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Sadržaj / Table of Contents

Effect of thyroid hormone levels on mortality in patients infected with Covid-19 in intensive care units

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Abstract

Objective: By examining the mortality rate of thyroid hormone levels and the factors affecting this rate during the follow-up of patients infected with Covid 19 in the intensive care unit, it was aimed to contribute to the literature on covid 19 disease, which is a new disease.

Material and methods: Covid 19-infected patients who were hospitalized in the intensive care unit between 18 August and 30 November 2020 according to the criteria of hospitalization in intensive care, such as age, gender, hospitalization periods, additional diseases, thyroid hormone levels, and inflammatory cytokine levels and mortality rates. Their clinical features were recorded, retrospectively analyzed, and compared.

Results: Data of 89 patients whose thyroid function tests were examined from 113 patients included in the study were collected. It was found that triiodothyronine levels in the group of patients who died were statistically lower than those who were discharged. Interleukin-6 and procalcitonin levels were found to be higher in the group of patients who died.

Conclusion: Triiodothyronine, interleukin-6, and procalcitonin levels affect mortality rate and may be useful in predicting mortality in Covid19-infected patients treated in intensive care.

Key words: Covid-19; Mortality; Thyroid hormone levels.

Introduction

Covid 19 infection has been spreading globally since the day it emerged and threatened human health. This epidemic, which occurred in China, spread throughout the world in a short time and affected countries' health systems [1]. Covid 19 infection infects many systems in the human body and causes organ dysfunction. In addition to causing respiratory distress, especially with the development of pneumonia, it is a disease that can affect the circulatory, hepatic, renal, and hematological systems [2-3]. However, the effect of covid 19 infections on thyroid functions is not clearly known. However, it is known that other types of coronavirus can infect the thyroid glands [4]. The S proteins on the surfaces of coronaviruses provide attachment and entry into cells. With the help of S protein, it attaches to the cells with angiotensin-converting enzyme 2 (ACE 2), which is present in the cells. In the thyroid gland, the number of receptors in the lungs (ACE 2) is high, and coronaviruses can bind via these receptors and cause infection development [5]. Thyroid hormones; Triiodothyronine (T3) and L thyroxine (T4) provide growth from birth, regulate metabolism, play a role in neuronal activations and take part in the immune system. Thyroid function abnormalities are frequently encountered in patients infected with coronavirus [6]. Decreased T3 and thyroid-stimulating hormone (TSH) concentrations have been shown to be associated with mortality in critical care patients and patients in intensive care units due to chronic renal failure, acute myocardial infarction, and sepsis [7-8–9]. It is known that Covid 19 infection progresses more severely due to reasons such as high C Reactive protein (CRP), d dimer, procalcitonin, lactate dehydrogenase (LDH) levels, and thrombocytopenia [10-11]. In this retrospective study, we aimed to investigate the role of thyroid functions in predicting death risk in patients with severe or critically ill COVID-19. We hypothesized that thyroid hormone levels could predict the death of severe COVID-19 patients.

Material method

A total of 113 patients who were followed up in adult intensive care units due to COVID 19 infection between 18 August and 30 November 2020 were screened, and data of a total of 89 patients who had thyroid function tests were collected. Our study

is getting retrospective and approved by the ethics committee and our ministry of health. The files of the patients were examined. The patients' age, gender, and comorbidities, and length of stay in the intensive care unit were analyzed and recorded. In addition, the discharge processes and mortality of the patients were examined. The ones studied after the patients were taken into intensive care; Leukocyte, neutrophil, lymphocyte count, procalcitonin, ferritin, albumin, fT3, fT4, TSH, interleukin-6 (IL-6), IGA, C-reactive protein (CRP), and D-dimer results were recorded. To investigate the effect of thyroid function tests on mortality in patients infected with covid 19; The patients who lost their lives were classified as Group 1. The patients were discharged from the intensive care unit as Group 2.

Inclusion criteria for the study

Patients who present to our hospital with complaints such as fever, cough and shortness of breath and whose diagnostic imaging findings of COVID-19 infection are confirmed by a radiologist will be included in the study. In addition, patients aged 18 and over who are supported by the diagnosis of covid-19 by detecting nucleic acid by polymerase chain reaction in the respiratory tract and meet the criteria for admission to intensive care.

Intensive care Inclusion criteria

Respiratory rate above 20 and oxygen saturation of 90 and below despite 5 lt / min 100% oxygen support with a reservoir oxygen mask or invasive mechanical ventilation support was applied to emergency departments with respiratory distress.

Results

The mean age of group 1 was 73 ± 11, and the mean age of group 2 was 70 ± 13. There was no difference between the groups in terms of average age (p: 0.29). There was no difference between the groups in terms of female and male ratio and length of stay. Respectively (p: 0.60, p: 0.24) (Table 1).

There was no significant difference between the groups in terms of comorbid diseases.

Procalcitonin, IL6, and fT3 were different between groups (Table 1). Other parameters were not d. A positive correlation was found between fT3 level and discharge (p: 0.018). There was no correlation between other parameters and discharge. Different between groups (Table 1).

In the regression analysis, it was seen that the rate of discharge and death was affected by the fT3 level. (Table 2).

Table 1. Average of age, gender, length of stay, and laboratory results of the groups

	GROUP 1		GROUP2		P
		N		N	
AGE	73±11	59	70±13	30	0,29
F/M	23/36	59	13/17	30	0,6
DURATION OF HOSPITAL	12±9	59	17±17	29	0,24
ALBUMIN g/dl	3,1±0,6	59	3,0±0,3	30	0,79
LEUKOCYTE cells/mm^3	11±6	59	9±4	30	0,22
NEUTROPHIL cells/mm^3	10±5	59	8±3	30	0,11
LYMPHOCYTE cells/mm^3	0,7±0,5	59	0,7±0,3	30	0,29
D DIMER ug/ml	3573±3679		3623±8096	30	0,29
CRP mg/L	133±81	59	108±62	30	0,49
FERRITINE µg/L	753±532	59	644±504	30	0,35
PROCALCITONINE ng/ml	4,05±13	56	0,6±1,8	28	0,02
IGA ng/ml	19,7±42	59	14,5±47	30	0,59
IL-6 ng/ml	324±938	59	151±420	30	0,00
Free T3 ng/L	1,6±0,4	59	1,7±0,6	30	0,01
FreeT4 ng/L	1,09±0,3	59	1,1±0,4	30	0,94
TSH mU /L	1,02±1,3	59	0,86±1,1	30	0,95

Group 1: patients who died. Group 2: patients discharged from intensive care. N: number of patients. F / M: Female to male ratio. CRP: C-Reactive protein. TSH: Thyroid-stimulating hormone.

Table 2. Regression analysis of variables

	B	Standard error	SIG	BETA
AGE	-,058	,031	,058	,943
GENDER	,432	,881	,624	1,541
ALBUMIN g/L	-,047	,067	,482	,954
LEUKOCYTE cells/mm^3	-,035	,178	,844	,966
NEUTROPHIL cells/mm^3	-,075	,171	,661	,928
LYMPHOCYTE cells/mm^3	-,276	,985	,779	,759
D-DIMER ug/ml	,000	,000	,195	1,000
CRP mg/L	-,005	,005	,321	,995
FERRITINE µg/L	,001	,001	,490	1,001
PROCALCITONINE ng/ml	-,099	,114	,384	,906
IGA ng/ml	,006	,007	,391	1,006
IL-6 ng/ml	,000	,001	,892	1,000
FT3 mu/L	1,386	,698	,047	3,999
FT4	,208	1,009	,837	1,231
TSH	-,061	,251	,809	,941

Statistical analysis

SPSS v20 program was used in the analysis of the data. Categorical variables were presented as number and percentage, numerical variables as mean and standard deviation. The distribution of categorical variables between groups was analyzed with the KI-Square test. The Kolmogorov-Smirnov test and graphing method investigated the compatibility of numerical variables to normal distribution. Mann Whitney-U was used for comparisons of numerical variables that were not normally distributed, and a t-test was used for data that fit normal distribution and were homogeneous. $P < 0.05$ was considered statistically significant. Spearman correlation analysis was performed to examine the correlation of the data. Logistic regression analysis was performed to examine which variables affected the discharge and mortality of the patients.

Discussion

The covid-19 disease can cause the release of pro-inflammatory cytokines such as IL-6. Besides, these cytokines are known to be higher in patients infected with covid-19, in severe and dying patients [12-13]. In a study investigating the ability of interleukin-6 (IL-6), C-reactive protein (CRP), and procalcitonin (PCT) to predict mild to severe COVID-19 cases, IL-6, CRP, and PCT are independent factors for predicting the severity of COVID-19. [14] Malik et al. In their study, IL-6 level was found to be statistically higher in the group with covid 19 compared to the non-covid-19 group [12].

In our study in critical intensive care patients, IL-6 and procalcitonin levels were found to be statistically higher in patients who died due to the severity of the disease compared to those who were discharged.

Thyroid hormones are involved in the functioning of many systems as well as in the functioning of the immune system. It is known that thyroid hormone abnormalities are very common in patients infected with coronavirus [6]. Wei et al. In a study they conducted, studies conducted on patients infected with 5 SARS coronavirus showed a decrease in the number of TSH-producing cells. It has been reported that despite decreased T3 and T4 levels in these patients, TSH secretion does not increase even when stimulated by negative feedback [15]. Chen et al. [16] TSH and serum total triiodothyronine (T3) levels were significantly lower in patients with COVID-19 than the healthy control group and non-COVID-19 pneumonia patients. The degree of decrease in TSH and T3 levels positively correlated with the severity of the disease. It has been shown that the total thyroxine (T4) level of patients with COVID-19 is not significantly different from the control group. Malik et al. [12] found that T3 and TSH values were statistically lower in the covid-positive group than the

non-covid group in a study where they compared patients who were positive for covid-19 PCR and those who were not.

In this study, the fT3 hormone level was found to be statistically lower in the patients in the group who lost their lives compared to the patients who were discharged. TSH and T4 hormone levels were similar in both groups of patients. Unlike other studies, the TSH level was not different in the groups because all of the patients in our study were critically ill, and a comparison was made in terms of mortality, unlike other studies.

Previous studies have shown that people with hypothyroidism are immunocompromised and have a higher risk of viral infection [17,18,19]. In their study, Kumari et al. [20] found that unregulated thyroid hormone may have a significant risk of exacerbating the infection and spread of SARS-CoV-2.

Our study found that fT3 levels were lower, and IL-6 and procalcitonin levels were higher in patients in the group who died compared to those who were discharged. In the regression analysis performed on this, it was seen that the rate of death with the discharge was affected only by fT3 values.

This study and other studies showing lower t3 hormone levels in covid patients [12,17] also show that t3 level is lower in intensive care patients who lost their lives. A lower fT3 level may be useful in predicting mortality in patients with covid 19. The fact that our study was conducted only in critical intensive care patients is one of the study's limitations.

Conclusions

Thyroid hormones play an important role in many systems of the human body. Changes in thyroid hormone levels may have important clinical consequences on human health by affecting the immune system. Low t3 level may increase mortality and be useful in predicting mortality in critically ill patients infected with covid-19. Studies with larger samples are needed.

References

1. *Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX,,at al Clinica lCharacteristics of Coronavirus Disease 2019 in China. N Engl J Med, 2020; 382: 1708–1720.*
2. *Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) 2020; 395(10223): 497-506.*
3. *Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet (London, England) 2020; 395(10223): 507-13.*
4. *Wang W, Su X, Ding Y, Fan V, Su J, Chen Z, Thyroid function abnormalities in COVID-19 patients medRxiv 2020.06.15.20130807*
5. *Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cellentrydepends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181(2): 271-80.e8.*
6. *Wei L, Sun S, Xu CH, et al. Pathology of thethyroid in severe acute respiratory syndrome. Hum Pathol, 2007; 38(1): 95–102.*
7. *P.M. Rothwell, P.G. Prediction of outcome in intensive care patients using endocrine parameters Crit. CareMed., 1995; 23: 78-83, 10.1097/ 00003246-199501000-00015*
8. *Todd SR, Sim V, Moore LJ, Turner KL, Sucher JF, Moore FA. The identification of thyroid dysfunction in surgical sepsis. J Trauma Acute Care Surg, 2012; 73(6): 1457–1460.*
9. *Wu Y, You S, Zang H, Liu H, Mao Y, Mao P, et al. Usefulness of serum thyroid-stimulation hormone (TSH) as a prognostic indicator for acute-on-chronic liver failure. AnnHepatol, 2015; 14(2): 218–224.*
10. *Zhang JJ, Cao YY, Dong X, et al. Distinct characteristics of COVID-19 patients with initialrRT-PCR positive and negative results for SARS-CoV-2. Allergy 2020.*
11. *Wu C, Chen X, Risk CY, et al. Factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA InternMed 2020; 180(7): 934.*
12. *Malik J, Malik A, Javaid M, Zahid T, Ishaq U, Shoaib M. Thyroid Function Analysis in COVID-19: A Retrospective Study from a Single Center, medRxiv 2021.02.09.21251435;*

13. *Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome Blood, 2014; 124(2): 188-195.*

14. *Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol. 2020; 127: 104370. doi:10.1016/j.jcv.2020.104370*

15. *Wei L, Sun S, Zhang J, et al. Endocrinecells of theadenohypophysis in severe acuterespiratorysyndrome (SARS). Biochemistryandcellbiology = Biochimie et biologiecellulaire 2010; 88(4): 723-30.*

16. *Chen M, Zhou W, Xu W. ThyroidFunction Analysis in 50 Patientswith COVID-19: A RetrospectiveStudy. Thyroid. 2021 Jan; 31(1): 8-11. doi: 10.1089/thy.2020.0363. Epub 2020 Jul 10. PMID: 32600165*

17. *Seyyedi N, Dehbidi GR, Karimi M, Asgari A, Esmaeili B, Zare F, et al. Human herpesvirus 6A activeinfection in patients with autoimmune Hashimoto's thyroiditis Braz. J. Infect. Dis., 2019; 23(6): 435 - 440.*

18. *Varedi M, Moattari A, Amirghofran Z, Karamizadeh Z, Feizi H. Effects of hypo- and hyperthyroid states on herpes simplex virus infectivity in therat Endocr. Res., 2014; 39(2): 50 - 55.*

19. *DiCrescenzo V, D'Antonio A, Tonacchera M, Carlomagno C, Vitale M. Human herpes virus associated with Hashimoto's thyroid it is InfezMed., 2013; 21(3): 224 – 228.*

20. *Kumari K, Chainy GBN, Subudhi U. Prospective role of thyroid disorders in monitoring COVID-19 pandemic. Heliyon. 2020 Dec; 6(12): e05712.*

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A visual method of sexing the hip bone and pelvis

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Abstract

Background/aim: The aim is to examine the correlations between the representation of qualitative (morphognostic) gender marks on the hip bone and pelvis, in relation to the values of the index of the upper part of the greater sciatic notch, based on which gender determination was performed, as well as monitor the percentage of individual morphognostic gender marks in relation to determination of male or female gender (based on the index).

Material and methods: The study was conducted prospectively on 98 adult hip bone of Bosnian population, of which 56 were single and 42 were within the pelvis. The gender of the bones are determined based on the index of the upper part of the greater sciatic notch. The research is based on the osteoscopic analysis of morphoscopic characteristics of the hip bones and pelvis.

Conclusion: Appearance of sciatic notch, appearance of bones and auricular surface, morphology of pelvic outlet and pelvic constitution stand out as the most powerful indicators of sexual dimorphism based on visual method of sexing the hip bone and pelvis.

Key words: Hip bone, pelvis, sexual dimorphism, visual method

1. Introduction

Assessment of gender based on human skeleton has its own importance and application in forensic medicine, anatomy, physical anthropology and archeology (1). Gender determination is one of the first steps in biological or forensic anthropological analysis. The main reason for this is the fact that other vital information, such as age and height, can not be obtained adequately without an initial gender assessment, as the male and female skeletons differ morphometrically. These differences are determined by the methods of determining age or height. Also, accurate gender assessment is crucial at all stages of the identification process allowing final conclusions to be reached (2-7). On the skeleton, it is best to assess gender after puberty after gender differences develop fully (8, 9). In adults, the bone material in which we find pronounced gender dimorphism are pelvis and skull. Numerous osteological indicators of gender can be observed on the pelvis. Differences between the pelvis of a male and a female have been confirmed by numerous studies using different methods such as morphoscopic and morphometric methods. The most noticeable differences are found in bone size, greater sciatic notch, auricular surface, acetabulum, and on the pubic bone (10, 11, 12, 13). Some authors suggest visualization of ten features on the pelvis: greater sciatic notch, pubic angle, the angle formed by auricular surface and greater sciatic notch, hip bone, obturator foramen, body of ischium, iliac crest, iliac fossa, greater pelvis and lesser pelvis (14). Research on the pelvis provides the most significant results in gender distinction for several reasons. Primarily because of the numerous details that can be detected and the ability to make comparisons between those details. The largest number of differences are found on the pelvis throughout all ages, starting from intrauterine, i.e. fetal development, all the way to old age (15).

2. Materials and methods

The study was designed as a prospective osteoscopic and it was conducted in osteological cabinets at the Department of Anatomy, Faculty of Medicine, University of Sarajevo. Total of 56 individual hip bones (34 left and 22 right) and 21 pelvis sample were observed (total of 98 hip bone - 43 right and 55 left). The pelvis and hip bones belonged to adults of the population in Bosnia and Herzegovina. The gender of the hip bones was determined based on the index of the upper part of the greater sciatic notch. All hip bones with an index I <0.70, were

characterized as reliably male hip bones, and if the index value was I> 0.70, hip bones were characterized as reliably female hip bones (16).

On individual hip bones, the following parameters were assessed: bone appearance, appearance of the iliac fossa, shape and size of the obturator foramen, appearance of the acetabulum, auricular surface and greater sciatic notch, and longitudinal-transverse ratio appearance of hip bones. On the pelvis a descriptive assessment was performed: pelvis constitution, appearances of individual bones, iliac fossa, pelvic cavity, sacrum, pelvic outlet and pubic symphysis, shape of pelvic inlet, expression of promontorium, descriptive assessment of distance between pubic tubercles and between the ischial tuberosities, the appearance of the pubic arch, the shape and size of the obturator foramen, the appearance of the acetabulum, and a description of the pelvic inclination.

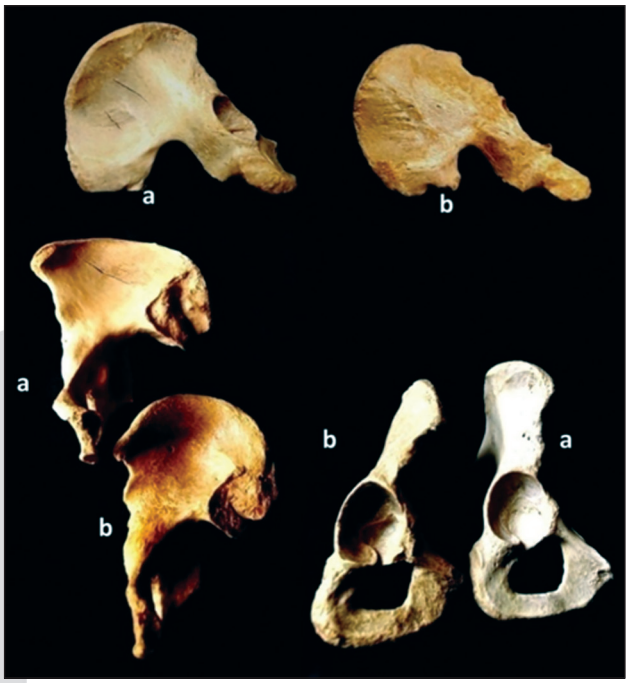

Figure 1. Hip bones - a-female, b-male determined by the value of the index of the upper part of the greater sciatic notch - Osteological Collection of the Department of Human Anatomy, Medical faculty University of Sarajevo

3. Results

3.1. Correlation relations of osteoscopic - qualitative (morphognostic) gender marks for individual hip bones, which are sexually determined based on the value of the index of the upper part of the greater sciatic notch

Kendall's tau-b (Correlation Coefficient) showed a statistically significant level of matching (on the total sample p <0.05) of the index of the upper part of the greater sciatic notch (male≤0.70 / female> 0.71) and morphognostic gender markings.

The highest matching coefficient was with: appearance of greater sciatic notch b = 0.640, followed with appearance of bone b = 0.508. Slightly weaker matching of index of upper part of greater sciatic notch was with morphognostic gender markings: appearance of iliac fossa b = 0.419, appearance of auricular surface b = 0.473 and the appearance of the hip bone - longitudinal-transverse ratio b = 0.419.

The least match of the index of the upper part of the greater sciatic notch is with the morphog-

Table 1. Correlation relations of qualitative gender markings with the index of the upper part of the greater sciatic notch – hip bone

		Bone appearance	Appearance of iliac fossa	Shape and size of obturator foramen	Appearanceaof the acetabulum	Appearance of the auricular surface	Longitudinal-transverse ratio appearance of hip bones	Appearance of the greater sciatic notch
Index of the upper part of the greater sciatic notch	Kendall's tau-b Correlation-Coefficient	0,508	0,419	0,234	0,373	0,473	0,419	0,640
	P.	0,0005*	0,0005*	0,021*	0,001*	0,001*	0,0005*	0,0005*
	N	98	98	98	78	53	98	98

nostic gender markings: the appearance of the acetabulum b = 0.373 and the shape and size of the obturator foramen b = 0.234.

3.2. Correlation relations of osteoscopic - qualitative (morphognostic) pelvic gender marks, sexually determined based on the value of the index of the upper part of the greater sciatic notch

Kendall's tau-b (Correlation Coefficient) showed a statistically significant level of matching (on the total sample) of the index of the upper part of the greater sciatic notch (male≤0.70 / female> 0.71) and morphognostic gender markings: appearance of aperture pelvic outlet, pelvic constitution, bone appearance and iliac fossa appearance.

The highest matching coefficient is with the following morphognostic gendrer characteristics: appearance of pelvic outlet b = 0.564, appearance of bones b = 0.564, pelvic constitution b = 0.552. Slightly weaker matching coefficient was with morphognostic appearance of iliac fossa b = 0.462.

Kendall's tau-b (Correlation Coefficient) did not show a statistically significant level of matching (on the total sample; p> 0.05; b <0.3) of the index of the upper part of the greater sciatic notch (male≤0.70 / female> 0.71) and morphognostic gender markings

Table 2. Correlations in the total sample of indices (I <0.70 / I> 0.70) and morphognostic gender

	Index of the upper part of the greater sciatic notch (categories)		
	Kendall's tau b Correlation Coefficient	**p**	**N**
Constitution of the pelvis	0,552	0,0005*	21/21
Appearance of the bones	0,564	0,0005*	21/21
Appearance of the iliac fossa	0,462	0,003*	42/42
Shape of the pelvic inlet	0,137	0,380	21/21
Shape of the pelvic cavity	0,462	0,003	21/21
Appearance of the sacrum	0,034	0,826	21/21
Promontorium expression	0,070	0,654	21/21
Appearance of the pelvic outlet	0,564	0,0005	21/21
Appearance of the pubic symphysis	0,005	0,972	21/21
Descriptive assessment of the distance between the pubic tubercles	0,034	0,826	21/21
Descriptive assessment of the distance between the ischial tuberosities	0,252	0,106	21/21
Appearance of the pubic arch	0,218	0,163	21/21
Shape and size of the obturator foramen	0,137	0,380	42/42
Appearance of the acetabulum	0,311	0,155	22/42
Description of the pelvic inclination	0,222	0,155	21/21

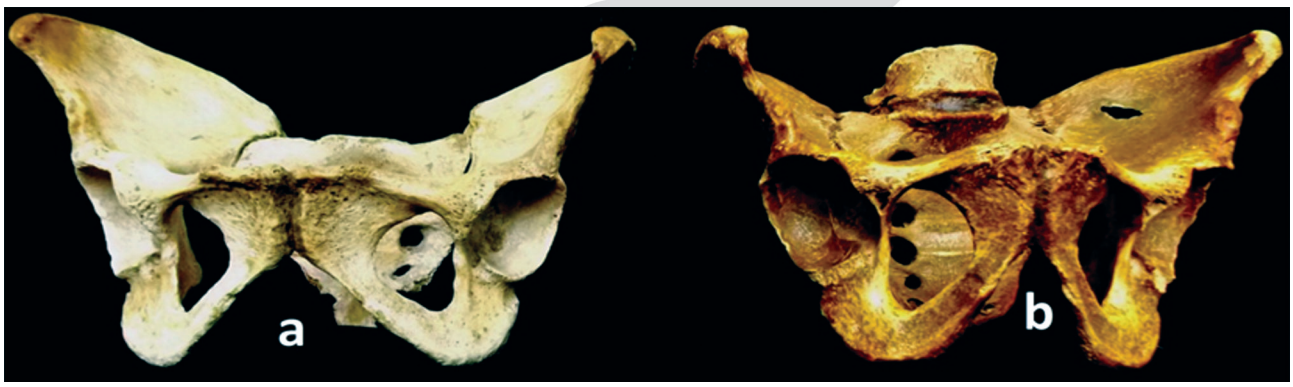

Figure 2. Pelvis (a-female and b-male, osteoscopically determined) - Osteological Collection of the Department of Human Anatomy, Medical Faculty University of Sarajevo

osteoscopically determined: shape of the pelvic inlet, appearance of pelvic cavity and sacrum axis, expression of promotorium, appearance of pubic symphysis, descriptive estimates of distance between pubic tubercles, descriptive estimates of distance between ischial tuberosity, appearance of pubic arch, obturator foramen and pubic inclination.

3.3. Percentage of morphological gender marks in gender determination based on the index of the upper part of the great sciatic notch

3.3.1. Percentage of morphological gender markers on individual hip bones, in gender determination based on the index of the upper part of the greater sciatic notch

Of the seven examined morphological characteristics of the hip bone (bone appearance, appearance of the iliac fossa, shape and size of the obturator foramen, appearance of the acetabulum, appearance of the auricular surface, appearance of the longitudinal-transverse ratio of the hip bone, and appearance of the greater sciatic notch), the most significant are shown in the tables 3,4 and 5.

Morphognostic gender marks of bone appearance (male / female) and the index of the upper part of the greater sciatic notch I <0.70, coincided in 89.7% of cases. A slightly weaker match, 57.5%, was with the index of the upper part of the greater sciatic notch with value higher of I> 0.71. This match is statistically significant and correlates with Kendall's tau-b = 0.508, p <0.0005.

Morphognostic gender markings of auricular surface appearance (male / female) and upper part of greater sciatic notch I <0.70, matched in 79% of cases. A slightly weaker, 68%, match was with greater sciatic notch index greater than I> 0, 71. This match is statistically significant and correlates with Kendall's tau-b = 0.473, p <0.0005.

Morphognostic gender markings of the hip bone appearance (male / female) and the index of

Table 3. Percentage of bone appearance in gender determination based on the index of the upper part of the greater sciatic notch - individual hip bone

			Bone appearance		Total
			Male	Female	
Index of the upper part of the greater sciatic notch	(I≤0 ,70) M	Count	52	6	58
		%	89,7%	10,3%	100,0%
	(I>0,71) Ž	Count	17	23	40
		%	42,5%	57,5%	100,0%

Table 4. Percentage of the appearance of auricular surface in gender determination based on the index of the upper part of the greater sciatic notch - individual hip bone

			Auricular surface appearance		Total
			Male	Female	
Index of the upper part of the greater sciatic notch	(I≤0 ,70) M	Count	27	7	34
		%	79,4%	20,6%	100,0%
	(I>0,70) Ž	Count	6	13	19
		%	31,6%	68,4%	100,0%

Table 5. Percentage of the appearance of the longitudinal-transverse ratio of the hip bones in gender determination based on the index of the upper part of the greater sciatic notch - individual hip bone

			Appearance of the longitudinal-transverse ratio of the hip bone		Total
			Male	Female	
Index of the upper part of the greater sciatic notch	(I≤0 ,70) M	Count	48	10	58
		%	82,8%	17,2%	100,0%
	(I>0,70) Ž	Count	17	23	40
		%	42,5%	57,5%	100,0%

the upper part of the greater sciatic notch I <0.70, coincided in 83% of cases. A slightly weaker match of 57.5% was with the index of the upper part of the greater sciatic notch higher than I> 0.71. This match is statistically significant and correlates with Kendall's tau-b = 0.419, p <0.0005.

3.3.2. Percentage of individual morphological gender marks on the pelvis, in gender determination based on the index of the upper part of the greater sciatic notch

Table 6. Percentage of certain qualitative characteristics of the pelvis in determining gender

	Appearance of the pelvic outlet	**Pelvis constitution**	**Bone appearance**	**Iliac fossa appearance**
Percentage of representation	80,1%	85,7%	80,1%	80,1%
Kendall's tau b Correlation Coefficient	0,564	0,552	0,564	0,462
N	21	21	21	21

Table 7. Percentage of individual qualitative characteristics of the pelvis in determining gender, for male and female separately, defined on the basis of the index of the upper part of the greater sciatic notch

Index of the upper part of the greater sciatic notch	**I<0,70**	**I>0,70**
Appearance of the pelvic outlet	100%	55,50%
Pelvis constitution	100%	66,70%
Bone appearance	100%	55,50%
Iliac fossa appearance	83,50%	77,80%
N	12	9

4. Discussion

In our sample on individual hip bones, of all seven assessed qualitative features, greater sciatic notch b = 0.640 proved to be the most significant in gender determination, followed by bone appearance b = 0.508. Somewhat less significant are gender markings of iliac fossa b = 0.419, appearance of auricular surface b = 0.473 and a descriptive assessment of the appearance of the hip bone longitudinal-transverse ratio b = 0.419. Gender was previously determined based on the index value of the upper part of the greater sciatic notch. These data were obtained using Kendall from the tau-b statistical correlation test which shows how important the individually observed features are in determining gender on the hip bone.

Regarding the percentage of individual qualitative features in determining gender, each of the seven observed traits is statistically significant and correlates with the Kendalls tau-b test. The highest degree of matching was recorded in greater sciatic notch and was 77.6% for males and 87.5% for females, and the corresponding Kendalls tau-b coefficient was b = 0.64 (gender determined based on the index of the upper part of greater sciatic notch).

A study conducted in Bordeaux on individual hip bones showed that osteoscopically, if the entire hip bone is preserved, gender can be determined with 98% accuracy, including all possible parameters that can be observed on one hip bone, which relate to gender dimorphism. In our study, a high percentage of correlation b = 0.508 was obtained for the appearance of the bone itself, so that both studies agree. The greater sciatic notch was also observed in this study and it was proven that when observed independently, with of course a slightly more detailed approach, gender can be differentiated with an accuracy level of 92% which also coincides with the high level of correlation we obtained b = 0.640 (17).

Fifteen qualitative features were assessed on the pelvis. After the Kendalls tau-b correlation test, the most statistically significant of all were: appearance of pelvic outlet b = 0.564, bone appearance b = 0.564, pelvis constitution b = 0.552 and slightly weaker appearance of iliac fossa b = 0.462. Other qualitative characteristics based on the Kendall's tau b correlation index do not show statistical coincidence with the index of the upper part of the greater sciatic notch on the pelvis. Note that the indices were mostly matched which means, that there were either only male or only female indices on one pelvis, except in three cases. These three cases mostly possessed limit values. The index characterized as male I <0.70 or as female I> 0.70 was obtained by calculating the average value on both sides of the pelvis.

Regarding the percentage of certain qualitative features in confirming gender in our sample, the most significant were as in Kendall with tau b coefficient: appearance of pelvic outlet where the

degree of matching was 100% in male and 55.5% in female pelvis (total 80.1%), pelvis constitution with a degree of matching in male pelvis 100% and in female pelvis 66.7% (total 85.7%), followed by bone appearance showing 100% matching in male pelvis and 55.5% in female pelvis (80.1% in total) and finally the appearance of the iliac fossa where the match for male pelvis is 83.5% and for female pelvis 77.8% (total 80.1%).

Researchers from the University of Sarajevo examined the characteristics of the pelvis in children and adults on radiographs, and came to slightly different conclusions compared to ours. The authors report that in male children, and thus in adults, the most characteristic qualitative feature is pubic arch, and as for females, in girls it is the curvature of the sacrum, and in adults the protrusion of the promontory (18).

According to our statistically processed data, these three parameters have no statistical significance (appearance of the sacrum b = 0.034, p = 0.826; appearance of the promontory b = 0.070, p = 0.654; pubic arch b = 0.137, p = 0.380). However, it should be emphasized once again that this is a different methodological approach. The mentioned research was performed on radiographs, unlike ours, which was conducted on osteological material. Furthermore, the mentioned research, besides adult participants, also included a group of children participants, which was not the case in our study, where we include only pelvis and individual hip bones of adults, of unknown gender and age. When it comes to gender determination in different age groups Rissech et al. found that the length of the ischium was the most reliable variable (19).

The osteoscopic data listed above in our sample lead to the conclusion that the percentage match of most qualitative features with the index of the upper part of the greater sciatic notch, both on individual hip bones and on the pelvis, is statistically significant and coincides with the Kendall's tau b correlation coefficient. In addition, a more detailed review of the tabelar data shows that in all parameters, except for greater sciatic notch in individual hip bones, it can be stated with a higher percentage of certainty that the same parameter belongs to the male, then can be confirmed to belong to the female.

In greater sciatic notch, this percentage is on the female side. This would essentially mean that in osteoscopic gender determination we prove with greater accuracy that some "male" characteristics belong to male bones than some "female" characteristics belong to female bones. In this context, papers should also be considered, which also refer to a number of transitional forms of coxae and pelvis in a wide range of gender dimorphism ranging between "purely" male and "purely" female sexual characteristics (20). Precisely this series of transitional shapes, performing osteometric and osteoscopic analyses, we noticed in our sample.

By analysing the tabelar data, we concluded in our study that all parameters had higher values in men, except for the values for greater sciatic notch, which are higher in females.

In our study by performing osteometric and osteoscopic analyses we noticed series of transitional shapes.

5. Conclusion

A statistically significant level of match between the index of the upper part of the greater sciatic notch on the basis of which the gender of the observed hip bone was determined and its morphognostic gender markings was found in: appearance of greater sciatic notch, appearance of bones and appearance of auricular surface

A statistically significant level of match between the index of the upper part of the greater sciatic notch on the basis of which the gender of the observed pelvis was determined and its morphognostic gender marks was found in: pelvic outlet appearance, bone appearance, pelvis constitution, and slightly weaker iliac fossa appearance.

We recommend a combination of osteometric and osteoscopic methods when determining gender given the large number of transitional forms that are difficult to classify into one or the other group.

A statistically significant difference, in the observed variables, between the left and right hip bones was not recorded during the study.

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References

1. *Sarač-Hadžihalilović A. Anatomically – anthropological significance of the skull. English edition (faculty textbook). Sarajevo: Medical faculty. 2017; 63-65.*

2. *Trotter M, Gleser GC. A re-evaluation of estimation of stature based on measurements of stature taken during life and of long bones after death. Am J Phys Anthropol. 1958; 16: 79–123.*

3. *Meindl RS, Lovejoy CO, Mensforth RP, Walker RA. A revised method of age determination using the os pubis, with a review and tests of accuracy of other current methods of pubic symphysis aging. Am J Phys Anthropol. 1985; 68: 29–45.*

4. *Brooks S, Suchey JM. Skeletal age determination based on the os pubis: a comparison of the Acsadi-Nemeskeri and Suchey-Brooks methods. Hum Evol. 1990; 5: 227–38.*

5. *Lovejoy CO, Meindl RS, Pryzbeck TR, Mensforth RP. Chronological metamorphosis of the auricular surface of the ilium: a new method for the determination of adult skeletal age at death. Am J Phys Anthropol. 1985; 68: 15–28.*

6. *Işcan MY. Osteometric analysis of sexual dimorphism in the sternal end of the rib. J Forensic Sci. 1985; 30: 1090–9.*

7. *Işcan MY, Loth SR, Wright RK. Metamorphosis at the sternal rib end: a new method to estimate age at death in white males. Am J Phys Anthropol. 1984; 65: 147–56.*

8. *Garvin HM. Adult sex determination: Methods and application. In: Dirkmaat DC, editor. A Companion to Forensic Anthropology. Malden, MA: Blackwell Publishing Ltd. 2012.*

9. *Osipov B, Harvati K, Nathena D, Spanakis K, Karantanas A, Kranioti EF. Sexual dimorphism of the bony labyrinth: A new age-independent method. American journal of physical Anthropology. 2013; 151: 290-301.*

10. *Phenice TW. A newly developed visual method of sexing the os pubis. Am J Phys Anthropol. 1969; 30: 297-301.*

11. *Iscan MY, Derrick K. Determination of sex from the sacroiliac joint: a visual assessment technique. Florida Sci. 1984; 47: 94-98.*

12. *Ferembach D, Schwidetzky I, Stloukal M. Recommendations for age and sex diagnoses of skeletons. J Hum Evol. 1980; 9: 517– 549.*

13. *Sutherland LD, Suchey JM. Use of the ventral arc in pubic sex determination. Journal of forensic sciences. 1991; 36: 501-511.*

14. *Ferembach D, Schwidetzky I, Stloukal M. Recommendations for age and sex diagnoses of skeletons. J Hum Evol. 1980; 9: 517– 549.*

15. *Holcomb, Susan, and Lyle W. Konigsberg. Statistical study of sexual dimorphism in the human fetal sciatic notch. Am J Phys Anthropol. 1995; 97(2): 113-125.*

16. *Jovanović S, Živanović S. Seksualne odlike velikog sjedalnog usjeka (incisura ischiadica major) kod čovjeka. Glas. Antropol. Druš. Jug. 1964; 1(1): 21-26.*

17. *Bruzek J. A method for visual determination of sex, using the human hip bone. Am J Phys Anthropol. 2002; 117(2): 157-168.*

18. *Bubić I, Šečerov D. Seksualni dimorfizam na rentgenogramima zdjelica kod djece i odraslih. Folia Anat Iugosl. 1982; 12(1): 55-63.*

19. *Rissech C, García M, Malgosa A. Sex and age diagnosis by ischium morphometric analysis. Forensic Sci Int. 2003; 135(3): 188-196.*

20. *Klonovski E. Određivanje spola. In E Klonovski editor. Uputstva za ekshumaciju i identifikaciju ljudskog skeleta. Sarajevo; Gik "Oko"; 1997; 21-26.*

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The effect of smoking and non-steroidal anti-inflammatory drugs on the stage of ulcerative colitis

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Abstract

Introduction: The aim of this study is to evaluate the influence of smoking and the use of nonsteroidal anti-inflammatory drugs on the stage of ulcerative colitis.

Methods: This is a cross-sectional study conducted in the period March-April 2013, which involved 99 outpatients of Gastroenterology Counseling Center, Clinical Center University of Sarajevo and the Association of Patients with Morbus Crohn and ulcerative colitis of B&H. Data was collected through a survey of outpatients and classification of ulcerative colitis is made according to Truelove and Witts. In the analysis a logistic regression model is used, by the procedure of binary logistic regression, backward method.

Results: Most of the respondents is the age between 15-39 years, 62 of them (62.6%). From the total of 99 patients 47 patients (47.5%) were smokers, and 35 (35.4%) were taking non-steroidal anti-inflammatory drugs. According to mentioned classification, 34 patients have a mild form of the disease, 20 moderately severe and 45 severe. There is a correlation between smoking and illness severity ($p<0.001$). Smoking and consumption of NSAIDs together increases the risk for more severe form of illness ($p\leq0.05$).

Conclusion: Smoking, the interaction of smoking and the use of nonsteroidal anti-inflammatory drugs, leads to an increased risk for manifestation of more severe forms of ulcerative colitis.

Key words: ulcerative colitis, smoking, nonsteroidal anti-inflammatory drugs.

Introduction

Ulcerative colitis (UC) as a concept, different from bacillary dysentery, was recognized in 1895. by Samuel Wilks at the Guy Hospital in London. Incidence of the UC is high in industrialized countries, and low in the third world countries, while it is stable since the fifties of the 20th century until today, maintaining a nearly ten-fold difference between areas with high and low incidence. In southern Europe epidemiological studies during the last years show no difference to northern Europe, which is probably a consequence of better recognition of the disease (1,2).

Study by Kappelman et al. (3) shows a prevalence of 241 and 263 per 100,000, and analysis data show that the prevalence of inflammatory bowel disease (IBD) slightly increases in recent years, while based on their studies, approximately 1,158,000 Americans have IBD (565,000 Crohn's disease and 593,000 UC). Most of the patients report to a doctor between the ages of 15-30 years, and the next wave are those 55-70 years old.

Although the exact causes and mechanisms of ulcerative colitis are not well understood, it is acceptable to be perceived as inadequate immune response of genetically prone person as result of a complex interaction of environmental, microbiological factors and immune intestinal system (2,4). This explains why the relative lack of microbiological pathogens early in life leads to reduced activity of the immune system, which later creates prolonged immune response with the inability to eliminate harmful agent (5).

Some studies indicate that smoking has a protective effect on the occurrence of ulcerative colitis,

while it is a risk factor for occurrence of Crohn's disease (6). It also shows that the risk for the occurrence of UC is in the 5 years' period after quitting smoking, but remains elevated for over 20 years and found that patients suffering from UC who smoke have an increased risk of events outside intestines (seronegative spondiloarthropaty and dermatological complications) compared to patient's non-smokers (7). The role of passive smoking in inflammatory bowel disease is still under evaluation. The researchers studied the systemic, cellular and humoral immune effects, changes in the mucous membrane, under the influence of smoking. To date, none of these studies does not adequately explain the observed changes (8).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the main group of medications that have been extensively investigated to a possible epidemiological or causal relationship with inflammatory bowel diseases. NSAIDs have been implicated not only in exacerbation of the disease, but also as a potential cause of new cases, likely acting through the blockade of protective prostaglandins, altering mucosal immune reactivity and increasing intestinal permeability (9).

Takeuchi et al. by clinical evaluation and the measurement of calprotectin in faeces demonstrated that non-selective NSAIDs are associated with a 17-28% relapse during nine days after ingestion of the drug in these patients (10), and Kvasnovsky et al. found that treatment with NSAIDs leads to relapse (11). Also, the study by Klein et Eliakim found that the use of NSAIDs leads to new cases of inflammatory bowel disease that is associated with increased disease activity index (12).

The central hypothesis of this study is that nonsteroidal anti-inflammatory drugs and smoking affect the stage of ulcerative colitis.

Methods

This is a cross-sectional study which involved respondents from Gastroenterology counseling center of the Clinical Center of University of Sarajevo (CCUS) and the Association of Patients with Morbus Chron and ulcerative colitis of B&H in the period from March to April 2013. The study involved 99 outpatients diagnosed with ulcerative colitis who have given their informed consent.

Inclusion criteria were patients' age from 15-89 years, both sexes, diagnosed with ulcerative colitis, and the criteria for exclusion were inadequate age, Crohn's disease, intermediate syndrome, primary sclerosing cholangitis, amoebiasis, infectious diseases with a similar clinical picture, or specific pathogens - salmonella, shigella, campylobacter jejuni and clostridium difficile, eosinophilic gastroenteritis, opportunistic infections, colitis caused by antibiotics, ischemic, radiation colitis, chemical laxative colitis.

Data were collected through a survey of outpatients, where was investigated mentioned parameters and their impact on the severity of the disease, and referred to the period before diagnosis.

The diagnosis of ulcerative colitis is confirmed on the basis of medical history, physical findings, colonoscopy and/or verified histological findings. In particular, recorded are the number of stools, rectal bleeding, fever, pulse rate, hemoglobin, erythrocyte sedimentation rate, due to the appropriate classification of diseases. Active disease was classified by severity as the mild, moderate and severe, relying on an index of disease activity according to Truelove and Witts (13). When classifying our respondents, we took the degree of disease which dominates in our patients.

Statistical analysis

Logistic regression model was created in *PASW statistics package version 18*. During this is selected procedure of binary logistic regression, backward method. Independent variables were smoking and the use of NSAIDs, and the dependent variable was describing the stage of disease activity according to above listed criteria according to Truelove and Witts.

Results

Of the total number of patients included in this study, 48 of them (48.4%) were men and 51 (51.6%) women. From the total of men, 25 (52.1%) falls into the age category of 15-39 years, 19 (39.6%) in the category of 40-64 years and 4 (8.3%) in the category of 65- 89 years. From the total of women, 37 (72.5%) of them are at the age of 15-39 years, 14 (27.5%) falls into the category of 40-64 years,

while there are no women in the age group from 65 to 89 years (Table 1.). The youngest patient was 17 and the oldest 81 years, while the largest number of respondents was 25 years old.

Table 1. Age and gender distribution of patients

Age	Women		Men		Total
	n	%	n	%	n
15-39	37	72,5	25	52,1	62
40-64	14	27,5	19	39,6	33
65-89	-	-	4	8,3	4
Total	51	100	48	100	99

Looking at the period from the first symptoms appearance until the moment of diagnosis of ulcerative colitis, in 70 (70.7%) of patients passed the period of 0-12 months (one year), in 12 (12.1%) passed the period of 13-24 months, and in 17 (17.2%) a period of 25 months or more (2 or more years).

Most of the patients, 89 of them (89,9%) does not have family history of the disease, while 10 (10,1%) have a family history, 6 of them (60%) have first degree relative, 2 (20%) patients second degree relative's kinship, and 2 (20%) the third generation of kinship.

Of the 99 patients included in the study, 47 (47.5%) were smokers and 52 (52.5%) patients were non-smokers. It is shown how many pack-years of cigarettes patients consume (a pack-year is defined as twenty cigarettes smoked everyday for one year) in the course of their life until the moment of diagnosis (Table 2.). Most of the patients, 17 of them (36.2%) consumed the least number of cigarettes or up to 5,5 pack-years, while 3 (6.4%) patients consumed the largest number of packages or over 27,5 pack-years which is over 200,000 cigarettes smoked in their lifetime. As seen the mean is 12,9 pack-years with a range from 0,1-60,2 (as calculated by the number of cigarettes amounts to 438,000).

Table 2. Number of pack-years of cigarettes

Number of pack-years of cigarettes	Patients	
	N	%
0-5,5	17	36.2
5,6-11,0	7	14.9
11,1-16,5	9	19.1
16,6-22,0	4	8.5
22,1-27,5	7	14.9
>27,5	3	6.4
Total	47	100.0

Nonsteroidal anti-inflammatory drugs were taking 35 patients (35.4%) and those who did not take were 64 (64.7%) before diagnosis. Of the total number of patients included in the study, 34 (34.3%) have a mild form of ulcerative colitis, 20 (20.2%) patients have moderately, while 45 (45.5%) have a severe form, by classifying disease according Truelove and Witts.

Applying backward (Wald) methods in PASW 18 software, we ultimately obtained regression model that is presented (Table 3.), * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ (original coefficient values are rounded to two decimal places).

Table 3. Characteristics of the regression model

	B (SE)	Odds ratio
Constant	-1.83 (0.97)	
Use of pain medication	1.28 (0.74)	3.60
Smoking***	2.01 (0.90)	7.47
Pain medications x Smoking*	-2.11 (1.09)	0.12

Discussion

For the majority of patients (70.0%) passed the period up to one year from onset of symptoms to diagnosis, whereas a period of one to two years passed the minimum number of patients (12.1%). Most respondents said that two months passed, with half of the respondents passed less than 6 months to diagnosis, with a range of 0-60 months.

Majority of patients in the survey stated there was no illness among family members, or, to have a negative family history. In a very small number of them exist a positive family history, where the largest representation of sick among family members is among the first line of consanguinity.

Of the total number of patients, the majority of them said that they smoked before diagnosis. Among patients who consumed tobacco (47.5%), the analysis of data revealed result of the total quantity of cigarettes consumed expressed in the number of pack-years. According to these figures, the highest number of smokers consumed up to 5,5 pack-years, while the lowest number of smokers consumed more than 27,5 pack-years until the diagnosis. Approximately 2/3 of the patients included in the study did not take non-steroidal anti-inflammatory drugs, while one-third of patients, in turn took and was probably insufficiently informed of the potential risk. Of the patients taking

the drugs listed, 34.2% were male, while according to this study, more females used these drugs.

As part of this study, we examined the extent of disease by the index of disease activity according to Truelove and Witts, and obtained the information that the largest number, or about half of patients, have severe form of the disease, a mild form has about one third of patients, while the smallest number has a moderate one. With a mild form of the disease was about two-thirds of female patients. Based on the fact that $\chi 2=24.4$, it can be concluded that the resulting model allows significantly more precise classification concerning the severity of the disease, in relation to the categorization that would be carried out so that we all respondents classified in the category that is most frequent according to empirical aspect.

Whether in the period before diagnosis was used non-steroidal anti-inflammatory drugs, or not in our patients, generally does not significantly affect whether a patient will be diagnosed with milder or more severe form of the disease. However, it has been shown that smoking significantly influences the severity of the disease. The chance to develop a more severe form of the disease is higher in smokers than in nonsmokers, provided that the other characteristics are expressed through the predictors are the same.

It is shown that the effect of NSAIDs on severity of the disease in our patients, significantly depends on whether or not the patient is smoking, although according to Ananthakrishnan (14) use of non-steroidal anti-inflammatory drugs increases the risk of ulcerative colitis with the mechanisms that are not well defined. According to our research, the majority of patients is in the age group of 15-39 years. Study by Martínez and associates also have similar results stating that the majority of their patients are in the younger age group (15).

Are they in the period before diagnosis used NSAIDs or not, generally does not significantly affect whether a patient will be diagnosed as mild or severe form of the disease, unless the use of NSAIDs is in combination with smoking in our study. The results which are similar to ours but using only NSAIDs can be found in study by Kvasnovsky et al. showed that treatment with conventional NSAIDs leads to more frequent relapse of patients with quiescent inflammatory bowel disease (11). Also Klein and Eliakim show that the use of non-steroidal anti-inflammatory drugs results in new cases of inflammatory bowel disease and is associated with increased disease activity index (12). A possible explanation for the difference between the results can be fewer respondents of our survey, which included 99 patients, of whom 35.4% used non-steroidal anti-inflammatory drugs. Opposed to mainly accepted belief, study Moninuola et al. did not find a consistent association between NSAIDs use and risk of Crohn's disease and ulcerative colitis exacerbation (16).

It has been shown that smoking among our respondents significantly influences the severity of illness, and it is stated that the opportunity to develop a more severe form of the disease is greater in smokers than in nonsmokers. In contrast to these results the cited study showing more benign form of the disease in smokers than in nonsmokers, with fewer hospitalizations, less number relapses and even smaller spread of the disease in the proximal parts of the intestine, but these observations have not been confirmed in other studies (6). According to Gearry et al. cigarette smoking at the time of diagnosis was also significantly associated with an increased incidence of ulcerative colitis (17). Also studies found that patients suffering from UC who smoke have an increased risk of events outside intestines (seronegative spondyloarthropathies and dermatological complications), which is also an indicator of severe symptoms and forms of the disease compared to non-smokers patients (7,18), which corresponds with the results our study.

Majority of patients with inflammatory bowel disease are unaware of the smoking risks associated with their disease, and the intent to quit smoking is strongly related to awareness. Better information through a therapeutic education programme and management of smoking cessation should be systematically undertaken in all smokers. (19,20)

In this study was observed the interaction of respondents who smoke and consume NSAIDs, and results suggests that the risk for the more severe form of the disease is greater in these patients. Other studies that integrate and compare these two environmental factors and examined their interaction and the degree of disease were unavailable to us.

Limitations of this study are relatively small sample of patients, as well as their follow-up period.

Conclusion

In conclusion, non-steroidal anti-inflammatory drugs does not affect the severity of ulcerative colitis, but in interaction with smoking increases the risk for more severeulcerative colitis. Smoking increases the risk for manifestation of severe forms of ulcerative colitis.

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References

1. *De Castro MM, Bitencourt Pascoal L, Steigleder KM, Piatezzi Siqueira B, Pires Corona L, de Lourdes Setsuko Ayrizono M et al. Role of diet and nutrition in inflammatory bowel disease. World J Exp Med 2021; 11: 1-16.*

2. *Rodrigues BL, Mazzaro MC, Kibune Nagasako C, de Lourdes Setsuko Ayrizono M, Fagundes JJ, Franco Leal R. Assessment of disease activity in inflammatory bowel diseases: Non-invasive biomarkers and endoscopic scores. World J Gastrointest Endosc 2020; 12: 504-20.*

3. *Kappelman MD, Moore KR, Allen JK, Cook SF. Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population; Dig Dis Sci. 2013; 58: 519-25.*

4. *Danese S, Fiocchi C. Etiopathogenesis of inflammatory bowel diseases. World J Gastroenterology 2006; 12: 4807-12.*

5. *Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med 2002; 347: 911-20.*

6. *Rosenfeld G, Bressler B. The truth about cigarette smoking and the risk of inflammatory bowel disease. Am J Gastroenterol 2012; 107(9): 1407-8.*

7. *Bastida G, Beltrán B. Ulcerative colitis in smokers, non-smokers and ex-smokers. World J Gastroenterol 2011; 17: 2740-7.*

8. *Apostolopoulos P. Environmental Factors in IBD. Annals of Gastroenterology 2006; 19: 152-4*

9. *Cipolla G, Crema F, Sacco S, Moro E, de Ponti F, Frigo G. Nonsteroidal antiinflammatory drugs and inflammatory bowel disease: current perspectives. Pharmacol Res 2002; 46: 1-6.*

10. *Takeuchi K, Smale S, Premchand P, Maiden L, Sherwood R, Thjodleifsson B et al. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2006; 4: 196-202.*

11. *Kvasnovsky CL, Aujla U, Bjarnason I. Nonsteroidal anti-inflammatory drugs and exacerbations of inflammatory bowel disease. Scand J Gastroenterol 2015; 50: 255-63.*

12. *Klein A, Eliakim R. Non steroidal anti-inflammatory drugs and inlammatory bowel diseases. Pharmaceuticals 2010; 3: 1084-92.*

13. *Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1955; 2(4947): 1041–48.*

14. *Ananthakrishnan AN. Environmental triggers for inflammatory bowel disease. Curr Gastroenterol Rep 2013; 15: 302.*

15. *Antón Martínez J, Ortega Gómez A, Arranz Carrero A, Molina Sánchez A, Alvarez García JF, Moreiras Jiménez JL, et al. Incidence of inflammatory bowel disease in the health area of Navalmoral de la Mata (Caceres, Spain) between 2000 and 2009. Gastroenterol Hepatol 2010; 33: 694-9.*

16. *Moninuola WM, Lochhead P, Khalili H. Systematic review with meta-analysis: association between acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) and risk of Crohn's disease and ulcerative colitis exacerbation. Aliment Pharmacol Ther 2018; 47: 1428-39.*

17. *Gearry RB, Richardson AK, Frampton CM, Dodgshun AJ, Barclay ML. Population-based cases control study of inflammatory bowel disease risk factors. J Gastroenterol Hepatol 2010; 25: 325-33.*

18. *Severs M, van Erp SJH, van der Valk ME, Mangen MJJ, Fidder HH, van der Have M, et al. Smoking is Associated With Extra-intestinal Manifestations in Inflammatory Bowel Disease. J Crohns Colitis 2016; 10: 455-61.*

19. *Ducharme-Bénard S, Côté-Daigneault J, Lemoyne M, Orlicka K, Lahaie R, Weber A, et al. Patients*

With Inflammatory Bowel Disease Are Unaware of the Impact of Smoking on Their Disease. J Clin Gastroenterol 2016; 50: 490-7.

20. *Saadoune N, Peyrin-Biroulet L, Baumann C, Bigard MA, WirthN, YvesM, et al. Beliefs and behaviour about smoking among inflammatory bowel disease patients. Comparative Study Eur J Gastroenterol Hepatol 2015; 27: 797-803.*

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Urinary tract infection in preterm and term newborn- epidemiology and risk factor

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Abstract

Introduction: Urinary tract infection in neonate is the first manifestation of more serious pathological conditions of the urinary system.

The aim of our study was to determine the frequency of urinary tract infections in preterm and term newborn, with the commonly isolated microorganisms, and the relationship with risk factors such as less gestation weeks, additional diseases, anomalies of the urinary system, prolonged stay on the intensive care and urinary tract infection of the mother during pregnancy.

Materials and methods: Our retrospective study included 250 newborns, 28 of them, had urinary tract infection. We divided neonates into two groups based on gestational age, the first group were preterm neonates, born from 28 GW to 36, the second group term newborn, born of ≥37GW, while both groups were further divided into two subgroups: Subgroup Ia were preterm neonates with urinary tract infection, Ib subgroup were preterm without. Subgroup IIa were term neonates with urinary tract infection and IIb term neonates without.

Results: The most common isolated microorganisms from urine culture of neonates were Escherichia coli, Staphylococcus coagulasa negative, Enterococcus faecalis, Pseudomonas aeruginosa, Candida species. We found a statistically significant difference in preterm infants compared to term according to: gestational age and birth weight, perinatal asphyxia and urinary tract infection in the mother (during pregnancy), in weight loss > 10%, hypodynamics.

Conclusion: Urinary tract infection in neonate is important cause of morbidity, the possible formation of kidney scars as long-term complications, and the development of hypertension and impaired renal function later in life.

Key words: neonate, urinary tract infection, urine culture, risk factors

Introduction

Urinary tract infection (UTI) in the neonatal period can be the first manifestation of more serious pathological conditions of the urinary system, that cann be congenital anomalies or various acquired diseases. Timely diagnosis of UTI and initiation of antibiotic therapy can prevent the damage of the kidney function, avoid the scars on kidney tissue, which can later lead to hypertension, proteinuria and kidney failure. However, increased antibiotic resistance may delay the the effect of the antibiotic therapy (1,2).

UTI in the early neonatal period (in the first 48 to 72 hours) is extremely rare, in developed European countries and the United States it ranges up to 1%, and in developing countries up to 2%. The most common manifestations of ITU are manifested in the period after 72 hours from birth (3). Etiologically, the most common isolated bacteria from urine culture in neonates is Escherichia coli. However, Escherichia coli as an isolated causative agent is more common in older children, while in newborns with congenital anomalies mostly gram-negative bacteria are Klebsiella pneumoniae et oxytoca, Proteus mirabilis, Enterobacter aerogenes, Pseudomonas aeruginosa and Morganella morgagnii (4,5). UTI caused by gram-positive bacteria, such as Enterococcus faecalis, Staphylococcus aureus, Sterptococcus group B, Streptococcus pneumoniae in neonates are less common (6). Coagulase-negative staphylococci can be isolated in premature infants, while in extremely immature infants Candida species is very often isolated from urine (7). Males are about 80% more likely to have UTI in the neonatal period than females, especially if they are premature.

The frequency of UTI is associated with the various risk factors, such as other bacterial and viral infection, wider use of antibiotics, mechanical ventilation, parenteral nutrition, the insertion of central

venous catheters, urinary catheters, longer stay in Intensive care unit and the anomalies of the urinary system (3,4,6). UTI in the mother during pregnancy is also associated with a higher risk of having a UTI in the newborn as well. The incidence of UTI in neonates born after premature rupture of fetal membranes is increased, due to the ascending transmission of uropathogenic bacteria (5,6).

In preterm and term infants, UTI may be asymptomatic and may present with nonspecific symptoms, such as a fever (≥38 ° C), refusal to feed, vomiting, diarrhea, and lethargy. Although more than 50% of preterm infants with UTI may also have respiratory symptoms, such as apnea, hypoxia, or tachypnea. Elevated temperature, higher than 39C, is more common in newborns with severe bacterial UTI than virus-induced infection (8). Neonatal UTI is often associated with jaundice, while in premature infants it is often associated with bacteremia and meningitis (7,8). UTI in neonatal period is very important while clinical presentation of UTI in neonates is often nonspecific, catheter urine sampling as a "more aggressive" method can be delayed, the diagnosis and timely treatment may be delayed, so that the children may have long term complication later in life (5,6,7).

The aim of our study was to determine the frequency of urinary tract infections in premature and term infants, with the most commonly isolated microorganisms, and the relationship of neonatal urinary tract infections with various risk factors such as less gestation weeks, additional diseases, anomalies of the urinary system, prolonged stay in intensive care and urinary tract infection of the mother during pregnancy.

Methods and subjects

We conducted the retrospective study at the Clinic for Children's Diseases, University Clinical Centre Tuzla, in the period from 01.01. 2020 to 01.01. 2021, which included 250 prematurely and term newborns hospitalised in ICU, 28 of them had UTI. All data were obtained from the medical records of newborns, hospitalized in the Intensive Care Unit, and then monitored on an outpatient basis. We divided neonates into two groups based on gestational age, the first group were preterm neonates, born from 28 GW to 36, and the second group was newborn of ≥37GW, while both groups of newborns were further divided into two subgroups in relation to UTI diagnosis: Subgroup Ia were preterm newborns with UTI, Ib subgroup were preterm newborns without UTI. Subgroup IIa were term neonates with UTI and IIb term neonates without UTI.

For the diagnosis of UTI in newborns the laboratory values of leukocytes, erythrocyte sedimentation rate and CRP (C Reactive Protein) values are not crucial (1,5). The most important for the diagnosis of UTI is the isolated pathogen from the urine culture. Urine sampling can collect in three ways: by urinary catheterization, suprapubic aspiration, and urine collection with a sterile bag. The greatest possibility is the contamination of urine culture by taking urine with a sterile bag. Definitions vary, although most urinary culture-positive authors declare an increase in identified urine bacteria of 100,000 CFU / ml in a bag sample, ≥ 10,000 CFU / ml in a catheter for a urine sample, while any presence of bacteria in urine in a suprapubic aspiration sample is also UTI.

From hospitalized newborns a urine sample was taken with a bag of newborns who had clinical symptoms: fever (> 38C), weight loss greater than 10% per day, refusal to feed, hypodynamics, irritability, jaundice (5). The urin was taken from sterile bag specimen collection of the genitals after antiseptic procedures. If the child did not urinate for a period of 30 minutes, the procedure was repeated. Urine samples were processed at the Department of Biochemistry, Polyclinic for Laboratory Diagnostics, University Clinical Centre Tuzla. For confirmation of UTI after pathological laboratory urine findings, a urine sample for urine culture was taken with a catheter. Urine cultures were processed at the Department of Microbiology, Polyclinic for Laboratory Diagnostics, University Clinical Centre Tuzla. Urine cultures were stored on MacConkey, Thayer-Martin and blood agar plates, at 35 to 37C, and readings were made 24 to 48 hours after seeding. If the result was positive, the antibiogram of the grown bacterium was determined. In the absence of growth of microorganisms in the culture, the urine culture was treated as negative.

We did not perform suprapubic urine aspirations during this study.

The risk factors were considered such as gestation week of the child at birth, sex, birth weight, perinatal asphyxia, longer stay in intensive care, and the presence of abnormalities of the urinary system, mothers UTI during pregnancy (4,5,6).

The statistical program SPSS, Windows is used to process the results. All data were analyzed by chi-square, Fischer exact test, Student's t test, with the significance as $p < 0.05$.

Results

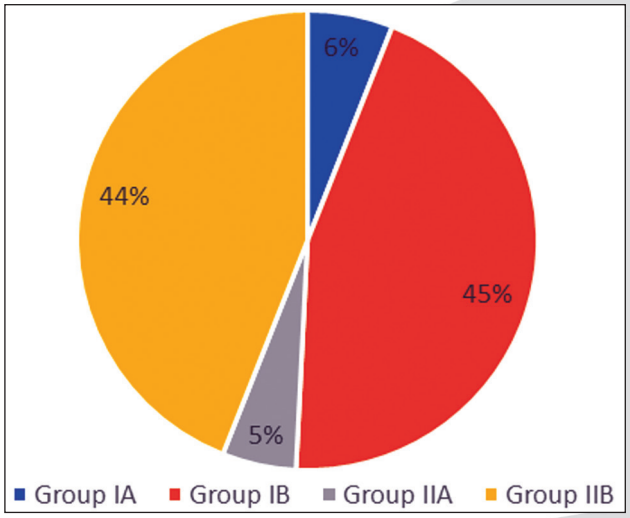

Figure 1. Clinical date of preterm and term neonates

Subgroup Ia had 15 (6%) preterm neonates with UTI, Ib subgroup were 112 (45%) preterm newborns without UTI. Subgroup IIa were 13 (5%) term neonates with UTI and IIb 110 (45%) term neonates without UTI.

The most common microorganisms isolated from the urine cultures of preterm and term infants with UTI are shown in Figure 2.

The Figure 2. presented the most common microorganisms isolated from urine cultures of preterm and term infants: Escherichia coli (30,9%), Staphylococcus coagulasa negative (15%), Enterococcus faecalis (23%), Klebsiella pneumoniae (15,3%), Pseudomonas aeruginosa (5,8%), Candida species (10%).

UTI had 28 neonates, 20 newborns (71,4%) were male, while 8 (28,6%) were female, with a ratio of 10 males: 5 females in the group born prematurely compared to 10: 3 in the group of term infants.

There was without significantly difference between male and female in our groups. We found a statistically significant difference in preterm infants compared to term according to gestational age and birth weight ($p = 0,05$; $p = 0,004$). A statistically significant difference was found in relation to perinatal asphyxia and UTI in the mother (during pregnancy) in the prematurely born ($p = 0,01$; $p = 0,03$) in relation to term neonate.

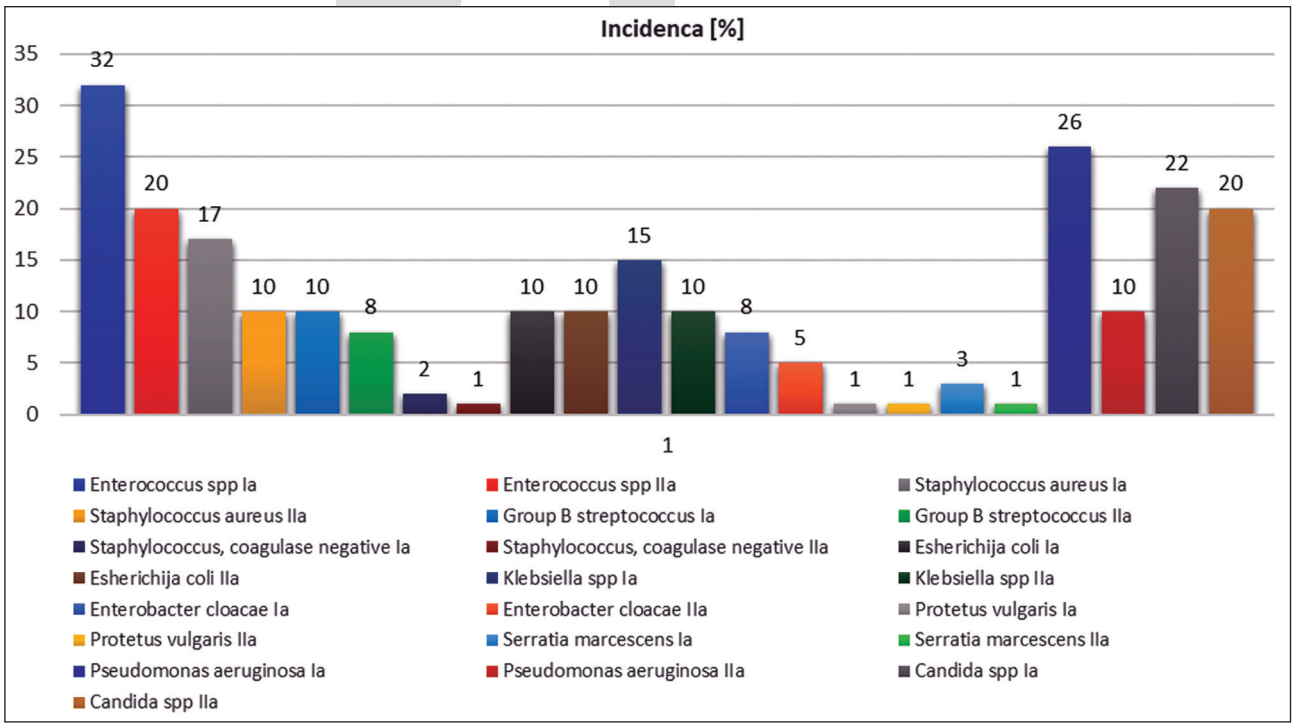

Figure 2. The most common microorganisms isolated from urine cultures of preterm and term infants

Table 1. Newborn demographics date

Characteristics	Group Ia (N=15; 6%)	Group Ib (N=112; 45%)	Group IIA (N=13; 5%)	Group IIB (N=110; 44 %)	p
Gender (Male: Female)	(10: 5)**	(72: 40)	(10: 3)**	(60: 50)	0,20** 0,28
Gestation week (GW)	29±8,7*	32±2,3	37±3,6*	38±2,6	0,05* 0,32
Birth weight (g)	980±19,9*	1320±123,2	2900±235,1*	3450±109,1	0,004 * 0,53
Perinatal asphyxia (5min<6)	15**	8	3**	1	0,01** 0,32
Mothers UTI (during pregnancy)	12**	4	2**	2	0,03** 0,72

Table 2. The most common clinical manifestations in newborns associated with UTI

Characteristics	Group Ia (N=15; 6%)	Group Ib (N=112; 45%)	Group IIA (N=13; 5%)	Group IIB (N=110; 44%)	P
Fever >38C	4 (26,6%)*	2 (1,8%)	3 (23%)*	1 (1,1%)	0,24 0,14
Weightloss >10%	14 (93%)*	9 (8%)	6 (46%)*	2 (2,2%)	0,05 0,13
Refusal to feed	13 (86,6)*	6 (5,3%)	10 (77%)*	3 (3,3%)	0,60 0,47
Hypodinamism	12 (80%)*	10 (8,9%)	4 (31%)*	3 (3,3%)	0,05 0,21
Irritability	13 (86,6%)*	10 (8,9%)	13 (100%)*	3 (3,3%)	0,65 0,21
Jaundice	15 (100)*	12 (10,7%)	13 (100)*	3 (3,3%)	0,19 0,20

Table 3. The common congenital anomalies in newborns associated with UTI

Characteristics	Group Ia (N=15; 6%)	Group Ib (N=112; 45%)	Group IIA (N=13; 5%)	Group IIB (N=110; 44%)	p
Difficult differentiation from the surrounding tissue, and the parenchyma and the duct system	15 (100%)*	14 (1,8%)	3 (23%)*	1 (1,1%)	0,44* 0,22
Dilated pyelon in AP diameter	13 (86,6%)*	9 (8%)	6 (46%)*	2 (2,%)	0,11* 0,13
Enlarged/smaller kidney	7 (46,6%)*	6 (5,3%)	10 (76,9%)*	3 (2,72%)	0,80* 0,47
Ectopio seu agenesio	2 (13,3%)*	1 (1,1%)	4 (30%)*	3 (2,72%)	0,15* 0,18
Enlarged ureter	3 (20%)*	3 (2,6%)	3 (23)*	3 (2,72%)	0,54* 0,13

No statistically significant difference was found in relation to fever, refusal to feed, jaundice of the skin and irritability between preterm and term infants with UTI. A statistically significant difference was found in weight loss > 10%, hypodynamics in the group of preterm neonates with UTI compared to the group of term (p = 0,05; p = 0,05).

No statistically significant difference was found in relation to congenital anomalies between preterm and term infants with UTI.

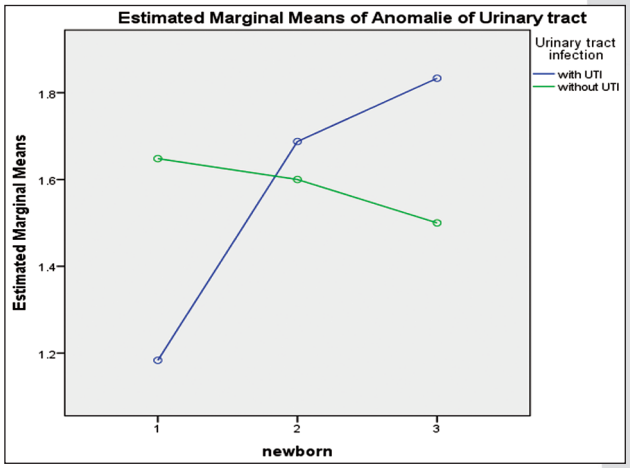

Figure 3. Correlation of UTI with associated risk factors

The two-factor analysis of the variance of different groups of newborns with UTI investigated the influence of age, gestation weeks of birth and the anomalies of the urinary tract to diagnose UTI. Newborns diagnosed with UTI were divided into three groups, in the first group were neonates born from 28 to 33 GN, in the second group neonates born from 34 to 36 GN, and the third group were neonates born ≥37 GN. The influence of the interaction between the earlier birth, less gestation weeks and diagnosed UTI in neonates was statistically significant F (2,549) = 1.44, p = 0.02. A statistically significant effect of the existence of renal and urinary bladder anomalies on UTI was found in preterm infants F (2,549) = 1.98, p = 0.01.

Discussion

Urinary tract infection in newborns has no specific clinical manifestations, it is diagnosed and confirmed by pathological urine findings, with the identification of the microorganism in the urine. Several different algorithms and procedures have been published, emphasizing the importance of accurate diagnosis, appropriate treatment, and a mandatory screening program after the first proven UTI (1,5,8).

In our study, 6% of preterm infants had a UTI, while 5% of term. The incidence of symptomatic UTI ranges from 1 to 3% for older children, while slightly higher in neonates about 5% (2,3,9). According to Shaikhs research, the highest incidence of UTI is in the first 4 months of life, especially in the first month of life, and then slowly decreases during the first year of life (4). The increase in the incidence of UTI in the earliest age has recently been attributed to better knowledge of the pathogenesis and earlier diagnosis of the disease (9).

The most common isolated microorganisms from urine cultures of our preterm and term infants were Escherichia coli (30,9%), Staphylococcus coagulasa negative (15%), Enterococcus faecalis (23%), Klebsiella pneumoniae (15,3%), Pseudomonas aeruginosa (5,8%), Candida species (10%). This diversity of microorganisms, the causative agents of UTI, can be explained by the widespread use of antibiotics in the treatment of unspecified infections in the neonatal period, which affects the natural flora and destroys opportunistic microorganisms. This is supported by the presence of Candida species with 10% in our respondents. Shaikh had similar results (2), as Riskin did (4). The natural defense of the urinary system includes an antibacterial barrier consisting of urine and mucous membranes of the urinary tract, an antiadherent mechanism, the mechanical effect of urinary lavage, the presentation of phagocytic cells and other immune mechanisms (5,10). In the neonatal period, these natural mechanisms may be absent, and newborns are therefore more prone to UTI (11).

Of the 250 hospitalised infants 28 (11,2%) had UTI, 71,4% were male, while 28,6% female, with a ratio of 10 males: 5 females in the group born prematurely compared to 10: 3 in the group of term infants. In both groups of our neonates with UTI we did not have significantly difference between the gender. Zorc et al. had similar results (6), while American authors, still had more represented boys with UTI than girls, as much as 4 to 20 times more uncircumcised boys (12). Although circumcision, according to research, may be a predisposing factor for the development of UTI

(5,10,11). The relatively small number and small difference among our respondents explains the non-existence of a statistical difference between the sexes in newborns with ITU.

Gestational age and birth weight of neonates were statistically significantly different in preterm infants compared to term infants (p = 0,05; p = 0,004). The more immature the newborn is, has the less developed the urinary system, and is more receptive for UTI. Also, small and earlier birth weight is one of the already known so-called classic risk factors for UTI (5). Also known risk factors for the development of UTI are reduced oxygenation and blood flow through the kidneys that occurs during perinatal asphyxia, but also ascending transmission of bacteria from mother to newborn, if the mother had UTI during pregnancy (8,9,10).

In our study we found a statistically significant difference in relation to perinatal asphyxia and UTI in the mother, during pregnancy in premature infants (p = 0.01; p = 0.03), similar to the Samayam et al (7).

During our study, 40 preterm and 15 term infants with UTI had nonspecific symptoms. The most common were fever (≥38 ° C), refusal to feed, vomiting, diarrhea and lethargy. All preterm infants with UTI had some of the respiratory disorders such as apnea, hypoxia, or tachypnea. Premature neonates were more likely to have UTI associated with sepsis (7). Prematurely born male children have a higher risk of developing sepsis and UTI (5,7). In our subjects, no statistically significant difference was found in relation to fever, refusal to feed, jaundice and irritability between preterm and term infants with UTI. A statistically significant difference was found in weight loss> 10%, hypodynamics in the group of preterm with UTI compared to term neonate. According to other study (12,2,4) the clinical manifestations of UTI are similar in preterm and term infants. All invasive procedures, even in antiseptic conditions, can be the cause of bacterial contamination, especially in the neonatal period (5,11,12). Intravascular catheterization, intubation, insertion of a urinary catheter are procedures that are associated with a higher risk of developing UTI. UTI is more common in preterm and term infants, who were on mechanical ventilation, along with parenteral nutrition. Prolonged stay in intensive care, combined with premature birth, perinatal asphyxia, mechanical ventilation and inadequate nutrition are in direct correlation with UTI in both premature and term neonate (10,12).

Congenital malformations of the kidneys and urinary system, especially obstructive anomalies, are more often associated with UTI (9,10). The influence of the interaction between the earlier birth, congenital anomalie and diagnosed UTI was statistically significant in preterm infants.

Kidney scarring is especially prevalent in the neonatal period, up to the second year of life, after acute pyelonephritis, inadequately treated and children with vesicoureteral reflux and obstructive anomalies (10,11)). It is important to diagnose in time and start early antibiotic therapy of the first UTI, but also repeated, in order to prevent permanent kidney damage.

As there is still no common consensus among the published procedures and algorithms for imaging of newborns and older children after the first UTI, it is recommended to do an ultrasound examination of the kidneys and bladder first. Based on the ultrasound findings, other imaging diagnostic procedures, such as MCUG, DMSA renal scintigraphy and MR urography, should be further decided, but also postponed until the first recurrence of UTI with fever. Ultrasound cystography is the latest method for diagnosing VUR. Its biggest advantage for children is that it does not use ionizing radiation! Cortical scintigraphy as an unavoidable test in the diagnosis of renal tissue scars and dynamic scintigraphy are recommended for the functional assessment of drainage disorders of obstructive anomalies (1,5).

Conclusion

The infants with risk factors have a higher frequency of UTI in the neonatal period. UTI in neonate is an important cause of morbidity, the possible formation of kidney scars as long-term complications, hypertension and impaired renal function. The most common symptoms are nonspecific and there is difficulty in taking urine samples, so there are the reasons for the late diagnosis of UTI at the earliest age. Proven and properly treated UTI prevents the recurrence of infection, further scarring and the development of complications later in life.

Reference

1. *Clinical practice guideline. Urinary Tract Infection: Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months. Pediatrics. 2011; 128(3): 595-610.*

2. *Ismaili K, Lolin K, Damry N, et al. Febrile urinary tract infections in 0- to 3-month-old infants: a prospective follow-up study. J Pediatr. 2011; 158: 91–4.*

3. *Shaikh N, Morone NE, Bost JE, et al. Prevalence of urinary tract infection in childhood: a meta-analysis. Pediatr Infect Dis J. 2008; 27: 302–8.*

4. *Riskin A, Toropine A, Bader D, et al. Is it justified to include urine cultures in early (<72 hours) neonatal sepsis evaluations of term and late preterm infants? Am J Perinatol. 2013; 30: 499–504.*

5. *American Academy of Pediatrics, Committee on Quality Improvement, Subcommittee on Urinary Tract Infection: The diagnosis, treatment and evaluation of the initial urinary tract infection in febrile infants and young children. Peditrics 1999; 103(4): 843-52.*

6. *Zorc JJ, Levine DA, Platt SL, et al. Clinical and demographic factors associated with urinary tract infection in young febrile infants. Pediatrics. 2005; 116: 644–8.*

7. *Samayam P, Ravi Chander B. Study of urinary tract infection and bacteriuria in neonatal sepsis. Indian J Pediatr. 2012; 79: 1033–6.*

8. *Morley EJ, Lapoint JM, Roy LW, et al. Rates of positive blood, urine, and cerebrospinal fluid cultures in children younger than 60 days during the vaccination era. Pediatr Emerg Care. 2012; 28: 125–30.*

9. *Lin Ky, Chiu MJ, Lai Ch, Huang JJ, Wang YT, Chiou YY. Acute pyelonephritis and sequelae of renal scars in pediatric first febrile urinary tract infection. Pediatr Nephrology 2003; 18: 362-5.*

10. *Subat- Dezulovic M, Saina G, Smokvina A. Renalna ultrasonografija- prva dijagnosticka pretraga u djece s dokazanom urinarnom infekcijom. Pediatr Croat 1998; 42: 139-44.*

11. *Stein R, Dogan H, Hoebeke P, et al. Urinary tract infections in children: EAU/ESPU guidelines. European Society for Pediatric Urology. Pediatrics. 2015; 67(3): 546-58.*

12. *Ellison J, WDy G, Fu B, et al. Neonatal circumcision and urinary tract infection in infants with hydronephrosis. Peditrics. 2018; 142.*

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Abstract

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Key words: Camera ready paper, Journal.

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Regular paper may be divided in a number of sections. Section titles (including references and acknowledgement) should be typed using 12 pt fonts with **bold** option. For numbering use Times New Roman number. Sections can be split in subsection, which should be typed 12 pt *Italic* option. Figures should be one column wide. If it is impossible to place figure in one column, two column wide figures is allowed. Each figure must have a caption under the figure. Figures must be a resolution of 300 DPI, saved in TIFF format, width 10 cm min. For the figure captions 12 pt *Italic* font should be used. (1)

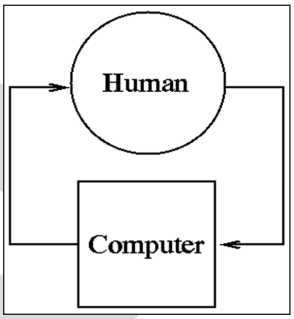

Figure 1. Text here

Conclusion

Be brief and give most important conclusion from your paper. Do not use equations and figures here.

Acknowledgements (If any)

These and the Reference headings are in bold but have no numbers.

References

1. *Sakane T, Takeno M, Suzuki N, Inaba G. Behcet's disease. N Engl J Med 1999; 341: 1284–1291.*
2. *Stewart SM, Lam TH, Beston CL, et al. A Prospective Analysis of Stress and Academic Performance in the first two years of Medical School. Med Educ 1999; 33(4): 243- 50.*

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