SANAMED

ISSN-1452-662X

Vol 16 (1) 2021.

MEDICAL JOURNAL

SANAMED

ISSN-1452-662X

IZDAVAČ

Udruženje lekara Sanamed, Novi Pazar

ČASOPIS IZLAZI TRI PUTA GODIŠNJE

ADRESA UREDNIŠTVA

„SANAMED“, Ul. Palih boraca 52, 36300 Novi Pazar, Srbija
email: sanamednp2006@gmail.com, www.sanamed.rs

ŠTAMPA

„OFSET“, Kraljevo

TIRAŽ

500

PRETPLATA

Godišnja pretplata: 4500 din. za domaće ustanove; 1500 din. za pojedince; za inostranstvo 75 eura (u dinarskoj protivrednosti po kursu na dan uplate). Pretplatu vršiti na račun 205-185654-03, Komercijalna banka. Za sve dodatne informacije kontaktirati Uredništvo.

ISSN-1452-662X

PUBLISHER
Association of medical doctors “Sanamed”, Novi Pazar

ISSUED THREE TIMES A YEAR

EDITORIAL ADDRESS
“SANAMED”, St. Palih boraca 52, 36300 Novi Pazar, Serbia
email: sanamednp@gmail.com, www.sanamed.rs

PRINT
“OFSET”, Kraljevo

CIRCULATION
500

SUBSCRIPTION
Annual subscriptions: 4500 RSD for domestic institutions and 1500 RSD for individuals. For readers abroad, annual subscription is 75 Euro (in Dinar equivalent at the exchange rate on the day of payment). For further instructions and informations, contact Editorial Board.

SANAMED

CONTENTS

PROFESSIONAL ARTICLE

CASE REPORT

SADRŽAJ

STRUČNI RAD

PRIKAZ SLUČAJA

A WORD FROM THE GUEST EDITOR

Poštovani čitaoci,

Sa posebnim zadovoljstvom sam se odazvala na poziv uredništva časopisa „Sanamed“ i prihvatila da budem gostujući urednik u martovskom broju koji je pred Vama.
Ovo nije početak naše saradnje. Već nekoliko godina pratim napredak časopisa i divim se entuzijazmu i naporima uredništva da podstaknu što veći broj lekara za publikovanje naučnih i stručnih radova.
Ono što polako postaje prepoznatljiv „pečat“ časopisa „Sanamed“ jesu upravo gostujući urednici, kojih je do sada bilo iz više različitih država. Ovo posebno pomaže promociji ovog medicinskog časopisa.
Moram istaći da je saradnja sa uredništvom iznad svega profesionalna i odgovorna, ali je protekla i u prijateljskoj, pozitivnoj i srdačnoj atmosferi.
Uzimajući u obzir kvalitet časopisa, njegovo kotiranje i potencijal, pozivam kolege da publikuju svoja naučna dostignuća u časopisu „Sanamed“ i uključe ga u svoje reference.
Na kraju, zahvaljujem se uredništvu na ukazanom poverenju i iskreno Vam želim napredak i uspeh u daljem radu, a u ovim vremenima borbe sa Covid-pandemijom.

Dear Readers,

With great pleasure, I have responded to the invitation of the Editors of Sanamed Journal and accepted to be a Guest Editor in the March 2021 issue of Sanamed. This is not the beginning of our cooperation. I've been following the progress of the Journal for several years, and I admire the enthusiasm and efforts of the Editors that they invest to encourage a greater number of doctors to publish scientific papers. Visiting editors is something that is slowly becoming a recognizable “signet” of Sanamed Journal. They were, so far, from several different countries. This is especially helpful for the general promotion of this medical Journal.
I must point out that cooperation with the Editors was, above all, professional and accurate, but also it has passed in a friendly, positive and cordial atmosphere.
Considering the quality of the Journal, its impact, and potential, I urge colleagues to publish their scientific achievements in Sanamed Journal and to include them in their references.
Finally, I thank the Editors for their trust, and I sincerely wish them prosperity and success in future work, and in these times of fighting the Covid-pandemic.

Ass. dr Katarina M. Janićijević
University of Kragujevac
Faculty of medical sciences

Čitaj da shvatiš

Piši da preneseš

Uradi da te pamte

* * *

Read to understand

Write to impart

Work to be remembered

Avdo Ćeranić

SANAMED
2021; 16(1): 11–18
ISSN-1452-662X

DOI: 10.24125/sanamed.v16i1.474
UDK:616.98:578.834]:617.3-089
ID:37473801
Original article

A COMPARISON OF ORTHOPAEDIC TRAUMA CASES OPERATED ON DURING THE COVID-19 PANDEMIC WITH DIFFERENT PERIODS: A SINGLE CENTRE STUDY

Akalın Yavuz, Ulusaloglu Can Armagan, Avci Ozgur, Cevik Nazan, Guler Olcay Burak, Ozturk Alpaslan

Health Sciences University, Bursa Yuksek Ihtisas Research and Training Hospital
Department of Orthopedics and Traumatology, Yıldırım, Bursa, Turkey

Primljen/Received 23. 11. 2020. god. Prihvaćen/Accepted 22. 01. 2021. god.

Abstract: **Introduction:** To compare orthopaedic trauma cases treated surgically in our clinic during the COVID-19 pandemic in Turkey with surgically-treated trauma cases in previous periods, and to discuss these in the light of literature.

Materials and Methods: Patient data of 3 different periods were compared. Group 1 included cases in the time period March 11 - May 30, when the hospital was operating as a pandemic hospital for the COVID-19 pandemic in Turkey. Group 2 included cases from the equivalent time period the year before the pandemic, thought to have similar patient characteristics, and Group 3 covered the time period immediately before 11 March when COVID-19 was known in the world but there had not been any cases diagnosed in Turkey. Operations performed in our clinic because of orthopaedic trauma counts 186 patients in Group 1, 262 patients in Group 2, and 261 patients in Group 3.

Results: A decrease of 29% was observed in trauma cases during the pandemic. In Group 1,62 of 186 patients were aged > 65 years, and 43 of these (69%) had a hip fracture, in Group 2,33 (58%) patients aged > 65 years underwent surgery for hip fracture, and in Group 3,60 (75%) patients. The time from hospital admission to surgery was mean 3.76 ± 3.55 days in Group 1, 3.18 ± 3.08 days in Group 2, and 2.68 ± 2.33 days in Group 3 ($p = 0.017$). The number of cases of attempted suicides was 6, 3, 3, respectively in the three groups ($p = 0.184$). 30-day mortality was determined in 5, 3, and 4 cases, respectively ($p = 0.460$).

Conclusions: A decrease in the number of trauma cases was observed during the pandemic. However, there was no such decrease in hip fractures in elderly patients despite the quarantine of those aged > 65 years. The workforce of the clinic was divided up during the pandemic for the diagnosis and follow-up of COVID-19 cases and thus there was no reduction in the workload of orthopedists as trauma surgery continued at the rate of 71%. Therefore, strict regulations must be applied which will decrease the risk of the spread of infection, and implement a multidisciplinary workflow for a more rapid discharge of trauma patients.

Keywords: Covid-19 pandemic, trauma, hip fracture, quarantine.

INTRODUCTION

The new coronavirus, first seen in China's Hubei province in December 2019, causes a disease progressing with severe acute respiratory failure (SARS-CoV-2), and was named corona virus disease 2019 (COVID-19) (1, 2). COVID-19 is spread by droplets and with symptoms such as fever, cough, dyspnea, and fatigue, which causes an upper respiratory tract disease similar to influenza. However, just as some patients may exhibit these symptoms, asymptomatic patients may also be seen. Cases of COVID-19 increased rapidly throughout the world, and on March 11, 2020, the World Health Organisation declared COVID-19 a pandemic. By March 11, 119.239 cases and 4287 deaths had been recorded in 115 countries (3).

Examining recent pandemics, the Spanish flu in the 20th century infected 50 million people, and the H1N1 outbreak in 2009 was the first pandemic of the 21st century (4, 5). After COVID-19 was first identified in China, in December 2019, it spread throughout the world rapidly and became a pandemic. Many

countries started to take different precautions, including social isolation, curfews, and regional quarantine (6). COVID-19 is known to cause greater morbidity and mortality in the elderly and those who are immune-compromised (7–11). In Turkey, the first COVID-19 case was diagnosed on March 10. The first precaution taken by the Turkish Ministry of Health on March 11 was to impose a partial curfew for citizens over 65 and under the age of 20, age groups known to be more severely affected by the disease.

As our hospital is a training and research centre, when COVID-19 cases started to be found, elective surgeries planned for March 17 - May 30 were postponed in accordance with the Ministry of Health instructions. During that period, the only operations performed were for spinal, pelvis, and upper and lower extremity trauma. In addition, throughout the pandemic, orthopaedic specialists and residents worked in wards with patients diagnosed with COVID-19 and in the COVID-19 emergency wards, as did all the physicians in the hospital.

Several guidelines have been published which show variations related to patients requiring surgery during the pandemic (12–15). The variability is caused by the continuously changing flow of information about the disease, and differences in health care infrastructures and demographic data in different countries. The aim of this study was to examine cases of orthopaedic trauma which had undergone surgery in our clinic during the COVID-19 pandemic in Turkey while curfew was in place and to compare and discuss these cases with those of previous periods.

MATERIAL AND METHODS

Approval for this study was granted by the Ministry of Health and the Local Ethics Committee (2011-KAEK-25 2020/06-19). The data for this retrospective study were retrieved from the hospital and clinic archives. The data which had been collected prospectively were compared retrospectively between the period of the pandemic and two previous cross-sectional periods. This research adhered to the principles of the Declaration of Helsinki.

Group 1 was formed from the time period March 11 - May 30, when the hospital was operating as a pandemic hospital. Group 2, in the same period from the year before the pandemic, and Group 3 covered an equivalent time period immediately before March 11 when COVID-19 was known in the world but there had not been any cases diagnosed in Turkey.

In Groups 2 and 3, elective cases and emergency operations, other than for trauma, were excluded. As the curfew implemented during the pandemic included individuals aged < 20 years and > 65 years, the patients in the 3 study groups were separated into subgroups of < 20 years, 20-64 years, and > 65 years. The groups were compared in respect of whether the trauma was low-energy or high-energy, the injured body region, time from trauma to surgery, and postoperative length of stay in hospital.

The daily working of the Orthopaedics and Traumatology Clinic changed during the COVID-19 pandemic, where basic changes were made because of the precautions taken. In addition to the general precautions instructed by the Ministry of Health, our hospital was designated as a pandemic hospital, so the A-block building was assigned for COVID-19 patients, and all the surgical clinics located in that block were transferred to another building.

In this period, all patients were treated using the necessary personal protective equipment (PPE), and no problems were experienced with PPE. All patients presenting at the Emergency Department were questioned and evaluated in respect of COVID-19 symptoms of fever, fatigue, respiratory problems, cough, nasal discharge, metallic taste in the mouth, loss of sense of smell, gastroenteritis, and flu-like symptoms. Patients with physical examination findings, a suspicious history, and low oxygen saturation were evaluated with pulmonary tomography and blood tests grouped as a COVID-19 panel, also nasopharyngeal swabs were taken for RT-PCR test.

Patients with suspected COVID-19 for whom surgery was planned were first admitted to the suspected cases ward and evaluations were made in respect of COVID-19. When the hospital bed capacity allowed, patients were isolated in single rooms. Special care was taken to isolate patients aged > 65 years as they were known to be affected more severely by COVID-19. Efforts were made to reduce the risk of infection spread by implementing the necessary measures aimed at reducing preoperative waiting time and accelerating discharge.

Statistical Analysis

Data obtained in the study were analysed statistically using SPSS for Windows vn. 15.0 software. Descriptive statistics were reported as number and percentage for categorical variables and as mean ± standard deviation (SD), minimum and maximum values for numerical variables. Rates in the groups were compared using the Chi-squared test. Multiple group comparisons of two of the numerical variables were made with the Kruskal-Wallis test, and the Mann-Whitney U-test was applied to subgroup analyses. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

Operations were performed in our clinic on 186 patients for orthopaedic trauma in Group 1, 262 patients in Group 2, and 261 patients in Group 3. The demographic data of the groups are shown in Table 1.

In Group 1, the 186 patients comprised 106 (56.9%) males and 80 (43.1%) females with a mean age of 45.2 years (range, 2-94 years); 46 (24.7%) in the ≤ 20 years age group, 78 (41.9%) in the 20-64 years age group and 62 (33.3%) in the ≥ 65 years age group. Operations were performed because of trauma on the upper extremity of 64 (34.4%) patients, on the lower extremity of 116 (62.4%), and on both upper and lower extremities of 6 (3.2%).

In Group 2, the 262 patients comprised 141 (53.8%) males and 121 (46.1%) females with a mean age of 47.1 years (range, 1-91 years); 84 (32.1%) in the ≤ 20 years age group, 122 (46.6%) in the 20-64 years age group and 56 (21.4%) in the ≥ 65 years age group. Operations were performed because of trauma on the upper extremity of 113 (43.1%) patients, on the lower extremity of 142 (54.2%), and on both upper and lower extremities of 7 (2.7%).

In Group 3, the 261 patients comprised 138 (52.8%) males and 123 (47.1%) females with a mean age of 46.1 years (range, 1-93 years); 65 (24.9%) in the ≤ 20 years age group, 116 (44.4%) in the 20-64 years age group and 80 (30.7%) in the ≥ 65 years age group. Operations were performed because of trauma on the upper extremity of 106 (40.6%) patients, on the lower extremity of 147 (56.3%), and on both upper and lower extremities of 8 (3.1%).

Examining the age distributions of the patients, a statistically significant difference was determined in Group 2, with the lowest number of patients in the > 65 years age group (56/262, 21.4%), and the most in the ≤ 20 years age group (84/262, 32.1%) (p = 0.035).

All the patients associated with 30-day mortality in all the groups were patients aged > 65 years with hip fracture. In Group 1, 5 patients, in Group 2, 3 patients, and in Group 3, 4 patients, died within 30 days. No significant difference was determined between the groups in respect of 30-day mortality (p = 0.460).

The cases were separated as low-energy and high-energy trauma. Fractures occurred as a result of high-energy trauma in 41/186 (22%) patients in Group 1, in 45/262 (17.2%) in Group 2, and in 44/261 (16.8%) in Group 3. No statistically significant difference was determined between the groups (p = 0.307).

When the mechanism of trauma was examined, no difference was determined between the groups in respect of the rate of traffic accidents (p = 0.890). A statistically significant difference was determined between the groups in respect of the numbers of falls from heights (p = 0.007). In the subgroup analyses, a statistically significant difference was determined between Group 1 and Group 2, and between Group 1 and Group 3 (p = 0.010).

The time from hospital admission to surgery was mean 3.76 ± 3.55 days in Group 1, 3.18 ± 3.08 days in

Table 1. *Demographic data and general information of the patients in the groups*

Total Patients (n)		**Group 1**	**Group 2**	**Group 3**
		186	262	261
Sex (n, %)	**Male**	106 (56.9%)	141 (53.9%)	138 (52.8%)
	Female	80 (43.1%)	121 (46.1%)	123 (47.2%)
Trauma Localization (n, %)	**Lower extremite**	116 (62.4%)	142 (54.2%)	147 (56.3%)
	Upper extremite	64 (34.4%)	113 (43.1%)	106 (40.6%)
	Lower + Upper	6 (3.2%)	7 (2.7%)	8 (3.1%)
Age (years) (n,%)	**≤ 20**	46 (24.7%)	84 (32.1%)	65 (24.9%)
	21-64	78 (41.9%)	122 (46.6%)	116 (44.4%)
	≥ 65	62 (33.3%)	56 (21.1%)	80 (30.7%)
Time to surgery (day), (Mean ± SD)		3.76 ± 3.55	3.18 ± 3.08	2.68 ± 2.33
Post-surgery hospital stay (day), (Mean ± SD)		2.83 (± 3.17)	2.78 (± 4.11)	2.81 (± 3.90)
30-day mortality rate (n, %)		5 (2.7%)	3 (1.1%)	4 (1.5%)
Trauma energy (n, %)	**High energy**	41 (22%)	45 (17.2%)	44 (16.8%)
	Low energy	145 (78%)	217 (82.8%)	218 (83.2%)

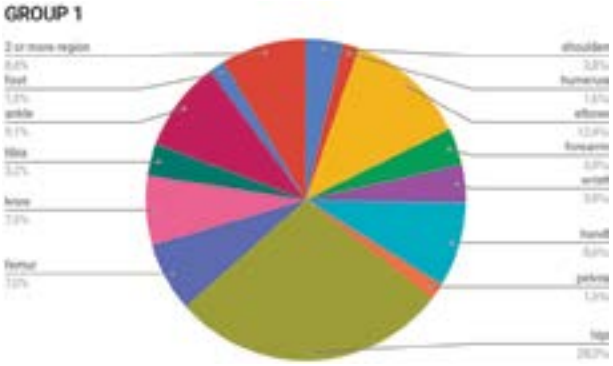


Figure 1. *Fracture localisation of the patients in Group 1*

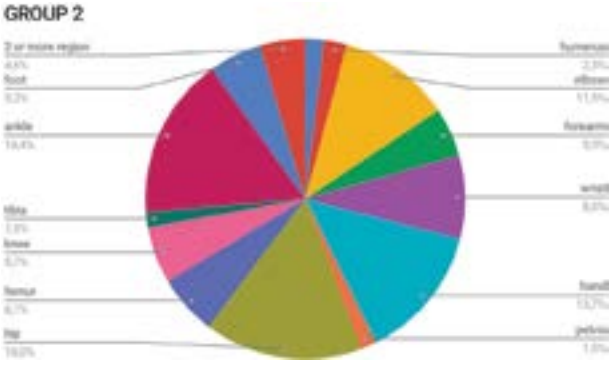


Figure 2. *Fracture localisation of the patients in Group 2*

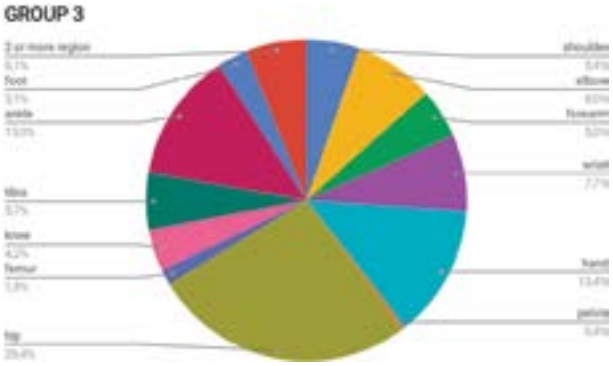


Figure 3. *Fracture localisation of the patients in Group 3*

Group 2, and 2.68 ± 2.33 days in Group 3 (p = 0.017). The length of postoperative stay in hospital was mean 2.83 ± 3.17 days in Group 1, 2.78 ± 4.11 days in Group 2, and 2.81 ± 3.90 days in Group 3 (p = 0.293). The preoperative time in the hospital was determined to be statistically significantly longer in Group 1 than in Group 3 (p = 0.004).

The patients aged > 65 years were compared in respect of the region of the traumatic fracture, and hip fractures were determined in 43/62 (69.4%) patients in Group 1, in 33/56 (58.9%) in Group 2, and in 60/80 (75%) in Group 3. No statistically significant difference was determined between the groups in respect of the rates of hip fractures in patients aged > 65 years (p = 0.137).

The distribution of the fracture localisation in the groups is shown in Figures 1-3. The number of cases of attempted suicide was 6 in Group 1, 3 in Group 2, and 3 in Group 3, with no statistically significant difference determined between the groups (p = 0.184).

DISCUSSION

The process of quarantine applied during the COVID-19 pandemic, which affected the whole world, was only applied as continuous quarantine to the < 20 years age group and the > 65 years age group in Turkey. In the later periods, with the aim of mobilisation, permission was granted to these individuals to go outside within walking distance of their home in specific time periods. At weekends and on official holidays, all age groups throughout the country were put into lockdown. The main aim of this study was to examine the effects of the COVID-19 pandemic and the quarantine on the distribution of orthopaedic trauma cases requiring surgery and the treatment processes and to discuss the pandemic in the light of literature from an orthopaedic perspective.

In comparison with the previous periods, a decrease in the number of trauma cases during the pandemics was recorded. However, despite this decrease, no difference was seen in the number of hip fractures in the elderly, which can occur as a result of trauma, such as a simple fall in the home. When the total trauma cases in the groups were examined, the vast majority were seen to be fractures in the hip region. This can be explained by the fact that hip fractures, especially in the elderly can be the result of minor trauma such as a simple fall at home. The number of cases of attempted suicide was seen to be 6, 3, and 3 in Groups, 1, 2, and 3, respectively. Although not to a statistically significant level, the number of attempted suicides was greater during the pandemic than in the other periods, which could be attributed to the activation of psychiatric disorders with the concerns of the pandemic and the quarantine process.

A study in Belgium reported a 32% decrease in trauma cases during the COVID-19 pandemic (16). In the current study, a total of 186 patients underwent surgery because of trauma during the pandemic, compared to 262 in Group 2, and 261 in Group 3. Thus a decrease of approximately 29% was determined in orthopaedic trauma cases during the pandemic and quarantine. When the reduction in cases was examined according to age groups, it was seen to be greater in the 20-64 years age group who were not included in the continuous quarantine. Although this seems to be con-

tradictory, it is thought that there was a reduced risk of workplace accidents during the pandemic because of flexible working hours and fewer people in the workplace. The reduction in orthopaedic trauma cases aged < 20 years is thought to be due to the restrictions on games and sports activities after school and at weekends. Furthermore, with the recommendation of the National Orthopaedics Association, cases where there was an option of conservative and surgical treatment, the conservative method should be applied to reduce the risk of COVID-19 infection spread, and this has also contributed to the decrease.

Of the 186 patients operated on in our clinic because of trauma during the pandemic, 62 were aged > 65 years, and of these 43 (69%) had a hip fracture. This rate of hip fracture in patients aged > 65 years was similar in Group 2 (n : 33,58%) and in Group 3 (n : 60,75%). No difference was determined between the groups in respect of patients aged > 65 years with a hip fracture. In a multi-centre study in Wuhan, China, it was reported that 58.3% of the fractures during the pandemic were hip fractures (17). In another single centre study in Belgium, it was reported that 23 (28%) of 80 trauma cases operated on during the pandemic were hip fractures in elderly patients (16). For reasons such as social distancing and restrictions on others entering the home if not necessary, there was thought to be an increase in jobs within the home undertaken by elderly individuals living alone, and therefore in future similar outbreaks or pandemics, the provision of social support is very important. There should also be more information and education given to the elderly about protective measures to be taken in these periods, such as sufficient lighting inside the house, sitting to take a bath, the use of non-slip shoes and slippers, and the techniques of slowly and carefully standing from a lying position.

In a multi-centre study in Spain during the pandemic, which evaluated mortality rates in hip fractures, it was reported that mortality developed in the follow-up period in 5 (4%) of 124 patients who were treated surgically and in 8 (66%) of 12 patients treated conservatively. In the same study, the mortality rate of COVID-19 patients was reported to be 7/23 (30.4%) (18). Another multi-centre study in New York reported 30-day mortality in 17/138 (12.3%) hip fracture patients (115 Covid negative, 17 Covid positive, 14 with suspected Covid), and the mortality rate for hip fractures in the previous year was 3/115 (3%) (19). Following surgery to hip fractures in elderly COVID-19 positive patients during the pandemic in Italy, Catellani et al. (20) reported 7-day mortality in 4 of 13 patients.

It can be understood from these studies that the mortality rate was increased because of the systemic effects created in patients with a weaker immune system such as the elderly with a hip fracture and a diagnosis of COVID-19. In contrast, in a study in Spain during the pandemic, the frequency of hip fractures and mortality rates were seen to be no different from those of previous periods (18). In the current study, 5 patients operated on because of hip fracture in the > 65 years age group in Group 1 during the pandemic, 3 patients in Group 2, and 4 patients in Group 3, were lost to 30-day mortality. According to these data, the frequency of hip fractures and mortality rates were similar in all three groups. Differences in the mortality rates in similar studies can be attributed to several reasons such as comorbidities.

That there was no increase in the mortality rates in the current study could also be associated with there not being COVID-19 positive patients as the test results of 9 suspected COVID patients were negative. In the study by Catellani et al. (20), although the mortality rate was high after surgery in COVID-19 positive patients, it was recommended that surgical treatment was applied early to these fractures during the pandemic for reasons such as patient mobilisation, the provision of physiological ventilation, and comfort in bed. We also believe that early surgery and early rehabilitation in COVID-19 positive or suspected patients was beneficial for the COVID-19 treatment, and therefore, surgery should be performed in the early period with the provision of the necessary protective equipment against the risk of COVID-19 infection spread.

Hospitals are high-risk areas in respect of infection spread during the pandemic. Moreover, the disease is known to be more severe in the elderly with higher morbidity and mortality rates (1, 7, 9, 11). Therefore, it is important that the preoperative preparation, treatment, and follow-up procedures are completed in as short a time as possible for all trauma patients, and especially for the elderly. In our clinic, it was aimed to reduce the length of stay in hospital to a minimal level for trauma patients during the pandemic. However, because of the potential requirement for intensive care, elective operations were postponed and the number of operating rooms was reduced. Accordingly, taking the existing precautions into consideration, there was only one operating room where it was possible to operate on orthopaedic trauma patients. In addition, there was a loss of manpower as orthopaedists were seconded to other clinics to deal with COVID-19 patients. The time from hospital admission to surgery was mean 3.76 ± 3.55 days in Group 1, 3.18 ± 3.08 days in Group 2, and 2.68 ± 2.33 days in Group 3, and thus it can be seen that there was no reduction in preoperative waiting time.

The preoperative waiting time of patients with 30-day mortality was seen to be mean 7.4 ± 1.81 (range,

5-10) days in Group 1, 3.66 ± 1.52 (2-5) days in Group 2, and 2.78 ± 1.70 (1-5) days in Group 3. The reason for the longer stay in hospital before surgery in Group 1 can be considered to be associated with prolonged evaluations because of the suspicion of COVID-19 positivity in 4 of the 5 patients who died. Vijay Kumar Jain et al. (21) reviewed COVID-19-positive trauma cases and recommended that especially because of proximal femur fractures and the presence of comorbidities in the elderly, early surgery in advanced centres with an intensive care unit would be more appropriate for the improvement of respiratory functions in this age group of patients.

Therefore, rather than postponing early surgery of fractures in patients aged > 65 years because of the suspicion of COVID-19, the implementation of conditions so that early surgery can be performed with the provision of the necessary PPE is of great importance in reducing morbidity and mortality. The physiological ventilation provided by early surgery and rehabilitation will be useful in improving the pulmonary functions affected by the COVID-19 virus. In addition, when planning internal and external hospital assignments in possible future outbreaks, it was seen that despite flexible working arrangements and quarantine, the workload of orthopaedic trauma cases during the pandemic continued in a course near to that of normal periods. Therefore, operating room conditions should be planned and organised accordingly. In this way, the preoperative waiting time can be reduced with arrangements to be made, and by increasing patient circulation, the risk of infection spread within the hospital can be reduced, and working conditions can be made easier.

There were some limitations to this study, primarily the retrospective design. Another limitation could be said to be that the 30-day follow-up was short for the examination of mortality, and comorbid diseases and the treatments applied were not compared. However, as the information records system of the patients is kept well there was no loss of data, and the fact that this was a single-centre study, unlike the majority of studies that have compared trauma cases during the COVID-19 pandemic, can be considered strong aspects of the study.

CONCLUSION

With the whole world affected by the COVID-19 pandemic, changes in daily life habits have led to many changes in healthcare management, hospital working organisation and the approach to patients, and these changes are continuing. Although the effect of the pandemic has decreased in some countries, as no definitive treatment or vaccine has yet been found, there is an increased risk of virus spread as a second wave, and there are concerns of further restrictions such as quarantine. Just as in examples from around the world, the results of this study showed that although there was a slight decrease in orthopaedic trauma cases, they continued at the rate of 71% during the pandemic. When it is considered that the priority in dealing with the virus is to reduce the spread of infection, it is important that hospital treatments and discharge of patients are completed in as short a time as possible. Therefore, when planning pandemic interventions, there must be an awareness that the workload of orthopaedic trauma will continue, and a shorter length of stay in hospital will significantly reduce the risk of COVID-19 infection spread.

Acknowledgment

None.

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Sažetak

UPOREĐIVANJE SLUČAJEVA ORTOPEDSKE TRAUME OPERISANIH TOKOM PANDEMIJE KOVID-19, SA RAZLIČITIM PERIODIMA: STUDIJA JEDNOG CENTRA

Akalın Yavuz, Ulusaloglu Can Armagan, Avci Ozgur, Cevik Nazan, Guler Olcay Burak, Ozturk Alpaslan

Health Sciences University, Bursa Yuksek Ihtisas Research and Training Hospital
Department of Orthopedics and Traumatology, Yıldırım, Bursa, Turkey

Uvod: Uporediti slučajeve ortopedske traume hirurški lečene u našoj klinici tokom pandemije KOVID-19 u Turskoj sa hirurški lečenim slučajevima traume u prethodnim periodima i razmotriti ih kroz literaturu.

Materijali i metode: Upoređeni su podaci o pacijentima iz 3 različita vremenska perioda. Grupa 1 obuhvatila je slučajeve u vremenskom periodu od 11. marta do 30. maja, kada je bolnica radila kao pandemijska bolnica za vreme pandemije KOVID-19 u Turskoj. Grupa 2 obuhvatala je slučajeve iz ekvivalentnog vremenskog perioda godinu dana pre pandemije, za koje se smatralo da imaju slične karakteristike pacijenta, a grupa 3 pokrivala je vremenski period neposredno pre 11. marta kada je KOVID-19 bio poznat u svetu, ali nije bilo dijagnostikovanih slučajeva u Turskoj. Operacije su rađene u našoj klinici zbog ortopedske traume i to: 186 pacijenata u grupi 1, 262 pacijenta u grupi 2 i 261 pacijentu u grupi 3.

Rezultati: Primećen je pad od 29% u slučajevima traume tokom pandemije. U grupi 1, 62 od 186 pacijenata bilo je starije od 65 godina, a 43 od njih (69%) imalo je prelom kuka. U grupi 2, 33 (58%) pacijenta starija od 65 godina operisano je zbog preloma kuka, a u grupi 3, 60 (75%) pacijenata. Vreme od prijema u bolnicu do operacije bilo je prosečno 3,76 ± 3,55 dana u grupi 1, 3,18 ± 3,08 dana u grupi 2 i 2,68 ± 2,33 dana u grupi 3 (p = 0,017). Broj slučajeva pokušaja samoubistava bio je 6, 3, 3, u naše tri grupe (p = 0,184). 30-dnevni mortalitet utvrđen je u 5, 3, odnosno 4 slučaja (p = 0,460).

Zaključak: Tokom pandemije primećen je pad broja slučajeva traume. Međutim, nije došlo do velikog smanjenja preloma kuka kod starijih pacijenata uprkos karantinu starijih od 65 godina. Radna snaga klinike bila je podeljena tokom pandemije na one koji rade na dijagnozi i praćenju slučajeva KOVID-19, i na one koji nisu, tako da nije došlo do smanjenja opterećenja ortopeda, jer je operacija trauma nastavljena po stopi od 71%. Stoga je veomo važno primeniti stroge propise koji će smanjiti rizik od širenja infekcije i primena multidisciplinarnog toka rada za brže otpuštanje pacijenata sa traumom.

Ključne reči: pandemija KOVID-19, trauma, prelom kuka, karantin.

REFERENCES

1. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020; 579(7798): 265–9. doi: 10.1038/s41586-020-2008-3.

2. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W et al. A pneumonia outbreak associated with a new corona virus of probable bat origin. Nature. 2020; 579(7798): 270–3. doi: 10.1038/s41586-020-2012-7.

3. The Lancet Infectious Diseases. COVID-19, a pandemic or not? Lancet Infect Dis. 2020; 20(4): 383. doi: 10.1016/S1473-3099(20)30180-8.

4. Trilla A, Trilla G, Daer C. The 1918 "Spanish Flu" in Spain. Clin Infect Dis. 2008; 47(5): 668–73. doi: 10.1086/590567.

5. Webster RG, Govorkova EA. Continuing challenges in influenza. Ann N Y AcadSci. 2014; 1323(1): 115–39. doi: 10.1111/nyas.12462.

6. Sarac NJ, Sarac BA, Schoenbrunner AR, Janis JE, Harrison RK, Phieffer LS, et al. A review of state guidelines for elective orthopaedic procedures during the COVID-19 Outbreak. J Bone Joint Surg Am. 2020; 102(11): 942–5. doi: 10.2106/JBJS.20.00510.

7. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of corona virus disease (COVID-19) outbreak. J Autoimmune. 2020; 109: 102433. doi: 10.1016/j.jaut.2020.102433.

8. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on corona virus disease 2019 (COVID-19) outbreak - an update on the status. Mil MedRes. 2020; 7(1): 11. doi: 10.1186/s40779-020-00240-0.

9. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J Infect. 2020; 80(6): e14–8. doi: 10.1016/j.jinf.2020.03.005.

10. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med. 2020; 382(18): 1708–20. doi: 10.1056/NEJMoa2002032.

11. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult patients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229): 1054–62. doi: 10.1016/S0140-6736(20)30566-3.

12. Rodrigues-Pinto R, Sousa R, Oliveira A. Preparing to perform trauma and orthopaedic surgery on patients with COVID-19. J Bone Joint Surg Am. 2020; 102(11): 946-50. doi: 10.2106/JBJS.20.00454.

13. Chang Liang Z, Wang W, Murphy D, Po Hui JH. Novel Coronavirus and orthopaedic surgery: early experiences from Singapore. J Bone Joint Surg Am. 2020; 102(9): 745-749. doi: 10.2106/JBJS.20.00236.

14. Ti LK, Ang LS, Foong TW, Ng BSW. What we do when a COVID-19 patient needs an operation: operating room preparation and guidance. Can J Anaesth. 2020; 67(6): 756–8. doi: 10.1007/s12630-020-01617-4.

15. Ozturk K, Unkar EA, Ozturk AA. Perioperative management recommendations to resume elective orthopaedic surgeries for post-COVID-19 "new normal": Current vision of the Turkish Society of Orthopaedics and Traumatology. Acta Orthop Traumatol Turc. 2020; 54(3): 228-33. doi: 10.5152/j.aott.2020.20183.

16. Hernigou J, Morel X, Callewier A, Bath O, Hernigou P. Staying home during "COVID-19" decreased fractures, but trauma did not quarantine in one hundred and twelve adults and twenty eight children and the "tsunami of recommendations" could not lockdown twelve elective operations. Int Orthop. 2020; 44(8): 1473-80. doi: 10.1007/s00264-020-04619-5.

17. Zhu Y, Chen W, Xin X, Yin Y, Hu J, Lv H, et al. Epidemiologic characteristics of traumatic fractures in elderly patients during the outbreak of coronavirus disease 2019 in China.

Int Orthop. 2020; 44(8): 1565-70. doi: 10.1007/s00264-020-04575-0.

18. Munoz Vives JM, Jornet-Gibert M, Camara-Cabrera J, Esteban PL, Brunet L, Delgado-Flores L, et al. Mortality rates of patients with proximal femoral fracture in a worldwide pandemic: preliminary results of the Spanish HIP-COVID observational study. J Bone Joint Surg Am. 2020;102(13): e69. doi: 10.2106/JBJS.20.00686.

19. Egol KA, Konda SR, Bird ML, Dedhia N, Landes EK, Ranson RA, et al. Increased mortality and major complications in hip fracture care during the COVID-19 pandemic: a New York city perspective. J Orthop Trauma. 2020; 34(8):395-402. doi: 10.1097/BOT.0000000000001845.

20. Catellani F, Coscione A, D'Ambrosi R, Usai L, Roscitano C, Fiorentino G. Treatment of proximal femoral fragility fractures in patients with COVID-19 during the SARS-CoV-2 outbreak in Northern Italy. J Bone Joint Surg Am. 2020; 102(12): e58. doi: 10.2106/JBJS.20.00617.

21. Kumar Jain V, Lal H, Kumar Patralekh M, Vaishya R. Fracture management during COVID-19 pandemic: A systematic review. J Clin Orthop Trauma. 2020; 11 (Suppl 4): S431-41. doi: 10.1016/j.jcot.2020.06.035.

Correspondence to/Autor za korespondenciju
Alpaslan Ozturk MD
Professor of Orthopaedics and Traumatology
Health Sciences University,
Bursa Yüksek IhtisasResearchand Training Hospital
Department of OrthopedicsandTraumatology,
Yıldırım, Bursa, Turkey.
Orcid: 0000-0001-7362-0284
Cell: +905323531031
Fax number: +902242955497
e-mail**:** ozturkalp16@gmail.com; alpaslan.ozturk@sbu.edu.tr

SANAMED
2021; 16(1): 19–27
ISSN-1452-662X

DOI: 10.24125/sanamed.v16i1.481
UDK:616.98:578.834(560)
616-089(560)
ID:37377289
Original article

THE EFFECT OF COVID-19 PANDEMIC ON THE FUNCTIONING OF A SURGICAL CLINIC: SINGLE CENTRE EXPERIENCE IN TURKEY

Ferahman Sina,[1] Donmez Turgut,[1] Surek Ahmet,[1] Akarsu Cevher,[1] Aydin Husnu,[1] Seyit Hakan,[1] Ozcevik Halim,[2] Tecir Harun,[1] Karabulut Mehmet[1]

[1] Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Department of General Surgery, Istanbul, Turkey
[2] Istanbul Provincial Health Directorate, Department of General Surgery, Istanbul, Turkey

Primljen/Received 04. 12. 2020. god.

Prihvaćen/Accepted 25. 01. 2021. god.

Abstract: **Introduction:** Covid-19 is a viral epidemic disease that causes serious health problems and death worldwide. The rapid expansion of Covid-19 infection led to the disruption of healthcare services and radical re-organisation of healthcare resources due to the healthcare workers' infection.

Aim: This clinical study investigated the effects of Covid-19 infection on emergency and elective cases in our general surgery clinic.

Material and methods: We retrospectively analysed the clinical data of 195 patients who underwent elective (Group Elective) and emergency (Group Emergency) surgery during the Covid-19 incubation period in the Bakırköy Dr. Sadi Konuk Training and Research Hospital between March 11 - May 18, 2020. Demographic features, symptoms, surgical diagnoses, surgical methods, complications, duration of surgery, length of hospital stay and mortality, the status of Covid-19 of all patients were recorded.

Results: 195 patients, including emergency and elective surgery cases, were operated on (104 and 91, respectively). The incidence of Covid-19 infection was 5.49% in patients scheduled for elective surgery and 4.8% in patients operated urgently, and all developed in the postoperative period. Two patients with emergency surgery died of respiratory failure, their mean age was 51 years. Two of 104 emergency-operated patients were positive from Covid-19 (1.92%) at the time of admission. Eighteen medical staff and nurses got Covid-19 infections.

Conclusions: Due to the rapid spread of Covid-19 infection, early precautions must be taken in surgical clinics to guarantee the safety of patients all healthcare providers, and personnel.

Key Words*:* Covid-19, General Surgery, Emergency, Operation.

INTRODUCTION

Following the notification of the first serious coronavirus disease 2019 (Covid-19) cases in Wuhan, China in December 2019, the virus began to spread all over the world, and this Covid-19 viral outbreak was declared a pandemic by the World Health Organisation (WHO) on March 11 (1). Studies show that 2% of the population are asymptomatic carriers of Covid-19 and these viruses are responsible for about 5% to 10% of acute respiratory infections (2, 3). Patients initially present with the complaint of fever with or without pulmonary symptoms, but varying degrees of pulmonary pathologies are detected with thorax computed tomography (CT) (4, 5, 6). Although it is mostly a common and mild disease in patients, approximately 15-20% of patients develop severe disease, and oxygenation is required in this severely ill group (6). This severe group has a high mortality rate and co-morbidities such as advanced age, diabetes mellitus, and medical procedures (such as endoscopic procedures, angiography procedures, and elective surgeons who operate and are infected in a hospital setting) increase mortality rate (6). The pathogenic mechanism leading to pneumonia appears complex. Data from studies show that viral infection causes an excessive immune reaction in the host. It produces a reaction that leads to extensive tissue damage, defined as a "cytokine release storm" (CRS). The main factor in this storm is interleukin 6 (IL-6). IL-6 is produced by activated leukocytes and acts on a large number of cells and tissues. It also stimulates the production of acute-phase proteins and plays an important role in thermoregulation, bone structure, and functionality of the central nervous system. IL-6 has anti-inflammatory effects in addition to its pro-inflammatory role. However, IL-6 also increas-

es in inflammatory diseases, infections, autoimmune disorders, cardiovascular diseases, and some types of cancer. It is also seen in the pathogenesis of CRS, an acute systemic inflammatory syndrome characterised by fever and multiple organ failure (7).

Governments are working hard to take measures to prevent the devastating effects of the Covid-19 pandemic. Many uncertainties persist regarding both the virus-host interaction and the trend of the outbreaking of the virus, such as when the outbreak will reach its peak, and the dangers of the 2nd or 3rd wave epidemics. Like all countries in the world, the Republic of Turkey Ministry of Health took extraordinary measures to get viral spread under control. As of March 11, 2020, when the first case was reported in Turkey, travel restrictions were introduced for all countries of the world where the epidemic had caused serious destruction, and then to other countries because of the spread of the epidemic. Elective surgical operations were stopped in all hospitals except for cancer patients. As a result, all surgical services in the surgical department were stopped, except for endoscopy and cancer cases with outpatient and oncological emergencies. However, the emergency room continued to accept surgical patients. All surgical branch physicians joined the Covid-19 treatment and follow-up team.

In parallel with the progressive increase in Covid-19 cases and lung findings consistent with Covid-19 in our society, patients with suspected Covid-19 infection started to be detected in the general surgery service parallel with the increase in consultations in the emergency department. Initial infection cases were recorded among surgical service nurses.

In this study, descriptive analysis was conducted about the impact of the first two months of the Covid-19 pandemic in the General Surgery department of a tertiary hospital in Istanbul (Turkey). The aim of this study was to analyse the surgical cases in the general surgical ward when the incidence of the Covid-19 epidemic increased in general population, to investigate the effect of the infection on the health services, and to evaluate the effect of the measures taken.

MATERIAL AND METHODS

Between March 11 and May 18, data were prospectively collected from the General Surgery service in Bakırköy Dr. Sadi Konuk Training and Research Hospital from patients in a clinic confirmed with Covid-19 and among surgeons with confirmed Covid-19. It is a 380-bed state hospital. There are 18 surgical residents, eight doctors, one professor, and 15 general surgery specialists in the General Surgery and Digestive Surgery Service.

This study was carried out in accordance with the 1964 Helsinki Declaration and its recent amendments. Written consent was obtained from all participants. Permission was obtained from the local ethics committee (Ref. Nr: 2020-09) and the Ministry of Health Scientific Research Institution (Ref. Nr: 2020-05-06T09_16_49).

The presence of at least one of the following symptoms: the onset of cough, shortness of breath, throat pain, chest pain, anosmia, muscle pain, or fever was accepted as compatible with Covid-19 (1). Suspected cases were confirmed with the reverse transcription-polymerase chain reaction (RT-PCR) technique using a nasopharyngeal swab sample (according to the method of the microbiology laboratory in the hospital). Patients and doctors with negative RT-PCR but maintaining clinical compatibility with Covid-19 had repeated their diagnostic tests with RT-PCR. Radiological signs compatible with Covid-19 were ground-glass appearance, diffuse alveolar consolidation pattern, bilateral patchy shading, and cobblestone pattern which were considered consistent with Covid-19 pneumonia. RT-PCR (+) or thoracic CT Covid-19 pneumonia findings (+) patients with any (+) received Covid-19 diagnosis and treatment.

Patients who were operated on during the Covid -19 pandemic in the General Surgery Clinic were divided into two groups as planned surgery (group elective) and emergency surgery (group emergency). Demographic features, symptoms, surgical diagnosis, surgical methods, complications, duration of surgery, length of hospital stay, and mortality of all patients were recorded. Laboratory and radiological evaluations were recorded.

Statistical analysis

Statistical analysis was performed with JMP® software version 9.0.1 (SAS® Institute, Inc, Cary, North Carolina, USA). Patient characteristics were analysed via descriptive statistics. Continuous variables were expressed as mean ± SD or median and interquartile ranges. Categorical variables were expressed as frequencies and percentages. Comparison of parametric continuous variables was performed using Student's t-test. The Mann-Whitney U test was used for non-parametric continuous variables. The Chi-square test was used for the comparison of categorical variables. p-values of 0.05 or less were considered statistically significant.

RESULTS

The usual healthcare service continued from March 11 to March 31, and surgical procedures for benign pa-

Table 1. *Patient characteristics and operative results*

	Emergency surgery (n: 104)	**Elective surgery (n: 91)**	**p value**
Age (y) (mean ± SD)	43.82 ± 19.45	54.53 ± 14.33	< 0.001
Gender Female/male	54/50	42/49	0.421
BMI* kg/m2 (mean ± SD)	26.24 ± 2.92	26.73 ± 3.21	0.192
ASA score**			
I	44	11	< 0.001
II	34	44	
III	23	32	
IV	3	4	
Comorbidity	37	66	< 0.001
Hypertension	18	31	
Diabetes Mellitus	9	19	
Cardiovascular disease	5	9	
Cerebrovascular disease	3	1	
COPD†	2	5	
Chronic kidney disease	0	1	
Surgical Time (min) (mean ± SD)	62.14 ± 26.43	152.24 ± 107.63	< 0.001
Hospital stay (day) (mean ± SD)	4.62 ± 0.56	5.86 ± 0.6	0.156
Preoperative covid-19 (+)	2 (1.92%)	0	0.098
Postoperative covid-19 (+)	5 (4.80%)	5 (5.49%)	0.416
Mortality	6 (5.76%)	8 (8.79%)	0.500
Covid-19 (+)	2 (1.92%)	0	
Covid-19 (-)	4 (3.84%)	8 (8.79%)	

*BMI: Body mass index, **ASA: American Society of Anesthesiologists, †COPD: Chronic obstructive pulmonary disease.

thologies were suspended from March 31. From March 31, patients with oncological pathology and emergency surgical cases were operated on.

The demographic data of the patients are given in Table 1. There was no statistically significant difference between the two groups in terms of gender, body mass index, and length of hospital stay. A statistically significant difference was detected between the two groups in terms of the American Society of Anesthesiologists (ASA) score and concomitant diseases ($p < 0.001$) (Table 1).

Between March 11 - May 18, 2020, 195 patients were operated on in the General Surgery Service, 104 were urgent and 91 were planned surgical cases (Table 2).

In emergency cases, laparoscopic appendectomy was the most performed surgery due to acute appendicitis, and emergency cases due to colon cancer were identified in second place. Among the planned surgeries, the most common surgery was identified as colorectal cancer cases (Table 2).

Emergency cases (colostomy necrosis, acute perforated diverticulitis, multiple small bowel perforations, toxic megacolon, and acute mesenteric ischemia) and elective cases (morbid obesity, splenectomies, adrenal adenoma, clastic skin cancer, hydatid cysts, and nutrition gastrostomy) were examined.

The age group was significantly higher in the elective surgery group than in the emergency surgery group ($p < 0.001$) (Table 1).

The mean age of Covid-19 positive patients undergoing planned surgery was 54.5 years, and the mean age of patients undergoing emergency surgery was 43.8 years ($p < 0.001$). Of infected patients, 56.25% were male. The most common comorbidities among these patients were hypertension (HT), diabetes mellitus (DM), and cardiovascular diseases, respectively (Table 1).

In terms of the duration of surgery between the two groups, it was found to be significantly higher in the elective surgery group compared to the emergency surgery group ($p < 0.001$) (Table 1).

There was no statistically significant difference between the two groups in terms of contracting postoperative Covid-19 (+) disease and mortality ($p =$

Table 2. *Distribution of cases in covid-19 pandemic*

Variable	Emergency surgery (n: 104)	Elective surgery (n: 91)	Total (n: 195)
Cholelithiasis (LC)	5	11	16
Abdominal wall hernia	5	4	16
Open technique	5	4	9
Laparoscopic	0	7	7
Colorectal cancer	13	20	33
Open technique	13	12	25
Laparoscopic/Robotic	0	8	8
Gastric Cancer (Open technique)	1	4	5
Peptic ulcus perforation	11	–	11
Open technique	6	–	6
Laparoscopic	5	–	5
Acute Appendicitis (LA) (UAA/CAA)	36/10	–	46
Pancreas cancer (Open Technique)	–	4	4
Breast cancer	–	16	16
Thyroid Cancer	–	9	9
Retroperitoneal sarcoma	–	2	2
Fournier gangrene	4	–	4
Benign anorectal disease	–	7	7
Gunshot injury	2	–	2
Blunt abdominal trauma	3	–	3
Intraabdominal knife injury	5	–	5
Others	8	7	15

*LC: Laparoscopic cholecystectomy, †LA: Laparoscopic appendectomy, ‡UAA: uncomplicated acute appendicitis, §CAA: complicated acute appendicitis.

0.416, p = 0.50, respectively) RT-PCR (+) and thorax CT (+) were two or two (+), and two of seven patients requiring emergency surgery were preoperatively Covid-19 (+). The first patient, a 49-year-old male with diabetes mellitus disease, was operated on due to Fournier gangrene in the bilateral inguinal region with RT-PCR + and thorax CT (-) ASA II. The patient, who was followed up in the postoperative ward, received Covid-19 treatment for seven days and vacuum-assisted wound closure (VAC) was applied three times. He was discharged after healing. In the second patient, a laparoscopic Miles operation was performed in October 2019 because of an anal canal tumor, and the ASA III case had segmented colon resection with end colostomy operation due to necrosis. The patient had preoperative thorax CT (+), RT-PCR (-) and Covid-19 treatment was additionally applied. He was discharged on the 10th day with healing.

In the postoperative period, for 102 patients undergoing other emergency surgeries, one patient had RT-PCR (+) and thorax CT (+), three patients had Thorax CT (+) and one patient had RT-PCR (+) for Covid-19 (7.14%). Two patients died in the postoperative intensive care unit (ICU). The first patient, a 51-year-old female patient, who was ASA IV, underwent perforation repair + mentoplasty due to peptic ulcer perforation(PUP), followed in ICU on the third day, thorax CT (+) - RT-PCR (-) and died on the 5th day. The second patient, a 51-year-old male patient with ASA III, underwent massive small bowel resection due to mesenteric panniculitis + multiple small bowel perforations as acute abdomen (Table 1).

In the emergency surgery group, the other three patients who developed a Covid-19 infection after surgery were discharged with healing after receiving additional treatment (Table 3).

Covid-19 was present in five(5.49%) of 91 patients who underwent planned surgery (Table 1). Between March 11 and May 15, 17 patients who underwent scheduled hospitalisation showed respiratory symptoms and fever between the 2nd and 8th postoperative days, all of them received RT-PCR and thorax CT, and

Table 3. *Data of patients with covid-19 infection in the postoperative period*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	No (%)
Age, years	51	86	61	56	51	55	56	62	67	58	N/A
Gender, Female/male	Female	Female	Male	Male	Male	Male	Male	Female	Female	Male	N/A
Comorbidities											
Cardiovascul. disease	No	No	No	No	Yes	No	No	No	No	No	1 (10)
Malignancy	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	9 (90)
Hypertension	No	Yes	Yes	Yes	No	Yes	No	No	No	Yes	5 (50)
Diabetes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	9 (90)
Cerebrovascul disease	No	Yes	No	No	No	No	No	No	No	No	1 (10)
COPD	No	Yes	No	No	No	No	No	No	No	No	1 (10)
ASA Class	IV	IV	III	III	III	III	III	III	III	III	N/A
Diagnosis	PUP	GC	CP-SCC	OCC	MSBP	DRC	SCC-CVF	PHC	DPC	DCC	N/A
Surgical type	Emergency	Emergency	Emergency	Emergency	Emergency	Elective	Emergency	Elective	Elective	Elective	N/A
Surgical treatment	GR-O	DSG	SCR-H	LC	MSBR	RLAR	SCR-VR	Whipple	DP-S	LH	N/A
Surgical time, min	74	190	145	65	175	162	286	285	180	134	N/A
ICU	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No	6 (60)
Day of first sypmtom	3	4	5	5	2	6	8	5	3	3	N/A
First symptom or sign	Fever	Cough	Cough	Cough	Fever	Fever	Cough	Fever	Cough	Fever	N/A
RT-PCR test	Negative	Positive	Negative	Negative	Positive	Negative	Positive	Positive	Positive	Positive	6 (60)
Toraks BT (Covid-19)	Positive	Positive	Positive	Positive	Negative	Positive	Positive	Negative	Negative	Positive	7 (70)
Complications											
Respiratory failure	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No	6 (60)
ARDS	No	No	No	No	Yes	No	No	No	No	No	1 (10)
Shock	Yes	No	No	No	Yes	No	No	No	No	No	2 (20)
Arrhythmia	Yes	No	No	No	No	No	No	No	Yes	No	2 (20)
Secondary infection	No	No	Yes	Yes	No	Yes	Yes	No	No	No	4 (40)
Mortality	Yes	No	No	No	No	No	No	No	No	No	2 (20)
Day of death	5	–	–	–	8	–	–	–	–	–	N/A
Hospital stay (day)	–	12	12	13	–	14	22	15	10	10	N/A

Abbreviations: COPD; Chronic obstructive pulmonary disease, ASA Class; American society of anesthesiologists classification, PUP; Peptic ulcus perforation, GC; Gastric cancer, CP-SCC; Colon perforation with sigmoid colon cancer, OCC; Obstructive colon cancer, MSBP; Multipl small bowel perforation, DRC; Distal rectum cancer, SCC-CVF; Sigmoid colon cancer with colovesical fistula, PHC; Pancreas head cancer, DPC; Distal pancreas cancer, DCC; Descenden colon cancer, DSG; Distal subtotal gastrectomy, SCR-H; Sigmoid colon resection + hartman procedure; GR-H;Grahamrafi + omentoplasty, LC; Loop colostomy, MSBR; Massive small bowel resection, RLAR; Robotic low anterior resection, SCR-VR; Sigmoid colo nresection + near total vesical resection, DP-S; Distal pancreatectomy + splenectomy, LH; Left hemicolectomy, ICU; Intensive Care Unit, ARDS; Acute Respiratory Distress Syndrome.

the patients used surgical masks from the moment of suspicion. In five cases, Covid-19 infection was confirmed (RT-PCR and thorax CT). The first patient, a 56-year-old ASA III male patient underwent colon resection + nearly total bladder resection + ileal bladder surgery for a sigmoid tumor with colovesical fistula. On the 5thpostoperative day, an intra-abdominal abscess was repeated, and on the 8th postoperative day RT-PCR (+)/ thorax CT (+), and Covid-19 treatment was started. He was discharged on the 22nd postoperative day. The other four patients who developed Covid-19 infection after surgery in the elective group were discharged with healing after receiving additional treatment (Table 3).

Confirmed Covid-19 patients were treated with an infection and pneumology team in a separate isolated room with clinical follow-up according to hospital protocol. None of these patients had to receive intensive care because of clinical deterioration and five patients were discharged.

Nineteen days after low anterior resection surgery due to rectum cancer, a patient aged 74 years was admitted with symptoms of fever and cough, and was

hospitalised due to bilateral Covid-19 pneumonia with RT-PCR (+) and Thorax CT (+) and treated in the infection clinic. This contamination was probably achieved in the community because it was beyond the maximum 14-day incubation period defined for Covid-19.

From March 11 to May 18, 104 emergency surgical interventions were carried out. Interventions were performed in 10 patients due to perforated appendicitis, 11 patients due to PUP, 4 patients due to large bowel tumor perforation, one patient for bowel perforation, and one patient for diverticulitis perforation. In other words, 26% of 104 patients who underwent emergency surgery since March 11 had a presentation of peritonitis at diagnosis.

During this period, consultations for Covid-19 patients with potential surgical pathology were also performed. Seven patients were evaluated: two had acute cholecystitis and two had appendicular plastron treated conservatively with antibiotics. The hernias of two patients who had incarcerated inguinal hernias were rejected. Conservative treatment was performed for one patient with a hematoma of the rectus sheath. Therefore, conservative treatment was provided for all patients with Covid-19 infection who were potentially hospitalised with surgical pathology.

The effects of the Covid-19 pandemic on healthcare workers were examined in the General Surgery Service and the operating room. These included five ward nurses, two operating room nurses, four anaesthesia residents, two anaesthesiologists, three operating room personnel, and two ward personnel. Eight (50%) of these employees were hospitalised and treated because they had serious problems. They were discharged with healing. Ten others spent the duration with Covid-19 in their homes asymptomatically.

Serious measures were taken since March 11. These measures include the suspension of clinical sessions and face-to-face multidisciplinary committees, wearing protective equipment and hospital shoes, surgical masks, face visors, avoiding touching the face, washing common work surfaces and washing in and out of the hospital before and after each patient. Washing hands with hydroalcoholic solution was tightly applied even when wearing gloves.

DISCUSSION

As an epidemic, the Covid-19 pandemic originated in Wuhan city in the People's Republic of China, and spread to Europe and the entire world, especially in neighbouring countries. After the detection of Covid-19 in Europe, Iran and Saudi Arabia in February, security and health screenings were increased at airports and border gates.

After the first identification of a citizen, who visited Europe, in Istanbul on March 11, education was interrupted, from early childhood education to university education, and the distant education program was started on March 16.

From March 11, when Covid-19 infection was announced, to May 18, 150.593 cases and 4.171 deaths were reported in the 80 million population in our country. Istanbul is the most populous city in the country with a population of 16 million, and it is the city where 60% of Covid-19 cases and deaths occurred due to being a center of tourism and trade.

In addition, all face-to-face meetings in the Bakırköy Dr. Sadi Konuk Hospital and all other hospitals were suspended from March 11 and these meetings were held by teleconference. Surgical interventions and surgeries planned for benign pathologies were suspended as of March 31 (8), and emergency or non-oncological consultation of our general surgery clinic was canceled. Precautionary measures were increased among hospital health and administrative staff. All appointments and procedures, except for emergency procedures, were canceled in the endoscopy section.

As of March 31, elective surgeries were planned for cancer patients who had the highest priority cases due to the risk of early complications and did not show fever or active respiratory pathology at the time of admission or in the previous days, with a negative Covid-19 test and no direct contact with Covid-19 (+) cases.

The Covid-19 epidemic has had a major impact on health worldwide. A) The importance of quarantine and home isolation of healthcare workers after Covid-19 transmission reduced the current workforce in healthcare and assistance among branches, B) There were significant reductions in the number of patients going to the emergency department during the epidemic period. Real emergency patients with emergency surgical pathology (appendicitis, cholecystitis, diverticulitis etc.) and with more or complex symptoms, reduced burden in surgical wards. C) There were reductions in planned surgical activity in cancer patients, selecting all cases with risk of obstruction or perforation and all elective surgeries for benign pathology were suspended (10).

In our highly suspected or confirmed Covid-19 patient series, five planned surgeries and seven urgent surgeries were performed. Two of the patients operated urgently died. The 1st patient, a 51-year-old female, was ASA IV with open raphy + omentoplasty surgery due to PUP and died on the 5th postoperative day in the ICU. The other patient who was operated due to acute abdomen and was treated in the ICU died on the 8th day. Other patients who were operated surgically

and operated on a planned basis had varying respiratory symptoms, but all responded to medical treatment in a regular hospital room without need for orotracheal intubation.

We cannot conclude that Covid-19 infection is the differential element between both patient groups, because the mean age, surgical diagnosis, and clinical severity of each group do not allow us to compare both groups.

In case of confrontation with the Covid-19 pandemic, it is preferable to turn to existing alternatives (antibiotic therapy, percutaneous drainage, cholecystitis, stent placement or delayed surgery) until the disease is less common for both emergency surgery and elective cancer patients (10, 11).

In hospitals serving in a region with high Covid-19 cases, it is recommended that all patients be scanned preoperatively with RT-PCR and/or chest CT for cases undergoing elective cancer surgery and emergency surgery (12). In this epidemic period, it is important for the patient to get the best available treatment (percutaneous drainage, antibiotic therapy, laparoscopy or laparotomy) as well as the necessary protective measures (8). However, there is a significant problem regarding open or laparoscopic method for the selection of the surgical technique for the patient. Since CO2 pneumoperitoneum is used in robotic, laparoscopic and single-port techniques, it poses serious risks for both the patient and the medical team. This is because aerosols formed during the operation tend to concentrate in the abdominal cavity because of the low gas mobility in pneumoperitoneum. Sudden release of trocar valves, airtight instrument replacement, and even small abdominal extraction incisions can expose the medical team to pneumoperitoneum aerosols. The risk due to laparoscopy is definitely higher than traditional open surgery (13, 14). If the operation is to be performed laparoscopically, it is recommended that the patient is kept at a low pressure and in trendelenburg oscillation as much as possible (14). In our clinic, we performed the laparoscopic technique in cases of acute appendicitis and acute cholecystitis and left the patient in trendelenburg position and low pressure (8 mmHg). While we performed emergency and elective surgery for colon cancer with the open method, we performed robotic surgery for elective rectum cancer cases. We did not detect Covid-19 cases in any of these patients.

In our study, our mortality was 12 (6.15%) patients with seven (3.58%) patients among emergency cases and five (2.57%) patients among elective cases (Table 1). Among emergency cases, two patients with postoperative Covid-19 (+) died. The first of these patients was a 51-year-old operated for breast cancer who underwent omentoplasty due to PUP and had ASA IV with bone, lung and liver metastases. The other patient had a massive small bowel resection due to multiple small bowel perorations with connective tissue disease. We do not think that these patients died primarily due to Covid-19. Preoperative and postoperative Covid-19 (-) in patients who died were elective cases.

There was no death among our Covid (+) patients in the postoperative period, who were operated electively. In a clinical study conducted by Lei et al., seven patients out of 34 patients with Covid-19 (+) after emergency and elective surgery were reported to die in the Covid-19 pandemic (8). However, since there is no data on the total number of surgeries performed in the hospital, no data on Covid-19 (+) transmission were included. In our study, despite our high case count, we think that the Covid-19 transmission rate and low mortality indicate the effectiveness of the measures and treatment used in our country.

The main purpose of patient safety is to intervene with patients who may have worsened respiratory conditions with oral intubation and Covid-19, and to prevent virus contamination of patients without Covid-19 in the postoperative period (15).

During this period when the peak of Covid-19 cases occurred, all basic measures were applied to protect healthcare workers. As a result of all the precautions taken, Covid-19 (+) was not detected in any faculty, specialist doctor and resident doctors among the surgeons in the general surgery department. However, five ward nurses and two ward personnel were Covid-19 positive. After the first confirmed cases in our health service, strict compliance with individual protection measures, disinfection of common areas and suspension of doctor meetings were enforced. These measures reduced the incidence of new cases, along with the isolation of all healthcare workers at home with suspected symptoms or confirmed infection.

Infection of health personnel is an additional cause of concern for the management of this social and health crisis (16). Action instructions were prepared for confirmed or very suspicious patients with Covid-19 infection. We all know what precautions should be applied in General Surgery wards based on available literature and subjects to review as the pandemic develops in our country in general (12,17).

CONCLUSION

The Covid-19 outbreak has a major impact on health systems worldwide. This epidemic has resulted in reorganisation of existing resources and questioning health systems. To cope with the rapid spread of the coronavirus and the severity of the clinical tableau it

produces, General Surgery services need to reconsider surgical and healthcare activities.

Since the beginning of the Covid-19 cases, no infection has been detected (0%) as a reward for our strict preventative measures among our surgeons and assistants. Ten **(**5.12%) of postoperative emergency and elective patients had COVID-19 infection. Death was concentrated in patients with high ASA scores with emergency surgical pathology.

Acknowledgment: None.

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Sažetak

UTICAJ PANDEMIJE KOVID-19 NA FUNKCIONISANJE HIRURŠKE KLINIKE: ISKUSTVO JEDNOG CENTRA U TURSKOJ

Ferahman Sina,[1] Donmez Turgut,[1] Surek Ahmet,[1] Akarsu Cevher,[1] Aydin Husnu,[1] Seyit Hakan,[1] Ozcevik Halim,[2] Tecir Harun,[1] Karabulut Mehmet[1]

[1] Bakirkoy Dr Sadi Konuk Training and Research Hospital, Department of General Surgery, Istanbul, Turkey
[2] Istanbul Provincial Health Directorate, Department of General Surgery, Istanbul, Turkey

Uvod: Kovid-19 je virusna epidemija koja uzrokuje ozbiljne zdravstvene probleme i smrt širom sveta. Brzo širenje infekcije Kovid-19 dovelo je do poremećaja u zdravstvenim ustanovama i radikalne reorganizacije zdravstvenih resursa zbog zaraze zdravstvenih radnika.

Cilj: U našoj kliničkoj studiji istražili smo posledice infekcije Kovid-19 na hitne i elektivne slučajeve u našoj Klinici za opštu hirurgiju.

Materijal i metode: Retrospektivno smo analizirali kliničke podatke 195 pacijenata koji su bili podvrgnuti elektivnoj (Grupa Elektivna) i hitnoj (Grupa Hitna) operaciji tokom perioda inkubacije Kovid-19 u Bolnici za obuku i istraživanje Bakırkoi Dr Sadi Konuk od 11. marta do 18. maja 2020. Zabeležene su demografske karakteristike, simptomi, hirurške dijagnoze, hirurške metode, komplikacije, trajanje operacije, dužina boravka u bolnici i mortalitet, status Kovid-19 svih pacijenata.

Rezultati: Operisano je 195 pacijenata, uključujući hitnu i elektivnu operaciju (104, odnosno 91). Incidencija infekcije Kovid-19 bila je 5,49% kod pacijenata kojima je zakazana elektivna operacija i 4,8% kod pacijenata koji su hitno operisani, a sve su se razvile u postoperativnom periodu. Dvoje pacijenata sa hitnom operacijom umrlo je od respiratorne insuficijencije, srednje starosni dobi od 51 godinu. Dva od 104 hitno operisana pacijenta bila su pozitivna na Kovid-19 (1,92%) u trenutku prijema. Osamnaest članova medicinskog osoblja i medicinskih sestara se inficiralo korona virusom.

Zaključci: Zbog brzog širenja infekcije Kovid-19, rane mere predostrožnosti moraju se preduzeti u hirurškim klinikama kako bi se garantovala bezbednost pacijenata, kao i svih zdravstvenih radnika i osoblja.

Ključne reči: Kovid-19, opšta hirurgija, hitna pomoć, operacija.

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med. 2020; 382(18): 1708-20. doi: 10.1056/NEJMoa2002032.

2. Chan JF, To KK, Tse H, Jin DY, Yuen KY. Interspecies transmission and emergence of novel viruses: lessons from bats and birds. Trends Microbiol. 2013; 21(10): 544-55. doi: 10.1016/j.tim.2013.05.005.

3. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary pathology of early-phase 2019 novel Coronavirus (COVID-19) pneumonia in two Patients with lung cancer. J Thorac Oncol. 2020; 28(5): 700-4. doi: 10.1016/j.jtho.2020.02.010.

4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223): 497-506. doi: 10.1016/S0140-6736(20)30183-5.

5. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel Coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382(8): 727-33. doi: 10.1056/NEJMoa2001017.

6. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020; 323(11): 1061-9. doi: 10.1001/jama.2020.1585. Erratum in: JAMA. 2021;325(11):1113.

7. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation and treatment Coronavirus (COVID-19). 2020 Apr 6. In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2020 Jan–PMID: 32150360.

8. Lei S, Jiang F, Su W, Chen C, Chen J, Mei W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. E Clinical Medicine. 2020; 21; 100331. doi: 10.1016/j.eclinm.2020.100331.

9. Aminian A, Safari S, Razeghian-Jahromi A, Ghorbani M, Delaney CP. COVID-19 outbreak and surgical practice: unexpected fatality in perioperative period. Ann Surg. 2020; 272(1): e27-e9. doi: 10.1097/SLA.0000000000003925.

10. Sica GS, Campanelli M, Bellato V, Monteleone G. Gastrointestinal cancer surgery and enhanced recovery after surgery (ERAS) during COVID-19 outbreak. Langenbecks Arch Surg. 2020; 405(3): 357-8. doi: 10.1007/s00423-020-01885-0.

11. Ti LK, Ang LS, Foong TW, Ng BSW. What we do when a COVID-19 patient needs an operation: operating room preparation and guidance. Can J Anaesth. 2020; 67(6): 756-8. doi: 10.1007/s12630-020-01617-4.

12. SAGES and EAES Recommendations Regarding Surgical Response to COVID-19 Crisis - SAGES [Internet] [consultado 1 Abr 2020]. https://www.sages.org/recommendations-surgical-response-covid-19.

13. Li CI, Pai JY, Chen CH. Characterization of smoke generated during the use of surgical knife in laparotomy surgeries. J Air Waste Manag Assoc. 2020; 70(3): 324–32. doi: 10.1080/10962247.2020.1717675.

14. Zeng MH, Boni L, Fingerhut A. Minimally invasive surgery and the novel Coronavirus outbreak: lessons learned in China and Italy. Ann Surg. 2020; 272(1): e5-e6. doi: 10.1097/SLA.0000000000003924.

15. Li R, Pei S, Chen B, Song Y, Zhang T, Yang W et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2). Science. 2020; 368(6490): 489-93. doi: 10.1126/science.abb3221.

16. Bedford J, Enria D, Giesecke J, Heymann DL, Ihekweazu C, Kobinger G et al. COVID-19: towards controlling of a pandemic. Lancet. 2020; 395(10229): 1015-18. doi: 10.1016/S0140-6736(20)30673-5.

17. Zhang Z, Liu S, Xiang M, Li S, Zhao D, Huang C et al. Protecting healthcare personnel from 2019-nCoV infection risks: lessons and suggestions. Front Med. 2020; 14(2): 229-31. doi: 10.1007/s11684-020-0765-x.

Correspondence to/Autor za korespondenciju
Sina Ferahman, MD.
Adress: Bakirkoy Dr. Sadi Konuk Training and Research Hospital,
General Surgery Department Zuhuratbaba Mah, Dr. Tevfik Sağlam Cd No: 11,
34147 Bakırkoy/Istanbul/Turkey.
Phone: +90 533 612 0201
E-mail: sinaferahmantr@hotmail.com
Orcid no: 0000-0003-1160-9156

SANAMED
2021; 16(1): 29–34
ISSN-1452-662X

DOI:10.24125/sanamed.v16i1.480
UDK: 613-056.24:616-006.6
616.89-008.454:616-006.6
ID:37391369
Original article

ASSESSMENT OF QUALITY OF LIFE PATIENTS SUFFERING FROM BREAST CANCER AND LUNG CANCER

Kalajdzic Olivera,[1] Pavlovic Jelena[2]

[1] Department of Psychology, University of East Sarajevo, Faculty of Medicine in Foca, Bosnia and Herzegovina
[2] Department of Nursing, University of East Sarajevo, Faculty of Medicine in Foca, Bosnia and Herzegovina

Primljen/Received 02. 12. 2020. god. Prihvaćen/Accepted 30. 01. 2021. god.

Abstract: **Introduction:** Assessment of quality of life is an important subject of research in various disciplines and today it is an integral part of the evaluation of rehabilitation and therapeutic procedures. The aim of the study was to assess the quality of life and to assess the impact of depression on the quality of life in patients with breast cancer and lung cancer.

Material and methods: The study included 60 people, of whom 30 were diagnosed with lung cancer and 30 with breast cancer. The questionnaire was constructed by researchers for this research. Quality of Life Assessment Questionnaire SF-36 and assessment of depression, Beck Depression Scale.

Results: The presence of complications is a statistically significant source of differences in the domain of the total physical score, and is not a statistically significant source of differences in other domains from the SF36 questionnaire. Based on the data from the previous table, we can see that the values on the Beck Depression Inventory range from 23 to 35, with AS = 30.00 and SD = 2.584.

Conclusion: Respondents who have a higher score on the Beck Depression Inventory also have a higher score on the dimension of physical functioning.

Keywords*:* quality of life, malignant diseases, depression, patients.

INTRODUCTION

Quality of life is a complex concept dealt with by various scientific disciplines. Health status is an important element of quality of life. One of the indicators of health status is self-assessment of health (1). A narrower term than general quality of life is health-related quality of life (HRQoL). It is a state of well-being that consists of the ability to perform the activities of everyday life and the patient's satisfaction with the degree of functioning and control of the disease. In addition to the four basic dimensions of quality of life, the existence of symptoms and side effects of medical treatments to which the patient is subjected (satisfaction with the treatment, emotional distress, spirituality, financial condition, etc.) is also important (2, 3). Quality of life in oncology looks at the subjective experiences of the positive and negative aspects of the disease on physical, emotional, social and cognitive functions, and the frequency of symptoms and side effects of treatment. Quality of life is specific for malignant diseases and is associated with all stages of the disease. Assessment of quality of life is an important subject of research in various disciplines and today it is an integral part of the evaluation of rehabilitation and therapeutic procedures. The issue of personal quality of life factors is very topical in the field of health care of chronic patients, as well as in the general population (4). Technological advances and new diagnostic methods and therapies have resulted in longer survival of patients with breast and lung cancer, and as a result, there is a growing interest in assessing the quality of life of these patients. Nowadays, there is an increasing problem in the competitive healthcare market, the problem of measuring the quality of care for certain diseases, as well as the quality of life (QOL) (5, 6). The study aimedto assess the quality of life and to assess the impact of depression on quality of life in patients with breast cancer and lung cancer.

MATERIAL AND METHODS

Respondents and type of study

The quality of life study,for patients diagnosed with lung or breast cancer, was designed as a cross-sectional study. The study included 60 people, of whom 30 were diagnosed with lung cancer and 30 with di-

agnosed breast cancer. The sample included the same number of men and women (30 women and 30 men), aged 32 to 83 years. The research was conducted at the University Hospital Foca, Department of Oncology in the period between April and September 2018. All respondents were informed about the goals of the research, and they agreed to participate with written consent.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving research study participants were approved by the Ethics Committee of the Faculty of Medicine Foca.

Instruments

The survey was conducted through a specially constructed questionnaire consisting of several units: sociodemographic characteristics, questionnaire on socio-demographic characteristics of respondents that provides data on personal, socio-status characteristics of respondents relevant to this research (gender, age, education, marital status, employment status, diagnosis, length of chemotherapy and the presence of complications). The questionnaire was constructed by researchers for the purposes of this research. Quality of Life Assessment Questionnaire SF-36 (7). The questionnaire contains 36 questions, which are classified into 8 domains: physical functioning (8 questions), limitations in functioning due to physical difficulties (4 questions), limitations in functioning due to emotional difficulties (three questions), energy, ie exhaustion (4 questions), emotional well-being (5 questions), social functioning (2 questions), pain (2 questions), general health (5 questions). Assessment of depression Beck Depression Scale (8), which consists of 21 items, which determine the presence or degree of symptoms of depression. The items are formulated to represent four groups of symptoms - emotional, cognitive, motivational, and physiological. Each item consists of four statements sorted by the severity of a particular symptom of depression and is scored from 0 to 3, so the range of results can range from 0 to 63. Respondents who score from 0 to 10 are included in the group of subjects without depressive problems, while respondents with a score of 11 or more belong to the group with depressive disorders.

Statistical analysis

The data processing procedure was performed through the software package SPSS version 20, and descriptive statistical measures, correlation analysis, Mann-Whitney U test, and Kruskal-Wallis test were used for the analysis of the collected data.

RESULTS

The study included 60 people diagnosed with lung or breast cancer. The sample included the same number of men and women (30 women and 30 men) (Figure 1).

The youngest respondent was 32 years old and the oldest 83. The average age of the respondents was 56.80 years (SD = 12.64). The differences in the average age of men (x = 33.50, SD = 13.18) and women (x = 54.63, SD = 11.89) were not statistically significant (p = 0.186). The largest number of respondents is in the age category up to 49 years (Figure 2).

The theoretical values of each of the SF domains can range from 0 to 100, with higher values indicating a better quality of life. From the data presented in Table 1, we notice that the maximum values of the distribution of all domains in our sample are less than the maximum theoretical value. In the total sample of respondents, the domain of physical functioning had the highest value with a median of 55, while the domain of energy/exhaustion had the lowest value with a median of 17.50. There is no statistically significant difference in the quality of life assessments between men and women.

The presence of complications is a statistically significant source of differences in the domain of total physical score and is not a statistically significant source of differences in other domains from the SF36 questionnaire (Table 2).

Based on the data from the previous table, we can see that the values on the Beck Depression Inventory range from 23 to 35, with AS = 30.00 and SD = 2.584.

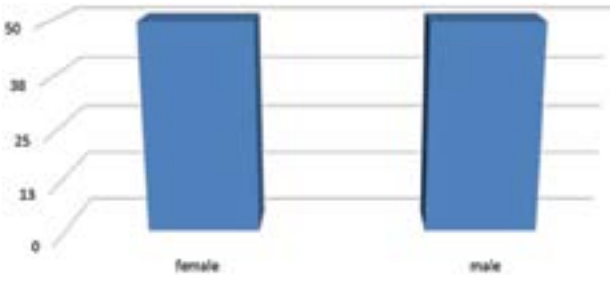


Figure 1. *Gender structure of patients*

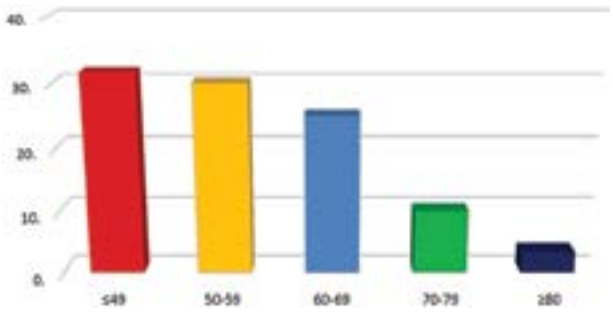


Figure 2*. Age structure of patients*

Table 1. *Values of all SF questionnaire domains*

Variables	AS	SD	M	Min	Max
Physical functioning	52.42	10.75	55	25	75
Restrictions due to physical t.	33.33	17.63	25	0	75
Limitations due to emotional problems	21.11	16.20	33.33	0	33
Energy / exhaustion	19.08	8.46	17.50	5	45
Emotional well-being	38.27	7.19	40.00	20	56
Social functioning	38.54	11.34	37.50	13	63
Pain	23.79	10.91	22.50	10	55
General health	27.67	7.22	27.50	15	45
Total physical score	34.30	5.78	35.00	21	54
Total mental score	29.25	5.25	30.46	15	40

AS - arithmetic mean, **SD** - standard deviation, **M** - median, **Min** - minimum, **Max** - maximum

Table 2. *Occurrence of complications and average values of domains from the SF36 questionnaire*

Variables		Median	Min	Max	Rang	Mann-Whitney U	z	p
FF	**Yes**	55	25	70	45	295.000	-0.734	0.463
	No	55	35	75	40			
OF	**Yes**	25	0	50	50	233.000	-1.952	0.051
	No	50	25	75	50			
OE	**Yes**	33.33	0	33	33	322.500	-0.307	0.759
	No	33.33	0	33	33			
E	**Yes**	15	5	40	35	230.500	-1.877	0.061
	No	20	5	45	40			
EB	**Yes**	40	20	52	32	285.500	-0.911	0.362
	No	36	24	56	32			
SF	**Yes**	37.50	13	50	37	258.000	-1.439	0.150
	No	37.50	13	63	50			
B	**Yes**	22.50	10	55	45	333.000	-0.079	0.937
	No	22,50	10	45	35			
OZ	**Yes**	25	15	45	30	251.000	-1.522	0.128
	No	30	15	45	30			
UF	**Yes**	33.75	21	43	22	204.000	-2.285	**0.022**
	No	35.63	24	54	30			
UM	**Yes**	30	15	38	23	286.000	-0.879	0.379
	No	46	24	40	16			

FF - physical functioning, **OF** - restrictions due to physical difficulties, **OE** - limitations due to emotional problems, **E** - energy/ exhaustion, **EB** - emotional well-being, **SF** - social functioning, **B** - pain, **OZ** - general health, **UF** - total physical score, **UM** - total mental score

Table 3. *Assessment of depression*

Depression	N	%
No depression	0	0
Mild depression	0	0
Mild to moderate depression	0	0
Moderate to severe depression	23	38.3
Expressed depression	37	61.7
Σ	60	100

Table 4. *Relationship between quality of life and value domains on the Beck Depression Scale*

The domain of quality of life	Beck Depression Scale	
	Ro	P
FF	0.263	**0.044**
OF	0.029	0.829
OE	-0.242	0.065
E	0.117	0.376
EB	-0.106	0.422
SF	-0.214	0.103
B	0.048	0.718
OZ	0.000	0.999
UF	0.153	0.248
UM	-0.280	**0.032**

FF - physical functioning, **OF** - restrictions due to physical difficulties, **OE** - limitations due to emotional problems, **E** - energy/ exhaustion, **EB** - emotional well-being, **SF** - social functioning, **B** - pain, **OZ** - general health, **UF** - total physical score, **UM** - total mental score

The obtained results tell us that all respondents from our sample had certain depressive disorders, namely 61.7% of respondents with pronounced depression, and 38.3% with moderate to severe depression (Table 3).

Based on the data presented in Table 4, it is possible to notice that the correlation between the score on the Beck Depression Inventory and physical functioning is statistically significant at the significance level of 0.05 and that it is positive. Respondents who have a higher score on the Beck Depression Inventoryalso have a higher score on the dimension of physical functioning. Since the obtained correlation coefficient is less than 0.30, it can be concluded that the level of correlation is low according to the Cohen criterion. Also, the obtained results show that there is a statistically significant correlation between the score on the Beck Depression Inventory and overall mental functioning and that this correlation is negative. The negative sign of the obtained correlation indicates that a high score on the Beck Depression Inventory is followed by a low score on the dimension of overall mental functioning and vice versa. The obtained correlation coefficient is less than 0.30, so it can be concluded that the level of correlation is low according to the Cohen criterion.

DISCUSSION

Quality of life is a comprehensive satisfaction/ dissatisfaction with one's own life. It is the subjective experience of every human being that undoubtedly depends on the circumstances in which one lives, as well as on the composition of values, expectations, and aspirations. Quality of life refers to personal well-being and life satisfaction, including mental and physical health (9). The study included 60 people diagnosed with lung or breast cancer. Patients facing a diagnosis of malignancy go through a difficult period of disease acceptance and adjustment (10). The conducted research verified the satisfaction of the respondents with everyday life, the obtained information on medical check-ups, the support of family members as well as the possibilities of self-care, as well as the presence of depression in patients with malignant diseases. The treatment and care of patients with malignant diseases are multidisciplinary, with particular emphasis on the role of the nurse who spends the most time with the patient. In order for the health care process to meet the needs of patients during hospitalisation and after discharge, an important factor is the continuous education of nurses to acquire new knowledge, skills, and abilities. Nurses, in order to improve the quality of life of patients with malignant diseases, must base their daily work on the science of nursing, verified scientific theories, and empiricism (10). Disturbed perception of the appearance of their body, which can result in lower self-esteem and lead to social isolation and impaired quality of life, with negative physical, mental and social consequences for themselves and their family members (11). In our research, the best quality of life was observed in the group of persons with the highest level of education (college and university), while in all three phases of the survey, statistically, significantly lower values were found in persons with completed or incomplete primary school. Lundy and co-workers believe that the level of education should be viewed in the context of income because it is largely conditioned, and lower-income has a negative impact on all aspects of quality of life (12).

Statistically significantly lower values were found in the domain of limitations in functioning due to emotional problems, which indicates that it is necessary to provide patients with psychosocial support after treatment. In the psychological sense, adaptation implies the adaptation of an individual to his environment or the circumstances in which he finds himself, and it includes physical, cognitive, and emotional factors. The obtained results tell us that all respondents from our sample have certain depressive disorders, namely 61.7% of respondents with pronounced depression, and 38.3% with moderate to severe depression. Aminisani and colleagues state in their paper that anxiety and depression are considered the most common mental disorders in people with malignant diseases, citing data from the literature that the prevalence of clinical depression among cancer patients ranges between 13-40%; depression is associated by some authors with higher mortality rates (13, 14). In our study, the highest values of the Beck Depression Scale were found in the elderly, respondents in the widow/widower group, and people with the lowest level of education; gender and

place of residence did not have a significant impact on the values of this instrument. Respondents who have a higher score on the Beck Depression Scale also have a higher score on the physical functioning dimension. Patients who have signs of depression have a significantly poorer quality of life. Women diagnosed with breast cancer face a number of challenges that impair their mental health and thus their quality of life. Factors that are important for mental health are the occurrence of depression and anxiety, stress, and a distorted body image. Diagnosis, treatment decisions, and outcome care and prognosis produce significant stress (15, 16, 17). Depression and anxiety occur depending on the treatment. Research has focused on the aspect of personality that is thought to support the mental health of women with breast cancer, and that aspect is optimism (18). As mental health intertwines with the quality of life, poorer mental functioning leads to lower quality of life. Quality of life based on the health of people with malignancy must be the goal and end result of the rehabilitation process for every patient with malignancy (19, 20, 21, 22).

CONCLUSION

Respondents who have a higher score on theBeck Depression Inventory also have a higher score on the dimension of physical functioning. Recognising the importance of the impact of physical health on mental health and the link between mental health and physical health, the treatment of breast cancer strives to maintain a quality of life as high as possible. To achieve this, health care must be at the highest possible level, and the education of medical staff is needed through regular education and additional education related to communication skills and psychological aspects of the health of people with cancer.

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Sažetak

PROCENA KVALITETA ŽIVOTA PACIJENATA OBOLELIH OD KARCINOMA DOJKE I PLUĆA

Kalajdzic Olivera,[1] Pavlovic Jelena[2]

[1] Department of Psychology, University of East Sarajevo, Faculty of Medicine in Foca, Bosnia and Herzegovina
[2] Department of Nursing, University of East Sarajevo, Faculty of Medicine in Foca, Bosnia and Herzegovina

Uvod: Procena kvaliteta života važan je predmet istraživanja u raznim disciplinama i danas je sastavni deo evaluacije rehabilitacionih i terapijskih postupaka. Cilj studije bio je proceniti kvalitet života i uticaj depresije na kvalitet života kod pacijenata s rakom dojke i pluća.

Materijal i metode: Studija je obuhvatila 60 osoba, od kojih je 30 sa dijagnostikovanim rakom pluća, a 30 sa dijagnostifikovanim rakom dojke. Upitnik su sastavili istraživači za potrebe ovog istraživanja. Procena kvaliteta života Upitnik za ocenu kvaliteta života SF-36. I procena depresije Beckova skala depresije.

Rezultati: Prisustvo komplikacija je statistički značajan izvor razlika u domenu ukupnog fizičkog rezultata i nije statistički značajan izvor razlika u drugim domenima iz upitnika SF36. Na osnovu podataka iz prethodne tablice možemo videti da se vrednosti na Beckovoj skali depresije kreću od 23 do 35, s AS = 30,00 i SD = 2,584.

Zaključak: Ispitanici koji imaju viši rezultat na Beckovoj skali depresije imaju i veći rezultat na dimenziju fizičkog funkcionisanja.

Ključne reči: kvalitet života, maligne bolesti, depresija, bolesnici.

REFERENCES

1. Lin JS, Piper MA, Perdue LA, Rutter C, Webber EM, O'Connor E, et al. Screening for colorectal cancer: updated evidence report and systematic review for the US preventive services task force. JAMA. 2016; 315(23): 2576-94. doi: 10.1001/jama.2016.3332.

2. World Health Report: life in the 21st century-a vision for all. Geneva: WHO. 1998. https://www.who.int/whr/1998/en/.

3. WHOQOL Group. Study protocol for the World Health Organization project to develop a quality of life assessment instrument (WHOQOL). Qual Life Res. 1993; 2(2): 153-9.

4. Hengelson VS. Social support and quality of life. Qual Life Res. 2003; 12 (Suppl 1): 25-31. doi: 10.1023/a:1023509117524.

5. Andrews L. Systematic review summary - Psychosocial interventions to improve quality of life and emotional well-being for recently diagnosed cancer patients. Singapore Nursing Journal 2013; 40(3): 12-33.

6. Barre VP, Padmaja G, Saxena RK, Rana S. Impact of medical intervention on stress and quality of life in patients with cancer. Indian J Palliat Care. 2015; 21(2): 203-8. doi: 10.4103/0973-1075.156503.

7. Ware JE, Snow KK, Kosinski M, Gandek B, New England Medical Center. The Health Institute. SF-36 Health Survey: Manual and Interpretation Guide. Boston: The Health Institute, New England Medical Center; 1993.

8. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961; 4:561-71. doi: 10.1001/archpsyc.1961.01710120031004.

9. Kugler S. Quality of life and standards for quality. E Quality 2001; 2:70-2.

10. Guldbrandt LM. The effect of direct referral for fast CT scan in early lung cancer detection in general practice. A clinical, cluster-randomised trial. Dan Med J 2015; 62(3): B5027.

11. Urbania TH, Dusendang JR, Herrinton LJ, Alexeeff S, Corley DA, Ely S, et al. Standardized reporting and management of suspicious findings on chest CT imaging is associated with improved lung cancer diagnosis in an observational study. Chest. 2020; 158 (5): 2211-20. doi: 10.1016/j.chest.2020.05.595.

12. Fevrier HB, Liu L, Herrinton LJ, Li D. A transparent and adaptable method to extract colonoscopy and pathology data using natural language processing. J Med Syst. 2020; 44(9): 151. doi: 10.1007/s10916-020-01604-8.

13. Aminisani N, Nikbakht H, Asghari Jafarabadi M, Shamshirgaran SM. Depression, anxiety, and health-related quality of life among colorectal cancer survivors. J Gastrointest Oncol. 2017; 8(1): 81-8. doi: 10.21037/jgo.2017.01.12.

14. Cordero A, Villar MJ, Sanchez NM, Pimentel MN, Garcia ML, Gomez V. Breast cancer and body image as a prognostic factor of depression: a case study in México City Nutr Hosp. 2014; 31(1):371-9. doi: 10.3305/nh.2015.31.1.7863.

15. Colby D, Shifren K. Optimism, mental health, and quality of life: A study among breast cancer patients. Psychol Health Med. 2013; 18(1): 10 –20. doi: 10.1080/13548506.2012.686619.

16. Corwin D, Wall K, Koopman C. Psychospiritual integrative therapy: Psychological intervention for women with breast cancer. The journal of specialists in group work 2012; 37(3): 252 –73.doi: 10.1080/01933922.2012.686961.

17. Fox JP, Philip EJ, Gross CP, Desai RA, Killelea B, Desai MM. Associations between mental health and surgical outcomes among women undergoing mastectomy for cancer. Breast J. 2013; 19(3): 276–84. doi: 10.1111/tbj.12096.

18. Gopie JP, Kuile MM, Timman R, Mureau MA, Tibben A. Impact of delayed implant and DIEP flap breast reconstruction on body image and sexual satisfaction: a prospective follow-up study. Psychooncology. 2014; 23(1): 100 –7. doi: 10.1002/pon.3377.

19. Kvillemo P, Branstrom R. Copingwith breast cancer: A meta-analysis. PLoS ONE. 2014; 9(11):e112733. doi: 10.1371/journal.pone.0112733.

20. McKean LN, Newman EF, Adair P. Feeling like me again: a grounded theory of the role of breast reconstruction surgery in self-image. Eur J Cancer Care (Engl). 2013; 22(4): 493-502. doi: 10.1111/ecc.12055.

21. Mosewich AD, Hadd V, Crocker P, Zumbo B. Invariance testing of the SF-36 health survey in women breast cancer survivors: Do personal and cancer-related variables influence the meaning of quality of life items? Soc Indic Res 2013; 110(2): 559–77.doi: 10.1007/s11205-011-9944-0.

22. Przezdziecki A, Sherman K, Baillie A, Taylor A, Foley E, Stalgis BK. My changed body: breast cancer, body image, distress, and self-compassion. Psycho-Oncology. 2013; 22(8): 1872 –9. doi: 10.1002/pon.3230.

Correspondence to/Autor za korespondenciju
Dr. Olivera Kalajdžić, Faculty of Medicine in Foca, University of East Sarajevo, Bosnia and Herzegovina, Department of Psychology
Studentska 5, 73300 Foca, Bosnia and Herzegovina
E-mail: olivera.kalajdzic@yahoo.com

SANAMED
2021; 16(1): 35–39
ISSN-1452-662X

DOI:10.24125/sanamed.v16i1.488
UDK: 616.523:616.13-002
ID:37392137
Original article

SHOULD GIANTCELL ARTERITIS SIGNS BE DETECTED IN PATIENTS WITH HERPES ZOSTER?

Kulakli Fazil,[1] Cayli Erdem,[2] Kulakli Sevgi,[3] Oguz Deniz Isil,[3]
Celik Canan,[1] Yildizgoren Turgut Mustafa[4]

[1] Department of Physical Medicine and Rehabilitation, Giresun University Faculty of Medicine, Giresun, Turkey
[2] Department of Radiology, Giresun University Faculty of Medicine, Giresun, Turkey
[3] Department of dermatology, Giresun University Faculty of Medicine, Giresun, Turkey
[4] Department of Physical Medicine and Rehabilitation, Mustafa Kemal University Faculty of Medicine, Hatay, Turkey

Primljen/Received 10. 01. 2021. god. Prihvaćen/Accepted 14. 02. 2021. god.

Abstract: **Objective:** This study aims to determine the clinical, laboratory, and ultrasonographic findings of giant cell arteritis in patients with Herpes Zoster.

Methods: The study included 36 consecutive patients (median age 59.0 years; range 19 to 76 years) who were admitted to the Dermatology Outpatient Clinic with the diagnosis of Herpes Zoster. Demographic and clinical features of the patients were recorded. The presence of ultrasonographic characteristics of giant cell arteritis such as halo sign, compression sign, occlusion, and stenosis was also recorded using ultrasound. The patients were evaluated at baseline and 6 months.

Results: A total of 36 patients were assessed. 4 patients had jaw claudication (11.1%), 5 patients had scalp tenderness (13.9%), 11 patients had a new-onset headache (30.6%) and, 23 patients had post-herpetic neuralgia (63.9%). No patients had elevated erythrocyte sedimentation rate and ultrasonographic findings of Giant cell arteritis.

Conclusion: Our data show that a small proportion of patients with Herpes Zoster may have clinical findings suggesting Giant cell arteritis. However, they do not have elevated erythrocyte sedimentation rate and sonographic findings of Giant cell arteritis.

Keywords: Giant cell arteritis, Herpes zoster, Vasculitis.

INTRODUCTION

Varicella zoster virus (VZV) is a member of *the Herpes viridae* family and results in two different clinical conditions. VZV, also colloquially known as chickenpox, is the primary clinical outcome, characterised by widespread exanthematous skin lesions. Shingles or herpes zoster (HZ) is a recurrent infection of latent VZV following the primary infection of the organism (1). HZ is diagnosed in 20-30% of healthy adults whereas this rate goes up to about 50% in immunosuppressed patients (2). Grouped vesicular lesions are seen on the innervated dermatome region of the ganglion (Generally thoracic-cervical dermatomes and the ophthalmic branch of the trigeminal nerve) where VZV is activated (3).

Giant cell arteritis (GCA) is a type of vasculitis diagnosed frequently in patients older than 50 years, which affects medium-to-large-sized arteries. It may produce a wide spectrum of clinical symptoms. New-onset headache is the most common symptom, followed by jaw claudication, vision problems, and scalp sensitivity (4). Diagnosis is usually made with clinical symptoms with additional diagnostic methods such as ultrasonography (USG) and other imaging techniques, laboratory parameters, and temporal artery biopsy. Temporal artery biopsy is considered the ‘gold standardfor GCA (5). USG is also shown to have a higher sensitivity and specificity rate in GCA diagnosis when compared with biopsy and is proven to be much more cost-effective (6).

VZV complications include chronic pain (post-herpetic neuralgia), myelopathy, and vasculopathy. Vasculopathy is usually seen on cerebral arteries and might have negative outcomes such as transient ischemic attacks and stroke (7). VZV mostly reactivates in the elderly (the same age group in which GCA predominates), often affects arteries, and produces multinucleated giant cells in acutely infected tissue.

In addition, VZV vaccines are reported to affect extracranial areas such as temporal, ophthalmic, and retinal arteries, which might cause GCA symptoms and results in some patients (8). In contrast, some studies report no sighting of VZV in the temporal artery and that VZV is not related to GCA etiology (9, 10). There is no study in the literature regarding whether there are any ultrasonographic changes on the temporal artery after HZ. Those opposing views found in the literature also cause more confusion about whether VZV plays a role in GCA etiology. Accordingly, this study aimsto determine the clinical, laboratory, and ultrasonographic findings of giant cell arteritis in patients with Herpes Zoster**.**

MATERIAL AND METHODS

36 consecutive patients over 18-years who were admitted to the Dermatology Outpatient Clinic in Giresun University Faculty of Medicine with a diagnosis of Herpes Zoster (HZ) were enrolled between June 2019 - March 2020. Subjects with diseases that might affect vascular structures (vasculitis, hypertension, diabetes mellitus, etc.), severe infection, fever, cognitive dysfunction or mental retardation, multiple systemic diseases, malignancy, and open wounds were excluded. Demographic and clinical features of the patients including age, gender, comorbid diseases, current medications, varicella vaccination status, presence of symptoms associated with the temporal artery (such as jaw claudication, new-onset headache, vision problems, sensitivity in the temporal region) were recorded. The patients were evaluated at baseline and at 6 months.

Ethics approval for the study was obtained from the Ethics Committee of Giresun University (Date/No: 2018/117). Written informed consent was obtained from each subject. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Ultrasonographic Evaluation

An ultrasound was performed by 10years experienced radiologist in vascular ultrasound using a Toshiba Aplio 500 Ultrasonography (Toshiba Medical System Corporation, Tokyo, Japan) a device with a high-frequency linear probe that supports doppler mode usage (PLT-1005 BT [4-14 MHz]). Colored Doppler frequency was set at 10 MHz, PRF 2-3 kHz, focus at 5mm and depth was set at 1-2 cm. Common superficial temporal arteries, their frontal and parietal branches were reviewed bilaterally on longitudinal and axial planes. The presence of GCA characteristics such as halo sign, compression sign, occlusion, and stenosis was recorded. Also, intima-media complex measurements, known to show higher values on vasculitis, were done using *Schäfer VS et al*'s study as reference (11). The cut-off value for diameters in halo sign was set at 0.42 mm for superficial temporal artery, 0.34 mm for frontal branch, 0.29 mm for parietal branch, and 0.2 mm for intima-media complex thickness. "Compression sign" was defined as artery not being compressed when pressed with US probe, "occlusion" was defined as temporal artery filled with hypoechoic material despite decreased PRF and increased color gain setting, unable to get doppler signal, and finally "stenosis" was defined as the presence of turbulent colored patterns and persistent diastolic refill on Doppler USG with increased maximum systolic flow force on pulse-wave Doppler USG. Results were recorded as "positive" or "negative".

Statistical analysis

Data were analysed using the SPSS version 21.0 (SPSS, Inc., Chicago, IL, USA) program. Data were expressed as median (minimum-maximum) or n (percentage). The correlation between clinical variables was analysed with the Kolmogorov-Smirnov Test. Mann-Whitney U test was used to compare differences between the groups. Chi-square test and Fisher test were used to compare the differences between the groups. The significance level was set at $p < 0.05$.

RESULTS

Demographic, clinical, and ultrasonographic features of the subjects are given in Tables 1, 2, and 3. None of the patients developed any signs of GCA. Although some patients described some symptoms given in Table 2 in detail, none of the patients showed GCA-specific findings. The mean value for intima-media complex thickness was found as 0.15±0.03 mm (min = 0.10 mm, max = 0.19 mm, median = 0.16 mm). The mean Erythrocyte Sedimentation Rate (ESR) value of the patients was calculated as 24.75 ± 10.86 mm/h. Clinical features of the patients according to the

Table 1. *Demographic features of the Herpes Zoster patients (n = 36)*

Demographic features	***n (%)***
Age – years	
Median (min-max)	59.0 (19-76)
Gender	
Female	17 (47.2)
Male	19 (52.8)

Table 2: *Clinical features of the Herpes Zoster patients (n = 36)*

Clinical features	n (%)
Jaw claudication	4 (11.1)
Scalp tenderness	5 (13.9)
New onset headache	11 (30.6)
Vision problems	2 (5.6)
Zostervaccinationstatus	0
Drug usage	
Brivudin	22 (66.1)
Valasiklovir	14 (38.9)
Postherpetic neuralgia	23 (63.9)

Table 3: *Ultrasonographic and Laboratory findings of the Herpes Zoster patients*

Ultrasonographic findings	Baseline	Followup
Halo sign	–	–
Compressionsign	–	–
Stenosis	–	–
Occlusion	–	–
Laboratory findings		
Erythrocyte sedimentation rate, mm/h		24.75 ± 10.86
CRP, mg/L		3.2 ± 0.4

Table 4. *Clinical features of the Herpes Zoster patients according to the presence of post-herpetic neuralgia, n (%)*

	PHN (-) (n = 13)	**PHN (+)** (n = 23)	**P value**
Age, years	57.0 (19-68)	65.0 (19-76)	**0.018**
Gender, Female/Male	6 (46.2) / 7 (53.8)	11 (47.8) / 12 (52.2)	0.923
Jawclaudication	1 (7.7)	3 (13.0)	1.000
Scalptenderness	1 (7.7)	4 (17.4)	0.634
New onsetheadache	4 (30.8)	7 (30.4)	1.000
Visionproblems	1 (7.7)	1 (1.3)	1.000

PHN: Post-HerpeticNeuralgia

presence of post-herpetic neuralgia (PNH) are shown in Table 4. There was no statistically significant difference between the groups, except age. Patients with post-herpetic neuralgia had older age.

DISCUSSION

There are various studies about the relationship between Varicella Zoster Virus (VZV) infections and Giant Cell Arteritis (GCA). In our study, none of the patients diagnosed with HZ showed clinical, laboratory, or ultrasonographic GCA signs both in baseline and follow-up, which might be interpreted as the absence of a relationship between HZ infections and GCA. However, we say further studies in this area are warranted due to the limitations mentioned below in detail.

Despite recent advances in immunology, GCA etiology is still unclear in the literature. Multiple environmental and genetic factors probably play a part in susceptibility to GCA. However, it is thought that the relationship between vascular walls and the immune system plays a role in the pathogenesis. Activated vascular dendritic cells gather CD4+ T-cells and macrophages towards the vessel wall (12, 13). Those cells then penetrate from the adventitia to the intima layer through vasa vasorum along with tissue space and this causes granuloma formation (12). As intracellular pathogens often cause a similar granulomatous inflammation response, infections are also thought to possibly trigger the same response in some of the patients (13). As HZ infections, which is one of the reasons thought to cause etiopathogenesis, are usually seen in elderly patients like GCA and cause a similar T-cell mediated immune response, it is thought that HZ and GCA show similar etiological properties. To elaborate this claim, VZV is known to cause vasculopathy, and the pathology samples from involved vessels are shown to contain multinucleated giant cells, similar to GCA (9). Previous studies have shown that a detailed review of temporal artery and aorta specimens of GCA patients with positive and negative biopsy results detected VZV antibodies and DNA in those samples. A recent case-control study showed no relationship between GCA and HZ, yet another case-control study reported an increased risk of GCA following HZ infections. (10, 14, 15).

Another recently published case report described polymyalgia rheumatica, very similar to GCA symptoms and thought to be a part of the disease, in a patient with HZ infection (16). The curiosity sparked by those contradicting results reported in the literature drew us

to conduct a study on whether GCA symptoms show up on HZ patients. In this direction, we assessed the presence of GCA symptoms in clinical, laboratory, and ultrasonography methods in those patients. Our study is a first in this regard which assessed this subject using USG. The main reason that we have chosen the USG review instead of temporal artery biopsy, which is the golden standard in GCA diagnosis, is due to the invasive nature and its association with high complication risks. In addition, it only assesses a part of a certain vein. Finally, ultrasonographic imaging was shown to have superior sensitivity and specificity for GCA diagnosis, not to overlook its cost-efficient nature (6). Ultrasonography can detect 4 characteristic pathologies in GCA. Those are thickening on the venous wall (halo sign), the artery cannot be compressed (compression sign), stenosis, and venous occlusion. Cellular infiltrates and edema can especially build up on intima and then spread out to media and adventitia layers in GCA. This thickening in the venous wall shows a hypoechoic image around the vein in USG and is named a "halo sign" (17, 18). The previous studies reported the cut-off value for halo sign diameter as 0.1-1 mm (19). Another recent study reported normal intima-media complex diameter in the temporal artery as 0.2 mm whereas those values increase up to 0.5-0.8 mm in vasculitis (20). USG halo sign was reported to have a sensitivity of 55-100% and a specificity of 78-100% in GCA diagnosis in a number of studies, yet this imaging method still did not replace temporal artery biopsy for GCA diagnosis (20). Temporal artery biopsy and colored doppler USG were compared prospectively in the TABUL study and sensitivity was reported as 39% to 54% and specificity was reported as 100% to 81% (21).

In our study, we used USG for the assessment of the temporal artery in HZ patients for the reasons stated above, however, this caused some limitations in the study. One of those limitations is that using the ultrasonographic assessment method, although performed by an experienced radiologist, is still a debated method in definitive GCA diagnosis despite being widely used, secure and reliable today. Another limitation is that we did not perform temporal artery biopsy, which is the key point in diagnosis, in any of the patients. Yet this is because an invasive procedure like temporal artery biopsy is ethically unjustified in patients without any GCA clinical and/or laboratory results just for the diagnosis. Finally, our last limitation is the relatively short follow-up period of six months for the included patients in the study. There is a chance that those patients can develop GCA in the future and we might diagnose this during their routine follow-up. Even though the patients were assessed not only by USG but also with clinical and laboratory results for GCA-related symptoms, further studies with fewer limitations are required for this subject.

In conclusion, a small proportion of patients with HZ may have symptoms suggesting GCA. However, they do not have elevated ESR and sonographic findings of GCA. Clinical examination, laboratory, and US may help us to exclude a GCA diagnosis and thus to spare these patients from unnecessary immunosuppression.

Abbreviations

VZV — Varicella zoster virus
HZ — herpes zoster
GCA — Giant cell arteritis

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Licensing

Sažetak

DA LI BI ZNACI GIGANTOCELULARNOG ARTERITISA TREBALI BITI DETEKTOVANI KOD PACIJENATA KOJI IMAJU HERPES ZOSTER?

Kulakli Fazil,[1] Cayli Erdem,[2] Kulakli Sevgi,[3] Oguz Deniz Isil,[3] Celik Canan,[1] Yildizgoren Turgut Mustafa[4]

[1] Department of Physical Medicine and Rehabilitation, Giresun University Faculty of Medicine, Giresun, Turkey
[2] Department of Radiology, Giresun University Faculty of Medicine, Giresun, Turkey
[3] Department of dermatology, Giresun University Faculty of Medicine, Giresun, Turkey
[4] Department of Physical Medicine and Rehabilitation, Mustafa Kemal University Faculty of Medicine, Hatay, Turkey

Cilj: Ova studija ima za cilj da utvrdi kliničke, laboratorijske i ultrasonografske nalaze gigantocelularnog arteritisa kod pacijenata sa herpes zosterom.

Metode: Studija je obuhvatila 36 pacijenata (srednja starost 59,0 godina; raspon od 19 do 76 godina) koji su primljeni u dermatološku ambulantu sa

dijagnozom herpes zoster. Zabeležene su demografske i kliničke karakteristike pacijenata. Prisustvo ultrasonografskih karakteristika gigantocelularnog arteritisa kao što su halo znak, znak kompresije, okluzija i stenoza takođe je zabeleženo korišćenjem ultrazvuka. Pacijenti su ispitani na početku i nakon 6 meseci.

Rezultati: Pregledano je ukupno 36 pacijenata. Četiri pacijenta su imala klaudikaciju vilice (11,1%), 5 pacijenata je prijavilo osetljivost kože glave (13,9%), 11 pacijenata je imalo novonastalu glavobolju (30,6%), a 23 pacijenta postherpetičnu neuralgiju (63,9%). Nijedan pacijent nije imao povišenu stopu sedimentacije eritrocita niti ultrasonografski nalaz gigantocelularnog arteritisa.

Zaključak: Naši podaci pokazuju da mali deo pacijenata sa herpes zosterom mogu imati kliničke nalaze koji ukazuju na gigantocelularni arteritis. Međutim, oni nemaju povišenu stopu sedimentacije eritrocita i sonografske nalaze gigantocelularni arteritisa.

REFERENCES

1. Mori I, Nishiyama Y. Herpes simplex virus and varicella zoster virus: why do these human alpha herpes viruses behave differently from one another? Rev Med Virol. 2005; 15(6): 393–406. doi: 10.1002/rmv.478.

2. Schmader K.Herpes Zoster. Clin Geriatr Med. 2016; 32(3): 539–53. doi: 10.1016/j.cger.2016.02.011.

3. Sterling JC. Viral infections. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. Rook's Text Book of Dermatology. 8th ed. Oxford: Wiley-Blackwell; 2010. pp. 33.22–8.

4. Keser G, Aksu K. Diagnosis and differential diagnosis of large-vessel vasculitides. Rheumatol. Int. 2019; 39(2): 169-85. doi: 10.1007/s00296-018-4157-3.

5. Banerjee PJ, Petrou P, Plant GT. Diagnostic and treatment challenges in giant cell arteritis. Lancet. 2014; 383(9936): 2210. doi: 10.1016/S0140-6736(14)61081-3.

6. Diamantopoulos AP, Haugeberg G, Hetland H, Soldal DM, Bie R, Myklebust G. Diagnostic value of color Doppler ultrasonography of temporal arteries and large vessels in giant cell arteritis: a consecutive case series. Arthritis Care Res. 2014; 66(1): 113-9. doi: 10.1002/acr.22178.

7. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. Lancet Neurol. 2009; 8(8): 731-40. doi: 10.1016/S1474-4422(09)70134-6.

8. Gilden D. Association of varicella zoster virus with Giant Cell Arteritis. Monoclon Antib Immunodiagn Immunother. 2014; 33(3): 168–72. doi: 10.1089/mab.2014.0020.

9. Nordborg C, Nordborg E, Petursdottir V, LaGuardia J, Mahalingam R, Wellish M, et al. Search for varicella zoster virus in giant cell arteritis. Ann Neurol. 1998; 44(3): 413–4. doi: 10.1002/ana.410440323.

10. Kennedy PGE, Grinfeld E, Esiri MM. Absence of detection of varicella-zoster virus DNA in temporal artery biopsies obtained from patients with giant cell arteritis. J Neurol Sci. 2003; 215(1-2): 27–9. doi: 10.1016/s0022-510x(03)00167-9.

11. Schäfer VS, Juche A, Ramiro S, Krause A, Schmidt WA. Ultrasound cut-off values for intima-media thickness of temporal, facial and axillary arteries in giant cell arteritis. Rheumatology (Oxford). 2017; 56(9): 1479-83. doi: 10.1093/rheumatology/kex143.

12. Patil P, Karia N, Jain S, Dasgupta B. Giant cell arteritis: a review. Eye Brain. 2013; 5:23-33. doi: 10.2147/EB.S21825.

13. Hilhorst M, Shirai T, Berry G, Goronzy JJ, Weyand CM. T cell-macrophage interactions and granuloma formation in vasculitis. Front Immunol. 2014; 5: 432. doi: 10.3389/fimmu.2014.00432.

14. Gilden D, White T, Khmeleva N, Heintzman A, Choe A, Boyer PJ, et al. Prevalence and distribution of VZV in temporal arteries of patients with giant cell arteritis. Neurology. 2015; 84(19): 1948-55. doi: 10.1212/WNL.0000000000001409.

15. Nagel MA, White T, Khmeleva N, Rempel A, Boyer PJ, Bennett JL, et al. Analysis of Varicella-Zoster Virus in Temporal Arteries Biopsy Positive and Negative for Giant Cell Arteritis. JAMA Neurol. 2015; 72(11): 1281-7. doi: 10.1001/jamaneurol.2015.2101.

16. Kulakli F, Kulakli S, Ilhanli I, Aslan A, Uysal E, Celik C. Polymyalgia rheumatica after herpes-zoster. Arch Rheumatol. 2018; 33(4): 494-5. doi: 10.5606/ArchRheumatol.2018.6859.

17. Schmidt WA. Role of ultrasound in the understanding and management of vasculitis. Ther Adv Musculoskelet Dis. 2014; 6(2): 39–47. doi: 10.1177/1759720X13512256.

18. Schmidt WA, Kraft HE, Volker L, Vorpahl K, Gromnica-Ihle EJ. Colour doppler sonography to diagnose temporal arteritis. Lancet. 1995; 345(8953): 866. doi: 10.1016/s0140-6736(95)93005-1.

19. Schmidt WA. Ultrasound in the diagnosis and management of giant cell arteritis. Rheumatology. 2018; 57(suppl 2): 22-31.doi: 10.1093/rheumatology/kex461.

20. Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia rheumatica and giant cell arteritis: a systematic review. JAMA 2016; 315(22): 2442–58. doi: 10.1001/jama.2016.5444.

21. Luqmani R, Lee E, Singh S, Gillett M, Schmidt WA, Bradburn M, et al. The role of ultrasound compared to biopsy of temporal arteries in the diagnosis and treatment of giant cell arteritis (TABUL): a diagnostic accuracy and cost-effectivenes sstudy. Health Technol Assess. 2016; 20(90): 1–238. doi: 10.3310/hta20900.

Correspondence to/Autor za korespondenciju
Kulakli Fazil
Giresun University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation
Phone: +904543102020
Email: drfzl46@gmail.com

SANAMED
2021; 16(1): 41–46
ISSN-1452-662X

DOI:10.24125/sanamed.v16i1.487
UDK: 616.72-002-085-053.2
615.357
ID:37500169
Original article

INTRAARTICULAR STEROIDS IN TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS: A SINGLE CENTER EXPERIENCE

Cosickic Almira,[1] Alic Adin,[1] Suljendic Sanimir,[1] Selimovic Amela,[1] Skokic Maida,[2] Delibegovic Dina,[1] Delibegovic Mirela[3]

[1] Clinic for Children's Diseases Tuzla, University Clinical Centre Tuzla, Bosnia and Herzegovina
[2] Clinic for Internal Medicine Tuzla, University Clinical Centre Tuzla, Bosnia and Herzegovina
[3] Clinic for Radiology and Nuclear Medicine, University Clinical Centre Tuzla, Bosnia and Herzegovina

Primljen/Received 17. 12. 2020. god. Prihvaćen/Accepted 26. 02. 2021. god.

Abstract: **Aim:** To evaluate the therapeutic response to triamcinolone acetonide (TA) and triamcinolone hexacetonide (TH) injections in the knee of children with JIA.

Material and methods: 46 joints of 42 children undergoing intra-articular injections were randomly treated with either TH or TA depending on the availability of the drug. A good response was defined as the decrease in articular score of 60% from the baseline and the ultrasound absence of synovitis. Clinical, laboratory variables were noted to examine possible predictive factors of the result.

Results: Of 42 children with JIA, the most common was the oligoarticular persistent form in 24 (57.1%) children. Six-month remission was observed in 21.4% of children, TA vs. TH: 36.8% vs. 8.7% (p = 0.02). The absence of signs of knee inflammation within 12 months was found in 23.8% of children, after the application of TA vs. TH: 31.6% vs. 17.4% (p = 0.28). However, long-term, a twenty-four-month remission was achieved in 52.4% of children – in twice as many children after TH (69.9%) than after TA application (31.6%) (p = 0.03). A statistically significant correlation was observed between articular score values and duration of remission after TH application, (r = 0.56, p = 0.006; 95%CI: 0.145-0.80). Two children developed side effects in the form of subcutaneous atrophy at the site of injection, one girl developed transient crystal synovitis after TH applications.

Conclusion: This study has shown that intraarticular steroid injections are safe for the treatment of joint inflammation in JIA, and TA is effective in short-term follow-up where TH is an optimum choice in long-term follow-up.

Key words: Intraarticularsteroids, Children, Idiopathicarthritis.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic rheumatic disease of unknown cause, most common in childhood and a significant cause of disability in children (1). Various therapeutic options have been recommended to control inflammation and prevent permanent loss of joint function (2). The intraarticular steroids (IASs) are a commonly used option for the treatment in children with JIA with a small number of affected joints as well as an effective way to reduce and/or avoid the use of systemic drugs, to treat an arthritis flare in children already maintained on second-line agents (3, 4). The most commonly used corticosteroid preparations for IAS administration are long-acting corticosteroids, triamcinolone acetonide (TA), and triamcinolone hexacetonide (TH).

Aim: To evaluate the therapeutic response to TA and TH injections in the knee joints of children with arthritis.

MATERIAL AND METHODS

This retrospective-prospective study was conducted at the Department of Rheumatology, Immunology and Allergy of the Clinic for Children's Diseases, University Clinical Center (UCC) Tuzla in the period from January 2018 to December 2020. The medical records of children with JIA oligoarticular (persistent

or extended) and polyarticular form of the disease who had received IAS injections were analyzed. The diagnosis and classification of JIA were made based on the classification and diagnostic criteria for JIA 2001 by the International League of Associations for Rheumatology (ILAR) (1). Inclusion criteria included the use of IAS injections either for an unsatisfactory response to NSAIDs, disease-modifying agents, and/or for persistent single-joint involvement. Exclusion criteria included failure to fulfill the diagnostic criteria, IAS treatment during the previous 12 months, and erosive joint changes on an X-ray. 42 children were included in the study, 12 boys and 30 girls; 19 children underwent therapy with TA and twenty-three with TH.

The following were analysed: gender, age at onset of JIA, the form of JIA, length of arthritis at the time of application of corticosteroids in the knee, values of inflammatory parameters, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). The results were considered normal: ESR ≤ 15 mm/h, CRP < 5 mg/L. Clinical and ultrasound assessments of synovitis of the knee were performed before and then every 3 months until 24 months after the injection. The clinical assessment included an evaluation of the articular score used to determine the presence of swelling, limitation of range of movements, pain on passive movement, and joint warmth to touch (4). Each of these variables was measured on a scale ranging from 0 to 3, and each variable was scored: 0 normal, 1 mild, 2 moderate, and 3 severe. The ultrasound examination of the knee assessed the presence of signs of synovitis: synovial thickening or enhancement, and effusion (5, 6). A good response to IAS injections was defined as the absence of signs of synovitis or if there was an articular score decrease of 60% when compared with the baseline. Relapse was defined as the reappearance of clinical or ultrasound signs of arthritis. The children's knee joints were injected with either TA or TH; the choice of drug was dependent on the availability of TH during the study period. The procedure was performed with ultrasound guidance. One hour before the procedure Eutectic lidocaine/prilocaine cream (EMLA) was applied to the skin above the joints and half an hour before the procedure children received oral midazolam. TA or TH at the dose of 20 mg, 30 mg, and 40 mg of steroids were administered in the knee joint for children weighing < 20 kg, > 20 kg, and > 40 kg, respectively.

Ethics Statement

The study protocol was approved by the Ethics Committee of UCC Tuzla. Informed consent was signed by the parents of all participants.

Statistical analysis

Statistical data analysis was conducted using the biomedical software application "MedCalc for Windows, Version 15.11.4" (Med Calc Software, Ostend, Belgium). The variables with distorted distribution were shown with the median as a measure of the central value. The $\chi 2$-test, the Mann-Whitney U test was used to test the statistical significance of the difference between the samples. Spearman's correlation coefficient was used to assess the correlation of variables. The difference was considered significant when $p < 0.05$.

RESULTS

Five out of 47 children with JIA met the exclusion criteria, i.e. 3 children had received IAS treatment during the previous 12 months, 1 child had erosive findings on joint X-ray, and for 1 child parents did not consent to participate in the study. The median age of 42 children was 7.1 years (minimum and maximum from 2.1 to 6.8 years). The median age at disease onset was 5.3 years (minimum and maximum from 2.1 to 6.8 years). The most common was an oligoarticular persistent form of JIA observed in 24 (57.1%) children, while 3 (7.1%) children had polyarticular rheumatic factor (RF) + JIA. 46 knee joints were injected with either TA or TH, and in 4/42 (9.5 %) children steroids were injected in both knees (TA in 1, TH in 3 children). The characteristics of the two treatment groups are summarized in Table 1.

All children injected with TA and TH initially improved, and five children had a prompt release of joint contractures, two with oligoarticular extended, and three children with a polyarticular form of diseases. One boy with oligoarticular extended JIA relapsed one month after injections of TH, who developed the clinical and ultrasound characteristics of synovitis. The number of children with a sustained response of 24 months was significantly higher with TH than with TA: 69.6% vs 31.6% ($p = 0.03$) (Table 1). Six joints were still in remission after the 24 month follow-up period, 2 joints after TA and 4 after TH injections, but without statistical significance $p = 0.52$.

Spearman's correlation coefficient was done to assess the correlation between articular score, the value of CRP, ESR, disease duration, and remission duration of synovitis in both groups of children, with TA and TH injections. A statistically significant correlation was observed only between articular score values and duration of remission after TH application ($r = 0.56$, $p = 0.006$; 95%CI: 0.145-0.80), while no statistically

Table 1. *Clinical characteristics of the two treatment groups of children with JIA**

	TA (n = 19)	**TH (n = 23)**	**p**
Gender N (%)			
Girls	13 (68.4)	17 (74.0)	0.47
Boys	6 (31.6)	6 (26.0)	
Age years, median (minimum-maximum)	6.8 (5.3-9.2)	7.2 (6.2-9.0)	0.3
Age disease onset (years, median) (minimum-maximum)	4.6 (3.4-5.2)	5.8 (2.1-6.6)	0.13
Form of disease N (%)			
Oligoarticular persistent form	9 (47.4)	15 (65.2)	0.24
Oligoarticular extended form	2 (10.5)	3 (13.0)	0.06
Polyarticular RF†+ form	1 (5.3)	2 (8.8)	0.66
Polyarticular RF- form	7 (36.8)	3 (13.0)	0.71
Disease duration months, median (minimum-maximum)	14.0 (3-28)	17.0 (2-27)	0.28
Articular score at baseline N (%) **≥ 5** **4** **3**			
ESR‡ mm/h, median (minimum-maximum)	15 (6-23)	20 (11-35)	0.002
CRP§ mg/dl, median (minimum-maximum)	7.8 (2.1-24.8)	17.4 (10.5-28.1)	0.01
Injected joins N (%)	20 (43.5)	26 (56.5)	
NSAID¶ N (%)	9 (47.4)	16 (69.6)	0.25
NSAID+MTX N (%)**	8 (42.1)	5 (21.8)	0.15
MTX+TNFi ††N (%)	2 (10.5)	2 (8.7)	0.15
Duration of response after IAS injections N (%)			
3 week	–	1 (4.3)	
6 months	7 (36.8)	2 (8.7)	0.02
12 months	6 (31.6)	4 (17.4)	0.28
24 months	6 (31.6)	16 (69.6)	0.03

*juvenile idiopathic arthritis; †rheuma factor; ‡erythrocyte sedimentation rate, §C reactive protein, ‖antinuclear antibody, a¶Non-steroidal anti-inflammatory drug, **methotrexate, ††tumor necrosis factor inhibitor.

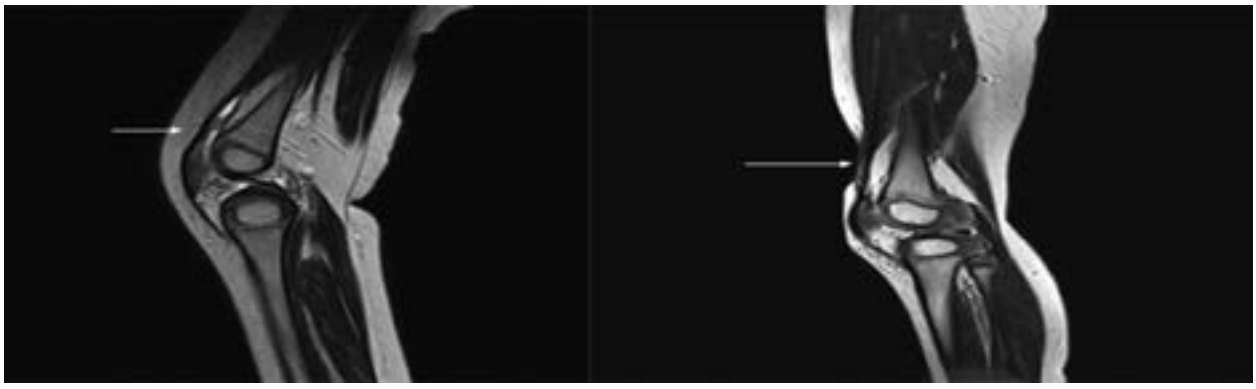


Figure 1A-B. *Magnetic resonance imaging T2 sagittal section, a knee of 2 year old girl.*
A: Normal subcutaneous tissue before corticosteroid application (arrow);
B: atrophic subcutaneous tissue 2 months after application of corticosteroids (arrow)

significant correlations were found between other analysed variables.

Two children, one in each group, developed side effects in the form of subcutaneous atrophy at the site of injection (Fig. 1). Resolution of subcutaneous atrophy was noted after 9 months in one child; while 14 months after the steroid injections, at the time of writing the article, there was no complete resolution of subcutaneous atrophy in the other child. One girl developed transient crystal synovitis following the application of TH, which spontaneously subsided within 14 days.

DISCUSSION

Intraarticular steroid usage is a safe treatment option in children with JIA (1, 5, 6). The intra-articular approach delivers a high concentration of corticosteroids to the primary site of pathology, where among other things down-regulates immunological processes production of proinflammatory cytokines (7). Ravelli et al. (8) reported that 52% of children achieved remission in injected joints, similar to Neidel et al. (9) and Cuncha et al. (10) who reported full remission of joint inflammation in 58–82% and more than 50% of large joints of children enrolled in their study. As TH has a lower solubility compared to TA, its absorption from the injected joint is slower, thereby maintaining synovial levels for a longer period, which may account for its enhanced efficacy (2, 11, 12). The results obtained by Zulian et al. (13) clearly showed that after 6 months 81.4% of joints injected with TH and 53.3% of joints injected with TA had no sign of inflammation. The six-month response rate after TH was similar to that reported in other studies, ranging from 67.6% to 82%, and regarding TA, researchers found a response rate lower (11, 14). However, Ravelli et al. (15), as well as Lapore et al. (16), observed a six-month arthritis remission in 69% and 68% of children after TA application. Our results were somewhat in accordance with the findings of the aforementioned studies. The short-term-six-month remission was observed in a large number of children following the application of TA than of TH. However, we noted twenty-four-month arthritis remission in 31.6% of children after TA, and in just about twice as many children after TH, 69.6% ($p = 0.03$). Six joints were still in remission after the twenty-four-month follow-up, four joints after TH, and two after TA injections. In a randomised controlled trial of TH versus TA in oligoarthritis, Martini et al. (16) observed that a significant improvement in the TH group was maintained over two years of follow-up. Neidel et al. (9) achieved two years remission in 78% of children after TH injections. Results obtained by some other researchers were similar, which showed that TH was more effective than TA in long-term follow-up (8, 10, 13). The studies showed thus longer response duration after IAS injections in children who developed arthritis at a younger age and had shorter disease duration at the time of IAS application, with higher activity of arthritis and in children with an oligoarticular form of the disease (13-16). Our findings were in accordance with that, the most frequent form of arthritis was oligoarticular in children enrolled in our study was oligoarticular, the median age was 7.1 years, median disease duration was 11 months (minimum and maximum from 2-28 months); in most children the activity of arthritis was moderate, and perhaps that explains why long term remission was achieved after IAS injections in a significant number of children included in our study. However, Leow et al. (2) and Zulian et al. (13**)** emphasised the difference between outcomes after the application of TA and TH, but they also did not find any difference in markers of inflammationor articular score. Our findings were somewhat different – considering the influence of the variables such as articular score, the value of ESR, CRP, and duration of disease – we only found a significant positive correlation between disease duration and remission duration in the group of children with TH. It seems that heterogeneity of the JIA children with different subtypes of arthritis may account for this different result. Studies showed an overall favorable adverse effect profile.Iatrogenic septic arthritis is very rare and can be avoided with aseptic precautionssince transient crystal synovitis is self-limited without any intervention (13-16). The most frequent adverse effects are atrophic skin changes at the site of injection, particularly of smaller joints such as wrists, ankles, and interphalangeal joints. Subcutaneous atrophy is a well-recognised adverse effect with resolution after two to four years (17,18). However, recent studies have shown a relatively high incidence of osteochondral lesions, and repetitive steroid injections need to be considered an associated risk factor (19, 20). In our study adverse effects of IAS in the form of subcutaneous atrophy at the site of injection developed in two children (remission occurred after nine months in one child, while the subcutaneous tissue was not completely recovered in another child); one girl developed transient crystal synovitis after TH applications, who underwent multiple IAS injections and spontaneous resolution of crystals occurred.

The Limitations of the Study

We presented the clinical outcomes of a small number of children in a short period for the assessment

of the final outcome. This can be evaluated many years after, not just after an initial follow-up.

CONCLUSION

This study has shown that IAS is safe for the treatment of joint inflammation in JIA, and TA is effective in short-term follow-up but TH is an optimum choice in long-term follow-up.

Abbreviations

CRP — C reactive protein
EMLA — Eutectic lidocaine/prilocaine cream
ESR — erythrocyte sedimentation rate
IAS — Intraarticular steroids
ILAR — International League of Associations for Rheumatology
JIA — juvenile idiopathic arthritis
MTX — Methotrexate
NSAID — Non-steroidal anti-inflammatory drug
RF — Rheuma factor
TA — triamcinolone acetonide
TH — triamcinolone hexacetonide
TNFI — Tumor necrosis factor inhibitor

Conflict of interest

All of the authors declare that they read and approved the final version of the manuscript. Additionally, there are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Funding: None

Licensing

Sažetak

INTRAARTIKULARNI STEROIDI U LEČENJU IDIOPATSKOG JUVENILNOG ARTRITISA: ISKUSTVO JEDNOG CENTRA

Ćosičkić Almira,[1] Alić Adin,[1] Suljendić Sanimir,[1] Selimović Amela,[1] Skokić Maida,[2] Delibegović Dina,[1] Delibegović Mirela[3]

[1] Clinic for Children's Diseases Tuzla, University Clinical Centre Tuzla, Bosnia and Herzegovina
[2] Clinic for Internal Medicine Tuzla, University Clinical Centre Tuzla, Bosnia and Herzegovina
[3] Clinic for Radiology and Nuclear Medicine, University Clinical Centre Tuzla, Bosnia and Herzegovina

Cilj: proceniti terapijski odgovor nakon aplikacije injekcije triamcinolon acetonida (TA) i triamcinolon heksacetonida (TH) u kolena dece s juvenilnim idiopatskim artritisom (JIA). **Materijal i metode:** U četrdeset šest zglobova od 42 dece aplikovan je TH ili TA u zavisnosti od dostupnosti leka. Dobar odgovor na aplikaciju steroida je definisan kao smanjenje zglobnog skora za 60% u odnosu na početnu vrednost, odsustvo ultrazvučnih karakteristika sinovitisa, dok su kliničke i laboratorijske varjable razmatrane kao prediktorni faktori ishoda. **Rezultati**: Najčešća forma JIA bila je oligoartikularna perzistenta u 24/42 (57.1%) dece. Šestomesečna remisija zabeležena je za 21.4% dece, nakon primene TA vs TH 36.8% vs 8.7% (p = 0.02). Odsustvo znakova upale kolena tokom 12 meseci imalo je 23.8% dece, nakon primene TA vs TH 31.6% vs 17.4% (p = 0.28). Dugoročna dvadesetčetvoromesečna remisija ostvarena je u 52.4% dece, u više od dvostrukog broja dece nakon TH (69.9%) nego nakon aplikacije TA (31.6%) (p = 0.03). Statistički značajna korelacija primećena je između vrednosti rezultata zglobnog skora i trajanja remisije nakon primene TH (r = 0.56, p = 0.006; 95% CI: 0.145-0.80). Dvoje dece razvilo je neželjene efekte u obliku atrofije potkožnog tkiva na mestu aplikacije, jedna devojčica je razvila prolazni kristalni sinovitis nakon primene TH. **Zaključak:** Naše skromno iskustvo pokazuje da je intraartikularna primena steroida siguran pristup lečenja upale zglobova dece s JIA, te da je TA efikasniji u kratkoročnom, ali da je TH optimalniji izbor u dugoročnom praćenju.

Ključne reči: Intraartikularni steroidi, deca, idiopatski artritis.

REFERENCES

1. Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol. 1998; 25(10): 1991-4.

2. Leow OM, Lim LK, Ooi PL, Shek LP, Ang EY, Son MB. Intra-articular glucocorticoid injections in patients with juvenile idiopathic arthritis in a Singapore hospital. Singapore Med J. 2014; 55(5): 248–52. doi: 10.11622/smedj.2014066.

3. Jennings H, Hennessy K, Hendry GJ. The clinical effectiveness of intra-articular corticosteroids for arthritis of the lower limb in juvenile idiopathic arthritis: a systematic review.

Pediatr Rheumatol Online J. 2014; 12:23. doi: 10.1186/1546-0096-12-23.

4. Bloom BJ, Alario AJ, Miller LC. Intra-articular corticosteroid therapy for juvenile idiopathic arthritis: report of an experiential cohort and literature review. Rheumatol Int. 2011; 31(6): 749-56. doi: 10.1007/s00296-010-1365-x.

5. D'Agostino MA, Terslev L, Aegerter P, Backhaus M, Balint P, Bruyn GA, et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce-Part 1: definition and development of a standardized, consensus-based scoring system. RMD Open. 2017; 3(1): e000428. doi: 10.1136/rmdopen-2016-000428.

6. Ruth NM, Passo MH. Juvenile idiopathic arthritis: management and therapeutic options. Ther Adv Musculoskelet Dis. 2012; 4(2): 99-110. doi: 10.1177/1759720X11413630.

7. Zulian F, Martini G, Gobber D, Agosto C, Gigante C, Zacchello F. Comparison of intra-articular triamcinolone hexacetonide and triamcinolone acetonide in oligoarticular juvenile idiopathic arthritis. Rheumatology (Oxford) 2003; 42(10): 1254-9. doi: 10.1093/rheumatology/keg358.

8. Ravelli A, Davì S, Bracciolini G, Pistorio A, Consolaro A, van Dijkhuizen EHP, et al. Intra-articular corticosteroids versus intra-articular corticosteroids plus methotrexate in oligoarticular juvenile idiopathic arthritis: a multicentre, prospective, randomised, open-label trial. Lancet. 2017; 389(10072): 909-16. doi: 10.1016/S0140-6736(17)30065-X.

9. Neidel J, Boehnke M, Küster RM. The efficacy and safety of intraarticular corticosteroid therapy for coxitis in juvenile rheumatoid arthritis. Arthritis Rheum. 2002; 46(6): 1620–8. doi: 10.1002/art.10313.

10. Cuncha ALG, Miotto E Silva VB, Osaku FM, Niemxeski LB, Furtado RN, Natour J et al. Intra-articular injections in patients with juvenile idiopathic arthritis: factor associated with a good response. Rev Bras Reumatol Engl Ed. 2016; 56(6): 490-6. doi: 10.1016/j.rbre.2016.01.001.

11. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken). 2011; 63(4): 465-82. doi: 10.1002/acr.20460.

12. Brown GT, Wright FV, Lang BA, Birdi N, Oen K, Stephens D, et al. Clinical responsiveness of self-report functional assessment measures for children with juvenile idiopathic arthritis undergoing intraarticular corticosteroid injections. Arthritis Rheum. 2005; 53(6): 897–904. doi: 10.1002/art.21599.

13. Zulian F, Martini G, Gobber D, Plebani M, Zacchello F, Manners P. Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial. Rheumatology (Oxford) 2004; 43(10): 1288–91. doi: 10.1093/rheumatology/keh313.

14. Ravelli A, Lattanzi B, Consolaro A, Martini A. Glucocorticoids in pediatric rheumatology. Clin Exp Rheumatol. 2011; 29(Suppl 68): S148-52.

15. Lepore L, Del Santo M, Malorgio C, Presani G, Perticarari S, Prodan M, et al. Treatment of juvenile idiopathic arthritis with intra-articular triamcinolone hexacetonide: evaluation of clinical effectiveness correlated with circulating ANA and T gamma/delta + and B CD5+ lymphocyte populations of synovial fluid. Clin Exp Rheumatol. 2002; 20(5): 719–22.

16. Martini G, Gobber D, Agosto C, Vianello A, Zulian F.. Comparison between intraarticular triamcinolone hexacetonide and acetonide in oligoarticular JIA. Ann Rheum Dis. 2001; 60(Suppl 11): ii, 12.

17. Lanni S, Bertamino M, Consolaro A, Pistorio A, Magni-Manzoni S, Galasso R, et al. Outcome and predicting factors of single and multiple intra-articular corticosteroid injections in children with juvenile idiopathic arthritis. Rheumatology (Oxford). 2011; 50(9): 1627-34. doi: 10.1093/rheumatology/ker165.

18. Papadopoulou C, Kostik M, Gonzalez-Fernandez MI, Bohm M, Nieto-Gonzalez JC, Pistorio A. et al. Delineating the role of multiple intra-articular corticosteroid injections in the management of juvenile idiopathic arthritis in the biologic era. Arthritis Care Res (Hoboken). 2013; 65(7): 1112-20. doi: 10.1002/acr.21947.

19. Heidt C, Grueberger N, Grisch D, Righini-Grunder F, Rueger M, Ramseier L. . The assessment of steroid injections as a potential risk factor for osteochondral lesions in children with juvenile idiopathic arthritis. Cartilage. 2020; doi:1947603520961173.

20. Kubo H, Oommen PT, Hufeland M, Heusch P, Laws HJ, Krauspe R, et al. Osteochondritis dissecans shows a severe course and poor outcome in patients with juvenile idiopathic arthritis: a matched pair study of 22 cases. Rheumatol Int. 2018; 38(9): 1705-12. doi: 10.1007/s00296-018-4100-7.

Correspondence to/Autor za korespondenciju
Adin Alić
Mehmedalije Maka Dizdara 35, 75000 Tuzla,
Bosna and Herzegovina
Tel: +387 61 64 96 54
Email: adin.alic@ukctuzla.ba

SANAMED
2021; 16(1): 47–54
ISSN-1452-662X

DOI:10.24125/sanamed.v16i1.485
UDK: 616.35-072.1(560)"2008/2018"
ID:37477129
Original article

WHEN AND FOR WHICH PATIENTS SHOULD WE PERFORM ILEAL INTUBATION AND ILEAL BIOPSY DURING COLONOSCOPY

Akturk Remzi,[1] Serinsoz Serdar[2]

[1] Department of Surgery, Istanbul Gelisim University, Avcılar, Istanbul, Turkey
[2] Department of Medical Imaging, Beykent University, Turkey

Primljen/Received 04. 01. 2021. god. Prihvaćen/Accepted 21. 02. 2021. god.

Abstract: **Background:** Terminal ileum intubation(TI) is an important part of a colonoscopy. In this study, we investigated whether patients should be selected according to their symptoms rather than taking a biopsy from all of them, or whether biopsies should be taken from patients with visual pathology only detected in the mucosa.

Material and methods: Between 2008 and 2018, patients who underwent colonoscopy and ileal biopsy in our Endoscopy Unit were investigated. We evaluated patients with right iliac fossa pain, diarrhoea, and anaemia as well as patients with a high incidence of suspected inflammatory bowel disease (IBD) and high ileal abnormality in patients undergoing colonoscopy (group A). Patients with other indications were included in another group (Group B).

Results: A total of 479 patients were planned for TI according to their symptoms and colonoscopy was performed. Both microscopic and macroscopic findings were found to be more prevalent in patients with right iliac fossa pain, diarrhoea (group A), and rectal bleeding, and significantly different from patients with other symptoms (group B) ($p < 0.05$).

Conclusion: We recommend that patients undergoing colonoscopy with gastrointestinal complaints also undergo ileoscopy as much as possible and that blind biopsies be taken, at least in patients with symptoms suggestive of IBD even if the mucosa is macroscopically normal. The negative results we found strengthened the diagnosis of Irritable Bowel Syndrome (IBS) and made it easier for us to proceed with IBS treatment.

Key words: Colonoscopy, ileal biopsy, ileal intubation, ileocolonoscopy, terminal ileum.

INTRODUCTION

Colonoscopy is an imaging modality that plays an important role in the diagnosis of many diseases. Terminal ileum intubation (TI) is also an important part of this examination (1). With successful TI, ileoscopy has become an important part of colonoscopy, especially in patients with inflammatory bowel disease, diarrhoea, small bowel lymphoma, cytomegalovirus (CMV), and tuberculosis ileitis (2-5). In ideal routine intubations, rare small bowel tumors such as carcinoids can also be detected (6). Furthermore, it is suggested that TI may be useful for the diagnosis of portal hypertension because hyperplasia is accompanied by hypertensive gastropathy and colopathy in a third of patients with portal hypertension (7). Ileal imaging and/or ileal biopsy (IB) is the best proof for TI such as colonic tenia unification (triradiate fold), appendiceal orifice, and ileocecal valve (ICV) photographs which are signs of arriving at the cecum suggested by the American Society of Gastrointestinal Endoscopy (ASGE) (3). Thus, it is shown that the colonoscopy was done completely. Otherwise, there may be serious diagnostic errors if one is not sure whether the colonoscopy was done properly, which would result in disadvantages for the patient. ICV intubation depends on factors primarily such as endoscopist experience and secondly colon cleansing, ICV morphology, patient age, sex, body mass index, diverticulosis, and past abdominopelvic operations and can be performed in 80-95% of patients (8). In our study, intussusception was difficult due to inadequate bowel cleansing and the anatomic placement of the ileocecal valve (9). However, when we detected ileocecal lips, we performed intubation using biopsy forceps as a guide in case of intubation difficulties (10). Sublingual glyceryl trinitrate is known to be used to facilitate Oddi cannulation in endoscopic retrograde cholangiopancreatography (ERCP). Hill PA and colleagues did not observe the difference between the two groups in their study with 800 micrograms of sublingual glyceryl trinitrate and 0.9% saline solution

before the procedure, and they attributed TI to the endoscopist's experience (11). Willcock and colleagues suggested that arriving at the cecum and intubating the ICV is easier in the modified lithotomy (supine) position than in the left lateral position (12). Some investigations have suggested that inflation of water and CO2 instead of air during colonoscopy in patients, especially with inflammatory bowel disease, will provide better post-procedural comfort, easier procedure, and easier TI (13, 14). The lack of image clarity in colonoscopy with water may increase the risk of colon perforation especially in patients with diverticulosis. Clark and colleagues suggested that ileum mucosa is also detected in ICV biopsies without TI but also agree that TI and IB are required (15). There are also studies showing that ileal imaging is more important than cecal imaging in confirming complete colonoscopy (16). However, IB is better for understanding complete colonoscopies, but if there is no visual pathology in the ileal mucosa, it is debated whether to take the biopsy from the ileum because the pathology detection rate is low (0.3-7%). However, in the current approach, the appearance of villus structure with TI is considered sufficient to demonstrate the completion of colonoscopy. The same investigations find routine IB unnecessary in patients with normal ileal mucosa, except for patients who are undergoing control colonoscopy because of inflammatory bowel disease (17, 18, 19). In this study, we investigated whether patients should be selected according to their symptoms rather than taking a biopsy from all of them, or whether biopsies should be taken from patients with visual pathology only detected in the mucosa.

MATERIAL AND METHODS

Between 2008 and 2018, patients who underwent colonoscopy and IB at the SAFA Hospital Group Endoscopy Unit (Istanbul/Turkey) with abdominal pain, chronic diarrhoea, chronic constipation, anaemia, rectal bleeding, weight loss, and proctological complaints were retrospectively reviewed. Clinical data and details of the histopathological diagnoses were obtained from the endoscopy database and patient records. We evaluated patients with right iliac fossa (RIF) pain, diarrhoea, and anaemia as patients with a high incidence of suspected IBD (Inflammatory Bowel Disease) and high ileal abnormality in patients undergoing colonoscopy (group A). Patients with other indications formed the other group (group B). They were evaluated for macroscopically significant findings of ulceration, erosion, stenosis, or inflammation on colonoscopy in the terminal ileum. The only nodularity in the distal ileum mucosa was accepted as a macroscopically nonspecific finding and recorded as a routine biopsy (20, 21). Attempts were made to take biopsies from lesions at least 5 cm distal to the lesions. Chronic nonspecific ileitis, oedema, hyperaemia, and lymphoid hyperplasia were accepted as nonspecific findings and evaluated as pathologically meaningless. Cases with active chronic ileitis, structural distortion, erosion, ulceration, cryptitis, crypt abscess, fibrosis, and Paneth cell hyperplasia were considered microscopically significant (21).

Post-biopsy pain complaining patients were evaluated by the radiology medical imaging department for determining possible complications and avoiding unnecessary surgical procedures.

Statistical analysis

The data were arranged as SPSS 18 data, and it was determined that the data were not normally distributed as a result of the measurements of skewness and kurtosis. As a result, mean, standard deviation, range, minimum and maximum values, and percentage were measured for the parameters of ileal intubation time. Symptom parameters were tested with the Kruskal-Wallis test for ileal pathology. Also, two groups with significant differences were compared again with the Mann-Whitney U test. A P value of < 0.05 was taken as statistically significant. However, the two groups with macroscopic and microscopic findings were also assessed with a correlation between themselves. All procedures performed were with the standard of the institutional research ethics committee and the 1964 Helsinki declaration and its later amendments.

Availability of data and materials

The data that support the findings of this study are available from SAFA Hospital Group but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of SAFA Hospital Group.

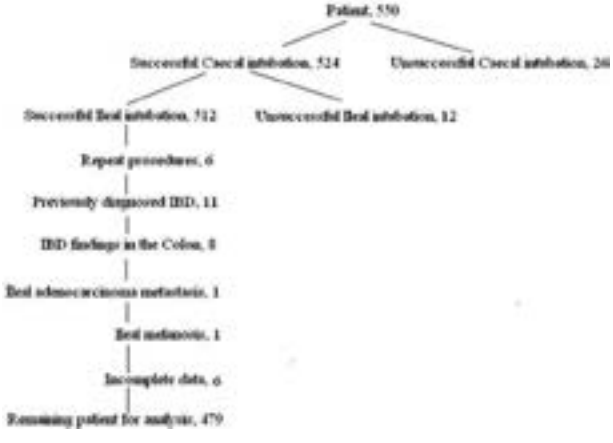


Figure 1. *Patient selection*

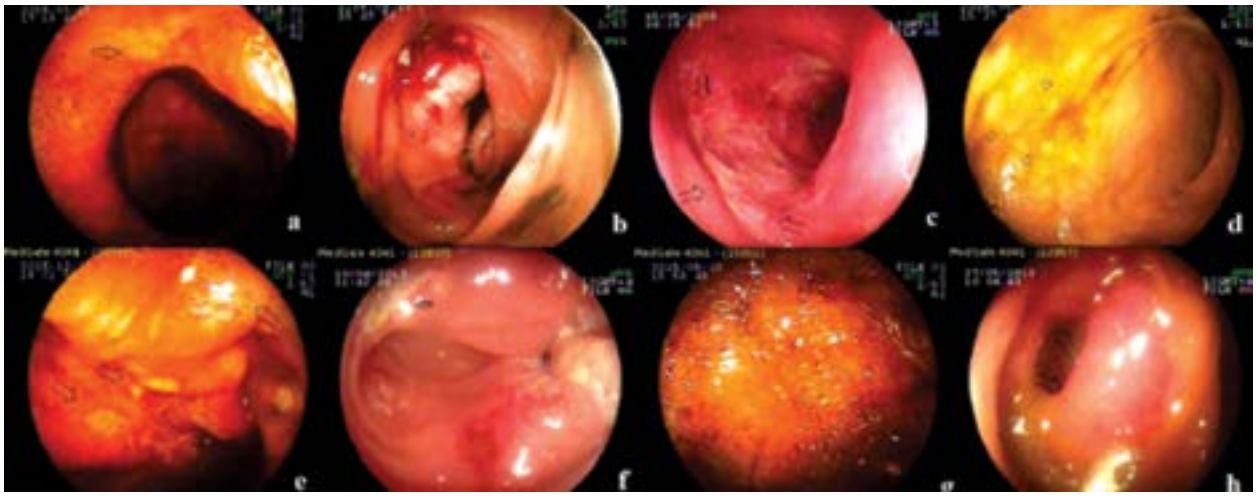


Figure 2. *Macroscopic abnormality of ileum; backwash ileitis (a, b, c), nodular ileitis (lymphoid hyperplasia, d), Crohn disease (CD) (e, f), ileal melanosis (g), ileal adenocarcinoma metastasis (h)*

RESULTS

Of the 5146 colonoscopies performed in 10 years, 550 patients with TI planned and applied according to their symptoms were evaluated.

The cecum was reached in the majority of patients (524/550, 95.27%). Only 22 patients had insufficient bowel cleansing, 3 patients had morbid obesity, and 1 patient had late adhesions due to recurrent abdominal surgery. Therefore, the cecum could not be reached in these patients. Almost all of the patients underwent TI (512/524, 97.71%). 33 patients were excluded from the study because inflammatory bowel disease macroscopic findings were detected in the colon (8/33), IBD was detected before (11/33), adenocarcinoma metastasis was detected in the pathology (1/33), ileal melanosis was present (1/33), and the procedure was repeated (6/33), or incomplete data (6/33) (Figure 1, Figure 2). For this reason, only 479/550 patients were included in the study. The mean age of the patients was 40.80 ± 14.807 (14-84) years and there was no significant difference between macroscopic findings and microscopic findings according to age ($P > 0.05$). The mean TI time of 3.16 ± 2.078 (1-15) was observed. There was no significant difference in terms of TI time between male and female patients ($p > 0.05$).

As seen in Table 1, the incidence of macroscopic findings was significantly higher in males than in females ($P < 0.05$).

As seen in Table 2, the incidence of macroscopic findings on colonoscopy was the same as microscopic findings in constipated patients ($p > 0.05$). Both microscopic and macroscopic findings were found to be more prevalent in patients with RIF pain, diarrhoea, and rectal bleeding, and significantly different from patients with other symptoms ($p < 0.05$). Microscopic findings and macroscopic findings can be seen together, and most microscopic findings are not accompanied by macroscopic findings ($P < 0.05$). Although there are more macroscopic findings in patients with proctologic symptoms, microscopic findings do not accompany this finding ($p > 0.05$).

As seen in table 3, microscopic pathology was observed in 70.3% (78/111) of the patients with macroscopic pathology, while macroscopic pathology was detected in 36.97% (78/211) of the patients with microscopic pathology. A weak correlation was found between macroscopic findings and microscopic findings (r: 0.290). As expected, there is a positive correlation between macroscopic findings and microscopic findings ($p > 0.05$).

Table 1. *Ileal pathology distribution according to gender*

Gender	Ileal Pathology									
	Normal		Mac. Signs		Mic. Signs		Mac.&Mic. Signs		Total	
	n	%	n	%	n	%	n	%	n	%
Woman	125	26.1	9	1.9	57	11.9	34	7.1	225	47.0
Man	110	23.0	**24**	**5.0**	76	15.9	44	9.2	254	53.0
Total	235	49.1	33	6.9	133	27.8	78	16.3	479	100

Table 2. *Distribution of macroscopic and microscopic findings between symptoms*

Major indication for colonoscopy	Ileal Pathology									
	Normal		Mac. Signs		Mic. Signs		Mac.&Mic. Signs		Total	
	n	%	n	%	n	%	n	%	n	%
Group A										
RIF Pain	14	2.9	1	0.2	**62**	**12.9**	**32**	**6.7**	109	22.8
diarrhoea	11	2.3	2	0.4	**29**	**6.1**	**15**	**3.1**	57	11.9
anaemia	10	2.1	0	0	1	0.2	0	0	11	2.3
Subtotal	35	7.3	3	0.6	94	19.6	47	9.8	179	37.4
Group B										
Nonspecific abdominal pain	32	6.7	2	0.4	3	0.6	0	0	41	8.6
Constipation	101	21.1	**17**	**3.5**	**17**	**3.5**	**16**	**3.3**	151	31.5
Rectal Bleeding	12	2.5	3	0.6	**16**	**3.3**	**11**	**2.3**	42	8.8
Proctological Symptoms	46	9.6	**7**	**1.5**	4	0.8	3	0.6	60	12.5
Weight Loss	7	1.5	0	0	2	0.4	1	0.2	10	2.1
Subtotal	200	41.8	30	6.3	39	8.1	31	6.5	300	62.6
Total	235	49.1	33	6.9	133	27.8	78	16.3	479	100

Table 3. *Crosstab comparison of macroscopic and microscopic findings*

			Microscopic pathology		Total
			Absent	Present	
Macroscopic pathology	**Absent**	**Count**	235	133	368
		Expected Count	205.9	162.1	368.0
		% within macroscopic pathology	63.9%	36.1%	100.0%
	Present	**Count**	33	78	111
		Expected Count	62.1	48.9	111.0
		% within macroscopic pathology	29.7%	70.3%	100.0%
Total		**Count**	268	211	479
		Expected Count	268.0	211.0	479.0
		% within macroscopic pathology	55.9%	44.1%	100.0%

Table 4. *Distribution of disease between the groups*

Disease	Group					
	Group A		Group B		Total	
	n	%	n	%	n	%
IBS	38	7.9%	230	48.0%	268	55.9%
Crohn disease	22	4.6%	9	1.9%	31	6.5%
TBC	2	0.4%	0	0.0%	2	0.4%
Infection	94	19.6%	47	9.8%	141	29.4%
Drug	23	4.8%	14	2.9%	37	7.7%
Total	179	37.4%	300	62.6%	479	100.0%

Figure 3. *Distribution of ileal pathology and disease*

When microscopic abnormalities are examined according to pathologies, drug use and abuse play an important role in infection (94/179) accounted for 19.6% of the patients in group A, while patients with irritable bowel syndrome (IBS) (230/300) accounted for 48% of group B. Drugs are especially important in both groups. This rate is close to inflammatory bowel diseases (Table 4, Figure 3).

DISCUSSION

In the vast majority of patients, the cecum was reached (524/550, 95.27%) and TI was performed in almost all patients (512/524, 97.71%). In different studies, it was reported that the rate of access to the cecum is 93.6% to 99% and the rate of TI is 87% to 97% (8, 9, 16, 22). We found that the mean TI time was 3.16 ± 2.078 (1-15) in our study. The incidence of macroscopic findings was significantly higher in males than in females ($p < 0.05$). In a study conducted in 2005, it was reported that many factors such as colon resection surgery and experienced endoscopy staff shortened the TI time, but most importantly, the large intestine must be adequately cleaned. In the same study, the meantime to reach the cecum was 10.5 ± 10.2 min (9). The mean TI duration was reported to be between 1 and 6.4 minutes, depending on the endoscopy team and patient-related factors (8, 9, 16). In our study, the experience of the colonoscopist, the technical characteristics of the device (especially the relaxation of the rotation mechanism over time), and the additional manoeuvre experience of the endoscopy nurse were factors that related to the procedure affecting the TI time. Morbid obesity, a previous abdominal operation, and most importantly, adequate bowel cleansing were the patient-related factors. There was no significant difference between male and female patients in terms of TI time ($p > 0.05$). While microscopic findings are detected with symptoms of IBD such as RIF pain, diarrhoea, and rectal bleeding, macroscopic findings may not accompany these microscopic findings. The reason for this may be that every patient can easily undergo colonoscopy nowadays so that the disease can be detected during the remission phase. Some studies have identified mucosal macroscopic pathology rate as 1.35% and histopathologic pathology rate as 0.33% in randomised IB cases, suggesting that routine TI is not necessary (17, 23). Kunrotas LW and colleagues showed that the diagnostic value of TI and IB is low if the colon is normal in colonoscopies performed in patients with chronic diarrhoea without rectal bleeding (17). A positive diagnosis rate is given as 2.7-5% with TI and IB in asymptomatic patients, and some studies suggest that TI is an important aid for colonoscopy, especially in diarrhoeal patients (18, 24). In our study, we found macroscopic and microscopic findings in patients with constipation and proctologic complaints, although there were no symptoms suggestive of IBD. Some studies have shown that patients with symptoms suggestive of IBD have a significantly higher incidence of histological ileal abnormalities than others (1, 2, 18, 25).

In some of the patients without macroscopic findings, microscopic findings appeared, which weakens the correlation between macroscopic findings and microscopic findings (r: 0,290). Misra SP and colleagues found that histological examination of biopsies taken from the normal-looking cecum and terminal ileum was useful in a small but significant number of patients with colonic tuberculosis (5). In some studies, histopathologic abnormalities were detected in 27/764 patients (3.53%) despite endoscopically normal terminal ileum. Of these patients, 82.46% did not have mucosal abnormality during endoscopy. However, significant ileal abnormality (Crohn's Disease, inflammation, and inflammation-related) was detected by TI and IB in 1.9% of these patients. They suggested that these patients who did not undergo TI and IB could not be diagnosed and that it could lead to misdiagnosis during diagnosis and treatment (2). Makkar L. et al. found the diagnostic values of TI and IB are low if the colon mucosa is normal during endoscopies in patients with chronic, non-bloody diarrhoea. However, they suggested that TI and IB may provide supportive evidence for patients with previously diagnosed ileocolonic Crohn's disease (21). Borcsh G et al. (19) proposed routine TI in all patients undergoing a colonoscopy as a diagnostic procedure with suspected or identified inflammatory bowel disease and/or persistent diarrhoea, lower gastrointestinal tract bleeding or IBS (19). Another study showed that TI has a high diagnostic yield and this study found 14% (8/57) of ileal abnormalities in patients with normal colonoscopy or barium enema (25).

While the negative results distanced us from IBD diagnosis, they brought us closer to IBS diagnosis and made it easier for us to proceed with IBS treatment. In a multicentre study, it was suggested that TI and IB should be an integral part of colonoscopy in patients with RIF pain, diarrhoea, anaemia, suspected

IBD, or elevated inflammatory markers. In this group of patients, even if the macroscopic appearance of the colon and the terminal ileum are sometimes normal, TI and IB can provide additional information for the colonoscopy diagnostic findings and effects. Also, TI and IB are relatively easy and there is no risk of additional adverse effects. However, they did not find strong enough evidence to recommend routine use in all cases, and they found that the diagnostic yield was low in patients without suspected IBD. Thus, in addition, they considered that the cost of routine ileal histology may be another disadvantage (2). Some studies suggest TI and IB in symptomatic patients as a diagnostic procedure for suspected or diagnosed IBD, IBS with chronic diarrhoea, and lower GI bleeding. In particular, they suggested that the nonpathological emergence of IB as a diagnostic procedure for IBS has diagnostic value in terms of showing the absence of organic pathologies (19, 22). Kundrotas LW and colleagues suggest that TI and IB should be performed in colonoscopies for screening purposes, although the detection rate of abnormal microscopic findings is too low to be considered, as TI and IB do not lead to time and cost loss (23).

When microscopic abnormalities are examined according to pathologies, drug use and abuse play an important role. Infections (94/179) accounted for 19.6% of the patients in group A, while IBS patients (230/300) accounted for 48% of group B. Drugs are especially important in both groups. This rate is close to inflammatory bowel diseases (Table 4). The similarity of inflammatory bowel disease and microscopic ileal pathology with drug use may also be the subject of a separate study. Kennedy G and colleagues showed poor abnormal macroscopic ileal findings in only 1% of patients and microscopic ileal abnormalities were detected in only 0.3% of all patients; thus, suggesting that TI should not be a necessary part of the screening colonoscopy (23). Mohammad Hassan Emami et al. stated that normal ileal findings in TI pathology+ helped to exclude IBD in diagnosis in 78 patients with abdominal pain, weight loss, low GI bleeding, or colonic inflammation, and in this study 82 patients (86.3%) showed that TI and IB were clinically valuable findings. TI is safe, fast and feasible; therefore, it is recommended in all symptomatic cases since normal findings are valuable in the clinical management of patients. Given normal findings, they came to the conclusion that routine TI has a surprisingly high diagnostic yield compared to the results of previous studies (22).

CONCLUSION

As a result, we recommend that patients undergoing colonoscopy with gastrointestinal complaints undergo ileoscopy as much as possible and that blind biopsies be taken, at least in patients with symptoms suggestive of IBD even if the mucosa is macroscopically normal. Besides, we do not believe that colonoscopy can be completed without ileoscopy. The negative results we found strengthened the diagnosis of IBS and made it easier for us to proceed with IBS treatment. These results made it possible to easily add antidepressants to IBS treatment.

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Licensing

Ethics approval and consent to participate: The study was approved by S.B.U. Istanbul Education and Research Hospital Clinical Research Ethics Committee (Approval no: 2159).

Authors' contributions: I would like to thank Serdar SERINSOZ MD, responsible for our radiology department, for his contributions to both data and writing. All authors read and approved the final manuscript.

Acknowledgments: I would like to thank everyone who contributed to this study, especially my family and author friends.

Sažetak

KADA I ZA KOJE PACIJENTE JE INDIKOVANA IILEOSKOPIJA I BIOPSIJA TOKOM KOLONOSKOPIJE

Akturk Remzi,[1] Serinsoz Serdar[2]

[1] Department of Surgery, Istanbul Gelisim University, Avcılar, Istanbul, Turkey

[2] Department of Medical Imaging, Beykent University, Turkey

Uvod: Intubacija terminalnog ileuma (TI) važan je deo kolonoskopije. U ovoj studiji istraživali smo da li pacijente treba birati prema njihovim simptomima, bez uzimanja biopsije od svih, ili treba uzimati biopsije kod pacijenata sa vizuelnom patologijom koja je otkrivena samo na sluznici.

Metode: Između 2008. i 2018. istraživani su pacijenti koji su bili podvrgnuti kolonoskopiji i biopsiji ileusa u našoj jedinici za endoskopiju.

Ispitivali smo pacijente sa bolom u desnoj ilijačnoj jami, dijarejom i anemijom, kao i pacijente sa velikom učestalošću sumnje na inflamatorno oboljenje creva (IBD) i abnormalnosti ileuma kod pacijenata podvrgnutih kolonoskopiji (Grupa A). Pacijenti sa drugim indikacijama bili su uključeni u drugu grupu (grupa B).

Rezultati: Obavljeno je ukupno 479 pacijenata kojima je planirano TI u skladu sa simptomima i kolonoskopijom. Utvrđeno je da su i mikroskopski i makroskopski nalazi zastupljeniji kod pacijenata sa bolom u desnoj ilijačnoj jami, dijarejom (grupa A) i rektalnim krvarenjem i značajno se razlikuju od pacijenata sa drugim simptomima (grupa B) ($p < 0,05$).

Zaključak: Preporučujemo da se pacijenti nakon kolonoskopije sa gastrointestinalnim tegobama takođe podvrgavaju ileoskopiji što je više moguće i da se uzimaju slepe biopsije, barem kod pacijenata sa simptomima koji sugerišu IBD, čak i ako je sluznica makroskopski normalna. Negativni rezultati koje smo pronašli ojačali su dijagnozu sindroma iritabilnog creva (IBS) i olakšali nam nastavak lečenja IBS.

Ključne reči: Kolonoskopija, biopsija ileala, intubacija ileala, ileokolonoskopija, terminalni ileum.

REFERENCES

1. Misra SP, Dwivedi M, Misra V. Ileoscopy in 39 hematochezia patients with normal colonoscopy. World J Gastroenterol. 2006; 12(19): 3101-4. doi: 10.3748/wjg.v12.i19.3101.

2. Wijewantha HS, de Silva AP, Niriella MA, Wijesinghe N, Waraketiya P, Kumarasena RS, et al. Usefulness of routine terminal ileoscopy and biopsy during colonoscopy in a tropical setting: a retrospective record-based study. Gastroenterol Res Pract. 2014; 2014: 343849. doi: 10.1155/2014/343849.

3. Rex DK, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE, et al. Quality indicators for colonoscopy. *Gastrointest Endosc.* 2006; 63(Suppl 4): S16-28. doi: 10.1016/j.gie.2006.02.021.

4. Mansuri I, Fletcher JG, Bruining DH, Kolbe AB, Fidler JL, Samuel S, et al. Endoscopic skipping of the terminal ileum in pediatric Crohn disease. *AJR Am J Roentgenol.* 2017; 208(6): W216-24. doi: 10.2214/AJR.16.16575.

5. Misra SP, Dwivedi M, Misra V, Gupta M, Kunwar BK.Endoscopic biopsies from normal-appearing terminal ileum and cecum in patients with suspected colonic tuberculosis. *Endoscopy.* 2004; 36(7): 612-6. doi: 10.1055/s-2004-814518.

6. Ten Cate EM, Wong LA, Groff WL, Miller AT. Post-surgical surveillance of locally advanced ileal carcinoids found by routine ileal intubation during screening colonoscopy: a case series. J Med Case Rep. 2014; 8:444. doi: 10.1186/1752-1947-8-444.

7. Rana SS, Bhasin DK, Jahagirdar S, Raja K, Nada R, Kochhar R, et al. Is there ileopathy in portal hypertension? *J Gastroenterol Hepatol*. 2006; 21(2): 392-7. doi: 10.1111/j.1440-1746.2005.04037.x.

8. Iacopini G, Frontespezi S, Vitale MA, Villotti G, Bella A, d'Alba L, et al.Routine ileoscopy at colonoscopy: a prospective evaluation of the learning curve and skill-keeping line. Gastrointest Endosc. 2006; 63(2): 250-6. doi: 10.1016/j.gie.2005.09.029.

9. Zuber-Jerger I, Endlicher E, Gelbmann CM.Factors affecting cecal and ileal intubation time in colonoscopy. Med Klin (Munich). 2008; 103(7): 477-81. doi: 10.1007/s00063-008-1071-6.

10. Abdulla HM, Bachar M, Chamberlain SM. Forceps-assisted intubation of the ileocecal valve. Gastrointest Endosc. 2016; 83(3): 662-3. doi: 10.1016/j.gie.2015.09.014.

11. Hill PA, Panteleimonitis S, McKay G, Watson C, Prach A, Macdonald A. Sublingual glyceryl trinitrate during colonoscopy and terminal ileal intubation: a randomized controlled trial. Scott Med J. 2017; 62(1): 11-15. doi: 10.1177/0036933017690465.

12. Willcock H, Gold DM. Supine colonoscopy: an advantage over left lateral in synchronous proctological surgery. J. Laparoendosc Adv Surg Tech A. 2016; 26(6): 475-7. doi: 10.1089/lap.2015.0609.

13. Falt P, Šmajstrla V, Fojtík P, Urban O, Hill M. Water-aided colonoscopy in inflammatory bowel disease patients-a randomised, single-centre trial. J Crohns Colitis. 2015; 9(9): 720-4. doi: 10.1093/ecco-jcc/jjv093.

14. Falt P, Šmajstrla V, Fojtík P, Hill M, Urban O. Carbon dioxide insufflation during colonoscopy in inflammatory bowel disease patients: a double-blind, randomized, single-centre trial. Eur J Gastroenterol Hepatol. 2017; 29(3): 355-9. doi: 10.1097/MEG.0000000000000791.

15. Clark DA, Rocker M, Reddy M, Aslam M, Owen SM. Confirmation of complete colonoscopy without intubation of the ileum. Colorectal Dis. 1999; 1(5): 283-5. doi: 10.1046/j.1463-1318.1999.00072.x.

16. Powell N, Knight H, Dunn J, Saxena V, Mawdsley J, Murray C, et al. Images of the terminal ileum are more convincing than cecal images for verifying the extent of colonoscopy. Endoscopy. 2011; 43(3): 196-201. doi: 10.1055/s-0030-1256174.

17. Kennedy G, Larson D, Wolff B, Winter D, Petersen B, Larson M. Routine ileal intubation during screening colonoscopy: a useful manoeuvre? Surg Endosc. 2008; 22(12): 2606-8. doi: 10.1007/s00464-008- 9843-x.

18. Zwas FR, Bonheim NA, Berken CA, Gray S. Diagnostic yield of routine ileoscopy. Am J Gastroenterol. 1995; 90(9): 1441-3.

19. Borsch G, Schmidt G. Endoscopy of the terminal ileum. Diagnostic yield in 400 consecutive examinations. Dis Colon Rectum. 1985; 28(7): 499-501. doi: 10.1007/BF02554095.

20. Tontini GE, Vecchi M, Pastorelli L, Neurath MF, Neumann H. Differential diagnosis in inflammatory bowel disease colitis: State of the art and future perspectives. World J Gastroenterol. 2015; 21(1): 21–46. doi: 10.3748/wjg.v21.i1.21.

21. Makkar R, Lopez R, Shen B. Clinical utility of retrograde terminal ileum intubation in the evaluation of chronic non-bloody diarrhoea. J Dig Dis. 2013; 14(10): 536-42. doi: 10.1111/1751-2980.12082.

22. Emami MH, Behbahan IS, Zade HD, Daneshgar H. A new interpretation for the diagnostic yield of ileoscopy: A prospective study and a brief review. J Res Med Sci. 2009; 14(3): 157–63.

23. Kundrotas LW, Clement DJ, Kubik CM, Robinson AB, Wolfe PA.A prospective evaluation of successful terminal ileum intubation during a routine colonoscopy. Gastrointest Endosc. 1994; 40(5): 544-6. doi: 10.1016/s0016-5107(94)70249-7.

24. Annese V, Daperno M, Rutter MD, Amiot A, Bossuyt P, East J, et al. European Crohn's and Colitis Organisation. European evidence-based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis. 2013; 7(12): 982-1018. doi: 10.1016/j.crohns.2013.09.016.

25. Bhasin DK, Goenka MK, Dhavan S, Dass K, Singh K. Diagnostic value of ileoscopy: a report from India. J Clin Gastroenterol. 2000; 31(2): 144-6. doi: 10.1097/00004836-200009000-00011.

Correspondence to/Autor za korespondenciju
Remzi Akturk
Address: Private Safa Hospital; Zafer Mh, Ahmet Yesevi cd. Gümüş sk No 9/11 Bahçelievler/Istanbul
Mobile Phone, Phone: +90 532 253 56 24, 0 850 878 7232 / 2137
E mail: dremzi@gmail.com
Orcid Id: 0000-0002-1951-2087

SANAMED
2021; 16(1): 55–63
ISSN-1452-662X

DOI:10.24125/sanamed.v16i1.503
UDK:616.98:578.834]-053.2(497.6)"2020"
ID:37501705
Original article

COVID-19 TRIAGE AMONG HOSPITALIZED NEONATES IN TUZLA CANTON

Devleta Hadzic,[1] Fahrija Skokic,[1] Selmira Brkic[2]

[1] Pediatric Clinic, University Clinical Center of Tuzla, Bosnia and Herzegovina
[2] Faculty of Medicine University of Tuzla, Bosnia and Herzegovina

Primljen/Received 16. 03. 2021. god. Prihvaćen/Accepted 16. 04. 2021. god.

Abstract: **Aim:** To evaluate the incidence, characteristics, transmission, and outcomes of COVID-19 infection in hospitalized neonates in Tuzla Canton and to emphasize the importance of quality triage in the prevention and control of infection.

Material and Methods: A retrospective cohort study, which included all consecutive neonates suspected of COVID-19 infection, and which required screening supervision in the triage department, from those who required hospital treatment at the Pediatric Clinic, University Clinical Center Tuzla for 12 months. (January 1 to December 31, 2020). Statistical analysis applied standard methods, and the research was approved by the Ethics Committee of the institution.

Results: In the observed period, in the neonatal triage department, 111 neonates suspected to COVID-19 were treated, with no gender difference. Among them were 92 neonates of mothers suspected of COVID-19 (66 admitted immediately after birth, 26 readmitted after discharge home), and 19 neonates of mothers positive for COVID-19 (16 admitted immediately after birth, 3 readmitted). Cesarean delivery was a more common delivery option, and fever a more common symptom in COVID-19 positive mothers, but without statistical significance. The neonates from COVID-19 suspected mothers formed a heterogeneous group, with common perinatal problems, while neonates from COVID-19 positive mothers, hospitalized immediately after birth, were almost term neonates with appropriate birth weight, without need for a lot of treatment. All neonates hospitalized immediately after birth were negative for COVID-19. The only three COVID-19 positive neonates were readmitted after previous discharge home, and they had mild symptoms, mostly one-day fever, and they all recovered completely. All of these neonates are under further follow-up after discharge from the hospital, and all are, for now, in good general condition, and all have continued to breastfeed.

Conclusion: Neonates born to mothers with positive COVID-19 infection generally have favorable outcomes, with no convincing case of vertical transmission. Neonatal COVID-19 is mostly asymptomatic, acquired postnatally, and associated with favorable outcomes. The importance of quality triage in the prevention and control of infection is crucial, with consistent implementation of safe practices including proper patient isolation and appropriate protective equipment.

Key words: neonatal COVID-19, triage, vertical transmission, horizontal transmission, neonatal outcome.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) as a global public health crisis is in the focus of numerous studies that have mainly evaluated the effects of COVID-19 on the general population, and there are insufficient data on its impact on vulnerable populations, such as neonates (1). By the end of the first pandemic year, it was estimated that about 300,000 neonates were born from pregnant women infected with the coronavirus, and millions of neonates were born into families that experienced stress due to the pandemic, even if they were not infected (2). Epidemiological data up to this point, have demonstrated that children, especially neonates, represent a minority of the overall cases, and data on the neonatal outcomes of pregnant women infected with the COVID-19 are limited (3, 4). New data accelerates health policy changes in pandemic-affected countries, continuously developing clinical management guidelines. The very rapid spread and increased mortality rate require exact information urgently, to identify and protect vulnerable popula-

Table 1. *Clinical, laboratory, and radiological findings in neonates with COVID-19*

Clinical manifestations in neonates with COVID-19	
Respiratory	**Gastroenterological**
Moaning, groaning	abdominal distension
fluttering of the nostrils	feeding problems
tachypnea	vomiting
chest retraction	diarrhea
pallor, cyanosis	**Neurological**
apnea	temperature instability
cough	lethargy
Laboratory findings	**Radiological findings**
Leukocytes normal or decreased, lymphopenia	Infiltration on Chest X-rays
Mild thrombocytopenia	
Elevated Serum enzymes CK, ALP, ALT, AST, LDH	

tions, to prevent infection, reduce the need for intensive care, and reduce mortality rates (5).

From the beginning, neonatal units and patients had to be protected from all sources of new viral infection, which immediately complicated the organization and functioning of neonatal units, with the need for epidemiological screening, which requires double resources. Reliable and unmistakable triage is fundamental to this concept. Clinical manifestations, laboratory and radiological findings in neonates with COVID-19 are shown in the following table (Table 1) (2). However, all of these clinical, laboratory, and radiological findings are not specific and are not sufficient for COVID-19 neonates triage. Therefore, the only valid diagnosis is microbiological testing (2). Strong recommendations are to test neonates only if the results of the mother's tests are positive (2, 6). Finally, testing rules may vary for each facility, especially in hospital admission triage. The determinant is the local epidemiological situation and in accordance with the recommendations of the competent Department for Infection Prevention and Control.

Intra-hospital transfer of neonates should be limited with responsible risk management. Risk assessment is crucial in clinical decisions about the need for clinical intervention, diagnostic (radiological examinations, computed tomography, magnetic resonance imaging, eye examination, etc.) or therapeutic (7, 8). If possible, they should be postponed until the test arrives. However, if the clinical intervention cannot be delayed, neonates must be transported in a closed incubator and then managed according to current protocols. It is mandatory to follow the recommendations of the local department for infection prevention and control, in order to reduce the possibility of spreading the infection. Treatment management may involve proactive care, such as intubation using personal protective equipment (5, 8). Supportive care is currently the only known effective therapy for COVID-19. Advanced support may be indicated if a severe deterioration in respiratory function occurs. There is no evidence of routine use of antiviral drugs, steroids, or interferons in neonates (9, 10, 11). If necessary, consultations with a pediatric infectiologist or with the department for infection prevention and control are desirable.

In conclusion, neonates differ from older children in their reactions to exposure to severe acute respiratory syndrome and COVID-19 infection. The previous data describing the appearance of COVID-19 in this group are rare, and the recommendations and guidelines from the authorities are variable. **The aim of this study** was to describe the incidence, characteristics, transmission, and outcomes of COVID-19 infection in neonates who were hospitalized in Tuzla Canton and to emphasize the importance of quality triage in the prevention and control of infection.

MATERIAL AND METHODS

Patients and study design

A retrospective cohort study, which included all consecutive neonates suspected of COVID-19 infection, and which required screening supervision in the triage department, from those who required hospital treatment, either in the Neonatal Intensive Care Unit (NICU) or in the Neonatology Department of the Pediatric Clinic, University Clinical Center Tuzla for 12 months. (January 1 to December 31, 2020). They were mostly neonates from COVID-19 suspected and covid-19 positive mothers, hospitalized immediately after birth, but also neonates readmitted (with mothers) after they had already been discharged and stayed

at home for a period. The study was approved by the Ethics Committee of the Institution.

Methods

Clinical and demographic data were obtained from medical records and electronic databases of patients treated in NICU and Neonatology Department, which included gender, gestational age, birth weight, perinatal risk factors, clinical presentation, laboratory findings, applied therapy, and the outcome. During admission, COVID-19 history data for mothers and neonates were specifically analyzed. All these neonates were first admitted to the neonatal triage department, respecting all the strict rules and recommendations for the prevention and control of infection. After clinical observation, including necessary diagnostic and therapeutic interventions, and including the COVID-19 test (Polymerase chain reaction - PCR of the nasopharyngeal swab), neonates were then selected according to the results and definitions of COVID-19 infection in neonates. The categories of COVID-19 disease in neonates are Confirmed Case, Suspected Case, and Case Contact. A confirmed case is a neonate who has laboratory confirmation for COVID-19. A suspected case is a neonate who has the symptoms of viral infection, with included COVID-19 in differential diagnosis, while testing is in progress. Contact with the case is a neonate that is asymptomatic but has been exposed to a healthcare professional or family member who is a symptomatic or confirmed case of COVID-19.

COVID-19 triage protocol

The first patient with COVID-19 in Bosnia and Herzegovina was confirmed on March 5, 2020. and on March 11, 2020, the World Health Organization (WHO) declared a COVID-19 pandemic (2). In order to preserve the free status of the COVID-19 neonatology department, another neonatology department with an intensive care unit (the neonatal triage department) was formed in our clinic, to treat neonates suspected of COVID-19. The operating principles and work in the neonatal triage department were organized with the implementation of all recommendations of the Department of Prevention and Infection Control. The only valid diagnosis for COVID-19 is microbiological testing. Strong recommendations are to test neonates only if the results of the mother's tests are positive, but we tested all hospitalized neonates. Neonates, COVID-19 Confirmed Case, Suspected Case or Case Contact, were admitted to the isolation room, in consultation with the local Infection Prevention and Control Department. Appropriate precautions against infection were taken, and neonates were, as ideally recommended, kept in a closed incubator until test results arrived.

In treated neonates, clinical presentation, applied therapy, length of hospitalization, and the outcome were analyzed. From laboratory findings, we particularly analyzed potential markers of infection, including C-reactive protein (CRP), Complete blood cell (CBC) counts, the highest and lowest value for white blood cell (WBC) count, absolute neutrophil count (ANC), platelet count, and coagulation status.

Statistical analysis

For statistical analysis standard methods of descriptive statistics (central tendency measures, dispersion measures) were used. Parametric and non-parametric significance tests (X^2-test, respectively, Fisher's exact test and Student's t-test) were used to test the significance of differences between the samples. Statistical hypotheses were tested at a significance level of $\alpha = 0.05$, i.e. The difference between the samples is considered significant if $p < 0.05$. We used Systat Software, Systat Inc, Evanston, IL, USA for statistical processing of data.

RESULTS

In the period from January 1 to December 31, 2020, 620 neonates were treated in the Pediatric Clinic of the University Clinical Center Tuzla, of which 370 in the Neonatology Department and 250 in the Neonatal Intensive Care Unit. This is slightly below the annual average from the experience of the previous five years but in line with the experiences of all departments and clinics in this year's COVID-19 environment.

In the observed period, in the neonatal triage department, 111 neonates suspected of COVID-19 were treated. Among them were 92 neonates of mothers suspected of COVID-19, and 19 neonates of mothers positive for COVID-19. Among 92 neonates of COVID-19 suspected mothers, 66 were admitted immediately after birth, while 26 were readmitted (with mothers) after they had already been discharged and stayed at home for a period. Among 19 neonates from COVID-19 positive mothers, 16 were admitted immediately after birth, while 3 were hospitalized as re-admission after discharge home after birth (Table 2).

Maternal perinatal data and COVID-19 history are shown in Table 3. There was no statistically significant difference in maternal perinatal data in the two observed groups (COVID-19 suspected and COVID-19 positive mothers). Maternal perinatal data and COVID-19 history in our study were not significantly different nor spe-

Table 2. *COVID-19 status of neonates hospitalized in the triage unit*

Time of neonatal hospital admission	**Maternal COVID-19 status**	
	COVID-19 suspected mother	COVID-19 positive mother*
Immediately after birth	66	16
COVID-19 neonatal status*	Negative 66	Negative 16
Readmission after discharge home	26	3
COVID-19 neonatal status	Negative 26	**Positive 3**
X^2-test $p < 0.001$; Yates corrected X^2-test: $p = 0.0005$; Fisher's exact test: $p = 0.001$		
*COVID-19 status tested by PCR of nasopharyngeal swab		

Table 3. *Maternal perinatal data and COVID-19 symptoms*

Maternal perinatal data of observing neonates			
Maternal perinatal data	COVID-19 suspected mother (n = 66)	COVID-19 positive mother (n = 16)	p
Primiparous, n (%)	34 (51.5)	8 (0.5)	0,9137
Multiparous, n (%)	32 (48.5)	8 (0.5)	0,9131
Vaginal delivery, n (%)	46 (69.7)	9 (56.2)	0,3048
Cesarean delivery, n (%)	20 (30.3)	7 (43.7)	0,3044
COVID-19 history and prepartum clinical presentation			
Asymptomatic, n (%)	11(16.7)	2 (12.5)	0,6827
Fever, n (%)	16 (24.2)	6 (37.5)	0,2828
Other mild symptoms, n (%)	39 (59.1)	8 (0.5)	0,5096

Table 4. *Neonatal-perinatal data and laboratory findings*

Parameter	Neonates from COVID-19 suspected mothers (n = 66)	Neonates from COVID-19 positive mothers (n = 16)	p
	mean ± SD	mean ± SD	
Gestational age (weeks)	37.10 ± 3.61	39.00 ± 1.68	**0.0457**
Birth weight (grams)	3042.76 ± 903.09	3503.53 ± 470.79	**0.0457**
AS in the 1st minute	8.21 ± 1.05	8.53 ± 0.87	0.229
AS in the 5th minute	8.55 ± 0.63	8.76 ± 0.56	0.2259
CRP (mg/L)	6.93 ± 11.73	7.16 ± 13.96	0.9461
Erythrocytes $\times 10^{12}$/L	4.58 ± 0.86	4.67 ± 0.89	0.6796
Hemoglobin (g/L)	165.51 ± 34.34	167.00 ± 37.26	0.8794
Hematocrit (proportion)	0.46 ± 0.09	0.47 ± 0.09	0.6942
Platelets $\times 10^9$/L	251.03 ± 89.10	279.82 ± 53.95	0.2207
Leukocytes $\times 10^9$/L	14.66 ± 7.36	17.39 ± 8.26	0.1974
Neutrophil content (proportion)	0.46 ± 0.15	0.48 ± 0.17	0.6588
ANC $\times 10^9$/L	6140.69 ± 3698.5	7469.41 ± 4144.2	0.2115
Lymphocyte content (proportion)	0.37 ± 0.15	0.35 ± 0.18	0.6627
Intensive treatment (days)	5.07 ± 9.42	0.82 ± 2.32	0.0742
SD - standard deviation; AS - Apgar score; CRP - c reactive protein; ANC - absolute neutrophil count			

Table 5. *Clinical presentation in the two observed groups of neonates*

Parameters n (%)	Neonates from COVID-19 suspected mothers (n = 66)	Neonates from COVID-19 positive mothers (n = 16)	p
Respiratory distress syndrome	11 (16.7)	2 (12.5)	0.6827
Pneumonia	9 (13.6)	3 (18.7)	0.6031
Intracranial hemorrhage	12 (18.2)	4 (25)	0.5368
Coagulation disorders	18 (27.3)	2 (12.5)	0.2171
Confirmed microbial isolates	9 (13.4)	4 (25)	0.2639
No antibiotic therapy	7 (10.6)	7 (43.7)	**0.0016**
First line of antibiotics	13 (19.7)	9 (56.2)	**0.0031**
Second line of antibiotics	9 (13.6)	0	0.1176
Blood products	13 (19.7)	2 (12.5)	0.5039
Phototherapy	11 (16.7)	2 (12.5)	0.6827
Inotropes	5 (7.6)	0	0.2561
Intravenous immunoglobulins	7 (10.6)	0	0.1733
Mechanical ventilation	6 (9.1)	0	0.2103
Exogenous surfactant	5 (7.6)	0	0.2561
Umbilical venous catheter	13 (19,7)	2 (12.5)	0.5039
Intensive Treatment (NICU)	14 (21.2)	2 (12.,5)	0.4303
NICU - neonatal intensive care unit;			

cific in their presentation. Cesarean delivery was a more common option in COVID-19 positive mothers but without statistical significance. As for COVID-19 history, fever was more commonly observed in COVID-19 positive mothers, compared to the group of COVID-19 suspected mothers, but this difference was not statistically significant. Related to COVID-19 symptomatology, mild to moderate symptoms dominated our study in mothers. There has not been a severe respiratory failure, need for ventilatory support for mothers, and maternal deaths due to COVID-19, until now.

Neonatal-perinatal data and laboratory findings are shown in Table 4. Clinical presentations in the two observed groups of neonates are shown in Table 5. If we analyze the data from neonates, treated immediately after birth, we conclude that the group of neonates from COVID-19 positive mothers was uniform, they were neonates with statistically better gestational age and birth weight, and these were neonates with better clinical status, and with significantly less required treatment options, compared to neonates from COVID-19 suspected mothers. All these neonates, finally, had a negative COVID-19 test and were recorded without significant laboratory and radiological deviations. After the observation in the triage department, all neonates continued their treatment in the Neonatology department with the promoted recommendations of the department for prevention and control of infection.

Results on neonatal COVID-19 status showed that all neonates hospitalized immediately after birth, from both COVID-19 suspect and COVID-19 positive mothers, were negative for COVID-19. In a group of neonates hospitalized as a re-admission after discharge home, 26 of them from COVID-19 suspected mothers, also were negative for COVID-19 (as well as their mothers finally). The only three COVID-19 positive neonates in our experience were precisely the neonates of the three positive mothers, admitted as re-admissions after previous discharge home, which showed statistically significant differences in horizontal transmission compared to vertical (X^2-test $p < 0.001$; Yates corrected X^2-test: $p = 0.0005$; and Fisher's exact test: $p = 0.001$). Three neonates with a positive COVID-19 test had mild symptoms of the disease, mostly one-day fever, and with isolation, monitoring, and symptomatic therapy, they all recovered completely. All of these neonates are under further follow-up after discharge from the hospital, and all are, for now, in good general condition, and all have continued to breastfeed.

DISCUSSION

Consistent with results and reports to date, children are not dominant among the diagnosed cases of COVID-19, and they usually count approximately 1%–5% (1). In general, COVID-19 appears to be a less se-

vere disease for children than for adults and almost 90% of pediatric patients are diagnosed as an asymptomatic or mild disease (1). However, 5-10% of cases can be severe, usually in patients younger than 1 year of age and in patients who have severe comorbidity (11). Despite many published pediatric reports, epidemiological, clinical patterns of COVID-19 and treatment approaches in pediatric patients are still unclear. There is little data related to neonates. We follow them through studies of infected pregnant women (12, 13). COVID-19 during pregnancy may be associated with severe maternal morbidity and the impact on the outcome of pregnancy and neonates is not completely clear, especially if the infection occurs early in pregnancy (3, 4). Because it is known how harmful viral infections can be during pregnancy, and that they can affect the fetus in several ways: from direct transmission through the placenta to inflammatory responses that can disrupt metabolism in the uterus and can negatively affect fetal growth (4). Some indications increased rates of preterm birth may be associated with maternal COVID-19 infections, and some studies suggest that severe disease in early pregnancy may be associated with a higher risk of stillbirths (12, 14).

Data for 2020 for our institution also suggest a slight increase in the prematurity rate, although there is a slight decrease in the total number of live births. We can only theoretically link this observation to this year's pandemic, and we cannot scientifically substantiate it because we did not conduct mass and repeated tests, so there was no permanent screening for COVID-19 in pregnant women throughout pregnancy. For now, it is considered that there is no strong evidence of vertical transmission of the infection from pregnant women to neonates, also, at this time, there are no reports of an increased risk of congenital anomalies in children born to COVID-19 positive pregnant women (6, 7, 12). According to the published case reports, it appears that the COVID-19 virus has a very low rate of infection among neonates, which is estimated at 1-5% worldwide (13, 14, 15). Most cases are considered to be the result of horizontal transmission from the environment, in the household by droplets from another family member, and therefore potentially possible from health professionals, as a potential healthcare-related infection (15, 16).

In our study among 111 neonates suspected of COVID-19, all neonates hospitalized immediately after birth, from both COVID-19 suspect and COVID-19 positive mothers, were negative for COVID-19, which is consistent with reports that there is no vertical transmission COVID-19 from mothers to neonates (4, 6, 7, 15). In a group of neonates hospitalized as readmission after discharge home, 26 of them from COVID-19 suspected mothers, also were negative for COVID-19 (as well as their mothers finally). The only three COVID-19 positive neonates in our experience were precisely the neonates of the three positive mothers, admitted as readmissions after previous discharge home, which is also consistent with the published experiences of others, that neonates are mostly infected by horizontal transmission from the environment and COVID-19 positive family members (15, 16).

Maternal perinatal data and COVID-19 history in our study were not significantly different nor specific in their presentation. Cesarean delivery in our study was a more common option in COVID-19 positive mothers, who mainly showed mild to moderate symptoms. There was no severe respiratory failure, no need for ventilatory support for mothers, and no maternal deaths due to COVID-19, until now. Smith et all (3) in their study conclude that COVID-19 positive pregnant women present with fewer symptoms than the general population, while the results of Juan et all (9) suggest that COVID-19 in pregnant women may increase the risk of maternal mortality. We can conclude that, despite the growing number of published studies, there is still not enough valid data on the severity and complications of COVID-19 in pregnant women.

According to published reports, especially those from the beginning of the pandemic, guidelines for the management of neonates born to mothers with COVID-19, confirmed or suspected infection, vary from country to country, and routine separation of mothers and neonates after birth has been recommended in many countries (16, 17). Our research supports international guidelines, suggesting avoiding the separation of mother and child after birth, in case of suspected or confirmed COVID-19 infection in mothers (16).

According to the clinical presentation, neonates from the mothers suspected of COVID-19, in our study, were a heterogeneous group, with different, but still common perinatal symptoms and problems. It is noticeable that neonates from COVID-19 positive mothers, hospitalized immediately after birth, were a uniform group of term neonates with appropriate birth weight and with a better general condition, and less need for any intervention and treatment. Almost all similar studies find that there is no evidence for vertical transmission. According to Golden et al (4), a possible explanation would be that immune cells in the placenta also have antiviral capacity. Even studies that report more serious clinical presentation in early-infected neonates suggest that in some cases it might have been related to other neonatal conditions, such as preterm birth. Therefore, the long-term effects of early exposure COVID-19 are still unknown, although the short-term outcomes are excellent in these studies (16). After the observation in the triage department, all neonates continued their treatment in the Neonatology department with the promoted recommendations of the department for prevention and control of

infection. Three neonates with a positive COVID-19 test had mild symptoms of the disease, mostly one-day fever, and with isolation, monitoring, and symptomatic therapy, they all recovered completely. Although COVID-19 is a new infectious disease, with still insufficiently known clinical manifestations in neonates, current findings suggest that in addition to having a lower incidence, they have mostly mild forms of the disease (11, 13, 18). This is in line with published results, that hyperthermia, signs of upper respiratory tract infection, and poor feeding were more commonly reported in neonates diagnosed with COVID-19 later than 7 days after birth (11, 16). In our study, all of these neonates are under further follow-up after discharge from the hospital, and all are, for now, in good general condition, and all have continued to breastfeed. This differs from some previously published studies that have observed laboratory deviations, and the most common biochemical and haematological abnormalities were raised lactate, raised C-reactive proteins and a low lymphocyte count, and some report chest x-ray abnormal findings, with ground-glass changes (11, 13, 16).

Neonates, in addition to treatment, require social contact with the mother and family members for their growth and development. It is very important, if possible, to practice skin-to-skin contact between mother and child, as the results of recent studies are encouraging (8, 16). Concerning nutrition, breastfeeding remains the best source of nutrition for most neonates. To date, there is no evidence of the presence of COVID-19 in breast milk. Therefore, on June 23, 2020, the World Health Organization (WHO) issued recommendations regarding breastfeeding and COVID-19. COVID-19 positive mothers are encouraged to breastfeed their children while wearing a mask and practicing all hygiene rules (2). Due to the current COVID-19 pandemic, the supply of donor milk is limited (16). Some studies report suspected nosocomial transmission of COVID-19 to neonates, within neonatal units, suggesting that such units should be reevaluated in procedures to isolate highly infectious cases (8). Further research is needed to understand the real effects of limiting hospital visits on the spread of this highly transmissible virus.

Family engagement and presence depend on current location-specific guidelines for visitors. The assessment should be done in collaboration with the Infection Prevention and Control Department. The family will need support, depending on the outcome and especially in less fortunate circumstances. Available support services should be made available as soon as possible. Memories of neonates should be provided to the family, if possible, such as photographs, or the use of other virtual connections between mother, family, and neonates should be considered.

When considering discharge from the hospital, continued isolation should be provided if the neonates are discharged before the end of the isolation period. If the neonates' tests are positive, then isolation is recommended for at least 10 days after the onset of symptoms; or, until the fever ceases without the use of antipyretic drugs or until symptoms improve (respiratory, gastrointestinal, and systemic). It is reasonable to postpone audiological and other examinations while neonates are under protective supervision. It should be ensured that the confirmed status of COVID-19 mothers and neonates has previously been explained and forwarded to the competent health service.

CONCLUSION

In conclusion, neonates born to mothers with positive COVID-19 infection generally have favorable outcomes, with no convincing case of vertical transmission. In our study, the proportion of neonates with the disease is extremely low. Moreover, neonatal COVID-19 appears to be acquired postnatally and associated with favorable respiratory outcomes. For those reasons, the provision of respiratory care in neonates should continue in accordance with current standards. However, to protect and to stop any spread of COVID-19 infection, it is critical to emphasize the importance of quality triage for the prevention and control of infection, consistently implement safe practices including proper patient isolation and appropriate protective equipment. Finally, information is rapidly changing, and clinicians should often look out for new updates as the state of our knowledge evolves.

Abbreviations

NICU — Neonatal intensice care unit
CRP — C-reactive protein
CBC — Complete blood cell
WBC — white blood cell
ANC — absolute neutrophil count
Htc — hematocrit
GA — Gestational age
BW — Birth weight
AS — Apgar score
SD — standard deviation
MV — mechanical ventilation

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Licensing

Sažetak

KOVID-19 TRIJAŽA HOSPITALIZOVANIH NEONATUSA U TUZLANSKOM KANTONU

Devleta Hadzic,[1] Fahrija Skokic,[1] Selmira Brkic[2]

[1] Pediatric Clinic, University Clinical Center of Tuzla, Bosnia and Herzegovina
[2] Faculty of Medicine University of Tuzla, Bosnia and Herzegovina

Cilj studije: da se proceni incidencija, karakteristike, prenos i ishodi infekcije COVID-19 kod hospitalizovanih novorođenčadi u Tuzlanskom kantonu i naglasi važnost kvalitetne trijaže u prevenciji i kontroli infekcije.

Metode: Retrospektivna kohortna studija koja je obuhvatila svu uzastopnu novorođenčad suspektnu na infekciju COVID-19 koja su zahtevala nadzor i skrining na odeljenju trijaže, među onim koji su zahtevali hospitalizaciju u Klinici za dečije bolesti Univerzitetskog kliničkog centra Tuzla, tokom 12 meseci. (od 1. januara do 31. decembra 2020. godine). U statističkoj analizi primenjene su standardne metode, a istraživanje je odobrio Etički komitet institucije.

Rezultati: U posmatranom periodu, na odeljenju za trijažu lečeno je 111 novorođenčadi pod sumnjom na COVID-19, bez razlike u polnoj zastupljenosti. Među njima je bilo 92 novorođenčadi od majki suspektnih na COVID-19 (66 primljenih odmah nakon rođenja, 26 ponovo primljenih nakon prethodnog otpusta kući) i 19 novorođenčadi od majki pozitivnih na COVID-19 (16 primljenih neposredno nakon rođenja, 3 ponovni prijem). Kod majki pozitivnih na COVID-19, carski rez bio je češća opcija porođaja, a febrilnost češće primećeni simptom, ali bez statističke značajnosti. Novorođenčad od majki suspektnih na COVID-19 su činila heterogenu grupu, sa uobičajenim perinatalnim problemima, dok su novorođenčad od pozitivnih majki, hospitalizovana odmah po rođenju, gotovo svi bili terminska novorođenčad sa odgovarajućom porođajnom težinom, bez potrebe za značajnim lečenjem. Sva novorođenčad hospitalizovana odmah nakon rođenja bila su negativna na COVID-19. Jedino troje novorođenčadi pozitivnih na COVID-19 bilo je hospitalizovano nakon izvesnog boravka kod kuće, svi su imali blage simptome, uglavnom jednodnevnu temperature i svi su se potpuno oporavili. Sva ova novorođenčad nakon hospitalizacije su na daljem praćenju i za sada su dobrog opšteg stanja i svi su na prirodnoj ishrani.

Zaključak: Novorođenčad rođena od majki sa potvrđenom infekcijom COVID-19 uglavnom ima povoljne ishode, bez ubedljivog dokaza vertikalnog prenosa. COVID-19 u novorođenčadi je uglavnom stečena postnatalno i povezana sa povoljnim ishodima. Značaj kvalitetne trijaže u prevenciji i kontroli infekcije je presudan, uz doslednu primenu bezbednih praksi, uključujući odgovarajuću izolaciju pacijenta i odgovarajuću zaštitnu opremu.

Ključne reči: neonatalna COVID-19, trijaža, vertikalna transmisija, horizontalna transmisija, neonatalni ishod.

REFERENCES

1. Tezer H, Bedir Demirdağ T. Novel coronavirus disease (COVID-19) in children. Turk J Med Sci. 2020; 50(SI-1): 592-603. doi: 10.3906/sag-2004-174.

2. World Health Organisation: WHO, www.who.int

3. Smith V, Seo D, Warty R, Payne O, Salih M, Chin KL, et al. Maternal and neonatal outcomes associated with COVID-19 infection: a systematic review. PLoS One. 2020; 15(6): e0234187. doi: 10.1371/journal.pone.0234187.

4. Golden TN, Simmons RA. Maternal and neonatal response to COVID-19. Am J Physiol Endocrinol Metab. 2020; 319(2): E315-9. doi: 10.1152/ajpendo.00287.2020.

5. Halliday HL, Speer CP. COVID-19 and neonatal resuscitation. Neonatology. 2020; 117(2): 132. doi: 10.1159/000508003.

6. Shalish W, Lakshminrusimha S, Manzoni P, Keszler M, Sant'Anna GM. COVID-19 and neonatal respiratory care: current evidence and practical approach. Am J Perinatol. 2020; 37(8): 780-91. doi: 10.1055/s-0040-1710522.

7. Griffin I, Benarba F, Peters C, Oyelese Y, Murphy T, Contreras D, et al. The Impact of COVID-19 Infection on labor and delivery, newborn nursery, and neonatal intensive care unit: prospective observational data from a single hospital system. Am J Perinatol. 2020; 37(10): 1022-30. doi: 10.1055/s-0040-1713416.

8. Chandrasekharan P, Vento M, Trevisanuto D, Partridge E, Underwood MA, Wiedeman J, et al. Neonatal resuscitation and postresuscitation care of infants born to mothers with suspected or confirmed SARS-CoV-2 Infection. Am J Perinatol. 2020; 37(8): 813-24. doi: 10.1055/s-0040-1709688.

9. Juan J, Gil MM, Rong Z, Zhang Y, Yang H, Poon LC. Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: systematic review. Ultrasound Obstet Gynecol. 2020; 56(1): 15-27. doi: 10.1002/uog.22088.

10. Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. Acta Obstet Gynecol Scand. 2020; 99(7): 823-9. doi: 10.1111/aogs.13867.

11. Sankar J, Dhochak N, Kabra SK, Lodha R. COVID-19 in children: Clinical approach and management. Indian J Pediatr 2020; 87(6): 433-42. doi: 10.1007/s12098-020-03292-1.

12. Karimi-Zarchi M, Neamatzadeh H, Dastgheib SA, Abbasi H, Mirjalili SR, Behforouz A, et al. Vertical transmission of coronavirus disease 19 (COVID-19) from infected pregnant mothers to neonates: a review. Fetal Pediatr Pathol. 2020; 39(3): 246-50. doi: 10.1080/15513815.2020.1747120.

13. de Rose DU, Piersigilli F, Ronchetti MP, Santisi A, Bersani I, Dotta A, et al. Novel Coronavirus disease (COVID-19) in newborns and infants: What we know so far. Ital J Pediatr. 2020; 46(1): 56. doi:10.1186/s13052-020-0820-x.

14. Jain P, Thakur A, Kler N, Garg P. Manifestations in neonates born to COVID-19 positive mothers. Indian J Pediatr. 2020; 87(8): 644. doi: 10.1007/s12098-020-03369-x.

15. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: An overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. Pediatr Infect Dis J. 2020; 39(5): 355-68. doi: 10.1097/inf.0000000000002660.

16. Gale C, Quigley MA, Placzek A, Knight M, Ladhani S, Draper ES, et al. Characteristics and outcomes of neonatal SARS-CoV-2 infection in the UK: a prospective national cohort study using active surveillance. Lancet Child Adolesc Health. 2021; 5(2): 113-21. doi: 10.1016/S2352-4642(20)30342-4.

17. Yeo KT, Oei JL, De Luca D, Schmolzer GM, Guaran R, Palasanthiran P et al. Review of guidelines and recommendations from 17 countries highlights the challenges that clinicians face caring for neonates born to mothers with COVID-19. Acta Paediatr. 2020; 109(11): 2192-207. doi: 10.1111/apa.15495.

18. Sporisevic L, Mesihović-Dinarevic S, Joguncic A, Pilav A. Coronavirus disease 2019 (COVID-19): a new pediatric challenge. JHSCI. 2020; 10(2): 103–8. doi: 10.17532/jhsci.2020.9720.

Correspondence to/Autor za korespondenciju
Devleta Hadžić
Univerzitetski klinički centar Tuzla, Klinika za dječije bolesti
Prof. dr. Ibre Pašić bb
75000 Tuzla, Bosna i Hercegovina
00 387 35 303 733
e-mail: devletahadzic@yahoo.com

SANAMED
2021; 16(1): 65–69
ISSN-1452-662X

DOI:10.24125/sanamed.v16i1.471
UDK:616.428-007.6-076.5(497.113)"1999/2019"
ID:37394185
Professional article

21 YEARS AFTER INTRODUCING SENTINEL LYMPH NODE BIOPSY IN CLINICAL PRAXIS AT THE ONCOLOGY INSTITUTE OF VOJVODINA

Selakovic Vladimir,[1] Ranisavljevic Milan,[1, 2] Lukic Dejan,[1, 2] Djuric Mladen[1]

[1] Oncology Institute of Vojvodina, Department for operative oncology, Novi Sad, Serbia
[2] Medical faculty of Novi Sad, University of Novi Sad, Novi Sad, Serbia

Primljen/Received 05. 11. 2020. god. Prihvaćen/Accepted 26. 01. 2021. god.

Abstract: **Introduction:** Sentinel lymph node biopsy (SLNB) is a standard procedure at the Oncology Institute of Vojvodina since 1999 and during this period we have done more than 1700 biopsies. **The aim** of this study was to present our results in SLNB in breast cancer surgery.

Materials and methods: This retrospective study was performed at the Department for Surgical Oncology at the Vojvodina Institute of Oncology in the period from January 1999 to December 2019. The study included 1762 patients who had undergone SLNB. The mean duration of the follow-up period was 121.89 months. All patients were women with clinically T1-2N0-1M0 breast cancer. Preoperatively, all patients were administered dual contrast media, radiotracer, and blue dye.

Results: The majority of tumors were T1c (955 (54.18%). The mean number of extirpated sentinel lymph nodes (SLN) in both groups was 1.84. In 199 (36.72%) patients SLN was the only metastatic lymph node in the axilla. Micro metastases were found in 113 (21.03%) patients. The overall diagnostic accuracy of SLNB was 96%.

Conclusion: Axillary SLN can serve as a reliable predictor of negativity of other ipsilateral axillary nodes. Micro metastases in the SLN are not an indication for complete axillary lymph node dissection.

Keywords: breast cancer, sentinel lymph node, complete axillary lymph node dissection.

INTRODUCTION

Between the Halsted and Fisher concept in breast cancer treatment, almost 100 years had passed. During that period of time, it has been recognised that breast cancer biology, is a major risk factor in the determination of both systematic and locoregional recurrence (1, 2).

Giuliano has introduced the concept of sentinel lymph node biopsy (SLNB) in breast cancer in 1997. After that, the use of complete axillary lymph node dissection (cALND) decreased from 94% to 36% (3, 4).

Sentinel lymph node biopsy in breast cancer has been a standard procedure at the Oncology Institute of Vojvodina since 1999 and we have done more than 3500 biopsies.

Complete cALND is an effective method of maintaining regional control of the disease but it is associated with a significant risk of complications like lymphedema.

The aim of this study is to present our results of SLNB in breast cancer surgery at the Department of Surgical Oncology, Oncology Institute of Vojvodina.

MATERIAL AND METHODS

This retrospective study was performed at the Department for Surgical Oncology at the Oncology Institute of Vojvodina in the period from January 1999 to December 2019. The study included 1762 patients who had undergone SLNB. 909 patients were postmenopausal (65.68%) and 763 (43.30%) premenopausal with the average age being 57 years (ranging from 25 to 84). The mean duration of the follow-up period was 121.89 months (median 95, range 12-252).

The preoperative diagnosis of breast cancer was obtained after core needle biopsy and supplementary physical examination, mammography, and breast ultrasonography. Mandatory at all verified breast cancers receptor status was determinate (estrogen (ER), progesterone (PR), humane epidermal growth receptor 2 (HER 2), and proliferation factor (Ki 67).

All patients were women with clinically T1-2N0-1M0 breast cancer.

Preoperatively, all patients were administered dual contrast media, **radiotracer** (*antimony sulfide nano colloid marked with technetium* 1.56 mg/ml; 0.3 mCi (11.1 MBq) – Institute for nuclear science „Vinča". Laboratory for radioisotopes. Belgrade, Republic of Serbia) and **blue dye** (Blu metilene® 1% – *S. A. L. F. S. p. A. Laboratorio farmacologico® Cenate Soto, Republic of Italy*)). Both contrasts were administered subcutaneously above the primary tumor and in some cases periareolar when the localisation of the primary tumor was near to the ipsilateral axilla and in cases of multifocal or multicentric tumors. The application was made with thin needles (25 G). The radiotracer was administered 2-16 hours preoperatively, and blue dye 15 minutes before the surgery.

For the detection of the accumulated radioactivity in the sentinel lymph node (SLN), we used an intraoperative handheld (wired or Bluetooth) gamma probe (10 mm) to identify nodes with the greatest numerical and sound activity (Figure 1) Europrobe® *3.2*, *Eurorad*

***Figure 1**. Gamma probe*

S.A. Ekbolsheim, Republic of France. Blue dye was identified visually (Figure 2).

After putting an incision in the axilla on the place with the highest radioactivity we performed extirpation of SLN. After extirpation of SLN, breast-conserving surgery was done and the extirpation of the primary tumor. The operation was performed in this order for the reason of not contaminating the SLN with tumor cells from the primary tumor and to obtaining false-positive results.

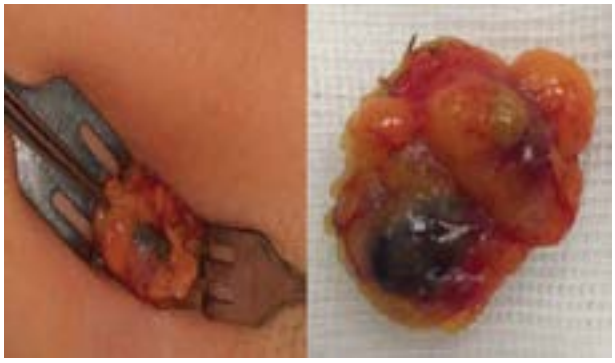


***Figure 2.** Colored SLN*

Immediately after the extirpation of the SLN specimen was sent for intraoperative frozen section evaluation (*ex tempore*). Depending on the results of the extempore SLN analysis dissection of other axillary lymph nodes was omitted or performed. In cases of micrometastases in the SLN axillary dissection was omitted.

RESULTS

Solitary tumors were found in 1662 (94.33%) and multifocal tumors in 100 (5.67%) patients. The most common histological type in both groups was ductal carcinoma found in 1089 (61.79%) patients. The majority of tumors were T1c (955 (54.18%). In the T2 group with positive SLN was 158 (8.96%) and negative SLN was 199 (11.29%) patients. SLN was negative in 1220 (69.24%) and positive in 542 (30.76%) patients (Table 1).

The mean number of extirpated SLNs in both groups (SLN positive and SLN negative) was 1.84 (median 1, range 1-6). The mean number of dissected axillary lymph nodes in the group with positive SLN on paraffin-embedded tissue sections was 18.49 (median 17, range 8-28 after cALND) (Table 2).

In 199 (36.72%) patients SLN was the only metastatic lymph node in the axilla after cALND. In the

***Table 1.** Tumor characteristic in groups with positive and negative SLN*

		Positive SLN		Negative SLN		Total	
		Number	Percent (%)	Number	(%)	Number	(%)
Tumor	Solitary	773	43.87	889	50.46	1662	94.33
	Multifocal	74	4.21	26	1.46	100	5.67
Histological type	Ductal	566	32.13	523	29.66	1089	61.79
	Lobular	266	15.08	323	18.35	589	33.43
	Other	76	4.33	61	3.45	137	7.78

Table 2. *Tumor characteristics (T) in groups with positive and negative SLN*

	Positive SLN		Negative SLN		Total	
	Number	Percent (%)	Number	(%)	Number	(%)
T1a: 0.1 - 0.5	33	1.90	99	5.57	132	7.47
T1b:0.5 - 1.0	69	3.89	249	14.21	318	18.10
T1c: 1.0 - 2.0	282	16.01	673	38.17	955	54.18
T2: 2.0 - 3.0	158	8.96	199	11.29	357	20.25
Total	542	30.76	1220	69.24	1762	100.00

Table 3. *Distant metastases according to SLN status*

	Positive SLN		Negative SLN		Total	
	Number	Percent (%)	Number	(%)	Number	(%)
Bones	56	38.35	9	6.77	65	48.87
Liver	32	24.06	8	6.02	40	30.08
Lungs	21	15.79	0	0.00	21	15.79
Brain	7	5.26	0	0.00	7	5.26
Total	116	83.46	17	12.79	133	100.00

group with positive SLN, micrometastases were found in 113 (21.03%) patients, and in these cases, we have omitted cALND. The overall diagnostic accuracy of SNB was 96% (Table 3).

In 65 patients tumors metastasized to bones in the SLN positive and negative groups. In the SLN negative group, we did not find metastases in the lungs and brain. Metastases were found in 133 patients (7.55% of the total number of patients). Fifteen patients died due to distant metastases in the SLN positive group during the follow-up period (Figure 3).

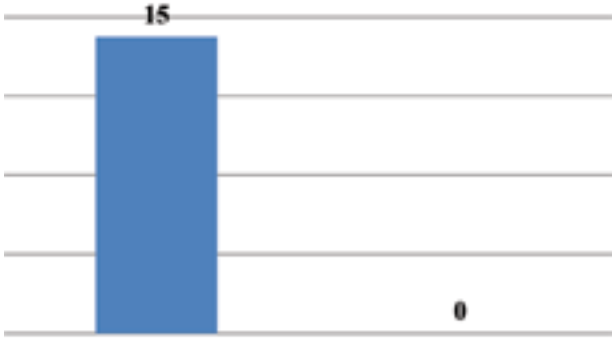


Figure 3. *Death due to metastases*

DISCUSSION

From the introduction of the SLNB into clinical practice in breast cancer surgery the use of cALND has decreased and the use of SLNB increased.

Histopathological classification of SLN defines three subtypes: macro metastases larger than 2 mm, micrometastatic foci smaller than 2 mm, and isolated tumor cells (5, 6). Novel studies have shown that only in cases where macrometastases are found in SLN, cALND is justified, in other cases, cALND should be omitted (6, 7).

The findings from the ACOSOG Z0011 study showed that at a median follow-up of 9.3 years, SLNB was non-inferior to cALND in both overall and disease-free survival, and routine use of cALND is not indicated (HR: 1.3) (5).

Some studies claimed several tumor factors indicated an early risk of recurrence, in first-line hormone-receptor negative and human epidermal growth factor receptor 2 positive and triple-negative tumors but ACOSOG Z0011 study in these cases (5, 6, 8). But in this last-mentioned study, high-risk patients were treated with neoadjuvant systemic therapy and the impact of it was significant.

Age of patients is also one of the respected criteria to omit cALND (patients older than 70 years). Younger patients with HER2-positive/triple-negative breast cancer would likely become cALND (5-8).

The role of the regional nodal irradiation for patients with breast cancer remains controversial, particularly based on nodal involvement. The study from Moreno et al concluded that whole breast irradiation with regional nodal irradiation did not affect 5-year overall survival rates for women with high-risk, early-stage breast cancer undergoing breast-conserving surgery and adjuvant chemotherapy, regardless of nodal status (9). On the opposite, the MA20 trial data showed that combined regional radiotherapy and cALND improved disease outcomes compared to standalone cALND (10).

The overall diagnostic accuracy of SNB in our study was 96% including patients with or without

neoadjuvant chemotherapy. A meta-analysis from El Hage Chehade et al after neoadjuvant systemic therapy show a false-negative rate of 13%, an SLN identification rate of 91%, and a pathological complete response (pCR) of 47% (11). The pathological complete response is defined as the 'absence of vital tumor cells. The SLNB is, therefore, a viable alternative to cALND provided that at least two nodes are sampled and there is radiological evidence of response to neoadjuvant systemic therapy. The high rate of PCR suggests that ALND may be over-treatment for these node-positive patients if performed routinely and SLNB after neoadjuvant therapy can lead to the omission of ALND in a significant proportion of patients who are node-positive prior to the initiation of therapy, resulting in reduced morbidity (especially lymphedema) and hospitalisation and better quality of life for patients (12, 13).

Our results in SLNB are constant and in correlation with our results from 2012 in terms of identification end extirpation of SLN using booth contrast media (14).

The question is, could we omit the use of SLNB and cALND in patients with node-positive disease after neoadjuvant systemic therapy? The MARI procedure is a novel technique where the largest (positive) node in the ipsilateral axilla is marked with an iodine-125 seed which is placed underultrasound guidance. This study found that 74% of patients could have avoided cALND (15). The negative side of this procedure is the cost of using positron emission tomography, computerised tomography and it is not applicable in most countries around the world.

CONCLUSION

To avoid a high rate of false-negative results, SLNB should be performed using the double-contrast method (radiotracer and color). The first performed should be SLNB and then breast-conserving surgery or mastectomy to avoid false-positive results due to the transportation of cancer cells from the primary tumor to SLN. Axillary SLN can serve as a reliable predictor of negativity of other ipsilateral axillary nodes, and cALND could be omitted to avoid postoperative complications associated with this procedure. Micrometastases in the SLN (real micrometastases or groups of isolated cells) are not an indication for cALND.

Abbreviations

SLNB — sentinel lymph node biopsy

cALND — complete axillary lymph node dissection

SLN — sentinel lymph node

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Licensing

Sažetak

21 GODINA OD UVOĐENJA BIOPSIJE LIMFNOG ČVORA STRAŽARA NA INSTITUTU ZA ONKOLOGIJU VOJVODINE

Selaković Vladimir,[1] Ranisavljević Milan,[1, 2] Lukić Dejan,[1, 2] Đurić Mladen[1]

[1] Oncology institute of Vojvodina, Department for operative oncology, Novi Sad, Serbia
[2] Medical faculty of Novi Sad, University of Novi Sad, Novi Sad, Serbia

Uvod: Biopsija limfnog čvora stražara je standardna procedura na Institutu za onkologiju Vojvodine od 1999. godine i do sada je urađeno više od 1700 biopsija. Cilj studije bio je da se prikažu naši rezultati u biopsiji limfnog čvora stražara u hirurgiji karcinoma dojke.

Materijal i metod: retrospektivna studija sprovedena na odeljenju operativne onkologije, Instituta za onkologiju Vojvodine u periodu od januara 1999. do decembra 2019. godine. Studija je uključila 1762 pacijenta kod kojih je bila urađena biopsija limfnog čvora stražara. Srednji period praćenja iznosio je 121,89 meseci. Svi pacijenti bili su ženskog pola i imali klinički T1-2N0-1M0 karcinom dojke. Preoperativno je kod svih pacijentkinja aplikovan dvojni kontrast radioobeleživa̧č i boja.

Rezultati: Najviše tumora bilo je T1c (955 (54.18%). Srednji broj ekstirpiranih limfnih čvorova stražara u obe grupe bio je 1,84. Kod 199 (36,72%) limfni čvor stražar bio je jedini limfni čvor u pazuhu sa metastatskim depozitom. Mikrometastaze pronađene su kod 113 (21.03%) pacijentkinja. Dijagnostička tačnost biopsije limfnog čvora stražara iznosila je 96%.

Zaključak: Pazušni limfni čvorovi stražari služe kao siguran prediktor negativnosti ostalih limfnih čvorova ipsilateralne aksile. Prisustvo mikrometastaza u limfnom čvoru stražaru nije indikacija za disekciju ostalih limfnih čvorova pazuha.

Ključne reči: karcinom dojke, limfni čvor stražar, kompletna disekcija limfnih čvorova aksile.

REFERENCES

1. Halsted WS. The results of radical operations for the cure of carcinoma of the breast. Ann Surg. 1907; 46(1): 1–19. doi: 10.1097/00000658-190707000-00001.

2. Fisher B, Redmond C, Poisson R, Margolese R, Wolmark N, Wickerham L, et al. Eight-year results of a randomised clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med. 1989; 320(13): 822-8. doi: 10.1056/NEJM198903303201302. Erratum in: N Engl J Med 1994; 330(20): 1467.

3. Giuliano AE, Jones RC, Brennan M, Statman R. Sentinel lymphadenectomy in breast cancer. J Clin Oncol. 1997; 15(6): 2345–50. doi: 10.1200/JCO.1997.15.6.2345.

4. Rescigno J, Zampell JC, Axelrod D. Patterns of axillary surgical care for breast cancer in the era of sentinel lymph node biopsy. Ann Surg Oncol. 2009; 16(3): 687–96. doi: 10.1245/s10434-008-0195-5.

5. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of axillary dissection vs. No axillary dissection on 10-Year overall survival among women with invasive breast cancer and sentinel node metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA. 2017; 318(10): 918-26. doi: 10.1001/jama.2017.11470.

6. Veronesi P, Corso G. Standard and controversies in sentinel node in breast cancer patients. Breast. 2019; 48 (suppl 1): 53-6. doi: 10.1016/S0960-9776(19)31124-5.

7. Zeitoun J, Babin G, Lebrun JF. Sentinel node and breast cancer: A state-of-the-art in 2019. Gynecol Obstet Fertil Senol. 2019; 47(6): 522-6. French. doi: 10.1016/j.gofs.2019.04.002.

8. Pan H, Gray RG, Davies C, Peto R, Bergh JCS, Pritchard KI, et al. Predictors of recurrence during years 5-14 in 46,138 women with ER+ breast cancer allocated 5 years only of endocrine therapy (ET). J Clin Oncol. 2016; 34(15): 505. doi: 10.1200/JCO.2016.34.15_suppl.505.

9. Moreno AC, Lin YH, Bedrosian I, Shen Y, Stauder MC, Smith BD, et al. Use of regional nodal irradiation and its association with survival for women with high-risk, early stage breast cancer: A National Cancer Database analysis. Adv Radiat OncoI. 2017; 2(3): 291–300. doi: 10.1016/j.adro.2017.04.008.

10. Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional nodal irradiation in early-stage breast cancer. N Engl J Med. 2015; 373(4): 307–16. doi: 10.1056/NEJMoa1415340.

11. El Hage Chehade H, Headon H, El Tokhy O, Heeney J, Kasem A, et al. Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving 3,398 patients. Am J Surg. 2016; 212(5):969–81. doi: 10.1016/j.amjsurg.2016.07.018.

12. Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol. 2013; 14(7): 609–18. doi: 10.1016/S1470-2045(13)70166-9.

13. Ranisavljević M, Selaković V, Lukić D, Radovanović Z, Vicko F. Impact of neoadjuvant chemotherapy on wound complications after breast surgery. Arch Oncol. 2013; 21(3-4): 105-8. doi:10.2298/AOO1304105R.

14. Golubovic A, Ranisavljevic M, Radovanovic Z, Selakovic V, Mandic A, Djilas D. Analysis of sentinel nodes biopsy in breast cancer: 12 years after introduction into clinical practice. Med Pregl. 2012; 65 (9-10): 363-7. doi: 10.2298/MPNS1210363G.

15. Koolen BB, Donker M, Straver ME, van der Noordaa MEM, Rutgers EJT, Valdes Olmos RA et al. Combined PET-CT and axillary lymph node marking with radioactive iodine seeds (MARI procedure) for tailored axillary treatment in node-positive breast cancer after neoadjuvant therapy. Br J Surg. 2017; 104(9): 1188–96. doi: 10.1002/bjs.10555.

Correspondence to/Autor za korespondenciju
Vladimir Selaković
Put doktora Goldmana 4; 21204 Sremska Kamenica; Serbia
Phone: +381 (0)21 480 5100
E-mail: selakovicvanja@gmail.com

SANAMED
2021; 16(1): 71–76
ISSN-1452-662X

DOI:10.24125/sanamed.v16i1.498
UDK:616.98:578.834] :614.253(560)
ID:37375497
Professional article

DEMOGRAPHIC CHARACTERISTICS OF COVID-19 POSITIVE HEALTHCARE WORKERS AND COMPARISON WITH THE LITERATURE

Durmus Ensar, Guneysu Fatih

Emergency Department, Sakarya University Training and Research Hospital, Sakarya, Turkey

Primljen/Received 26. 01. 2021. god. Prihvaćen/Accepted 21. 02. 2021. god.

Abstract: **Aim:** It is aimed to examine the status and demographic characteristics of COVID-19 Reverse Transcription Polymerase Chain Reaction (RT-PCR) positive staff working in the hospital during the pandemic period.

Material and methods: This is retrospective, descriptive research. All hospital personnel working at Sakarya Training and Research Hospital and tested positive for COVID-19 RT-PCR between 01/11/2020-30/11/2020 were included in the study.

Results: During the study period, the number of hospital staff who tested positive for COVID-19 RT-PCR was 340 people. Of the personnel, 228 (67.1%) were female, the mean age of all healthcare workers was 32.7 (± 8.3) years. The number of non-physician healthcare workers was 162 (47.6%), workers were 143 (42.1%), and physicians were 35 (10.3%). Among all hospital personnel, the COVID-19 RT-PCR test was positive in emergency room workers, with a maximum of 61 people (17.9%). It was followed by 43 (12.6%) people working in non-COVID clean wards.

Conclusions: It would be beneficial for all staff working in the hospital during the pandemic to pay attention to apply personal protective equipment during their work, notwithstanding whether the COVID-19 patient is caring or not. Simultaneously, healthcare professionals should be careful about COVID-19 transmission in their social life outside of the hospital.

Key words: COVID-19, healthcare workers, emergency service.

INTRODUCTION

The COVID-19 pandemic appeared in China in 2019's last weeks, then spread to the world quickly; moreover, was eventually declared a pandemic by the World Health Organisation (WHO) on March 11, 2020 (1). During the pandemic period, with the increasing number of patients, healthcare facilities have suffered accelerated patient admission and workload. Thus, negative images were reflected by the press because of the inadequate personnel and deficiency of physical facilities. Healthcare workers were also affected both psychologically and physically during the pandemic process (2, 3). Working in personal protective equipment (PPE) for long periods has been problematic, however, in some hospitals, healthcare workers (HCW) have not been able to protect themselves adequately due to insufficient PPE (4). On September 2, the WHO Pan American Regional Office in Washington DC reported that 570,000 healthcare workers were infected with Covid-19, and 2500 of them died. (5). While some HCW who had COVID-19 disease survived the disease outpatient, some had to be hospitalised and treated. Unfortunately, some healthcare professionals passed away due to COVID-19they contracted during this period. WHO has reported that thousands of HCW worldwide died due to COVID-19 by September 17, 2020 (6). Publications state that these mortality rates are observed less in HCW who had a reasonable adaptation period and had adequate PPE compared to those who did not have this opportunity (7).

Due to the increasing workload, each healthcare worker's need has become more evident during the pandemic period. Therefore, it is also essential to ascertain healthcare professionals' status in the COVID-19 pandemic, in which units are riskier, to protect HCW and maintain health service delivery.

This study aimed to reveal the demographic characteristics of HCW who tested positive for COVID-19 at Sakarya University Training and Research Hospital (SEAH) between November 1, 2020, and November 30, 2020. The patients' age, gender, occupation and unitthey worked in, hospitalisation status, and mortality were examined, so the contribution to literature is to tell us which occupational group should be of greater

concern, and in which areas; furthermore, to ascertain which healthcare professionals should be paid attention to more in the pandemic.

MATERIAL AND METHODS

This research is a retrospective, descriptive study.

In this study, the demographic data of the HCW working at SEAH between November 1, 2020 to November 30, 2020 who were positive for the COVID-19 RT-PCR test were analysed. SEAH has a total of 4818 health workers. RT-PCR positive HCW who worked actively in all the hospital's campuses and units were included in the study. HCW who were not on active duty but found a positive COVID-19 RT-PCR test were excluded from the research.

Definitions

The wards in which RT-PCR tested positive or clinically suspected COVID-19 patients hospitalised were accepted as "COVID-19 Service" and intensive care units as "COVID-19 intensive care". Units that are not associated with the diagnosis, follow-up, or treatment of COVID-19 patients were called "clean". Warehouses and technical units that were not in direct contact with patients were grouped as "support areas". All laboratory areas such as pathology, microbiology, biochemistry, or emergency laboratory were grouped as "laboratories". Areas including, corridors, waiting rooms, public toilets, entrance foyer areas where patients could be found for a short time while passing through were classified as "General Areas".

While hospital personnel is grouped according to their staff, all specialist physicians, assistant physicians, and general practitioners were grouped as "doctors". Except for the doctor, employees such as nurses, physiotherapists, and orthopaedic technicians who contact patients were grouped as "non-physician healthcare workers". Cleaning personnel, security guards, technical service personnel, and secretaries, who did not have a diagnosis or treatment relationship with the patient, were sometimes needed in the patients' areas, were included in the "worker" group.

Data collecting

The data were obtained by scanning from the hospital automation system and patient files.

Permissions

Approval was obtained from the Ethics Committee of Sakarya University Faculty of Medicine (E-71522473-050.01.04-6065 43).

Statistical analysis

IBM Statistical Product and Service Solutions (SPSS) V21.0 was used concerning statistical analysis. A Chi-square test was acquired for the association of categorical data. Results with $p < 0.05$ were interpreted as statistically significant. The skewness and kurtosis scores were expected to be in the ± 2 value range to specify whether the decentralised data match the regular distribution (8). Mann-Whitney U test was appropriated to compare independent data that did not submit to the normal distribution; moreover, results with $p < 0.05$ were acknowledged notable.

RESULTS

In SEAH, the number of COVID-19 positive HCW during the study period is 340 people. 112 (32.9%) of this personnel were male, and 228 (67.1%) were female. The average age of the personnel included in the study was 32.7 (± 8.3), the median age value was 32 (min. 26 years, max. 56 years).

The number of hospitalised and treated patients among all COVID-19 positive HCW was 13 (3.8%), 6 of them were men, and 7 were women. The average length of stay in hospital was 4.2 days (min. 2, max. 9 days). Of the 13 patients hospitalised, 2 (0.6%) were treated in the intensive care unit and 11 (3.2%) in the service. See Table 1 for inpatient data.

No deaths were observed among healthcare workers who tested positive for the PCR during the study period.

There was no statistically significant relationship between the gender of the patients and their hospitalisation status (Fisher's Exact Test, $p = 0.368$).

Table 1. *Inpatient Demographic data and length of stay of the patients*

Gender	Mean Age	Inpatient		Outpatient	Length of[1] Stay	p Value[2]
		Service	**Intensive care**			
Male	38	4	2	106	4	0.379
Female	34	7	0	222	4	0.379
Total	36	11	2	328	4	

[1] Average number of days spent in the hospital

[2] The result of comparing the gender and length of stay in hospital with the Kruskal Wallis Test

Table 2. *Distribution of COVID-19 Positive Healthcare Personnel*

		Inpatient	Outpatient	Total	Percent %[1]
Job Groups	Doctor	2	33	35	10.3
	Non-doctor staff	6	156	162	47.6
	Worker	4	139	143	42.1
Unit[2]	Emergency Service	2	59	61	17.9
	Clean Service	3	40	43	12.6
	COVID-19 Service	4	36	40	11.8
	Clean Intensive Care	2	35	37	10.9
	COVID-19 ICU	0	33	33	9.7
	General Areas	0	31	31	9.1
	Administrative units	1	23	24	7.1
	Outpatient Clinics	0	24	24	7.1
	Operating Room	0	12	12	3.5
	Support Units	0	7	7	2.1
	Hospital Pharmacy	0	5	5	1.5
	Laboratory	0	5	5	1.5
	Laundry	0	4	4	1.2
	Central	0	4	4	1.2
	Delivery Room	0	4	4	1.2
	Radiology	0	3	3	0.9
	Home Health Services	0	3	3	0.9

[1] Percentage of allCOVID-19 RT-PCR positive staff
[2] Hospital unit where staff work

When the occupational groups of healthcare professionals were examined, it was found that COVID-19 RT-PCR positive non-physician healthcare workers number was 162 (47.6%), the number of workers was 143 (42.1%), the number of doctors was 35 (10.3%).

No statistically significant difference was found between healthcare personnel's occupational groups and their hospitalisation status (Pearson Chi-Square, $p = 0.651$).

When the patients' conditions were examined according to their working units in the hospital, it was observed that the emergency service workers were most infected from COVID-19 with 61 cases (17.9%). After that respectively, 43 people (12.6%) who worked in clean wards, 40 people (11.8%) in COVID-19 wards, 37 people (10.9%) in clean intensive care units, and 33 people (9, 7%) in COVID-19 intensive care units accompanied the group. The number and rates of staff who were COVID-19 RT-PCR positive according to the work units are shown in Table 2.

When physician's workplaces were analysed, it was observed that the maximum rate of COVID-19 RT-PCR positive physicians was in COVID-19 services (16 people, 45.7%) and emergency services (13 people, 37.1%). On the other hand, the units where 162 non-physician healthcare professionals worked positively were the emergency service (32 people, 19.8%), clean service (31 people, 19.1%), clean intensive care units (27 people, 16.7%), COVID-19 service (18 people, 11.1%) and COVID-19 intensive care units (18 people, 11.1%).

The distribution of all other RT-PCR positive personnel according to their working areas were general areas (31 people, 23.5%), emergency service (15 people, 11.4%), polyclinic (15 people, 11.4%), clean wards (11 people, 8.3%), COVID-19 intensive care units (11 people, 8.3%).

Thus, 134 (39.4%) HCW were working in the emergency department, COVID-19 services, COVID-19 intensive care units; besides a total of 206 (60.6%), HCW were working in non-COVID-19 areas.

DISCUSSION

In the COVID-19 pandemic, health workers were physically and psychologically challenged; furthermore, sometimes they had COVID-19 infection. Albert and Rozita stated that 12 393 HCW infected with SARS-CoV-2 in Germany by May 25, 2020, and 567 (4.6%) of these health workers were hospitalised,

20 (0.2%) of them died; moreover, 63.9% of infected HCW were nurses (9). Jameela et al. checked 16,912 health workers in 14 hospitals in Qatar between March 10, 2020 and June 26, 2020, and they noted that 1799 (10.6%) tested positive for COVID-19, and 65.6% of them were male (10). It was recorded that 11.6% of these cases were hospitalised, and 0.6% required intensive care unit, while there were no deaths (10). In a retrospective study conducted in Wuhan, China, Jie Lu et al. observed that 64 HCW infected with COVID-19, but none of them needed intensive care (11). Kasper and colleagues analysed 28,792 HCW between April 15, 2020 to April 23, 2020 in an observational cohort study conducted in Denmark and asseverated that 1163 (4.04%) HCW tested positive for COVID-19 and 71% of them were women (7). Kramer et al. notified that 2.8% of 3669 HCW in Germany infected with COVID-19 between April 15, 2020 and May 1, 2020, of which 61% were women (12). Nicola et al. also reported that 82 (13.8%) HCW were COVID-19 positive, of which 68.3% were women in a survey of 595 health workers; furthermore, most of them were young and nurses. According toour research's results, 340 HCW in SEAH infected with COVID-19 between November 1, 2020 and November 30, 2020. The above studies and this study did not cover the whole pandemic period but were conducted over specific periods. However, 67.1% of the HCW infected in our study were women correlated with other research, except Jameela et al. The reason female employees contracted COVID-19 at such a prevailing rate may be that women frequently perform the nursing profession. In support of this, Albert and Rozita published that 63.9% of infected medical personnel, Nicola 70.1%, Kasper 34.5%, Liu and colleagues 67%, and Stock et al. 33.2% were nurses (7, 9, 11, 13, 14). Contrary to these studies and our study, in Jameela et al.'s research, COVID-19 positivity was predominately found in male health workers (10). This may be because 75% of the Qatar population is made up of men (15). However, it is impossible to conclude this issue due to the limited data on the HCW's gender distribution in Qatar hospitals. Besides, in Jameela et al.'s study, midwives and nurses rates among the healthcare workers infected with COVID-19 are at the top with 33.2% (10).

Jameela et al. reported that only 5% of HCW infected with COVID-19 work in healthcare facilities where COVID-19 patients were cared for (10). Besides, in the early days of the pandemic, data from China indicated that healthcare workers infected with COVID-19 from healthcare facilities, while later research in German hospitals declared that HCW contaminated with COVID-19 might have acquired the disease from the community (16). Jie Lu et al. also ascertained that just 18% of HCW infected with COVID-19 had a history of touch with COVID-19 cases or patients' samples (11). Albert and Rozita affirmed that 80% of the 224 HCW who were COVID-19 RTPCR positive until April 11, 2020 in Malaysia acquired the infection from the community (9). In our study, it was observed that 60.4% of the infected HCW were serving in clean areas, where there were no COVID-19 patients. Thus, the results of our study agreed with the conclusions of the above research. On the other hand; Kasper et al. reported that COVID-19 seroprevalence was significantly higher in those working in the COVID wards than other healthcare professionals (7).

Kramer et al., COVID-19 positivity was found more frequently in the emergency department, intensive care unit, and COVID wards than those working in other hospital's non-COVID areas (12). In our study, the high rate of positivity in healthcare professionals working in non-COVID areas supports the result of HCW acquired COVID-19 from the community. Also, Albert and Rozita are the fundamental reasons HCW in Malaysia infected with COVID-19; designated that insufficient PPE was used and there was no suspicion of COVID-19 in the patient (9). This study result can be interpreted that, HCW working in the non-COVID areas are not more concerned about wearing PPE.

CONCLUSION

The COVID-19 outbreak has negatively influenced healthcare workers as well as the whole society. HCW are at risk of COVID-19 infection in addition to the enhanced workload. Especially all HCW who are in close contact with any patient should be extra careful. Throughout the COVID-19 pandemic, healthcare professionals working in non-COVID areas should also provide healthcare service cautiously. As well as healthcare professionals are circumspect about infection transmission in their social lives outside of the hospital, it may help decrease the number of healthcare workers infected with COVID-19.

Abbreviations

HCW — healthcare workers

PPE — personal protective equipment

RT-PCR — Reverse Transcription Polymerase Chain Reaction

SEAH — Sakarya University Training and Research Hospital

Acknowledgment

None.

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Sažetak

DEMOGRAFSKE KARAKTERISTIKE POZITIVNIH ZDRAVSTVENIH RADNIKA NA KOVID-19 I POREĐENJE SA LITERATUROM

Durmus Ensar, Guneysu Fatih

Emergency Department, Sakarya University Training and Research Hospital, Sakarya, Turkey

CILJ: Cilj je da se ispitaju status i demografske karakteristike KOVID-19 RT-PCR pozitivnog osoblja koje radi u bolnici tokom perioda pandemije.

Metode i materijal: Ovo je retrospektivno, deskriptivno istraživanje. Sve osoblje bolnice koje radi u bolnici za obuku i istraživanje Sakaria i ima pozitivan test na KOVID-19 RT-PCR u periodu od 01.11. je uključeno u istraživanje.

Rezultati: Tokom perioda ispitivanja, broj bolničkog osoblja koje je imalo pozitivan test na KOVID-19 RT-PCR bio je 340 ljudi. Od osoblja, 228 (67,1%) su bile žene, prosečna starost svih zdravstvenih radnika bila je 32,7 ± 8,3) godina. Broj zdravstvenih radnika koji nisu lekari bio je 162 (47,6%), radnika 143 (42,1%), a lekara 35 (10,3%). Među svim bolničkim osobljem, test KOVID-19 RT-PCR bio je pozitivan kod radnika hitne pomoći, sa maksimalno 61 osobom (17,9%). Zatim 43 (12,6%) ljudi koji rade u ne-KOVID odeljenjima za čišćenje.

Zaključci: Bilo bi korisno da osoblje koje radi u bolnici tokom pandemije obrati pažnju da tokom svog rada primenjuje ličnu zaštitnu opremu, bez obzira na to da li pacijent sa KOVID-19 to isto čini ili ne. Istovremeno, zdravstveni radnici trebaju bit oprezni u pogledu prenošenja KOVID-19 u svom društvenom životu van bolnice.

Ključne reči: KOVID-19, zdravstveni radnik, Hitna služba.

REFERENCES

1. WHO announces COVID-19 outbreak a pandemic [Internet]. World Health Organization; 2020 [cited 2020 Apr 11]. Available from: http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic.

2. Vizheh M, Qorbani M, Arzaghi SM, Muhidin S, Javanmard Z, Esmaeili M. The mental health of healthcare workers in the COVID-19 pandemic: A systematic review. J Diabetes Metab Disord. 2020; 19(2):1–12. doi: 10.1007/s40200-020-00643-9.

3. Lucchini A, Iozzo P, Bambi S. Nursing workload in the COVID-19 era. Intensive Crit Care Nurs. 2020; 61:102929. doi: 10.1016/j.iccn.2020.102929.

4. Shaukat N, Ali DM, Razzak J. Physical and mental health impacts of COVID-19 on healthcare workers: a scoping review. Int J Emerg Med. 2020; 13(1): 40. doi: 10.1186/s12245-020-00299-5.

5. Pan American Health Organization (PAHO)/World Health Organization (WHO) 2020. COVID-19 has Infected Some 570.000 Health Workers and Killed 2,500 in the Americas. [cited 2020 Sep 27]. Available from: https://www.paho.org/en/news/2-9-2020-covid-19-has-infected-some-570000-health-workers-and-killed-2500-americas-paho.

6. Erdem H, Lucey DR. Healthcare worker infections and deaths due to COVID-19: A survey from 37 nations and a call for WHO to post-national data on their website. Int J Infect Dis. 2021; 102: 239–41. doi: 10.1016/j.ijid.2020.10.064.

7. Iversen K, Bundgaard H, Hasselbalch RB, Kristensen JH, Nielsen PB, Pries-Heje M, et al. Risk of COVID-19 in health-care workers in Denmark: an observational cohort study. Lancet Infect Dis. 2020; 20(12): 1401–8. doi: 10.1016/S1473-3099(20)30589-2.

8. George D, Mallery P. IBM SPSS statistics 25 step by step: a simple guide and reference. Fifteenth edition. New York ; London: Routledge, Taylor & Francis Group; 2019. 404 p.

9. Nienhaus A, Hod R. COVID-19 among Health Workers in Germany and Malaysia. Int J Environ Res Public Health. 2020; 17(13): 4881. doi: 10.3390/ijerph17134881.

10. Alajmi J, Jeremijenko AM, Abraham JC, Alishaq M, Concepcion EG, Butt AA, et al. COVID-19 infection among healthcare workers in a national healthcare system: The Qatar experience. Int J Infect Dis. 2020; 100: 386–9. doi: 10.1016/j.ijid.2020.09.027.

11. Liu J, Ouyang L, Guo P, Wu H, Fu P, Chen Y, et al. Epidemiological, clinical characteristics and outcome of medical staff infected with COVID-19 in Wuhan, China: A Retrospective Case Series Analysis [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Mar [cited 2020 Dec 31]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.03.09.20033118.

12. Kramer V, Papazova I, Thoma A, Kunz M, Falkai P, Schneider-Axmann T, et al. Subjective burden and perspectives of German healthcare workers during the COVID-19 pandemic. Eur Arch Psychiatry Clin Neurosci. 2021; 271(2): 271-281. doi: 10.1007/s00406-020-01183-2.

13. Magnavita N, Tripepi G, Di Prinzio RR. Symptoms in health care workers during the COVID-19 epidemic. A

cross-sectional survey. Int J Environ Res Public Health. 2020; 17(14): 5218. doi: 10.3390/ijerph17145218.

14. Stock AD, Bader ER, Cezayirli P, Inocencio J, Chalmers SA, Yassari R, et al. COVID-19 infection among healthcare workers: serological findings supporting routine testing. Front Med. 2020; 7: 471. doi: 10.3389/fmed.2020.00471.

15. Woman and Man- A Statistical Portrait 2018 [Internet]. Doha: Planning and Statistics Authority; 2018 Dec [cited 2020 Jan 6] p. 22. Available from: https://www.psa.gov.qa/en/statistics/Statistical%20Releases/Social/GenrealSocialStatistics/MenWomenProfile/2018/Woman_Man_2018_EN.pdf.

16. Bielicki JA, Duval X, Gobat N, Goossens H, Koopmans M, Tacconelli E, et al. Monitoring approaches for health-care workers during the COVID-19 pandemic. Lancet Infect Dis. 2020; 20(10): e261–7. doi: 10.1016/S1473-3099(20)30458-8.

Correspondence to/Autor za korespondenciju
Ensar Durmus, MD
Sakarya Training and Research Hospital
Department of Emergency Medicine
Sakarya, TURKEY
Phone: +90505 866 57 82
e-mail: muhalefet@hotmail.com

SANAMED
2021; 16(1): 77–83
ISSN-1452-662X

DOI:10.24125/sanamed.v16i1.500
UDK:616.5:[616.98:578.828
ID:37504777
Professional article

SKIN MANIFESTATIONS IN HIV/AIDS PATIENTS – OUR EXPERIENCE

Djurovic Milena,[1] Andric Bogdanka,[2] Djurovic Milica,[1] Bojic Milos[3]

[1] Clinic of Dermatology and Venereology, Clinical Center of Montenegro, Faculty of Medicine, University of Montenegro, Podgorica, Montenegro
[2] Clinic of Infectious Diseases, Clinical Center of Montenegro, Faculty of Medicine, University of Montenegro, Podgorica, Montenegro
[3] Clinic of Plastic Surgery, Clinical Center of Montenegro, Podgorica, Montenegro

Primljen/Received 19. 02. 2021. god. Prihvaćen/Accepted 10. 04. 2021. god.

Abstract: **Objective**: HIV/AIDS represents a significant public health issue since the number of cases is continuously on the rise. Even though contemporary medicine is rapidly developing, there is currently no effective cure for HIV. Mucocutaneous manifestations often represent the first recognized clinical manifestation. This study was carried out to note different presentations of HIV/AIDS on the skin.

Material and Methods: The study included 150 patients who were hospitalized and have been confirmed as HIV positive either before the hospitalization or during the hospitalization.

Results: Out of 150 patients, 50 of them had mucocutaneous presentations. Frequently, mucocutaneous lesions are the first manifestation of HIV/AIDS and a pointer toward setting up HIV/AIDS diagnosis. Moreover, the same patient was admitted more than once, because of a variety of skin manifestations.

Conclusion: It was recognized that the greater the destruction of the immune system is, the more severe forms of mucocutaneous diseases occur. It is considered that cutaneous manifestations are rarely considered life-threatening in people living with HIV, but they can undoubtedly impair their quality of life.

Keywords*:* Mucocutaneous lesions, HIV/AIDS, immune system activation, HIV pandemic, ART.

INTRODUCTION

HIV / AIDS are two stages of a deadly infectious disease of viral etiology. The causative agent, HIV was discovered in 1983. It belongs to the family of non-oncogenic retroviruses, subfamilies of lentiviruses. Studies have shown the inhomogeneity of HIV and the majority belong to the HIV-1 variant. The HIV-2 variant is present only in West Africa and represents a less virulent form than HIV-1 (In HIV-1 and HIV-2, only about 40% of the sequences are identical.) (1, 2, 3).The basic effect of HIV infection is the progressive destruction of the immune system, up to the terminal phase of AIDS, which is characterized by pronounced suppression of the immune system and the development of fatal coinfections, opportunistic infections, and tumors (4). After entering the body, HIV binds to receptors on the surface of CD4 lymphocytes and other cells: Langerhans cells, cells of the monocyte-macrophage line, which serve as reservoirs and carriers of the virus (5, 6, 7).

In order to enter the cell, HIV requires a cofactor: CCR-5 (for tropic macrophages) and CXCR-4 (for lymphotropic variants of HIV). The first step of HIV entry into the cell is the fusion of proteins (GP 120) with CD4.

A strong Th1 response can keep the virus under control for a long time. (asymptomatic period lasts about 10 years). However, in most infected people, this cellular response does not last that long. The production of specific antibodies (Th2 response) is activated, which are significantly less effective. The number of viruses gradually increases and progressively destroys CD4 cells. Cells that are not destroyed are damaged, which also reduces the body's defense possibilities. The virus itself is capable of destroying CD4 cells, by triggering the mechanisms of programmed death (apoptosis). By destroying key defense cells, a complete breakdown of the immune system and the manifestation of AIDS occurs. It attacks and kills the regulatory T cells needed for the immune response (when there are no CD4 cells, the ability to make CD8 cells is lost) (8).

AIM

Skin changes are common in people living with HIV and may be the first manifestation of HIV. It is reported that up to 90% of people living with HIV

around the world have or had skin changes (5). It is considered that cutaneous manifestations are rarely considered life-threatening in people living with HIV, but they can undoubtedly impair their quality of life. Although the use of HAART prolongs life expectancy, many people living with HIV suffer from facial lipoatrophy as a result of a response to therapy and many other dermatological manifestations, such as psoriasis-like syndrome. In addition to cosmetic disfigurement, in eosinophilic folliculitis, intense pruritus can seriously impair the quality of life of the infected (1, 2, 3).

Most commonly, there is no difference between the treatment of skin manifestations in HIV/AIDS positive and negative patients. However, systemic administration of high-dose steroids in longer runs should be used with caution due to its immunosuppressive effects.

According to numerous studies, and generally accepted rules, the spectrum of skin manifestations depends on: the immune stage of the disease, the number of CD4 cells, the simultaneous use of HAART, and the pattern of endemic infections. These changes are also influenced by the geographical distribution of various infectious agents. (e.g. penicilliosis is more frequent in Southeast Asia and Hong Kong than in the Western world). In advanced stages of HIV infection, skin changes often have an unusual appearance, which makes setting up the diagnosis difficult.

During the study of skin manifestations, some authors came to the conclusion that the introduction of HAART, due to the improvement of host immunity, changed the spectrum of skin manifestations in HIV/AIDS people. It is reported to reduce the incidence of Kaposi's sarcoma, eosinophilic folliculitis, dermatophyte infections, molluscum contagiosum, and others, and increase the number of HIV-positive people with herpes viruses: HZ, HSV, CMV, EBV, and some other agents with skin affinity (1).

Due to all previously mentioned, it is important to keep in mind the importance of skin manifestations. Not rarely, skin manifestations could be the pointer for revealing HIV status. It seems that a large number of physicians do not have that in mind. Skin conditions are usually not life-threatening, but it is important not to neglect them. Instead, health professionals should observe them and try to find the eventual underlying condition that triggered skin changes.

MATERIAL AND METHODS

Comprising the period from 1995 to 2015, we observed 150 patients diagnosed with HIV/AIDS to identify the type, frequency, and severity of skin

Table 1. *The frequency of dermatologic manifestations in our HIV/AIDS patients*

No.	Dermatological manifestation	Number of patients (total number of patients = 50)*	Percentage of patients that had certain skin manifestation
1.	Skin changes due to primary HIV infection	15	30%
2.	Hairy leukoplakia	2	4%
3.	Herpes simplex (HSV-1 and HSV-2)	9	18%
4.	Disseminated bullous herpes zoster	3	6%
5.	Cutaneous CMV infection	2	4%
6.	Molluscum contagiosum	7	14%
7.	HPV condylomata	3	6%
8.	Oral candidiasis	23	46%
9.	Cutaneous candidiasis and Onychomycosis	2	4%
10.	Hystoplasmososcutanea	1	2%
11.	Scabies	5	10%
12.	Angiomatosis bacillaris	1	2%
13.	Dermatitis seborrhoea	11	22%
14.	Kaposi sarcoma	2	4%
15.	Non-Hodgkins lymphoma cutis	1	2%

*Single patients had more than one mucocutaneous manifestation

manifestations. Among this group, we registered skin changes in 50 patients. After a deep analysis of skin changes, our experience has shown that the most commonly registered skin changes in the study group were due to herpes virus infections (HSV, VZV, EBV, and CMV) and fungal infections. Less common were parasitic, bacterial infections, and tumors.

The diagnostic examinations were performed at the Infectious and Dermatology Clinic of the Clinical Center of Montenegro, among the patients who were admitted due to the worsening of clinical signs. Among the respondents, the youngest was 18 years old, and 85% were on ART. Epidemiological data, clinical and laboratory examinations were performed during the study. Routine laboratory examinations included Complete Blood Count, CD4 Count, and Liver Functional Tests. In cases where it was needed tissue samples for biopsy were obtained, chest X-ray, microbiological tests, serological tests, etc. All the tests were used to evaluate the overall being of patients. Diagnostic tests (ELISA, Western Blot) were also used for etiological confirmation of HIV/AIDS.

RESULTS

The first case of HIV infection in Montenegro was registered in 1986 (sailor from the seaside). Data from 50 patients were included in our observation. The most common dermatologic manifestations were skin changes due to primary HIV infection, represented by exanthems. According to the epidemiological data, the most common way of transmission was the sexual route of transmission. Not all the patients had just one skin manifestation. Thus, some of them looked for help because of skin issues more than once due to different skin diseases. Out of 50 patients, 15 had just one skin disease or 30% of patients had one skin manifestation. 31 patients (62%) were admitted twice, and just 3 patients (8%) had three different skin manifestations. Among the respondents, the youngest was 18 years old, and 85% were on HART/ART therapy. In Table 1 we presented dermatologic manifestations of HIV/AIDS according to our experience.

DISCUSSION

Primary HIV infection (Acute Seroconversion Syndrome)

Primary HIV infection (Acute Seroconversion Syndrome) is similar to EBV infection. Fever, laryngitis, cervical adenopathy are often accompanied by polymorphic exanthem (in 70% of cases) (9). It can be manifested as erythematous, maculopapular rash, often with a tendency to confluent. The eruption is distributed throughout the trunk, sometimes on the palms and soles (similar to secondary syphilis). During this phase of infection, oral and genital erosions were also found. Histologically, nonspecific mononuclear infiltrates are found in the upper dermis (10).

Oral hairy leukoplakia

It manifests with the formation of thick, whitish adherent deposits, which cannot be removed. The lesions are located on the buccal mucosa, the bottom of the oral cavity, or on the tongue. The etiological cause of hairy leukoplakia is considered to be Epstein Bar Virus (EBV), although other infectious agents have been found. Leukoplakia may appear as one of the first symptoms of HIV infection (11).

Herpes simplex viral (HSV) infections (HSV-1 and HSV-2)

Symptomatic and asymptomatic reactivated HSV infections are common even nowadays among the HIV population and can be the cause of significant morbidity and even lethality in the HIV/AIDS population in conditions of severe immunodeficiency (12).

Disseminated bullous herpes zoster

The clinical occurrence of HZ among HIV-positive individuals is usually no different from that in individuals without HIV infection. Nevertheless, lesions affecting more dermatomes are more common in advanced stages. Atypical manifestations, like necrotic ulcers or hyperkeratotic ulcerated nodules, are reported to be more common when the immune system is more destroyed (13).

Cutaneous manifestations in people living with HIV, caused by cytomegalovirus (CMV)

Systemic CMV infection is common in people living with HIV, while mucosal and skin lesions are rare. If mucocutaneous lesions occur, oral or perianal ulcers are the most frequent clinical image. Papulovesicular eruptions, purpura, nodules, and verrucous lesions on the skin have also been registered (14).

Molluscum contagiosum (MC)

The causative agent is the Poxvirus, which selectively infects human epidermal cells. The disease has a benign course in immunocompetent, but severe and long-lasting in immunodeficient. In the advanced stages of immune system destruction, giant and verrucous forms of MC may occur. MC in HIV/AIDS patients

is persistent, hard to cure and treat, and tends to be chronic (15).

Cutaneous manifestations of human papillomavirus infection in people living with HIV/AIDS

Both HIV and HPV viruses can survive in the body for years in a latent state without manifest symptoms of the disease. In people who have both HPV and HIV infection, both viruses can make a person more susceptible to other diseases or complications. The extent of the disease depends on the state of the immune system and numerous types of HPV, of which some are at low-risk types for the development of malignancies and some are at high risk (16).

Fungal Infections

1. Oral candidiasis

Mucocutaneous candidiasis is usually caused by Candida albicans. It is one of the most common mucocutaneous findings in HIV disease. It manifests as oral thrush, cutaneous cheilitis, balanitis, intertrigo, paronychia, and vaginal thrush. Oropharyngeal candidiasis may present as an erythematous or hyperplastic type (17).

2. Dermatophytosis and onychomycosis

The clinical image of these fungal infections is generally similar to those of non-HIV-infected individuals. Tinea unguium is often associated with tinea pedis. “Proximal white subungual onychomycosis” is a regularly less common presentation, but more specific for HIV infection. The administration of systemic therapy is usually needed, as topical therapy is not effective (18).

Scabies

In people with HIV/AIDS who suffer from scabies, skin changes are generally similar to those without HIV infection but are usually more extensive and severe (exaggerated).In one case of advanced HIV/AIDS infection, manifestations of scabies were similar to Norwegian scabies. Norwegian scabies occurs mainly in people with a significantly weakened immune system. The treatment of the disease is very difficult, and the contagiousness is great. Thick crusts appear on the skin which often cover large areas of the body. The changes were not accompanied by itching (19).

Seborrhoeic dermatitis

Seborrhoeic dermatitis is a common skin condition that mainly affects the hairy part of the head. It is manifested by scaly changes, reddish skin, and stubborn dandruff. The tendency to recur is also one of the common features of seborrhoeic dermatitis. ART decreases the prevalence of seborrhoeic dermatitis and those who are under ART treatment may experience milder and less severe clinical presentation (20).

Bacillary angiomatosis

Bacillary angiomatosis is a systemic infectious disease that affects both the skin and internal organs. It is characterized by the development of angiomatous lesions, which can be clinically reminiscent of Kaposi’s sarcoma (21).

Kaposi’s sarcoma

Kaposi’s sarcoma (KS) is a soft tissue malignant tumor. Skin lesions are usually purple. They may occur in a limited area or be disseminated. Tumor deterioration may occur very rapidly or gradually. Although the etiology of these changes is not yet fully known, human herpesvirus 8 is found in lesions. Four clinical forms of this tumor have been described: classic, endemic, immunosuppressive - therapeutic, and epidemic (HIV related). The classic form usually occurs in older males, progresses slowly, and is usually located on the skin of the lower extremities. Endemic form occurs in young adult males in Africa and may be more aggressive. KS associated with immunosuppressive therapy usually occurs in humans after organ transplantation and mainly affects the skin. The KS epidemic form occurs in people living with AIDS and represents the second most common tumor in HIV/AIDS people (22).

Dermatological manifestations could appear in all stages of HIV/AIDS, regardless of the severity of infection/disease. They appear as skin infections or inflammations, immune and malignant diseases. After the introduction of antiretroviral therapy, some dermatological manifestations became rare, but new diseases appeared, such as immune restoration diseases, then lipodystrophic skin disorders, etc (6).

Manifestations such as MC, oral leukoplakia, oral candidiasis, chronic ulcerative HS, and KS are strongly associated with the progression of HIV immunodeficiency. In the last decade, highly active ART has significantly changed the course of HIV infection by empowering the immune system and improving the clinical signs of dermatological manifestations (7).

Symptoms of skin disorders, which are more frequent among HIV-positive patients compared to HIV-negative patients, are also characterized by their complexity, atypia, and therapeutic resistance in any case affecting the quality of life of HIV-positive patients.

Of the non-infectious skin disorders in HIV-positive patients, lesions represented as pruritic papular eruption were the most frequent cutaneous manifestation (1, 2).

Studies conducted in Pakistan to determine the pattern and prevalence of mucocutaneous lesions in HIV patients revealed that fungal infections prevailed, starting with the most frequent oral candidiasis and onychomycosis. Herpes zoster and HPV infections had the highest prevalence among HIV-accompanying viral diseases. Bacterial infections in these patients were mainly of the folliculitis type. Among other clinical manifestations, photosensitivity, scabies, and hyperpigmentation were less common (23).

A study conducted in Iran showed that 32% of HIV-infected patients had a CD4 cell count lower than 300 cells/ml. Participants with lower CD4 had more frequent symptoms and more severe clinical presentation. In this study, CD4 cell counts were found to have a positive and significant correlation with skin diseases and that these skin disorders can help in faster HIV diagnosis. Information was accepted with reservations, given the differences in the results of examinations by other authors, which do not find a relationship between the number of CD4 cells (P = 0.274) and the severity of clinical manifestations, with the explanation that many skin disorders can occur in HIV patients with normal CD4 cell counts. In our series of Bartonella henselae infection studies, extensive disseminated changes (on the skin, liver) were found in a patient with a normal CD4 cell count, without signs of immunodeficiency of any etiology (24).

CONCLUSION

Since the discovery up to this day, HIV/AIDS issue remains the main challenge in the field of medical sciences, and the subject of intensive scientific research, in particular, the immuno-pathogenetic characteristics of the infection, effective prevention, and treatment. Mucocutaneous manifestations of HIV/AIDS were first registered in patients in the early 1980s. A handful of researches have shown that no skin disease is caused specifically by HIV/AIDS. However, diseases such asKS and eosinophilic folliculitis strongly suggest the HIV etiology of the changes. In HIV/AIDS, skin diseases usually present with more severe clinical presentations, tending to become chronic, recurrent, and resistant to treatment. At the end of 2019, 81% of people living with HIV knew their status. It is estimated that 67% of people received ART and 59% achieved HIV control without the risk of infecting others. At the end of 2019, 25.4 million people started ART. Between 2000 and 2019, new HIV infections fell by 39%, HIV-related deaths fell by 51%, and 15.3 million lives were saved due to ART. These results were achieved due to the tough efforts of national and international HIV programs and the strong actions of major health institutions and civil societies

Abbreviations

AIDS — acquired immunodeficiency syndrome
HIV — human immunodeficiency virus
CCR — C-C chemokine receptor type 5
CXCR — C-X-C chemokine receptor type 4
EBV — Epstein Bar Virus
ART — antiretroviral therapy
HAART — highly active antiretroviral therapy
HZ — herpes zoster
VZV — Varicella zoster virus
HSV — herpes simplex virus
CMV — Cytomegalovirus
HPV — Human papillomavirus
KS — Kaposi's sarcoma

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Sažetak

DERMATOLOŠKE MANIFESTACIJE KOD HIV/AIDS PACIJENATA – NAŠE ISKUSTVO

Đurović Milena,[1] Andrić Bogdanka,[2] Đurović Milica,[1] Bojić Miloš[3]

[1] Clinic of Dermatology and Venereology, Clinical Center of Montenegro, Faculty of Medicine, University of Montenegro, Podgorica, Montenegro
[2] Clinic of Infectious Diseases, Clinical Center of Montenegro, Faculty of Medicine, University of Montenegro, Podgorica, Montenegro
[3] Clinic of Plastic Surgery, Clinical Center of Montenegro, Podgorica, Montenegro

Cilj: HIV/AIDS predstavlja značajno javno-zdravstveno pitanje, jer je broj zaraženih/obolelih u stalnom porastu. Iako se savremena medicina ubrzano razvija, trenutno ne postoji efikasan lek za HIV. Kutane manifestacije često predstavljaju prvu prepoznatu kliničku manifestaciju HIV/AIDSa, a neretko se kožne manifestaciju zanemaruju. Ova studija je sprovedena kako bi se zabeležile različite prezentacije HIV/AIDS-a na koži.

Materijal i metode: Studija je obuhvatila 150 stacionarnih bolesnika koji su bili hospitalizovani i kojima je potvrđeno da su HIV pozitivni ili pre hospitalizacije ili tokom hospitalizacije.

Rezultati: Od 150 pacijenata, 50 pacijenata su imali kožne manifestacije. Neretko su kožne i sluzokožne lezije prva manifestacija HIV/AIDS-a i vodič ka postavljanju dijagnoze HIV/AIDSa. Štaviše, u našoj studiji i isti pacijent je primljen više puta zbog različitih kožnih manifestacija.

Zaključak: Prepoznato je da što je veća destrukcija imunološkog sistema, to se javljaju teži oblici mukokutanih bolesti. Smatra se da se kožne manifestacije retko smatraju opasnim po život ljudi koji žive sa HIV-om, ali nesumnjivo mogu narušiti njihov kvalitet života.

Ključne reči: mukokutane lezije, HIV/AIDS, aktivacija imunog sistema, HIV pandemija, ART.

REFERENCES

1. Richman DD,Bozzette SA. The impact of the syncytium – inducinephenothype of human immunodeficiency virus on disease progression. J Infect Dis. 1994; 169(5): 968–74. doi: 10.1093/infdis/169.5.968.

2. O'Donovan D, Ariyoshi K, Milligan P, Ota M, Yamuah L, Sarge-Njie R, et al. Maternal plasma viral RNA levels determine marked differences in mother-to-child transmission rates of HIV-1 and HIV-2 in The Gambia. MRC/Gambia Government/University College London Medical School working group on mother-child transmission of HIV. AIDS. 2000; 14(4): 441–8. doi: 10.1097/00002030-200003100-00019.

3. Dean M, Carrington M, Winkler C, Huttley GA, Smith MW, Allikmets R, et al. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. Science. 1996; 273(5283). 1856-62. doi: 10.1126/science.273.5283.1856.

4. Ndour M, Sow PS, Coll-Seck AM, Badaine S, Ndour CT, Diakhate N et al. AIDS caused by HIV1 and HIV2 infection: are there clinical differences? Results of AIDS surveillance 1986–97 at Fann Hospital in Dakar, Senegal. Trop Med Int Health. 2000; 5(10): 687–91. doi: 10.1046/j.1365-3156.2000.00627.x.

5. Sharp PM, Hahn BH. Origins of HIV and the AIDS Pandemic. Cold Spring Harbor Perspect Med. 2011; 1(1): a006841. doi: 10.1101/cshperspect.a006841.

6. Centers for Disease Control and Prevention. (2014) HIV/AIDS: Statistics Overview. Accessed at www.cdc.gov/hiv/statistics/basics/index.html on July 21.

7. Joint United Nations Programme on HIV/AIDS (UNAIDS); World Health Organization. AIDS epidemic update: December 2009. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2009.

8. Matsiyeuskaya VN, Tsyrkunov MV. Activation of blood T-cells in HIV/HCV co-infected patients. Sanamed. 2013; 8 (1): 11-8.

9. Moir S, Chun TW, Fauci AS. Pathogenic ,echanisms of HIV disease. Annu Rev Pathol. 2011; 6: 223-48. doi: 10.1146/annurev-pathol-011110-130254.

10. Sullivan PS, Fideli U, Wall KM, Chomba E, Vwalika C, Kilembe W et al. Prevalence of seroconversion symptoms and relationship to set-point viral load: findings from a subtype C epidemic, 1995-2009. AIDS. 2012; 26(2): 175-84. doi: 10.1097/QAD.0b013e32834ed8c8.

11. Tappuni AR. The global changing pattern of the oral manifestations of HIV. Oral Dis. 2020; 26(Suppl 1): 22-7. doi: 10.1111/odi.13469.

12. Munawwar A, Grupta S, Sharma SK, Singh S. Seroprevalence of HSV-1 and 2 in HIV-infected males with and without GUD: Study from a tertiary care setting of India. J Lab Physicians. 2018; 10(3): 326-31. doi: 10.4103/JLP.JLP_7_18.

13. Kakitha R, Shanmugam S. Bullous pemphigoid-like presentation of disseminated Herpes Zoster: a case report. Indian J Dermatol. 2020; 65(3): 234-5. doi: 10.4103/ijd.IJD_337_18.

14. Perello R, Vergara A, Monclus E, Jimenez S, Montero M, Saubi N et al. Cytomegalovirus infection in HIV-infected patients in the era of combination antiretroviral therapy. BMC Infectious Diseases. 2019; 19(1): 1030. doi: 10.1186/s12879-019-4643-6.

15. Gaurkar SP, Pund PB, Dindore PR, Bhoi UY. Extensive molluscum contagiosum causing obstruction of vision in HIV-positive women. Indian Dermatol Online J. 2016; 7(3): 190-1. doi: 10.4103/2229-5178.182360.

16, Clifford GM, Tully S, Franceschi S. Carcinogenicity of Human Papilloma virus (HPV) types in HIV-positive women: a meta-analysis from HPV infection to cervical cancer. Clin Infect Dis. 2017; 64(9): 1228-35. doi: 10.1093/cid/cix135.

17. Patil S, Majumdar B, Sarode SC, Sarode GS, Awan KH. Oropharyngeal candidosis in HIV-infected patients-an update. Front Microbiol. 2018; 9: 980. doi: 10.3389/fmicb.2018.00980.

18. Ali SY, Gajjala SR, Raj A. Study of the prevalence of dermatophytes among human immunodeficiency virus/AIDS patients in Shadan Institute of Medical Sciences and Teaching Hospital and Research Centre, Hyderabad, Telangana, India. Indian J Sex Transm Dis AIDS. 2018; 39(2): 98-101. doi: 10.4103/ijstd.IJSTD_103_16.

19. Tirado-Sánchez A, Bonifaz A, Montes de Oca-Sánchez G, Araiza-Santibañez J, Ponce-Olivera RM. Escabiosis costrosa en pacientes con infección por VIH/SIDA. Reporte de 15 casos

[Crusted scabies in HIV/AIDS infected patients. Report of 15 cases]. Rev Med Inst Mex Seguro Soc. 2016; 54(3): 397-400.

20. Forrestel AK, Kovarik CL, Mosam A, Gupta D, Maurer TA, Micheletti RG. Diffuse HIV-associated seborrheic dermatitis – a case series. Int J STD AIDS. 2016; 27(14): 1342-5. doi: 10.1177/0956462416641816.

21. Balaban M, Ioana Nedelcu R, Balmes G, Adela Todorovic T, Brinzea A, Nichita Let al. Bacillary angiomatosis triggered by severe trauma in a healthy Caucasian patient: A case report. Exp Ther Med. 2020; 20(1): 56-60. doi: 10.3892/etm.2019.8260.

22. Curtiss P, Strazzulla LC, Friedman-Kien AE. An Update on Kaposi's Sarcoma: Epidemiology, Pathogenesis, and Treatment. Dermatol Ther (Heidelb). 2016; 6(4): 465-70. doi: 10.1007/s13555-016-0152-3.

23. Azfar NA, Khan AR, Zia MA, Humayun A, Malik LM, Jahangir M. Frequency of mucocutaneous manifestations in HIV positive Pakistani patients. J Pak Assoc Dermatol 2011; 21: 149–53.

24. Foroughi M, Koochak HE, Roosta N, Paydary K, Khatami A, Shahriari S et al. Prevalence of dermatologic manifestations among people living with HIV/AIDS in Imam Khomeini Hospital in Tehran, Iran. Journal of AIDS and HIV Research. 2012; 4(2): 56-9.

Correspondence to/Autor za korespondenciju
Milena Djurovic
Deparment of Dermatovenerology, Clinical Center of Montenegro,
Podgorica, Montenegro
email: milena.djurovic@kccg.me
phone: 00382 69 544 000

SANAMED
2021; 16(1): 85–90
ISSN-1452-662X

DOI:10.24125/sanamed.v16i1.501
UDK:616.24-074
619.98:578.834]:577.1
ID:37486857
Case report

HIGH D-DIMER VALUES AND POST-DISCHARGE ACUTE PULMONARY EMBOLISM IN YOUNG PATIENTS WITH COVID-19: A CASE SERIES

Calin Pop,[1, 2] Ionuț Ferenț[1]

[1] Emergency Clinical County Hospital of Baia Mare, Baia Mare, Romania
[2] "Vasile Goldis" University, Faculty of Medicine Arad, Arad, Romania

Primljen/Received 22. 02. 2021. god. Prihvaćen/Accepted 10. 04. 2021. god.

Abstract: **Introduction**: The coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is associated with an inflammatory and prothrombotic state that increases the risk of thromboembolic events. High levels of D-dimer are associated with the severity of the disease and acute pulmonary embolism (PE) is the most common thrombotic complication.

Material and methods: We analyzed a series of four cases of COVID-19 in young patients (under 45 years) who developed PE with a delay of two to four weeks after hospital discharge.

Results: These patients had elevated D-dimer (at least 10 times the upper limit of normal) at the initial admission and at the time of the PE diagnostic, while other parameters which involved inflammation and coagulation (C-reactive protein — CRP; lactate dehydrogenase — LDH; fibrinogen; international normalized ratio — INR) were normal. There were no pre-existing risk factors for PE and all the patients were anticoagulated with prophylactic intermediate doses of enoxaparin.

Conclusions: PE is a complication of the COVID-19 disease which may occur later, especially in young patients with no other risk factors for the condition. The highly elevated levels of D-dimer at COVID-19 admission seem to be associated with the post-discharge apparition of PE. This data suggests the role of extended anticoagulation in selected COVID-19 patients and warrants further investigations.

Key words: D-dimer, COVID-19, young patients, pulmonary embolism, post-discharge.

INTRODUCTION

COVID-19, caused by the SARS-CoV-2 coronavirus, is an infectious disease that usually presents respiratory symptoms, predisposing patients to venous thromboembolic (VTE) complications (1). COVID-19 was associated with an inflammatory status, cytokine and chemokines secretion, endothelial injury, or coagulation abnormalities, with marked elevations seen in C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, interleukin levels, and D-dimer (2). The result is the development of diffuse endothelial damage that predisposes to widespread thrombotic vascular lesions with microangiopathy, disrupted cell membranes, and new vessel growth (3). Patients with the elevation of D-dimer and fibrin degraded products have the worst prognosis (p = 0.003, for in-hospital death in the multivariable analysis) and higher severity of COVID-19 (4). The prevalence of pulmonary embolism (PE) was 15.8% [95% CI (6.0–28.8%)] in a meta-analysis of nine studies which included 3066 patients with COVID-19 (5). PE was the most frequent thrombotic complication from the reported VTE events in hospitalized patients with COVID-19.

Our case series of four young COVID-19 patients (under 45 years) described the appearance of PE post-discharge. We present the most important clinical and laboratory findings with the aim that this data may help clinicians in identifying the patients at risk for late thromboembolic complications.

MATERIAL AND METHODS

Four patients with suspected COVID-19, initially hospitalized (diagnosis made via SARS-CoV-2 PCR in a certified laboratory) and discharged from two COVID-19 dedicated hospitals, were admitted to the Intensive Cardiac Care Unit of the Emergency County Hospital in Baia Mare because of the new onset of intense dyspnea. This hospital usually provides the treatment for suspected and proven PE patients in Baia Mare and Maramureș County. The Ethics Com-

mittee of the Baia Mare Clinical County Emergency Hospital reviewed and approved the study (decision no. 34978/2020), which was done retrospectively with data collected from patients' records.

RESULTS

The clinical and laboratory characteristics of the patients are presented in Table 1.

Three of the four patients were male and all of them were between 31 and 45 years of age. None of them had medical antecedents, however, two were overweight with a BMI of 29 and 30. The symptoms were initially respiratory with cough and fever (37.5–38.5 °C); and one of the patients had arthralgia, myalgia, abdominal pain, diarrhea, and dyspnea. CT images displayed the presence of ground-glass opacities in all patients. Two of them had multi-affected lobes, one had two lobes, and the female patient had only one lobe affected. SpO2 was between 84–90% in two patients who had pressurized oxygen therapy for five days, 88–92% in one who had basal oxygen therapy

Table 1. *Clinical and laboratory characteristics of PE patients*

Variables/ Patients	1	2	3	4
Age	45	42	35	29
Sex	male	male	female	male
Medical history	none	none	none	none
BMI kg/m^2	29	30	24.5	25
ECG	110 b/min, sinus tachycardia	115 b/min, sinus tachycardia	incomplete right bundle branch	incomplete right bundle branch
PE symptoms	acute dyspnea, right thoracic pain, hemoptysis,	left thoracic pain, hypoxia 90 %	acute dyspnoea	acute dyspnoea
PE after ...days of Covid onset	22	18	32	16
PE localisation at angio CT	distal bilateral segmental and subsegmental	distal left lower lobe and central lobar right superior	distal bilateral segmental	distal unilateral lower left lobe
SARS-CoV-2 PCR at PE diagnosis	negative	negative	negative	positive
D-Dimer at Covid -19 diagnostic RR: 0.00−0.49 mg/L FEU	4.2	14.4	5.2	8.1
D-Dimer, at PE diagnostic, RR: 0.00−0.49 mg/L FEU	4.8	16.8	14.3	13.4
h-CRP (mg/dl) RR: up to 5 mg/L	12	25	10	4
Fibrinogen (g/L) RR: 2.0 to 4.0 g/L	4.3	5.2	4.6	3.7
LDH (U/l) RR: 100 - 250 IU/L	270	320	260	230
Serum ferritin RR; 12-300 ng/ml	80	450	–	–
BNP (pg/mL) RR: < 100 pg/ml	485	630	350	180
Haemoglobin (g/L), RR: 13-15 g/l	15	ı4	12.5	15
White-cell count (per mm) RR: 5000-10000	10300	11000	9600	9400
Platelets (per mm) RR: 150000-450000	410000	520000	245000	375000
INR, RR: 0.8-1.1	1.1	1.05	1.2	1
Anticoagulation before PE onset	Enoxaparin 0.6 ml once daily/ 7 days	Enoxaparin 0.6 ml once daily/ 7 days	none	none
PE treatment	Enoxaparin therapeutic doses, Dabigatran	Enoxaparin therapeutic doses, Dabigatran	Enoxaparin therapeutic doses, Dabigatran	Enoxaparin therapeutic doses, Apixaban

Legend: BMI – body mass index, ECG – electrocardiogram, bpm – beats per minute, PE – pulmonary embolism, FEU – Fibrinogen equivalent units, CRP – C reactive protein, LDH – Lactate dehydrogenase thromboplastin time, BNP – brain natriuretic peptide, INR – international normalized ratio, LWMH – low weight molecular heparin, RR – reference range.

for many days, and more than 92% in the female patient who had only intermittent oxygen therapy. The patients were initially managed in two COVID-19 dedicated hospitals and had anticoagulation therapy for VTE prevention (enoxaparin 0.6 ml or 0.8 ml, or 1 ml SC, once a day–q.d) for 10 days. All of them were treated with antimicrobial therapy for secondary bacterial infection and with hydroxychloroquine (400 mg/day). They were discharged after a second negative SARS-CoV-2 PCR test made after 10 days of hospitalization. All the patients developed dyspnea of acute onset and/or chest pain 16 to 32 days after discharge, and they had to be hospitalized at the Emergency County Hospital Baia Mare under suspicion of PE. One of the four patients was, surprisingly, COVID-19 positive in the nasopharyngeal swab on the admission day. Biomarkers usually involved in inflammation were only slightly elevated in three of them, while the common coagulation test international normalized ratio (INR) was normal. The electrocardiogram presented sinus tachycardia (110–120 bpm) in two patients, while the other two had new development of an incomplete right bundle branch. None of them had signs of deep vein thrombosis at the venous duplex ultrasound scan (VDUS). The angio-CT scans revealed distal bilateral pulmonary emboli in three patients and smaller distal unilateral PE in one. There is no data for the D-dimer values on hospital discharge after COVID-19 treatment. The D-dimer were highly elevated (levels vary between 1.06 and 16.96 mg/L, reference range – RR: 0.00−0.49 mg/L FEU) on the second hospital admittance, being the highest in patients with bilateral PE. All patients were started on anticoagulation therapy with enoxaparin SC at therapeutic doses, followed by oral administration of Dabigatran or Apixaban; all of them recovered well.

DISCUSSION

We report four cases of late PE in young patients (under 45 years), which appeared 16 to 32 days after discharge after being infected with the COVID-19 virus: the median time delay to the onset of symptoms was 20 days (interquartile range 4–12); the median age of patients was 38.5 years (interquartile range 9.5–6.5) — presented in Table 1. A series of 15 case reports and small series (altogether 26 patients) were retrieved from a PubMed search for papers published up to November 31, 2020, concerning post-discharge PE events after mild COVID-19 cases. These cases reported the occurrence of late thromboembolic complications, especially in young patients (most of them under 50 years), with the absence or with various modalities of thromboprophylaxis during the COVID-19 course (6–20). Patients under 65 years (younger cohort) had a significantly higher PE prevalence of 20.5%, compared to the 14.3% ($p < 0.05$) observed in those older than 65 years (5).

In a retrospective study, a VTE post-discharge rate of 4.8 per 1000 discharges was found within 42 days, following 1877 hospital discharges associated with COVID-19. The post-discharge rate of PE associated with other medical conditions was 3.1 per 1000 discharges within 42 days. The risk of VTE post-COVID-19 discharge was not significantly higher (odds ratio 1.6) compared with the risk of VTE after other acute diseases. This study was limited to those with symptomatic thromboembolic events and possibly underestimated the total burden of post-discharged VTE after COVID-19, as many events are mild or asymptomatic (21, 22).

The main characteristic of patients with post-discharge PE was the highly elevated D-dimer values, a five to 200-fold increase above the cut-off level used in different studies. The D-dimer values were significantly increased at the initial COVID-19 hospitalization, being the highest at PE admission (7, 10–15, 17–20). They had the same pattern in our patients, with values from 10 to 20 times above the upper limit of normal at first admission and even greater at PE diagnostic, with values from 10 to 34 times higher (Table 1). Therefore, when the patients came with acute dyspnea or respiratory distress after an initial clinical improvement or after discharge, extremely high levels of D-dimer (at least five times higher than normal values) suggested late PE development (6, 9–14, 19). A French retrospective study in 394 COVID-19 patients, proposes a D-dimer cut-off of 2500 ng/ml (normal range < 400 ng/ml) for the PE diagnostic. The study also presented that D-dimer is associated with an increased risk of death (if > 1000) and has an important prognostic role (22). However, a prospective study is required to assess the frequency of late PE and validate the proposed D-dimer cut-off of 2500 ng/mL to indicate the presence of PE in COVID-19 patients.

Another characteristic in our case series is a disproportionally elevated D-dimer value in comparison to other coagulation or inflammatory blood parameters (Table 1). This pattern is like other case series reports of post-discharge PE and should, hence, raise suspicion for pulmonary or venous embolism even in the absence of symptomatology (9, 10, 11).

An important characteristic of most patients was the absence of pre-existing risk factors for VTE and the absence of signs of deep vein thrombosis at VDUS, suggesting that COVID-19 itself – by promoting a prothrombotic status – may be a risk factor (2, 3, 22, 23).

Apart from a female patient in one study, none were found to have inherited thrombophilia to explain the occurrence of the thromboembolic event (10). In our cases, none of the patients had thromboembolic risk factors, and VDUS were performed on all patients with none found with venous thrombosis. Thus, the probable triggers for thrombotic events are the inflammatory status and diffusing the endothelial damage that predisposes to widespread thrombotic vascular lesions (2, 3).

All the patients in our case series during hospitalization had thromboprophylaxis (not full doses) with enoxaparin SC 0.6, 0.8, or 1 ml once daily for seven days. The recommendations of the 2020 - American College of Chest Physicians (ACCP) guideline and expert panel report for the prevention, diagnosis, and treatment of VTE in patients with COVID-19 suggest the current standard dose of anticoagulant (not intermediate) thromboprophylaxis during hospitalization and extended thromboprophylaxis after hospital discharge for those with low risk of bleeding (24). We do not have data for D-dimer values on hospital discharge after COVID-19 treatment and none of the patients had post-discharge oral anticoagulation. This issue could be related to the apparition of late PE. However, until now, no trials were addressing the role and duration of thromboprophylaxis in COVID-19 patients after discharge and no trial evaluating the predictive value of D-dimer for the risk of VTE after anticoagulation withdrawal.

Finally, our patients had a favorable therapeutic evolution to parenteral and oral anticoagulants. Usually, much of the late PE after COVID-19 is segmental or subsegmental, and, therefore, the evolutions are generally good (9–11, 22, 23, 25). The pulmonary angio-CT in our patients showed filling defects of the distal segmental and subsegmental arterial branches (two cases) and left lower pulmonary artery (two cases). Pulmonary inflammation caused by COVID-19 and the absence of signs of venous thrombosis at VDUs suggests a pulmonary thrombosis rather than a PE. In a series of 109 hospitalized COVID-19 patients who had suspicions of PE, the patients with confirmed PE were 41/101 (40.6%), while those with deep venous thrombosis at VDUs were 5/41 (12.2%). Thus, the authors hypothesized that the thrombosis due to diffuse pulmonary inflammation explained the PE, rather than the thromboembolism. The question could not be solved due to the limited number of available autopsy studies. Additionally, further research is required to clarify the different PE scenarios seen in the current studies (25).

Limitations

Our series was retrospective with only four patients presented at the hospital with PE suspicion after the initial COVID-19 discharge. There is no data for the D-dimer values on hospital discharge after the COVID-19 treatment. Therefore, our data should be interpreted cautiously until larger studies bring in more parameters to predict the apparition of late PE in COVID-19 patients.

CONCLUSION

PE is a complication of the COVID-19 disease which may occur later, especially in young patients with no other risk factors for pulmonary embolus. The highly elevated levels of D-dimer at COVID-19 admission are correlated not only with the prognostic but also with the risk of thromboembolic complications and seem to be associated with the post-discharge apparition of PE. This data suggests the role of extended anticoagulation in selected COVID-19 patients and warrants further investigations addressing the role and duration of thromboprophylaxis in COVID-19 patients after discharge.

Abbreviations

SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2
COVID-19 — Coronavirus Disease
PE — pulmonary thromboembolism
VTE — venous thromboembolism
CRP — C reactive protein
LDH — lactate dehydrogenase
INR — international normalized ratio
SC — subcutaneous
BMI — body mass index
ECG — electrocardiogram
Bpm — beats per minute
FEU — Fibrinogen equivalent units
BNP — brain natriuretic peptide
RR — reference range
CI — confidence interval

Authors' contributions

Both authors CP and IF were involved in conceptualization, data collection, interpretation of data, writing – original draft, review drafting, and reviewing the submitted manuscript.

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Licensing

Sažetak

VISOKE VREDNOSTI D-DIMERA I AKUTNA PLUĆNA EMBOLIJA NAKON OTPUSTA IZ BOLNICE KOD MLADIH PACIJENATA SA KOVID-19: SERIJA SLUČAJEVA

Calin Pop,[1, 2] Ionuț Ferenț[1]

[1] Emergency Clinical County Hospital of Baia Mare, Baia Mare, Romania
[2] "Vasile Goldis" University, Faculty of Medicine Arad, Arad, Romania

Uvod: Koronavirusna bolest (KOVID-19), izazvana teškim akutnim respiratornim sindromom koronavirusom 2 (SARS-KoV-2), povezana je sa inflamatornim i protrombotičkim stanjem koje povećava rizik od tromboembolijskih događaja. Visok nivo D-dimera povezan je sa težinom bolesti, a akutna plućna embolija (PE) je najčešća trombotička komplikacija.

Materijal i metode: Analizirali smo seriju od četiri slučaja KOVID-19 kod mladih pacijenata (mlađih od 45 godina) koji su razvili PE sa zakašnjenjem od dve do četiri nedelje nakon otpusta iz bolnice.

Rezultati: Ovi pacijenti su imali povišeni D-dimer (najmanje 10 puta od gornje granice normale) pri prijemu i u vreme dijagnostike PE, dok su ostali parametri, koji su uključivali zapaljenje i koagulaciju (C-reaktivni protein - CRP, laktat dehidrogenaza — LDH, fibrinogen, INR) bili normalni. Nije bilo prethodno postojećih faktora rizika za PE i svi pacijenti su bili antikoagulirani sa profilaktičkim srednjim dozama enoksaparina.

Zaključak: PE je komplikacija bolesti KOVID-19 koja se može javiti kasnije, posebno kod mladih pacijenata bez drugih faktora rizika za to stanje. Čini se da su visoko povišeni nivoi D-dimera pri prijemu KOVID-19 povezani sa pojavom PE nakon otpuštanja. Ovi podaci sugerišu ulogu produžene antikoagulantne terapije kod nekih pacijenata sa KOVID-19 i zahtevaju dalja istraživanja.

Ključne reči: D-dimer, COVID-19, mladi pacijenti, plućna embolija, otpust pacijenata.

REFERENCES

1. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel Coronavirus pneumonia. J Thromb Haemost. 2020; 18(6): 1421–4. doi: 10.1111/jth.14830.

2. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. J Thromb Haemost. 2020; 18(7): 1559–61. doi: 10.1111/jth.14849.

3. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endotheliosis, thrombosis, and angiogenesis in COVID-19. N Engl J Med. 2020; 383(2): 120-128. doi: 10.1056/NEJMoa2015432.

4. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course, and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020; 395(10229): 1054-62. doi: 10.1016/S0140-6736(20)30566-3.

5. Desai R., Gandhi Z., Singh S, Sachdeva S, Manaktala P, Savan S, et al. Prevalence of pulmonary embolism in COVID-19: a pooled analysis. SN Compr Clin Med. 2020: 1-4. doi: 10.1007/s42399-020-00605-5. Epub ahead of print.

6. Vadukul P, Sharma DS, Vincent P. Massive pulmonary embolism following recovery from COVID-19 infection: Inflammation, thrombosis, and the role of extended thromboprophylaxis. BMJ Case Rep. 2020; 13(9): e238168. doi: 10.1136/bcr-2020-238168.

7. Oflar E, Caglar FN. Pulmonary embolism after successful COVID-19 treatment. Int J Cardiovasc Acad. 2020; 6(3): 137–9. doi: 10.4103/IJCA.IJCA_24_20.

8. Di Tano G, Moschini L, Loffi M, Testa S, Danzi GB. Late pulmonary embolism after COVID-19 pneumonia despite adequate rivaroxaban treatment. Eur J Case Rep Intern Med. 2020; 7(7): 001790. doi:10.12890/2020_001790.

9. Karolyi M, Pavelka E, Omid S, Kelani H, Mader T, Baumgartner S, et al. Late-onset pulmonary embolism in young male otherwise healthy COVID-19 patients. Eur J Clin Microbiol Infect Dis. 2021; 40(3): 633-5. doi: 10.1007/s10096-020-04044-x. Epub 2020 Sep 23.

10. Vechi HT, Maia LR, Alves MDM. Late acute pulmonary embolism after mild Coronavirus disease 2019 (COVID-19): A case series. Rev Inst Med Trop Sao Paulo. 2020; 62: e63. doi: 10.1590/S1678-9946202062063.

11. Greenan-Barrett J, Perera A. COVID-19 and Pulmonary Emboli: A case series and literature review. Clin Pract Cases Emerg Med. 2020; 4(3): 299–303. doi: 10.5811/cpcem.2020.7.48174.

12. Beckman, M., Nyrén, S, Kistner, A. A case report of widespread pulmonary embolism in a middle-aged male seven weeks after asymptomatic suspected COVID-19 infection. Thrombosis J. 2020; 18: 19. doi: 10.1186/s12959-020-00235-w.

13. Touré A, Donamou J, Camara A, Dramé B, BAH, O. Post-COVID-19 late pulmonary embolism in a young wom-

an about a case. OJEM. 2020; 8(4): 79–85. doi: 10.4236/ojem.2020.84009.

14. Koche M, Bechmann S, Omoruyi IS. Bilateral pulmonary embolism in a discharged patient with resolved COVID-19 pneumonia. Cureus. 2020; 12(7): e9406. doi: 10.7759/cureus.9406.

15. Akiyama Y, Horiuchi K, Kondo Y, Kabata H, Ishii M, Fukunaga K. A case of non-severe COVID-19 complicated by pulmonary embolism. Respirol Case Rep. 2020; 8(7): e00622. doi: 10.1002/rcr2.622.

16. Kanso M, Cardi T, Marzak H, Schatz A, Faucher L, Grunebaum L, et al. Delayed pulmonary embolism after COVID-19 pneumonia: a case report. Eur Heart J Case Rep. 2020; 4(6): 1-4. doi: 10.1093/ehjcr/ytaa449.

17. Vitali C, Minniti A, Caporali R, Del Papa N. Occurrence of pulmonary embolism in a patient with mild clinical expression of COVID-19. Thromb Res. 2020; 192: 21–2. doi: 10.1016/j.thromres.2020.05.002.

18. Bellieni A, Intini E, Taddei E, Baldi F, Larosa L, Murri R, et al.Challenges in COVID-19: Is pulmonary thromboembolism related to overall severity? Infect Dis (Lond). 2020; 52(8): 585–9. doi: 10.1080/23744235.2020.1769854.

19. Tveita A, Hestenes S, Sporastřyl ER, Pettersen SA, Neple BL, Myrstad M, et al. Pulmonary embolism in cases of COVID-19. Tidsskr Nor Laegeforen. 2020; 140: 0526. doi: 10.4045/tidsskr.20.0366.

20. Roberts LN, Whyte MB, GeorgiouL, Giron G, Czuprynska J, Rea C, et al. Postdischarge venous thromboembolism following hospital admission with COVID-19. Blood. 2020; 136 (11): 1347–50. doi: 10.1182/blood.2020008086.

21. Mouhat B, Besutti M, Bouiller K, Grillet F, Monnin C, Ecarnot F, et al. Elevated D-dimers and lack of anticoagulation predict PE in severe COVID-19 patients. Eur Respir J. 2020; 56(4): 2001811. doi:10.1183/13993003.01811-2020.

22. Graziani A, Domenicali M, Zanframundo G, Palmese F, Caroli B, Graziani L: Pulmonary artery thrombosis in COVID-19 patients. Pulmonology. 2020:S2531-0437(20)30185-9. doi: 10.1016/j.pulmoe.2020.07.013. Epub ahead of print.

23. Cavagna E, Muratore F, Ferrari F. Pulmonary Thromboembolism in COVID-19: venous thromboembolism or arterial thrombosis? Radiol Cardiothorac Imaging. 2020. 9; 2(4): e200289. doi: 10.1148/ryct.2020200289.

24. Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, et al. Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019: CHEST Guideline and Expert Panel Report. Chest. 2020; 158(3): 1143-63. doi: 10.1016/j.chest.2020.05.559.

25. Lax SF, Skok K, Zechner P, Kessler HH, Kaufmann N, Koelblinger C, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: Results from a prospective, single-center, clinicopathologic case series. Ann Intern Med. 2020; 173(5): 350–61. doi: 10.7326/M20-2566.

Correspondence to/Autor za korespondenciju
Călin Pop MD. PhD
Emergency Clinical County Hospital of Baia Mare,
"Vasile Goldis" University, Faculty of Medicine Arad
Romania. e-mail: medicbm@yahoo.com, tel – 0744515794

SANAMED
2021; 16(1): 91–94
ISSN-1452-662X

DOI:10.24125/sanamed.v16i1.502
UDK:616.98:578.825
616.36-002-053.2
ID:37394441
Case report

INFECTIOUS MONONUCLEOSIS AND AUTOIMMUNE HEPATITIS

Skoric Jasmina, Pavkovic Bojan

Health Centre "Dr Simo Milošević", Belgrade, Serbia

Primljen/Received 02. 03. 2021. god. Prihvaćen/Accepted 10. 04. 2021. god.

Abstract: **Introduction**: The case report shows a sick nine-year-old girl whose disease initially manifested as infectious mononucleosis. Encountering infectious mononucleosis in pediatrics is quite common and it is estimated that as much as 50% of children are infected with the Epstein-Barr virus before the age of 5. Suspicion of mononucleosis emerges every time there is a patient with swollen neck lymph nodes, fever, painful and difficult swallowing. However, the laboratory findings in the second month of the onset of the disease raised suspicion for autoimmune disease.

Case report: Based on the clinical manifestations, the patient underwent a series of examinations such as biochemical analyses, blood count, and Epstein-Barr virus serology, as well as abdominal ultrasound and testing of ceruloplasmin and Alpha-1 antitrypsin values. The autoimmune disorder was confirmed after detecting elevated IgG levels, the presence of anti-LKM antibodies, and interface hepatitis as a pathoanatomic substrate of liver bioptates.

Conclusion: The case report presents the Epstein-Barr virus as a direct trigger of autoimmune hepatitis. This DNA virus known for its cytopathic effect on B lymphocytes induced the swelling of lymph nodes, liver, and spleen. Its overall impact on B lymphocytes and the liver led to producing specific autoantibodies and infiltrating hepatic nodes with lymphocytes.

Key words: antibodies, hepatitis, biopsy, Epstein-Barr virus.

INTRODUCTION

Infectious mononucleosis is an acute, viral disease caused by the Epstein-Barr virus (EBV), a member of the herpes virus family. Transmission occurs by a fecal-oral route with an incubation period of 30-50 days. The infection is often asymptomatic or is encountered as pharyngitis with clinical characteristics in the forms of exudative tonsillitis and cervical lymphadenopathy. An enlarged liver and spleen can be found in 75% of patients, as well as elevated transaminase levels. In a smaller number of patients, a maculopapular rash can also occur, as well as urticaria, petechiae, or scarlet fever. Characteristic hematologic findings are absolute lymphocytosis and atypical lymphocytes that last 2-3 weeks. The diagnosis is confirmed with the use of the Paul-Bunnell-Davidsohn test that examines Immunoglobulin G (IgG) antibodies and heterophile antibodies (1, 2). Epstein-Barr virus infections frequently affect the liver and cause hepatitis. Infectious triggers are often associated with certain autoimmune diseases whereby EBV is well-known for being the causative agent. Numerous reports are showing evidence of autoimmune hepatitis (AIH) following the EBV infection (3). AIH is a chronic liver disease which, if untreated, can lead to liver cirrhosis. Most commonly it affects female children and adolescents (4). There are three types of AIH: type 1, type 2, and seronegative AIH. Type 1 is a classic and most common form of the disease that is characterized by positivity for antinuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA). The illness usually occurs after the age of 10. Type 2 AIH is characterized by the presence of anti LKM1 (liver-kidney microsomal type 1 antibody) and it mainly affects younger children. The disease is likely to present with severe clinical manifestations and it appears in a more progressive form. Seronegative AIH is characterized by the absence of antibodies. However, in such cases, the liver biopsy can reveal features compatible with autoimmune hepatitis. The standard treatment is based on administering corticosteroids and azathioprine (5, 6).

CASE REPORT

A nine-year-old girl was examined for the first time by a pediatrician due to fever, sore throat, and abdominal pain. The examination detected tonsillar hypertrophy and exudates, slightly swollen neck glands measuring up to 1 cm, as well as liver and spleen pal-

pable 1.5 cm below the costal margin. The serology testing showed positive EBV results: immunoglobulin M (IgM)1/ 250, IgG 1/ 60, transaminase AST 134 IU/L, ALT 459 IU/L. Routine blood testing showed no signs of significant deviations. The patient underwent abdominal ultrasound imaging whereby no abnormalities were detected. The follow-up analysis performed two weeks later showed an increase in transaminase levels AST 599 IU/L, ALT 1,234 IU/L. Further analyses were conducted to exclude the potential diagnoses of Wilson disease (ceruloplasmin 29.4 mg/dL) and Alpha-1 antitrypsin deficiency (Alpha-1 antitrypsin concentration 162 mg/dL), and the obtained results showed no evidence of such diagnoses. However, significantly elevated levels of total IgG were detected, 21.2 g/L, which could be an important diagnostic marker for autoimmune disorders. Having established AIH as a potential diagnosis and after obtaining anti-LKM1 antibodies < 200 U/ml, the patient underwent liver biopsy.

Percutaneous liver biopsy revealed mildly to significantly expanded portal zones. The lobular architecture was disturbed by the septa of connective tissue, portal tracts were somewhere joined with central veins and somewhere surrounded by small parenchymal nodules. Mild lymphocytic infiltration was detected as well as moderate interface hepatitis. Stage of severe fibrosis was diagnosed (Figure 1).

Prednisone and azathioprine therapy was initiated which led to the normalization of transaminase levels. After three months, prednisone was discontinued and allopurinol was introduced to reduce azathioprine. The patient then experienced epigastric pain and underwent a proximal gastrointestinal endoscopy examination. The obtained results were found in order**.** However, allopurinol therapy was discontinued whereas prednisone and azathioprine were reintroduced. Seven months later, clinical and lab remission was achieved. The patient was taken off prednisone and remained on azathioprine. However, four years after the diagnosis was established, new clinical manifestations arose such as muscle weakness of lower extremities, insecure walking, and falling. As proposed by the neurologist, electromyography was performed: motor nerve conduction velocity (MCV) for the peroneal nerve bilaterally and right tibial nerve, whereby distal latency, amplitude, and velocity were within normal range.

Sensory conduction velocity (SCV) examination of the sural nerve showed prolonged latency, normal amplitude, and slowed nerve conduction velocity. Electromyography (EMG) of the right leg rectus femoris muscle did not show pathological spontaneous activities, adenosine monophosphate **(**AMP) characteristics were found normal at muscle contraction, with some of them polyphasic. The obtained examination findings indicated the development of sensory neuropathy for the right sural nerve as well as potentials characteristic of a myopathic disorder in the examined muscle rectus femoris. At this stage, there was a clinical suspicion of corticosteroid-induced myopathy, but this diagnosis was not corroborated by the creatine kinase levels that were tested within the normal range. Additional three months of prednisone were prescribed as well as physical therapy. The combined treatment resulted in full recovery of standing and walking abilities. Currently, the girl reports no clinical symptoms. She is regularly attending high school and is taking azathioprine therapy.

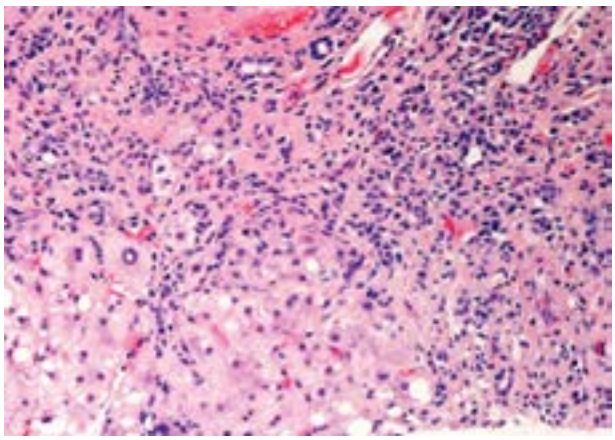


Figure 1. *Interface hepatitis*

DISCUSSION

EBV is a highly prevalent infectious trigger that affects a vast number of the worldwide population. Among others, it is the usual cause of infectious mononucleosis and is known for targeting B lymphocytes which can lead to lymphoid hyperplasia involving lymph nodes, liver, and spleen (2). Taking into consideration the disease onset of the case presented and its clinical manifestations, the initial suspicion of infectious mononucleosis was heavily grounded in the existing clinical research and case reports, as depicted in Dunmire et al. (2). Additionally, EBV can trigger fulminant infectious mononucleosis in some children due to the mutation of the X- chromosome gene responsible for encoding intracellular signaling protein, a mediator of signal transduction in lymphocyte activation (7). However, the subsequent clinical work-up redirected the diagnostic process towards the link between EBV and autoimmune hepatitis as its sequelae. Autoimmune hepatitis is a rare liver disease with an unknown etiology. Evidence in support of EBV in the pathogenesis of autoimmune hepatitis (AIH) is largely based around case reports noting the development of

AIH following EBV infection, as was the case with our patient (8, 9).

The clinical presentation that included, elevated transaminase levels, interface hepatitis on histology, presence of LKM-1, liver inflammation, massive lymphocytic portal infiltrates extending into the surrounding lobules, accompanied by the patient's age and gender, all represent features of AIH type 2 pathogenesis. The most comprehensive analysis up to date focusing on the pediatric AIH as well as on the analysis of the treatment response has been described in the article from Porta et al. The clinical, histological, and laboratory findings of our patient coincide with the results presented in the article. The same combination treatment consisting of prednisone and azathioprine was administered to over 90 % of the patients, whereby more than 76 % of them achieved biochemical remission (10).

As for the muscle weakness of lower extremities, the conclusion has been reached that it was most likely *atrophia ex inactivity* due to prolonged bed rest,lack of physical activity, and excessive weight gain which the patient successfully managed to reverse.

Due to the highly variable clinical manifestations, it can be challenging to establish an AIH diagnosis. However, to achieve full remission, early detection and treatment can be of utmost importance. Conducting routine biochemical check-ups can help identify elevated ALT and AST levels, thus contributing to an early diagnosis. Steroids and azathioprine course of therapy requires administering a long-term treatment with strict adherence that can lead to a successful outcome and fully recovered patient.

Abbreviations

AIH — Autoimmune hepatitis
AMP — Adenosine monophosphate
ANA — Antinuclear antibodies
ASMA — Anti-smooth muscle antibodies
EMG — Electromyography
EBV — Epstein-Barr virus
LKM1 — Liver-kidney microsomal type 1 antibody
MCV — Motor nerve conduction velocity
SCV — Sensory conduction velocity

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Licensing

Sažetak

INFEKTIVNA MONONUKLEOZA I AUTOIMUNI HEPATITIS

Skoric Jasmina, Pavkovic Bojan

Health Centre "Dr Simo Milošević", Belgrade, Serbia

Uvod: U radu je prikazan slučaj obolele devetogodišnje devojčice kod koje se bolest inicijalno manifestovala kao infektivna mononukleoza. Vrlo često u pedijatrijskoj populaciji srećemo infektivnu mononukleozu i smatra se da je čak 50% dece do 5 godina prokuženo Epstein Barr virusom. Sumnja na infektivnu mononukleozu postoji uvek kada imamo dete sa uvećanim limfnim čvorovima vrata, temperaturom, otežanim i bolnim gutanjem. Međutim, usled daljih analiza u drugom mesecu nakon pojave prvih simptoma, posumnjano je na autoimuni poremećaj.

Rezultati: Na osnovu prikazanih simptoma, pored rutinskih analiza kao što su krvna slika, biohemijske analize, serologija na Epstein Barr virus, takođe je urađen ultrazvučni pregled abdomena, a određene su i vrednosti ceruloplazmina i alfa 1 antitripsina koje su bile uredne. Autoimuna priroda bolesti potvrđena je nalazom povišenih vrednosti ukupnog IgG, pozitivnim anti LKM antitelima i „interface" hepatitisom koji je utvrđen kao patoanatomski supstrat bioptata jetre.

Zaključak: U ovom radu prikazan je Epstein Barr kao neposredni uzrok autoimunog hepatitisa. Ovaj DNK virus poznat je po citopatogenom efektu na B limfocite. Otuda su se kao posledica infekcije ovim virusom javili uvećani limfni čvorovi, slezina i jetra. Sveukupan uticaj i na B limfocite i na jetru doveo je do stvaranja specifičnih antitela i infiltracije hepatičnih nodusa limfocitima.

Ključne reči: antitela, hepatitis, biopsija, Epstein Barr virus.

REFERENCES

1. Womack J, Jimenez M. Common questions about infectious mononucleosis. Am Fam Physician, 2015; 15;91(6): 372-6.

2. Dunmire SK, Hogquist KA, Balfour HHJ. Infectious Mononucleosis. Curr Top Microbiol Immunol. 2015; 390(Pt 1): 211–40. doi: 10.1007/978-3-319-22822-8_9.

3. Peng H, Lim T, Nam J, Lee J. Autoimmune hepatitis following Epstein-Barr virus infection: a diagnostic dilemma. BMJ Case Rep. 2019; 12(7): e229615. doi: 10.1136/bcr-2019-229615.

4. Alvarez F. Autoimmune hepatitis in children. J Pediatr (Rio J). 2019; 95(4): 382-4. doi: 10.1016/j.jped.2018.08.001.

5. Della Corte C, Mosca A, Vania A, Alterio A, Alisi A, Nobili V. Pediatric liver diseases: current challenges and future perspectives. Expert Rev Gastroenterol Hepatol. 2016;10(2): 255-65. doi: 10.1586/17474124.2016.1129274.

6. Salih MM, Ibraheem MF, Nader KE. Etiology and clinical pattern of liver diseases in children. JFac Med Bagdad. 2018; 60(2): 76-9.doi: 10.32007/jfacmedbagdad.6028.

7. Houldcroft CJ, Kellam P. Host genetics of Epstein–Barr virus infection, latency, and disease. Rev Med Virol. 2015 Mar; 25(2): 71–84. doi: 10.1002/rmv.1816.

8. Liberal R, Vergani D, Mieli-Vergani G. Update on autoimmune hepatitis. J Clin Transl Hepatol. 2015; 3(1): 42-52. doi: 10.14218/JCTH.2014.00032.

9. Rigopoulou EI, Smyk DS, Matthews CE, Billinis C, Burroughs AK, Lenzi M, et al. Epstein-barr virus as a trigger of autoimmune liver diseases. Adv Virol. 2012; 2012: 987471. doi: 10.1155/2012/987471.

10. Porta G, Carvalho E, Santos J, Gama J, Borges CV, Seixas RBPM, et al. Autoimmune hepatitis in 828 Brazilian children and adolescents: clinical and laboratory findings, histological profile, treatments, and outcomes. J Pediatr (Rio J). 2019; 95(4): 419-27. doi: 10.1016/j.jped.2018.04.007.

Correspondence to/Autor za korespondenciju
Jasmina Škorić
Health Centre “Dr Simo Milošević”, Belgrade, Serbia
Poručnika Spasića i Mašere 53, 11030 Belgrade
Cell phone: +381 637111603
E-mail: jasmina.skoric1979@yahoo.com

SANAMED
2021; 16(1): 95–100
ISSN-1452-662X

DOI:10.24125/sanamed.v16i1.504
UDK:615.213.035.7
615.213.099
ID:37507337
Case report

ACUTE LAMOTRIGINE OVERDOSE IN ADULTS: A CASE REPORT

Janicijevic Katarina[1], Kovacevic Zoran[2], Glisic Milos[3], Janicijevic Petrovic A. Mirjana[4], Lazarevic Tatjana[5]

[1]Department of Social Medicine, Faculty of Medical Sciences University of Kragujevac, Serbia
[2]Department of Internal medicine, Clinical Centre Kragujevac, in Kragujevac, Serbia
[3]Department of Physiology, Faculty of Medical Sciences University of Kragujevac, Serbia
[4]Department of Ophthalmology, Faculty of Medical Sciences University of Kragujevac, Serbia
[5]Department of Internal medicine, Faculty of Medical Sciences University of Kragujevac, Serbia

Primljen/Received 15. 03. 2021. god. Prihvaćen/Accepted 20. 04. 2021. god.

Apstrakt

Introduction: Self-treatment with Lamotrigine rarely ends with toxicity, regardless of the suicidal intentions of the patient. The authors hereby present an illustrative case of the patient who has been treated with epilepsy therapy with Dandy-Walker syndrome and congenital epidermolysis bullosa (potentially skin-unwanted). Lamotrigine is a phenyltriazine-class, broad-spectrum antiepileptic and therapy of bipolar depression. Dandy-Walker syndrome is a pathological entity and represents the set of developmental, cerebral, but also other abnormalities of the organism. Epidermolysis bullosa is a hereditary, non-inflammatory skin disease with a mucous membrane of characteristic "bubbles".

Case report: Our patient, a 37-year-old male was first admitted to the hospital department of Urgent Medicine of Clinical Center Kragujevac because he consumed two boxes of Lamotrigine tablets. In the receiving clinic, the patient showed respiratory failure and was urgently intubated. From medical documentation and hetero-anamnesis (obtained by his father), the authors found out that he was treated for epilepsy, Dandy-Walker syndrome, and congenital epidermolysis bullosa, which deteriorated with the use of Lamotrigine through potentially undesirable skin effects. During clinical observation, a lavage of gastric contents was conducted. The medical coal was used via nasogastric intubation as a detoxification method because of the patient's comatose state. Causative metabolic pathway of lamotrigine, the hemodialysis was performed.

Conclusion: The case report of our patient points to the necessity of a multidisciplinary approach of the expert team, consisting of the clinical pharmacologist and toxicologist, neurologist, dermatologist, nephrologists, and other specialists, if necessary. Patients with Dandy-Walker syndrome require adequate socio-medical care.

Keywords: Lamotrigine, acute overdose, Dandy-Walker syndrome, congenital epidermolysis bullosa, clinical manifestations, diagnostic and therapeutic interventions

INTRODUCTION

Self-treatment with Lamotrigine rarely ends with overdose toxicity, regardless of the suicidal intentions of the patient. The patient from our case study is a 37-year-old male who was hospitalized because of a Lamotrigine overdose. He was sent to Clinical Center Kragujevac from the Health Center of Arandjelovac. We hereby present the illustrative case of the patient who has been treated for epilepsy (with potentially unwanted therapy), Dandy-Walker syndrome, and congenital epidermolysis bullosa. He used Lamotrigine for treatment (*Phenyltriazine-class*), a broad-spectrum antiepileptic drug along with the therapy for bipolar depression. Dandy-Walker syndrome is the pathological entity of developmental abnormalities in the brain and other organs. Bullous epidermolysis is a hereditary, non-inflammatory skin disease with persistent mucous membrane, characteristic as "bubbles". According to action-mechanism, Lamotrigine blocks sodium channels, and during clinical exposure, it can cause, toxicity in overdose (≥23 mcg/mL) as the newer genera-

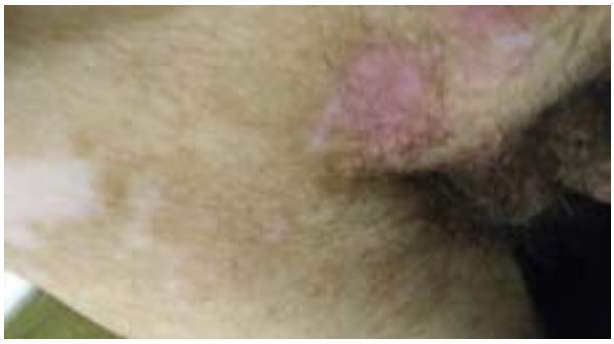
tion of anti-epileptics (respiratory depression, cardiac arrest, coma, and death) which required endotracheal intubation as an effective procedure in overdose cases (1). This syndrome diagnosis (her father provided diagnosis) was followed by clinical symptoms, that have previously been reported as epilepsy, intellectual incompetence, and other. The case report illustrates the complexity of the observation of the syndrome in an adult male, which presents the diagnostic and the therapeutic challenge in acute overdose with Lamotrigine. The constellation of symptoms and structural abnormalities of the brain should be taken into consideration when dealing with patients with neuropsychiatric manifestations, systemic diseases, and specific skin diseases, especially if diagnosed in childhood and adolescence and chronically treated with Lamotrigine.

CASE REPORT

A patient of 37 years was conducted as an emergency admission to The Department of Urgent Medicine of Clinical Center Kragujevac in Kragujevac because he had consumed two boxes of Lamotrigine tablets (overdose). From his medical documentation and hetero-anamnesis, the authors discovered that he was treated for epilepsy, Dandy-Walker syndrome, and congenital (epidermolysis bullosa), which worsened with the use of Lamotrigine, through undesirable skin effects.

At admission, the patient was disoriented, agitated, a-febrile of medium osteomuscular build and nutrition, no signs of hemorrhagic syndrome and peripheral adenopathy. Auscultatory over lungs weakened respiratory murmur. Rhythmic heart action, well-audible tones, no noise; the abdomen was soft, palpably painless, without defense, and peritoneal reaction. Bullous changes bleeding when touched were seen on the mucous membrane of the oral cavity, two erosions covered with thin crusts were seen on the inner side of the left hand, and one bulla filled with serous contents was observed in the pubic area (Figure 1).

Figure 1. Epidermolysis bullosa (Lamotrigine-overdose), as potentially undesirable skin effects.



Initially, due to the patient's non-cooperation, it was not possible to perform an electrocardiographic recording, which was subsequently performed and shallow negative T-waves from V1 to V4 were recorded, with sinus rhythm and heart rate 90/min. Immediately, after the examination, breathing ceased, and the patient was urgently intubated and connected to an assisted ventilation device. Biochemical laboratory tests were regular except for inflammations parameters. The gas analyses indicated hypoxemia (Table 1).

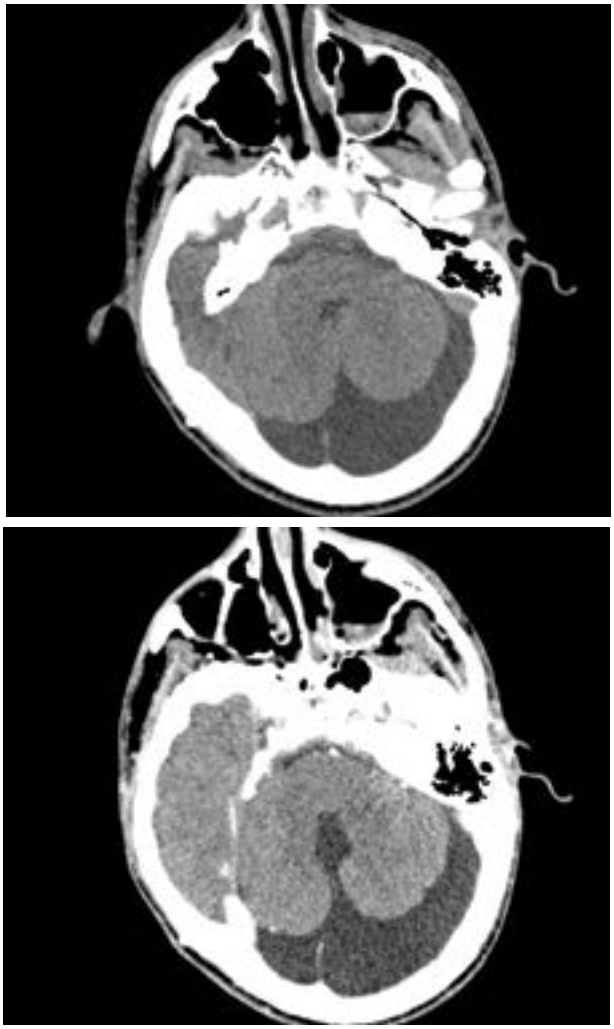
During the clinical observation, the lavage of gastric contents was performed. Medical coal was used via nasogastric intubation as a detoxification method since the patient was in a comatose state. Causative metabolic pathway of Lamotrigine the double hemodialysis with the minimal ultrafiltration was also performed.

Additionally, a computerized tomography (CT) scan of the brain discovered: cerebral hemiatrophy including cerebellum hypo-atrophy with skull thickening/widening of the vermis (dysgenesis) and communication of ventricle (IV) with arachnoid-cisternal - spaces in fossa crani posterior (Figure 2).

As for clinical characteristics, a radiography of the heart and lungs performed several times showed regular findings. The concentration of Lamotrigine in blood was determined at a reference institution in Belgrade of Serbia (toxicological laboratory of Military Medical Academy), which was elevated to a toxic concentration of 20.82 g/l (reference value 4-11 g/l).

On the fourth day of hospitalization, the state of consciousness stabilized, and gas exchange normalized, after which the patient was separated from assisted ventilation and extubated. The patient had normal vital signs: blood pressure was 110/55 mm Hg, heart rate was 54/min, respiratory rate was 15/min, and the temperature was about 36°C. Ophthalmological signs showed minor nystagmus, degenerative myopia, and characteristic retinal defects with vitreous fenestrated membranes in the retinal periphery. The virus tests were negative, as well as the psychoactive substance test. Due to clinical improvement and normalization of all basic-laboratory analyzes, so no control level of Lamotrigine was performed. Finally, since *Lamiktal*® tablets (brand name of medicament) can cause skin changes exacerbating its condition, the doctors decided to opt for gradual exclusion of this medicament while continuing the treatment of epilepsy with *Kepra*® tablets (brand name). To treat depression, *Elice*® tablets (brand name) were introduced. The patient was discharged for 16 days of hospitalization in good general condition.

Figure 2. The computerized tomography with neuro-anatomic structural changes in Dandy-Walker syndrome.



DISCUSSION

Our case reported the illustrates-nature of Dandy-Walker syndrome and congenital epidermolysis bullosa in an adult male and represented the diagnostic and therapeutic challenge in acute overdose of Lamotrigine. Our patient was of depressed mood resulting in suicidal ideation/suicidal attempts and developed the status of epileptic.

The spectrum of clinical effects of Lamotrigine in acute overdose was not precisely established. Several cases of overdose had serious effects such as coma, respiratory depression, and intraventricular conduction disturbances.

Serum evaluation revealed high Lamotrigine levels without any other etiology for mental dysfunction. After the prompt supportive treatment with early intubation, use of potassium chloride for hypokalemia, and the administration of sodium bicarbonate, the condition of the overdosed patients improved (2). Encephalopathy is the secondary cause of serious Lamotrigine-toxicity, as the clinical manifestation (3). Lamotrigine-overdose was usually benign, mild, or with no toxicity, but large exposures were associated with severe central nervous system depression, cardiac conduction delays, seizures, and death (4).

Other toxic effects include hypersensitivity reactions, QRS-complex prolongations, rhabdomyolysis, serotonin syndrome, seizures, and/or agitation (5), with these effects of the other author's opinion, we also agree. Today, many document treatment-refractory Lamotrigine cardiotoxicity among dogs by applying intra-lipid emulsion therapy (6). Dandy-Walker malformation or syndrome occurs sporadically. Some patients remain clinically asymptomatic for years, while others may exhibit a variety of co-morbidities leading to earlier diagnosis and multidisciplinary research. Treatments are generally focused on posterior fosse symptoms, often including surgical interventions, like ventriculoperitoneal and cystoperitoneal shunting (7), but the surgical possibility of intervention was excluded from our patient.

In case reports, many authors described the neuropsychological and behavioral profile of patients, usually in adult males (8), as in our case report.

Brain computed tomography and brain magnetic resonance imaging have shown cyst in posterior fosse, hydrocephalus, hypoplasia of corpus callosum, syringomyelia, absence of cerebellar vermis, etc. Surgery involving arachnoid adhesiolysis and endoscopic third ventriculostomy was performed (9).

The progression of associated morbidities in Dandy-Walker syndrome requires an early, multidisciplinary diagnosis, so that clinically asymptomatic cases, over the many years (10,11), would not remain undiagnosed, as in our case.

Bullous dermatitis in infants and adults is a clinical term used for several disorders associated with primary neonatal pemphigus. The common symptoms of the disorder regardless of etiologic factors are redness of skin and formation of bubbles of various sizes filled with serous or serous-bloody content. Bursting bubble patches peel off, leaving bare, sometimes oozing surface (12). Bullous dermatitis in neonates and adults associated with primary neonatal pemphigus should be ruled out as a differential diagnosis. It is characterized by irritation and hyperemia of dry skin, with the formation of bubbles with serous or serous-bloody contents, which are emptied and moisturize skin (12).

Immune-Fluorescence-Antigen-Mapping testing is morphological verification of diagnosis and targeted genetic analysis of the mutations by the molecular

method in Dandy-Walker syndrome (13).

De Crecchio, et al pointed to the association of high myopia and unusual changes in the retina of the eye in Dandy-Walker syndrome (14), which statement authors agree.

Getova and Mihaylova analyzed the effects of Lamotrigine on specific epi-seizure models: neurotransmitters (Glutamate and GABA) are actors in seizure-control, and Lamotrigine has an anticonvulsant effect, reducing intensity and timing of epi-seizures (control with *bicucul*line and *pentylenetetrazole*) (15).

Lamotrigine is reported to have linear kinetics so that the elimination rate is linearly proportional to blood concentration. Measurement and close monitoring of lamotrigine levels are vital for discovering new symptoms that could be consistent with lamotrigine toxicity, particularly when the baseline serum concentration is >10 mg/l (16), indefinitely to our experience in this case report.

The rate of elimination of Lamotrigine is the linear proportion of its concentration in the blood. Measurement of concentration is important for symptom relief and toxicity of Lamotrigine (initial serum concentration >10 mg/L (16)).

In conclusion, the case report of our adult patient (acute Lamotrigine-overdose) once again confirms that successful treatment of Dandy-Walker syndrome can only be achieved through a multidisciplinary approach, including a medical team consisting of clinical pharmacologist and toxicologist, neurologist, dermatologist, nephrologist, neurosurgeon, ophthalmologist, and social worker. Patients with Dandy-Walker syndrome require adequate socio-medical care of society.

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Sažetak

AKUTNO TROVANJE LAMOTRIGINOM KOD ODRASLIH: PRIKAZ SLUČAJA

Janicijevic Katarina[1], Kovacevic Zoran[2], Glisic Milos[3], Janicijevic Petrovic A. Mirjana[4], Lazarevic Tatjana[5]

[1]Department of Social Medicine, Faculty of Medical Sciences University of Kragujevac, Serbia
[2]Department of Internal medicine, Clinical Centre Kragujevac, in Kragujevac, Serbia
[3]Department of Physiology, Faculty of Medical Sciences University of Kragujevac, Serbia
[4]Department of Ophthalmology, Faculty of Medical Sciences University of Kragujevac, Serbia
[5]Department of Internal medicine, Faculty of Medical Sciences University of Kragujevac, Serbia

Uvod: Samotrovanje lamotriginom je retko trovanje, nezavisno od suicidne namere bolesnika. Autori prikazuju ilustrativni slučaj bolesnika, koji je lečen (potencijalno kožno-neželjenom terapijom) za epilepsiju, sa Dandy-Walkerovim sindromom i kongenitalnom buloznom dermolizom. Lamotrigin je antiepileptik klase feniltriazina u terapiji bipolarne depresije. Dandy-Walkerov sindrom je patološki entitet i predstavlja skup razvojnih, moždanih, ali i drugih abnormalnosti organizma. Bulozna epidermolize je nasledna, nezapaljenjska bolesti kože i sluzokože sa karakterističnim "mehurićima".

Prikaz bolesnika: Naš bolesnik, star 37 godina prvi put je primljen u hospitalni odsek Centra za urgentnu medicine, Kliničkog Centa Kragujevac u Kragujevcu, jer je konzumirao dve kutije Lamotrigina tableta U prijemnoj ambulanti bolesnik pokazuje respiratornu insuficijenciju, prestanak disanja i u besvesnom stanju je hitno intubiran. Iz referente medicinske dokumentacije i heteroanamneze (od njegovog oca) saznajemo da je lečen od epilepsije, Dandy-Walkerovim sindroma i kongenitalne bulozne dermolize, koja se se sa terapijom Lamotriginom pogoršala, kroz potencijalno neželjeno dejstvo na koži. U toku kliničke observacije urađena je lavaža želudačnog sadržaja. Kao metod detoksikacije primenjen je medicinski ugalj putem nazogastrične sonde zbog komatoznog stanja svesti bolesnika. Uzročno metaboličkom putu lamotrigina, sprovedena je hemodijaliza.

Zaključak: Prikaz slučaja ovog bolesnika ukazuje na neophodnost multidiciplinarnog pristupa tima eksperata, u sastavu kliničkog farmakologa i toksikologa, neurologa, dermatologa, nefrologa i drugih specijalista. Pacijenti sa Dandi-Walkerovim sindromom zahtevaju adekvatnu društvenomedicinsku brigu.

Table 1. The gas, blood and laboratory analyzes (biochemical parameters).

Gas analyzes	Blood analyzes	Laboratory analyzes
Ph 7.24	Le 11.10	Glycosa 5.1
pO_2 6.2	Er 3.95	Urea 1.6
pCO_2 3.7	Hgb 124	Kreatinin 72
Na 139	Hct 0.327	CK 195
K 3.3	Tr 182	CRP 15.5
Ca 1.14	PTT 36.3	
HCO_3 19.3	INR 1.590	
SpO_2 87%	Albumin 44	

Ključne reči: Lamotrigin, akutno predoziranje, Dandy-Walker sindrom, kongenitalna bulozna dermoliza, kliničke manifestacije, dijagnostičke i terapijske intervencije

REFERENCES

1. Griswold A, Tully B, Katz K, Beauchamp G, Cook M, Cannon R. Lamotrigine ODT-induced seizure in a 3-year-old child after accidental ingestion. Case Rep Emerg Med. 2019; 2019: 2675931. doi: 10.1155/2019/2675931.

2. Hajiali F, Nassiri-Asl M. Report of severe menorrhagia following the maximum amount of Lamotrigine overdose. Iran J Pharm Res. 2015; 14(4):1289-93.

3. Lambea Gil A, Caldu Agud R, Rodríguez Gascon D, Garayoa Irigoyen V. Encephalopathy secondary to lamotrigine toxicity. Neurologia. 2018; S0213-4853(18):30146-34. English, Spanish. doi: 10.1016/j.nrl.2018.03.017.

4. Alyahya B, Friesen M, Nauche B, Laliberte M. Acute lamotrigine overdose: a systematic review of published adult and pediatric cases. Clin Toxicol (Phila). 2018; 56(2):81-9. doi: 10.1080/15563650.2017.1370096.

5. Alabi A, Todd A, Husband A, Reilly J. Safety profile of lamotrigine in overdose. Ther Adv Psychopharmacol. 2016; 6(6):369-81. doi: 10.1177/2045125316656707.

6. Bellis TJ, Gibeon L. The use of intralipid emulsion therapy to treat severe cardiotoxicity secondary to lamotrigine ingestion in a dog. Clin Case Rep. 2018; 6(10):1982-8. doi: 10.1002/ccr3.1733.

7. Zamora EA, Ahmad T. Dandy Walker Malformation. Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2019.

8. Belser-Ehrlich J, Adrian Lafo J, Mangal P, Bradley M, Wicklund M, Bowers D. Neurocognitive profile of a man with Dandy-Walker malformation: evidence of subtle cerebellar cognitive affective syndrome. Clin Neuropsychol. 2020;34(3):591-610. doi: 10.1080/13854046.2019.1569724.

9. Zhang N, Qi Z, Zhang X, Zhong F, Yao H, Xu X, et al.. Dandy-Walker syndrome associated with syringomyelia in an adult: a case report and literature review. J Int Med Res. 2019; 47(4):1771-7. doi: 10.1177/0300060518808961.

10. Stambolliu E, Ioakeim-Ioannidou M, Kontokostas K, Dakoutrou M, Kousoulis AA. The most common comorbidities in Dandy-Walker syndrome patients: a systematic review of case reports. J Child Neurol. 2017; 32(10):886-902. doi: 10.1177/0883073817712589.

11. Agrawal S, Dave M, Mahur H, Aswani M, Goyal R, Pansari N, et al. Dandy-Walker syndrome: a rare presentation in adult. J Assoc Physicians India. 2016; 64(10):112.

12. Konefał H, Gawrych E, Czeszyńska MB. Congenital epidermolysis bullosa - a case report. Ginekol Pol. 2012; 83(10):792-4.

13. Smolyannikova VA, Kubanova AA, Albanova VI, Nefedova MA, Karamova AE. Current approaches to the morphologic diagnosis of different types of congenital epidermolysis bullosa. Arkh Patol. 2016; 78(6):9-16. doi: 10.17116/patol20167869-16.

14. Crecchio G, Cennamo G, de Leeuw N, Ventruto ML, Lonardo MC, Friso P, et al. Severe myopia with unusual retinal anomalies and Dandy-Walker sequence in two sibs. A distinct new neuro-ocular disorder. Ophthalmic Genet. 2013; 34(4):254-7. doi: 10.3109/13816810.2013.763992.

15. Getova DP, Mihaylova AS. A study of the effects of lamotrigine on mice using two convulsive tests. Folia Med (Plovdiv). 2011; 53(2):57-62. doi: 10.2478/v10153-010-0038-6.

16. Ramey P, Osborn MR, Lowen KM, Reed RC, Abou-Khalil B. Unexplained spikes in lamotrigine serum concentration: nonlinear elimination? Acta Neurol Scand. 2017; 135(2):240-6. doi: 10.1111/ane.12588.

Correspondence to/Autor za korespondenciju
Mirjana A. Janicijevic Petrovic, full professor
Department of Ophthalmology, Faculty of Medical Sciences University of Kragujevac, Serbia
Svetozara Markovica 69, 34000 Kragujevac, Serbia
E-mail: mira.andreja@yahoo.com
Tel: +381 64 8065048
Fax: +381 34 306 800

ERRATUM

Erratum for article: Emced K. Comparing the outcomes of routine and selective epicardial pacing wire placement: a single -center experience of 237 patients. Sanamed.2019;14(3):247-52. doi:10.24125/sanamed.v14i3.360

Author of this paper informed us about existence of an error.

On page 247, in Abstract, section Method, the sentence:

"A total of 237 patients undergoing OHS in our clinic (ORDU UNVERSTY TRAINING AND RESEARCH HOSPTAL) were enrolled in this study."

should be replaced with:

"A total of 237 patients undergoing OHS in our clinic (DR ERSIN ARSLAN EDUCATION AND RESEARCH HOSPTAL, GAZIANTEP, TURKEY) were enrolled in this study."

UPUTSTVO AUTORIMA

SANAMED je medicinski časopis osnovan 2006. godine. Časopis objavljuje: originalne naučne i stručne članke, prikaze bolesnika, revijske radove, pisma uredniku, članke iz istorije medicine, prikaz objavljenih knjiga i druge medicinske informacije.

Rukopise slati na adresu:
Prim. dr Avdo Ćeranić,
(za Sanamed)
Ul. Palih boraca 52, 36300 Novi Pazar
Email: sanamednp2006@gmail.com
www.sanamed.rs

Prispeli rukopis Uređivački odbor šalje recenzentima radi stručne procene. Ukoliko recenzenti predlože izmene ili dopune, kopija recenzije se dostavlja autoru s molbom da unese tražene izmene u tekst rada ili da argumentovano obrazloži svoje neslaganje s primedbama recenzenta. Konačnu odluku o prihvatanju rada za štampu donosi glavni i odgovorni urednik.

Časopis se štampa na engleskom jeziku, sa kratkim sadržajem prevedenim na srpski jezik.

OPŠTA UPUTSTVA

Tekst rada kucati u programu za obradu teksta *Word*, latinicom, sa dvostrukim proredom, isključivo fontom *Times New Roman* i veličinom slova 12 tačaka (12 pt). Sve margine podesiti na 25 mm, a tekst kucati sa levim poravnanjem i uvlačenjem svakog pasusa za 10 mm, bez deljenja reči (hifenacije).

Rukopis mora biti organizovan na sledeći način: naslovna strana, sažetak na srpskom jeziku, sažetak na engleskom jeziku, ključne reči, uvod, cilj rada, bolesnici i metodi/materijal i metodi, rezultati, diskusija, zaključak, literatura, tabele, legende za slike i slike.

Svaki deo rukopisa (naslovna strana, itd.) mora početi na posebnoj strani. Sve strane moraju biti numerisane po redosledu, počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u zagradama, i to onim redosledom kojim se pojavljuju u tekstu.

Obim rukopisa. Celokupni rukopis rada, koji čine naslovna strana, kratak sadržaj, tekst rada, spisak literature, svi prilozi, odnosno potpisi za njih i legenda (tabele, slike, grafikoni, sheme, crteži), naslovna strana i sažetak na engleskom jeziku, mora iznositi za originalni rad, saopštenje, rad iz istorije medicine i pregled literature do 5.000 reči, a za prikaz bolesnika, rad za praksu, edukativni članak do 3.000 reči; radovi za ostale rubrike moraju imati do 1.500 reči.

Provera broja reči u dokumentu može se izvršiti u programu *Word* kroz podmeni *Tools-Word Count* ili *File-Properties-Statistics*.

Sva merenja, izuzev krvnog pritiska, moraju biti izražena u internacionalnim SI jedinicama, a ako je neophodno, i u konvencionalnim jedinicama (u zagradi). Za lekove se moraju koristiti generička imena. Zaštićena imena se mogu dodati u zagradi.

Naslovna strana. Naslovna strana sadrži naslov rada, kratak naslov rada (do 50 slovnih mesta), puna prezimena i imena svih autora, naziv i mesto institucije u kojoj je rad izvršen, zahvalnost za pomoć u izvršenju rada (ako je ima), objašnjenje skraćenica koje su korišćene u tekstu (ako ih je bilo) i u donjem desnom uglu ime i adresu autora sa kojim će se obavljati korespondencija.

Naslov rada treba da bude sažet, ali informativan.

Ako je potrebno, može se dodati i podnaslov.

Kratak naslov treba da sadrži najbitnije informacije iz punog naslova rada, ali ne sme biti duži od 50 slovnih mesta.

Ako je bilo materijalne ili neke druge pomoći u izradi rada, onda se može sažeto izreći zahvalnost osobama ili institucijama koje su tu pomoć pružile.

Treba otkucati listu svih skraćenica upotrebljenih u tekstu. Lista mora biti uređena po abecednom redu pri čemu svaku skraćenicu sledi objašnjenje. Uopšte, skraćenice treba izbegavati, ako nisu neophodne.

U donjem desnom uglu naslovne strane treba otkucati ime i prezime, telefonski broj, broj faksa i tačnu adresu autora sa kojim ce se obavljati korespodencija.

Stranica sa sažetkom. Sažetak mora imati do 350 reči. Treba koncizno da iskaže cilj, rezultate i zaključak rada koji je opisan u rukopisu. Sažetak ne može sadržati skraćenice, fusnote i reference.

Ključne reči. Ispod sažetka treba navesti 3 do 8 ključnih reči koje su potrebne za indeksiranje rada. U

izboru ključnih reči koristiti Medical Subject Headings — MeSH.

Stranica sa sažetkom na engleskom jeziku. Treba da sadrži pun naslov rada na engleskom jeziku, kratak naslov rada na engleskom jeziku, naziv institucije gde je rad urađen na engleskom jeziku, tekst sažetka na engleskom jeziku i ključne reči na engleskom jeziku.

Struktura rada. Svi podnaslovi se pišu velikim slovima i boldovano.

Originalni rad treba da ima sledeće podnaslove: uvod, cilj rada, metod rada, rezultati, diskusija, zaključak, literatura.

Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura.

Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

Treba navesti statističke metode koje su korišćene u obradi rezultata.

Rezultati. Rezultati treba da budu jasni i sažeti, sa minimalnim brojem tabela i slika neophodnih za dobru prezentaciju.

Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

Reference se citiraju prema tzv. Vankuverskim pravilima, koja su zasnovana na formatima koja koriste *National Library of Medicine* i *Index Medicus*.

Primeri:

1. **Članak:** (svi autori se navode ako ih je šest i manje, ako ih je više navode se samo prvih šest i dodaje se *"et al."*)

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

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad.

Slike. Sve ilustracije (fotografije, grafici, crteži) se smatraju slikama i označavaju se arapskim brojevima u tekstu i na legendama, prema redosledu pojavljivanja. Treba koristiti minimalni broj slika koje su zaista neophodne za razumevanje rada. Slova, brojevi i simboli moraju biti jasni, proporcionalni, i dovoljno veliki da se mogu reprodukovati. Pri izboru veličine grafika treba voditi računa da prilikom njihovog smanjivanja na širinu jednog stupca teksta neće doći do gubitka čitljivosti. Legende za slike se moraju dati na posebnim listovima, nikako na samoj slici.

Ako je uveličanje značajno (fotomikrografije) ono treba da bude naznačeno kalibracionom linijom na samoj slici. Dužina kalibracione linije se unosi u legendu slike.

Uz fotografije na kojima se bolesnici mogu prepoznati treba poslati pismenu saglasnost bolesnika da se one objave.

Za slike koje su ranije već objavljivane treba navesti tačan izvor, treba se zahvaliti autoru, i treba priložiti pismeni pristanak nosioca izdavačkog prava da se slike ponovo objave.

Pisma uredniku. Mogu se publikovali pisma uredniku koja se odnose na radove koji su objavljeni u SANAMEDU, ali i druga pisma. Ona mogu sadržati i jednu tabelu ili sliku, i do pet referenci.

Propratno pismo. Uz rukopis obavezno priložiti pismo koje su potpisali svi autori, a koje treba da sadrži: izjavu da rad prethodno nije publikovan i da nije istovremeno podnet za objavljivanje u nekom drugom časopisu, te izjavu da su rukopis pročitali i odobrili svi autori koji ispunjavaju merila autorstva. Takođe je potrebno dostaviti kopije svih dozvola za: reprodukovanje prethodno objavljenog materijala, upotrebu ilustracija i objavljivanje informacija o poznatim ljudima ili imenovanje ljudi koji su doprineli izradi rada.

Troškovi pripreme rada

Svi autori radova, imaju obavezu da pre nego što dobiju potvrdu da će rad biti objavljen u Sanamedu, izvrše uplatu za pokriće dela troškova štampe koja za autora rada iznosi 2500 dinara, a za koautore po 1500 dinara, za svaki prihvaćeni rad. Za autora rada iz inostranstva naknada za štampanje iznosi 40 eura (u dinarskoj protivrednosti po kursu na dan uplate), a za koautore 20 eura. Dodatno će biti naplaćena svaka stranica na kojoj se nalaze slike u boji, po ceni od 30 eura; crno bele slike se ne naplaćuju.

Za sva dalja uputstva i informacije kontaktirajte Uredništvo.

Napomena. Rad koji ne ispunjava uslove ovog uputstva ne može biti upućen na recenziju i biće vraćen autorima da ga dopune i isprave. Pridržavanjem uputstva za pisanje rada za SANAMED znatno će se skratiti vreme celokupnog procesa do objavljivanja rada u časopisu, što će pozitivno uticati na kvalitet i redovnost izlaženja svezaka.

INSTRUCTIONS TO AUTHORS

SANAMED is a medical journal, published since 2006. The journal publishes: original papers, case reports, review articles, letters to the Editor, other articles and information concerned with practice and research in medicine.

Address manuscripts to:
Prim. dr Avdo Ćeranić,
(for Sanamed)
Ul. Palih boraca 52, 36300 Novi Pazar
Email sanamednp2006@gmail.com
www.sanamed.rs

Arrived manuscript is sent to reviewers for expert assessment by the Editorial Board. If reviewers propose changes or amendments, copies of reviews are submitted to authors with a request to enter the required changes to the text or explain its disagreement with the remarks of the reviewer. The final decision of acceptance for publishing is given by Editor in chief.

The journal is published in English, with the summary translated into Serbian.

GENERAL GUIDELINES

Text of the paper should be typed in a word processing program *Word*, written in Latin, double-spaced, only in *Times New Roman* font size 12 points. All margins should be set at 25 mm, and the text should be typed with the left alignment and paragraph indentations of 10 mm, without dividing the words.

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.

Each manuscript component (title page, etc.) begins on a separate page. All pages are numbered consecutively beginning with the title page.

References in the text are designated with Arabic numerals in parentheses, and the order in which they appear in the text.

Manuscript volume. The complete manuscript, which includes title page, short abstract, text of the article, literature, all figures and permisions for them and legends (tables, images, graphs, diagrams, drawings), title page and abstract in English, can have the length up to 5000 words for original paper, report, paper on the history of medicine and literature overview, while for patient presentation, practice paper, educative article it can be up to 3000 words, and other papers can be up to 1500 words.

The word count check in a document can be done in *Word* processor program in submenu *Tools Word Count* or *File Properties Statistics*.

All measurements, except blood pressure, are reported in the System International (SI) and, if necessary, in conventional units (in parentheses). Generic names are used for drugs. Brand names may be inserted in parentheses.

Title page. The title page contains the title, short title, full names of all the authors, names and full location of the department and institution where work was performed, acknowledgments, abbreviations used, and name of the corresponding author. The title of the article is concise but informative, and it includes animal species if appropriate. A subtitle can be added if necessary.

A short title of less than 50 spaces, for use as a running head, is included.

A brief acknowledgment of grants and other assistance, if any, is included.

A list of abbreviations used in the paper, if any, is included. List abbreviations alphabetically followed by an explanation of what they stand for. In general, the use of abbreviations is discouraged unless they are essential for improving the readabillity of the text.

The name, telephone number, fax number, and exact postal address of the author to whom communications and reprints should be sent, are typed at the lower right corner of the title page.

Abstract page. An abstract of less than 180 words concisely states the objective, findings, and conclusion of the studies described in the manuscript. The abstract does not contain abbreviations, footnotes or references.

Below the abstract, 3 to 8 keywords or short phrases are provided for indexing purposes.

The structure of work. All headings are written in capital letters and bold.

Original work should have the following headings: introduction, aim, methods, results, discussion, conclusion, references.

A case report include: introduction, case report, discussion, references.

Review of the literature include: an introduction, subheadings, conclusion, references.

Patients and methods/Material and methods. The selection of patients or experimental animals, including controls is described. Patients' names and hospital numbers are not used.

Methods are described in sufficient detail to permit evaluation and duplication of the work by other investigators.

When reporting experiments on human subjects, it should be indicated whether the procedures followed were in accordance with ethical standards of the Committee on human experimentation of the institution in which they were done and in accordance with the Declaration of Helsinki. Hazardous procedures or chemicals, if used, are described in detail, including the safety precautions observed. When appropriate, a statement is included verifying that the care of laboratory animals followed the accepted standards.

Statistical methods used, are outlined.

Results. Results are clear and concise, and include a minimum number of tables and figures necessary for proper presentation.

Discussion. An exhaustive review of literature is not necessary. The major findings should be discussed in relation to other published works. Attempts should be made to explain differences between results of the present study and those of the others. The hypothesis and speculative statements should be clearly identified. The discussion section should not be a restatement of results, and new results should not be introduced in the discussion.

References. References are identified in the text by Arabic numerals in parentheses. They are numbered consecutively in the order in which they appear in the text. Number of references should not exceed 30, except in the literature review, which is allowed to be to 50.

Avoid using abstracts as references and abstract older than two years are not cited.

References are cited by the so-called Vancouver rules, which are based on formats that use the National Library of Medicine and Index Medicus. The following are examples:

1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first six are listed followed by *"et al."*)

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

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

Tables. Tables are typed on separate sheets with figure numbers (Arabic) and title above the table and explanatory notes, if any, below the table.

Figures and figure legends. All illustrations (photographs, graphs, diagrams) are to be considered figures, and are numbered consecutively in the text and figure legend in Arabic numerals. The number of figures included is the least required to convey the message of the paper, and no figure duplicates the data presented in the tables or text. Letters, numerals and symbols must be clear, in proportion to each other, and large enough to be readable when reduced for publication. Figures are submitted as near to their printed size as possible. Legends for figures should be given on separate pages.

If magnification is significant (photomicrographs), it is indicated by a calibration bar on the print, not by a magnification factor in the figure legend. The length of the bar is indicated on the figure or in the figure legend.

Photographs of identifiable patients are accompanied by written permission from the patient.

For figures published previously, the original source is acknowledged, and written permission from the copyright holder to reproduce it is submitted.

Letters to the Editor. Both letters concerning and those not concerning the articles that have been published in SANAMED will be considered for publication. They may contain one table or figure and up to five references.

Cover letter. The letter signed by all authors must be attached with the manuscript. The letter should consist of: the statement that the paper has not been published previously and that it is not submitted for publication to some other journal, the statement that the manuscript has been read and approved by all the authors who fulfill the authorship criteria. Furthermore, authors should attach copies of all permits: for reproduction of previously published materials, for use of illustrations and for publication of information about pub-

licly known persons or naming the people who contributed to the creation of the work.

Costs of paper preparation

All authors of papers, have obligation, before they receive confirmation that the paper will be published in Sanamed, to pay part of expenses of printing, which is 2500 RSD for author, 1500 RSD for co-authors, for each paper.

For paper author from abroad printing fees are 40 Euro (in Dinar equivalent at the exchange rate on the day of payment), and 20 Euro for co-authors. Additionally will be charged each page with pictures in color, costing 30 Euro; black and white pictures will not be charged.

For any further instructions and information, contact Editorial Board.

Note. The paper which does not fulfill the conditions set in this instruction cannot be set to reviewers and will be returned to the authors for amendments and corrections. By following the instructions for writing the papers for Medical Journal, the time needed for the process of publication of papers in the journal will be shortened, which will have positive impact on the quality and regularity of publication of volumes.

CIP — Каталогизација у публикацији
Народна библиотека Србије, Београд

61

SANAMED / glavni i odgovorni urednik Avdo Ćeranić. — God. 1, br. 1 (2006)– . — Novi Pazar : Udruženje lekara Sanamed, 2006– (Kraljevo : Ofset). — 30 cm

Tri puta godišnje. — Tekst na engl. jeziku. — Drugo izdanje na drugom medijumu: Sanamed (Online) = ISSN 2217-8171

ISSN 1452-662X = Sanamed

COBISS.SR-ID 135154444

ISSN 1452-662X