH, therapeutic hypothermia; PPV, positive predictive value; NPV, negative predictive value, CI, confidence interval; OR odds ratio

Table 2. *Significance of clinical parameters for prediction of 'severely abnormal' brain MRI*

Clinical parameter	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*P-value (QR, 95%CI)*
Inability of oral feeding	83	54	38	92	0.013 5.5,1.3-21.5
Hystory of clinical seizure	92	36	39	95	0.032 9.5,1.2-78.5

Abbrevations: PPV, positive predictive value; NPV, negative predictive value, CI, confidence interval; OR odds ratio

clei in 7, abnormal signal in the cortex in 16, abnormal signal both in the cortex and in the basal nuclei in 23 neonates. MRI scans showing injury of both basal nuclei and cortex were considered 'severely abnormal'.

Univariate analysis showed that all three selected clinical parameters evaluated 10 days after completion of therapeutic hypothermia were significantly associated with abnormal brain MRI scans the inability of oral feeding (P < 0.001, OR 10.2, 95% CI 3.4 – 25.7), deviation in muscle tone (P < 0.001, OR 8.9, 95% CI 2.5 – 29.7) and a history of clinical seizures (P < 0.001, OR 12.5, 95% CI 3.4 – 41.7). When we performed the multivariate analysis, only feeding difficulty ($P < 0.001$, OR 8.3, 95% CI 2.9 - 28.9) and a history of seizure ($P < 0.001$, OR 11.95, 95% CI 3 - 44.5) was linked with an increased risk of abnormal brain MRI findings.

Out of 23 neonates with 'severely abnormal' MRI, 20 neonates had difficulties with oral feeding, and 22 had a history of seizures. When we repeated multivariate regression analysis with all three clinical parameters for the outcome of 'severely abnormal' brain MRI, feeding difficulty and a history of seizures were again associated with the outcome, with negative predictive values of 92% and 95%, respectively (Table 2).

DISCUSSION

Currently, there are several clinical scoring systems in the early neonatal period proposed for the prediction of neurological outcomes after therapeutic hypothermia (10, 11). Many of these tests incorporate feeding ability and history of seizures, which appear to be significant predictors of neurodevelopmental outcomes following perinatal asphyxia (12, 13). The clinical assessment immediately after the therapeutic hypothermia treatment may result in false prediction due to the postponed removal of medication or impaired neuronal activity because of a briefly preceding hypoxic-ischemic incident and delaying clinical examination is more informative (14). Our study suggests that deferring clinical evaluation until ten days after therapeutic hypothermia completion provides significant prognostic information on neurodevelopmental outcomes.

The brain MRI scans after therapeutic hypothermia assure that there is no other pathology (e.g. hemorrhage, ischemia, congenital anomalies,…) and have a prognostic value. Early MRI abnormalities may not represent the final pathology, but the injury that is still evolving and studies show that delaying brain MRI scans to 4 months of age has the highest correlation with a long-term neurodevelopmental outcome (4). In our study, the negative predictive values of oral feeding ability and a history of seizures ten days after the completion of therapeutic hypothermia for prediction of 'severely abnormal' MRI were 92% and 95%. respectively. This signifies that neonates who attain oral feeding and have no history of seizures are unlikely to have severe changes on brain MRI. According to our results, brain MRI scans before discharge in such cases are not necessary and can be postponed to a period of life when MRI scans are more informative regarding the long-term neurodevelopmental outcome.

In conclusion, oral feeding ability and history of clinical seizures 10 days after completion of therapeutic hypothermia may be used for a selective and targeted approach to the brain MRI evaluation of the asphyxiated neonates. This approach may be more useful since delayed brain MRI scans are more informative in terms of long-term neurodevelopmental outcomes.

Abbreviations

MRI — magnetic resonance imaging
CI — confidence interval
NPV — negative predictive value
OR — odds ratio
PPV — positive predictive value
TH — therapeutic hypothermia;

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Sažetak

ZNAČAJ RANIH KLINIČKIH PARAMETARA U PREDIKCIJI MRI NALAZA NA MOZGU KOD NOVOROĐENČADI LEČENIH TERAPIJSKOM HIPOTERMIJOM

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Uvod: Nalaz MRI mozga ima prediktivnu vrednost za neurorazvojni ishod kod novorođenčadi lečenih terapijskom hipotermijom. Uobičajena klinička praksa je da se uradi MRI mozga pre otpusta, ali MRI mozga u dobi od oko 4 meseca života ima bolju prognostičku vrednost za dugoročni neurološki ishod kod novorođenčadi sa asfiksijom.

Cilj: Identifikovati koji od odabranih kliničkih parametara (sposobnost oralnog hranjenja, mišićni tonus, konvulzije) procenjeni 10 dana nakon terapijske hipotemije mogu predvideti primarni ishod abnormalnog MRI mozga.

Metode: Pregledali smo medicinsku dokumentaciju novorođenčadi ≥ 36 navršenih sedmica gestacije koja su uzastopno lečena terapijskom hipotermijom i bila podvrgnuta MRI mozga. Klinički parametri 10 dana nakon terapijske hipotermije bili su u korelaciji sa nalazima MRI mozga učinjenim u prvih 7-14 dana života. Urađena je logička regresiona analiza korištenjem sve tri kovarijante kliničkog statusa, sa abnormalnim MRI nalazom kao primarnim ishodom.

Rezultati: MRI mozga je bio abnormalan kod 42 (51,85%) novorođenčadi sa sledećom distribucijom obrazaca oštećenja mozga: abnormalni signal u bazalnim jedrima kod 6, abnormalni signal u korteksu kod 16, abnormalni signal i u korteksu i bazalnim jedrima kod 20 novorođenčadi. Od tri analizirana klinička parametra, samo poteškoće pri hranjenju ($P < 0,001$, OR 8,3, 95% CI 2,9 - 28,9) i konvulzije ($P < 0,001$, OR 11,95, 95% CI 3 - 44,5) su bili značajno povezani sa abnormalnim MRI nalazom.

Zaključak: Novorođenčad koja su bila sposobna za potpuno oralno hranjenje do 10. dana života nakon terapijske hipotermije i nisu imala konvulzije, imala su malu verovatnost da će imati abnormalni nalaz MRI mozga. Ovo se može koristiti u selektivnom planiranju MRI mozga pre otpusta kod asfiksiranih novorođenčadi.

Ključne reči: terapijska hipotermija, klinički parametri, poteškoće pri hranjenju, napadi, magnetna rezonanca mozga.

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TREATMENT ADHERENCE OF COVID-19 PATIENTS GETTING MEDICATION AT HOME

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Abstract: **Introduction**: Turkey has adopted outpatient treatment of COVID-19 since the beginning of the pandemic. In the outpatient treatment of COVID-19 in Turkey, only hydroxychloroquine was initially used, favipiravir was added to the treatment, and finally, hydroxychloroquine was removed from the treatment and only favipiravir was used. Our study aims to examine the adherence to the recommended treatment of people diagnosed with COVID-19 who have received outpatient treatment without hospitalization and their attitudes and declared behaviors towards using the medications they were given free of charge.

Methods: This follow-up study was conducted between February 15, 2021, and May 15, 2021, by telephone survey method in the Lüleburgaz District of Kırklareli City. The study participants were 4368 people who were diagnosed with COVID-19 with a positive PCR test in Lüleburgaz District between February 15 and May 15, 2021, and were given hydroxychloroquine and/or favipiravir drugs for home use after being deemed suitable for outpatient treatment according to the guidelines of the Republic of Turkey Ministry of Health.

Results: 88.1% (n = 3849) of the survey respondents reported using the given medications regularly, while 11.9% (n = 519) did not use them regularly. The most important socio demographic factor affecting the regular use was age, and the patient-centered factor was the sense of trust. Conclusion: In the fight against COVID-19, measures to increase the sense of trust of patients who are expected to adhere to the treatments should be considered a priority.

Keywords: COVID-19, Favipiravir, Hydroxychlorochine, Medication Adherence, Outpatient Therapy.

INTRODUCTION

Since the World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020, the disease has remained on the world's number one health agenda. On the same day as the WHO pandemic declaration, the first case of COVID-19 in Turkey was officially announced (1). The first case initiated discussions about the treatment of people diagnosed with COVID-19 because, as of the date of the first case in Turkey, there is no proven and approved treatment agent for the treatment of Covid-19 (2). Since then, COVID-19 treatment recommendations have been published by the Republic of Turkey Ministry of Health. These recommendations can be examined in two groups of hospitalized patients and for follow-up at home (outpatient treatment) (3). In the first published guidelines for outpatient treatment, only hydroxychloroquine was recommended, favipiravir was added to the treatment with the phrase "and/or", and finally hydroxychloroquine was removed from the treatment guidelines and only favipiravir was recommended for outpatient treatments (4). This study aims to examine the adherence to the recommended treatment of people diagnosed with COVID-19 who have received outpatient treatment without hospitalization and their attitudes and declared behaviors towards using the given medications free of charge.

The Republic of Turkey Ministry of Health Treatment Recommendations for Outpatient COVID-19 Patients

In the first guidance published by the Republic of Turkey Ministry of Health on March 23, 2020, it was recommended that patients with the following characteristics be hospitalized and monitored for possible severe disease and complications (3):

- Those over 50 years old
- Those with underlying diseases (cardiovascular diseases, immunosuppressive conditions, especially DM, HT, cancer, chronic lung diseases),

• Those with heavy pneumonia criteria (confusion or tachycardia (> 125/min) or respiratory distress or tachypnea (> 30/min) or hypotension < 90/60 mmHg or SpO2 < 92% or extensive bilateral lung involvement in chest scans),

• Sepsis, septic shock,

• Those who develop cardiomyopathy, arrhythmia, or acute kidney damage,

• Those with poor prognostic criteria in the blood tests taken in the application (Blood lymphocyte count < 800/µl or CRP > 40 mg/l or ferritin > 500ng/ml or D-Dimer > 1000 ng/ml etc.) Reports showed that patients without these symptoms could be identified as asymptomatic definitive cases or symptomatic (uncomplicated or with mild pneumonia) possible/definitive cases, and they could use hydroxychloroquine 200 mg tablets twice a day for five days without hospitalization if the physician-approved (3).

The treatment guidelines published by the Republic of Turkey Ministry of Health have changed dynamically during the pandemic and were changed frequently according to the recommendations of the science council established by the ministry (5). For the use of hydroxychloroquine in the guide published on April 12, 2020, it is mentioned: *"The available scientific data are asymptomatic and do not strongly support the start of hydroxychloroquine for individuals who have tested positive for COVID-19 PCR. However, based on general information that early start of medications is more effective, hydroxychloroquine can be started if the physician evaluating the patient approves and on the condition of being careful about side effects"* (4). In the guideline published on July 31, 2020, favipiravir was added to the treatment of outpatient patients with the phrase "and/or", to load 2 x 1600 mg (8 tablets of 200 mg) on the first day and then 2 x 600 mg (3 tablets of 200 mg) for the four following days (4, 5, 6).

The Republic of Turkey Ministry of Health's recommendation for outpatient treatment continued for some time as hydroxychloroquine and/or favipiravir. In the "COVID-19 Adult Patient Treatment" guideline updated on May 7, 2021, the Ministry removed the recommendation of hydroxychloroquine for patients with asymptomatic, uncomplicated, or mild-moderate pneumonia treated on an outpatient basis but recommended the use of favipiravir only with the dose table mentioned earlier (4).

All inpatient and outpatient treatments within the scope of COVID-19 in Turkey are ruled to be free by a presidential decree issued on April 14, 2020. In this context, free hydroxychloroquine and/or favipiravir drugs have been delivered to the patients' residences for free (7).

Treatment Adherence

The adherence of patients to regulated treatments has been discussed for many years. At a meeting of the World Health Organization in 2001, the concept of treatment adherence was defined as "the extent to which the patient follows the medical instructions" (8). According to this definition, patients are perceived as people who are instructed by health care providers and who must follow these instructions. However, in the modern treatment approach, it is envisaged that health care providers will inform the patients, offer alternative methods of treatment and leave the choice to the patient. In other words, there should be cooperation between the service providers and the service receivers regarding the nature of the health service to be provided (9). In this context, the concept of treatment adherence has been redefined, and the definition of "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" has been adopted (10). Patients' adherence to regulated treatment is one of the most crucial factors affecting treatment success. Low treatment adherence increases morbidity and mortality rates and therefore creates a great additional cost for health systems. Numerous studies prove the negative consequences of low treatment adherence for chronic diseases such as asthma, diabetes, and cardiovascular disorders, as well as infectious diseases such as HIV and tuberculosis (11).

MATERIAL AND METHODS

Study Design

This follow-up study was conducted between February 15, 2021, and May 15, 2021, by telephone survey method in the Lüleburgaz District of Kırklareli City. Kırklareli is a city of approximately 360.000 residents in northwest Turkey. Approximately 42% of the total population of Kırklareli lives in Lüleburgaz, the largest district of the city. There are a total of five hospitals in Lüleburgaz, one public and four private. Primary health services are provided by 48 family physicians working in 16 family health centers, in addition to a healthy life center affiliated with the District Health Directorate. There are also private physician and dentist offices, as well as medical centers in the district. In addition, five ambulance stations for emergency medical services are available.

Target Population and Sampling

The target population of the study consists of 5322 people who were diagnosed with COVID-19

by testing positive for PCR in Lüleburgaz District between February 15 and May 15, 2021, and who were given hydroxychloroquine and/or favipiravir drugs for use at home, deemed suitable for outpatient treatment according to the guidelines of the Republic of Turkey Ministry of Health. In our study, there was no sampling, and the aim was to reach all patients who started outpatient medication. People who were called twice on two different days after their drug use ended but could not be contacted by phone or who refused to participate in the study were excluded from the scope of the study. 4368 people who could be reached by phone agreed to participate in the study (N = 4368). The participation rate of the study is 82.1%.

Data Collection

The telephone survey method was applied in the collection of data. A two-stage questionnaire developed by researchers consisting of questions about demographic information and disease processes was applied to the people who agreed to participate in the study. In the demographics section, age, gender, marital status, number of children, education status, occupation, health insurance, and economic status are included. We asked participants about the drugs given to use in relation to disease processes, whether they used the given drugs regularly, the factors affecting their regular use of their medications, whether the drugs had side effects, and the factors that affected their decisions if they did not use their medications regularly, and their recent status.

Ethical Consideration

For the study, permissions were obtained from the Ethics Committee of The Institute of Health Sciences of Kırklareli University dated 15. 02. 2021 and numbered 2021/9 and from the Research Applications Review and Evaluation Commission of the Kırklareli Provincial Health Directorate dated 05. 04. 2021 and numbered 2021/6.

Statistical Analysis

SPSS 22 (Statistical Program for Social Sciences) software was used in the analysis of the data. Descriptive statistics are presented as numbers, percentages, standard deviations, and averages. The distribution of data was verified by Kolmogorov Smirnov and Shapiro Wilk Tests. Chi-square and binary logistic regression modeling were used in the analysis of the data that were not normally distributed. The suitability and efficiency of the model were evaluated by the Hosmer and Lemeshow test.

RESULTS

The average age of the respondents was 42.7 ± 14.9 (min 18, max 102), with an average age of 43.2 ± 15.3 (min 18, max 102) for women and 42.2 ± 14.4 (min 18, max 92) for men. It is seen that 1.1% (n = 50) of the respondents were treated only with hydroxychloroquine, 59.4% (n = 2596) only with favipiravir, and 39.4% with a combination of hydroxychloroquine and favipiravir. 88.1% (n = 3849) of the respondents reported that they used the given medications regularly, while 11.9% (n = 519) reported not using them regularly. The distribution of the medications given to the respondents for use and their status of use is seen in Table 1.

The three most common responses of the respondents who reported regular use of the medications when asked about the factors affecting their regular use were detected as “because I trusted the medical team that came home” with 49.7% (n=2170), “because the Ministry of Health recommends so” with 19.8% (n=865) and “because of having symptoms of the disease” with 10.3% (n = 449). When respondents who reported not regularly taking the medications they were given (n = 519) “what they meant by not taking them regularly”, the three most common responses were “given one drug, I never used it” with 37.2% (n = 193), “I was given two drugs, I never used both” with 16.0% (n = 83) and “given one drug, I started using it,

Table 1. *Distribution of the medications given to the respondents for use and their status of use*

Status of use	Recommended Medications			
	(Only) Hydroxychloroquine n (%)	(Only) Favipiravir n (%)	Hydroxychloroquine + Favipiravir n (%)	Total n (%)
Used all the medications as recommended	33 (0.8)	2354 (53.9)	1461 (33.5)	3848 (88.1)
Didn’t use the Hydroxychloroquine	17 (0.4)	0 (0.0)	113 (2.6)	130 (3.0)
Didn’t use the Favipiravir	0 (0.0)	242 (5.5)	9 (0.2)	251 (5.7)
Didn’t use both Hydroxychloroquine and Favipiravir	0 (0.0)	0 (0.0)	138 (3.2)	138 (3.2)
Total	50 (1.1)	2596 (59.4)	1722 (39.4)	4368 (100.0)

Table 2. *Comparison of some sociodemographic characteristics of the respondents with the regular use of medications for outpatient treatment of COVID-19*

Sociodemographic characteristics	Were the medications used regularly?		
	Yes n (%)	No n (%)	Total n (%)
Gender			
Female	1902 (43.5)	277 (6.3)	2179 (49.9)
Male	1947 (44.6)	242 (5.5)	2189 (50.1)
Age by group average (Average age of the group = 42.7)			
Younger	1881 (43.1)	341 (7.8)	2222 (50.9)
Older	1968 (45.1)	178 (4.1)	2146 (49.1)
Marital status			
Single	745 (17.1)	154 (3.5)	899 (20.6)
Married	2898 (66.3)	336 (7.7)	3234 (74.0)
Widow / Divorced	206 (4.7)	29 (0.7)	235 (5.4)
Children			
None	944 (21.6)	181 (4.1)	1125 (25.8)
1 child	815 (18.7)	118 (2.7)	933 (21.4)
2 children	1525 (34.9)	151 (3.5)	1676 (38.4)
3 or more	565 (12.9)	69 (1.6)	634 (14.5)
Education			
Below high school degree	1794 (41.1)	172 (3.9)	1966 (45.0)
High school degree	1142 (26.1)	180 (4.1)	1322 (30.3)
Above high school degree	913 (20.9)	167 (3.8)	1080 (24.7)
Total	3849 (88.1)	519 (11.9)	4368 (100.0)

Table 3. *Comparison of some socioeconomic characteristics of the respondents with the regular use of medications for outpatient treatment of COVID-19*

Socioeconomic characteristics	Were the medications used regularly?		
	Yes n (%)	No n (%)	Total n (%)
Income generating job			
Yes	2249 (51.5)	339 (7.8)	2588 (59.2)
No	1600 (36.6)	180 (4.1)	1780 (40.8)
Health insurance			
No	483 (11.1)	55 (1.3)	538 (12.3)
General health insurance (for unemployed citizens without social security)	446 (10.2)	62 (1.4)	508 (11.6)
Other*	2920 (66.8)	402 (9.2)	3322 (76.1)
Monthly income			
None	606 (13.9)	109 (2.5)	715 (16.4)
Below the national min. wage	256 (5.9)	22 (0.5)	278 (6.4)
National min. wage	917 (21.0)	119 (2.7)	1036 (23.7)
Above the national min. wage	2070 (47.4)	269 (6.2)	2339 (53.5)
Perceived economic status			
Very bad / bad	458 (10.5)	67 (1.5)	525 (12.0)
Middle	2872 (65.8)	376 (8.6)	3248 (74.4)
Good / very good	519 (11.9)	76 (1.7)	595 (13.6)
Total	3849 (88.1)	519 (11.9)	4368 (100.0)

* Social security, private health insurance, etc.

Table 4. *Association between the respondents' use of given medications and some sociodemographic and socioeconomic characteristics*

	B	S.E.	Wald	Sig.	Exp(B)	95% C.I. for EXP(B)	
						Lower	Upper
Gender							
Female / Male	0.155	0.100	2.436	0.119	1.168	0.961	1.420
Age							
Respondent's age	-0.022	0.005	16.527	< 0.001	0.978	0.968	0.989
Marital status							
Single			6.367	0.041			
Married	-0.289	0.298	0.940	0.332	0.749	0.418	1.343
Other (Widow, divorced)	-0.507	0.222	50.221	0.022	0.602	0.390	0.930
Children							
None			8.140	0.043			
1 child	-0.541	0.246	4.838	0.028	0.582	0.359	0.943
2 children	-0.325	0.183	3.149	0.076	0.723	0.505	1.035
3 or more	-0.431	0.161	7.130	0.008	0.650	0.474	0.892
Education							
Below high school degree			8.392	0.015			
High school degree	-0.378	0.146	6.752	0.009	0.685	0.515	0.911
Above high school degree	-0.043	0.123	0.120	0.728	0.958	0.753	1.219
Income generating job							
Yes / No	0.091	0.121	0.564	0.453	1.095	0.864	1.388
Health insurance							
None			1.760	0.415			
General health insurance (for unemployed citizens without social security)	-0.203	0.154	1.750	0.186	0.816	0.604	1.103
Other*	-0.011	0.148	0.005	0.943	0.990	0.741	1.321
Monthly income							
None			3.821	0.281			
Below the national min. wage	0.211	0.149	20.009	0.156	1.235	0.922	1.654
National min. wage	-0.217	0.255	0.728	0.393	0.805	0.489	1.325
Above the national min. wage	0.085	0.130	0.431	0.512	1.089	0.844	1.404
Perceived economic status							
Very bad / bad			0.822	0.663			
Middle	0.023	0.212	0.012	0.913	1.023	0.676	1.549
Good / very good	-0.087	0.146	0.356	0.550	0.917	0.689	1.219
Constant	-0.232	0.453	0.262	0.608	0.793		

* Social security, private health insurance, etc.
Hosmer and Lemeshow Test: 8.312; p > 0,05

but I quit" with 14.5% (n = 75). When respondents who reported not taking the medications regularly were asked about the factors that affected their lack of regular use of their medications, the three most common responses were mild symptoms with 50.9% (n = 264), distrust of medications with 17.5% (n = 91) and side effects of medications with 16.4% (n = 85). The three most common side effects reported by those who reported quitting the medications due to side effects were nausea and vomiting 34.1% (n = 29), palpitations with 17.6% (n = 15), and abdominal pain 16.5% (n = 14).

A comparison of some sociodemographic characteristics of the respondents with the regular use of medications for outpatient treatment of COVID-19 is seen in Table 2.

A comparison of some socioeconomic characteristics of the respondents with the regular use of medications for outpatient treatment of COVID-19 is seen in Table 3.

Table 5. *Comparison of the respondents' regular use of the given medications with the ending of their complaints due to COVID-19*

Were the medications used regularly?	Current health status			
	Fully recovered	Still have some complaints	Total	p*
Yes	3331 (76.3)	518 (11.9)	3849 (88.1)	
No	455 (10.4)	64 (1.5)	519 (11.9)	0.478
Total	3786 (86.7)	582 (13.3)	4368 (100.0)	

* Chi-square test was used.

Some sociodemographic and socioeconomic factors that are thought to affect the regular use of the given medications by the respondents were analyzed by the binary logistic regression method. The results of the binary logistic regression analysis are shown in Table 4.

When respondents were asked about their current health status as of the moment the survey was conducted, 86.7% (n = 3786) reported that they had fully recovered, while 13.3% (n = 582) still had some complaints. The usual complaints reported to be ongoing, weakness and loss of appetite with 5.2% (n = 228), cough with 2.5% (n = 111), general muscle and joint pain with 2.2% (n = 96), shortness of breath with 1.6% (n = 72) and loss of smell and taste with 1.2% (n = 53) were detected. The comparison of the respondents' regular use of the given medications with the ending of their complaints due to COVID-19 is seen in Table 5.

DISCUSSION

Discussions are still ongoing about the outpatient treatment of the COVID-19 pandemic that has affected the world. Various medications have been tried alone or in combinations in different countries, and numerous publications have been issued (12, 13). Several medications have even been tried to be used for pre-exposure prophylaxis against COVID-19 (14). Although Turkey has not supported the use of medications for pre-exposure prophylaxis since the beginning of the pandemic, it is a country that has adopted the outpatient treatment of COVID-19. In the outpatient treatment of COVID-19 in Turkey, only hydroxychloroquine was initially used, favipiravir was added to the treatment and finally, hydroxychloroquine was removed from the treatment and only favipiravir was used in the outpatient treatment (4). Naturally, the first question that comes to mind here is to what extent the patients who are prescribed outpatient treatment adhere to the treatments arranged for them. Many studies have been conducted to examine the factors affecting patients' adherence to treatments related to various diseases. In a systematic review examining these studies, factors affecting treatment compliance are categorized as "patient-centered factors", "therapy-related factors", "social and economic factors", "healthcare system factors", and "disease factors" (15). Our study observed that among the patient-centered factors such as demographic, psychosocial, and economic characteristics, age is the most affecting factor for the treatment adherence, and the treatment adherence increases as the age of the patients increases. Again, the fact that the patient is educated at least at the high school level increases the treatment adherence compared to being less educated.

One of the crucial discussions in the outpatient treatment of COVID-19 is how to decide which patient will take outpatient treatment and which patient will be hospitalized. Some studies envisage supporting the decision to be made in this regard with laboratory examinations (16). However, no laboratory examination was suggested in the guidelines of the Republic of Turkey Ministry of Health to make this decision, and the decision-making was left to the initiative of the physicians working in the field, provided that they complied with the algorithms in the guidelines (4). Some studies report that it is important for the patient to have confidence in the physician and accept and adhere to the treatment (17). When respondents of our study survey were asked about the factors affecting their regular use of their medications, the most common response was "because I trust the medical team that comes home". Of course, it is not enough that patients have confidence only in the physician, but also that they have confidence in the recommended treatment methods and medications. As in many countries of the world, research on the effectiveness and reliability of medications was carried out also in Turkey (18, 19, 20). The results have been discussed not only within the academic community but by the whole society, especially through social media platforms (21). The wariness of medications was the second most common cause of the respondents reporting that they did not use the medications regularly, while two of the most important reasons for regular use of the medications reported by respondents was their trust

in the healthcare team visiting them at home and the recommendation of the Ministry of Health. In light of these findings, it has been confirmed once again that psychosocial factors, one of the patient-centered factors are effective in the regular use or non-use of the medications, and that the sense of trust in the society is one of the most important factors affecting adherence to the treatment given.

The third most common reason of the respondents who reported that they did not regularly use the medications was the "side effects of the medications", one of the treatment-related factors included taste, method of application, duration, and complexity of the treatment and side effects. Studies have been carried out in the past years to examine factors affecting compliance with medications used for various diseases, and the results are that side effects are one of the most negatively affecting causes of therapy compliance (22, 23). Therefore, when setting strategies in cases that require widespread medication use such as outpatient treatment of COVID-19, it is once again understood that the side effects of medications should be taken into account.

In our study, the effect of the social and economic factors such as patient income and cost of the medication on the treatment adherence has not been observed, and such an effect was not expected anyway. Because, as previously emphasized, all outpatient medications are provided free of charge by the healthcare system and delivered to the residences of patients by medical teams. Similarly, since all patients diagnosed with COVID-19 who decided to take an outpatient treatment at their residences are served where they are without long waiting periods, as expected, no negative feedback was received on the healthcare system-related factors.

Disease-related factors such as disease symptoms and the severity of the disease were found to affect the regular use or non-use of the medications. Respondents who reported using the medications regularly indicated that there were signs of the disease in the third place as the reason for their regular use, whereas the participants who reported that they did not use the medications regularly indicated that the symptoms of the disease were mild, causing their behavior most often. A Danish study reported that physicians had a significant impact on patient adherence (24). Therefore, it is thought that by extending the time that physicians can allocate to patients as much as possible and taking measures to increase patient-physician communication, patients can be made more conscious about using medications according to recommendations, not symptoms, and thus the treatment adherence can be increased.

Many studies examining the efficiency of hydroxychloroquine and/or favipiravir treatment have been conducted and it has been reported that these medications can be used effectively in the treatment of COVID-19 (25, 26, 27). In our study, no statistically significant difference between the regular use of the given medications by the respondents and the ending of their complaints due to COVID-19 was detected. Since our study is based on the statements of the respondents, in other words, since the current conditions of the respondents were not determined by medical consultations and examinations, it is thought that this finding cannot be used to interpret the effectiveness of the medications.

Our study was carried out based on the statements of people who have been diagnosed with COVID-19 and who have been called by phone. It is not known whether those who refused to participate in the study used the medications given to them or not or how their final health conditions are. This is the crucial limitation of our research.

CONCLUSION

In our study, we determined that age is the most critical sociodemographic factor affecting the use of free medications by patients taking outpatient treatment after receiving a COVID-19 diagnosis and psychosocial factors are the most important determinants that positively or negatively affect the treatment adherence. It has been concluded that these factors should be taken into account in the planning for future measures against the disease. Measures to increase patients' trust expected to adhere to the treatments should be a priority.

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Sažetak

PRIDRŽAVANJE PREPORUČENOG TRETMANA KOD KUĆNOG LEČENJA COVID-19 PACIJENATA

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Uvod: Turska je usvojila ambulantno lečenje KOVID-19 od početka pandemije. U ambulantnom lečenju KOVID-19 u Turskoj, prvobitno je korišćen samo hidroksihlorokin, tretmanu je onda dodat favipiravir, a na kraju, hidroksihlorokin je uklonjen iz lečenja i korišćen je samo favipiravir. Naša studija ima za cilj da ispita koliko su se osobe sa dijagnozom KOVID-19 koji su bili na ambulantnom lečenju bez hospitalizacije pridržavali preporučenog tretmana i njihove stavove i ponašanje prema korišćenju lekova koje su dobili besplatno.

Metode: Ova studija praćenja sprovedena je između 15. 2. 2021. i 15. 5. 2021. metodom telefonskog istraživanja u okrugu Luleburgaz, grada Kirklareli.

Učesnici studije su 4368 pacijenta kojima je dijagnostikovan KOVID-19 pozitivnim PCR testom u okrugu Luleburgaz između 15. februara i 15. maja 2021. godine, kojima su izdati lekovi hidroksihlorokin i/ili favipiravir za kućnu upotrebu nakon što su smatrani pogodnim za ambulantno lečenje prema smernicama Ministarstva zdravlja Republike Turske.

Rezultati: 88,1% (n = 3849) ispitanika navodi da redovno koristi date lekove, dok ih 11,9% (n = 519) ne koristi redovno. Najvažniji socio-demografski faktor koji je uticao na redovnu upotrebu bila je starost, a faktor usredsređen na pacijenta bio je osećaj poverenja.

Z**aključak:** U borbi protiv KOVID-19, mere za povećanje osećaja poverenja pacijenata od kojih se očekuje da se pridržavaju lečenja treba da budu prioritet.

Ključne reči: KOVID-19, Favipiravir, hidroksihlorokin, pridržavanje lekova, ambulantna terapija.

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SERUM C3 AND SERUM C4 COMPLEMENT IN PATIENTS WITH BURN TRAUMA AND CORRELATION WITH BURN INJURY SEVERITY

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Abstract: **Introduction:** Burns, depending on the degree of severity, induce a significant pathophysiological response in the body. The complement system participates in the body›s defenses as well as in immune responses after burn-induced trauma.

Objectives: The main objective of the study was to examine how burn severity affects serum C3 and serum C4 complement values; whether burn severity correlates with serum C3 and C4 complement, and establish the predictive value of the serum C3 complement and serum C4 complement for assessing the severity of the burn.

Patients and methods: According to the degree of TBSA, patients were classified into three groups: group with %TBSA < 15% (30 patients), group with %TBSA > 15%-25% (30 patients), and group with %TBSA > 25% to 40% (30 patients). According to the depth of burns, patients were classified into two groups partial-thickness burns (39 patients) and full-thickness burns (51 patients). We followed laboratory parameters: value serum C3 complement and serum C4 complement on the first and seventh day after burn trauma.

Results: Serum C3 complement was significantly lower in patients with %TBSA > 25%-40% and in the group with %TBSA > 15%-25% compared to patients with %TBSA < 15% on the first and seventh day after burn trauma. Serum C3 complement was significantly lower in patients with %TBSA > 15%-25% compared to patients with %TBSA < 15% on day one and day seven after burn trauma. Serum complement C4 was not significantly different between burn groups on the first and seventh day. Full-thickness burns have significantly lower levels of serum complement C3, compared to partial-thickness burns, on the 1st and 7th day. Full-thickness burns result in a decrease in serum C4 complement compared to partial-thickness burns on the 7th day after burn trauma, but this decrease is not significant. On the 1st day after burn trauma, we found a negative correlation between %TBSA with serum C3 complement. Serum C4 complement was not correlated with %TBSA on the day 1st.

Conclusions: %TBSA and depth of burn result in a significant decrease in serum C3 complement but not serum C4 complement. There is a negative correlation of %TBSA and C3 complement but not serum C4 complement on the 1st day after burn trauma. Serum C3 complement is a significant predictor of burn severity. The predictory significance of the C4 complement is not statistically significant.

Keywords: burns, %TBSA, depth of burns, serum C3 complement, serum C4 complement, predictory significance.

INTRODUCTION

In the daily clinical practice of treating burnt patients, it is crucial to accurately assess the severity of the burn based on exact laboratory parameters. One of these parameters is the level of serum complement.

The complement system participates in the body's defenses as well as in immune responses after burn-induced trauma. Complement activation can result in opsonization, then activation of leukocytes, which have receptors for complement components, and finally lysis of the target cell, e.g. burn-damaged tissue cells. Serum C3 complement is involved in the process of complex formation and apoptosis as well as the defense against microorganisms, and thus in the creation of a desirable immune response. These components of complements are involved in the defense against microorganisms and the process of creating immune complexes and apoptosis.

RESEARCH OBJECTIVES

The objectives of the study are to examine how different degrees of %TBSA (Total Body Surface Area) and depth of burns affect serum C3 and serum C4 complement; to monitor the dynamics of these parameters in the 1st and 7th days after burns and monitor how serum C3 and serum C4 component of complement correlate with %TBSA. The objectives of the study are to determine the predictor significance of serum C3 and serum C4 components for assessing the severity of the burn.

PATIENTS AND METHODS

The study is a prospective clinical study of patients with burns conducted at the Clinic for Reconstructive and Plastic Surgery of the University Medical Center (UCC) in Sarajevo.

The study included 90 patients with varying degrees of severity of thermal trauma, aged 18 to 65 years, of both sexes, with %TBSA to 40%. The study was conducted from 2010 to 2017. The study did not include patients younger than 18 or older than 65 or patients with other acute and chronic diseases.

Patients with burns were classified according to the generally accepted classification of burns by the American Burns Association (1). According to the %TBSA of the burn, patients were classified into three groups: group with %TBSA < 15% (30 patients), group with %TBSA > 15%-25% (30 patients) and group with %TBSA > 25% to 40% (30 patients); according to the depth of the burn, the group I, partial-thickness burns (39 patients), and in group II, full-thickness burns, (51 patients). We did not have patients with grade IV in this study.

Serum complement C3 and serum C4 complement were laboratory determined on the 1st and 7th day after burn trauma at the Institute of Clinical Immunology, UCC in Sarajevo. Serum C3 complement and serum C4 complement were determined by nephelometry by measuring the turbidity of a water sample by passing a beam of light through the measured sample. A Siemens BN II nephelometer was used for this study Ser. Br. 292714, year of manufacture 2010.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration.

Statistical data

All data collected by this survey were prepared for statistical evaluation and stored in the Exel 2010 program, Microsoft Office software package (Microsoft USA), while statistical processing was done in the statistical data processing program SPSS ver.20.

The following tests were performed for inferential statistics depending on the sample distribution: Student T-test, Mann-Whitney U test, AVENE test, and Kruskal-Wallis test. The Pearson test or Spearman's test was used in the correlation analysis depending on the distribution of the samples.

A linear multivariate regression model was used to assess the predictor effect of individual variables on the dependent outcome variable (% TBSA). Values of $p < 0.05$ were accepted as statistically significant.

RESULTS

We statistically analyzed the values of serum C3 complement individually in each group with different %TBSA (%TBSA < 15%; %TBSA > 15%-25%; %TBSA > 25-40%) on the 1st and 7th day. Serum C3 complement was significantly lower in the patients with %TBSA < 15% on day 7th, compared to day 1, $p = 0.043$. In the group with %, TBSA > 15%-25% serum C3 complement was significantly lower on the 7th day, compared to the 1st day, $p = 0.038$. In the group of patients with %TBSA > 25%-40%, serum C3 complement was significantly lower on the day 7th compared to the day 1st after burn trauma, $p < 0.005$ (Table 1).

Statistical analysis of serum C3 complement between 3 groups of patients with different %TBSA (%TBSA < 15%; %TBSA > 15%-25%; % TBSA > 25-40%) on the first day, we found a significant difference between the groups, $p < 0.005$. Seventh day after the burn we found a significant difference between the groups (%TBSA <1 5%; %TBSA > 15%-25%; %TBSA > 25-40%), $p < 0.005$.

Table 1. *Serum C3 complement and %TBSA*

%TBSA	DAYS				P
	1 st day		7 th day		
	X	± SD	X	± SD	
%TBSA < 15%	1.44	0.19	1.27	0.26	p = 0.043
%TBSA > 15-25%	1.02	0.22	0.87	0.21	p = 0.038
%TBSA > 25-40%	0.83	0.19	0.59	0.12	p < 0.005

Legenda: X -mean value, SD - standard deviation

Table 2. *Serum C4 complement and %TBSA*

% TBSA	DAYS				p
	1 st day		7 th day		
	M	IQR	M	IQR	
%TBSA < 15%	0.24	0.17-0.32	0.23	0.19-0.32	p = 0.976
%TBSA > 15-25%	0.23	0.19-0.30	0.2	0.16-0.30	p = 0.977
%TBSA > 25-40%	0.21	0.16-0.26	0.18	0.15-0.30	p = 0.331

Legend: M - median, IQR - interquarterly rang

Table 3. *Serum C3 and serum C4 complement on the 7th day*

Serum complement	BURN DEPTH		p
	Partial thickness burn	Full thickness burn	
	M (IQR)	M (IQR)	
C3	1.2 (1.02-1.52)	0.7 (0.54-0.90)	p < 0.005
C4	0.25 (0.18-0.31)	0,23(0.18-0.31)	p = 0.497

Legend: M - median, IQR - interquartile rang

Table 4. *Predictor importance of C3 and C4 complement for the assessment of %TBSA*

Model	Non-standard coeff.		Standard coeficient	t	p	95% CI for B	
	B	Std. error	Beta			lower limit	upper limit
1 cont.	11.464	4.429		2.588	0.011	2.65	20.277
C3	-1.623	2.287	-0.05	-2.68	0.012	-6.175	2.929
C4	-0.087	0.063	-0.073	-2.379	0.064	-0.212	0.039

Legend: Dependent variable: % TBSA, Confindence interval (CI)

We analyzed the behavior of serum C3 complement between groups on the 1st and 7th day. By statistical analysis, we obtained the data that serum C3 complement on day 1st after burn trauma was significantly lower in the patients with %TBSA > 25-40% compared to the patients with %TBSA > 15%-25%, p = 0.004. Serum C3 complement on the 1st day after burn trauma were significantly lower in patients with %TBSA > 25-40% compared to patients with %TBSA < 15%, p < 0.005. On the 1st day, serum C3 complement were significantly lower in the patients with %TBSA > 15%-25% compared to the patients with %TBSA < 15% , p < 0.005.

On the 7th day, the serum C3 complement were significantly lower in the patients with %TBSA > 25%-40% compared to the patients with %TBSA > 15%-25%, p < 0.005, as well as compared the patients with %TBSA > 25%-40% to the patients with %TBSA < 15% ,p < 0.005. On the 7th day, serum C3 complement were significantly lower in the patients with %TBSA > 15%-25% compared to the patients with %TBSA < 15%, p < 0.005.

We statistically analyzed the values of serum C4 complement individually in each group with different %TBSA (%TBSA < 15%; %TBSA > 15%-25%; %TBSA > 25-40%) on the 1st and 7th days. Serum C4 complement values decreased on the 7th day compared to the 1st day in all groups of burns, but this decrease was not significant (in the group with %TBSA < 15%, p = 0.976; in the group with %TBSA > 15%-25%, p = 0.977; in the group with %TBSA > 25%-40%, p = 0.331) (Table 2).

On the 1st day, serum C4 complement values did not differ significantly between group whit %TBSA < 15% compared to group whit %TBSA > 15%-25%, p > 0.05 , and compared to the patients whit %TBSA > 25%-40%, p = 0.077. Serum C4 complement values did not differ significanty between the patients with %TBSA < 15%, compared to the patients with %TBSA > 15-25%, p > 0.05, and compared to the patients with %TBSA > 25%-40%, p = 0.318 on the day 7th after burn trauma.

On the 7th day after burn trauma, full-thickness burns resulted in a significant decrease in serum C3 complement compared to partial-thickness burns, p < 0.005. Full-thickness burns result in a decreased serum C4 complement compared to partial-thickness burns on the 7th day after burn trauma, but this decrease is not significant, p = 0.497 (Table 3).

On the 1st day after burn trauma, % TBSA negatively correlated with serum C3 complement, $p < 0.005$. On the 1st day after burn trauma, we found no correlation of %TBSA with serum C4 complement, $p > 0.005$.

On the 7th day after burn trauma, we proved that serum C3 complement is the greater predictor for the assessment of burn severity compared to serum C4 complement. The predictor importance of serum C4 complement is insignificant. The statistical model classified 84% of the variability of the dependent variable, which can be explained by independent parameters (Table 4).

DISCUSSION

The management of burn patients is always challenging for the clinician due to the high risk of bacterial sepsis, multi-organ failure, and death. Thermally devitalized tissue is a potent complement activator. Complement activation can be triggered by thermally damaged cell proteins, polysaccharides, bacterial endotoxins, fungi, or serum proteins.

This research proved that serum C3 complement is significantly activated on the first day after burn trauma. The intensity of serum C3 complement activation depends on the %TBSA and the duration of the burn trauma.

On the 1st and 7th day after burn trauma, C3 complement is more activated in burns with %TBSA > 25%-40% compared to groups with %TBSA > 15%-25% and also compared to patients with %TBSA < 15%. On the 1st and 7th day after burn serum C3 complement is more activated in a group with %TBSA > 15%-25% compared to patients with %TBSA < 15%.

Serum complement C4 is also activated on the first day after burn trauma. The activation of serum C4 complement depends on the % of TBSA and the duration of the burn but the decrease in C4 complement value, i.e.its activation, is not significant between individual groups with different % of TBSA. How long the the burn lasts affects the activation of serum C4 complement. In each group individually, serum C4 complement was lower on the seventh day when compared to the first day after the burn, but this reduction was not significant. Greater burn areas have the consequence of the higher complement consumption and the significantly lower serum C3 complement values, but do not significantly lower the serum C4 complement.

The results of our research are similar to experimental works of Gelfand et al (2). They found massive activation of an alternative complement pathway but not the classical activation pathway in a mouse experiment, %TBSA 25%–60%. The authors found de novo immunoelectrophoretic conversion of C3 complement 15 minutes to 2 hours after the burn. The activation of the alternative complement pathway was associated with increased aggregation of neutrophils in plasma and lungs, but also with increased permeability of blood vessel walls in the lungs and the formation of pulmonary edema. Decomplementation with one factor of cobra venom, or in the case of a genetic defect of the C5 component of complement, reduced complement activation by an alternative route, reduced aggregation of neutrophils in pulmonary blood vessels, reduced pulmonary edema, and reduced mortality from burns in the first 24 hours after the burn. The same authors followed the activation of the classical and alternative complement activation pathways, measuring the hemolytic activity of CH50 complement in 8 burnt patients with %TBSA 30% -90%. In the first 24 hours after the burn, they found primary activation of an alternative complement activation pathway in seven patients who developed bacteremia, pneumonia, and acute respiratory distress syndrome (ARDS). The classical complement activation pathway was not significantly activated. In the serum of burnt patients, the activating products, i.e. de newly created proteins, which activate an alternative pathway of complement activation, the mentioned authors, failed to prove. The authors hypothesize that these are the consequences of rapid in vivo clearance of de newly created substances that activate an alternative pathway of complement activation in humans.

The degree of complement reduction may be one of the indicators of the survival of the burnt patient (3). In burn patients a massive inflammatory response is induced that negatively affects the healing process of the burn wound and additionally exerts systemic effects. An important factor here is the complement system (4).

Bjornson et al. (5) experimentally examined the opsonic activity of C3 complement against E. coli in the serum of five patients with burns, with %TBSA of 40%-80%, for three weeks after the burn. Opsonic activity and serum C3 levels were reduced in all patients during the first seven days after the burn. The opsonic activity of the C3 complement remained significantly reduced for three weeks after the burn injury. By adding the serum of healthy persons, and the serum of burnt patients, the opsonic activity of the C3 complement returned to normal limits, but the ability to activate the C3 complement did not return. The authors believe that the reduced opsonization is a consequence of serum protein deficiency in patients with burns, and the decrease in C3 conversion may also be caused by some inhibitor present in the circulation. Mc Cabe (6) found in his studies that reduced complement values

are important predictors of immune suppression and concluded that immunosuppression is stronger if the %TBSA is greater.

Some authors attribute a direct role in the lethal outcome of an extensively burnt patient to the activation of the alternative complement pathway. Gelfand et al. (7) believe that, in extensive burns, shock does not occur as a result of protein loss over burnt surfaces, but due to increased aggregation of neutrophils in plasma and lungs, increased permeability of blood vessel walls in the lungs, formation of pulmonary edema and lethal outcome, and all changes as a consequence of complement activation by an alternative pathway. Kang et al. (3) found, in patients with extensive burns with a lethal outcome, simultaneous activation of both the classical and alternative complement activation pathways. The function of the complement system may be determined by a delicate balance between positive and negative regulation. Bain et al. have shown that increased alternative complement pathway function is associated with improved survival during critical illness, possibly due to improved host immune capacity (8). The immune response of the organism after a burn is very complex and is caused by several factors. The serum complement is one of these crucial factors. Our earlier research shows that the behavior of T lymphocytes in patients with different %TBSA is similar to the behavior of serum complement in this research. During the burns, several changes in the T-lymphocyte population were observed. The suppression of the immune response is greater the more severe the burn is (9).

CONCLUSIONS

Our research has shown that complement activation occurs on the first day after the burn trauma. Patients with a higher %TBSA already on the first day after the burn had lower complement values compared to patients with a lower %TBSA. On the 1st day after burn trauma, we found a negative correlation between %TBSA and serum C3 complement. Complement C3 was significantly lower on 7th day compared to day 1 after the burn in all burnt patients with different %TBSA, but not serum C4 complement. Full-thickness burns resulted in a significant decrease in serum C3 complement compared to partial-thickness burns. The larger burn area has the consequence on the higher complement consumption and the significantly lower serum C3 complement values, but not significantly lower the serum C4 complement. Serum C3 complement is a significant predictor of burn severity on the 1st day. Predictory significance of serum C4 complement is not significant on day 1.

TBSA-**Authors statement:** The authors state that the article is original, has not been submitted for publication in other journals and has not yet been published either wholly or partially. The authors claim that all authors are responsible for the research that all authors have designed and carried out; all authors have participated in drafting and revising the manuscript submitted, whose contents we approve. The study was approved by the UCC Bioethics Committee No. 1893/2009.

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Sažetak

SERUMSKI C3 I SERUMSKI C4 KOMPLEMENT KOD PACIJENATA SA OPEKOTINAMA I KORELACIJA SA TEŽINOM OPEKOTINE

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Uvod: Opekotina, ovisno o stepenu težine, indukuje značajan patofiziološki odgovor organizma. Serumski complement učestvuje u imunološkom odgovoru opečenog organizma u sklopu opšteg imunološkog odgovora indukovanog opekotinskom traumom.

Ciljevi istraživanja: Ciljevi istraživanja su ispitati kako težina opekotine utiče na vrednosti serumskog C3 i C4 komplementa, da li težina opekotine korelira sa vrednostima serumskog C3 i C4 komplementa, i proceniti prediktivnu važnost serumskog C3 i C4 komplementa za procenu težine opekotine.

Pacijenti i metod rada: Prospektivno ispitivanje je sprovedeno kod 90 pacijenata. Prema stepenu %TBSA, pacijente smo klasifikovali u 3 grupe: pacijente sa %TBSA < 15% (30 pacijenata), pacijente sa %TBSA od 15%-25% (30 pacijenata) i pacijente sa %TBSA 25%-40% (30 pacijenata). Partial-thickness burns, imalo je 39 pacijenata , a full-thickness burns 51 pacijent. Kod svih pacijenata određivali smo serumski C3 i C4 komplement prvog i sedmog dana nakon opekotine.

Rezultati i straživanja: Serumski C3 komplement signifikantno je niži kod grupe sa %TBSA 25%-40% i grupe sa %TBSA 15%-25% prvog i sedmog dana u odnosu na pacijente sa %TBSA < 15%, $p < 0.005$. Serumski C4 komplement nije se signifikantno razlikovao između ispitivanih grupa prvog i sedmog dana. Serumski C3 komplement signifikatno je niži u grupi pacijenata sa full- thickness burns u poređenju sa grupom pacijenata sa partial-thickness burns, $p < 0.0005$. Serumski C4 komplement bio je niži u grupi pacijenata sa full-thickness burns u poređenju sa pacijentima sa partial-thickness burns, ali to sniženje nije signifikantno. Već prvog dana nakon opekotinske traume, %TBSA je u negativnoj korelaciji sa serumskim C3 komplementom, ali ne i sa serumskim C4 komplementom.

Zaključak: Naše istraživanje pokazalo je da se serumski C3 komplement aktivira već prvog dana opekotine. Pacijenti sa većim %TBSA već prvog dana imali su niže vrednosti komplementa u odnosu na pacijente sa nižim %TBSA. Prvog dana opekotine prisutna je negativna korelacija serumskog C3 komplementa i %TBSA. Serumski C3 komplement signifikantno je niži sedmog dana u poređenju sa prvim danom opekotine kod svih pacijenata sa različitim %TBSA. Full-thickness burns pacijenti imaju signifikantno niži serumski C3 komplement u poređenju sa pacijentima koji su imali partial-thickness burns. Veći stepen %TBSA i dubina opekotine signifikantno smanjuju serumski C3 komplement, ali ne i serumski C4 komplement. Serumski C3 komplement je značajan prediktor težine opekotine već prvog dana nakon opekotinske traume. Prediktorni značaj težine opekotine serumskog C4 komplementa prvog dana opekotinske trauma nije značajan.

Ključne reči: opekotine, %TBSA, dubina opekotine, serumski C3 komplement, serumski C4 komplement, prediktorni značaj serumskog komplementa.

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Case report

LARGE SOLITARY ENCAPSULATED NEUROFIBROMA F UPPER ARM – A CASE REPORT

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Abstract: **Introduction**: Neurofibromas are benign tumors of neuronal origin, occurring most commonly in young adults, with no gender predilection. The connection of neurofibroma with disorders on a general level as von Recklinghausen's disease makes its diagnosis critical. **Case report:** A 32-old female patient was administered to the Clinic of Plastic surgery, Clinical Center of Montenegro in Podgorica, with a 10-year history of painless, subcutaneous tumor of the right upper arm that grew in size over the last ten years. The patient reported progressive pain and tingling in her right forearm and right hand for the last 12 months. An MRI showed a non-homogenous tumor of the middle third portion of the triceps muscle, in close contact with the humerus but without infiltrating it. The tumor was removed, with a definitive histopathological result of a solitary benign neurofibroma. **Conclusions:** This example of successful treatment of solitary neurofibroma may serve to increase the awareness of surgeons and radiologists in small countries regarding benign peripheral nerve sheath tumors. The patient is under observation for two years with no signs of relapse and no other features indicative of neurofibromatosis type 1.

Keywords: peripheral nerve sheath tumors, neurofibroma, magnetic resonance imaging, surgery, upper arm.

INTRODUCTION

Neurofibromas are benign peripheral nerve sheath tumors that can develop as solitary tumors or as a part of neurofibromatosis type 1 (NF-1). We report an uncommon case of a large solitary neurofibroma with no neurofibromatosis type 1 presence. Radical surgery remains the choice of treatment in such cases, providing low recurrence and the best long-term results.

CASE REPORT

A 32-year-old woman presented to the Clinic of Plastic surgery Clinical Center of Montenegro in Podgorica, with a palpable subcutaneous tumor of the right upper arm. She stated that the mass grew slowly over the last ten years, without any symptoms until last year when periodical tingling of the forearm and right hand (thumb) pain occurred. The symptoms worsened in the recent couple of months. Her previous medical history and laboratory results were unremarkable, and the patient denied a family history of NF-1. The clinical examination revealed in the middle portion of the right upper arm an irregularly-oval-shaped subcutaneous tumor, approximately 6 cm in its diameter. It was palpably painless, there wasn't a vascular deficit on that arm, and Tinel's sign on the median nerve was positive. An magnetic resonance imaging (MRI) of the right arm showed an irregularly oval-shaped, non-homogenous, necrotic tumor measuring 70 x 36 mm, with extension to subcutis in one direction, and in other close contacts with the cortex of humerus, without infiltration of the bone in the middle third of the triceps muscle (Figures 1 and 2). No detectable vascular or bone injuries and associations were seen on the MRI. The patient was examined for clinical signs of NF-1, and from a minimum of two of seven suggested criteria for confirming the diagnosis of NF-1, in our patient all criteria were negative (explained in further text). Then, under general anesthesia, the extirpation of the tumor was performed. Surgery revealed an irregularly dome-shaped tumor measuring 60x53mm, with a smooth surface and skin-like color, with medium firm consistency (Figure 3), located in the middle portion of the triceps muscle, with no visible infiltration of adjacent bone and muscle tissue. The tumor was removed and subjected to definitive histopathological examina-

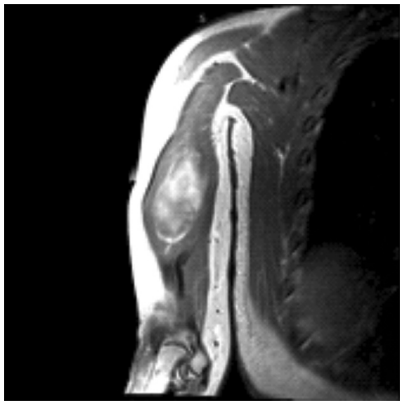

Figure 1. *Sagital plane MRI: showing tumor in the right upper arm*

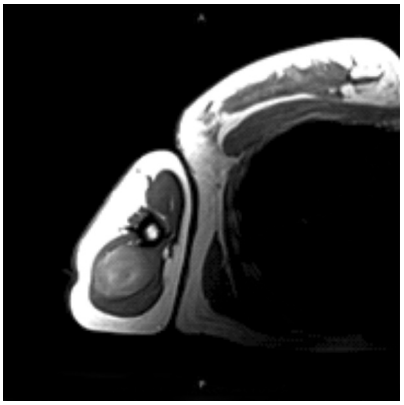

Figure 2. *Transversal plane MRI: showing tumor in the right upper arm*

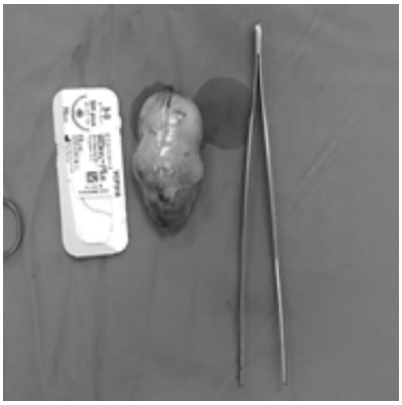

Figure 3. *Extirpated tumor*

tion. The postoperative period was uneventful, without relapse of the tumor. Histopathology reported regular histological and cytological built - a tumor made of spindle-shaped fibroblasts and Schwann cells, normochromic wavy nuclei, with no mitosis included in the mostly hyalinized and partially myxoid stroma, encapsulated by a thin capsule. The further immunohistochemical analysis stated s-100 positive, neuron-specific enolase, vimentin, and negative immunoreactivity to pan-cytokeratin and desmin. All this considered, the tumor was defined as a benign neurofibroma, without evidence of neurofibromatosis.

DISCUSSION

Clinically, neurofibromas arise in two possible patterns: either as sporadic tumors or in association with neurofibromatosis, Von Recklinghausen's disease.

Neurofibromatosis, Von Recklinghausen's disease is a direct consequence of a defect on chromosome 17, encoding for a tumor suppressor gene NF1, which is transmitted in an autosomal dominant pattern. It affects the skin, nervous, musculoskeletal system, and eyes. Two of the seven criteria are required to confirm the diagnosis of NF-1 (1): six or more café au lait macules, freckling in the axillary or inguinal lentigines, two or more neurofibromas of any type or a plexiform neurofibroma, two or more Lisch nodules (iris hamartomas), osseous lesions, an optic glioma and an affected first-degree relative (sibling or parent) (2, 3, 4).

Histologically three subtypes of neurofibroma are: solitary, diffuse, and plexiform. Solitary, sporadic neurofibromas are most common, with no racial and gender predilection, most often occurring in adults in the third decade. They present as usually slowly growing, skin-colored, rubbery tumors (5). Diffuse neurofibromas are most common in children, usually located within the subcutaneous tissue of the head and neck. Plexiform neurofibromas are characterized by diffuse involvement of the nerve segment and its branches, often accompanied by massive soft tissue overgrowth and consequently functional impairment. They are pathognomonic of NF-1, and unlike solitary and diffuse types, the plexiform type is associated with an increased risk of malignant transformation.

Solitary neurofibromas are usually clinically silent at the beginning, but as they inchmeal increase in diameter, compression effects occur on adjacent structures and organs, which exactly had happened in our patient, with Tinel sign positive. Giant variants of solitary neurofibroma exceeding 2 cm in diameter are rare, and those which are not associated with type I neurofibromatosis (NF-1) are even rarer. Such cases were reported in head & neck (6, 7), preperitoneal (8), retroperitoneal (9, 10), oral cavity (11), thoracic cavity and extremities.

The exact etiopathogenesis of solitary sporadic neurofibroma is still unknown, with the most acceptable theory considering it as a hyperplastic hamartoma (12, 13, 14).

Preoperative imaging (ultrasound, CT, MRI) is often inadequate to provide a definitive diagnosis, although data received from preoperative imaging facilitates the surgeon's job (ex. to determine the general morphology of the tumor, its location, and correspondence with adjacent structures) and therefore helps to prevent intraoperative complications.

When possible, if an incisional biopsy is performed with consequent pathohistological confirmation of neurofibroma, opinions concerning further treatment options are divided between clinicians. Few authors argue that only when the tumor is a cause of neurological deficiencies and/or its malignant potential is suspected radical surgery indicated (15). Authors of this text believe that if there are no vital con-

traindications, surgical excision in toto should always be performed. Besides functional impairment, solitary neurofibroma can also destructively engage adjacent structures, leading to irreversible loss of function in damaged structures, leading to worse outcomes, such as amputation of the limb (16).

A definitive diagnosis can only be provided by a pathologist after conventional histological analysis and immunohistochemistry. Histopathological examination confirms the proliferation of Schwann cells, perineural cells, and fibroblasts are seen among the stroma, sometimes myxomatous and micro -vacuolation. Differentiating neurofibroma from schwannoma is focal S-100 positivity which is a characteristic of neurofibroma. Histopathological findings show proliferation of Schwann cells, perineural cells, and fibroblasts amid a myxomatous stroma. The differential diagnosis for painful subcutaneous tumors should include myxoma, neurofibrosarcoma, angiolipomas, rhabdomyoma, and especially schwannomas, with preoperative imaging often being insufficient in differentiating them (17, 18).

CONCLUSION

Regarding soft tissue tumors, especially in young adults, it is recommended to include neurofibromatoses as part of differential diagnosis. A follow-up is fundamental for younger adult patients who were diagnosed with a solitary neurofibroma so that diagnosis of NF-1 can be excluded with certainty. In our patient, the absence of distant metastases, the absence of required signs of NF-1, as well as no relapse after surgery, and uneventful follow-up - confirmed the nature of the tumor.

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Sažetak

VELIKI SOLITARNI NEUROFIBROM NADLAKTICE-PRIKAZ SLUČAJA

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Uvod: Neurofibromi su benigni tumori nervnog tkiva, javljaju se najčešće kod mlađih odraslih osoba, podjednako kod oba pola. Potencijalna povezanost neurofibroma sa sistemskim poremećajem poput neurofibromatoze tip 1 (von Recklinhausen-ova bolest) čini dijagnozu neurofibroma izuzetno značajnom. **Prikaz slučaja:** Prikazujemo32-godišnju pacijentkinju sa prisutnom potkožnom tumefakcijom u predelu desne nadlaktice, koja je prisutna unazad oko 10 godina, uz postepen rast. Pacijentkinja se žali na osećaj bola i trnjenja u desnoj podlaktici i šaci unazad oko 12 meseci, sa progresivnim pogoršanjem tegoba. MR dijagnostika potvrđuje prisustvo nehomogenog tumora u predelu srednje trećine tricepsa desne nadlaktice, koji je u bliskom kontaktu sa humerusom, ali ga ne angažuje. Tumor je ekstirpiran u celini, sa histopatološkom verifikacijom solitarnog benignog neurofibroma. **Zaključak:** Ovaj prikaz slučaja uspešnog lečenja solitarnog neurofibroma služi kao podsticaj za podizanjem svesti za neurofibrome i tumore omotača perifernih nerava među hirurzima i radiolozima u manjim centrima. Pacijentkinja je redovno kontrolisana tokom dve godine postoperativno, bez recidiva i znakova razvoja NF-1.

Ključne reči: tumori omotača perifernih nerava, neurofibrom, magnetna rezonanca, hirurgija, nadlaktica.

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Case report

PRIMARY SPONTANEOUS PARTIAL PNEUMOTHORAX IN A PATIENT WITH COVID-19 PNEUMONIA. HAVE WE UNDERESTIMATED THIS COMPLICATION? A CASE REPORT

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Abstract: **Introduction and case report**: We described a case of primary spontaneous partial pneumothorax in a middle-aged man with COVID-19 pneumonia who presented with fever, loss of appetite, and malaise. Laboratory results revealed higher levels of inflammatory markers, as well as sterile urine and blood cultures. On admission, a chest X-ray revealed bilateral patchy consolidations in the lung parenchyma, as well as a left-sided partial pneumothorax. Throughout his hospitalization, the patient was closely examined by a thoracic surgeon, and a chest X-ray was taken on multiple occasions. There was spontaneous resorption of air from the pleural space. **Conclusion**: Pneumothorax is a rare but serious complication of the COVID-19 infection that has recently been documented in patients with no comorbidities, requiring various types of ventilatory support. The precise mechanism of primary spontaneous pneumothorax in COVID-19 infection is unknown, but it will undoubtedly pose a challenge to future researchers.

Keywords*:* primary spontaneous pneumothorax, partial, COVID-19, treatment.

INTRODUCTION

The presence of air in the pleural space that is not produced by trauma or another clear triggering factor is referred to as spontaneous pneumothorax (trauma or iatrogenic during a procedure). Secondary spontaneous pneumothorax is a consequence of preexisting lung disease, whereas primary spontaneous pneumothorax (PSP) occurs without a clinically detectable lung ailment (1). According to the literature, spontaneous pneumothorax is a rare and infrequent complication of Coronavirus disease (COVID-19) pneumonia (2). A few authors discovered that while the frequency in hospitalized patients is extremely low, about 0.3%, in those who required invasive mechanical ventilation (IMV), the incidence climbed to 12.8-23.8 %, with a mortality rate of up to 100% (3). This case presentation aims to stress this complication and explore potential risk factors associated with this phenomenon.

CASE REPORT

A 46-year-old man was admitted to the pulmonology department after complaining of a five-day fever, malaise, and loss of appetite. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) real-time polymerase chain reaction (RT-PCR) test resulted in a positive result. On admission, he was afebrile, with a blood pressure of 130/85 mmHg and a heart rate of 120 beats per minute. In room air, the pulse oximeter saturation was 87%. He had weakened breath sounds and no cardiac murmurs on auscultation. The patient disputed having drug allergies or a chronic condition, nor was a heavy smoker. On admission, laboratory findings revealed that C reactive protein (CRP) was 71.6 mg/l, leucocytes 14.8 cells/mcl, neutrophils 92%, lymphocytes 4.5%, erythrocytes 4.5 million cells/mcl, hemoglobin 142 g/l, platelets 243 cells/mcl, ferritin 1463 ng/ml, and IL-6 was 36.3 pg/ml. The D-dimer concentration was 1630 ng/ml. The blood gas analysis was within normal limits. Blood and urine cultures were both sterile. On admission, a chest X-ray revealed bilateral patchy consolidations in the lung parenchyma, as well as a left-sided partial pneumothorax (Figure 1). He was given ceftriaxone 2g once a day, levofloxacin 400 mg once a day, dexamethasone 6mg three times a day, low molecular weight heparin

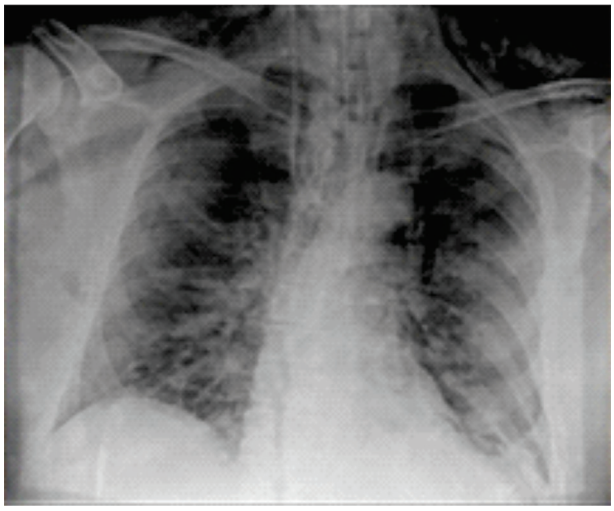

Figure 1. *Chest X-ray on admission showed bilateral spotty consolidations in lung parenchyma with left-sided partial pneumothorax*

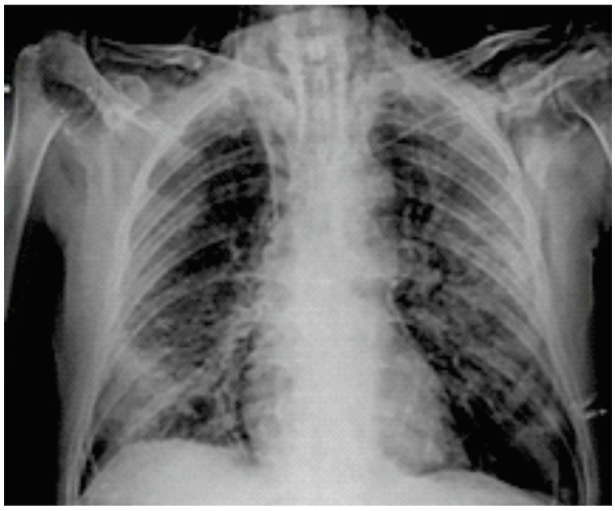

Figure 2. *Control chest- X-ray showed slightly regression of inflammatory changes and left-sided pneumothorax only in the apicoposterior segment*

(LMWH) 80mg twice a day, vitamins C, B6, and D, pantoprazole 20 mg twice a day, and oxygen therapy at 2-4 l/min. The patient's condition was closely monitored during his hospitalization; he was examined by a thoracic surgeon who did not indicate drainage, a chest X-ray was conducted on several occasions, and there was no worsening of respiratory symptoms. Blood, gas analyses were always within normal limits. On the tenth day of hospitalization, the patient had a control chest X-ray, which revealed a slight regression of inflammatory changes and a left-sided pneumothorax only in the apicoposterior segment (Figure 2). In the weeks that followed, the patient had two chest X-rays that revealed complete removal of the pneumothorax.

DISCUSSION

PSP symptoms might be mild or non-existent. These clinical symptoms are based on the proportion and size of the pneumothorax. Patients may suffer a sudden onset of pleuritic chest pain with dyspnea and shortness of breath, and some may experience shoulder tip pain (4). PSP is frequent in young people, with men having a higher frequency than women (7.4-18 per 100.000 men and 1.2-6 per 100.000 women). Being a male, having a slim and tall stature, and smoking are all risk factors (5). Some studies observed that PSP in COVID-19 pneumonia is usually associated with hypertension (37.5%), asthma (20%), and diabetes (17.5%), none of which were present in our patient (6). In laboratory findings, higher levels of inflammatory markers, particularly IL-6, were found, which value, according to data from some researchers, matches levels seen in COVID-19 infection (7). A chest X-ray revealed bilateral pneumonia with partial pneumothorax on the left side. According to the literature, the most prevalent chest-X-ray findings in COVID-19 are: lower lung zone involvement (50%) bilaterality (50%) consolidations (47%) peripheral infiltrates (41%), and ground-glass opacities (33%). A chest X-ray should be considered a viable imaging method for detecting COVID-19 pneumonia (8). However, a chest X-ray has been shown to have low sensitivity in detecting pneumothorax, particularly in the spine position, and computed tomography (CT) represents the "gold standard" diagnostic test for pneumothorax, but it is well limited by its high exposure to radiation, and can be unsafe to transport unstable patients (9). According to several experts, lung ultrasonography (LUS), particularly the BLUE protocol, can now cover some of the most critical disorders, including pneumothorax, with an accuracy of about 90% (10). We decided to monitor pneumothorax only through control chest X-rays due to the patient's symptomatology and overall good health. Given that he was not a smoker and had no other risk factors, we suspect that our patient developed PSP as a result of pulmonary lesions induced by COVID-19 infection.

CONCLUSION

Pneumothorax is a rare but serious complication of COVID-19 infection that has recently been documented in patients with no comorbidities and who are receiving various types of ventilatory support. The precise mechanism of PSP in COVID-19 infection is unknown, but it will undoubtedly pose a challenge to future researchers.

Abbreviations

CT — computed tomography
CRP — C reactive protein

IMV — invasive mechanical ventilation
LUS — lung ultrasound
LMWH — low molecular weight heparin
PSP — primary spontaneous pneumothorax

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Sažetak

PRIMARNI SPONTANI PARCIJALNI PNEUMOTORAKS KOD BOLESNIKA SA DIJAGNOSTIKOVANOM COVID-19 UPALOM PLUĆA. DA LI SMO POTCENILI OVU KOMPLIKACIJU? PRIKAZ SLUČAJA

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Uvod i prikaz slučaja: Opisali smo slučaj bolesnika srednjih godina sa primarnim spontanim parcijalnim pneumotoraksom kod koga je dijagnostikovana COVID-19 pneumonija sa tegobama u vidu povišene temparature, gubitka apetita i malaksalosti. U laboratorijskim rezultatima zabeležene su povišene vrednosti markera zapaljenja, urino i hemokulture su bile sterilne. Na radiografiji srca i pluća opisana je obostrana upala pluća sa konsolidacijama i levostranim parcijalnim pneumotoraksom. Tokom hospitalizacije bolesnik je pregledan od strane grudnog hirurga, radiografija srca i pluća je ponovljena više puta. Na poslednjem snimku došlo je do potpune resorpcije vazduha iz pleuralnog prostora. **Zaključak**: Pneumotoraks je retka ali ozbiljna komplikacija COVID-19 infekcije koja je zabeležena kod bolesnika bez komorbiditeta i onih koji nisu zahtevali bilo koji vid ventilatorne podrške. Tačan mehanizam razvoja primarnog spontanog pneumotoraksa još uvek nije poznat, ali će nesumljivo predstavljati izazov budućim istraživačima.

Ključne reči: primarni spontani pneumotoraks, parcijalni, COVID-19, lečenje.

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Hostory of medicine

DEVELOPMENT OF SERBIAN MEDICINE IN THE 19TH CENTURY

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Abstract: With the fall of the medieval Serbian state under Turkish rule, every culture, including medicine, died out, and the people resorted to folk medicine and self-taught doctors, i.e. empiricists. Serbs began to get educated in Vienna and Pest, and there were Serbian doctors in Novi Sad already at the beginning of the 18th century. At that time, the first doctors with diplomas appeared in Serbia, but mostly as personal doctors of the Belgrade pasha or Knez Miloš, i.e. his brother Jevrem in Šabac. In the fourth decade of the 19th century, the first military doctors set out, and the newly created four military district commands got their doctors. The Serbian Medical Association started the first medical journal, "Serbian Archives" in 1874. Josif Pancic is writing the first textbook in natural sciences, and Dr. Acim Medovic is writing the first textbook on forensic medicine. Before the First Serbian-Turkish War, the civilian ambulance numbered 69 doctors, 10 medical assistants, 26 pharmacists, and five pharmacy assistants, while the military ambulance had 19 doctors, five medical assistants, one pharmacist, and four pharmacy assistants. Health was initiated but also the establishment of the Ministry of Health and the higher education institution of the Medical Faculty in Belgrade. Guided by the oath, expertise, and experience, the doctors of that time made a significant effort to improve and develop medicine in Serbia in the 19th century.

Keywords: history of medicine, Serbia, 19th century.

INTRODUCTION

"I swear that I will come to the aid of the poor and the rich with equal zeal, that I will not deviate from the zealous performance of the duties of a district physician neither by bias, nor by friendship, nor by bribery," states the first medical oath from 1839 taken by district physicians and doctors. With the fall of the medieval Serbian state under Turkish rule, every culture, including medicine, died out, and the people resorted to folk medicine and self-taught doctors, i.e. empiricists (1). There were no trained doctors in the First or Second Serbian Uprising, but empiricists provided help. In the Serbia post-uprising, these empiricists even competed with trained doctors, because they were widely known (grandmother Stanija, gendarme Aleksa, uncle Dimitrije and others), and at the beginning of the 19th century the most famous were dolly Mana, lady Mother, and her son hakim Toma (1). Folk medicine has left written traces in the form of a medicinal book "Lekarusha" written by literate folk doctors who changed and augmented them over time. "Lekarusha" presents advice and instructions on diseases, medications, and treatments. The writings were passed from generation to generation anonymously, and it is unknown where or who wrote them. Recent research has shown that various therapeutic anthologies of medieval Serbia are not anthologies of folk medicine but writings created under the influence of Western European scientific medicine from Montpellier. These anthologies contained transcripts from the work of Joanes Platearius called Practica Brevis. These therapeutic anthologies were widely used in our country and were considered folk medicine, when in fact were the medicine of the Montpellier school (2). The most important achievement of folk medicine is variolation against smallpox from scabies of the sick to the healthy. At first, it was done by self-taught the people, and only from 1870 by hakims. Vuk Stefanovic Karadzic wrote in 1837 that Montenegrins knew how to inoculate smallpox by taking pus from patients, and they claimed that

they learned to do that from Bishop Petar First. While working in Cetinje, Dr. Milan Jovanovic Batut studied folk medicine in Montenegro and discovered that in the old days, priests used to remove dried scabs from patients, turned them into powder, and used bird feathers to put them in the noses of healthy people or gave them a snort. Later they transferred the pus with a thin silver needle to the scratched skin (1). During the migration of Serbs under Ottoman pressure, a part of Vojvodina was inhabited, which acquired certain political and civil rights from Austria only in the middle of the 18th century. Among other things, Serbs began to get an education in Vienna and Pest, and there were Serbian doctors in Novi Sad already at the beginning of the 18th century (1, 2, 3).

THE ARRIVAL OF LEARNED DOCTORS TO SERBIA FROM THE END OF THE 18TH AND THE BEGINNING OF THE 19TH CENTURY

The first doctor, a Serb, was Dr. Jovan Apostolovic, born in Budim. He studied medicine in Germany, and in 1759 he began to practice medicine in Novi Sad, which was declared a free town only a decade before. Novi Sad did not have a city physician but only a surgeon-healer, Andrija Leb. Only in 1762 was Dr. Jovan Apostolovic appointed the first city physician of Novi Sad. By the second half of the 18th century, there were four Serbian doctors in Vojvodina, and in the first half of the 19th century, there were already thirty (4). In the vassal principality of Serbia, Hatisherif from 1830 allowed the opening of the first hospitals. At the time, the first doctors with diplomas appeared in Serbia, but usually as personal doctors of the Belgrade pasha or Knez Miloš, i.e. his brother Jevrem in Šabac. Not having favorable conditions for work and life, these doctors stayed in Serbia for a short period (1). Among the first to persist in the principality for a long time were Bartolomeo Kunibert from Italy, Dr. Jovan Stejic from Arad, Dr. Carlo Pacek from Slovakia, Dr. Emerich Lindenmeier, an Austrian from Banat, and Carlo Belloni, a Slovak from Upper Hungary, and others. Hence, in 1838, before the end of the first reign of Knez Miloš, there were nine doctors and four medical assistants in Serbia, and the first pharmacies opened in Belgrade. One was opened by Mata Ivanovic, a pharmacist from Zemun, in 1830, and another by pharmacist Pavle Ilic, a native of Veliki Beckerek in Kragujevac, in 1836 (3). In the fourth decade of the 19th century, the first military doctors set out, and the newly created four military district commands got their doctors. In 1836, the first border quarantines were established, the most important one in Aleksinac (5). During the rule of The Defenders of the Constitution (1838-1958), the civil and military medical service became part of the Ministry of Interior, in which the Quarantine Department with medical care was formed. Dr. Karlo Pacek for quarantine affairs and Dr. Jovan Stajic for medical affairs were appointed as the head of that department. After the departure of Dr. Pacek with Knez Mihajlo from the country in 1842, Dr. Stajic remained alone as the head of that department and remained there until 1845, when he was appointed Secretary of the State Council. He was replaced by Dr. Lindenmeyer. Dr. Pacek drafted the Law on the Establishment of District Physicians, but in the absence of doctors, some positions of district physicians were filled by medical assistants (5). The newly-organized medical service began to solve many problems rapidly, such as combating infectious diseases in humans and livestock, introducing smallpox variolation, increasing the number of doctors, opening hospitals and pharmacies, appointing the first municipal doctors and midwives, sending state cadets abroad to study medicine, inspecting the composition and effect of mineral waters, etc.

THE DEVELOPMENT OF SERBIAN MEDICINE IN THE SECOND HALF OF THE 19TH CENTURY

As early as 1862, three new laws were passed: the Law on the Organization of the Central State Administration, which established ministries, the Law on the Organization of the People's Army, and the Law on General Conscription (1). With this legal transformation, the Military Medical Administration became a department in the Ministry of the Interior, which gave them more favorable conditions for work and development. The number of doctors in the city ambulance increased, and doctors began to come from the universities: Dr. Stevan Milosavljevic in 1855, who after Lindenmeier in 1859 was appointed head of the civilian ambulance and remained there for almost two decades; then Dr. Milosav Pavlovic in 1859, Dr. Filip Tajsic in 1864, and Dr. Josif Pancic and Dr. Vuk Marinkovic. Apart from the increase in the number of trained doctors, other changes are taking place in Serbian health care (1). In 1863, the Lyceum of the Year became the Great School within which the Department of Forensic Medicine and Public Hygiene was established. The first "bosses" of the department were Dr. Acim Medovic, and then Milan Jovanovic-Morski. With the enactment of the Law on Hospitals and Pharmacies in 1865, the Hospital Fund was formed, and the resources for the functioning of the fund were

provided from the annual tax of 1.60 dinars per tax head. The General State Hospital in Paliule in Belgrade was formed in 1867, and with the efforts of Dr. Vladan Djordjevic, the Serbian Medical Association was founded in 1872, and the Serbian Red Cross Society in 1876. The Serbian Medical Association started the first medical journal "Serbian Archives" in 1874. At the same time, the era of printing medical books began; textbooks whose authors were first foreigners or Serbs from Vojvodina. Dr. Vladan Djordjevic is among the first most published authors. The most famous works created in that period are the descriptions of Banja and the history of Serbian medicine by Lindenmeyer, the textbook of hygiene by Dr. Milan Jovanovic-Morski. Dr. Jovan Stojic, Dr. Vuk Marinkovic, and Dr. Josif Pancic are writing the first textbooks in natural sciences, and Dr. Acim Medovic is writing the first textbook on forensic medicine. With the development of medicine in civilian life, the military ambulance is also advancing. Before the First Serbian-Turkish War, the civilian ambulance numbered 69 doctors, 10 medical assistants, 26 pharmacists, and five pharmacy assistants, whereas the military ambulance had 19 doctors, five medical assistants, one pharmacist, and four pharmacy assistants (5). In 1879, Dr. Vladan Djordjevic was appointed head of the medical department of the Ministry of the Interior, and he remained in that position for five years. Thanks to him, Serbian health care has undergone thorough reform. Immediately after being appointed head of the medical department, this experienced and gifted doctor and organizer, who was a military doctor until then, drafted two laws (6). First, the Law on the People's Sanitary Fund was adopted by the Assembly by the end of December 1879. This law united all district hospital funds (established by the law in 1865) into one National Sanitary Fund that increased the hospital surtax by 0.50 dinars per tax head. The revenues of this fund also included the funds of the regular annual state aid and the income of the surtax for district doctors. In this way, the financial basis for the implementation of sanitary reform was created. The second law, the Law on the Regulation of the Medical Profession and the Protection of Public Health, was adopted in 1881. Although the roots of reforms in Serbian health care have been initiated, due to insufficient funds, by a small number of doctors and other medical workers, and especially the low level of health culture of the people, civilian health care has developed quite slowly. At the end of the 19th century and especially the beginning of the 20th century, the first surgical department opened in the improvised space of the General State Hospital in Palilula in Belgrade. Dr. Vojislav Subotic, the former head of the surgical department of the Zemun hospital, has been appointed the first head of the department. That was the first surgical department in the principality of Serbia. Along with this, the number of doctors significantly increased to 360 before the Balkan wars, and there were about thirty specialists among them. So, before the Balkan wars, we had the first specialists from various branches of medicine and surgery (7). All of this contributed to improving the health service, whose benefits were mostly available to the urban population, while the rural population, with very poor health conditions, remained unprotected. This, as well as the significantly slow development of the health service, was the subject of discussion at the sessions of the Serbian Medical Association, and every year it was the main item on the agenda of its annual assemblies. During one of the annual assemblies, the adoption of the new Law on Health was initiated, but also the establishment of the Ministry of Health, and the higher education institution of the Medical Faculty in Belgrade. However, the Balkan Wars and the First World War delayed the implementation of these initiatives (7). However, the military medical service developed much faster because the war conditions demanded it. From 1886 to 1903, the military ambulance experienced a revival, all under the leadership of Dr. Mihajlo Mike Markovic. His role in the military ambulance was as dominant as the role of Dr. Vladan Djordjevic in the civilian ambulance. As an active participant in the Serbian-Turkish wars, using his experiences, he focused his work on the development of war surgery, neglecting the hygienic-epidemiological service. He brought from Krakow an experienced surgeon, Dr. Roman Sendermayer, as the head of the military-surgical department, which opened in improvised premises at the old Belgrade military hospital. He sent several Serbian doctors to Vienna for specialization, and upon their return, he opened many surgical wards in five divisional hospitals in Belgrade, Nis, Kragujevac, Valjevo, and Zajecar. These surgeons also worked part-time in civilian hospitals, which contributed to the development of civilian medical care (1).

CONCLUSION

Guided by the oath, expertise, and experience, the doctors of that time made a significant effort to improve and develop medicine in Serbia in the 19th century. Unfortunately, the Balkan Wars and the First World War prevented them from further improving their health conditions in that period.

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Sažetak

RAZVOJ SRPSKE MEDICINE U XIX VEKU

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Padom srednjovekovne srpske države pod tursku vlast, svaka kultura, i medicina izumire, a narod je pribegao narodnoj medicini i samoukim lekarima, empiričarima. Srbi su se počeli školovati u Beču i Pešti, a već početkom 18. veka u Novom Sadu je bilo srpskih lekara. U to vreme pojavljuju se prvi lekari sa diplomama u Srbiji, ali uglavnom kao lični lekari beogradskog paše, ili kneza Miloša, odnosno njegovog brata Jevrema u Šapcu. U četvrtoj deceniji 19. veka postavljeni su prvi vojni lekari, a novostvorene četiri komande vojnih okruga dobile su svoje lekare. Srpsko lekarsko društvo pokrenulo je prvi medicinski časopis „Srpski arhiv“ 1874. Josif Pančić piše prve udžbenike iz prirodnih nauka, a dr Aćim Medović prvi udžbenik sudske medicine. Pre Prvog srpsko-turskog rata, civilna ambulanta je brojala 69 lekara, 10 lekarskih pomoćnika, 26 farmaceuta i pet apotekarskih pomoćnika, dok je vojna ambulanta imala 19 lekara, pet saniteta, jednog apotekara i četiri apotekarska pomoćnika. Pokrenuto je zdravstvo i osnivanje Ministarstva zdravlja, te visokoškolske ustanove Medicinskog fakulteta u Beogradu. Vođeni zakletvom, stručnošću i iskustvom, tadašnji lekari su uložili značajan napor da unaprede i razviju medicinu u Srbiji u 19. veku.

Ključne reči: istorija medicine, Srbija, 19. vek.

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Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

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GENERAL GUIDELINES

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The manuscript should be arranged as following: title page, abstract, key words, introduction, patients and methods/material and methods, results, discussion, conclusion, references, tables, figure legends and figures.

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