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**Novi Centralni medicinski blok - Klinički centar Univerziteta u Sarajevu**
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## Novi Evropski vodič za prevenciju tromboembolizma kod A Fib

### $CHA_2DS_2$-VASc skor za procjenu rizika od tromboembolizma kod A Fib!

**Risk factor-based point-based scoring system - $CHA_2DS_2$ -VASc**

| Risk factor | Score |
|---|---|
| Congestive heart failure/LV dysfunction | 1 |
| Hypertension | 1 |
| Age ≥75 | 2 |
| Diabetes mellitus | 1 |
| Stroke/TIA/thrombo-embolism | 2 |
| Vascular disease* | 1 |
| Age 65–74 | 1 |
| Sex category (i.e. female sex) | 1 |
| **Maximum score** | **9** |

*Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.

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### Major i non-major riziko fakori za procjenu tromboembolizma kod A Fib!

**Risk factors for stroke and thrombo-embolism in non-valvular AF**

| Major risk factors | Clinically relevant non-major risk factors |
|---|---|
| Previous stroke | CHF or moderate to severe LV systolic dysfunction [e.g. LV EF ☒ 40%] |
| TIA or systemic embolism | Hypertension |
| Age ☒75 years | Diabetes mellitus |
| | Age 65-74 years |
| | Female sex |
| | Vascular disease |

AF = atrial fibrilation; EF = ejection fraction (as documented by echocardiography, radio nudide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV = left venticular; TIA = trasient ischaemic attack.

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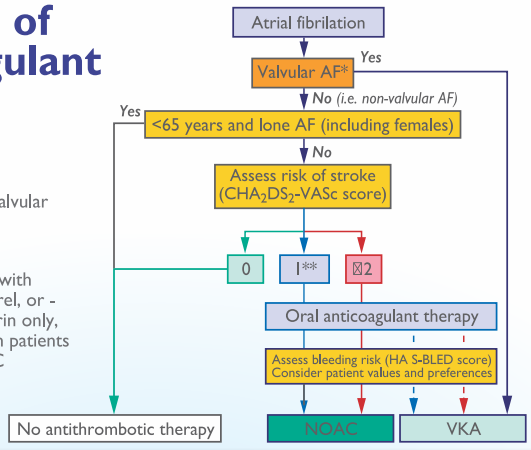
### Algoritam antikoagulantne terapije nakon procjene $CHA_2DS_2$VASc i major risk faktora!

**Choice of Anti-coagulant**




* Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc.

** Antiplatelet therapy with aspirin plus clopidogrel, or - less effectively - aspirin only, may be considered in patients who refuse any OAC

NOAC - Novel Oral Anticoagulants, VKA - Vitamin K Antagonists

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The Medical Journal aims to publish the highest quality materials, both clinical and scientific, on all aspects of clinical medicine. It offers the reader a collection of contemporary, original, peer-reviewed papers, professional articles, review articles, editorials, along with special articles and case reports.



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# Content



## Original articles



## Professional articles



## Case series



## Case reports

# Immediate two-stage breast reconstruction with and without TiO2Mesh ™ BRA: comparing safety outcomes of the first phase of subpectoral implant-based breast reconstruction

# Primarna dvofazna rekonstrukcija dojke sa i bez implementacije TiO2MeshTM BRA hirurške mrežice: komparacija sigurnosti nakon prve faze protetske rekonstrukcije dojke u subpektoralnom maniru

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## ABSTRACT

Introduction: breast cancer is the most common cancer among women, and since 1989 breast cancer deaths have decreased by 43%, reflecting significant advances in treatment. Aim: this study aimed to compare the complication rates and need for revision surgeries between the traditional two-staged implant-based breast reconstruction technique, which did not use surgical mesh, and breast reconstruction utilizing relatively new TiO2Mesh™ BRA alloplastic material in order to assess their safety. Materials and methods: at our institution, a prospective open-label, non-randomized controlled clinical trial with 70 patients was carried out between January 2020 and July 2023. The initial phase of a two-stage prosthetic breast reconstruction was performed on the patients. There were 55 breasts (63.2%) in the control group that had reconstruction without mesh, and 32 breasts (34.8%) in the experimental group that underwent reconstruction with mesh added. Results: during postoperative follow-up after the first stage of breast reconstruction with an expander, 7.3% of breasts in the control group experienced complications requiring a revision surgery. In the experimental group, 40.6% of breasts experienced complications, with 31.25% of all experimental group breasts requiring revision surgery. According to regression analysis, the experimental group's likelihood of problems after the first stage is seven times higher. Conclusion: the experimental group experienced a statistically significant higher rate of complications leading to the conclusion that usage of $TiO_2$Mesh™ BRA is not a valid option for two-stage prosthetic reconstruction. The benefits and potential complications associated with synthetic mesh in breast reconstruction remain a topic of on-going debate.

**Keywords:** TiO2Mesh™ BRA, synthetic mesh, alloplastic breast reconstruction, prosthetic breast reconstruction, two-staged implant-based breast reconstruction (IBBR)

## SAŽETAK

Uvod: rak dojke je najčešći rak kod žena, a od 1989. godine smrtnost od raka dojke smanjena je za 43%, što predstavlja značajan napredak u liječenju. Cilj: ova studija je imala za cilj usporediti stopu komplikacija i stopu potrebe za revizionim operativnim zahvatom između tradicionalne tehnike dvostepene rekonstrukcije dojke protetskim materijalom gdje nije korištena hirurška mrežica i rekonstrukcije dojke korištenjem relativno novog TiO2Mesh ™ BRA aloplastičnog materijala u svrhu procjene njegove sigurnosti. Materijali i metode: u našoj ustanovi sprovedeno je prospektivno „open-label", nerandomizirano, kontrolirano kliničko ispitivanje, koje je uključivalo 70 pacijenta u periodu od januara 2020. godine do jula 2023. godine. Pacijenti su podvrgnuti prvoj fazi dvostepene protetske rekonstrukcije dojke. Ukupno 55 dojki (63.2%) u kontrolnoj grupi je povrgnuto rekonstrukciji bez upotrebe hirurške mrežice, dok su u eksperimentalnoj grupi 32 dojke (34.8%) podvrgnute rekonstrukciji uz upotrebu TiO2Mesh ™ BRA hirurške mrežice. Rezultati: tokom postoperativnog praćenja nakon prve faze rekonstrukcije dojke ekspanderom, 7.3% dojki eksperimentalne grupe pretrpjelo je komplikaciju i svaka od tih komplikacija je iziskivala revizioni operativni zahvat. U eksperimentalnoj grupi 40.6% dojki pretrpjelo je komplikaciju, a ukupno 31.25% dojki ekperimentalne grupe je zahtijevao revizioni

operativni zahvat. Sudeći po rezultatima regresione analize, vjerovatnoća komplikacija u ekperimentalnoj grupi nakon prve faze rekonstrukcije je sedam puta veća u odnosu na kontrolnu grupu. Zaključak: u eksperimentalnoj grupi je zabilježena statistički signifikantna veća stopa komplikacija i revizionih operativnih zahvata, što promovira činjenicu da upotreba $TiO_2$Mesh™ BRA hirurških mrežica nije validna opcija u dvostepenoj protetskoj rekonstrukciji. Upotreba sintetskih hiurških mrežica u rekonstrukciji dojke i dalje ostaje tema rasprave.

**Ključne riječi**: TiO2Mesh™ BRA, sintetske hirurške mrežice, aloplastična rekonstrukcija dojke, protetska rekonstrukcija dojke, dvostepena protetska rekonstrukcija dojke

## INTRODUCTION

Breast cancer is the most common cancer among women, with 2.26 million new cases and 658.000 deaths globally in 2020 (1,2). Since 1989, breast cancer deaths have decreased by 43%, reflecting significant advances in treatment (3). Bosnia and Herzegovina lacks precise statistics due to the absence of a central registry (4). Breasts are integral to female sexuality and beauty, so changes due to breast cancer can deeply affect a woman's psychological health and body image (5). While life-saving, breast cancer surgery can lower quality of life, making breast reconstruction a crucial part of treatment (6). Given that reconstruction is elective, it is vital to assess its risks, including potential impacts on oncological treatment and vice versa (7). Reconstruction methods vary, with no standardized protocol, requiring an individualized approach (7). Options include autologous, alloplastic, or a combination of both (8). A thorough discussion between the surgeon and patient is necessary, although alloplastic reconstruction is most common in Western countries (9). In alloplastic reconstruction, synthetic meshes or biological matrices are used (10). TiO2Mesh™ BRA, a newer material, is used in subpectoral or prepectoral reconstructions but lacks sufficient data on efficacy and safety (11).

## AIM

The aim of this study was to compare the complication rates and need for revision surgeries between the traditional two-staged implant-based breast reconstruction technique (IBBR), which did not use surgical mesh, and breast reconstruction utilizing relatively new TiO2Mesh™BRA alloplastic material in order to assess their safety.

## MATERIALS AND METHODS

A prospective open-label non-randomized controlled clinical trial with 70 patients ranging from 27 to 55 years of age was carried out at our institution between January 2020 and July 2023. In a single procedure, patients received a skin-sparing mastectomy and the initial phase of a two-stage prosthetic breast reconstruction. There were 55 breasts (63.2%) in the control group that had reconstruction without TiO2Mesh™ BRA, and 32 breasts (36.8%) underwent reconstruction in the experimental group that included TiO2Mesh™ BRA (Figure 1). The safety of using the mesh was assessed by comparing complication revision rates between the two groups. According to national guidelines, each patient received individualized surgical treatment which took into account all factors that could affect the therapeutic approach, including the patient's general health, the features of the tumor, and the size of the tumor or breast. Along with the surgeon, the patient's wishes were considered when planning the surgical procedure.

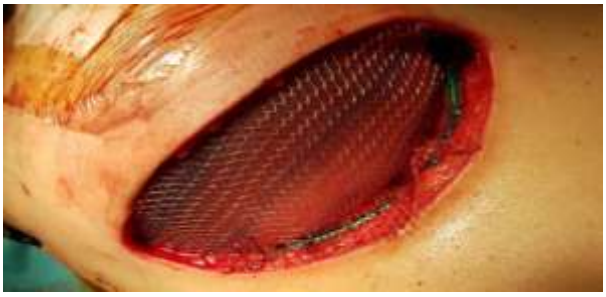

Figure 1 **TiO2Mesh™ BRA: intraoperative view**.

*Inclusion criteria:*

- Indicated primary two-stage reconstruction after skin-sparing mastectomy;
- Subpectoral placement of the implant;
- Completion of the first phase of reconstruction after the successful expansion;
- Termination of the first stage of reconstruction after expander explantation due to some of the complications;
- The expansion after the first stage is in progress but has lasted at least 12 months;

*Exclusion criteria:*

- Prepectoral placement of the implant;
- Indicated secondary reconstruction;
- Indicated single-stage prosthetic reconstruction;
- Reconstruction following subcutaneous mastectomy;
- Autologous reconstruction;
- The expansion after the first stage of reconstruction is in progress but has lasted less than 12 months;

The analyzed data were collected from patient medical records and included details about the patient's age, smoking status, body mass index (BMI), existing comorbidities, the specifics of the axillary lymph node dissection, the length of the expansion, the administered oncological treatments, occured complications and the need for unplanned return to the operating room for revision. Additionally, the individual impact of postmastectomy radiation, the impact of BMI >30 kg/m2, and the influence of multiple risk factors on wound healing were analyzed. This study did not address complications unrelated to the breast (e.g., embolism, arm lymphedema), as well as minor complications including "red breast syndrome," burns of postmastectomy flaps, and subjective difficulties like loss of sensation in the postmastectomy flap and cosmetic concerns (12).

*Surgical intervention*

In the study, the oncological surgeon excised the breast tissue while preserving the pectoral major muscle. The glandular and fatty tissue was removed from the skin flap using surgical scissors, adhering to the skin-sparing mastectomy principle. The breast tissue was then carefully separated from the pectoral muscle with an electrocautery instrument. The plastic surgeon performed two-stage breast reconstruction using an expander, followed by a permanent silicone implant. In the control group, a pocket for the expander was created by cutting and lifting the pectoral muscle, with lateral dissection beneath the serratus muscle. The inferior rectus muscle fascia was raised to achieve full submuscular coverage for the prosthesis. In the experimental group, TiO2Mesh™ BRA was used to create a dual-plane pocket (partial submuscular coverage) by suturing it to the pectoral muscle and thoracic wall. The expander was placed in the pocket, irrigated with an antibiotic solution, and sealed with resorbable sutures. Expansion began one month later, continuing biweekly unless tissue radiation was needed, in which case expansion paused for one to two months. After achieving the desired breast size, a permanent silicone implant was inserted during a second procedure (Figure 2). The use of TiO2Mesh™ BRA was at the surgeon's discretion.

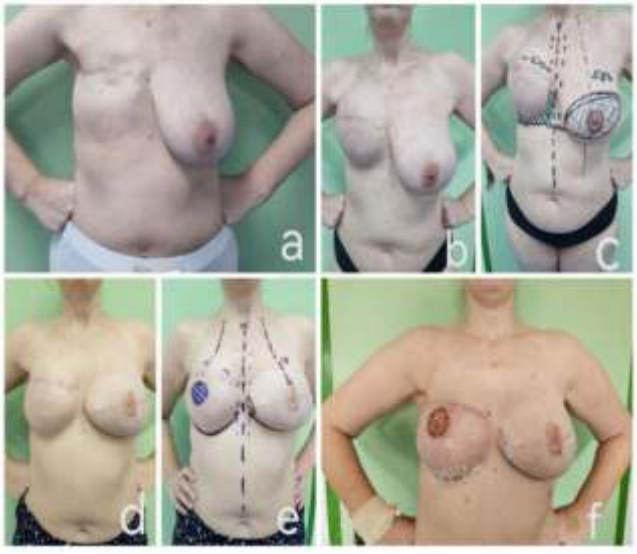


Figure 2 **Two-staged implant-based breast reconstruction: a) first stage postoperative photo; b) first stage expansion; c) second stage planning; d) second stage postoperative photo showing reduction of the left breast and reconstructing of the right breast using implant; e) third stage planning; f) third stage postoperative photo**.

*Statistical analysis*

Depending on the type of data, the data are displayed as tables and figures with the number of cases, percentage, mean with standard deviation, and range of values. The nonparametric Chi-square tests were used to examine the differences between the groups. Multivariate logistic regression was used to generate the odds ratio (OR), which was used to determine the combined and individual effects of potential risk factors. The relative risk (RR) between the groups was computed using the risk ratio. A p-value of less than 0.05 was regarded as statistically significant. Analysis was conducted using the statistical package, IBM Statistics SPSS (Version 23, Chicago, IL, USA).

## RESULTS

The study included 70 patients (87 breasts) undergoing two-stage breast reconstruction. The control group, without TiO2Mesh™ BRA, had 55 breasts (63.2%), while the experimental group, with mesh, had 32 breasts (36.8%) (Table 1).

Table 1 **Frequency of represented methods of prosthetic reconstruction in the control and experimental groups.**

| | | Group | | |
|---|---|---|---|---|
| | | Control | Experimental | Total |
| | N | 0 | 32 | 32 |
| | % | 0.0 | 100.0 | 36.8 |
| | N | 55 | 0 | 55 |
| | % | 100 | 0.0 | 63.2 |
| Total | N | 55 | 32 | 87 |
| | % | 100.0 | 100.0 | 100.0 |
| $\chi^2$=87.000; p=0.0001 | | | | |

*$X^2$ test.*
*Significance is shown as p<0.05.*

Follow-up discontinued due to implant loss in 28.1% of the experimental group, compared to 5.5% in the control group. The expansion phase is ongoing in 20% of control group cases and 3% in the experimental group. The second stage of reconstruction was completed in 74.5% of the control group and 68.8% of the experimental group, showing statistical significance (p=0.0001).

The control group's expansion lasted 13.5 months on average, compared to 10 months in the experimental group (p=0.026).

Table 2 **Representation of recorded complications in the control and experimental groups.**

| | | | Group | | |
|---|---|---|---|---|---|
| | | | Control | Experimental | Total |
| Complications | No complication | N | 51 | 19 | 70 |
| | | % | 92.7 | 59.4 | 80.5 |
| | Hematoma | N | 1 | 0 | 1 |
| | | % | 1.8 | 0.0 | 1.1 |
| | Infection | N | 2 | 5 | 7 |
| | | % | 3.6 | 15.6 | 8.0 |
| | Skin necrosis, prosthesis extrusion | N | 0 | 2 | 2 |
| | | % | 0.0 | 6.3 | 2.3 |
| | Pain | N | 0 | 1 | 1 |
| | | % | 0.0 | 3.1 | 1.1 |
| | Prosthesis rupture | N | 1 | 2 | 3 |
| | | % | 1.8 | 6.3 | 3.4 |
| | Seroma | N | 0 | 3 | 3 |
| | | % | 0.0 | 9.4 | 3.4 |
| | Total | N | 55 | 32 | 87 |
| | | % | 100.0 | 100.0 | 100.0 |
| $\chi^2$=18.457; p=0.005 | | | | | |

*$X^2$ test.*
*Significance is shown as p<0.05.*

Postoperative complications requiring revision occurred in 7.3% of the control group and 40.6% of the experimental group, with 31.25% of the latter needing revision surgery (p=0.005) (Figure 3 and 4). These findings were statistically significant.

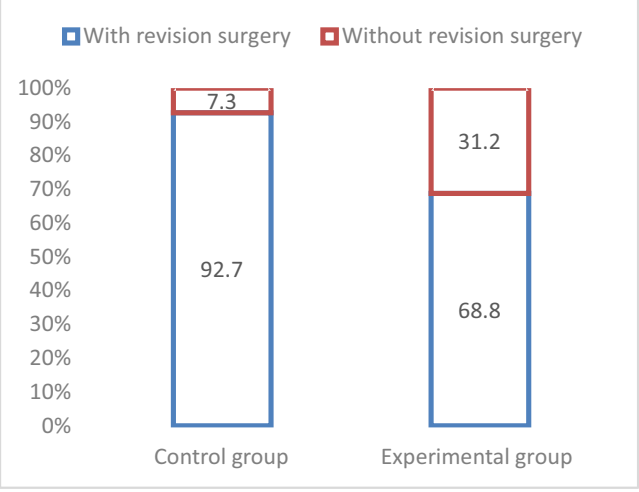


Figure 3 **Rate of revision surgeries (control versus experimental group).**

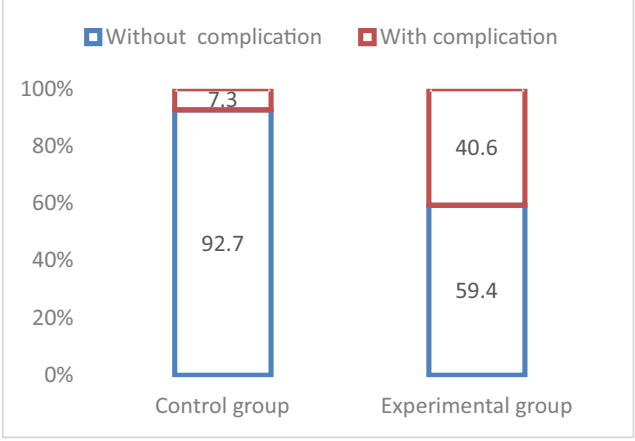


Figure 4 **Rate of complications (control versus experimental group).**

Preventive mastectomy was performed in 13.8% of cases, while 86.2% underwent skin-sparing mastectomy with axillary lymph node dissection. Sentinel lymph nodes were removed in 10.3% of cases, and axillary lymph nodes in 75.9% (p=0.149).

In the control group, 12.7% of breasts were in patients under 35 years old, compared to 18.8% in the experimental group. The 35-45 age group accounted for 45.5% of control cases and 43.8% of experimental cases, while the 45-55 group included 41.8% of control cases and 37.5% of experimental cases (p=0.742).

Chemotherapy was administered to 76.4% of control group cases and 87.5% of the experimental group (p=0.163).

Chronic smokers made up 25% of the experimental group and 29.1% of the control group (p=0.439).

Complications occurred in 6.2% of non-PMRT cases and 27.3% of PMRT cases, a significant difference (p=0.023).

Complications were observed in 17.1% of cases with BMI 30 kg/m² (p=0.043).

Cases with fewer than three risk factors had a 15.8% complication rate, compared to 45.5% with three or more risk factors (p=0.035) (Table 3).

Table 3 **Effects of risk factors on complications.**

| | | | Complications after the I[st] phase | | |
|---|---|---|---|---|---|
| | | | No | Yes | Total |
| Radiation therapy $\chi^2$=5.687; p=0.023 | No | N | 30 | 2 | 32 |
| | | % | 93.8 | 6.2 | 36.8 |
| | Yes | N | 40 | 15 | 55 |
| | | % | 72.7 | 27.3 | 63.2 |
| BMI $\chi^2$=4.967; p=0.043 | <30kg/m² | N | 63 | 13 | 76 |
| | | % | 82.9 | 17.1 | 87.4 |
| | >30kg/m² | N | 7 | 4 | 11 |
| | | % | 63.6 | 36.4 | 12.6 |
| More than 3 risk factors $\chi^2$=5.379; p=0.035 | No | N | 64 | 12 | 76 |
| | | % | 84.2 | 15.8 | 87.4 |
| | Yes | N | 6 | 5 | 11 |
| | | % | 54.5 | 45.5 | 12.6 |
| | Total | N | 70 | 17 | 87 |
| | | % | 80.5 | 19.5 | 100.0 |

BMI- body mass index
*$X^2$ test.*
*Significance is shown as p<0.05.*

Regression analysis ($R^2$=0.622) explains 62.2% of complications. Analysis of variance (F=10.162, p=0.00001) supports the model's reliability. Patients in the experimental group have a sevenfold higher chance of complications after the first stage, and those with more than three risk factors have a twofold higher chance. The relative risk (RR=5.59, 95% CI=1.99-15.69) indicates a fivefold higher complication risk in the experimental group (z=3.266, p=0.001).

## DISCUSSION

Two-stage tissue-expander breast reconstruction is the most commonly used reconstruction modality after mastectomy, being performed in three-quarters of breast reconstruction cases for early-stage cancer (13). The use of expanders has its drawbacks, including physical and psychological discomfort due to repeated outpatient expansions, potential rotation of the prosthesis, damage to the expander and the need for additional surgical treatment. The latter is particularly problematic because the expander is only temporarily placed, and the final appearance of the breast is achieved after the second stage, which is another psychological hurdle for the patient (13).

Recently, there has been a shift towards direct-to-implant (DTI) single-stage breast reconstruction with the insertion of the final implant at the time of mastectomy, especially in cases of nipple- or skin-sparing mastectomy (14,15). DTI is suitable for small to medium-sized breasts. The drawback of this type of reconstruction is that it requires preserving most of the breast skin and the fact that radiation after this type of reconstruction leaves unforeseen consequences (14,15). Subpectoral placement is technically more demanding in DTI reconstruction compared to subpectoral placement in two-stage tissue expander reconstruction. Additionally, there is a greater possibility of implant protrusion and control over the symmetry of the contralateral breast is more challenging (14). Recent reports in the literature have supported the safety and short-term cost-effectiveness of DTI breast reconstruction when compared to a multi-stage approach utilizing tissue expanders, but not all patients are candidates for this type of reconstruction (15).

Autologous reconstruction leads to greater patient satisfaction, but this type of reconstruction has more serious and more numerous complications (16). Disadvantages include longer surgical time, more complex technical procedure, longer hospital stay and complications at the donor site. Additionally, it is not suitable for all patients, especially in patients with multiple comorbidities (17).

The use of implants for reconstruction has increased for several reasons, including patient and operator preferences, changes in oncologic practice, and an increased incidence of bilateral mastectomies (18). For alloplastic breast reconstruction, implants are placed under the skin envelope with or without mesh (19). Total or partial submuscular placement of the prosthesis prevents infection following skin flap/wound dehiscence and prosthesis exposure, and for many years, it has been considered the safest choice, whether for single-stage or two-stage alloplastic breast reconstruction, thus having an advantage over prepectoral placement (20). Other advantages are minimal implant visibility and minimal palpability of implant edges at the upper pole. However, detachment of the pectoralis major leads to morbidity in terms of reduced pectoral muscle strength, animation deformity, postoperative pain, longer postoperative recovery and a less natural breast appearance (21).

The decision regarding when to add a biologic matrix or a synthetic mesh to an alloplastic reconstruction is controversial. Mesh promotes human body to produce more collagen in the form of scar tissue that weaves in and out of the mesh. More collagen equals more strenght. Benefits of their usage include prevention of prosthesis displacement, minimizing the prominence of the implant edge, reduced extent of tissue dissection required during surgery, lengthening of the pectoralis muscle, support for the device at the lower pole, more rapid expansion, improved definition of breast boundaries and folds and possible modification of capsule formation (22,23). Disadvantages include added risk of infection, skin necrosis, seroma formation, risk of material exposure, added surgical time and increased cost (22,23). Mesh was approved for IBBR in Europe in 2008, but only limited clinical data are available (24). According to a meta-analysis comparing complications between biologic and synthetic meshes, the latter group showed a lower likelihood of seroma and infection development, while the rate of capsular contracture and serious complications did not differ between the two groups (25). However, some studies indicate that the use of biologic meshes is associated with a higher rate of postoperative complications. Biologic meshes incur higher financial costs but yield better aesthetic results, particularly when forming a ptotic breast of mild to moderate degree (26). Major and minor complication rates, as well as total costs, were higher in the ADM group (12). According to Faulkner et al., synthetic absorbable mesh is a safe alternative to acellular dermal matrix in prosthetic breast reconstruction and provides stable results along with significant cost savings (27).

Judging by the narrative review of the management of complications after IBBR, which was performed by reviewing the

literature using the PubMed, OVID MEDLINE and Cochrane Library databases from 2000 to 2023, overall complication rates for IBBR range between 26.6–31.3%, while reoperation rates are 15.5–18.8% (28). Exactly 40.6% of the breasts in our experimental group where we used synthetic mesh Tio2Mesh™BRA had complications and 31.25% of those breasts needed revision surgery. Complication rate in the experimental group was nearly six times higher than that of the control group. These results were statistically significant. These data from our study refer only to the outcomes of the first stage of reconstruction and short-term complications and reoperations, so these data are therefore more dramatic.

Meta-analyses have shown that risk factors like age and smoking history significantly affect complications after breast reconstruction (7). An elevated risk of complications is associated with older patients for a number of reasons, chief among them being a 70% reduction in cardiac output and a 50% reduction in renal function in those over 65 compared to the average thirty-year-old (29,30). Smoking increases tissue hypoxia, cutaneous vasoconstriction, and platelet aggregation (31). In our study, the age groups and groups of smokers between the two analyzed groups were comparable, making it impossible to examine their impact on the incidence of complications.

Generally, chemotherapy and radiotherapy prolong the survival of patients (32). Research assessing the effect of chemotherapy on breast reconstruction has yielded inconsistent findings. Some reported that chemotherapy increases the risk of complications, while others noted that chemotherapy has no negative effects on reconstruction or that such effects are negligible (32). It was not possible to evaluate the effect of chemotherapy on the complication rate in our study since the percentage of patients subjected to chemotherapy was similar in the two groups. The distribution of post-mastectomy radiation exposure, BMI > 30 kg/m2, and the existence of three or more risk variables for healing-related problems (obesity, thyroid disease, PMRT, chronic cigarette consumption, diabetes mellitus, coagulopathy, significant heart disease, asthma, chronic obstructive lung diseases, systemic lupus erythematosus, scleroderma) were unevenly distributed in our study. Since these variables skew the evaluation of the influence of employing meshes on revision and complication rates, their separate effects on the incidence of complications were examined. Given the higher risk of problems and lower patient satisfaction, particularly in the case of alloplastic breast reconstruction, the detrimental effects of radiation are well reported in the literature. Radiation harms vascularization and promotes discomfort, poor cosmesis, capsular contracture, and necrosis of the flap following mastectomy (33, 34). On the other hand, the state of the skin flap and blood supply can stabilize with sufficient time following PMRT, allowin g for delayed reconstruction (33). Implant use in patients exposed to radiation is debatable. According to our research, the irradiated group experienced complications at a rate that was around four times higher than the non-irradiated group.

A BMI of 30 kg/m² or more is considered obese. Because of their weakened immune systems and high blood sugar, obese people are more likely to experience slower wound healing (35). Our study demonstrated the detrimental effects of higher BMI on outcomes and complication rates, with obese patients incurring complications at a rate twice that of non-obese individuals.

According to our study, patients who had three or more risk factors for wound healing difficulties experienced a statistically significant greater rate of complications than patients who had less than three risk factors. Regression analysis revealed that the presence of at least three risk factors that promote wound healing complications was associated with a twofold increased risk of complications. Other studies have similarly demonstrated the impact of risk factors on implant rejection (36-39).

Regression analysis revealed that the experimental group had a sevenfold increased risk of complications during the expansion phase after mastectomy and primary breast reconstruction with an expander.

## CONCLUSION

This was the first study to investigate the impact of $TiO_2$Mesh™ BRA meshes on complication and revision rates. Obesity, post-mastectomy radiation, and the presence of at least three risk factors for complications in wound healing of post-mastectomy skin flaps had a statistically significant effect on complication rates, and these factors also acted as confounding variables in evaluating the impact of $TiO_2$Mesh™ BRA on reconstruction in our study. The experimental group experienced a statistically significant higher rate of complications (40.6% vs. 7.3%), leading to the conclusion that these meshes are not a valid option for two-stage prosthetic reconstruction. The use of $TiO_2$Mesh™ BRA should be directed toward resorbable alternatives or considered only for carefully selected patients with fewer comorbidities or risk factors. Further research is needed to confirm this hypothesis. The assessment of potential complications in the first phase of alloplastic prosthetic reconstruction with $TiO_2$Mesh™ BRA in our study is limited by the small sample size. Nevertheless, a larger patient cohort analysis, including those undergoing breast reconstruction using a broader range of methods, as well as prospective, multicenter, and long-term outcome studies, are needed to further evaluate the benefits of such treatments. The benefits and potential complications associated with synthetic mesh in breast reconstruction remain a topic of ongoing debate.

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# Pulmonary embolism in patients diagnosed with malignancy - past, present and future findings - single center experience

# Plućna embolija kod pacijenata sa dijagnozom maligniteta - prošli, sadašnji i budući nalazi - iskustvo jednog centra

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## ABSTRACT

Introduction: pulmonary embolism (PE) and cancer represent significant causes of morbidity and mortality worldwide. Cancer-associated PE is often more severe, with higher rates of recurrence and mortality compared to PE in non-cancer patients. Aim: to compare the clinical profile and the treatment outcome of patients with and without malignant disease hospitalized for PE. Materials and methods: the cross-sectional, observational analysis of the patients diagnosed with the pulmonary thromboembolism hospitalized in the Intensive Care Unit of the Clinic of Lung Diseases and Tuberculosis of the Clinical Centre University of Sarajevo was performed in the period from 1 January 2023 to 1 July 2024. Patients' information was obtained via the medical histories. The obtained data were compared between the two groups of PE patients, group one diagnosed with malignancy, and group two without the previous malignant disease diagnosis. The general and demographic data of patients, data on the comorbidities, risk factors, the clinical presentation on admission, the laboratory findings were analyzed. The diagnostic and therapeutic approach and survival rate (one and three-months survival outcome) were also evaluated. Results: the previous diagnosis of heart and cerebrovascular disease, diabetes mellitus and chronic kidney disease was established in 51.5%, 18.8%, 24.8% and 15.8% of patients, respectively. The immobilization, as one of the main risk factors for PE onset, was identified in 57.6% of patients. The decreased mean levels of hemoglobin (125.75 ± 25.28) and hematocrit (40.21 ± 27.81) in PE patients were also identified. Statistically more trombophilic patients and more ECG changes as well as higher three months survival, higher values of the variables ALT and hemoglobin and lower value of the variable haematocrit were identified in non-malignant group of patients (12(11.2%) vs. 0 (0%), p=0.001**; 58 (54.2%) vs. 19 (32.8%), p=0.003; 75 (75%) vs. 32(59.3%); p=0.044; p=0.033; p=0.000**; p=0.000 respectively), than in the group of patients diagnosed with malignant disease. Statistically significant higher presentation of the infiltration on computed tomography (CT) (35(59.3%) and atelectasis on CT (29(49.2%) (p=0.002, 0.032 respectively) was identified in patients with malignant disease compared to the group of patients non-diagnosed with malignancy (33(31.1%); 37 (34.9%)). Also, statistically significant positive correlation was identified between neutrophyls and systemic immune inflammation index (SII) with parameters of one month survival and three months survival in either malignant and non-malignant group of patients (p<0.001). Conclusion: the diagnosis and management of PE in cancer patients requires a multidisciplinary approach, to optimize diagnostic and treatment strategies and avoid complications.

**Keywords**: pulmonary embolism, cancer, survival, treatment

## SAŽETAK

Uvod: plućna embolija (PE) i karcinom predstavljaju značajne uzroke morbiditeta i mortaliteta širom svijeta. PE povezana s karcinomom je često teža, s većom stopom recidiva i mortaliteta u

poređenju s PE kod pacijenata bez raka. Cilj: uporediti klinički profil i ishod liječenja pacijenata sa i bez maligne bolesti hospitaliziranih zbog PE. Materijali i metode: presječna, opservaciona analiza bolesnika s dijagnozom plućne tromboembolije hospitaliziranih na Odjeljenju intenzivne njege Klinike za plućne bolesti i tuberkulozu Kliničkog centra Univerziteta u Sarajevu, obavljena je u periodu od 01.01.2023. do 01.07.2024. godine. Podaci o pacijentima su dobijeni putem istorije bolesti pacijenata. Dobijeni podaci su upoređeni između dvije grupe pacijenata sa PE, prve grupe sa dijagnozom malignitеta i grupe 2 bez prethodne dijagnoze maligne bolesti. Analizirani su opšti i demografski podaci pacijenata, podaci o komorbiditetima, faktorima rizika, kliničkoj slici pri prijemu, kao i laboratorijski nalazi. Dijagnostički i terapijski pristup i stopa preživljavanja (jednomjesečni i tromjesečni ishod preživljenja) također su evaluirani. Rezultati: prethodna dijagnoza srčanih i cerebrovaskularnih bolesti, dijabetes melitusa i hronične bolesti bubrega postavljena je kod 51,5%, 18,8%, 24,8% i 15,8% pacijenata. Imobilizacija, kao jedan od glavnih faktora rizika za nastanak PE, identifikovana je kod 57,6% pacijenata. Identifikovani su i sniženi prosječni nivoi hemoglobina (125,75 ± 25,28) i hematokrita (40,21 ± 27,81) kod pacijenata sa PE. Statistički više pacijenata sa trombofilijom i više EKG promjena, kao i duže tromjesečno preživljavanje, veće vrijednosti ALT i hemoglobina i niža vrijednost hematokrita utvrđeni su u nemalignoj grupi bolesnika (12(11,2%) naspram 0 (0). %), p=0,001** nasuprot 19 (32,8%), p=0,003; ** p=0,000), nego u grupi pacijenata sa dijagnozom maligne bolesti. Statistički značajno veća zastupljenost infiltracije na kompjuterizovanoj tomografiji (CT) (35(59,3%) i atelektaze na CT-u (29(49,2%)) (p=0,002, 0,032 respektivno) utvrđena je kod pacijenata sa malignom bolešću u odnosu na grupu pacijenata bez dijagnosticiranog malignitеta (33 (31,1%); 37 (34,9%). Takođe je utvrđena statistički značajna pozitivna korelacija između neutrofila i indeksa sistemske imunološke upale (SII)) sa parametrima jednomesečnog preživljavanja i tromesečnog preživljavanja, bilo maligne, ili nemaligne grupe pacijenata (p<0,001). Zaključak: dijagnoza i liječenje PE kod pacijenata s karcinomom zahtijeva multidisciplinarni pristup, kako bi se optimizirale strategije dijagnostike i liječenja i izbjegle komplikacije.

**Ključne riječi**: plućna embolija, karcinom, preživljavanje, liječenje

## INTRODUCTION

Pulmonary embolism (PE) is a critical and potentially life-threatening medical condition defined by the blockage of one or more pulmonary arteries, significantly compromising the health of patient. This obstruction is typically a consequence of the migration of a blood clot to the lungs, resulting in compromised blood flow. Despite the progress in medical science and technological advancements, PE still presents a serious diagnostic and therapeutic challenge for healthcare workers worldwide.

The clinical manifestations of PE vary from mild symptoms such as breathlessness and chest discomfort to more severe ones like hemodynamic instability and sudden cardiac arrest (1,2). PE can develop in individuals with various risk factors, both acquired and inherited, contributing to the formation of blood clots that may travel to the lungs.

Some of them include: prolonged immobility, major surgery (particularly orthopedic surgeries), trauma (such as trauma to blood vessels), cancer (some types of cancer and certain cancer treatments can predispose individuals to blood clot formation), obesity, smoking, previous history of blood clots (patients with a history of deep vein thrombosis (DVT) or previous PE), pregnancy and postpartum period, use of hormonal contraceptives, inherited blood clotting disorders (factor V Leiden mutation, prothrombin gene mutation, and anticoagulant proteins deficiencies can predispose individuals to clot formation (3,4,5).

PE can present with a variety of symptoms, from subtle to severe, and sometimes may even be asymptomatic. The common symptoms of PE include: sudden shortness of breath which may be severe and can occur at rest or with exertion, chest pain: often sharp or stabbing, may worsen with deep breathing, coughing, or movement, cough, sometimes a hemoptysis, tachycardia due to the body's response to decreased oxygen delivery, leg swelling or pain, profuse sweating, anxiety possibly due to decreased oxygen levels, wheezing (6,7).

It is important to note that the presentation of PE can vary widely among individuals, and some people may have atypical or asymptomatic cases.

PE and cancer represent significant causes of morbidity and mortality worldwide. The mutual relationship between PE and cancer poses clinical challenges due to the overlapping risk factors, shared pathophysiological mechanisms, and complex management. Understanding the relationship between PE and cancer is essential for improving clinical outcomes and guiding therapeutic decision-making in affected patients (8).

Cancer-related hypercoagulability plays a central role in the pathogenesis of PE among cancer patients. Malignant tumors can trigger a prothrombotic state through various mechanisms, including the release of procoagulant factors, activation of platelets, and disruption of the balance between coagulation and fibrinolysis (9). Additionally, chemotherapy, surgery, and immobility associated with cancer treatment further increase the risk of venous thromboembolism, including PE. The presence of cancer significantly impacts the clinical course and prognosis of PE. Cancer-associated PE is often more severe, with higher rates of recurrence and mortality compared to PE in non-cancer patients. The diagnosis and management of PE in cancer patients requires a multidisciplinary approach, integrating oncology, hematology, and cardiovascular expertise to optimize treatment strategies and mitigate complications. Diagnosing PE in cancer patients can be challenging due to overlapping symptoms, such as dyspnea, chest pain, and cough, which may mimic cancer-related complications or treatment side effects. Imaging modalities, such as computed tomography pulmonary angiography (CTPA) and ventilation-perfusion (V/Q) scanning play a crucial role in confirming the diagnosis of PE and determining the extent of thromboembolic burden in cancer patients. The management of PE in cancer patients requires a tailored approach that balances the risks of anticoagulation therapy with the potential benefits of preventing recurrent thromboembolic events. Novel oral anticoagulants (NOACs) and low molecular weight heparin (LMWH) are commonly used anticoagulants, considering their efficacy and safety profiles. In select cases, adjunctive therapies, such as inferior vena cava (IVC) filters or systemic thrombolysis, may be considered to manage high-risk or recurrent PE episodes in cancer patients (10).

## AIM

The aim of the study was to compare the clinical profile and treatment outcome of 171 patients with and without malignant disease hospitalized for pulmonary thromboembolism (PE) in the Intensive Care Unit of the Clinic of Lung Diseases and Tuberculosis, Clinical Centre University of Sarajevo in the period from 1 January 2023 to 1 July 2024. The obtained data were compared between the two groups of PE patients, group one diagnosed with malignancy, and group two without the previous malignant disease diagnosis.

## MATERIALS AND METHODS

The cross-sectional, observational analysis of the patients diagnosed with the pulmonary thromboembolism hospitalized in the Intensive Care Unit of the Clinic of Lung Diseases and Tuberculosis, Clinical Centre University of Sarajevo, was performed in the period from 1 January 2023 to 1 July 2024. Patients' information was obtained via the medical histories.

The general and demographic data of patients (age, gender), data on malignant disease (the type of malignancy), smoking status, data on the comorbidities (confirmed ischemic heart disease, cerebrovascular disease, diabetes mellitus, chronic kidney disease), risk factors such as the use of oral contraceptives, hormonal therapy, immobilization, older age, presence of thrombophilia, previous pulmonary thromboembolism or venous thromboembolism episodes were analyzed. The clinical presentation on admission (dyspnea, chest pain, hemoptysis, syncope, hypotension, tachycardia), the laboratory findings (D-dimer, troponin, complete blood cell count, differential blood cell count, urea, creatinine, lactate dehydrogenase-LDH, aspartate transaminase-AST, alanine transaminase-ALT, bilirubin levels) were also analyzed. Systemic immune-inflammation index (SII) was also calculated. SII was defined as the product of peripheral platelet count, neutrophil count, divided by lymphocyte count: SII = (P x N) / L, where P, N, L represent peripheral platelet count, neutrophil count, and lymphocyte count respectively. The use of imaging modalities (chest computed tomography scan- CT scan with contrast medium, lung ventilation perfusion scintigraphy-V/P spect), the radiological presentation of the pulmonary embolism (infarction, pleural effusion, infiltration, atelectasis), the extent of the pulmonary thromboembolism (massive, lobar, segmental, subsegmental), electrocardiogram (ECG) changes (pathological, normal), echocadiography (pathological, normal), the therapeutic results according to the radiological findings on follow-up chest CT imaging (partial regression, complete regression, no changes detected, the progression of radiological findings) were analyzed as well. The therapeutic modalities use (unfractionated heparin-UFH, low molecular weight heparin-LMWH), the hospital treatment outcome (died, recovered), the duration of hospitalization (days of hospital stay), survival rate (one and three-months survival outcome) were also notified and evaluated.

### *Statistical analysis*

Statistical analysis was performed by two different programs, MS Excel (Microsoft Office Excel 2010) and SPSS (SPSS-Statistical Package for 27 Social Sciences) version 22.0. The Shapiro-Wilk tests was used to assess the normality of variable distribution. The mean value (X) and standard deviation (SD) for continuous independent variables that followed the normal distribution were determined, and the median and interquartile range for independent continuous variables did not follow the normal distribution. The Student t-test tested the significance of the difference for the independent variables that followed the normal distribution. In contrast, the Mann - Whitney U- test tested the significance of the difference for the independent variables that did not follow the normal distribution. We used Reciever. A $p<0.05$ was considered statistically significant.

## RESULTS

Table I **Sociodemographic and clinical presentations of patients with PE in the whole population.**

| | |
|---|---|
| Age (years) | 69 (62 - 75) |
| Gender (Male/Female) | 75(45.1%)/91(54.9%) |
| Smoking status (smoker/ex/non-smoker) | 50(30.5%)/56(34.1%)/57(35.4%) |
| Heart disease (Yes/No) | 85 (51.5%)/80(48.5%) |
| Cerebrovascular disease (Yes/No) | 31 (18.8%)/134(81.2%) |
| Diabetes mellitus (Yes/No) | 40 (24.8%)/124 (75.2%) |
| Chronic kidney disease (Yes/No) | 26 (15.8%)/139 (84.2%) |
| Immobilisation (Yes/No) | 95 (57.6%)/70 (42.4%) |
| Thrombophilia (Yes/No/Non tested) | 14(8.5%)/8(4.8%)/144(86.7%) |
| Electrocardiogram (ECG) changes (Yes/No/Non described) | 77 (46.7%)/59(35.8%)/29(17.6%) |
| Symptoms (Dispnoea/Chest pain/Hemoptysis/Sincopa/Hypotension/Palpitation/No) | 53(32.1%)/48(29.1%)/7(4.2%)/6(3.6%)/0(0%)/3(1.8%)/48(28.9%) |
| Echocardiography (Pathologic/No/Did not performed) | 34(20.6%)/10(6%)/121(72.3%) |
| Malignant disease (Yes/No) | 107(64.5%)/59(35.5%) |
| One month survival (Yes/No)*** | 128(78%)/36(22%) |
| Three months survivals (Yes/No)*** | 107(69%/48(31%) |

*** - *no data for all patients*

Sociodemograhic and clinical presentation of PE in patients with PE was presented in Table 1.

The mean age of patients with PE was 69 years, with 45.1% of males and 54.9% of females. The previous diagnosis of the heart disease, cerebrovascular disease, diabetes mellitus and chronic kidney disease was established in 51.5%, 18.8%, 24.8% and 15.8% of patients, respectively. The immobilisation, as one of the main risk factors for PE onset, was identified in 57.6% of patients. Unfortunately, thrombophilia analysis was performed in only 8.5% of cases. The most common symtoms among analyzed patients were dyspnea (32.1%) and chest pain (29.1%). Although ECG changes were identified in 46.7% of cases, experiencing the lack of diagnostic and medical staff resources, echocardiography was performed in only 20.6% of cases. The diagnosis of accompaning malignant disease was identified in the majority of patients amounting 64.5% of cases.

Table 2 **Laboratory parameters of patients with PE in the whole population.**

| | |
|---|---|
| LDH | 267 (216 - 343.5) |
| AST | 27 (19 - 39) |
| ALT | 24 (14 - 40) |
| D-dimer | 10.86 (6.09 - 18.63) |
| Fibrinogen | 5 (3.75 - 5.9) |
| Thrombocytes | 226 (175.5 - 300) |
| Leukocytes | 10.53 ± 9.05 |
| Hemoglobin | 125.75 ± 25.28 |
| Hematocrit | 40.21 ± 27.81 |
| Neutrophyls | 6.5 (4.63 - 9.37) |
| Lymphocytes | 0.6 (0 - 1.42) |
| Monocytes | 0.65 (0.5 - 0.9) |
| Basophils | 0 (0 - 0.85) |
| Eosinophils | 0 (0 - 0.1) |
| Troponin | 40 (15 - 85) |

*LDH – lactate dehidrogenase; AST – aspartate aminotranspherase; ALT – alanine aminotranspherase*

Basal values of laboratory paratemers in patients with PE in the whole population was presented in Table 2.

Among all the analyzed laboratory parameters' mean values in patients with PE, D-dimer, Troponin, Fibrinogen and Leukocyte count were increased or on the upper limit of the reference range (10.86, 40, 5, 10.53 ± 9.05) respectively. The decreased mean levels of hemoglobin (125.75 ± 25.28) and hematocrit (40.21 ± 27.81) in PE patients were also identified.

Table 3 **The relationship of sociodemographic and clinical presentations of patients with PE between patients with malignant disease and without malignant disease.**

| | Malignant disease | Non-malignant disease | p |
|---|---|---|---|
| Age (years) | 71 (65 – 74) | 67 (57 – 76) | 0.429 |
| Gender (Male/Female) | 20(33.9%)/39(66.1%) | 54 (50.9%)/52(49.1%) | 0.035* |
| Smoking status (smoker/ex/non-smoker) | 13(22.4%)/23(39.7%)/23(39.7) | 37(34.9%)/33(31.1%)/36 (34%) | |
| Heart disease (Yes/No) | 29(49.2%)/29(49.2%) | 55(51.4%)/52(48.6%) | 0.818 |
| Cerebrovascular disease (Yes/No) | 10(17.2%)/49(82.8%) | 20 (18.7%)/86(80.4%) | 0.797 |
| Diabetes mellitus (Yes/No) | 11(19%)/48(81%) | 29 (27.1%)/77 (72.%) | 0.233 |
| Chronic kidney disease (Yes/No) | 10 (17.2%)/39 (82.8%) | 16(15%)/90 (85%) | 0.720 |
| Immobilisation (Yes/No) | 10(17.2%)/49 (82.8%) | 25(22.6%)/81(76.4%) | 0.400 |
| Thrombophilia (Yes/No/Non tested) | 0(0%)/1(1.7%)/58(98.3%) | 12(11.2%)/7(6.5%)/85 (80.3%) | 0.001** |
| Electrocardiogram (ECG) changes (Yes/No/Non described) | 19(32.8%)/23(39.7%)/16 (27.6%) | 58(54.2%)/35(32.7%)/14 (13%) | 0.003** |
| Symptoms (Dispnoea/Chest pain/Haemoptysis/Sincopa/Hypotension/Palpitation/No) | 17(29.3%)/16(27.1%)/0(0%)/1 (1.7%)/0(0%)/0(0%)/24(40.7%) | 36(34%)/31(29.2%)/7 (6.6%)/5(4.7%)/3(2.8%)/24(22.6 %) | 0.163 |
| Ecocardiography(Pathologic/No/ Did not performed) | 10(17.2%)/3(5.2%)/46(77.6%) | 24(22.6%)/7(6.5%)/73 (68.2%) | 0.217 |
| One month survival (Yes/No)** | 43(74.1%)/15(25.9%) | 85(81%)/20(19%) | 0.312 |
| Three months survivals(Yes/No)*** | 32 (59.3%)/22(40.7%) | 75(75%)/25(25%) | 0.044* |

* - p<0.05; **p<0.01; *** - no data for all patients

Statistically significant difference in the variable gender was identified, where it was shown that there was statistically higher number of the male patients and statistically lower number of the female patients in non-malignant group (54(50.9%); 52(49.1%)), (20(33.9%); 39(66.1%)), p=0.035. Also, statistically more trombophilic patients were identified in non malignant group of patients (12(11.2%), p=0.001**), than in the group of patients diagnosed with malignant disease (0 (0%)). Statistically, more ECG changes were identified in non malignant group of patients (58 (54.2%), p=0.003) than in patients diagnosed with malignancy (19 (32.8%)). Also, there was statistically higher three months survival in patients non diagnosed with malignancy (75 (75%)), than in patients with malignant disease (32(59.3%); p=0.044). Other variables did not reach statistically significant difference (Table 3).

Table 4 **The relationship of laboratory parameters of patients with PE between patients with malignant disease and without malignant disease.**

| | Malignant | Non-Malignant | p |
|---|---|---|---|
| LDH | 289 (212.5 - 339.75) | 265 (216 - 339) | 0.820 |
| AST | 24.5 (16.75 - 39) | 27 (20 - 39) | 0.202 |
| ALT | 18 (12 - 35.25) | 26 (17 - 40) | 0.033* |
| D dimer | 12.9 (8.57 – 27.6) | 10 (5.2 - 15.5) | 0.896 |
| Fibrinogen | 4.25 (3.17 - 5.8) | 5.4 (4 - 5.9) | 0.562 |
| Thrombocytes | 234 (166 - 310) | 222 (176 - 282) | 0.277 |
| Leukocytes | 9.26 ± 3.89 | 11.27 ± 17.28 | 0.076 |
| Haemoglobin | 120.22 ± 22.73 | 128.74 ± 26.23 | 0.000** |
| Haematocrit | 41.61 ± 45.72 | 39.39 ± 7.67 | 0.000** |
| Neutrophyls | 6.5 (4.75 - 8.8) | 6.5 (4.25 - 9.6) | 0.751 |
| Lymphcytes | 1 (0.75 - 1.4) | 1.6 (1.1 - 2) | 0.595 |
| Monocytes | 0.6 (0.5 - 0.95) | 0.6 (0.6 - 0.9) | 0.346 |
| Basophils | 0.005 (0 - 0.1) | 0.07 (0 - 0.1) | 0.797 |
| Eosinophils | 0.1 (0 - 0.1) | 0.1 (0 - 0.2) | 0.834 |
| Troponin | 34 (19 - 62.5) | 56 (17.75 - 124.5) | 0.053 |
| SII | 1434.4 (519.16 - 2938.233) | 863.82 (528.35 - 1589.75) | 0.124 |

*LDH – lactate dehidrogenase; AST – aspartate aminotranspherase; ALT – alanine aminotranspherase*
*SII- systemic immune-inflammation index*

Statitistically significant higher values of the variables ALT and hemoglobin were identified in non malignant group of patients (26 (17 – 40); (128.74 ± 26.23) than in patients diagnosed with malignancy (18(12 – 35.25); (120.22 ± 22.73) (p=0.033; p=0.000** respectively).

Also, statistically lower value of the variable Haematocrit (39.39 ± 7.67) was identified in non-malignant disease group of patients than in patients diagnosed with malignancy (41.61 ± 45.72) (p=0.000). Other variables did not reach statistically significant difference (Table 4).

Table 5 **The relationship between PE patients with malignant disease and without malignant disease in CT presentation of the disease, diagnostic and treatment approach and the treatment outcome**.

| | Malignant disease | Non-Malignant disease | p |
|---|---|---|---|
| Extent of PE (massive/lobar/segmental/subsegmental) | 33(55.9%)/26(45.1%) | 74(69.8%)/30(28.3%)/2(1.9%) | 0.072 |
| Infarction on CT (Yes/No) | 9(15.3%)/50(84.7%) | 24(22.6%)/82(77.4%) | 0.283 |
| Effusion on CT (Yes/No) | 23(39%)/36(61%) | 33(31.1%)/73(68.9%) | 0.278 |
| Infiltration on CT (Yes/No) | 35 (59.3%)/24(40.7%) | 37(34.9%)/69(65.1%) | 0.002* |
| Atelectasis on CT (Yes/No) | 29(49.2%)/30(50.8%) | 35(33%)/71(67%) | 0.032* |
| Previous PE (Yes/No) | 16 (27.6%)/42(72.4%) | 36(34%)/70(36%) | 0.381 |
| CD of veins (Yes/No/Did not performed) | 9(15.5%)/1(1.7%)/48 (82.8%) | 20(18.9%)/4(3.8%)/82 (77.4%) | 0.441 |
| Dignostic procedure (CT aniography/VP spect) | 57(96.6%)/1(1.7%) | 106(100%)/0(0%) | 0.176 |
| Method of treatment (UFH/LMWH/Vitamin K Antagonist) | 40(69%)/18(31%) | 83(78.3%)/23(21.7%) | 0.188 |
| Treatment outcome (Recovered/Death) | 52(89.7%)/6(10.3%) | 91(85.8%)/15 (14.2%) | 0.478 |

*CT-Computing Tomography; CD- Color Doppler; VP spect-Ventilation/Perfusion scintigraphy*
*UFH- unfractionized heparin; LMWH- low molecular weight heparin*

Statistically significant higher presentation of the Infiltration on CT (35(59.3%) and Atelectasis on CT (29(49.2%) (p=0.002, 0.032 respectively) was identified in patients with malignant disease compared to the group of patients non diagnosed with malignancy (33(31.1%); 37 (34.9%)). Other variables did not reach statistically significant difference (Table 5).

Table 6 **Relationship between one month survival, three months survival and laboratory parameters between PE patients with malignant disease and without malignant disease**.

| | | Malignant | | Non-Malignant | |
|---|---|---|---|---|---|
| | | One month survival | Three months survival | One month survival | Three months survival |
| Neutrophyls | p (rho) | 0.430 (0.01)** | 0.470 (0.006)** | 0.439 (0.001)** | 0.444 (0.001)** |
| Lymphcytes | p (rho) | -0.012 (0.928) | -0.055 (0.694) | -0.023 (0.816) | -0.148 (0.141) |
| Monocytes | p (rho) | -0.171 (0.323) | -0.175 (0.329) | -0.045 (0.749) | -0.049 (0.728) |
| Basophils | p (rho) | 0.182 (0.171) | 0.093 (0.503) | 0.044 (0.656) | -0.043 (0.669) |
| Eosinophils | p (rho) | 0.217 (0.102) | 0.182 (0.189) | -0.027 (0.783) | -0.117 (0.246) |
| SII | p (rho) | 0.524 (0.001)** | 0.605 (0.000)** | 0.417 (0.002)** | 0.421 (0.002)** |

Statistically significant positive correlation was identified between Neutrophyls and SII with parameters of one month survival and three months survival in eather malignant and non-malignant group of patients ($p<0.001$). Other variables did not reach statistically significant correlation.

## DISCUSSION

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are one of the most common complications in patients with malignancy. In the various worldwide studies and databases in Europe and North America, 17–29% of new venous thromboembolism (VTE) episodes occurred in patients with malignancy (11). In our study, the diagnosis of PE accompaning malignant disease was identified in 64.5% of cases. However, these data correlate with *RIETE* registry (Registro Informatizado de Enfermedad TromboEmbólica) which identified 44% of cancer patients with PE while in the *TESEO* Spanish cohort PE was present in 60.8% out of 939 evaluated patients (12,13).

The mean age of 171 patients with PE and malignant disease in our study is 71 (65 - 74) with higher incidence of female gender (66.1%) compared to males (33.9%), whereas smokers amounted 22.4% and ex-smokers 39.7%. PE in patients with non-malignant disease occured more frequently in male gender (50.9%) with predomination of smokers (34.9%). The study of Au C, et al., evaluated 581 patients, out of which 33.0% had a diagnosis of cancer. Patients diagnosed with malignancy tended to be older (64.8 vs. 58.5 years, $p < 0.01$) and were less likely to be active smokers (9.2% vs. 21.1%, $p < 0.01$), as compared to non-cancer subjects, which correlates with the results of our study (14).

Patients with cancer in the study of Au C, et al., were also less likely to present with chest pain (18.2% vs. 37.4%, $p < 0.01$) and syncope (2.7% vs. 6.6%, $p = 0.05$) (14). These data also correlate with the results of our study, where dyspnea, chest pain and syncope occurred more frequently in patients not diagnosed with malignancy 34% vs. 29.3%; 29.2% vs. 27.1%; 4.7% vs. 1.7%, respectively.

In the study of Gok M, et al., multivariable analysis showed that SII (systemic immune-inflammation index) defined as platelet × neutrophil/lymphocyte counts was an independent predictor for massive acute pulmonary embolism (OR 1.005 (95% CI 1.002-1.007), $p < .001$), as well as C-reactive protein and cardiac troponin (15). Also, in our study, the mean value of cardiac troponin level was increased in overall population diagnosed with PE 40 (15 – 85), whereas higher mean values were identified in non-malignant 56 (17.75 - 124.5) compared to patients with malignancy 34 (19 - 62.5), but the results did not reach statistical significance.

Our study did not result in positive correlation between the range of PE and differential blood cell count. However, statistically positive correlation, in our study, was identified between neutrophyls and SII with parameters of one month survival and three months survival in eather malignant and non-malignant patients ($p<0.001$).

Patients with malignancy and PE in our study had higher mean D-dimer values 12.9 (8.57 – 27.6) compared to non-malignant patients 10 (5.2 – 15.5), but the results did not reach statistical significance. Elevated D-dimer levels are independently associated with the diagnosis of cancer. The study of Felix G, et al., identified that patients with D-dimer >15 μg/mL presented a >2-fold higher risk of being diagnosed with a cancer condition in the upcoming 2 years. D-dimer was independent predictor of future cancer diagnosis: OR = 1.07 ((95 % CI: 1.01-1.14) per each 5 ng/mL increase; for patients with D-dimer >15.0 μg/mL the OR of future cancer was 2.10 (1.05-4.18) (16).

Our study identified statitistically higher value of hemoglobin in non malignant disease group of patients (128.74 ± 26.23) than in patients diagnosed with malignancy (120.22 ± 22.73) (p=0.000*). Also, statistically lower value of hematocrit (39.39 ± 7.67) was identified in non-malignant disease group of patients than in patients diagnosed with malignancy (41.61 ± 45.72) (p=0.000). In the study of Felix G, et al., anaemia was also used to predict the unknown cancer [OR = 2.13 (1.08-4.16)] (16).

The study of Jimenez-Fonseca P, et al., evaluated intrathoracic radiological findings that could have significant impact on prognosis in patients with PE and cancer. Among the most common findings atelectasis amounted 19.0% (17). Never the less, in our study, significantly higher presentation of infiltration (59.3%) and atelectasis on CT (49.2%) (p=0.002, 0.032) was identified in patients with malignant disease than in the group of patients not diagnosed with malignancy (31.1%; 34.9%, respectively). However, in the study of Taşçı F, et al., in patients with late-period mortality, atelectasis (32.6%) was found to be statistically significantly higher (18). This study included 389 patients out of which 11.6% had a fatal outcome in the early period following hospitalization, while 22.6% had a fatal outcome within the 90-day period after diagnosis.

In our study, there was statistically significant higher three months survival in patients without malignant disease (75 (75%)), compared to patients with malignant disease (32(59.3%); p=0.044). Peris M, et al., in the *ERJ* evaluated data from the *RIETE* registry to compare the 3-month outcomes in patients with active cancer and incidental PE versus those with clinically suspected and confirmed PE. The study identified that cancer patients with incidental PE had a lower mortality rate than those with clinically suspected and confirmed PE (19).

Liu J, et al., identified that the rate of all-cause death and PE-related death in patients with cancer were significantly higher than those without cancer (9.6% [86/899] *vs.* 2.6% [168/6539], *P* <0.001; 3.3% [30/899] *vs.* 1.3% [88/6539], *P* <0.001, respectively). Among 899 patients with PE and cancer, 86 (9.6%) died during hospitalization. Initial anticoagulation and surgery within 1 month were independent protective factors for all-cause in-hospital death (OR: 0.201, 95% CI: 0.114– 0.352, *P* <0.001; OR: 0.367, 95% CI: 0.137–0.981, *P* = 0.046, respectively) (20).

In the study of Au C, et al., cancer increased the risk of one-year mortality (adjusted HR 9.7, 95% CI 4.8-19.7, p < 0.01); without affecting in-hospital mortality (adjusted HR 2.9, 95% CI 0.86-9.87, p = 0.086). Patients with malignancy are generally presented with less severe PE and the diagnosis of malignancy did not independently increase the risk of in-hospital mortality among PE patients (14). However, in our study, the extent of PE, medicamentous treatment options nor treatment outcome did not result in any statistical significance between patients diagnosed with or without malignancy.

Recurrent PE in our study was identified in 16 (27.6%) patients with malignant disease and in 36(34%) patients without malignant disease, not resulting in statistical significance. In the study of Kraaijpoel N, et al., amounting 695 patients, anticoagulation therapy was initiated in 97% of patients, out of which 89% were treated with low-molecular-weight heparin. In patients with cancer with incidental pulmonary embolism, risk of recurrent venous thromboembolism is significant despite anticoagulant treatment. Patients with subsegmental pulmonary embolism seemed to have a risk of recurrent venous thromboembolism comparable to that of patients with more proximal clots (21).

There was no statisticaly significant difference in the treatment modality (UFH, LMWH or Vitamin K antagonists) between the patients diagnosed with or without malignant disease in our study. Therefore, treatment options, treatment prophylaxis for PE patients with malignant disease still remain the greatest challenge of all. However, thrombopro phylaxis is not routinely recommended for all outpatients with cancer. Thromboprophylaxis with NOAC or LMWH should be provided to selected high-risk outpatients with cancer. Most hospitalized patients with cancer and an acute medical condition require thromboprophylaxis throughout hospitalization. Patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days (22).

## CONCLUSION

The diagnosis and management of PE in cancer patients requires a multidisciplinary approach, to optimize diagnostic and treatment strategies and avoid complications. Diagnostic approach to the new onset or recurrent findings of acute PE, taking into consideration the extent of the entity, remains a challenge. The future findings related to the treatment of acute episodes of PE will most certainly refer to the systemic markers of inflammation, complete and differential blood cell count.

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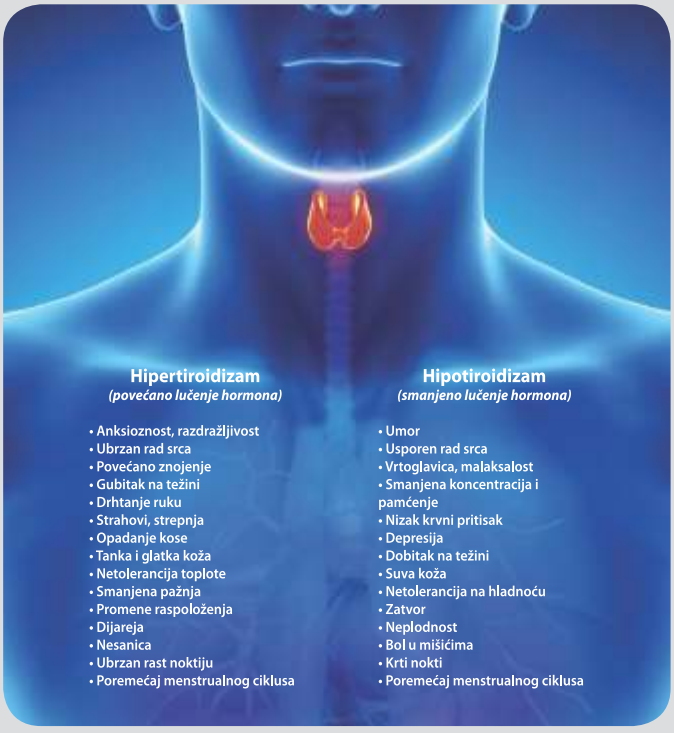

# Correlation between cytopathology and pathohistology of thyroid nodules-an institutional study

# Korelacija citološkog i patohistološkog nalaza kod tireoidnih čvorova-institucijska studija

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## ABSTRACT

Introduction: fine-needle aspiration (FNA) cytology has been an important diagnostic tool in the management of thyroid nodules. Introduced in 2017, revisedThe Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) set six categories (I-VI) for establishing diagnosis in order to standardize reporting and optimize clinical management. Aim:to evaluate the correlation between TBSRTC-based cytology and pathohistology results in the management of thyroid nodules in a tertiary referral center. Within TBSRTC, major diagnostic conandrums exist for indeterminate categories (III-V) with high levels of intra- and interobserver variability. Each TBSRTC category is assigned a risk of malignancy (ROM) calculated from the large meta-analyses, while the institutions are encouraged to calculate their own ROMs, reflecting the population. Our study tests a small fraction of Bosnian and Herzegovinian population as a part of the wider European population. Materials and methods: a descriptive, cross-sectional study of 50 patients with thyroid nodules, referred for FNA to the Clinic of Nuclear Medicine, Clinical Center University of Sarajevo. Each patient was assigned a TBSRTC category (I-VI), which guided the further management. All patients underwent surgery, and pathohistology was used for correlation.To assess FNA diagnostic performance, sensitivity, specificity, PPV and NPVwere calculated. Overall and category-based ROM were calculated. Results: study included 50 patients, 4 (8%) male and 46 (92,0%) female, age range 20-80 years, mean age 49.3 years. Overall sensitivity of FNA was 86.7%, specificity 100,0%, PPV 100,0% and NPV 83,3%. Overall rate of thyroid malignancy was 60%. According to Bethesda, six categories were distributed as follows (I-VI): 2 patients (4.0%), 4 (8,0%), 20 (40.0%), 15 (30.0%), 6 (12.0%) and 3 (6.0%). Calculated ROM per Bethesda category was (I-VI): 50%, 25%, 40%, 73.3%, 100%, and 100%, respectively. Conclusion: our results can be used for comparison purposes with TBSRTC. FNA sensitivity and NPV remain lower than clinically ideal, which is attributed to the cohort size, but also to the lack of routine molecular testing for thyroid cancer. Our rate of indeterminate (III-V) FNA results exceeds recommendations from TBSRTC and should be adjusted accordingly. Molecular testing for genetic alterations in thyroid cancer is recommended to be introduced in our clinical practice.

**Keywords:** thyroid nodule, FNA, cytology, Bethesda System, molecular testing

## SAŽETAK

Uvod: citološka aspiracija finom iglom (FNA) je značajna dijagnostička alatka u obradi tireoidnih čvorova. Uveden 2017. godine, Bethesda sistem klasifikacije citoloških nalaza štitnjače (TBSRTC) je uspostavio šest kategorija za dijagnosticiranje sa ciljem standardizacije i optimizacije liječenja. Cilj istraživanja: korelirati citološke nalaze prema TBSRTC sa patohistološkim nalazima kod tireoidnih nodusa u tercijarnom zdravstvenom centru. U TBSRTC su osnovni dijagnostički problem neodređene (III-V) kategorije za koje postoji visok stupanj intra- i interopservacijske varijabilnosti. Svaka TBSRTC kategorija nosi određeni rizik maligniteta (ROM) izračunat prema rezultatima meta-analiza. Zdravstvene ustanove se podstiču na izračunavanje svojih vlastitih ROM vrijednosti koje bi odražavale matičnu populaciju. Naše istraživanje ispituje mali uzorak bosansko-hercegovačke populacije kao dijela šire europske populacije. Materijali i metode: deskriptivno, presječno istraživanje na 50 pacijenata sa tireoidnim nodusima koji su upućeni na FNA na Kliniku za nuklearnu medicinu Kliničkog centra Univerziteta u Sarajevu. Pacijenti su svrstani u TBSRTC kategorije (I-VI) što je odredilo daljnji tok liječenja. Kod svih pacijenata je izvedena operativna resekcija, a patohistološki nalazi su korišteni za korelaciju. U svrhu procjene dijagnostičke preciznosti FNA, određeni su senzitivnost, specifičnost, PPV i NPV. Izračunati su ukupni rizici maligniteta i rizici maligniteta za pojedine Bethesda kategorije (I-VI). Rezultati: istraživanje je uključilo 50 pacijenata, 4 (8%) muškarca i 46 (92,0%) žena starosti 20-80 godina, u prosjeku 49,3 godine. Ukupna senzitivnost FNA je iznosila 86,7%, specifičnost 100,0%, PPV 100,0% i NPV 83,3%., a ukupna incidenca maligniteta 60%. Prema Bethesdi, ispitanici su razvrstani u kategorije (I-VI): 2 pacijenta (4,0%), 4 (8,0%), 20 (40,0%), 15 (30,0%), 6 (12,0%) i 3 (6,0%). ROM za

Bethesda kategorije (I-VI) je iznosio: 50%, 25%, 40%, 73,3%, 100% i 100%. Zaključak: rezultati istraživanja se mogu koristiti za usporedbu sa TBSRTC. Senzitivnost i NPV FNA su niži od klinički idealnih, što se pripisuje maloj kohorti i nedostatku rutinskog molekularnog testiranja kod karcinoma štitnjače. Broj pacijenata u neodređenim kategorijama (III-V) prevazilazi preporuke TBSRTC, i trebao bi biti prilagodjen. U budućnosti se preporučuje primjena molekularnog testiranja karcinoma štitnjače u svakodnevnoj kliničkoj praksi.

**Ključne riječi**: tireoidni čvor, FNA, citologija, Bethesda sistem, molekularno testiranje

## INTRODUCTION

In 2017, revised Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was introduced into clinical practice, firstly in the United States, and then worldwide, superseding the previously used 2007 Bethesda System. The Bethesda System is a standardized, category-based reporting system for thyroid fine-needle aspiration biopsy (FNA) (1,2).At our Institution, revised Bethesda System was put into practice shortly after its introduction.

Diagnostic algorithm for the management of thyroid nodules contains clinical examination, ultrasound, nuclear scan, FNA, and pathohistology, if surgery is performed. Necessary is to apply this algorithm step-wise, so that the evidence-based clinical steps are made according to the results of the diagnostic procedures performed at the earlier stages of the work-up (3).

Thyroid nodules are very common pathology with the reported incidence of 8-65% in the autopsy reports (4). Such incidence is multifactorial, and primarily depends on the population studied. Majority of thyroid nodules are benign, but due to their potential malignancy, they require a thorough work-up. Ultrasound is the most commonly used diagnostic method, with the advantages of high sensitivity, good safety profile, wide availability, reproducibility and low cost. Its role is important not only in characterization of palpable nodules, but also for detection of previously undetected nodules. Further characterization of thyroid nodules is achieved by fine-needle aspiration biopsy (5,6).Once the cytology specimens are obtained by FNA, TBSRTC is used for reporting. Newlyintroduced and revised TBSRTC version from 2017sets standardized and categorized criteria for establishing a diagnosis, together with the risk of malignancy, in order to aid further clinical management.

TBSRTC has six categories (Table 1): (I) nondiagnostic (ND) or unsatisfactory (US), (II) benign, (III) atypia of undetermined significance (AUS)/ follicular lesion of undetermined significance (FLUS), (IV) follicular neoplasm (FN) or suspicious for a follicular neoplasm (SFN), (V) suspicious for malignancy (SUSP), and (VI) malignant. Categories III-V are considered indeterminate as they fail to fulfill criteria for benignity or malignity, and present the biggest diagnostic conandrums.

Table 1 **The 2017 Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). Recommended Diagnostic Categories, Risk of Malignancies (ROMs) and Treatment Recommendations.**

| Bethesda Category | Definition | ROM (%) | Recommendation |
|---|---|---|---|
| I. Nondiagnostic (ND) or unsatisfactory (US) | Cyst fluid only; virtually acellular specimen; other (obscuring blood, clotting artifact, etc.) | | Repeat FNA with US guidance |
| II. Benign | Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.); consistent with lymphocytic (Hashimoto) thyreoiditis in the proper clinical context; consistent with granulomatous (subacute) thyreoiditis; others | 0-3% | Clinical and sonographic follow-up |
| III. Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) | | 5-15 % | Repeat FNA, molecular testing, or lobectomy |
| IV. Follicular neoplasm (FN) or suspicious for a follicular neoplasm (SFN) | | 15-30% | Molecular testing, lobectomy |
| V. Suspicious for malignancy (SUSP) | Suspicious for papillary carcinoma; suspicious for medullary carcinoma; suspicious for metastatic carcinoma; suspicious for lymphoma; others | 60-75% | Near-total thyreoidectomy or lobectomy |
| VI. Malignant | Papillary thyroid carcinoma; poorly differentiated carcinoma; medullary thyroid carcinoma; undifferentiated (anaplastic) carcinoma; squamos cell carcinoma; carcinoma with mixed features; metastatic carcinoma; non-Hodgkin lymphoma; others | 97-99% | Near-total thyreoidectomy or lobectomy |

*Source: Cibas SE, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology*

Each category of TBSRTC is assigned a risk of malignancy (ROM) that ranges from 0-3% for the benign category to 100% for the malignant category (1).Recommendation is for ROM tobe institution-based, and the large body of evidence must be collected for calculation(1). Innovations in 2017 TBSRTC are multiple. Much larger body of evidence is used for calculation of ROMs. Also, follicular variant of papillary thyroid cancer (PTC) is renamedtononinvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) due its indolent behavior. Even though NIFTP must be treated surgically, 2017 TBSRTC assigns different risks of malignancy, particularly to indeterminate categories (III-V), pending whether NIFTP is benign or malignant (1). Finally, molecular profiling is recommended based on the genomic research of thyroid oncogenesis (1).

When cytology report is created, the Bethesda category (I-VI) is added to the descriptive section of the report. The purpose of using Bethesda hereis to enable straightforward communication between cytologists and clinicians with maximum clarityin order to avoid different interpretations and patient treatment short of the optimal.

There is a very high concordance when reporting clearly benign and clearly malignant nodules. However, for indeterminate categories (III-V), a significant intra- and interobserver variability was noted. Moreover, categories III and IV have two subcategories each (AUS/FLUS and FN/SFN)that are synonymous, and should not be used interchangebly. The recommendation from 2017 TBSRTC is that every institution opts for one subcategory within categories III and IV, and uses themwith the descriptive section of the cytology findings (7).

Further management of thyroid nodules depends on FNA results, but also clinical examination and radiological imaging. It includes repeated FNA, follow-upand surgery.Clinicians face most diagnostic dilemmas in the management of categories III and IV, when the treatment options include repeated FNA, lobectomy and thyreoidectomy.When perofrmed, surgical treatment must be of an adequate extent in order to provide the best outcome for patients.

Treatment decisions are facilitated by developments in molecular biology and genomics.Advances in molecular and genomic research gave rise to an array of biological markers and their profiling. Biological markers (biomarkers) are quantifiable characteristics of biological processes that can be physiological, pathological or pharmacological (8). Biomarkers may play diagnostic or prognostic roles. When used in correlation with FNA, biomarkers of thyroid nodules,represented by alterations in genetic material,increase its sensitivity in detecting malignancy.There are different techniques of molecular testing of thyroid nodules: (a) testing for point mutations or translocations in genomic DNA from thyroid nodules, and (b) profiling of gene expression using mRNA (7). Most common mutations found in thyroid cancer are BRAF and RAS mutations as well as RET/PTC and PAX8/PPAR$\gamma$ chromosomal rearrangements, which together account for about 70% of genetic alterations in differentiated thyroid cancer (9,10).Molecular testingis very useful from the surgical point of viewbecause it helpsdeciding on the extension of thyroid surgery (lobectomy vs. thyreoidectomy) even before the operation.

## MATERIALS AND METHODS

We conducted a descriptive, cross-sectional study on50 patients with previously detected thyroid nodules by ultrasound who were referred to the Clinic of Nuclear Medicine, Clinical Center University of Sarajevo for further diagnostic work-up. We performed Tc-99m-pertechnetate nuclear scan, and then FNA under the ultrasound guidanance. Using TBSRTC, the cytology findings were categorized as: (I) nondiagnostic (ND) or unsatisfactory (US), (II) benign, (III) atypia of undetermined significance (AUS)/ follicular lesion of undetermined significance (FLUS), (IV) follicular neoplasm, including Hurthle cell neoplasm (FN)/suspicious for follicular neoplasm, including suspicious for Hurthle cell neoplasm (SFN), (V) suspicious for malignancy (SUSP) and (VI) malignant. Each Bethesda category was assigned a risk of malignancy (ROM) for the studied population. Cytology results, together with clinical and radiological findings, guided the further management. In all patients, surgery of different extent was performed, and pathohistology results obtained from different pathology labs were used for correlation purposes, as a gold standard. To assess FNA diagnostic performance, sensitivity, specificity, PPV and NPV were calculated. Overall and Bethesda category-based risk of malignancy was calculated. Descriptive statistical methods were used to calculate rates and percentages, where appropriate. MS Excel was used for statistical analysis.

## RESULTS

Our study included 50 patients, 4 (8%) males and 46 (92,0%) females, in the age range of 20-80 years, mean age 49,3 years. Stratification according to TBSRTC demonstrated: 2 (4%) patients in Category I, 4 (8%) in Category II, 20 (40%) in Category III, 15 (30%) in Category IV, 6 (12%) in Category V and 3 (6%) in Category VI (Table2).

All categories (I-VI) were included in the calculations because all patients underwent thyroid surgery, while patients from Category I were not subject to repeated FNA.

Table 2 **Stratification of patients according to TBSRTC.**

| Bethesda category | | Number | Percent | Cumulative Percent |
|---|---|---|---|---|
| | I | 2 | 4.0 | 4.0 |
| | II | 4 | 8.0 | 12.0 |
| | III | 20 | 40.0 | 52.0 |
| | IV | 15 | 30.0 | 82.0 |
| | V | 6 | 12.0 | 94.0 |
| | VI | 3 | 6.0 | 100.0 |
| | Total | 50 | 100.0 | |

When assessing diagnostic performance of FNA, true positives were Bethesda V or VI on FNA and positive on pathohistology, as well asthose positive for malignancy on pathohistology and Bethesda III or IV on FNA. False positives were Bethesda V or VIon FNA and negative for malignancy on pathohistology. True negatives were Bethesda I-IV on FNA and negative on pathohistology. False negatives were Bethesda I-IV on FNA, but positive on pathohistology.Using the appropriate formulas, sensitivity, specificity, PPV and NPV were calculated: sensitivity=TP/(TP+FN)]; specificity= [TN/(TN+FP)]; PPV=[TP/(TP+FP)]; NPV=[TN/(TN+FN)].

Overall diagnostic performance for FNA in detection of malignancy was: sensitivity 86,7%, specificity 100,0%, PPV 100.0%

and NPV 83,3%.The overall rate of thyroid malignancy was 60..0% (Table 3).

Table 3 **Diagnostic accuracy of FNA in detection of malignancy in thyroid nodules according to TBSRTC.**

| | P-H positive | P-H negative | |
|---|---|---|---|
| FNA positive | 26 | 0 | 26 |
| FNA negative | 4 | 20 | 24 |
| | 30 | 20 | 50 |

For each Bethesda category, we calculated the following ROM: 50% for Category I, 25% for Category II; 40% for Category III; 73.3% for Category IV, 100% for Category V and 100% for Category VI (Table 4).

Table 4 **Risk of malignancy (ROM) according to 2017 TBSRTC.**

| Bethesda category | | Number (% *) | | Total (%) |
|---|---|---|---|---|
| | | PH+ | PH- | |
| | I | 1 (50.0) | 1 (50.0) | 2 (4.0) |
| | II | 1 (25.0) | 3 (75.0) | 4 (8.0) |
| | III | 8 (40.0) | 12 (60.0) | 20 (40.0) |
| | IV | 11 (73.3) | 4 (26.7) | 15 (30.0) |
| | V | 6 (100.0) | 0 (0.0) | 6 (12.0) |
| | VI | 3 (100.0) | 0 (0.0) | 3 (6.0) |
| | Total | 30 (60.0) | 20 (40.0) | 50 (100.0) |

* Risk of malignancy was calculated for each Bethesda category

In our study, all patients underwent thyroid surgery based on cytology findings, clinical exams and radiological findings. Pathohistology results revealed malignancy in 30 (60,0%) cases and nonmalignancy in 20 (40,0%). Malignant diagnoses included papillary (23 patients), follicular (4) and medullary (2) thyroid cancer and one case of carcinoma NOS (nototherwise specified). All of them were treated with oncologic thyreoidectomy. Nonmalignant diagnoses included hyperplastic nodules (2 patients), nodular/multinodular goiter (9) and follicular adenoma (5). Follicular tumor of uncertain malignant potential (FT-UMP) in 3 patients was considered benign,surgically treated with lobectomy in two patients and referred to active follow-up, and total thyreoidectomy in one patient. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in 1 patient was also considered benign and treated with lobectomy and referred to follow-up.

As for surgery, total thyreoidectomy was performed in 35 (70%) patients, all 30patients with malignancies and 5 patientswho had hyperplastic nodules, multinodular goiter, follicular adenoma and one case of FT-UMP. In the remaining 15 (30% of patients), lobectomy was performed.

## DISCUSSION

Thyroid nodules account for majority of thyroid cases in referral to our Institution, which is a tertiarylevelhealth care facility. All patients presented with ultrasound findingsand were subject to diagnostic work-up if > 1 cm, but also if <1 cm if raised suspicion. Further evaluation of nodules >1 cm, but not exclusively, was done by FNA so that cytology results couldaid further management.American Thyroid Association (ATA) Guidelines (2015) include recommendations for initial evaluation, clinical and ultrasound criteria for FNA, interpretation of FNA results, use of molecular markers, and management of benign thyroid nodules (3). Studies suggest that 7-15% of thyroid nodules are malignant, depending on age, sex, history of head and neck irradiation, family history, and other factors (6). For this reason, it is of the utmost importance to evaluate thyroid nodules to exclude malignancy.

Our study included 50 patients, 4 (8%) males and 46 (92,0%) females. Such predominance of female patients is in accordance with the female prevalence in thyroid pathology,in general. According to ATA, thyroid pathology is 5-8% more prevalent in females (3).Calculated sensitivity, specificity, PPV and NPV were86,7%, 100%, 100%, and 83,3%, respectively. Such sensitivityis lower then desirable, but still clinically acceptable, most likely influenced by the inclusion of all six Bethesda categories into the calculation, and the small cohort. Our resuts are in part of sensitivitycomparable to the results of Acharya K, et al., (14) on 134 patients, who reported sensitivity and specificity of 89,4% and84,4%, respectively.

FNA results were categorized according toTBSRTC, andfor each Bethesda category, a ROM was calculated (Table 4).Our study included Category I (ND or US) in the calculations for the research purposes, and because both patients from this category underwent surgery without repeating FNA, having had clinical symptoms associated with enlarging goiters. Even though Category I delays making a diagnosis because it requiresrepeating FNA, the studies suggest that most nodules in this category are benign (11,12). Studies performed on large cohorts suggest that 2%-16% of all FNA samples fall in this group, with final resection in up to 26% and malignancy rate up to 32% (11,12). High ROM (50%) for this category (1 patient with medullary thyroid cancer) in our study exceeds by far the result of 5-10% from the large cohort studies referred to by TBSRTC (3), and could most probably be attributed to the small cohort. Category II refers to benign cytology, and the studies on large cohorts indicate a very low ROM (<3%) for this group (1,3,13).In our study, the assigned ROM forCategory II is 25,0%, and is caused by one case of papillary microcarcinoma. Cibas SE, et al., in TBSRTC report 0-3% (1), Acharya K, et al., on 134 patients report 11,7% (14), and Linhares SM, et al., on 1228 patients 11% (15). The higher rate from our study couldbe attributed to the very small cohort, but also the size of the malignant nodule. Categories III-V are considered indeterminate, as they do not fully qualify for malignancy. According to different studies, 10-40% of nodules are found indeterminate on cytology (10). All indeterminate categories (III-V) demonstrate high levels of intra- and interobserver variability. Reported are wide ranges of ROMs, somewhat lower within a category if NIFTP is notcancer then when it is (6%-18% and 10%-30%, respectively for III; 10-40% and 25-40%, respectively for IV; and 45-60% and 50-75%, respectively for V) (1). Our study assigned the following ROMs for indeterminate categories, with no discrimination toward NIFTP:45% for III, 73,3% for IV, and 100% for V. Our categories III and IVhave very high ROMs, which by far exceed the Bethesda risks. Also, in our study, Category III with 20 patients accounted for 40% of overall cases, and Category IV with 15 patients to 30%. Categories III and IV account for 70% of all cases in our study, while all indeterminate categories (III-V) account for 82%. Such valuesare considered very high, and are most probably attributable to the small cohort, less than optimal sample quality and discriminatory abilities of cytology for interpretation. For comparison purposes, in the study of Acharya K, et al., (14) on 134 patients, indeterminate

categories account for 40,3% of all cases, which is as low as half a value fromour study. According to Bethesda (1), only 20-30% of findings remain indeterminate (III-V). General 2017 TBSRTC recommendation is that AUS frequency in reporting is below 10% of cytology reports (1), which is by far exceededin our study.Reviewed literature reveals varyingROMs for Category III: Acharya K, et al., (14) and Abdulah N, et al., (17) reported 25.0%, Mahajan S, et al., (13) reported 33.3%, and Linhares SM, et al., 51%. According to Liu X, et al., (16), male sex, aspect ratio>1, microcalcification and BRAF mutationare strong predictors in AUS/FLUS, and indicate surgery. Recommendation here is to try to achieve the 2017 TBSRTC recommendations for all indeterminate categories, and Category III *per se*, when categorizing cytology results. For Category VI, calculated ROM is 100%, which is in a complete concordance with TBSRTC.

Correlation of pathohistology and ultrasound revealed that 45.1% of malignant nodules were hypoechogenic. Correlation of pathohistologyandscintigraphy revealed that 32% of nodules were cold, and 45.1% relatively cold, which is in accordance with the data from literature.

In 2017, revised TBSRTC introduced molecular testing of thyroid nodules as the further course of action, which is not available at our Institution. The aim is to increase specificity of FNA and ensure optimal clinical management (1). It is primarily recommended for indeterminate Bethesda categories (III-V), with the risks of malignancy of 10%-75% (1,2,9,10,18,19). The studies suggest that negative results of molecular testing reduce the risk of malignancy of Bethesda III and IV to 3-4%, which equals therisk of Bethesda II (benign).In that case, such nodules can be clinically followed-up and thyroid surgery avoided (18). Molecular testing is based on detection of genetic alterations that play role in thyroid oncogenesis. Most important are point mutations in BRAF and RAS oncogenes and gene rearrangements of RET/PTC and PAX8-PPAR$\gamma$. Established is that PTC most commonly harbors BRAF, than RAS and RET/PTC, while FTC harbors RAS or PAX8-PPAR$\gamma$.BRAF mutation is a valid diagnostic and prognostic marker. RAS mutation when present in a nodule, increases a cancer risk to 85% (18).

Advantage of our study is that it is the first of such design studies conducted in Bosnia and Herzegovina. It included a small fraction of the Bosnian and Herzegovinian population, as a part of the wider European population. It stratified FNA results into the Bethesda categories, and also assigned the ROMs to each Bethesda category, as per recommendation of 2017 TBSRTC that every institution should calculate its own ROMs based on the local population. We explored this idea, and found our ROMs to exceed the TBSRTC risks for all Bethesda grups. We attributed such findings to the very small cohort studied, as the main disadvantage of our study, but also to less than optimal cytology samples, and inherent limitations of cytology. Despite this, we are of the opinion that our results can be used for comparison purposes, and not as standard references for the clinical practice. Also, they could be indicative of pathology trends and related genetic alterationswithin the population, since the panel of oncogenic mutations emerging at a place primarily depends on the population. In order to be able to calculate clinically relevant institution-based ROMs for Bethesda categories, much larger cohort must be tested, which is our recommendation for future research. As the results of our study demonstrated high ROM's for indeterminate Bethesda categories, recommendation is also that we aim atreducingtheir frequency in reporting, particularly Category III (AUS/FLUS) to below 10% of the results, when diagnostically justifiable.In order to furtherly increase the specifity of FNA of thyroid nodules and assist clinical decision-making, we recommend molecular testing to be introduced. There are few available testing methods, most commonly applied is a 7-gene MT panel, for which commercially available kit exists. This kit tests for the most common alterations (BRAF, RAS, RET/PTC and PAX8-PPAR$\gamma$) and has a high sensitivity and PPV, but somewhat lower specificity of >90%. For that reason, the 7-gene MT panel cannot be considered a rule-out test. More recent 10-gene MT panel tests for more alterations, and has a higher specificity (18, 20). The results of molecular testing are interpreted in the context of Bethesda category of a nodule and the assigned ROM. Positive results escalate the risk of malignancy, indicating surgical treatment in a form of lobectomy or oncologic thyreoidectomy, pending the FNA results. Negative results deescalate the risk of malignancy, and the clinical management is adjusted accordingly. Molecular diagnostics, recognized in thyroid clinical practice and introduced into the National Comprehensive Cancer Network guidelines (NCCN) (21)remains our recommendation for thefuture development.By introducing molecular testing, thyroid carcinomas could be detected earlier, and unnecesarry invasive and costly surgical procedures could be avoided.

## CONCLUSION

Some adjustments to the current categorization rates of FNA results for thyroid nodules should be made per TBSRTC recommendations.Introduction of molecular testing in thyroid cancer on a wider basisis recommended in our clinical practice.

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# Malnutrition in liver cirrhosis: evaluating the relationship between subjective global assessment, Child-Turcotte-Pugh, and MELD-Na Scores

# Malnutricija kod ciroze jetre: procjena odnosa između PG SGA, Child-Turcotte-Pugh i MELD-Na rezultata

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## ABSTRACT

Introduction: cirrhosis, a chronic and irreversible liver disease, presents significant health and economic burdens. Malnutrition is related to the progression of liver dysfunction, leading to early complications, increased morbidity, and mortality. Aim: to compare nutritional status PG SGA (Patient generated Subjective Global Assessment) and the clinical scores (Child-Pugh) and (MELD-Na-Model of End-stage Liver Disease) in adult patients with liver cirrhosis. A comprehensive assessment of the relationship between these scores and the PG-Subjective Global Assessment can provide valuable insight into the interplay between malnutrition and liver disease progression. Materials and methods**:** demographic data (age, gender, cirrhosis etiology), Child-Pugh scores, and Model for End-Stage Liver Disease Na (MELD-Na) scores were collected from 114 patients. Nutritional status was evaluated using the Subjective Global Assessment tool, categorizing patients into A, B, and C based on the PG-SGA questionnaire. Statistical significance was set at $p \leq 0.05$. Results: significant correlations were found between PG-SGA scores and both Child-Pugh and MELD-Na scores ($p < 0.001$), indicating the utility of PG-SGA in assessing liver disease severity and nutritional status. Results revealed a significant gender disparity, with alcohol being the leading cause among males and autoimmune or biliary causes more common in females. Significant correlations were found between liver disease severity (Child-Pugh and MELD-Na scores) and nutritional status, as assessed by the PG-SGA rating, although no notable differences in PG-SGA ratings were observed across various etiologies. Conclusion: the PG-SGA assessment provides a simple and accessible means of identifying malnutrition in liver cirrhosis patients.

**Keywords:** cirrhosis, malnutrition, PG-Subjective Global Assessment

## SAŽETAK

Uvod: ciroza, hronična i ireverzibilna bolest jetre, predstavlja značajno opterećenje zdravstvenog i ekonomskog sistema. Malnutricija je povezana sa napredovanjem disfunkcije jetre, što dovodi do ranih komplikacija, povećanog morbiditeta i mortaliteta. Cilj: komparacija nutritivnog statusa PG SGA (Subjektivna globalna procjena generisana od strane pacijenata) i rezultata kliničkih testova (Child-Pugh i MELD Na) kod odraslih pacijenata sa cirozom jetre. Sveobuhvatna procjena odnosa između ovih rezultata i PG SGA može pružiti vrijedan uvid u međusobnu povezanost malnutricije i stadija jetrenog oboljenja. Materijali i metode: demografski podaci (starost, pol, etiologija ciroze), Child-Pugh skor i MELD. Na skor su prikupljeni na uzorku od 114 pacijenata. Nutritivni status je procijenjen korištenjem PG SGA upitnika, nas osnovu koje su pacijenti kategorizirani u A, B ili C grupu. Statistička značajnost je postavljena na $p \leq 0,05$. Rezultati: potvrđene su značajne korelacije između PG-SGA rezultata i Child-Pugh i MELD Na skora ($p < 0,001$), što ukazuje na korisnost PG-SGA u procjeni stepena jetrenog oboljenja i nutritivnog statusa. Rezultati ukazuju da je alkohol vodeći uzrok bolesti kod pacijenata muškog pola, dok su autoimuni ili bilijarni uzroci češći kod pacijenata ženskog pola. Pronađene su značajne korelacije između klinički verificiranog stadija bolesti (Child-Pugh i MELD-Na rezultati) i nutritivnog statusa koji je određen putem PG-SGA upitnika. Nisu uočene značajne razlike u PG SGA ocjenama kod različite etiologije ciroze. Zaključak: PG SGA procjena nutritivnog statusa pruža jednostavan i pristupačan način za otkrivanje malnutricije kod pacijenata s cirozom jetre.

**Ključne riječi:** ciroza, malnutricija, PG-SGA, MELD-Na, Child-Pugh skor

## INTRODUCTION

Cirrhosis is the incurable late and irreversible stage of chronic liver disease. During progression from the compensation to the decompensation stage, many morbidities and mortality can occur (1).

Liver cirrhosis (LC) decompensation is characterized by the development of ascites, gastrointestinal bleeding, hepatic

encephalopathy, kidney dysfunction, and infectious complications, dramatically affecting the disease course and patients' survival (2). Liver diseases account for approximately 2 million deaths worldwide per year with about half the numbers due to complications related to liver cirrhosis (3).

The Hepahealth report from 2018 reported a prevalence of chronic liver disease and cirrhosis in Europe between 500 and 1100 cases per 100.000 inhabitants (4).

There are many causes and risk factors that can cause liver diseases. In the 20th century, viral hepatitis was the most common cause of chronic endemic liver disease (5). However, due to the effective prevention of hepatitis virus, there are still many other causes that can be involved in developing liver disease, such as alcohol, drugs, poisons, and parenteral nutrition. There are also many causes with unknown etiology, but they are being discovered more in the present. At present, with the increasing prevalence of obesity and diabetes, and the use of powerful drugs in treating diabetes agents, the risk of nonalcoholic fatty liver disease (NASH) is increased and has the potential to become one of the leading causes of liver disease

Malnutrition is a significant concern and common complication among patients with liver cirrhosis, as it can contribute to various adverse health outcomes, including increased susceptibility to infections, prolonged hospital stays, and even higher mortality rates (6).

Identifying these patients is crucial, as malnutrition has been associated with increased risk of complications, such as hepatic encephalopathy, ascites, and infection.

Nutritional assessment is the systematic process of collecting and interpreting information in order to make decisions about the nature and cause of nutrition related health issues that affect an individual (British Dietetic Association, 2012).

The Subjective Global Assessment (SGA) is a widely used tool for assessing nutritional status in cirrhotic patients, and it has been shown to correlate with disease severity and prognosis (7).

The Patient-Generated Subjective Global Assessment (PG-SGA) was created by Faith Ottery in 1996 on the basis of SGA for nutritional assessment of cancer patients and was further improved (8,9).

In PG-SGA system, the components of the medical history are completed by the patient himself, and physical examination is performed by health professional either nurses/technician or health-care professionals. The scored PG-SGA is a further advancement of PG-SGA which provides numerical scoring as well as a global rating in form of well nourished, moderately malnourished, or severely malnourished. For each component of the scored PG-SGA, points (0-4) are awarded depending on the impact of the symptom on nutritional status. A sum of total score provides a guideline to the level of nutritional intervention.

Today, the PG-SGA is considered a reference method for the assessment of malnutrition in cancer patients [9]. This tool was also validated in intensive care unit patients, ischemic stroke and chronic kidney disease patients (8-10).

The Child-Turcotte-Pugh (CTP) score and the Model for End-Stage Liver Disease Na (MELD-Na) score are commonly used clinical scores to evaluate the severity of liver disease and predict the prognosis of patients with cirrhosis.

The Child-Pugh scoring system (also known as the Child-Pugh-Turcotte score) was designed to predict mortality in cirrhosis patients. Originally conceptualized by Child and Turcotte in 1964 to guide the selection of patients who would benefit from elective surgery for portal decompression, it broke down patients into three categories: A – good hepatic function, B – moderately impaired hepatic function, and C – advanced hepatic dysfunction. Their original scoring system used five clinical and laboratory criteria to categorize patients: serum bilirubin, serum albumin, ascites, neurological disorder, and clinical nutrition status (10). The original Child-Turcotte scale recognized the prognostic importance of nutritional status, but Pugh subsequently replaced it with the prothrombin time in 1973 (11).

Additionally, they introduced variable points for each criterion based on increasing severity (12).

The Child-Pugh score has been validated as a predictor of postoperative mortality after portocaval shunt surgery and predicts mortality risk associated with other major operations. After abdominal surgery, Child class A patients have a 10% mortality rate; Child class B patients have a 30% mortality rate, and Child class C patients have a 70 to 80% mortality rate (13,14).

The Model for End-Stage Liver Disease, or MELD, is a scoring system for assessing the severity of chronic liver disease. MELD uses the patient's values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time (INR) to predict survival. It is calculated according to formula: MELD = 3.78 × ln [bilirubin (mg/dL)] + 11.2 × ln [INR] + 9.57 × ln [creatinine (mg/dL)] + 6.43: MELD scores are reported as whole numbers, so the result is rounded (15).

The MELD-sodium (MELD-Na) score has replaced MELD for organ allocation for liver transplantation (16).

## AIM

The aim of this study was to compare nutritional status assessed by PG-SGA (Patient Generated Subjective Global Assessment) and the clinical scores CP (Child-Pugh) and MELD Na (Model of End-stage Liver Disease) in adult patients with liver cirrhosis. As a second aim we tried to emphases the importance of nutritional assessment in patients with liver cirrhosis, especially those with advanced disease.

## MATERIALS AND METHODS

This was a cohort study conducted in the period from September 2018 to September 2020. The study included 114 patients hospitalized at the Clinical Centre University of Sarajevo with LC diagnosis.

Written consent was obtained for all the patients included in this study, which was approved by the Ethical Committee of the CCUS.

PG-SGA version used in the study (available at http://pt-global.org) was translated into Bosnian language.

PG-SGA was used to assess the nutritional status of patients. PG-SGA allocates patients to 3 categories: well-nourished (Stage A), moderate/suspected malnutrition (Stage B), and severely malnourished (Stage C).

The remaining portions of the PG-SGA are to be completed by a professional (physician, nurse, or dietitian).

Physical components include loss of subcutaneous fat (e.g., triceps region and midaxillary line at the level of the lower ribs), muscle wasting (e.g., temporal areas, deltoids, and quadriceps with a loss of bulk and tone by palpation), and edema (e.g., ankle or sacral) or ascites.

An additive numerical PG-SGA score is used to define specific nutritional interventions. The triage based on the PG-SGA numeric score includes the following: no intervention required at this time

(0–1); patient and family education by dietitian, nurse, or other clinician with pharmacological intervention as indicated by the symptom survey and lab values as appropriate (2–3); requires intervention by a dietitian, in conjunction with a nurse or physician as indicated by symptoms (4–8); and indicates a critical need for improved symptom management and/or nutrient intervention options (≥ 9).

The numerical PG-SGA score provides professionals with clearer guidelines as to the level of medical nutrition therapy needed in a given case, while the A, B, or C rating provides an overall picture of a patient's current status.

CTP and MELD-Na score as clinical tools for estimation of the severity LD.

CTP score: This scoring was done using format of CTP scoring (12). Child Pugh's Score was classified as: A (5–6), B (7–9) and C (10–15). MELD-Na score: Model for End Stage Liver Diseases scoring was done by using preset format. This will be calculated by using following formula (17):

$$MELD\text{-}Na = MELD + 1.32 \times (137 - Na) - [0.033 \times MELD \times (137 - Na)]$$

The maximum MELD score is 40. MELD-Na is a continuous score, the higher score the patient gets, the more severe is the liver cirrhosis and the patient is prioritized more for liver transplantation.

For easy interpretation, MELD-Na score is classified into three categories (18): Mild liver disease (score 6–15), Moderate liver disease (score 16–24), and severe liver disease (score ≥ 25).

All statistical analyses were conducted using the appropriate software. To assess the normality of the age distribution, the Kolmogorov-Smirnov test was performed. For normally distributed data, the mean ($x$) and standard deviation ($\sigma$) were used to express central tendency and dispersion, respectively, while for non-normally distributed data, the median ($\tilde{x}$) and interquartile range ($\Delta Q$) were employed. Comparisons of means ($x$) between groups were carried out using Student's t-test for normally distributed data. For categorical variables, differences between groups were evaluated using the Pearson chi-square ($\chi^2$) test. The Spearman rank correlation ($\rho$) was employed to examine the association between non-parametric variables, while the Independent-Samples Mann-Whitney $U$ Test was used to compare medians between two independent groups. A one-sample binomial test was applied to assess the gender distribution within the cohort. Statistical significance was set at $p < 0.05$ for all analyses.

## RESULTS

The study included a cohort of 114 patients, with 77 (67.5%) males and 37 (32.5%) females (Table 1). The overall average age in the study cohort was 60, with a standard deviation of 12. Notably, the male proportion was significantly higher, as confirmed by a one-sample binomial test ($p$ <0.001). The age distribution was assessed to be normal based on the Kolmogorov-Smirnov test ($p = 0.084$), which can be visualized in the histogram (Figure 1). Furthermore, no statistically significant difference in mean values was observed, as determined by Student's $t$-test ($p = 0.064$).

Table 1 **Gender distribution and age statistics of patients in the study cohort**.

| | | | | Age (years) | |
|---|---|---|---|---|---|
| | | $N$ | % | $x$ | $\sigma$ |
| Gender | Male | 77 | 67.5% | 59 | 11 |
| | Female | 37 | 32.5% | 63 | 13 |
| | Total | 114 | 100.0% | 60 | 12 |

Number of males is significantly larger (one-sample binomial test, $p < 0.001$), age distribution is normal (Kolmogorov-Smirnov test, $p = 0.084$).

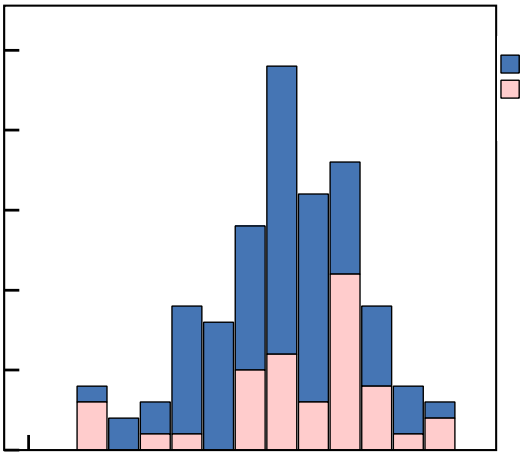

Figure 1 **Age by gender. Distribution is normal (Kolmogorov-Smirnov test, $p = 0.084$).**

The information provided in Figure 2 suggests a notable gender-based difference in the frequency of liver disease etiologies. The data was analyzed using a Pearson $\chi^2$ test, and the results indicated a significant distinction between the two genders ($p <$ 0.001).

For males, alcohol appears to be the predominant cause of liver diseases, accounting for 50.6% of cases. Following closely behind is viral etiology at 37.7%. Alcohol is a much less common primary cause for liver diseases among females, representing only 8.1% of cases. Viral etiologies contribute to 45.9% of cases. Additionally, autoimmune (24.3%) and biliary (13.5%) etiologies are more prominent among females.

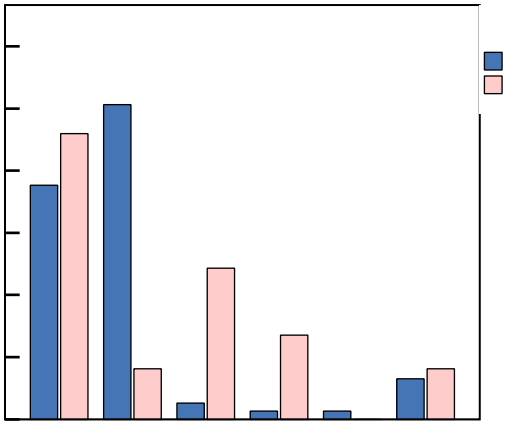

Figure 2 **Etiology of liver disease by gender in the examined group. The differences between genders are significant (Pearson $\chi^2$ test, $p < 0.001$).**

The information provided in Figure 3 demonstrates the mean Model for End-Stage Liver Disease -Na (MELD-Na) scores for each Child-Pugh Score class. The analysis indicates a strong correlation between MELD-Na scores and Child-Pugh classes, and this correlation has been deemed statistically significant according to the Spearman $\rho$ test ($p < 0.001$).

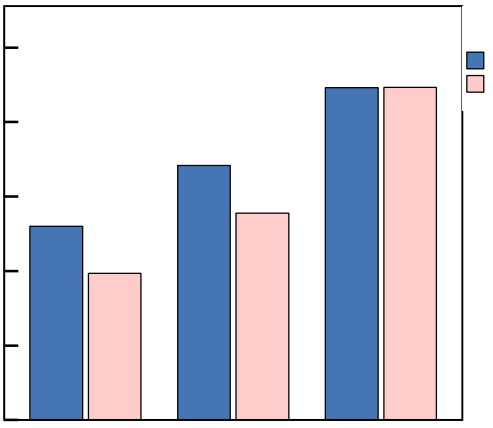

Figure 3 **Mean Model for End-Stage Liver Disease-Na (MELD-Na) scores for each Child-Pugh Score class. The strong correlation between MELD-Na scores and Child-Pugh classes is statistically significant (Spearman $\rho$ test, $p < 0.001$).**

Table 2 displays the distribution of liver cirrhosis severity using the Child-Pugh score across various etiologies. A significant proportion of patients with biliary cirrhosis (83.3%) are classified under Child-Pugh Class A, indicating less severe disease. In contrast, patients with alcohol-related and autoimmune cirrhosis have higher proportions in Child-Pugh Class C, suggesting more severe disease.

Table 2 **Distribution of liver cirrhosis severity by Child-Pugh score across different etiologies.**

| | | Etiology Type | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Viral | | Alcohol | | Autoimmune | | Biliary | | Cardiogenic | | Cryptogenic | | Total | |
| | | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % |
| **Child-Pugh score** | A | 15 | 32.6 | 5 | 11.9 | 4 | 36.4 | 5 | 83.3 | 0 | 0.0 | 0 | 0.0 | 29 | 25.4 |
| | B | 18 | 39.1 | 18 | 42.9 | 2 | 18.2 | 0 | 0.0 | 0 | 0.0 | 6 | 75.0 | 44 | 38.6 |
| | C | 13 | 28.3 | 19 | 45.2 | 5 | 45.5 | 1 | 16.7 | 1 | 100.0 | 2 | 25.0 | 41 | 36.0 |
| | Total | 46 | 100.0 | 42 | 100.0 | 11 | 100.0 | 6 | 100.0 | 1 | 100.0 | 8 | 100.0 | 114 | 100.0 |

Table 3 shows the distribution of liver cirrhosis severity according to the MELD-Na score across various etiologies. Among patients with auto-immune liver disease, 72.7% are classified as having mild disease, while 66.7% of biliary etiology cases fall under mild disease as well. In contrast, severe liver disease is most prevalent in the alcohol-related group (26.2%) and the cryptogenic group (37.5%).

Table 3 **Distribution of liver cirrhosis severity based on Model for End-Stage Liver Disease-Na (MELD-Na) score by etiology type.**

| | | Etiology Type | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Viral | | Alcohol | | Auto-immune | | Biliary | | Cardio-genic | | Crypto-genic | | Total | |
| | | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % |
| **MELD-Na** | Mild liver disease | 23 | 50.0 | 16 | 38.1 | 8 | 72.7 | 4 | 66.7 | 1 | 100.0 | 3 | 37.5 | 55 | 48.2 |
| | Moderate liver disease | 17 | 37.0 | 15 | 35.7 | 2 | 18.2 | 1 | 16.7 | 0 | 0.0 | 2 | 25.0 | 37 | 32.5 |
| | Severe liver disease | 6 | 13.0 | 11 | 26.2 | 1 | 9.1 | 1 | 16.7 | 0 | 0.0 | 3 | 37.5 | 22 | 19.3 |
| | Total | 46 | 100 | 42 | 100 | 11 | 100 | 6 | 100 | 1 | 100 | 8 | 100 | 114 | 100 |

Figure 4 illustrates a boxplot of PG-SGA score distribution in relation to PG-SGA stage rating. The analysis indicates a strong positive correlation between the two variables, and this correlation is found to be statistically significant for both male and female patients according to the Spearman $\rho$ test ($p < 0.001$). This correlation implies that as PG-SGA stage ratings increase, there is a corresponding increase in PG-SGA scores. Indeed, the PG-SGA score ($x \pm \sigma$) increases progressively across the groups, rising from

6.8±4.2 in group A, to 8.9±5.2 in group B, and further to 12.6±4.8 in group C.

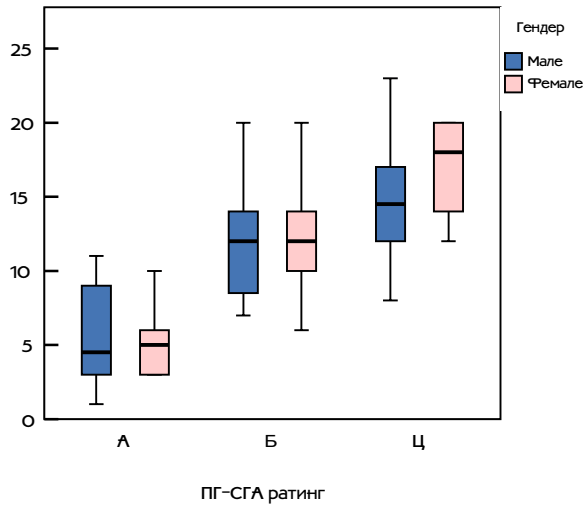


Figure 4 **Boxplot of Patient-Generated Subjective Global Assessment (PG-SGA) score distribution with respect to PG-SGA stage rating. The strong correlation between two variables is significant for both male and female patients (Spearman $\rho$ test, $p < 0.001$). No significant difference between male and female patients in PG-SGA score exists (Independent-Samples Mann-Whitney $U$ Test, $p = 1.000$).**

Table 4 presents the median ($\tilde{x}$) and interquartile range (IQR) of MELD-Na scores for each PG-SGA rating and gender. The $p$ value for PG-SGA rating A indicates that there is a statistically significant difference in the median scores between male and female patients, as tested by the Independent-Samples Mann-Whitney $U$ Test. For PG-SGA rating A, the median MELD-Na score is lower in females (9) compared to males (12), with a statistically significant difference ($p = 0.026$). There is no significant difference in MELD-Na scores between genders for PG-SGA ratings B and C, where the median scores (20) are similar across both groups.

Table 4 **Median ($\tilde{x}$) and interquartile range (IQR) of Model for End-Stage Liver Disease-Na (MELD-Na) scores for each Subjective Global Assessment (SGA) rating and gender**.

| | | MELD-Na score | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Gender | | | | Total | | $p$ |
| | | Male | | Female | | | | |
| | | $\tilde{x}$ | IQR | $\tilde{x}$ | IQR | $\tilde{x}$ | IQR | |
| SGA rating | A | 12 | 10 | 9 | 6 | 12 | 7 | 0.026 |
| | B | 20 | 9 | 20 | 6 | 20 | 9 | 1.000 |
| | C | 21 | 13 | 17 | 21 | 20 | 15 | 0.685 |

The correlation between PG-SGA rating and MELD-Na score is significant (Spearman $\rho$ test, $p < 0.001$), The $p$ value indicates if there is a statistically significant difference in the median scores between male and female patients, as tested by the Independent-Samples Mann-Whitney $U$ Test.

Table 5 shows the number of patients with different nutritional statuses as evaluated using the PG-SGA rating system across various Child-Pugh score categories. As expected, the proportion of well-nourished patients is highest in those with a Child-Pugh score of A (47.1%), decreases to 45.1% for those with a score of B, and drops further to only 7.8% for score C. Meanwhile, the number of moderately or severely malnourished patients increases as the Child-Pugh score rises. The correlation between two variables is reported as significant (Spearman $\rho$ test, $p < 0.001$). This indicates a strong relationship between the nutritional status assessed by PG-SGA rating and the severity of liver disease assessed by Child-Pugh score.

Figure 5 displays the frequency of different PG-SGA ratings across various etiologies of liver disease. The graph illustrates how the distribution of PG-SGA ratings varies across different causes of liver disease. According to the results of the Pearson $\chi^2$ test, the differences in the distribution of PG-SGA ratings among the various etiology categories were found to be not statistically significant ($p = 0.771$). This suggests that there are no substantial variations in the distribution of PG-SGA ratings across different causes of liver disease.

Table 5 **Number (*N*) and frequency (%) of Patient-Generated Subjective Global Assessment (PG-SGA) rating scores for patient groups with different Child-Pugh scores.**

| | | Child-Pugh score | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | A | | B | | C | | Total | |
| | | *N* | % | *N* | % | *N* | % | *N* | % |
| PG-SGA rating | A: Well-nourished | 24 | 47.1% | 23 | 45.1% | 4 | 7.8% | 51 | 100.0% |
| | B: Mild/moderately malnourished | 4 | 11.1% | 11 | 30.6% | 21 | 58.3% | 36 | 100.0% |
| | C: Severely malnourished | 1 | 3.7% | 10 | 37.0% | 16 | 59.3% | 27 | 100.0% |
| | Total | 29 | 25.4% | 44 | 38.6% | 41 | 36.0% | 114 | 100.0% |

The correlation between PG-SGA rating and Child-Pugh score is significant (Spearman $\rho$ test, $p < 0.001$), The differences amongst different Child-Pugh score classes are significant (Pearson $\chi^2$ test, $p < 0.001$).

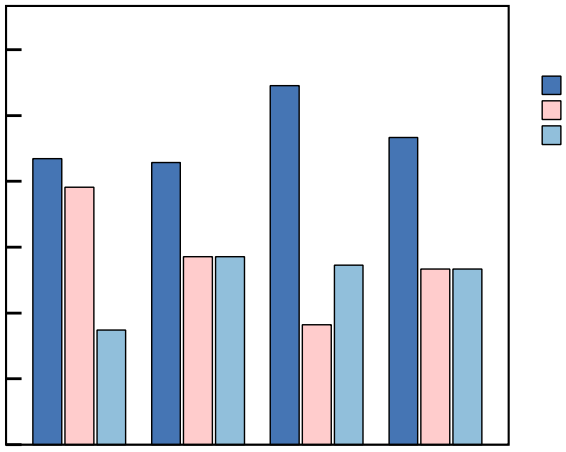

Figure 5 **Frequency of different PG-SGA ratings in different etiologies of liver disease. No significant differences amongst etiology categories were found (Pearson $\chi^2$ test, $p = 0.771$).**

## DISCUSSION

Malnutrition is a prevalent and often underdiagnosed issue among patients with liver cirrhosis (19) and has been shown to be closely associated with increased risk of mortality and morbidity in this patients (20,21).

The average malnutrition prevalence in CLD measured using different diagnostic tools is 36.4% (10-80.3%) respectively. Some studies reporting prevalence rates ranging from 20% to 80% (22). Malnutrition prevalence in patients with compensated and decompensated cirrhosis was 39.9% and 44.1%, respectively.

The results of our study showed a much higher percentage of males (67.5%) compared to females (32.5%), as confirmed by a one-sample binomial test ($p < 0.001$). Other studies also have found similar results highlighted the predominance of males in liver cirrhosis cases (23-25). In our study alcohol appears to be the predominant cause of liver diseases, accounting for 50.6% of cases as reported in study by Durazzo M, et al. (26).

As for the female patients, a different pattern was noticed. Viral etiologies contributed up to 45.9% of cases. In the study by Mishra D et al., viral hepatitis, particularly hepatitis B and C, accounts for a significant proportion of liver cirrhosis cases, with some studies reporting that approximately 20% of cirrhosis is related to viral hepatitis (27). This could be explained by variations in study populations and regional prevalence of viral infections.

There is statistically significant correlation between MELD-Na scores and Child-Pugh classes, as demonstrated by the Spearman $\rho$ test ($p < 0.001$). This underscores the strong correlation between these two widely used scoring systems for assessing liver disease severity. While the MELD Na score offers a more dynamic view of liver function by relying on objective laboratory values, the Child-Pugh score includes clinical features that provide further insights into the patient's condition. In clinical practice, the combined use of these scoring systems can improve decision-making in managing patients with end-stage liver disease. By recognizing the strengths of each system, healthcare providers can better tailor treatments and interventions for patients with advanced liver disease.

As shown in Table 2, analysis of the distribution of liver cirrhosis severity across various etiologies offer important insights into how different causes of cirrhosis impact disease progression. Our findings indicating that the majority of patients with biliary cirrhosis (83.3%) are classified in Child-Pugh Class A, indicating that this group tends to have less severe disease.

In contrast, patients with alcohol-related cirrhosis and autoimmune cirrhosis show a much higher prevalence of severe liver disease, with 45.2% and 45.5% of patients, respectively, falling into Child-Pugh Class C. This aligns with existing literature, as alcohol-related cirrhosis is often diagnosed at an advanced stage due to delayed presentation and continued alcohol consumption (28). Autoimmune cirrhosis, despite immunosuppressive therapy, can also progress rapidly in some patients, leading to higher rates of severe liver dysfunction (29).

The ESPEN 2006 guidelines estimate malnutrition prevalence in cirrhotic patients ranging from 65% to 90%, recommending tools such as SGA, hand grip strength, and anthropometric analysis for nutritional assessment (30).

SGA is a widely recognized tool for evaluating nutritional status in patients with cirrhosis and correlates with the severity and prognosis of the disease. Accurate nutritional assessment allows early identification and management, improving patient outcomes and quality of life (7).

The PG-SGA is recognized as the gold standard for oncology patients by the Oncology Nutrition Dietetic Practice Group of the American Dietetic Association, with a score above 9 indicating a need for intervention (31). PG-SGA is also suitable for detecting nutritional issues in gynecological cancer patients (32). In a study by Bauer et al., the PG-SGA demonstrated a sensitivity of 98% and a specificity of 82% for predicting malnutrition in 71 cancer patients (33). According to above mentioned studies PG SGA is highly effective in screening for malnutrition, identifying risk factors, assessing nutritional status, and recommending interventions.

The first four sections of the PG-SGA - weight history, food intake, symptoms, and activities/function were completed by the patient. This patient-generated component has two purposes: to directly engage the patient in their care, fostering both problem identification and patient empowerment and secondly to use a minimal amount of time from health professionals. Such engagement helps address the root cause of the problem, giving the patient better awareness of their nutritional status.

Ideally, patients should complete the PG-SGA themselves, as their performance regarding food intake, symptoms, and functional status can be reliably assessed but, in some cases, different circumstances like severe visual impairment, illiteracy, or language barriers may make it difficult for patients.

As shown in Figure 4, the strong correlation between PG-SGA scores and stage ratings supports PG-SGA's reliability in assessing nutritional status in liver cirrhosis patients. As the stage rating increases from A (well-nourished) to C (severely malnourished), there is a corresponding rise in PG-SGA scores, which is expected knowing that worsening of nutritional status is typically seen in patients with advanced liver disease. This finding aligns with previous studies that have validated the use of PG-SGA in cirrhotic patients with malnutrition as a critical factor affecting clinical outcomes (34).

The consistency of PG-SGA scores across genders suggests that the tool is equally applicable to both male and female patients in assessing malnutrition. This implies that clinicians can apply this tool uniformly in both male and female patients when planning nutritional interventions and managing complications related to malnutrition.

The analysis of MELD-Na scores by PG-SGA rating and gender, as shown in Table 4, provides further insights into the relationship between liver disease severity and nutritional status.

Well-nourished female patients (PG-SGA rating A) tend to have lower median MELD-Na scores (9) compared to males (12), indicating that females may exhibit less severe liver disease at this stage. This difference could reflect gender-related physiological variations in liver disease progression or differences in responses to nutritional interventions.

However, for patients with moderate to severe malnutrition (PG-SGA ratings B and C), there were no significant gender differences in MELD-Na scores, suggesting that as malnutrition worsens, liver disease severity becomes comparable in both males and females. This has important clinical implications. While gender may influence early-stage liver disease, in patients with moderate to severe malnutrition, the focus should be on aggressive nutritional interventions and liver disease management, as the severity is similarly high across genders.

Also, there is strong correlation between the PG-SGA rating system and Child-Pugh score categories, where we presented the close relationship between nutritional status and the severity of liver disease (Table 5).

These results align with previous research showing that as liver disease progresses malnutrition becomes more prevalent due to factors such as reduced appetite, metabolic disturbances, and malabsorption (35).

Sapkota Y, et al, in their study (36) also revealed statistically significant association of PG-SGA with CTP class and MELD-Na which is similar to the results obtained from study conducted in Romania by significantly correlated with Child-Pugh, and MELD-Na scores (37).

Interestingly, no significant differences were observed in PG-SGA rating distribution across various liver disease etiologies ($p = 0.771$), as shown in Figure 5, suggesting that the cause of liver disease whether alcohol-related, viral, biliary, or autoimmune does not significantly affect nutritional status. This indicates that malnutrition is a critical issue across all forms of liver cirrhosis. Reisman Y, et al. (38) in their study also reported that malnutrition prevalence was not different according to etiology, and if any, is negligible.

The main limitation of our study has been the relatively small number of patients. The present study explicitly relates to the nutritional status of chronic liver disease patients.

## CONCLUSION

Our findings suggest that malnutrition is prevalent across all etiologies of liver cirrhosis, regardless of the etiology. The PG-SGA proves to be a reliable tool for assessing nutritional status. Early nutritional interventions, along with the combined use of Child-Pugh and MELD Na scored are essential in optimizing patient care, preventing malnutrition, and improving outcomes in patients with liver cirrhosis.

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# The outcomes and complications of pancreaticoduodenectomy (Whipple procedure): cross sectional study

# Ishodi i komplikacije pankreatikoduodenektomije (Whipple postupak): studija presjeka

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## ABSTRACT

Introduction: pancreaticoduodenectomy or Whipple's operation is one of the most complex and difficult operations with a very high rate of complications in terms of pancreatic fistulas, bleeding, anastomosis dehiscence, wound infection, wound dehiscence, dumping syndrome. Aim: this study attempted to show the results of complication rates in patients operated on by the surgical team of the Clinic of General and Abdominal Surgery of the Clinical Center University of Sarajevo (CCUS). Materials and methods: this is a retrospective study conducted by the surgical team on 28 patients who had Whipple's surgery from January 2017 to January 2022 at the Clinic of General and Abdominal Surgery of the CCUS. Data were taken from patients' medical histories. Previously, all patients underwent preoperative preparation. None of the patients had previously received oncology therapy. Results: out of a total of 28 patients who underwent surgery, the most common complication was wound infection (23%), followed by anastomotic dehiscence (21.42%), bleeding (0%), wound dehiscence (7.14%). About 80% of patients who had preoperative ERCP had difficulty with bile duct dissection. An association was found between preoperative ERCP and difficult bile duct dissection (P value < 0.001). Conclusion: outcomes of the surgical team of the Clinic of General and Abdominal Surgery were compared with published data from other hospitals. During Whipple surgery, ERCP seems to make bile duct dissection quite difficult.

**Keywords**: pancreaticoduodenectomy, Whipple procedure, outcomes, complications

## SAŽETAK

Pozadina: pankreatikoduodenektomija ili Whippleova operacija je jedna od najsloženijih i najtežih operacija sa jako visokom stopom komplikacija u smislu fistula gušterače, krvarenja, dehiscence anastomoze, infekcije rane, dehiscence rane, dumping sindroma. Cilj: ova studija je pokušala pokazati rezultate stope komplikacija kod pacijenata koji su operisani od strane hirurškom tima Klinike za opštu i abdominalnu hirurgiju. Materijali i metode: ovo je retrospektivna studija koju je radio hirurški tim na 28 pacijenata koji su imali Whippleovu operaciju od januara 2017 do januara 2022 godine na Klinici za opštu i abdominalnu hirurgiju Kliničkog centra Univerziteta u Sarajevu. Podaci su preuzeti iz medicinskih istorija pacijenata. Prethodno je svim pacijentima urađena preoperativna priprema. Ni jedan pacijent prethodno nije primao onkološku terapiju. Rezultati: od ukupno 28 pacijenata koji su bili podvrgnuti operaciji, najčešća komplikacija bila je infekcija rane (23%), zatim dehiscenca anastomoze (21,42%), krvarenje (0%), dehiscenca rane (7,14%). Oko 80% pacijenata koji su imali preoperativno učinjen ERCP imali su teškoću sa disekcijom žučnog kanala. Utvrdila se povezanost između preoperativnog ERCP-a i otežane disekcije žučnog kanala (P vrijednost < 0,001). Zaključak: ishodi hirurškog tima Klinike za opštu i abdominalnu hirurgiju je poređen sa objavljenim podacima drugih bolnica. Tokom Whippleove operacije čini se da ERCP dosta otežava disekciju žučnog kanala.

**Ključne riječi**: pankreatikoduodenektomija, Whipple operacija, ishodi, komplikacije

## INTRODUCTION

Pancreaticoduodenectomy or Whipple's operation is a very demanding operation, mainly performed in malignant tumors of the pancreatic head, ampulla, and bile ducts, although it can also be performed in non-malignant cases, in traumatic injuries of the pancreatic head and duodenum. Very rarely, it can also be performed in chronic pancreatitis (1). Whipple surgery is associated with significant postoperative mortality with incidence rates of 30-65% (2,3,4). The leading postoperative complications are: fistulas,

leakage of bile contents, abscesses, postoperative bleeding, delayed gastric emptying and complications related to wound infection and dehiscence (3,4,5). The very progress of surgical techniques and the improvement of intensive medical care brings a decrease in mortality and morbidity rates.

Analyzing was usually reduced to the knowledge of other centers in Western countries, where there was a significant difference between the Clinical Center University of Sarajevo and Western centers regarding perioperative care, which can really affect the rate of complications and the treatment itself. The purpose of this paper is to estimate the rate of complications arising as a result of the Whipple operation we performed at KCUS, as well as to compare our outcomes with Western centers despite significant differences in perioperative management.

## AIM

The aim of this study was to show the results of complication rates in patients operated on by the surgical team of the Clinic of General and Abdominal Surgery of the CCUS.

## MATERIALS AND METHODS

This retrospective study was conducted on 28 patients who underwent classic Whipple pancreaticoduodenectomy by the surgical team of the Clinic of General and Abdominal Surgery of the CCUS, from January 2017 to January 2022.

Data collection: patient data were obtained from medical histories with reference to demographic data, intraoperative findings, and postoperative complications. Preoperative treatment: Blood counts, liver function, kidney function, thyroid function, minerals, coagulogram, EKG, lung X-ray were taken into consideration for all patients as part of preoperative preparation. The tumor stage was assessed preoperatively, based on CT analysis, MRI and endoscopic ultrasound for some patients. Some underwent preoperative ERCP with implantation of a biliary stent as a treatment modality for icterus. Surgical technique: All patients preoperatively received antibiotics as prophylaxis (Cefazolin 2gr, Metronidazole 500 mg), for 60 minutes before the surgical procedure. For exploration, we used a supraumbilical medial laparotomy incision. Peritoneum and liver were explored for the presence of metastases. The surgical team considered the structure of the pancreatic tissue, the size of the pancreatic duct and any difficulties in dissection of the biliary ducts. The reconstruction was followed by making a pancreaticojejuno anastomosis. In cases where there were small pancreatic ducts, we used 4 stitches, while in dilated ones we used 6-8 stitches. Then we made gastrojejuno anastomosis and Roux-en-hepaticojejuno termino-lateral anastomosis. In all patients, we placed an abdominal drain in the hepatorenal recess (Morrison's space). All patients had a nasogastric tube. None of the operated patients received neoadjuvant therapy. The samples were sent for pathohist ological analysis to confirm the type of tumor. Mortality and morbidity within 30 days postoperatively or during hospital stay or rehospitalization were assessed. Using imaging techniques such as ultrasound and CT, we monitored the appearance of any collections in the abdomen.

Data analysis was done using the SPSS program (version 22). Qualitative variables were expressed as percentage and number, while continuous variables were expressed with mean, median and standard deviation (SD). Chi square test was used to find the relationship between variables. A P-value < 0.05 was considered statistically significant.

## RESULTS

In the period from 2017 to 2022 we treated 28 patients who underwent Whipple's surgery. The average age was 55.9 ± 14.7 years, ranging from 30 to 80 years. Nine patients were men and nineteen patients were women. The most common age groups were between 51 and 60 years old (Figure 1). The most common reason for a patient to visit a doctor is because of symptoms of icterus (85,7 %), followed by loss of appetite followed by weight loss (71 %), while signs of gastrointestinal hemorrhage were the least present (0%) Table 1.

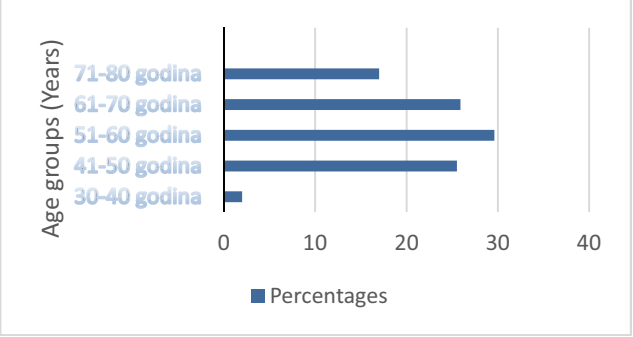


Figure 1 **Distribution of patients by age groups.**

Table 1 **Patients' demography and symptoms.**

| Variables | Values | |
|---|---|---|
| Age | 55,9±14,7 (30-80) | |
| Sex (%) | | |
| Male | 9 | 38,29% |
| Fimale | 19 | 61,71% |
| Smoker (%) | 15 | 53,60% |
| Symptoms (%) | | |
| Jaundice | 24 | 85,70% |
| Anorexia&Wight loss | 20 | 71% |
| GI bleeding | 0 | 0% |

### *Preoperative factors*

The median preoperative serum bilirubin is 12 mg/dl and about 80% of patients were referred for preoperative ERCP as a temporary method of biliary drainage.

Table 2 **Preoperative and intraoperative factors.**

| Values | Variables |
|---|---|
| Laboratory readings: Median (range) | |
| Total serum bilirubin (mg/dl) | 12(0.6-31) |
| Preoperative ERCP (%) | 80% |
| Intraoperative factors | |
| Pancreatic texture (%) | |
| Firm pancreas | 22 (78.5) |
| Soft pancreas | 6 (21.4) |
| Pancreatic duct status (%) | |
| Dilated caliber | 71.2% |

*Intraoperative factors*

Out of 28 patients, 22 of them had a hard pancreas, while soft pancreases were found in 6 patients. We were able to measure the diameter of the pancreatic ducts intraoperatively and found dilated ducts in the patients (71.2%) (Table 2). 10.33% of patients had benign tumors, while the most common malignant tumor was periampullary (51.88%), followed by pancreatic head cancer (20%), and the least with ampullary cancer (3%). Resections were extended in 4 patients; one underwent portal vein resection and the others colonic resections.

*Postoperative complications*

The most common postoperative complications were wound infections (23%), followed by anastomosis dehiscence (21.42%) (Table 3). Postoperative hemorrhage did not occur in any patient.

Table 3 **Complications and their percentages.**

| Complications | Total (%) |
|---|---|
| Wound infection | 23% |
| Pancreatic leak | 21.42% |
| Postoperative Hemorrhage | 0% |

About 80% of patients who underwent preoperative ERCP had difficult bile duct dissection and a strong association between ERCP and difficulty with bile duct dissection was shown (P value < 0.001) (Table 4).

Table 4 **Association between ERCP & difficult bile duct dissection**.

| Preoperative ERCP | Bile duct dissection | | |
|---|---|---|---|
| | Difficult | Easy | p-value |
| Performed | 77.3% | 22.7% | <0.001 |
| Not performed | 9.2% | 90.8% | |

## DISCUSSION

Pancreaticoduodenectomy or Whiple's operation is an extremely complex and demanding operation with many complications (6,7). Morbidity and mortality have improved slightly, and after improvements in care and advanced surgical techniques, mortality has decreased significantly, while the prevalence of postoperative complications remains very high. (8,9). In our circles, there are still doubts as to whether it is better to do surgery because it is very complex, very demanding and mostly with bad outcomes and good intensive care is necessary for success. Some time ago, a large number of patients went to other countries for this operation. At the very beginning, there were complicating factors for performing this operation in certain aspects, and then we noticeably improved the surgical technique, reduced the number of complications, despite the lack of equipment in the intensive care unit.

In this study, the age of patients ranged from 30 to 80 years, with the average age of patients being 55.9 years, which was lower than in other studies (1-9).

Unfortunately, we do not have data on dumping syndrome due to a poor data registration system. The results of this work show that the most common complications were wound infections with a rate of 23%. This result is higher than the data we get from other countries, for example, one of the studies in the United States shows a wound infection rate of 7-13.3% (10), while one of the studies in Germany shows a wound infection rate of 7.2%. (11). Due to the relative lack of data, we were unable to assess risk factors for wound infection. This rate of wound infection could be partly explained by inappropriate sterilization techniques. In our patients, the pancreaticojejunal anastomosis dehiscence rate was 21.42%, while this figure is variable in other centers where it ranges from 14-36%. (12,13), where our result is quite acceptable. There are many factors that affect anastomotic dehiscence, such as age, sex, ph findings, anorexia, type of procedure (2,13) There are various methods and advocates for preventing anastomotic leakage, but none of them are perfect, but the use of a surgical loupe significantly contributes to better results. Using a magnifying glass, the rate of anastomosis leakage was 23%, while the rate when using a microscope was 4.2% (13).

During this analysis, we noticed that not a single patient developed postoperative intra-abdominal bleeding, while in other centers it ranged from 0.7% to 25% (2,3,5). There are no data to define the cause or factors that contribute to a higher rate of bleeding, but it can certainly be related to hemostasis techniques, for which we standardly use electrocautery and ligatures for hemostasis, since we rarely have a harmonic scalpel or ligation device available, etc. Our results showed that 77.3% of patients who underwent preoperative ERCP had difficulties in bile duct dissection and that there was a strong association between preoperative ERCP and difficult bile duct dissection, partly due to adhesions, which could be a consequence reactions of the body to contrast during cholangiography or even more logically due to the biliary stent acting as a foreign body resulting in an inflammatory reaction. The very notion of severe bile duct dissection was an observation of the surgical team and could not be measured by standard measures, which is considered a limitation of the study. Previous research does not mention it in the literature.

## CONCLUSION

Whipple surgery has a high complication rate. The surgical team of the Clinic for General and Abdominal Surgery of the CCUS had quite good results. For the first time, data is being published in terms of comparison with other hospitals in Western countries. We have a very low rate of wound infections and post-operative bleeding, but we still have to work to achieve the best possible results. Preoperative ERCP seems to be associated with difficulties in bile duct dissection, which further prolongs operative time.

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# Antibiotic resistance in bacterial isolates at the Clinical Center University of Sarajevo in 2023

# Rezistencija bakterija na antibiotike u Kliničkom centru Univerziteta u Sarajevu u 2023 godini

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## ABSTRACT

Introduction: in the Clinical Center University of Sarajevo antibiotic resistance monitoring was initiated in 2013. Detection and reporting of bacterial resistance, as well as monitoring the use of antibiotics in hospital and outpatient settings, is an obligation of all countries today. Aim: to show the trend of increasing resistance to antibiotics through the analysis of the pattern of antimicrobial sensitivity of clinical isolates in 2023 and comparison with the data from 2016. Materials and methods: testing the sensitivity to antimicrobial drugs was done using the standard disk-diffusion method, VITEK 2 Compact System (BioMerieux) and broth microdilution, following the standards of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Results: a total of 5884 isolates were detected from different clinical samples. The most commonly reported species among Gram- positive bacteria was *Enterococcus faecalis* and among Gram- negative *Escherichia coli* (17,1%). Among Enterobacteriaceae incidence of resistance to third-generation cephalosporins (ESBL strains) increased from 10.4% to 20.81% for *E. coli*, 45,2% to 66,67% for *K. pneumoniae* and 39,4% to 49,09% for *E. cloacae*. The percentage of carbapenem-resistant *K.pneumoniae* increased to 34,69% . 8.48% strains of *Klebsiella pneumonia* resistant to carbapenems were resistant to colistin, too. Among non-fermenters resistance to carbapenems in *Pseudomonas aeruginosa* increased significantly from16,4% to 30,41% , and in *A. baumannii* is still extremely high and similar to the previous year's results. Compared to 2016 tobramycin resistance has increased from 66.3% to 93.16%. Among gram positive bacteria vancomycin resistance in *E. faecium* shows an increasing trend from 20,8% to 44,78% . Incidence of MRSA strains in CCUS decreased from 14,6% to 9,78% . There is still no resistance to vancomycin. Conclusion: resistance to third-generation cephalosporins, carbapenems and vancomycin shows an increasing trend in CCUS. The emergence of colistin-resistance creates a therapeutic challenge since polymyxins, including colistin, are an important "last-line" treatment option. Rational antimicrobial therapy and infection prevention and control strategies are the basis of effective intervention, with the aim of preventing the emergence and transmission of resistant bacteria.

**Keywords:** antimicrobial sensitivity, resistance monitoring, ESBL, carbapenem-resistance, VRE, MRSA

## SAŽETAK

Uvod: u Kliničkom centru Univerziteta u Sarajevu praćenje rezistencije na antibiotike započelo je 2013. godine. Dokazivanje i prijavljivanje rezistencije bakterija, kao i praćenje upotrebe antibiotika u bolničkoj i vanbolničkoj sredini je obaveza svih zemalja. Cilj: prikazati trend porasta rezistencije na antibiotike analizom obrasca antimikrobne osjetljivosti kliničkih izolata u 2023. i uporedbom s podacima iz 2016. godine. Materijali i metode: ispitivanje osjetljivosti na antimikrobne lijekove provedeno je standardnom metodom disk-difuzije, primjenom VITEK 2 Compact System (BioMerieux) i mikrodilucijom, prema standardima Europskog odbora za ispitivanje osjetljivosti na antimikrobne lijekove (EUCAST). Rezultati: iz različitih kliničkih uzoraka dokazano je ukupno 5884 izolata. Među Gram-pozitivnim bakterijama najčešće je detektovan *Enterococcus faecalis*, a među Gram-negativnim *Escherichia coli*. Među enterobakterijama učestalost rezistencije na cefalosporine treće generacije (ESBL sojevi) povećala se sa 10,4% na 20,81% za *E. coli*, 45,2% na 66,67% za *K. pneumoniae* i 39,4% na 49,09% za E. *cloacae*. Postotak karbapenem-rezistentne *K. pneumoniae* porastao je na 34,69%. 8,48% sojeva *Klebsiella pneumoniae* rezistentnih na karbapeneme bili su rezistentni i na kolistin. Kod nefermentatora rezistencija *Pseudomonas aeruginosa* na karbapeneme je značajno porasla sa 16,4% na 30,41%, a kod *A. baumannii* je i dalje izrazito visoka i slična rezultatima prethodnih godina. U usporedbi s 2016. rezistencija na tobramicin je porasla sa 66,3% na 93,16%. Među gram pozitivnim bakterijama otpornost na vankomicin u *E. faecium* pokazuje trend porasta sa 20,8% na 44,78%. Učestalost sojeva MRSA u KCUS je smanjena sa 14,6% na 9,78%. Još uvijek nema rezistencije na vankomicin. Zaključak: rezistencija na cefalosporine treće generacije, karbapeneme i vankomicin pokazuje trend porasta u KCUS. Pojava rezistencije na kolistin predstavlja terapijski izazov budući da su polimiksini, uključujući kolistin, važna "zadnja linija" u terapiji. Racionalna antimikrobna terapija, te strategije prevencije i kontrole infekcija temelj su efikasne intervencije, s ciljem sprječavanja nastanka i prijenosa rezistentnih bakterija.

**Ključne riječi:** antimikrobna osjetljivost, praćenje rezistencije, ESBL, rezistencija na karbapeneme, VRE, MRSA

## INTRODUCTION

Antimicrobial resistance is one of the biggest challenges to global public health. It is very well documented that the resistance of bacteria to antibiotics is very different in different areas of the world, in other parts of the same country, and finally, in various departments of the same hospital. Therefore, regardless of the knowledge of general trends, in every hospital, it is necessary to know the local resistance of certain bacterial species to the antibiotics used. Since the sensitivity of microorganisms changes over time, doctors need to be up-to-date with current information about the sensitivity of bacteria isolated in their environment, both in hospitals and in general practice, precisely for the reason that it is possible for these bacteria to spread from hospitals to the environment and vice versa (1).

According to the recommendations of the World Health Organization (WHO) from 2001, monitoring of bacterial resistance in a health institution implies a complete analysis of the use of antibiotics, the structure of the causative agents of infections, the map of resistance (phenotypic expression of multiresistance), as well as the identification of the spread of resistant and multiresistant strains. Detection and reporting of bacterial resistance, as well as monitoring the use of antibiotics in hospital and outpatient settings, is an obligation of all countries today (2).

In the Clinical Center University of Sarajevo (CCUS), antibiotic resistance monitoring was initiated in 2013. From the beginning of the monitoring, the microbiological laboratory applies the testing methodology by the standards of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and participates in external quality control. This paper shows a set of data that is processed at the local level per isolate with great care to include only one isolate per patient and to test all isolates for all given antibiotics during the study period.

The inclusion of a large number of isolates from different samples enables consistent monitoring of resistance rates and timely detection of strains with rare resistance mechanisms.

## AIM

The aim of the paper was to show the trend of increasing resistance to antibiotics through the analysis of the pattern of antimicrobial sensitivity of clinical isolates in 2023 and comparison with the data from 2016.

## MATERIALS AND METHODS

During 2023 antimicrobial surveillance in the CCUS was monitored for the following bacterial species: *Staphylococcus aureus, Enterococcus faecium, Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Acinetobacter baumannii, Pseudomonas aeruginosa*.

The basic principles of the surveillance methodology included:

a. all isolates of a certain bacterial species were tested for antibiotics based on EUCAST standards.
b. all isolates from clinical materials were tested with the agreed range of antibiotics.
c. duplicate strains, defined as isolates of the same bacterial species, isolated from the same patient, in any sample, within 30 days, were excluded from the data.

Isolates of special importance were: methicillin-resistant staphylococci (MRSA), *Staphylococcus* resistant to vancomycin and/or linezolid (VRSA), vancomycin-resistant enterococci (VRE), *E. coli* and *K. pneumoniae* that produce extended spectrum beta-lactamases (ESBL), Enterobacterales resistant to carbapenems, *Acinetobacter* and *Pseudomonas* resistant to colistin.

Testing the sensitivity of isolated bacterial colonies to antimicrobial drugs was done using the standard disk-diffusion method according to Kirby-Bauer on Mueller-Hinton agar, following the standards of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (3).

This test included the following antibiotics: penicillin (P), ampicillin (AMP), amoxicillin (AMX), amoxicillin+clavulanic acid (AMC), cefoxitin (FOX), erythromycin ( E), azithromycin (AZM), clarithromycin (CLR), cefazolin (CN), cefuroxime (CXM), ceftazidime (CAZ), cefepime (CFEP), piperacillin/tazobactam (PTZ), gentamicin (GM), amikacin (AN), chloramphenicol (CL), trimethoprim/sulfamethoxazole (SXT), ciprofloxacin (CIP), levofloxacin (LEV), vancomycin (VA), imipenem (IMP), meropenem (MEM), fusidic acid (FA), tetracycline (TE), linezolid (LZD), colistin (COL), tobramycin (TOB), teicoplanin (TEI), tigecycline (TIG).

For each tested antibiotic, bacteria were classified according to the zone of inhibition into three groups: sensitive - S, susceptible, increased exposure – I and resistant - R, following the guidelines from the European Committee for Antimicrobial Susceptibility Testing (EUCAST) (4,5,6).

Minimum inhibitory concentration (MIC) was performed using the VITEK 2 Compact System (BioMerieux) with a VITEK AST card, and for colistin, MIC was measured using broth microdilution with MIC-Strip Colistin (Merlin Diagnostika GmbH, Germany). The results were interpreted based on EUCAST breakpoints (3).

The quality of processed antibiograms is regularly checked and validated using reference strains of bacteria from the American Type Culture Collection (ATCC) as recommended by EUCAST.

### *Detection of resistance mechanisms*

To confirm ESBL production, phenotypic methods based on in vitro inhibition of ESBL activity by clavulonic acid were used: double disk synergy test (DDST), disk combination test (CDT), E-test ESBL or automatic system for detection of sensitivity to antibiotics VITEK 2 COMPACT (BioMerieux). The screening cut-off point was determined in accordance with EUCAST guidelines (3).

Carbapenemase production was detected using a combined-disk test (CDT) containing meropenem and various inhibitors (ROSCO Diagnostica A/S, Denmark), where class A carbapenemases are inhibited by boronic acid and class B by dipicolinic acid and ethylenediaminetetraacetic acid (EDTA). OXA-48-like carbapenemase was identified using temocillin with an MIC >128 mg/L as a phenotypic marker. However, due to its low specificity, this was verified by additional methods (3).

Methicillin/oxacillin resistance is detected by MIC determination, disk diffusion test, or latex agglutination to detect PBP2a protein. Disk diffusion test is performed with a Cefoxitin (30 µg) disk, which is a sensitive and specific marker of mecA/mecC-mediated resistance. A zone diameter < 22 mm was considered methicillin resistance.

The resistance of staphylococci to glycopeptide antibiotics is detected by the broth microdilution method which is recommended by EUCAST. The cut-off value for vancomycin resistance in *S. aureus* is MIC > 2 mg/L.

Vancomycin resistance in enterococci is detected by MIC determination, disk diffusion and/or the automatic antibiotic susceptibility detection system VITEK 2 COMPACT (BioMerieux). In the first two methods, the plates are incubated for a full 24 hours, in order to detect isolates with inducible resistance (3).

## RESULTS

A total of 5884 isolates were detected from different clinical samples received in the period from January to December 2023 at the Clinical Microbiology Laboratory of the Clinical Center University of Sarajevo.

The proportion of isolates in the total number of detected was as follows: *Enterococcus faecalis* 1370 (23,2%), *Staphylococcus aureus* 1166 (19,8%), *Escherichia coli* 1008 (17,1%), *Klebsiella pneumoniae* 810 (13,8%), *Pseudomonas aeruginosa* 438 (7,4%), *Enterobacter cloacae* 333 (5,6%), *Acinetobacter baumannii* complex (ACB) 280 (4,7%), *Proteus mirabilis* 249 (4,2%) and *Enterococcus faecium* 230 (3,9%)

The pattern of antimicrobial susceptibility/resistance for all isolates is presented in tables 1-9 and figures 1-9.

Table 1 **The pattern of antimicrobial resistance of *Escherichia coli.***

| Antibiotics | Amikacin | Amoxicillin/clav.acid | Ampicillin | Cefazolin | Cefepime | Ceftazidime | Cefuroxime | Ciprofloxacin | Gentamicin | Imipenem | Levofloxacin | Meropenem | Nitrofurantoin | Piperacillin/tazobaxctam | Trimethoprim/sulfo methoxazole |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R (N) | 18 | 550 | 796 | 501 | 164 | 206 | 292 | 248 | 193 | 0 | 131 | 0 | 28 | 71 | 396 |
| R (%) | 4.35 | 55.06 | 83.00 | 49.70 | 19.64 | 20.81 | 30.01 | 34.69 | 21.05 | 0.00 | 37.22 | 0.00 | 4.66 | 17.19 | 41.21 |
| Total tested | 414 | 999 | 959 | 1008 | 835 | 990 | 973 | 715 | 917 | 332 | 352 | 438 | 601 | 413 | 961 |

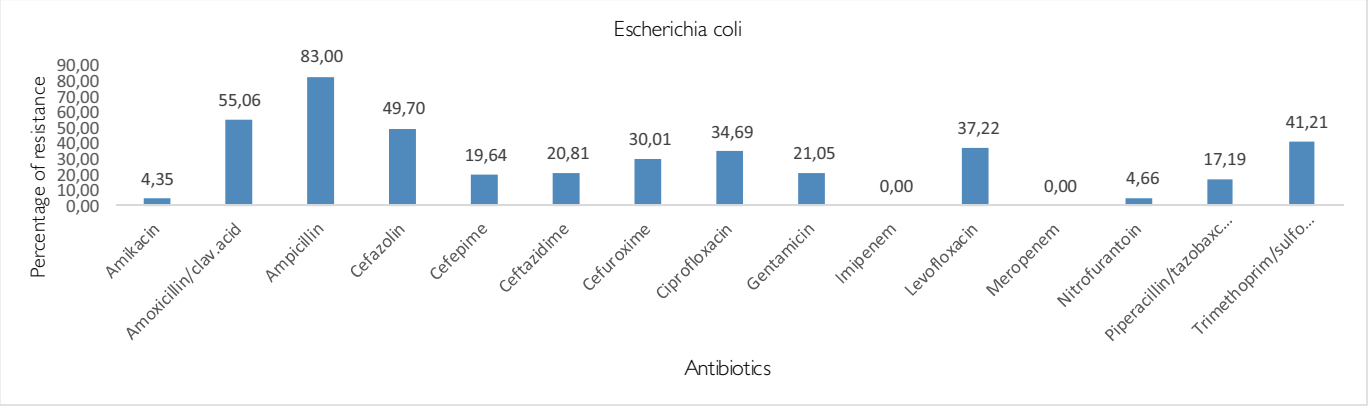


Figure 1 **Percentage of resistance of *Escherichia coli* to the tested antibiotics.**

Table 2 The pattern of antimicrobial resistance of *Klebsiella pneumoniae* .

| Antibiotics | Amikacin | Amoxicillin/clav. Acid | Ampicillin | Cefazolin | Cefepime | Ceftazidime | Cefuroxime | Ciprofloxacin | Gentamicin | Imipenem | Levofloxacin | Meropenem | Piperacillin/tazobactam | Trimethoprim/sulfomethoxazole | Colistin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R (N) | 76 | 608 | 810 | 472 | 507 | 498 | 477 | 386 | 407 | 220 | 291 | 255 | 451 | 400 | 24 |
| R (%) | 11.53 | 76.96 | 100.00 | 72.84 | 64.75 | 66.67 | 68.14 | 62.76 | 61.85 | 36.54 | 56.50 | 34.69 | 66.32 | 50.13 | 8.48 |
| Total tested | 659 | 790 | 810 | 648 | 783 | 747 | 700 | 615 | 658 | 602 | 515 | 735 | 680 | 798 | 283 |

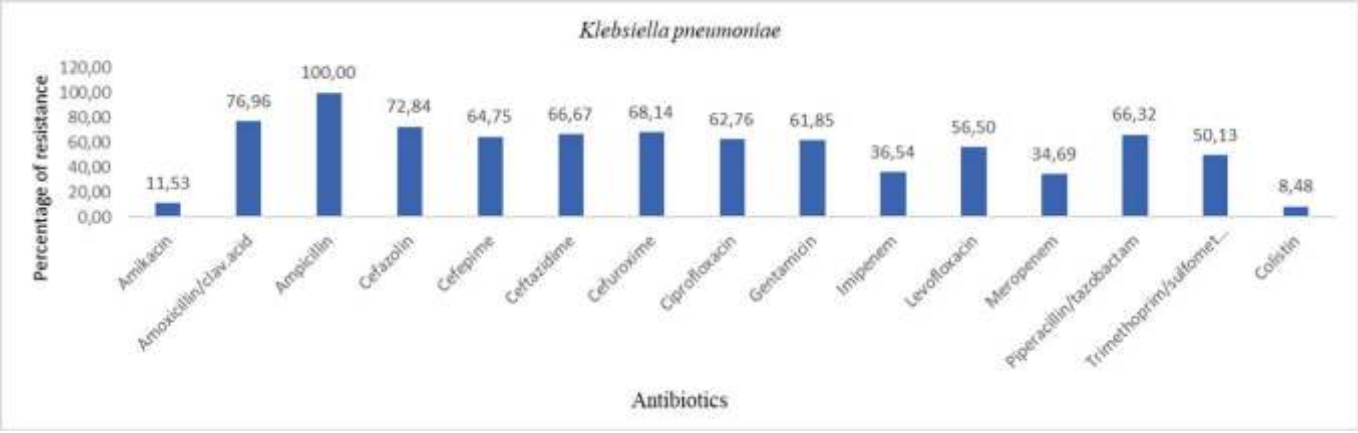


Figure 2 Percentage of resistance of *Klebsiella pneumoniae* to the tested antibiotics.

Table 3 The pattern of antimicrobial resistance of *Enterobacter cloacae* .

| Antibiotics | Amikacin | Amoxicillin/clavacid | Ampicillin | Cefazolin | Cefepime | Ceftazidime | Ciprofloxacin | Gentamicin | Imipenem | Levofloxacin | Meropenem | Piperacillin/tazobactam | Trimethprim/sulfomethoxazole |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R (N) | 22 | 333 | 322 | 306 | 148 | 161 | 104 | 112 | 25 | 36 | 26 | 120 | 130 |
| R (%) | 11.11 | 100.00 | 100.00 | 100.00 | 45.26 | 49.09 | 38.10 | 56.28 | 15.53 | 16.59 | 12.32 | 62.83 | 42.76 |
| Total tested | 198 | 333 | 322 | 306 | 327 | 328 | 273 | 199 | 161 | 217 | 211 | 191 | 304 |

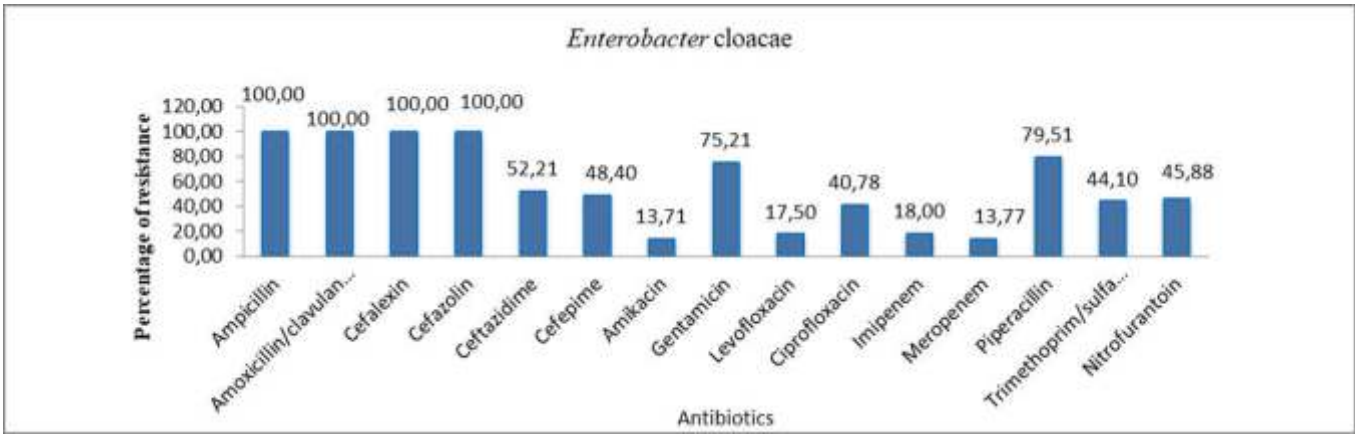


Figure 3 Percentage of resistance of *Enterobacter cloacae* to the tested antibiotics.

Table 4 The pattern of antimicrobial resistance of *Proteus mirabilis.*

| Antibiotics | Amikacin | Amoxicillin/clavacid | Ampicillin | Cefazolin | Cefepime | Ceftazidime | Cefuroxime | Ciprofloxacin | Gentamicin | Imipenem | Levofloxacin | Meropenem | Piperacillin/tazobactam | Trimethoprim/sulfomethoxazole |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R (N) | 12 | 91 | 183 | 126 | 30 | 51 | 75 | 58 | 52 | 0 | 44 | 0 | 12 | 105 |
| R (%) | 8.33 | 39.22 | 85.92 | 50.60 | 14.35 | 21.98 | 32.33 | 34.94 | 23.53 | 0.00 | 31.43 | 0.00 | 7.59 | 45.65 |
| Total tested | 144 | 232 | 213 | 249 | 209 | 232 | 232 | 166 | 221 | 110 | 140 | 167 | 158 | 230 |

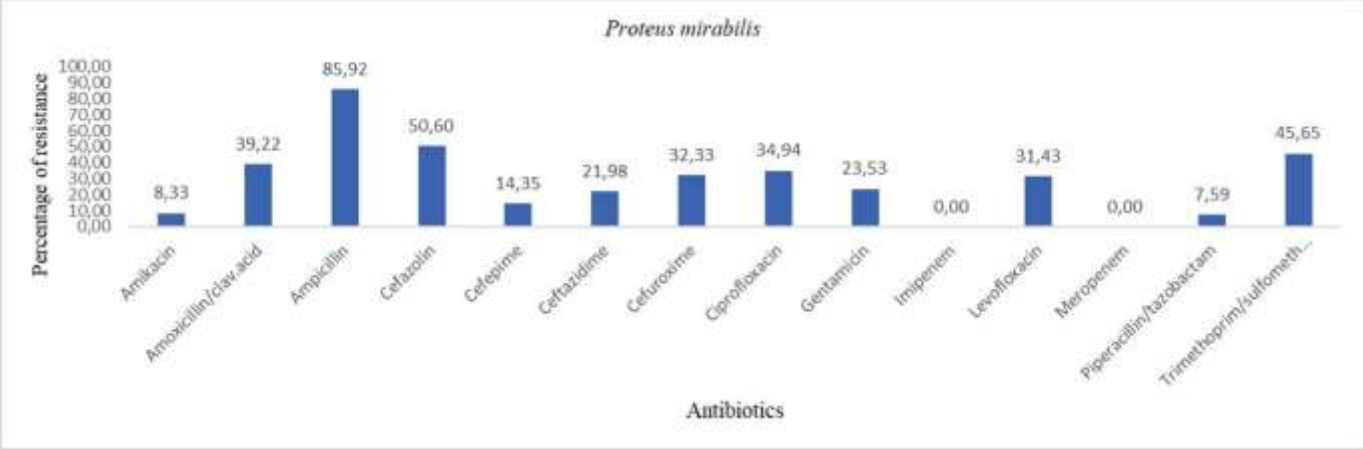


Figure 4 Percentage of resistance of *Proteus mirabilis* to the tested antibiotics.

Table 5 The pattern of antimicrobial resistance of *Pseudomonas aeruginosa.*

| Antibiotics | Amikacin | Cefepime | Ceftazidime | Ciprofloxacin | Colistin | Imipenem | Levofloxacin | Meropenem | Piperacillin/tazobactam |
|---|---|---|---|---|---|---|---|---|---|
| R (N) | 64 | 118 | 159 | 148 | 0 | 105 | 125 | 132 | 126 |
| R (%) | 14.78 | 26.94 | 37.15 | 39.26 | 0.00 | 30.09 | 40.06 | 30.41 | 29.10 |
| Total tested | 433 | 438 | 428 | 377 | 105 | 349 | 312 | 434 | 433 |

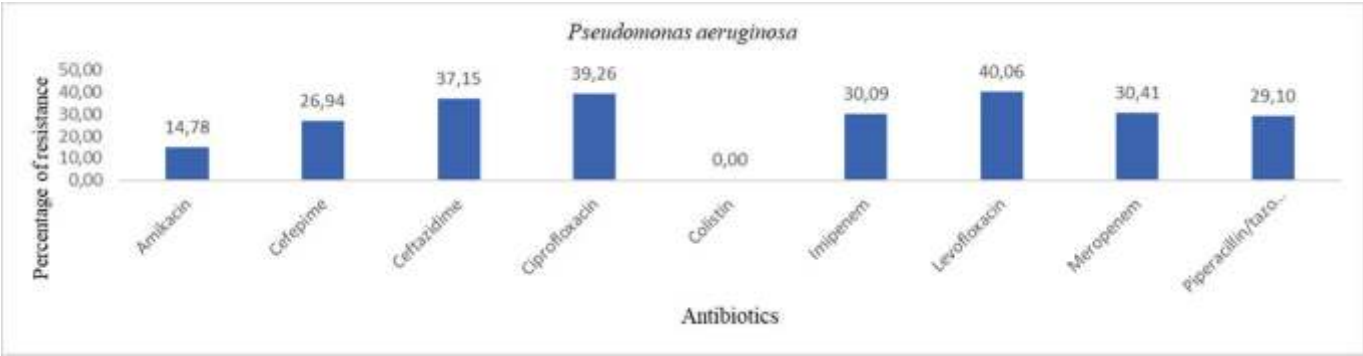


Figure 5 Percentage of resistance of *Pseudomonas aeruginosa* to the tested antibiotics.

Table 6 **The pattern of antimicrobial resistance of *Acinetobacter baumannii* complex (ACB).**

| Antibiotics | Amikacin | Ciprofloxacin | Colistin | Gentamicin | Imipenem | Levofloxacin | Meropenem | Tobramycin | Trimethoprim/sulfomethoxazole |
|---|---|---|---|---|---|---|---|---|---|
| R (N) | 275 | 246 | 0 | 255 | 251 | 254 | 281 | 218 | 255 |
| R (%) | 98.57 | 99.60 | 0.00 | 98.84 | 99.21 | 99.61 | 99.29 | 93.16 | 93.75 |
| Total tested | 279 | 247 | 280 | 258 | 253 | 255 | 283 | 234 | 272 |

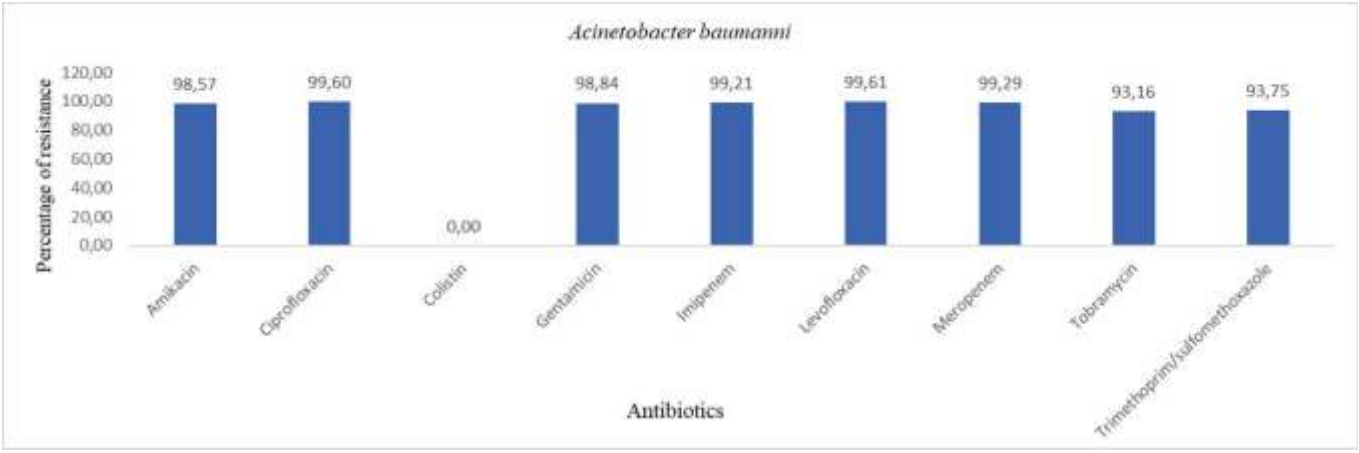


Figure 6 **Percentage of resistance of *Acinetobacter baumannii* complex (ACB) to the tested antibiotics.**

Table 7 **The pattern of antimicrobial resistance of *Staphylococcus aureus.***

| Antibiotics | Benzilpenicillin | Oxacillin | Ciprofloxacin | Erithromycin | Fucidinska kiselina | Gentamycin | Chloramphenicol | Clarithromycin | Tetrycline | Trimethprim/sulphomethoxazole | Vancomycin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| R (N) | 152 | 114 | 7 | 131 | 5 | 77 | 3 | 37 | 145 | 7 | 0 |
| R (%) | 17.82 | 9.78 | 2.60 | 11.73 | 0.43 | 7.10 | 1.06 | 11.14 | 13.06 | 0.69 | 0.00 |
| Total tested | 853 | 1166 | 269 | 1117 | 1161 | 1085 | 282 | 332 | 1110 | 1019 | 588 |

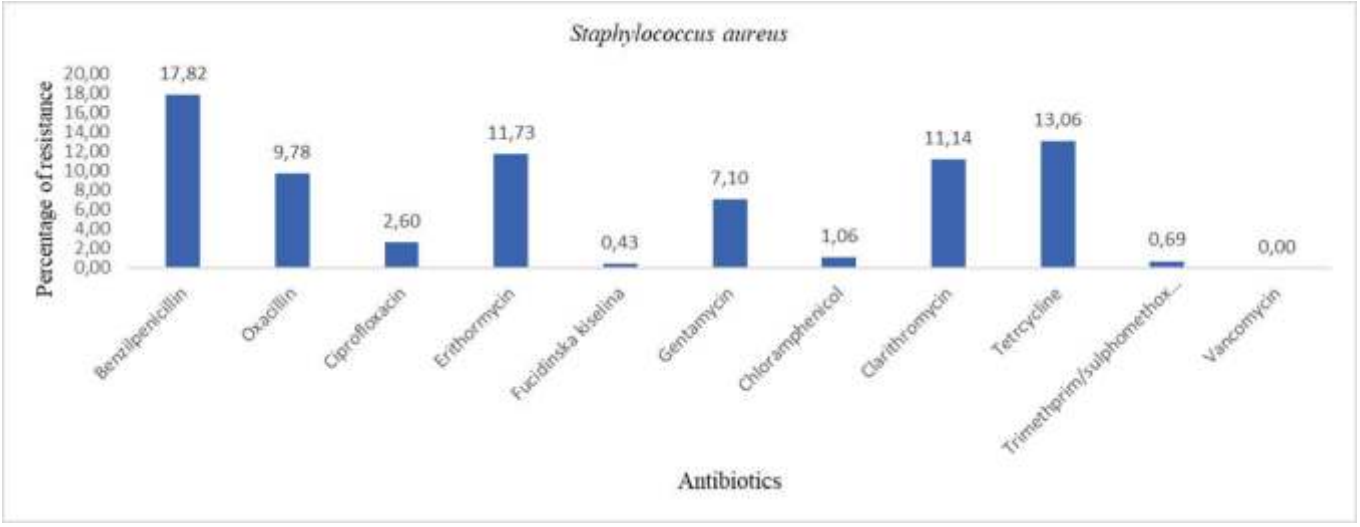


Figure 7 **Percentage of resistance of *Staphylococcus aureus* to the tested antibiotics.**

Table 8 The pattern of antimicrobial resistance of *Enterococcus faecalis.*

| Antibiotics | Ampicillin | Amoxicillin | Amoxicillin/clav.acid | Ciprofloxacin | Nitrodurantoin | Vancomycin |
|---|---|---|---|---|---|---|
| R | 0 | 0 | 0 | 240 | 62 | 0 |
| % | 0 | 0 | 0 | 33.6 | 8.3 | 0 |
| Total tested | 510 | 1030 | 361 | 713 | 741 | 1370 |

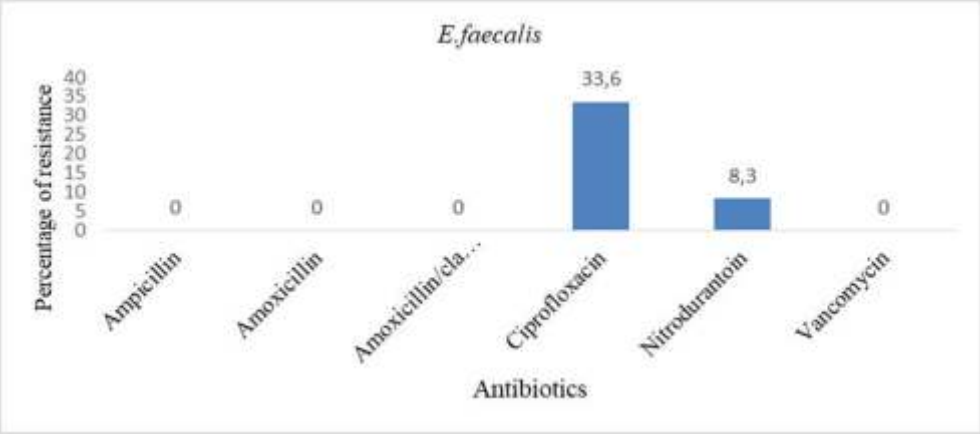


Figure 8 Percentage of resistance of *Enterococcus faecalis* to the tested antibiotics.

Table 9 The pattern of antimicrobial resistance of *Enterococcus faecium.*

| Antibiotics | Amoxicillin | Amoxicillin/clavacid | Ampicillin | Linezolid | Nitrofurantoin | Teicoplanin | Tigecycline | Vankomycin |
|---|---|---|---|---|---|---|---|---|
| R(N) | 150 | 77 | 122 | 0 | 79 | 44 | 4 | 103 |
| R(%) | 100.00 | 97.47 | 100.00 | 0.00 | 81.44 | 38.94 | 2.84 | 44.78 |
| Total tested | 150 | 79 | 122 | 166 | 97 | 113 | 141 | 230 |

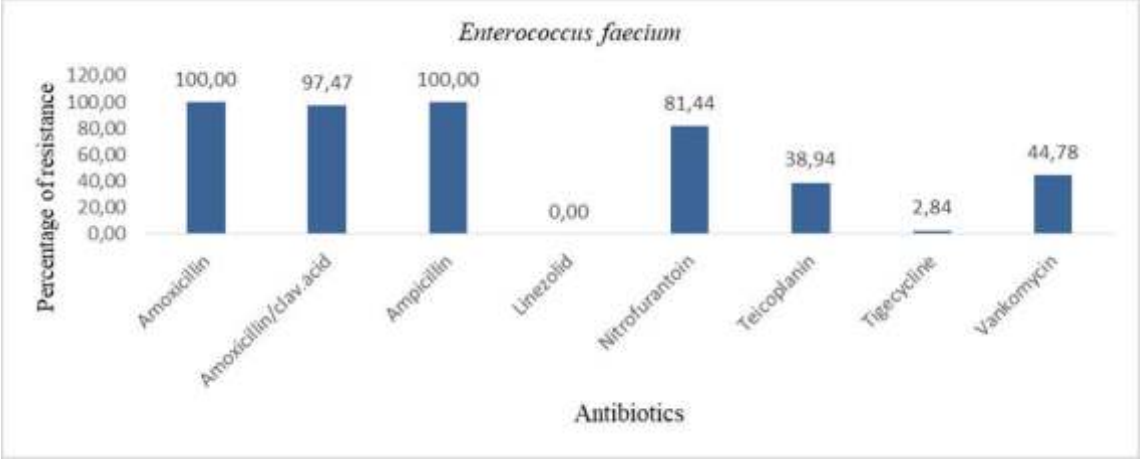


Figure 9 Percentage of resistance of *Enterococcus faecium* to the tested antibiotics.

## DISCUSSION

The development of resistance worldwide is becoming a priority problem. Therefore it is necessary to establish such a resistance monitoring system, which would provide relevant data, and according to which recommendations would be made for the use of antibiotics to reduce existing resistance, or to try to prevent or, at least, slow down the development of new resistance. These data can also be used as a guide in empiric antibiotic therapies, especially in very serious patients.

Recognizing the importance of the problem of bacterial resistance to antibiotics, its monitoring at the Clinical Center University of Sarajevo (CCUS) began in 2013 and has continued to this day. The pathogen testing methodology is the result of inter-laboratory standardization and high quality in the preparation of bacterial sensitivity tests (7).

With the aim of monitoring the increase in resistance, the pattern of antimicrobial susceptibility of clinical isolates in 2023 was analyzed and compared with the data from 2016. The AMR surveillance focuses on isolates of eight key bacterial species (*Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Acinetobacter species, Staphylococcus aureus, Enterococcus species*). Compared to 2016, the total number of reported isolates has increased from 5361 to 5884. The most commonly reported bacterial species were *Enterococcus faecalis* (23,2%), followed by *Staphylococcus aureus* (19,8%), *Escherichia coli* (17,1%), *Klebsiella pneumoniae* (13,8%), *Pseudomonas aeruginosa* (7,4%), *Enterobacter cloacae* (5,6%), *Acinetobacter baumannii* complex (ACB) (4,7%), *Proteus mirabilis* (4,2%) and *Enterococcus faecium* (3,9%). This ranking differs from the ranking in 2016, when isolates of *Staphylococcus aureus* were the most common (7).

Among the gram-negative bacteria, *Escherichia coli* is one of the most common causes of blood infections, as well as outpatient and hospital-acquired urinary infections. Antimicrobial resistance of this pathogen arouses great interest because the percentage of isolates resistant to the most commonly used antimicrobial agents is continuously increasing throughout Europe. More than half of the isolates that were reported to the EARS network (European Antimicrobial Resistance Surveillance Network) were resistant to at least one group of monitored antibiotics (aminopenicillins, fluoroquinolones, III-generation cephalosporins, aminoglycosides and carbapenems). The highest percentage of resistance was recorded in southern and southeastern Europe. Of particular importance is the increase in resistance to third-generation cephalosporins, as well as co-resistance to fluoroquinolones and aminoglycosides. Carbapenem resistance is still low and is <0.1% in Europe.

In our study, *E.coli* showed an increase in resistance to ampicillin from 68.3% to 84%. Resistance to the first and second generation of cephalosporins was 49,7% and 30,01% respectively, which is an increase when compared to 2016 when it was 35,1% and 11,6% respectively. The incidence of resistance to third-generation cephalosporins (ESBL strains) increased from 10.4% to 20.81%. Also, resistance to fluoroquinolones is rising and for ciprofloxacin increased from 21.4% in 2016 to 34.69% in 2023. There was no carbapenem resistance detected.

*Klebsiella* spp. and *Enterobacter* spp. usually cause healthcare-associated infections and for many years demonstrate high rates of resistance. *K.pneumoniae* has innate resistance to ampicillin but resistance to other beta-lactams is acquired due to high antibiotic exposure. Third- and fourth-generation cephalosporin resistance rates (64,75% for cefepime and 66,6% for ceftazidime) are higher than in 2016 (59,1% for cefepime and 54,8% for ceftazidime). Resistance to co-amoxiclav is similar to 2016 rates (53,1% in 2016 and 50,13 % in 2023).

An increasing trend of resistance has been noted to the following antibiotics: piperacillin/tazobactam (2016: 53,5%, 2023: 66,32%), ciprofloxacin (2016: 50%, 2023: 62,76%)), second-generation cephalosporins (2016: 51.5 %, 2023: 68,14%), cephalosporins of the first generation (2016: 59.7 %, 2023: 72,84%), gentamicin (2016: 51%, 2023: 61,85%). The incidence of ESBL strains has increased from 45,2% in 2016 to 66,67% in 2023. There is a decrease in resistance to amikacin, from 19,8% in 2016 to 11,53% in 2023. The number of carbapenem-resistant *K.pneumoniae* (CRKp) reached the level visible as a percentage of resistance to imipenem and meropenem (1%) for the first time in 2016, but the rates in 2023 increased to 34,69% (8,9).

This is very worrying considering that this resistance in invasive isolates according to the EARS-Net report from 2022 was 10.9% (10). The highest percentages of carbapenem resistance in *K. pneumoniae* were observed in southern and eastern Europe. Numerous reports on outbreaks demonstrate the transmission potential of this isolate in the healthcare systems. Outbreaks and clusters also highlight the importance of detecting this isolate early in settings due to high transmissibility (11-16).

According to the report from the Committee for antibiotic resistance surveillance in Croatia- Croatian Academy of medical sciences 13% of *K. pneumonia* isolates in 2022 were resistant to carbapenems (17). Since the total number of *Klebsiella* in CCUS continued to increase (595 isolates in 2016, 810 isolates in 2023), this indicates the danger of further spread of CRKp.

The emergence of colistin-resistant (ColR) in CRKp (8.48% in 2023) creates a therapeutic challenge since polymyxins including colistin are an important "last-line" treatment for infections caused by carbapenem-resistant *Klebsiella pneumoniae*. These infections can be associated with an increased risk for in-hospital mortality. With the rise in consumption of colistin, cases of colistin-resistant *K. pneumoniae* carbapenemase (KPC)-producing strains are reported globally (18). The results of some studies showed a strong association between the carbapenem-producing *K. pneumoniae* and increased resistance to colistin (19).

*Enterobacter* spp. poses innate inducible cephalosporinases and demonstrates resistance not only to ampicillin but to co-amoxiclav and 1st generation cephalosporins as well. Cefuroxime is marginally active against this bacterium and EUCAST standards do not include cefuroxime interpretation for it. Wild-type isolates are susceptible to the 3rd generation of cephalosporins but resistant derepressed mutants that hyperproduce AmpC cephalosporinases often emerge during therapy with these agents. In the period of our investigation, resistance to most antibiotics is increasing in *Enterobacter cloacae* isolates, namely: piperacillin/tazobactam (2016: 34,1%, 2023: 62,83%%), ciprofloxacin (2016: 21.1%, 2023: 38,10%), second-generation cephalosporins (2016: 52.4%, 2023: 75,42%), gentamicin (2016: 36.5%, 2023: 56,28%). Compared to 2016, the percentage of ESBL strains rise from 39,4% to 49,09% in 2023. Resistance to carbapenems in 2016 was 1%, while in 2023 has increased to 12.32% (7).

*Proteus mirabilis* still causes predominantly community-acquired infections and should naturally be a bacterial species well-susceptible to all beta-lactam antibiotics directed at gram-negative bacteria. Unfortunately, resistance to beta-lactam antibiotics has already reached high rates and in 2023 resistance is 86 % for

ampicillin, 39,22% for co-amoxiclav, 14,35 % (cefepime) to 21,9 % (ceftazidime) for the 3rd and 4th generation cephalosporins. Rates of resistance to ciprofloxacin (34,9%), gentamicin (23,5%), amikacin (8,3%) and co-trimoxazole (45,6%) are similar or equal to 2016. Incidence of ESBL strains decreased from 36,8% in 2016 to 21,98% in 2023 (7). Due to their innate resistance to colistin, tigecycline and lower susceptibility to imipenem, *Proteus mirabilis* and other *Proteus* spp. could represent an increasing problem in the future, especially in urological patients and infections associated with hospital care (17).

*Pseudomonas aeruginosa* is an opportunistic Gram-negative non-fermenting rod responsible for a variety of infections, particularly in hospitalized patients, including septicemia, orthopedic infections, burns, respiratory tract infections, corneal infections, and infections in patients with compromised immune systems. It is one of the most common colonizers of medical devices. It is intrinsically resistant to a majority of antimicrobial agents. Multiple-resistant *Pseudomonas aeruginosa*, especially carbapenem-resistant isolates, have been one of the biggest resistance problems for many years, especially in southern and eastern Europe (10).

Resistance to imipenem and meropenem in CCUS increased significantly in 2023 (16,4% in 2016, 30,41% in 2023). Resistance to amikacin in 2023 decreased from 28.1% to 14.78%. Resistance to fluoroquinolones increased (ciprofloxacin 31.35 % to 39.26% and levofloxacin 34.4% to 40.06% ), as well as to the fourth-generation of cephalosporins (7.4% to 26.94%). From 2020 EUCAST standards do not include testing of *P. aeruginosa* for gentamicin because this antibiotic is not effective for pseudomonas infections. For aminoglycosides, it is generally recommended that they should be used only in combination with other antibiotics for infections outside the urinary tract. It is common knowledge that higher doses of antibiotics are used to treat pseudomonas infections, and since 2020 this has been clearly stated in EUCAST standards for pseudomonas there is no "S" category (susceptible, standard dosage) for many antibiotics (ceftazidime, cefepime, piperacillin/tazobactam, imipenem, ciprofloxacin). Colistin susceptibility testing requires the use of a broth microdilution test, which is significantly more demanding and expensive than disk diffusion testing, and therefore the rule to test all isolates to all antibiotics under surveillance, in this case, is modified and only multiply, in particular carbapenem-resistant isolates are tested with colistin (7).

*Acinetobacter baumannii* is a non-fermenting multidrug-resistant bacteria, which is considered an opportunistic pathogen for years. But its ability to survive in a hospital environment makes it a frequent cause of infections such as pneumonia, bacteremia, meningitis, urinary tract infections and wounds. It shows high resistance to all tested antimicrobials (93-99%), except for colistin. Carbapenem resistance in *A. baumannii* has rapidly spread and in 2023 resistance rates to imipenem and meropenem (99%) are still extremely high and similar to the previous year's results.

Compared to 2016 anitmicrobial surveillance in CCUS, we observe that tobramycin resistance has increased from 66.3% in 2016 to 93.16% in 2023 (7).

As with *Pseudomonas*, colistin is tested only on carbapenem-resistant isolates, but since for several years such isolates constitute >90% of the total *Acinetobacter* isolates, it can be considered that colistin is tested on almost all isolates and the rates of colistin resistance can be compared with the rates for other antibiotics. According to the EARS-Net *Acinetobacter* resistance rates to colistin are still low (10) and such an isolate was not detected in CCUS in 2023.

Over the last seven years, the number of reported isolates of *E. faecalis* in CCUS has increased by +60% from 824 isolates in 2016 to 1370 in 2023. In addition to the fact that infections caused by resistant strains are difficult to treat, enterococci are also easily disseminated in healthcare settings. They are naturally resistant to many antibiotic classes, and all our isolates of *Enterococcus faecium* show resistance to ampicillin. There is no vancomycin resistance in *E. faecalis*, while vancomycin resistance in *E. faecium* (VRE) shows an increasing trend from 20.8% in 2016 to 44,78% in 2023. There is no linezolid resistance detected and resistance to teicoplanin and tigecycline is 38,94% and 2,84% respectively.

More than nine-tenths (92.5%) of the *E. faecium* isolates reported by all EU/EEA countries to EARS-Net for 2022 were resistant to at least one of the antimicrobial groups under surveillance (aminopenicillins, gentamicin (high-level resistance and vancomycin) (10). All enterococci show innate low-grade resistance to aminoglycosides, but aminoglycosides in wild-type enterococci can still be used in therapy combined with ampicillin or glycopeptides to achieve a synergistic effect. In strains highly resistant to aminoglycosides, these antibiotics cannot be used even in combination therapy. In 2014 EUCAST introduced susceptibility testing of enterococci to quinolones using norfloxacin as an indicator of susceptibility to ciprofloxacin and levofloxacin (3). Quinolones are intended to treat enterococcal infections only in case of uncomplicated urinary tract infections. Resistance to quinolones in *E. faecalis* was 33,6% in 2023. For uncomplicated urinary tract infections caused by *E. faecalis*, nitrofurantoin can also be used and resistance to this antibiotic is still low (8,3%).

*Staphylococcus aureus* is the main cause of skin and soft tissue infections and as such is also the most common cause of surgical site infections and bloodstream infections, exhibiting a high burden in terms of morbidity and mortality (20).

Methicillin-resistant *Staphylococcus aureus* (MRSA) strains are resistant to all beta-lactam antibiotics (except newer cephalosporins, ceftaroline, and ceftobiprole), and often show cross-resistance to other classes of antibiotics. Incidence of MRSA strains in CCUS decreased from 14,6% IN 2016 to 9,78% in 2023. There is still no resistance to vancomycin. Resistance of other tested antimicrobials is at a low level.

According to the EARS-Net report (10), the EU/EEA population-weighted mean MRSA percentage was 15.2% in 2022. This denotes a significantly decreasing trend for the period 2018–2022, from 17.8% to 15.2%.

With MRSA, combined resistance to another antimicrobial group was quite common. The most common AMR combination was MRSA and resistance to fluoroquinolones.

Large inter-country variations were noted for MRSA, with higher AMR percentages generally reported from southern and Eastern Europe than from northern Europe (10).

The shortcoming of the methodology presented in this report is that it is not possible to analyze the data according to the demographic characteristics of the patients, but the inclusion of a large number of isolates from different samples enables consistent monitoring of resistance rates and timely detection of strains with rare resistance mechanisms.

## CONCLUSION

Resistance to carbapenems in *Klebsiella pneumoniae* and *Pseudomonas* aeruginosa and vancomycin resistance in *E. faecium* shows an increasing trend in CCUS.

The emergence of colistin-resistant *Klebsiella pneumoniae* creates a therapeutic challenge since polymyxins, including colistin, are an important "last-line" treatment option.

A resistance monitoring system, which provides relevant data and according to which recommendations for the use of antibiotics are made, can reduce existing resistance, or prevent or at least slow down the development of new resistance.

Rational antimicrobial therapy and infection prevention and control strategies are the basis of effective intervention, with the aim of preventing the emergence and transmission of resistant bacteria

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# One-stage vs. two-stage revision knee endoprosthesis surgery

# Jednofazni vs. dvofazni revizioni operativni zahvat ugradnje endoproteze koljena

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## ABSTRACT

Introduction: a prosthetic joint infection (PJI) is possibly the most significant potential complication of total knee arthroplasty (TKA) and is associated with substantial morbidity and socioeconomic burden. Due to the fact that population generally has been more active in the last decade, demand for primary knee arthroplasty (PKA) has been increasing which will increase the number of PJI and revision surgeries. Aim: to compare the number of patients requiring one stage versus two stage revision endoprosthesis surgery at the Clinic of Orthopedicis and Traumatology of the Clinical Center University of Sarajevo (CCUS) in the period from 2023 to 2024. Material and methods: we assessed 143 patients with primary total knee endoprosthesis treated at the Clinic of Orthopedics and Traumatology of the CCUS, in the period from 2023 to 2024. Out of the total number of patients, 10 required revision endoprosthesis surgery. Patients were divided into two groups (one stage vs. two stage) depending of the reason requiring revision surgery. Results: the study included 100 female (69.3%) and 43 male patients (30.7%). Out of all patients treated with PKA, only 10 patients required revision arthroplasty or 6.9% of all TKA implanted. Out of 10 patients, only 2 (1.3%) required two-stage surgery by the criteria used for group selection. Regarding knee aspiration, only two patients had positive aspirates where *St.epidermidis* was isolated in one patient while *St. aureus* was isolated in other patient. Other knee aspirations were negative for patients demanding revision arthroplasty. Conclusion: joint infection after total knee arthroplasty is a serious complication that can significantly affect a patient's physical, emotional, social, and financial well-being. Therefore, achieving an early and accurate diagnosis of PJI is paramount in order to maximize the chances of successful treatment.

**Keywords**: intertrochanteric fracture, surgical procedure, functional outcome

## SAŽETAK

Uvod: infekcija endoproteze koljena (PJI) je možda najznačajnija potencijalna komplikacija nakon ugradnje totalne endoproteze koljena (TKA) i povezana je sa značajnim morbiditetom i socioekonomskim opterećenjem. Zbog činjenice da je populacija sve aktivnija u posljednjoj deceniji, potražnja za primarnom artroplastikom koljena (PKA) je u porastu što povećava broj infekcija i revizionih operativnih zahvata. Cilj: uporediti koliko pacijenata je zahtjevalo jednofazni ili dvofazni revizioni operativni zahvat endoproteze koljena na Klinici za ortopediju i traumatologiju u periodu od 2023. do 2024. godine. Materijal i metode: u studiju je uključeno 143 pacijenta sa primarnom totalnom endoprotezom koljena koji su liječeni na Klinici za ortopediju i traumatologiju Kliničkog centra Univerziteta u Sarajevu, u periodu od 2023. do 2024. godine. Od ukupnog broja pacijenata, 10 je zahtijevalo revizioni operativni zahvat. Pacijenti su podijeljeni u dvije grupe (jedna faza naspram dvije faze) u zavisnosti od uzroka revizionog operativnog zahvata. Rezultati: istraživanjem je obuhvaćeno 100 pacijenata ženskog pola (69,3%) i 43 pacijenta muškog spola (30,7%). Od svih pacijenata liječenih PKA, samo 10 pacijenata je zahtijevalo revizijsku artroplastiku ili 6,9% svih implantiranih TKA. Od 10 pacijenata, samo 2 pacijenta (1,3%) zahtijevalo je dvoetapnu operaciju prema kriterijima korištenim za odabir grupe. Svim pacijentima koji su zahtijevali revizioni operativni zahvat učinjena je aspiracija koljena gdje je kod samo dva pacijenta aspirati bio pozitivan. St.epidermidis izolovan kod jednog pacijenta, dok je St. aureus izolovan kod drugog pacijenta. Ostale aspiracije koljena bile su negativne za pacijente koji su zahtijevali revizijsku artroplastiku. Zaključak: infekcija zgloba nakon totalne artroplastike koljena je ozbiljna komplikacija koja može značajno uticati na fizičko, emocionalno, socijalno i finansijsko stanje pacijenta. Stoga je postizanje rane i tačne dijagnoze PJI najvažnije kako bi se maksimizirale šanse za uspješno liječenje.

**Ključne riječi:** primarna endoproteza koljena, reviziona artroplastika koljena, infekcija endoproteze

## INTRODUCTION

A prosthetic joint infection (PJI) is possibly the most significant potential complication of total knee arthroplasty (TKA) and is associated with substantial morbidity and socioeconomic burden (1). PJI is a relatively rare complication post-TKA, with registry data suggesting that the risk of PJI is 1.03% following a primary TKA (2). Due to the fact that population generally has been more active in the last decade, demand for primary knee arthroplasty has been increasing which will increase the number of PJI and revision surgeries. Revision arthroplasty for PJI is associated with increased mortality when compared to revision surgery for other causes such as aseptic loosening (3). Treatment of a PJI involves a multidisciplinary approach with input from specialized microbiologists, physiotherapists and revision arthroplasty surgeons. There is also evidence to suggest that outcomes can be improved when patients with PJI are treated in specialised arthroplasty centres with high volume revision arthroplasty specialists (4,5,6,7,8). The treatment of PJI involves the use of antibiotics and surgical intervention. Surgical management can involve a DAIR (debridement, antibiotics and implant retention), a single-stage revision arthroplasty, a two-stage revision arthroplasty and excision arthroplasty (9,1). A two-stage exchange revision is considered the standard treatment option for PJI, however, single-stage revision is becoming increasingly popular. The treatment of periprosthetic infection requires carefully structured multidisciplinary input. The vast majority of PJIs occur within a year of the index procedure. The most common cause of infection is the introduction of microorganisms during surgery either by direct contact or via aerosols colonising the prosthesis (10). PJI may also be secondary to haematogenous spread from other system such as the respiratory or renal systems. Lastly, PJI can originate from adjacent sources of infection such as infected soft tissue and osteomyelitis (11). The colonization of the prosthesis occurs in stages. Initially the single planktonic organisms adhere to the prosthesis' surface (12). The formation of a complex collection of microorganisms with a protective outer membrane, called a biofilm, then ensues. PJI can be broadly divided into early (<4 weeks postoperatively), delayed (4 weeks to 24 months postoperatively) or late (>24 months postoperatively) (13). Patients with early PJI typically present with a hot, swollen and erythematous joint. This can very well be associated with a fever which is commonly caused by highly virulent organisms such as *Staphylococcus Aureus* and gram-negative *bacilli*. Delayed PJI presentations are classically more subtle in nature and can be difficult to differentiate from aseptic loosening/failure. Delayed PJI are usually caused by less virulent organisms (14). Late PJIs usually present as subacute infections or with unforeseen onset of systemic features and these infections frequently arise from bacteria from the skin or other systems such as the respiratory system (15). An exchange arthroplasty is generally indicated in the non-acute setting of infection (>6 weeks postoperatively).

## AIM

The aim of the research was to compare how many patients required one stage versus two stage revision endoprosthesis surgery at the Clinic of Orthopedicis and Traumatology of the CCUS in the period from 2023 to 2024.

## MATERIALS AND METHODS

We assessed 143 patients with primary total knee endoprosthesis treated at the Clinic of Orthopedics and Traumatology of the CCUS, in the period from 2023 to 2024. Out of the total number of patients, 10 required revision endoprosthesis surgery. Patients were divided into two groups (one stage vs. two stage) depending of the reason requiring revision surgery. Criteria used for the group selection were: clinical presentation (pain, fever, swelling, skin redness, discharging sinus), serological testing (erythrocyte sedimentation rate [ESR] > 30 mm/hour; C-reactive protein [CRP] > 10 mg/L), knee aspiration, and biopsy samples. We graded all patients according to a standardized protocol for chronic hip and knee PJIs based on the criteria set out by Haddad and considered them for either a single- or two-stage revision procedure accordingly. The indications for using a single-stage approach during research period included insignificant bone loss or a soft tissue defect that could be closed primarily; patients who were not rheumatoid or diabetic or on immunosuppressant medication and did not have ongoing sepsis elsewhere or chronic disease such as anemia or cancer.

Statistical data processing was done through IBM SPSS Version 20.0 for Windows. Analysis of categorical variables was performed using Pearson's $\chi^2$-test or Fisher's exact probability test. Spearman rank correlation coefficients were used to examine the linear correlation. Statistical significance was set at the conventional level ($\alpha = 0.05$). The results were shown in the graph and contingency tables (numbers with three decimal places). The level of significance is $p < 0.05$.

## RESULTS

The study included 100 female patients (69.3%) and 43 male patients (30.7%) (Figure 1). The analysis revealed that the average age of the patients was 77.38±5.20 years. The average age of female patients was 77.42±5.41 years, and the average age of male subjects was 77.31±4.90. No significant statistical difference was found in relation to age (p=0.092). Out of all patients treated with PKA, only 10 patients required revision arthroplasty or 6.9% of all TKA implanted. Out of 10 patients, only 2 patients (1.3%) required two-stage surgery by the criteria used for group selection and no statistical significance was found (p=0.01.)

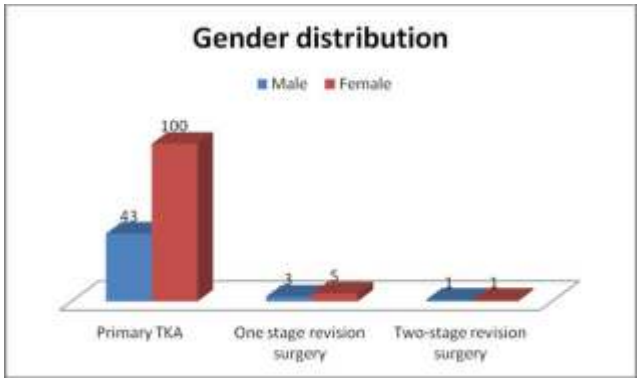


Figure 1 **Gender distribution**.

Out of 10 patients who required revisional arthroplasty, 2 patients had positive criteria for a two-stage surgery in terms of clicial presentation and higher rates of ESR and CRP, knee

aspiration was positive for both patients. Other patients had normal ESR and CRP, knee aspiration was negative.

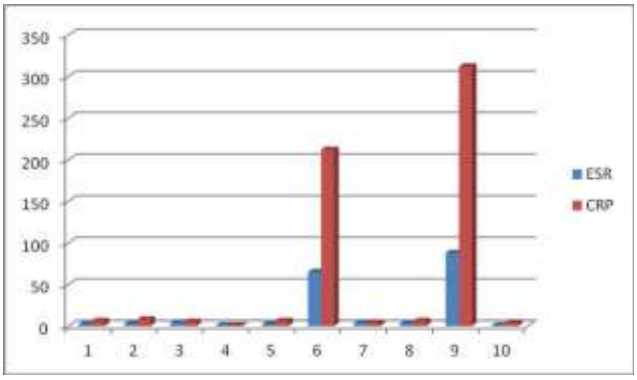


Figure 2 **Serological testing for revision arthroplasty.**

Regarding knee aspiration, only two patients had positive aspirates where St. Epidermidis was isolated in one patient while Staphyloccus aureus was isolated in other patients. Other knee aspirations were negative for patients demanding revision arthroplasty.

Table I **Knee aspiration isolates in group 2 requiring revision arthroplasty.**

| Knee aspiration isolates/Pt | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Staphylococcus aureus | neg | neg | neg | neg | neg | neg | neg | neg | neg | neg |
| Escherichia coli | neg | neg | neg | neg | neg | neg | neg | neg | neg | neg |
| Enterococcus faecalis | neg | neg | neg | neg | neg | neg | neg | neg | neg | neg |
| Pseudomonas aeruginosa | neg | neg | neg | neg | neg | neg | neg | neg | neg | neg |
| Staphylococcus aureus | neg | neg | neg | neg | neg | pos | neg | neg | neg | neg |
| Enterococcus faecium | neg | neg | neg | neg | neg | neg | neg | neg | neg | neg |
| Enterobacter cloacae | neg | neg | neg | neg | neg | neg | neg | neg | neg | neg |
| Streptococcus agalactiae | neg | neg | neg | neg | neg | neg | neg | neg | neg | neg |
| Staphylococcus epidermidis | neg | neg | neg | neg | neg | neg | neg | neg | pos | neg |

## DISCUSSION

Despite the relatively low rates of PJIs after TKAs, they remain a leading cause of revision surgery as a result of an ever increasing number of knee arthroplasties performed yearly for an aging population. Periprosthetic joint infection is a serious complication that can be associated with a reduction in quality of life and significant costs. Staphylococci were the predominant microorganisms causing early PJI in our study, which is also seen in PJI after primary arthroplasty (16). MRSA rate is as low as <1% in the general population and therefore early PJI after arthroplasty is rarely caused by MRSA. The antimicrobial mismatch rate between the empirical treatment and causative microorganism was not found in our cohort. This was mainly due to β-lactam-resistant S. epidermidis (MDR-SE), while Cefazolin was predominantly used as empirical antimicrobial treatment. Although resistance patterns differ locally, the emerging resistance rate of S. epidermidis to β-lactam antibiotics in PJI is of concern (17). In the study of Claret G, et al., an increase in MDR-SE PJI from 39% to 62% was seen between 2006 and 2015 (18). There are several diagnostic algorithms for PJI. One of the most widely used is the one proposed by the American Association of Orthopedic Surgeons (AAOS) in which they suggest that if a normal CRP and normal ESR are both normal, PJI is discounted (19). However, there are several studies that have proven that CRP and ESR are very non-specific PJI markers and can misdiagnose some 20% of PJI (20). The risk of unsuspected positive cultures has not been widely studied. A recent study by Bloom A, et al., showed that 7.9% of TKA and 12.1% of THA of the supposed aseptic revisions were really PJI (21). Grammatopolous G, et al., found that between 4 and 13% of patients with the preoperative diagnosis of aseptic loosening were infected (22). PJI should be diagnosed or excluded by performing joint aspiration before revision. Doing so ensures planning of the most appropriate treatment strategy. Joint aspiration is recommended to try to determine the causative microorganism and its antibiotic susceptibility before revision. This is important to tailoring the antibiotics to the bone cement and/or planning revision in one or two stages.

## CONCLUSION

Joint infection after total knee arthroplasty is a serious complication that can affect a patient's physical, emotional, social, and financial well-being. Therefore, achieving an early and accurate diagnosis of PJI is paramount in order to maximize the chances of successful treatment. The diagnosis of PJI involves a comprehensive approach that combines clinical assessment, serologic testing, synovial fluid aspiration, radiographic evaluation, and microbiologic finding. While some orthopedic surgeons and researchers have attempted to identify a single gold standard test for PJI diagnosis, such a test has not yet been established.

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# Clinical significance of coagulation factor gene mutations

# Klinički značaj mutacija gena koagulacijskih faktora

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## ABSTRACT

Introduction: the normal process of blood coagulation takes place under the control of protein coagulation molecules or coagulation factors, which are encoded by the corresponding protein-coding genes. The abnormal coagulation course, often cause of thromboembolic pathological conditions. Detection of pathological mutations of these genes has high importance in clinical medicine. Aim: The prevalence determination of specific coagulation gene mutations, important for timely anticoagulation therapy in personalized clinical medicine. Materials and methods: specimens of peripheral blood, taken from clinically selected patients, were analyzed to presence of specific gene mutations, by PCR and DNA sequencing methods. Results: after analysis of a total 121 specimens, determined total percentage mutation values were: 71%PAI-1(4G/5G); 23,6% MTHFR (C677T); 19% MTHFR (A1298C); 12,7% F13(G100T); 9,9% F5(G1691A); 1,6% F2(G20210A). Conclusion: the determination of these mutations is very important predictive molecular anticoagulant biomarkers for pregnant women and patients with autoimmune disorders.

**Keywords**: coagulation factor genes, DNA sequencing, pathological mutations, thrombophilia, clinical importance

## SAŽETAK

Uvod: normalan proces zgrušavanja krvi, odvija se pod kontrolom proteinskih molekula koagulacije ili faktora koagulacije, kodiranih odgovarajućim *protein-coding* genima. Abnormalni tok koagulacije, često je uzrok tromboembolijskih patoloških stanja. Detekcija patoloških mutacija ovih gena ima veliki značaj u kliničkoj medicini. Cilj: određivanje prevalencije specifičnih mutacija gena koagulacije, važnih za pravovremenu antikoagulacijsku terapiju u personaliziranoj kliničkoj medicini. Materijali i metode: uzorci periferne krvi, uzeti od klinički odabranih pacijenata, analizirani su na prisustvo specifičnih genskih mutacija, metodom PCR i DNK sekvenciranja. Rezultati: nakon analize od ukupno 121 uzorka, utvrđene su sljedeće ukupne procentualne vrijednosti mutacija: 71%PAI-1(4G/5G); 23,6% MTHFR (C677T); 19% MTHFR (A1298C); 12,7% F13(G100T); 9,9% F5(G1691A); 1,6% F2(G20210A). Zaključak: određivanje ovih mutacija je veoma važan prediktivni molekularni antikoagulantni biomarker za trudnice i pacijente sa autoimunim poremećajima.

**Ključne riječi:** geni koagulacijskih faktora, DNA sekvenciranje, patološke mutacije, trombofilija, klinički značaj

## INTRODUCTION

For normal process of blood coagulation are responsible several protein molecules or coagulation factors. All of them are encoded by protein coding genes, located on several human chromosomes. Our investigations of pathological mutations responsible for thrombophilia induction, included PAI-1, MTHFR, F-13, F-2 and F-5 genes. PAI-1 or SERPIN gene (7q22) encode PAI-1 or plasminogen activator inhibitor regulatory 40 kDa protein molecule. PAI-1 (4G/5G) mutation cause higher level production of abnormal PAI-1 proteins and a slower process of blood clots decomposition. It is caused by dysfunctional process of converting plasminogen into plasmin.

The PAI-1 protein molecule is in the form of heterodimer, with a molecular mass of 40 kDa structured by 402 amino acids. A significant number of people in the world dies, each year, from cardiovascular complications (myocardial infraction, pulmonary embolism) due to obstruction of blood vessels and impairment of normal blood flow. Mutations of the PAI-1 gene, mean an increased risk for pathological these events, especially for early abortion in pregnant women. In general, genetic analysis of PAI-1 gene polymorphisms is important for personalized biomedicine, in the meaning of appropriate clinical selection of patients with coronary complications and high-risk pregnancy.

Two mutated alleles for MTHFR gene (C677T and A1298C) may be present as two heterozygotes or one homozygote and mean a significant risk for thromboembolic events in pregnancy or other coagulation disorders. Concomitant heterozygosity for various factors manifests as high-risk hereditary thrombophilia. The

gene, located on first human chromosome (1p36.22), encodes a 74.5 kDa protein molecule, structured by 656 amino acids. Mutations of this gene are often associated in induction of vascular diseases, colon cancer and acute leukemia, as well.

F13B (Coagulation Factor 13B Chain) protein-coding gene, located on the first human chromosome, encodes a coagulation protein with a molecular weight of 75.5 kDa, structured from 661 amino acids. Mutations cause dysfunction of this protein molecule, resulting in the induction of diseases, such as F13B deficiency. It exists in the blood in an inactive or zymogenic form. F5 (Coagulation Factor 5) protein-coding gene (1q24), encode protein molecule structured from 2224 amino acids with molecular mass about 25.1 kDa. F2 (Coagulation Factor 2, Thrombin) protein-coding gene (11p11.2), encodes a heterodimeric protein with a molecular mass of 70 kDa, which consists of 622 amino acids. Mutations in this gene cause prothrombin deficiency, thrombophilia and dysprothrombinemia (1-5).

## AIM

The detection of coagulation genes specific mutations in clinically selected patients. It is important in determining the timely anticoagulation therapy of rheumatological and cardiovascular patients. The established prevalence of gene mutations represents a significant contribution to the field of molecular population genetics and personalized medicine, as well.

## MATERIALS AND METHODS

For screening to specific thrombophilia mutations presence, we analyzed a total 121 periferal blood specimens. DNA extraction is performed by using of Qiagen DNA mini extraction kit, according to the manufacturer's instructions. By using of specific detection primers (GML SNP Detectiv Panel Thrombophilia) the amplified specific gene nucleotide sequences obtained in thermal cycler, were analyzed by ABI 3130 sequencer. The reliability of this test is 99%.The genes, analyzed polimorphisms and obtained results interpretation are presented in tables 1 and 2.

Table 1 **Genes, mutations and polimorphisms.**

| GENE | MUTATIONS | POLYMORPHISMS |
|---|---|---|
| MTHFR | C677T | C T |
| PAI-1 | 4G/5G | 4G 5G |
| MTHFR | A1298C | A C |
| Factor-XIII | G100T | G T |
| Factor-II Prothrombin | G20210A | G A |
| Factor-V Leiden | G1691A | G A |

Table 2 **Possible interpretation of obtained results after DNA sequencing.**

| GENES | NORMAL GENOTYPE | POSSIBLE GENONOTYPE VARIANTS | DETECTED GENONOTYPE VARIANTS |
|---|---|---|---|
| MTHFR C677T | CC | CT (heterozygous)<br>TT (homozygous mutated) | Homozygous (CC) |
| PAI-1 | 5GG | 4G/5G (heterozygous)<br>4GG(homozygous mutated) | Heterozygous (4G/5G) |
| MTHFR A1298C | AA | AC (heterozygous)<br>CC (homozygous mutated) | Homozygous(AA) |
| Factor XIII | GG | GT (heterozygous)<br>TT (homozygous mutated) | Heterozygous (GT) |
| Factor II Protrombin | GG | GA (heterozygous)<br>AA (homozygous mutated) | Homozygous (GG) |
| Factor V Leiden | GG | GA (heterozygous)<br>AA (homozygous mutated) | Homozygous (GG) |

The analysis established the presence of heterozygotes at the PAI-1. Heterozygotes for mutated factor PAI-1 have increased activity of PAI-1 which acts as an inhibitor of fibrinolysis and thus an increased risk for thromboembolic event in pregnancy or other coagulation disorder. Heterozygote for mutated factor XIII has no clinical or therapeutic significance. Concomitant heterozygosity for various factors manifests as high-risk hereditary thrombophilia. Two mutated alleles for MTHFR (which may be present as two heterozygotes or one homozygote) have phenotypic manifestations in the form of hyperhomocysteinemia and a significant risk of thromboembolic event in pregnancy or other coagulation disorder. (6-8)

## RESULTS

We analyzed a total 121 of peripheral blood specimens to presence of patological mutations, which means predictive risk for thrombophilia, by PCR and DNA sequencing. In this paper, we presented the results of detected mutations for following genes:

MTHFR (C677T), PAI-1 (4G/5G), MTHFR (A1298C), Factor-13 (G100T), Factor-2 Prothrombin (G20210A), Factor-5 Leiden (G1691A) (Table 3.).

Table 3 **Obtained results to presence of specific pathological thrombophilia mutations.**

| Genes polymorphisms | Total specimens number | |
|---|---|---|
| | Homozygous | Heterozygous |
| PAI | 55 | 32 |
| MTHFR | 18 | 7 |
| MTHFR | 26 | 7 |
| F-13 | 18 | 2 |
| F-5 | 3 | 9 |
| F-2 | 0 | 3 |

Therefore, the analyzes showed the presence of heterozygosity in 37 specimens (30.58%) of peripheral blood samples, of which 5 have multiple heterozygosity, which indicates patients with a high or very high risk level for potential thromboembolic disorders. Most of the analyzed peripheral blood samples showed heterozygosity for one or two genes. Heterozygosity was most often determined for the PAI-1 gene and mutational variants of the MTHFR gene (A1298C, C677T). Samples 74, 84, 90, 119 and 121 had established multiple heterozygosity in the analyzed genes (Tables 4 and Figure 1).

Table 4 **Determined multiple heterozygosity in the analyzed genes.**

| Specimen number | PAI-1 | MTHFR (C677T) | MTHFR (A1298C) | F13 | F5 | F2 |
|---|---|---|---|---|---|---|
| 74 | HE | HE | HE | - | - | - |
| 84 | HE | HE | HE | HE | HE | - |
| 90 | HE | HE | HE | - | - | - |
| 119 | - | HE | HE | - | - | - |
| 121 | HE | - | - | - | HE | HE |

Table 5 **Obtained total incidence percentage mutation values.**

| Gene/Polimorphism | Total % | HM% | HE% |
|---|---|---|---|
| PAI-1 | 72 | 45,45 | 26,44 |
| MTHFR (C677T) | 27,3 | 21,48 | 5,78 |
| MTHFR (A1298C) | 21,5 | 15,7 | 5,78 |
| F13 | 14,87 | 13,2 | 1,65 |
| F5 | 9,97 | 2,47 | 7,43 |
| F2 | 2,47 | 0 | 2,47 |

Legend: HM-homozygous mutated; HE- heterozygous

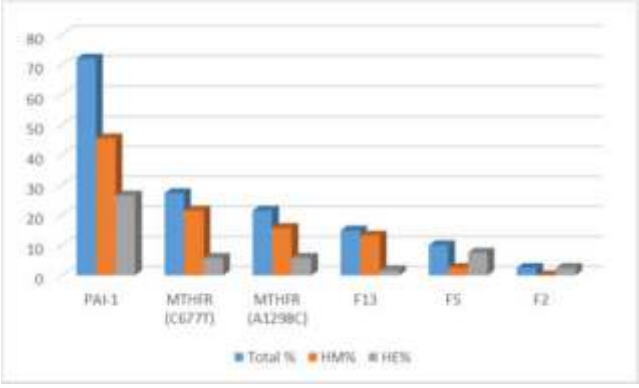


Figure 1 **Obtained total incidence percentage mutation values.**

## DISCUSSION

A significant number of people in the world die, each year, from cardiovascular complications such as heart attack and pulmonary embolism, because of vessel obstructions. Risk factors for that are pathological mutations of PAI-1 gene which encode plasminogen activator inhibitor type 1(PAI-1). PAI-1 is responsible for normal process of thrombus redissolution in the blood. The specific pathological mutation of this gene H(4G/5G), lead to increased PAI-1 level and slower decomposition od the blood clot. The clinically important PAI-1 gene polymorphisms H(4GG) and H(4G/5G) means increased risk for thrombophilia, myocardial infarcts and early miscarriage. Genetic analysis of PAI-1 gene polimorphisms is generally important for individual thrombophilia risk determination at patients with coronary complications and high-risk pregnancies as well.

Individual with 4G/5G polymorphism of PAI-1 gene have high risk for thrombosis development. Some investigations suggest that PAI-1 4G/4G polymorphism could be used as strong risk thrombophila factor (9-12).

Our investigations showed the highest incidence (71%) of this gene. This is all the more reason for the introduction of this molecular polymorphism gene screening, into everyday clinical practice, especially in the field of rheumatology and cardiovascular diseases. Often, thrombosis predisposition factors at pregnant women can be used mutations of MTHFR (C677T ; A1298C) and F5 (G1691) genes. The presence of these mutations means high risk factor for thrombosis development. A single mutation e.g. MTHFR (A1298C) generally cannot serve alone, as a risk factor for a thromboembolic event, but only can be significant, together with MTHFR (C677T) mutation (12-16).

Determined incidence of these polymorphisms was 23.6% and 19%. Also, mutations of F5(GA), F2(GG) and F8(GT) genes can serve as reliable thrombophilia prognostic factors. Thrombin or serin protease is key enzyme in the process of blood coagulation. Their precursor is prothrombin or F2 and G20210A mutation directly indicates dominantly inherited thrombophilia. The prevalence mutation determination of these genes in Bosnia people, represent important information in public health and contribute health improvement in prognostic sense and health care as well. Determination of thrombosis predisposition is very important in the protection of pregnant women especially those with a history of recurrent pregnancy loss.

Special attention should be paid to timely anticoagulant treatment of rheumatological patients in order to prevent arterial and venous thrombosis. Some current clinical trials have shown that people with antiphospholipid syndrome develop induction of venous thromboembolism in 18% of cases. The determined cumulative incidence percentages for other autoimmune diseases are: systemic lupus erythematosus (8%), vasculitis (7%), dermatomyositis (4%), rheumatoid arthritis (3%), autoimmune haemolytic anemia (3.4%), systemic sclerosis (3.1%), Sjogren's syndrome (2.1%) (17-21).

In clinical rheumatology, the MTHFR test detects specific mutations of this gene which mean a high risk for thromboembolic pathological disorders, which are caused by a disorder in the breakdown of the amino acid homocysteine. In fact, MTHFR protein molecules have their function for the normal metabolism of vitamin B-9 (folate), which is crucial in the process of normal functioning, cell growth, and the formation of erythrocytes.

It is also necessary in early pregnancy. Mutated MTHFR genes encode dysfunctional protein molecules, which causes the

accumulation of homocysteine in the blood, because of its untimely and rapid breakdown. Too high a concentration of homocysteine in the blood causes damage of blood vessels.

This means an increased risk for blood clots formation, cardiovascular diseases and stroke. A high level of homocysteine in the blood of pregnant women can cause a baby to be born with a neural tube defect. The two most common MTHFR gene mutations (C677T and A1298C) can be detected in people without any health problems. A negative test result means that none of the common MTHFR gene changes were detected. If, regardless of a negative MTHFR gene test, the level of homocysteine in the patient's blood is increased, it indicates that the cause may be a lack of B vitamins, consumption of certain drugs, age, hypothyroidism or some kidney disorders. Some mutations of the MTHFR gene are the cause of the weak effect of methotrexate in the treatment of patients with rheumatoid arthritis (RA nonresponder patients to methotrexate therapy). Research into new polymorphisms of the MTHRF gene is therefore very intensive in the world, especially in the field of rheumatology (22,23). Some researches, in terms of molecular personalized rheumatology, has shown that the MTHRF (C677T) polymorphism can be an important predictive biomarker of toxicity in methotrexate therapy. PAI-1(4G/4G) polymorphism may be useful disease activity predictor biomarker at patients with lupus nephritis and possible development of necrotizing lesions as well (24,25).

## CONCLUSION

Heterozygotes for mutated factor PAI -1 have increased activity of PAI-1, which acts as an inhibitor of fibrinolysis and mean an increased risk for thromboembolic event in pregnancy or other coagulation disorder. Heterozygote for mutated factor XIII has no clinical or therapeutic significance. Concomitant heterozygosity for various factors manifests as high-risk hereditary thrombophilia. The determined total incidence heterozygosity percentage values per gene were: PAI-1(26,5%), MTHFR (C677T)(4G/5G)(5,8%), MTHFR(A1298C)(5,8%), F-13 (G100T)(1,7%), F-5 Leiden (G1691A)(7,5%), F-2 Prothrombin (G20210A)(2,47%). Multiple heterozygosity showed five specimens under following numbers: 74, 84, 90, 119 and 121. This indicates the need for preventive anticoagulation therapy in these patients. The MTHRF (C677T) polymorphism can be used as toxicity predictive biomarker in rheumatology for methotrexate drug. The PAI-1(4G/4G) polymorphism can be useful disease activity predictor biomarker in lupus nephritis clinical management.

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# Comparison of knowledge about health care of chronic wounds in nurses - technicians of different level of education

# Komparacija znanja o zdravstvenoj njezi hroničnih rana kod medicinskih sestara - tehničara različitog nivoa obrazovanja

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## ABSTRACT

Introduction: chronic wounds significantly impact the health and quality of life of patients and their families. It is believed that nurses who are well-versed in best practices can influence the prevalence, frequency, and care of chronic wounds. Aim: to assess the knowledge of nurses regarding chronic wound care in relation to their level of education. Materials and methods: the study involved 699 nurses from Bosnia and Herzegovina. A questionnaire was used, created in Google Forms, based on a review of the available professional and scientific literature on chronic wounds. The questionnaire consisted of 64 questions, with 17 questions focused on the nurses' knowledge about chronic wounds. Results: it was found that 59.08% of respondents had secondary education, 6.15% had higher education, and 6.01% had advanced education. A certificate in chronic wound care was not possessed by 70.24% of respondents. The study found that 11.6% of respondents demonstrated unsatisfactory knowledge, while 31.2% showed knowledge with significant deficiencies. Satisfactory knowledge was demonstrated by 51.9% of respondents, and excellent knowledge was found in 5.3% of respondents. The study determined that there is no significant difference in the distribution of respondents based on knowledge criteria in relation to education level; p=0.19. Conclusion: overall, the knowledge and attitudes of the respondents were rated as satisfactory, with a minor presence of respondents with low knowledge. The level of education did not significantly impact the quality of nurses' knowledge about chronic wounds.

**Keywords:** chronic wounds, knowledge, education level, nurses

## SAŽETAK

Uvod: hronične rane imaju značajan utjecaj na zdravlje i kvalitetu života pacijenata i njihovu porodicu. Koliko je važno obrazovanje u njezi hroničnih rana vjeruje se da medicinske sestre koje poznaju najbolju praksu mogu utjecati na prevalencu, učestalost i njegu hroničnih rana. Cilj ovog rada je procjeniti znanje medicinskih sestara-tehničara o zdravstvenoj njezi hronične rane u odnosu na stručnu spremu. Materijali i metode: u istraživanje je uključeno 699 medicinskih sestara-tehničara sa teritorije Bosne i Hercegovine. Za istraživanje je korišten upitnik kreiran (google obrazac) na osnovu pregleda dostupne stručne i naučne literature vezano za hronične rane. Upitnik je prilagođen i modificiran prema preporukama European Wound Management Association (EWMA) i Hrvatske udruge za rane (HUR), čime je omogućeno ispitivanje znanja, stavova i prakse medicinskih sestara-tehničara o kroničnim ranama. Dio pitanja upitnika preuzet je iz "Quality of Life with Chronic Wounds – Wound-QoL Questionnaire", "Wound Care Survey" i znanstvene literature vezane uz temu (9-16). Rezultati: utvrđeno je da je 59,08% ispitanika s srednjom stručnom spremom, a višu stručnu spremu imalo je 6,15. Visoku stručnu spremu imalo je 6,01% ispitanika. Certifikat o zbrinjavanju hroničnih rana nije posjedovao 70,24% ispitanika. Utvrđeno je da je 11,6% ispitanika pokazalo nezadovoljavajuće znanje, a znanje sa značajnim nedostacima pokazalo je 31,2% ispitanika. Zadovoljavajuće znanje pokazala su 51,9% ispitanika. Odlično znanje imalo je 5,3% ispitanika. U ovom istraživanju je utvrđeno da ne postoji značajna razlika u distribuciji ispitanika na osnovu kriterija znanja, u odnosu na stručnu spremu; p=0,19. Zaključak: ukupno znanje i stavovi ispitanika su procjenjeni kao zadovoljavajući, uz manje prisustvo ispitanika sa niskim znanjem. Stepen stručne spreme nije značajno utjecao na kvalitet znanja medicinskih sestara o hroničnim ranama.

**Ključne riječi:** hronične rane, znanje, stručna sprema, medicinske sestre

## INTRODUCTION

It is estimated that chronic wounds affect 1-2% of the world's population (1). Chronic wounds have a significant impact on the health and quality of life of patients and their families, causing pain, loss of function and mobility, depression and anxiety, stigmatization and social isolation, financial burden, longer hospital stays, and chronic morbidity or even death (2,3).

The management of chronic wounds has significantly advanced over the past decade, requiring nurses to be particularly efficient and up-to-date with the latest best practice recommendations. As a result, nurses are offered continuous education and university degrees focused on developing wound care skills (4). The Organization of Wound Care Nurses (OWCN) was established in 2010 and provides basic and free training for all licensed nurses practicing in various care facilities. Wound and stoma care nurse education programs are increasingly becoming available in an effort to improve the quality of care among nurses (5).

The management of chronic wounds is complex, and to maximize patient outcomes, it is recommended that those involved in their care and treatment possess appropriate knowledge and skills, which include understanding the anatomy and physiology, tissue regeneration, and the etiology of chronic wounds, as well as knowledge about selecting the appropriate products and interventions to achieve positive outcomes (6,7).

Nurses are at the forefront of implementing innovations that can create positive outcomes in the prevention and treatment of chronic wounds in patients admitted to acute care hospitals. Given the importance of education in chronic wound care, it is believed that nurses who are knowledgeable about best practices can influence the prevalence, incidence, and care of chronic wounds. In the Canadian healthcare system, an educational program has been developed to inform and empower nurses who provide skin and wound care (8).

## AIM

The aim of this study was to assess the knowledge of nurse-technicians regarding the health care of chronic wounds in relation to their professional qualifications.

## MATERIALS AND METHODS

The study is a quantitative, cross-sectional, observational-analytical, comparative study. A total of 699 nurse-technicians from the territory of Bosnia and Herzegovina across all levels of healthcare were included in the research, with the sample collected using the "snowball" method. Distribution was carried out based on the recommendations of nurse-technicians. The research was conducted in collaboration with the Chambers of Nurse-Technicians and the Association of Nurse-Technicians in Bosnia and Herzegovina. The study was conducted from 24 November 2021 to 24 February 2022.

A questionnaire was used for the research, created based on a review of available professional and scientific literature related to chronic wounds. The questionnaire was adapted and modified according to the recommendations of the European Wound Management Association (EWMA) and the Croatian Wound Association (HUR), allowing for the examination of the knowledge, attitudes, and practices of nurse-technicians regarding chronic wounds. Part of the questionnaire's questions was taken from the "Quality of Life with Chronic Wounds - Wound-QoL Questionnaire," the "Wound Care Survey," and scientific literature related to the topic (9-16). The questionnaire consisted of 64 questions, with 17 questions focusing on the knowledge of nurse-technicians about chronic wounds.

The Cronbach's alpha test was conducted to check the adequacy of the questionnaire for assessing knowledge. Through the reliability analysis of the questions aimed at measuring knowledge, a Cronbach's alpha value of 0.615 was shown, which is characterized as an acceptable value, indicating the questionnaire can be used for knowledge assessment.

Approval for the research was obtained from the registered Chambers and Associations of Nurse-Technicians in Bosnia and Herzegovina. After the research was conducted, the collected data was entered into an electronic database created using Microsoft Office Excel 365. For statistical data processing, the IBM SPSS Statistics 26.00 program (IBM Corporation, Armonk, New York) was used.

## RESULTS

### *Distribution of participants by gender*

The study included 699 participants. Based on gender distribution, it was found that 153 participants (21.89%) were male and 546 participants (78.11%) were female. The distribution corresponds to the structure of employees in healthcare institutions in Bosnia and Herzegovina.

### *Distribution of participants by educational level*

Based on educational level, it was determined that 413 participants (59.08%) had a secondary education. 43 participants (6.15%) had a higher vocational education. A total of 243 participants (34.7%) had a university-level education. Among the participants with a university-level education, 192 were graduate nurses or had a bachelor's degree in nursing, 42 (6.01%) held a master's degree in their field, 7 (1.00%) held a master's degree in science, and 2 (0.29%) held a doctoral degree.

### *Proportion of certified nurse-technicians for chronic wound care*

Based on the data regarding certification for chronic wound care, 208 (29.76%) respondents were certified in wound care, while the remaining 491 (70.24%) did not possess the certification.

Table 1 **Scores on knowledge about wound treatment.**

| KNOWLEDGE | Mean | SD |
|---|---|---|
| **Average grade** | 12.49 | 2.29 |
| **Relative knowledge score (%)** | 73.50 | 13.46 |
| Knowledge classification | **N** | **%** |
| Unsatisfactory knowledge | 81 | 11.6 |
| Knowledge with significant gaps | 218 | 31.2 |
| Satisfactory knowledge | 363 | 51.9 |
| Excellent knowledge | 37 | 5.3 |

Overall, the average knowledge score was 12.49 ± 2.29 points, equivalent to 73.50 ± 13.46% in percentage terms. Based on the classification of knowledge, it was found that 81 participants (11.6%) demonstrated unsatisfactory knowledge, and 218 participants (31.2%) showed knowledge with significant gaps. Satisfactory knowledge was demonstrated by 363 participants (51.9%). Excellent knowledge (correct answers to more than 90% of the questions) was shown by 37 participants (5.3%).

Table 2 **Analysis of knowledge based on educational level.**

| Variable | Description | Knowledge points | | Proportion of correct answers | | p |
|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | |
| **Education Level** | SE | 12.33 | 2.37 | 72.51 | 13.93 | 0.065 |
| | VSE | 12.70 | 2.03 | 74.69 | 11.94 | |
| | University-level education | 12.74 | 2.18 | 74.97 | 12.80 | |

The analysis of knowledge based on participants' educational levels revealed that those with secondary education (SE) had an average score of 12.33 ± 2.37 points, with correct answers on 72.51 ± 13.93% of the questions. Participants with higher vocational education (VSE) scored an average of 12.70 ± 2.03 points, with correct answers on 74.69 ± 11.94% of the questions. Participants with university-level education showed an average knowledge score of 12.74 ± 2.18 points, with correct answers on 74.97 ± 12.80% of the questions. No significant difference in knowledge was found based on the level of education (p=0.065).

Table 3 **Classification of knowledge in relation to educational level.**

| Education level | Unsatisfactory knowledge | | Knowledge with significant gaps | | Satisfactory knowledge | | Excellent knowledge | | $x^2$ | p |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | | |
| **SE** | 58 | 14.0 | 130 | 31.5 | 206 | 49.9 | 19 | 4.60 | 8.723 | 0.19 |
| **VSE** | 3 | 7.0 | 14 | 32.6 | 25 | 58.1 | 1 | 2.30 | | |
| **University-level education** | 20 | 8.2 | 74 | 30.5 | 132 | 54.3 | 17 | 7.00 | | |

Among participants with secondary education (SE), 58 (14%) demonstrated unsatisfactory knowledge, 130 participants (31.5%) showed knowledge with significant gaps. Satisfactory knowledge, or correct answers on 75-90% of questions, was demonstrated by 206 participants with SE (49.9%). Excellent knowledge was shown by 19 participants with SE. Overall, satisfactory and excellent knowledge was present in 54.5% of participants. Among participants with higher vocational education (VSE), 3 (7%) demonstrated unsatisfactory knowledge, 14 participants (32.6%) showed knowledge with significant gaps. Satisfactory knowledge, or correct answers on 75-90% of questions, was demonstrated by 25 participants with VSE (58.1%). Excellent knowledge was shown by 1 participant (2.3%) with VSE. Overall, satisfactory and excellent knowledge was present in 60.4% of participants. Among participants with university-level education, 20 (8.2%) demonstrated unsatisfactory knowledge, 74 participants (30.5%) showed knowledge with significant gaps. Satisfactory knowledge, or correct answers on 75-90% of questions, was demonstrated by 132 participants with university-level education (54.3%). Excellent knowledge was shown by 17 participants with university-level education (7.0%). Overall, satisfactory and excellent knowledge was present in 61.3% of participants. The analysis showed no significant difference in the distribution of participants based on knowledge classification in relation to educational level; Chi-square=8.723; p=0.19.

Table 4 **The necessity of additional professional education in relation to knowledge.**

| Knowledge | Yes | | I am not sure | | No | | $x^2$ | p |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | Ne | % | | |
| Unsatisfactory knowledge | 57 | 10.7 | 14 | 15.1 | 10 | 13.7 | 14.888 | 0.021 |
| Knowledge with significant gaps | 168 | 31.5 | 31 | 33.3 | 19 | 26 | | |
| Satisfactory knowledge | 283 | 53.1 | 46 | 49.5 | 34 | 46.6 | | |
| Excellent knowledge | 25 | 4.7 | 2 | 2.2 | 10 | 13.7 | | |

Among the participants who stated that they needed additional education, 10.7% demonstrated unsatisfactory knowledge, 31.5% showed knowledge with significant gaps, 53.1% demonstrated satisfactory knowledge, and 4.7% showed excellent knowledge. Overall, satisfactory and excellent knowledge was present in 57.8% of participants. In the group of participants who believed they did not need additional education, 13.7% had unsatisfactory knowledge, and 26% had knowledge with significant gaps. Satisfactory knowledge was present in 46.6% of participants, and excellent knowledge was shown by 13.7% of participants. Overall, satisfactory and excellent knowledge was present in 60.3% of participants. Among participants who were unsure whether they needed additional education, satisfactory and excellent knowledge was present in 51.7% of participants. A significant difference was found in the necessity of education in relation to knowledge classification, with participants who stated that they did not need education showing the highest levels of satisfactory and excellent knowledge (Chi-square=14.888; p=0.021).

## DISCUSSION

A review of the literature and scientific databases reveals that little is known about the knowledge and skills of nurses in wound care, both in terms of formal evidence and education and what is gathered from experiential learning and clinical practice (15,16).

In this study, an analysis of demographic data based on gender distribution found that 153 (21.9%) respondents were male and 546 (78.1%) were female. This is expected, as nursing is predominantly a female profession in our region. The majority of respondents had a secondary education level, with 413 respondents (59.1%) having this qualification, while 243 respondents (34.7%) had a higher education level. In a study by Obilor HN, et al., which involved 182 nurses, the majority of participants were women (n=166, 91.2%), correlating with our study's results. However, in their study, 75% of participants were registered nurses, but none had postgraduate education, suggesting that our nurses may be more educated, as our study included nurses with both second and third cycles of higher education (17).

In this study, the overall average knowledge score was 12.49 ± 2.29 points, which corresponds to 73.50 ± 13.46 percent. Based on the classification of knowledge in this study, 11.6% of respondents showed unsatisfactory knowledge, and 31.2% showed knowledge with significant deficiencies. Satisfactory knowledge was demonstrated by 51.9% of respondents, while excellent knowledge (correct answers to more than 90% of questions) was shown by 5.3% of respondents. Insufficient knowledge of nurses in the basic components of wound assessment could lead to inappropriate treatment decisions, delayed wound healing, poor quality of life, and increased healthcare costs (17). The study by Bilal M, et al. aimed to assess the knowledge and attitudes of nurses regarding chronic wound care. Using a cross-sectional study design, a previously validated and tested questionnaire was used to collect data from a sample of 250 nurses working in two tertiary care hospitals in Karachi, Pakistan. Only 54% of nurses had adequate knowledge of chronic wounds, correlating with the results of our study. This study highlights significant gaps in nurses' knowledge and sheds light on the lack of evidence-based practice. Poor knowledge can compromise healthcare standards, even in the presence of positive attitudes. Therefore, a comprehensive revision of nursing curricula in local tertiary hospitals is warranted to enable nurses to update their knowledge (18).

In this study, no significant difference in knowledge was found based on the level of education (p=0.065). In a study by Surme Y, et al., it was found that the average knowledge score on wound healing was 62.0 ± 8.4. The study also found that as the educational level of nurses increased, so did their average knowledge score ($p < 0.05$), which does not correlate with the results of this study. The author noted that nearly half of the nurses did not regularly practice chronic wound healing, and more than half did not regularly conduct wound care education (19).

In this study, analysis demonstrated a significant difference in the distribution of respondents based on the possession of a certificate in chronic wound care (p=0.008). Additionally, a significant difference was observed in the need for further education relative to the classification of knowledge (p=0.021). Possession of a certificate in chronic wound care was directly and positively correlated with the amount of knowledge. Dugdall H, et al., conducted a study that did not explicitly investigate knowledge; however, they identified a link between higher and specialized wound care education and a positive attitude towards scientific evidence, which later led to better practice and wound care (20).

## CONCLUSION

Overall knowledge of the respondents was rated as satisfactory, with a minor presence of respondents with low knowledge. The analysis showed that 92.7% of respondents know what chronic wounds are, and 74.2% of respondents are also familiar with the different types of chronic wounds. This still indicates that there is likely a person on each team whose lack of knowledge could compromise the rules of good clinical practice. A significant difference was also found in the need for further education relative to the classification of knowledge, with respondents who stated that further education was not necessary showing the highest level of satisfactory and excellent knowledge. The level of education did not significantly affect the quality of nurses' knowledge about chronic wounds.

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**Declaration of patient consent**: the author certifies that they obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal.

**Authors' contributions:** AA, ĐO, MT, MG, AŠ, ADž, BK and AL gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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# Retrospective assessment of Dupuytren's disease patients surgically treated with partial fasciectomy

# Retrospektivna analiza pacijenata sa Dupuytrenovom bolesti koji su hirurški tretirani parcijalnom fasciektomijom

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## ABSTRACT

Introduction: Dupuytren's disease is a fibrosing disorder that results in slowly progressive thickening of the palmar fascia and leads to debilitating digital contractures, particularly of the metacarpophalangeal joints or the proximal interphalangeal joints. Current treatment for Dupuytren's disease is mainly limited to surgery. Aim: to evaluate the risk factors and analyze the characteristics of Dupuytren's disease patients who underwent partial fasciectomy, describe clinical and epidemiological behavior of Dupuytren's disease and to compare the results with other series published in the literature. Materials and methods: a retrospective descriptive study of 67 hands of 58 patients surgically treated with partial fasciectomy between 2018 and 2022 in Cantonal hospital Zenica. Information on involved hand and fingers, comorbidities, smoking history, anesthesia type, surgery duration, and postoperative complications was sought. Results: the mean age at surgery was 61.45 with a higher prevalence of man (81% of cases). The most common form of presentation was unilateral in right hand followed by bilateral and left hand involvement. The most commonly affected fingers were the ring finger (49.3%) and the little finger (41.8%). 26.9% of the patients were active smokers. Hypertension and diabetes mellitus were the most common accompanying diseases. Out of 67 surgeries, 58 were performed under regional anaesthesia and the rest under general aneaesthesia. During postoperative follow-up, 3 patients had wound dehiscence and one patient had localized postoperative hematoma. Number of affected fingers demonstrated a statistically significant positive correlation with hospitalization duration. Conclusion: partial fasciectomy is a safe and successful method for the treatment of Dupuytren's contracture with low rate of complications.

**Keywords**: Dupuytren's disease, contracture, palmar fibromatosis, partial fasciectomy

## SAŽETAK

Uvod: Dupuytrenova bolest je fibrozni poremećaj koji uzrokuje sporo progresivno zadebljanje palmarne fascije i vodi do iscrpljujućih digitalnih kontraktura, posebno metakarpofalangealnih zglobova ili proksimalnih interfalangealnih zglobova. Trenutni tretman za Dupuytrenovu bolest uglavnom je ograničen na hirurški zahvat. Cilj: procijeniti faktore rizika i analizirati karakteristike pacijenata s Dupuytrenovom kontrakturom koji su podvrgnuti parcijalnoj fasciektomiji, opisati kliničko i epidemiološko ponašanje Dupuytrenove bolesti i uporediti rezultate s drugim serijama objavljenim u literaturi. Materijali i metod: retrospektivna deskriptivna studija 67 šaka 58 pacijenata koji su operativno tretirani parcijalnom fasciektomijom između 2018. i 2022. godine u Kantonalnoj bolnici Zenica. Prikupljene su informacije o zahvaćenim šakama i prstima, komorbiditetima, historiji pušenja, vrsti anestezije, trajanju operacije i postoperativnim komplikacijama. Rezultati: prosječna starost pri operaciji bila je 61,45 godina s većom prevalencijom kod muškaraca (81% slučajeva). Najčešći oblik prezentacije bio je unilateralni na desnoj šaci, praćen bilateralnim i zahvaćenjem lijve šake. Najčešće zahvaćeni prsti bili su prstenjak (49,3%) i mali prst (41,8%). 26,9% pacijenata su bili aktivni pušači. Hipertenzija i dijabetes melitus bili su najčešće prisutni komorbiditeti. Od 67 operacija, 58 je izvedeno pod regionalnom anestezijom, a ostatak pod općom anestezijom. Tokom postoperativnog praćenja, 3 pacijenta su imala dehiscenciju rane, a jedan pacijent je imao lokalizovani postoperativni hematom. Broj zahvaćenih prstiju pokazao je statistički značajnu pozitivnu korelaciju s trajanjem hospitalizacije. Zaključak: parcijalna fasciektomija je sigurna i uspješna metoda za liječenje Dupuytrenove kontrakture s niskom stopom komplikacija.

**Ključne riječi**: Dupuytrenova bolest, kontraktura, palmarna fibromatoza, parcijalna fasciektomija

## INTRODUCTION

Dupuytren's disease is a prevalent benign fibromatosis affecting the palmar and digital fascia. Typically, it manifests with a fibrotic nodule on the palmar fascia, commonly found near the base of the 4th or 5th fingers. As the condition progresses, this nodule may gradually enlarge over several years, forming fibrous bands that extend into the fingers. These bands have the potential to contract, resulting in a flexion contracture of the small hand joints, known as Dupuytren's contracture, most frequently involving the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. This can lead to difficulties in fully extending the affected fingers and can impact hand function (1). Although the disease is not dangerous, it can cause disability in patients. People with Dupuytren's disease face many difficulties including washing hands, picking up objects, wearing gloves, holding objects with hands, putting hands in pockets, keeping hands straight and pain. These difficulties can reduce the quality of life of the patients (2). The prevalence of Dupuytren disease in the world is found as 8.2%. The highest rate of the prevalence of Dupuytren is related to the African continent with 17.2%, and the lowest is related to the American continent with 2.3% (2). Several risk factors have been identified for the development of Dupuytren's disease, including advanced age, male gender, familial history of the condition, diabetes mellitus, heavy alcohol consumption, smoking, and occupational exposure to manual labor (3). Dupuytren's disease tends to affect men more frequently and typically becomes apparent after the age of forty. While the incidence is notably higher in men, with reported ratios as extreme as 9:1, the condition often manifests less severely in women. Consequently, it may remain undetected until later stages of life (4). Treatment approaches vary depending on the severity and may include non-surgical options like steroid injections or collagenase injections, as well as surgical procedures to release the contracted bands and restore finger mobility (1). Today, several treatment options are available, including percutaneous fasciotomy, fasciotomy using collagenase (from Clostridium histolyticum), partial or selective fasciectomy, total fasciectomy, and dermofasciectomy (5). Surgical intervention is indicated after functional impairment, and it is typically recommended for patients with at least 30° of metacarpophalangeal joint contracture and/or proximal interphalangeal joint contracture associated with functional impairment (6). The literature is inconsistent in defining the percentage of contracture correction and recurrence rate, making it difficult to assess the effectiveness and safety of surgical interventions for Dupuytren disease (7). Dupuytren's disease, characterized by its genetic and cellular basis, lacks a definitive cure. Surgical interventions play a crucial role in managing hand impairment caused by this condition. While these procedures can significantly enhance hand function for many patients, they are not without risks, as both intraoperative and postoperative complications are frequently encountered. Moreover, recurrence of the disease remains a possibility following various treatments, including fasciectomy techniques. Therefore, while surgical techniques offer effective relief from symptoms, ongoing monitoring and potential additional interventions may be necessary to manage recurrent Dupuytren's disease effectively (11).

## MATERIALS AND METHODS

This study presents a retrospective observational analysis of patients with Dupuytren's disease who underwent surgical treatment at the Department of Plastic and Reconstructive Surgery of the Cantonal Hospital Zenica between 1 January 2018 and 31 December 2022. The study protocol received approval from the Institutional Research Ethics Committee (Approval No. 00-03-35-426-6/23). Demographic data were collected through an active search of medical records. The data collection instrument recorded various parameters, including sociodemographic features such as gender, age, and smoking status, as well as medical history elements such as diabetes mellitus, dyslipidemia, epilepsy, cardiovascular diseases, and hypertension. Clinical aspects of Dupuytren's disease, such as unilateral or bilateral involvement, affected rays, age at onset of symptoms, intra- and postoperative complications, length of surgical treatment, and anesthesia type, were also documented. The surgical procedure employed in this study was partial fasciectomy, which involved limb exsanguination using a pneumatic cuff. A skin incision was made on the volar aspect of the hand, creating skin flaps (z-plasty) extending to the affected area. Following the mobilization of skin flaps, neurovascular bundles and the thickened palmar fascia were dissected, identified, and protected. Subsequently, the affected fascia was excised, and the specimen was sent for histopathological examination to confirm characteristic changes associated with Dupuytren's disease.

### *Statistical analysis*

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS), version 23.0 for Windows (SPSS Inc. Chicago, USA). Categorical variables were presented as counts and percentages, and continuous variables were reported as mean ± standard deviation. Relevant variables were analyzed using descriptive statistics. Spearman's r data analysis was performed to evaluate the correlation. A statistical significance level of $p<0.05$ was set for all analyses.

## RESULTS

In a retrospective analysis, we examined the outcomes of surgical treatment with partial fasciectomy in 58 patients presenting with Dupuytren's disease. A total of 67 hands were surgically treated, with a predominant male representation (81%) and a male-to-female ratio of 4.3:1. The mean age at the time of surgery was 61.45 ± 9.25 years, ranging from 31 to 82 years. Comorbidities associated with Dupuytren's disease were prevalent in the patient cohort. Hypertension was the most common comorbidity, affecting 43.1% of patients, followed by diabetes mellitus type 2 (19%), dyslipidemia (12.1%), hypothyroidism (4.5%), pulmonary fibrosis (3.4%), and epilepsy (1.5%). Additionally, 26.9% of patients were active smokers.

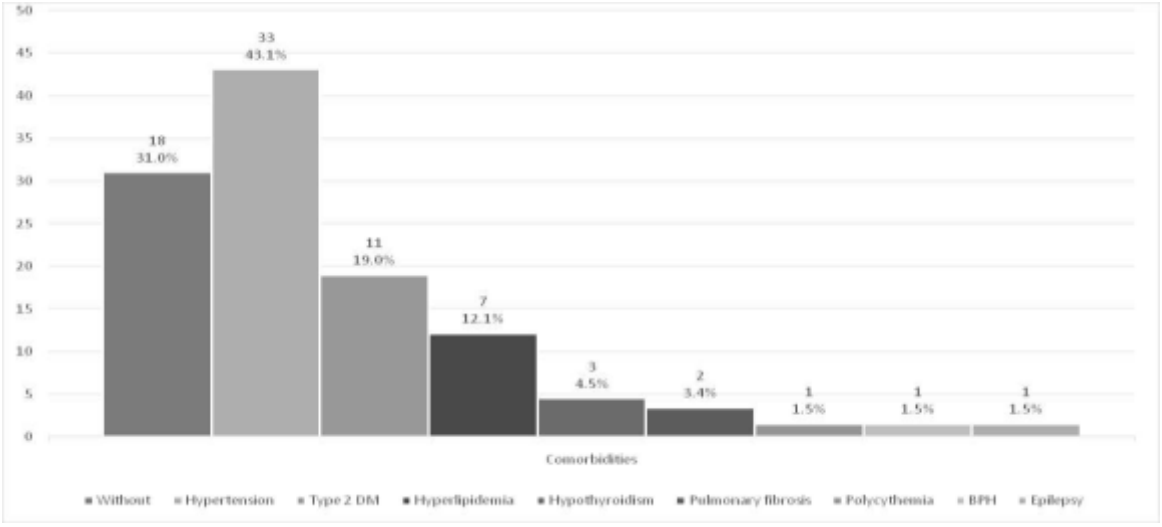


Figure 1 **Summary of the comorbidities among 58 individuals, indicating hypertension as the most prevalent (43.1%).**

| | | N | % |
|---|---|---|---|
| Bilateral presentation (N=58) | Yes | 21 | 36.2 |
| Affected hand (N=67) | Left | 25 | 37.3 |
| | Right | 42 | 62.7 |
| Affected finger (N=67) | 1 | 4 | 6.0 |
| | 2 | 5 | 7.5 |
| | 3 | 12 | 17.9 |
| | 4 | 33 | 49.3 |
| | 5 | 28 | 41.8 |
| Number of affected fingers (N=67) | One | 39 | 58.2 |
| | Two | 19 | 28.4 |
| | Three | 2 | 3.0 |
| | Four | 2 | 3.0 |
| | Palmar | 5 | 7.5 |
| Duration of complaints (years) (N=22) | Mean | 3.48 | |
| | Std. Deviation | 3.282 | |
| | Minimum | 0.5 | |
| | Maximum | 12 | |

Figure 2 **The distribution of affected fingers.**

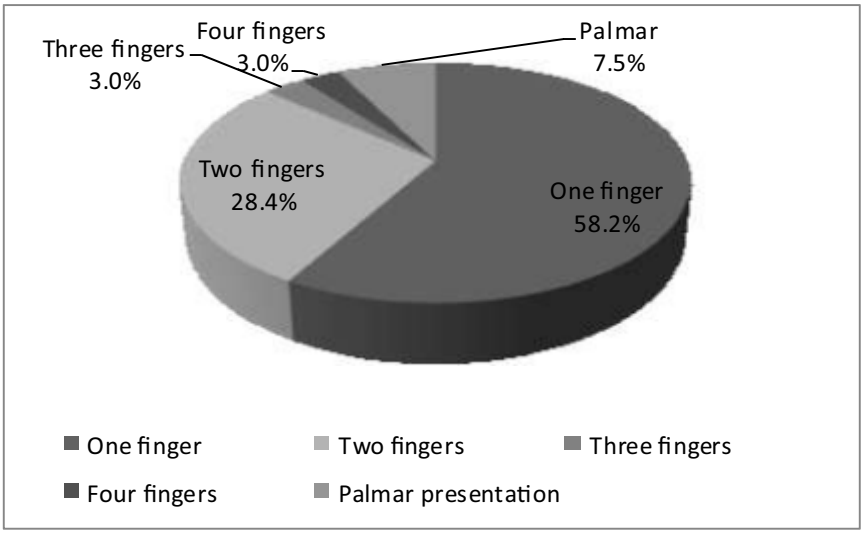


Figure 3 **The number of affected fingers**.

The primary mode of presentation documented in medical records was finger contracture, observed in 92.5% of patients, while palmar nodules were present in the remaining cases. Right-hand involvement was more frequent (43.1%) than left-hand involvement (20.7%) . Bilateral hand involvement was noted in 36.2% of patients, with 9 individuals undergoing bilateral hand surgery. Patients experienced symptoms for an average duration of 3.48 ± 3.28 years before undergoing surgery. Analysis of affected rays revealed that the ring (49.3%) and little (41.8%) fingers were most commonly affected, followed by the middle finger, index finger, and thumb. The majority of patients (58.2%) exhibited involvement of one affected ray, while 28.4% had involvement of two rays. A smaller proportion of patients had three or more affected rays. The majority of surgeries (88.1%) were conducted under regional anesthesia, while the remaining procedures were performed under general anesthesia. The mean duration of surgery was 53.2 ± 13.1 minutes, and patients experienced a mean hospital stay of 2.8 ± 1.1 days. Notably, no intraoperative complications were reported. However, during postoperative follow-up, three cases of wound dehiscence and one incidence of postoperative localized hematoma formation were observed. Among the various factors analyzed, only the number of affected fingers demonstrated a statistically significant correlation with hospitalization duration (rho = 0.266, p = 0.029). This finding suggests that patients with a

greater number of affected fingers are more likely to experience a longer hospital stay. These findings highlight the safety and efficacy of partial fasciectomy as the primary surgical approach for Dupuytren's disease, with a low incidence of postoperative complications.

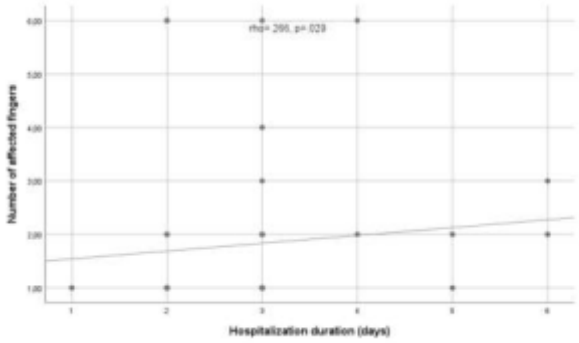


Figure 4 **Significant positive correlation between the number of affected fingers and the duration of hospitalization**.

## DISCUSSION

Classically, Dupuytren disease mainly affects white males, > 50 years old and its prevalence increases with age. We noted a predominance of individuals aged > 50 years old. A 4.3:1 ratio between men and women was observed, which is consistent with previous descriptions (5.9:1) (8). Multiple factors, including age, gender, and ethnicity, play an important role in the prevalence of the disease. The prevalence of this disease in white males, especially in northern European countries, is evidenced by the predominant age group between the fifth and seventh decades of life, with a male to female incidence ratio of 7:1-15:1 (9). In this study the seventh decade was predominant with mean age of 61.45. In terms of gender distribution, Dupuytren's disease exhibits a higher prevalence among males. This observation is consistent with findings by de Alencar FHU, et al., who reported 83.8% prevalence among males. Similarly, our Bosnian series demonstrates a predominance of males, with 81% of cases being male patients (6). In our study, bilateral involvement was noted in 36.2% of the cases, aligning with previous literature documenting the bilateral nature of Dupuytren's disease. Regarding unilateral involvement, the right side was more frequently affected, observed in 43.1% of cases, while the left side was affected in 20.7% of cases. This distribution is consistent with existing literature on the asymmetrical presentation of the disease (9). Furthermore, our findings revealed a notable predominance of involvement of fingers on the ulnar side of the hand. Specifically, the ring finger exhibited the highest involvement at 49.3%, followed closely by the little finger at 41.8%. These observations mirror patterns documented in the literature, reaffirming the characteristic distribution of Dupuytren's disease across the hand (9). Overall, our study's findings corroborate existing literature on the laterality and finger involvement patterns in Dupuytren's disease. Understanding these clinical features is crucial for accurate diagnosis and effective management strategies (9). In comparison to findings from a Brazilian study where 55% of patients exhibited cords and 45% presented with the nodular stage, our study demonstrates a notably higher prevalence of the nodular stage, with 92.5% of patients showing this characteristic (9). Among conditions associated with Dupuytren disease, 19% of the patients presented diabetes mellitus. In a series with only 58 cases of Brazilian patients with Dupuytren disease, Mansur et al. found a 44.8% prevalence of diabetes, with 62% of insulin-dependent subjects (9). Recently, a meta-analysis observed an approximately three-fold risk association between Dupuytren disease and diabetes mellitus (10). Furthermore, a majority of patients in our study also exhibited arterial hypertension, aligning with findings from Mansur et al. where 55% of subjects were reported to have this condition (9). Both Dupuytren disease and arterial hypertension predominantly affect elderly patients; however, the underlying cause of their association has not been elucidated in the current literature. Only one patient (1.5%) among this series presented with epilepsy. Historical literature has suggested a potential association between epilepsy and Dupuytren's disease; however, recent analyses indicate that this predisposition may be more closely linked to barbiturate therapy. Specifically, phenobarbital, a barbiturate used in epilepsy treatment, exhibits a dose and time-dependent profibrotic effect (12). In a study by Couto Gonzalez I, et al., epilepsy was found to have a prevalence of merely 1.6% among 184 patients in their series (13). In a comprehensive review, Denkler K, et al., reported a range of surgical complications following primary selective fasciectomy, with rates varying from 4% to 39%. In our study, we did not encounter any intraoperative complications. Specifically, there were no instances of digital nerve injury, which contrasts with the average rate reported in the literature of approximately 3% (11). This study provides valuable insights into the demographic characteristics, comorbidities, clinical presentation, and affected rays associated with Dupuytren's disease in patients undergoing surgical treatment with partial fasciectomy. These findings contribute to our understanding of the disease and may inform clinical management strategies.

## CONCLUSION

Our retrospective analysis underscores the efficacy and safety of partial fasciectomy as the primary surgical treatment for Dupuytren's disease. With a focus on demographic characteristics, comorbidities, clinical presentation, and surgical outcomes, our findings highlight minimal intraoperative complications, a brief hospital stay, and favorable postoperative outcomes. These insights contribute valuable evidence supporting the use of partial fasciectomy in managing Dupuytren's disease, emphasizing its role in achieving successful surgical outcomes with low complication rates.

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**Declaration of patient consent**: the author certifies that they obtained all appropriate patient consent forms. In the form, the patients have given their consent for the images and other clinical information to be reported in the journal.
**Authors' contributions:** HM, SS and AK gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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# Compounded suspensions in Galenic Laboratory of Clinical Pharmacy of the Clinical Center University of Sarajevo: a rewiew 2023

# Magistralno izrađene suspenzije u Galenskom laboratoriju Kliničke apoteke Kliničkog centra Univerziteta u Sarajevu: pregled 2023

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## ABSTRACT

Introduction: compounding suspensions are liquid pharmaceuticals forms that are widely used in variety of therapeutic applications in patients with special needs. Due to the ease of application of suspension, which is primarily reflected in the flexibility of dosing by volume measures, suspensions have an important role in hospital pharmacy, but also in public pharmacies. Aim: this paper represents an overview of compounding process, as well as analysis of the mostly common made suspensions in the previous year. Materials and methods: statistical evaluation of compounding suspensions from previous year, classified according to ATC clas sification. Presenting compounding process with significant facts that can affect outcome of therapy. Results: during 2023 year total of 734 suspensions were compounded in Galenic laboratory of the Clinical Pharmacy, Clinical Center University of Sarajevo. Out of total number 404 compounded suspensions are from group N - that affects Nervous system and is used for premedication and sedation. Total of 266 suspensions were prepared from group C that affects cardiovascular system. 32 suspensions are from group H - systemic hormonal preparations excluding sex hormones and insulin, 17 from group A - alimentary tact and metabolism, 11 from group J - anti-infective drugs for systemic use and 4 from group G - genitourinary system and sex hormones. Conclusion: compounding suspension is daily practice in hospital pharmacies. By understanding key components of formulation process, therapeutic needs and preferences of patients, pharmacists are able to compound safe and effective suspensions. Difficulties in drug chain supply, which causes medicine shortages in years after COVID-19, represent global problem. Related to this there is increased need for variety of compounding medicines such as suspensions.

**Keywords**: compounding suspensions, stability, dose unit uniformity

## SAŽETAK

Uvod: magistralno pripremljene suspenzije su tečni farmaceutski oblici koji se široko koriste u različitim terapijskim indikacijama kod pacijenata sa specifičnim potrebama. Zbog lakoće primjene suspenzije, koja se prvenstveno ogleda u fleksibilnosti doziranja volumnim mjerama, suspenzije imaju važnu ulogu u bolničkoj farmaciji, ali i u javnim apotekama. Cilj: ovaj rad predstavlja pregled postupka formulacije suspenzija, kao i analizu najčešće rađenih suspenzija u prethodnoj godini. Materijali i metode: statistička evaluacija magistralnih suspenzija iz prethodne godine, klasificiranih prema ATC klasifikaciji. Prikaz procesa izrade magistralnih preparata sa značajnim činjenicama koje mogu uticati na ishod terapije. Rezultati: tokom 2023 godine, u Galenskom laboratoriju Kliničke apoteke Kliničkog centra Univerziteta u Sarajevu, pripravljeno je ukupno 734 suspenzije. Od ukupnog broja 404 magistralno pripremljene suspenzije pripadaju grupi N - koja utiče na nervni sistem i koristi se za premedikaciju i sedaciju. Iz grupe C koja utječe na kardiovaskularni sistem pripremljene su ukupno 266 suspenzije. 32 suspenzije su iz grupe H -sistemskih hormonskih preparata izuzev spolnih hormona i inzulina, 17 iz grupe A-alimentarni takt i metabolizam, 11 iz grupe J-antiinfektivni lekovi za sistemsku upotrebu i 4 iz grupe G-lijekovi sa djelovanjem na genitourinarni sistem i spolni hormoni. Zaključak: magistralno pripravljanje suspenzija je svakodnevna praksa u bolničkim apotekama. Razumjevanje ključnih komponenti procesa formulacije, terapijskih potreba i preferencija pacijenata omogućava magistrima farmacije da priprave sigurne i efikasne suspenzije. Poteškoće u lancu snadbijevanja lijekovima, koje uzrokuju nestašicu lijekova u godinama nakon pandemije COVID-19, predstavljaju globalni problem. S tim u vezi bilježi se povećana potreba za različitim magistralno pripremljenim preparatima i suspenzijama.

**Ključne riječi**: magistralne suspenzije, stabilnost, ujednačenost doze

## INTRODUCTION

Suspensions are liquid pharmaceuticals forms that are widely used in variety of therapeutic applications in patients with special needs. In general, pediatric population mostly needs dosage adjusting. However, application of this form of drug is encountered in the geriatric population, the patients with dysphagia, as well as the patient fed through the tube. With the development of pharmacogenomics and increasing need for „tailored made" drugs, use of suspensions for patients allergic to a particular type of excipient is increased.

Due to the ease of application of suspensions which is primarily reflected in the flexibility of dosing by volume measures, suspensions have an important role in hospital pharmacy, but also in public pharmacies. Compounding suspensions have almost completely suppressed compounding of triturates (divided powders), which is considered an obsolete method of dose adjustment for patients and it is used only in the cases where it is not possible to ensure use of suspensions.

According to pharmaceutical profession, licensed drug is first choice to use in pharmacotherapy, or its equivalent, available on the market. If there is no such drug, possibility of compounding magistral or galenic medication is considered (1).

Suspension is form of medicine that is rearly commercially produced. In addition to physical stability such as prevention of precipitation and cake formation and enable redispersion, it is necessary to ensure both chemical and microbiological stability, as well as uniformity of dose through „shelf life" period and in use stability .

## AIM

The aim of the study was to evaluate most common compounded suspensions in Galenic laboratory in Clinical pharmacy classified according to ATC classification in previous year. The most significant characteristics of the formulation process, that can affect therapeutic outcome, are presented.

## MATERIALS AND METHODS

Compounding suspensions is a daily practice in the Galenic laboratory of the Clinical Pharmacy. In its work, pharmacists compound suspensions for oral use from various drug forms, in different dosage units. Mostly, during compounding process, licensed medicines from essential medicine list or commercially available medicines are used. This paper represents an overview of compounding process, as well as analysis of the mostly common made suspensions in the previous year, classified according to the ATC classification.

## RESULTS

Among variety of magistral and galenic medications during 2023 year, in Galenic laboratory of Clinical Pharmacy KCUS, were compounded total 734 suspensions in different concentrations and dosage. Drugs are classified according to the ATC classification.

Figure 1 **Compounded suspensions**

Table 1 **ATC Classification of compounded suspensions.**

| ANATOMICAL GROUP ON WICH THE DRUG AFFECTS | NUMBER OF PRODUCED SUSPENSIONS |
|---|---|
| C – CARDIOVASCULAR SYSTEM | 266 |
| J – ANTIINFECTIVE FOR SYSTEMIC USE | 11 |
| N – NERVOUS SYSTEM | 404 |
| G – GENITOURINARY SYSTEM AND SEX HORMONES | 4 |
| H – SYSTEMIC HORMONAL PREPARATIONS, EXCLUDING SEX HORMONES AND INSULINS | 32 |
| A – ALIMENTARY TRACT AND METABOLISM | 17 |

Most commonly produced suspensions were drugs from group N - Nervous System (404 suspensions) and C- group - Cardiovascular system (266 suspensions) (Table 1).

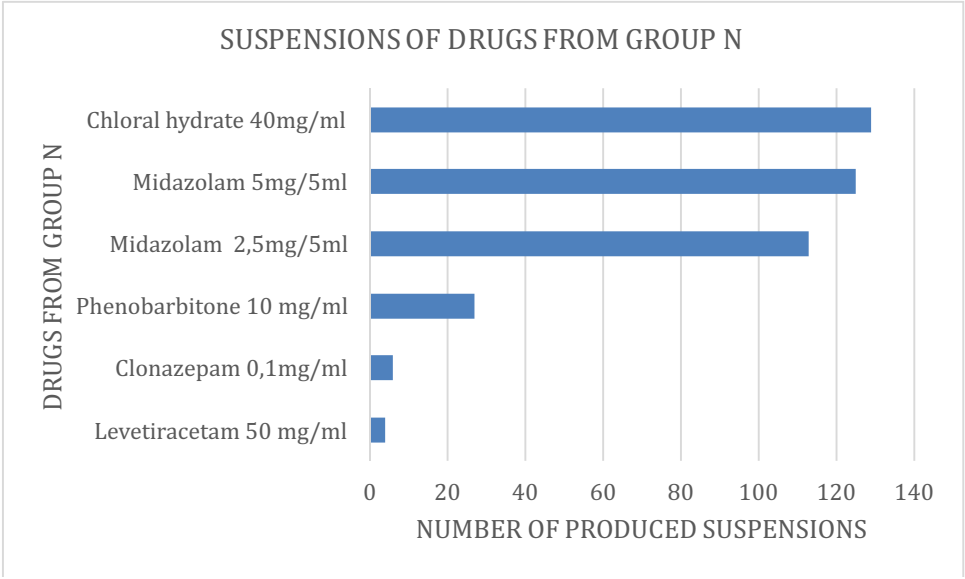


Figure 2 **Suspensions from group N.**

From the group N, which represent group of drugs that effects nervous system, 238 suspensions of Midazolam have been compounded, in two different concentrations 5mg/mL and 2,5mg/mL, and 129 Chloral hydrate suspensions at concentration of 40 mg/mL (Figure 2).

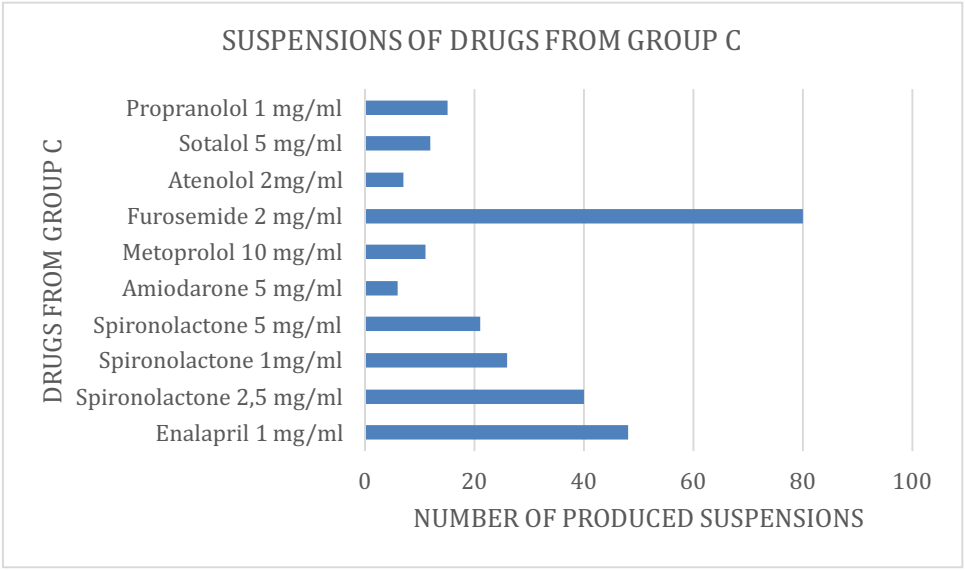


Figure 3 **Suspensions from group C.**

Among suspensions made from drugs that undergo C group, drugs that affects cardiovascular system, Furosemid suspension 2 mg/ml was mostly common compounded with total 80 in 2023 year. During two months period Furosemide triturates were made in order to „bridge the gap" in compounding material shortages. The amount of triturate is not represented in this analysis, but it is stated that number of produced furosemide suspensions would be significantly higher. Total 48 suspensions of Enalapril 1 mg/ml were compounded, and 87 suspensions of Spironolacton in different concentration 2,5 mg/ml, 1 mg/ml and 5 mg/ml (Figure 3).

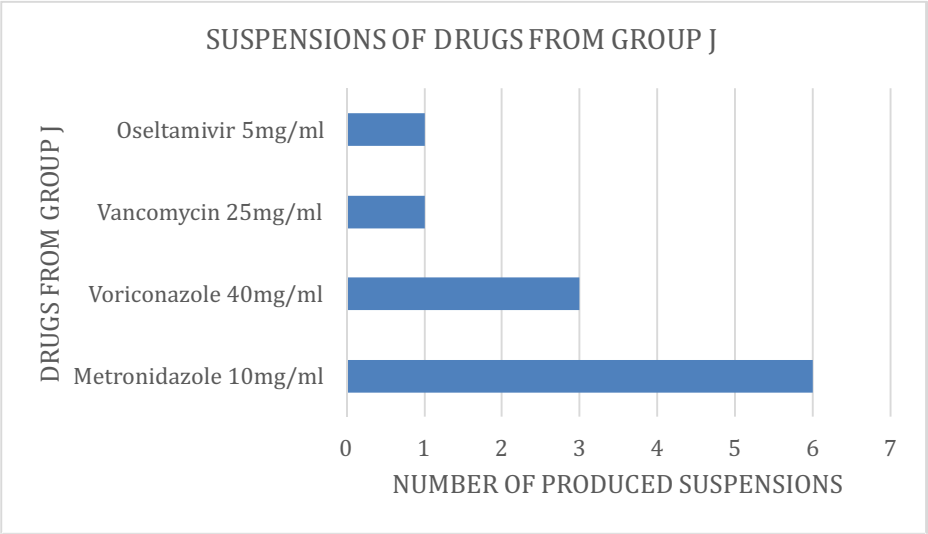


Figure 4 **Suspensions from group J.**

According to the anatomical-therapeutic-chemical classification, from group J -Anti-infective drugs for systemic use, 11 suspensions were produced, of which 6 were metronidazole suspensions in concentration of 10 mg/ml (Figure 4).

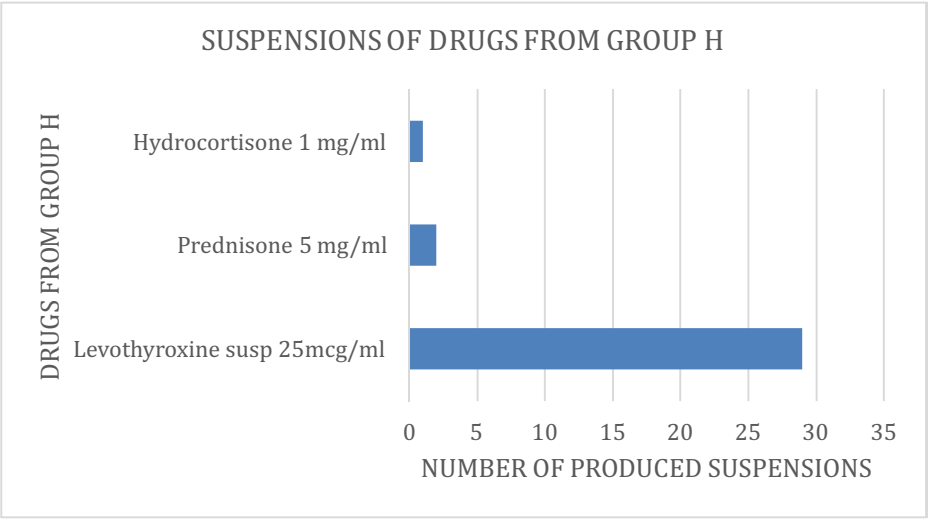


Figure 5 **Suspensions from group H.**

Pharmacists in Galenic laboratory have made 29 suspension of levothyroxine in concentration of 25 mcg/ml which is used in treatment of disorders and disease of thyroid gland (Figure 5).

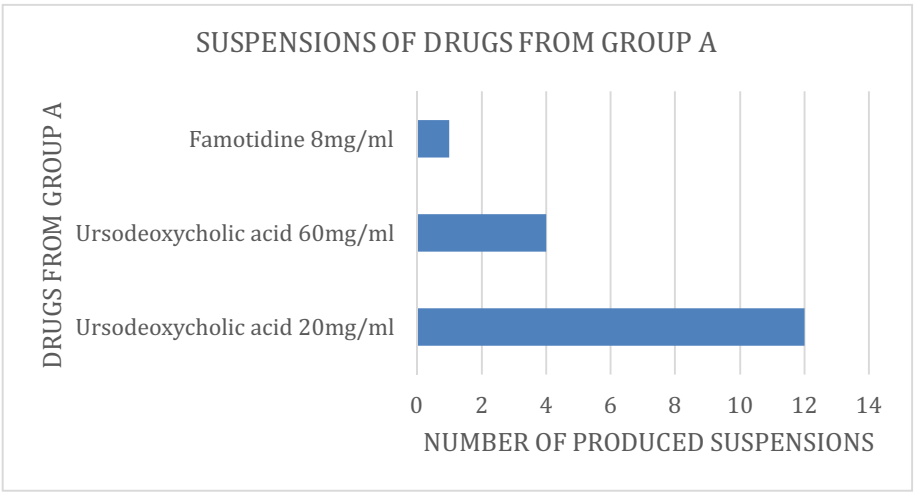


Figure 6 **Suspensions from group A.**

From group A- Drugs for the treatment of gastrointestinal tract diseases and metabolism, 17 suspensions were compounded, of which 16 were suspensions of ursodeoxycholic acid at concentrations of 60 mg/ml and 10 mg/ml, which is indicated in the pediatric population for the treatment of hepatobiliary disorders associated with cystic fibrosis (Figure 6).

The suspensions compounded in Galenic laboratory of CCUS, were mainly intended for the pediatric populations needs, but they are also suitable for use in all age groups with appropriate adjustment of the dose.

## DISCUSSION

The need for compounded preparation, in order to exceed lack of licensed oral liquid formulation for pediatric population, was demonstrated in this study. Total of 734 suspensions were compounded, regarding 23 different active substances, which have been used in the treatment of pediatric population in 2023.

The most commonly produced suspensions were midazolam and chloral hydrate that are indicated for use in pediatric population for sedation, anxiolysis and amnesia before diagnostic or therapeutic procedures or prior to the induction of anesthesia.

Worldwide, the prevalence of essential hypertension in the pediatric population is increasing.

Furosemide is a diuretic frequently used in the therapeutic management of edema associated with cardiac, renal and hepatic failure and hypertension. However, there is very low number of pharmaceutical dosage forms containing furosemide that are suitable for administration in pediatric population. Therefore, there is a real need for the development of furosemide suspension preparations, especially in the hospital.

Pharmaceutical industry is mainly oriented for target adult population and manufacture due to standardized protocol and as such cannot meet all patient needs. Compounded medications, prepared individually, have an important role in meeting the singe patient therapeutic needs and pediatric patients. The pharmacists are responsible for the preparation, control and dispensing of compounded preparations and they have a key role in interaction with patients and other health care professionals (2).

Prescribing drugs in pediatric is a critical issue due to the small number of clinical trials conducted on the pediatric population, which means that the therapeutic doses recommended for pediatric pharmacotherapy are not tested, or do not exist at all. So, it is necessary to apply pharmaceutical preparations that are available in a dose and forms intended for adult patients (3).

### *Formulating suspensions*

From a pharmacokinetic perspective, the advantage of suspensions lies in their large specific surface area. It can directly influence bioavailability, which can be greater compared to solid forms that undergo disintegration before absorption. Although the suspensions have numerous advantages typical for liquid pharmaceutical forms, their stability and effectiveness are not easily achieved (4).

Chemical structure of the drug (salt, ester) or active component is considered along with its characteristics, potency, stability and compatibility. Not comprehending these characteristics can lead to the degradation of active component which result in under dosed medication and ineffective therapy, even if the patient has taken the correct dose.

Compounding process starts by grinding tablets or capsules, and its transformation into a fine, smooth powder. While doing so, it is necessary to keep in mind that too much grinding can lead to higher adhesiveness compared to larger particles. If possible, it is preferable to use contents of capsules or crushed tablets. If tablets are coated, it is necessary to determine the solubility of the coating in water (4).

The required viscosity and flowability can be achieved by adding various excipients. To reduce interfacial tension and expel air from hydrophobic materials in dispersed mass, surfactants such as wetting are used. Excipients in all formulations are used only if there is justified need. They should be pharmacologically inert, while giving favorable physical properties and enable delivery of the active substance at the desired concentration. Since this suspension vehicle could be used in chronic treatment, certain excipients may accumulate with time. Therefore, special attention is needed in order to select excipients known for their innocuity and long-term safety. Choice of excipients depends on dose, type of active component, physiochemical properties, compatibility, desired effects and interaction with other component of the formulation system (5,6).

### *Organoleptic properties*

Organoleptic properties such as taste, sweetness, smell have significant influence on consistency of therapeutic dosage regime. Aromatic excipients are used to mask taste and smell of the active substance, as well as sweeteners and flavorings. Sweetened in suspensions should be use at lowest possible dose of sweetener, especially for the patients on a low-sugar diet. Commercially available vehicles with no added sugar are appropriate for diabetic patients. In patients receiving medication via enteral feeding tubes, organoleptic properties are less important.

### *Osmolality*

The osmolality of the physiological fluids of the gastrointestinal tract ranges from 100 mOsm/kg to 400 mOSm/kg. Depending on used sweeteners certain suspending vehicles have high osmolality. Natural polyol sweeteners such as sorbitol have much lower sweetness than artificial sweetener and require higher concentration in the formulation which consequently leads to hyperosmolality and osmotic diarrhea. Additionally sorbitol and sugar alcohols in general are only partially absorbed from gastrointestinal tract an can cause disorders, such as abdominal pain, swelling, flatulence, vomiting and osmotic diarrhea. Unabsorbed sorbitol ferments and metabolizes to fructose, therefor should be avoided in children with fructose intolerance and hypoglycemia. Pharmacist should ensure that the sorbitol intake during suspension dosing is kept below 20 g/ day for adults. Appropriate choice for patients who do not tolerate hypertonic solutions is to use unsweetened vehicles (7).

### *Viscosity*

Increased viscosity can reduce rate of sedimentation but also can affect re-dispersion and the possibility of pouring from the bottle influencing the dosing and its administration. If suspensions are administrated through narrow cannulas physiochemical properties are crucial since suspensions with inappropriate viscosity and large particles can clot the tube. Viscosity of these vehicles can be adjusted by diluting them with purified water, rather than with another vehicle with high osmolality.

### *pH value*

Drugs are usually week electrolytes, acids and bases. pH of the formulation greatly affects the ionization process, solubility and physiochemical stability of the suspensions. It is necessary to prevent sudden changes of pH in order to control ionization process of preservatives. Most drugs and preservatives require an acid pH. However if the drug is unstable in acid pH, the suspension should be prepared in basic pH environment in order to stabilize the active substance and the system.

### *Preservatives and Colors*

Preservatives are often included in liquid vehicles formulations for oral administration to ensure long term stability during the products shelf life. Parabens are frequently used because they offer broad spectrum antimicrobial protection, even in small concentrations. Methylparaben is effective in oral vehicles in wide range of pH value, but in combination with propylparaben achieve synergistic effect. Both have poor solubility in water and require use of co-solvents such as alcohol or propylene glycol (7).

In addition to parabens the most commonly used preservatives in oral preparations include sodium benzoat and potassium sorbate. Unlike parabens, these preservatives are water -soluble. The effectiveness depends on the pH value of the final preparation.

Colors provide smoothness and pharmaceutical elegance to the compounded liquid preparation. Due to the limited newborns metabolism, patients allergies or hypersensitivity often are used vehiculum without this excipients. Complex oral suspensions for this population are mainly prepared *ex temporaneus*, to be administrated immediately or within a short period of time, to avoid the use of preservatives as well.

### *Suspension stability*

Drug stability is essential quality parameter that not only determinates effectiveness but also safety of the drug during period of use. Side effects do not necessarily correlate with the pharmacological activity of the active substances, but may be related to the presence of impurities. Related substances or degradation products are impurities caused by chemical changes of substance that occurred during production and / or storage of the drugs (8).

Drug impurities are regulated by ICH guidelines and define level of impurity that should be reported, qualified or identified during the drug development and manufacturing processes (9).

By identifying related substances it is possible to determine their origin and properties. With correct analyze of degradation products, is possible to optimize conditions during production and storage in order to maintain their concentration remained within the declared limits.

### *Physical stability of the suspensions*

Physically stable liquid products should preserve, within the declared limits, color, viscosity clarity, taste and smell over the shelf life. Physical stability of the product is also affected by the type of packaging. Suspensions are distributed in multi dose glass or plastic bottles with screw caps, which can lead to moisture loss and evaporation of the product as well as microbial contamination, proliferation and/or physiochemical degradation after system has been broken (10).

Ideally the system should be pseudoplastic and thixotropic, with high viscosity during storage and low viscosity during shaking, pouring or spreading.

### *Chemical stability of the suspension*

Compared to solid and semisolid forms, liquid drug forms are more chemically unstable due to molecular interactions present in a liquid environment. The nature of water and other liquids is to accelerate all chemical processes, microbiological contamination and oxidative degradation. Temperature, pH value, presence of oxidants, certain trace metals and effect of light are parameters that can start chemical and physical changes. Increasing temperature of 10 degrees can result in 2 to 5 time faster degradation rate (7).

Drugs containing more than one functional group undergo the process of oxidation (in presence of oxygen) and hydrolysis (in presence of humidity). An example is atenolol which contains amide and alcohol groups. Active components that contain ester functional groups, such as aspirin and penicillin, degraded by

hydrolysis while those that containing aldehyde or hydroxyl groups, such as testosterone and dopamine, are subjected to oxidative decomposition (11).

### *Uniformity of dose units*

Degree of uniformity of dose units is essential considering that variability in delivered doses can lead to underdosed or overdosing therapy. Pharmacist must ensure homogenous suspension with equally distributed active ingredient so that every volume measure contains active substance within a narrow range around the declared value.

Dosage units are defined as pharmaceutical forms that contain one dose, or part of a dose of the active substance in each dosage unit. The term "uniformity of dosage units" is defined as the degree of uniformity of the amount of active substance among dosage units (12).

Figure 7 **Uniformity of suspensions.**

Considering that suspension is two phase system, which undergo precipitation process during time, they are dispensed with label „shake before use". It is important that end user, either nurse or patient, keep in mind that accuracy of delivered dose depends of this act.

## CONCLUSION

Oral suspensions are convenient and patient friendly way of administering medications. By understanding key components of formulation process, therapeutic needs and preferences of patients, pharmacists are able to compound safe and effective suspensions. As a result of global medicine shortages in years after COVID-19 pandemic increased need for compounding medicines is notable.

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# Characteristics of hemorrhagic fever outbreak during COVID-19 pandemic in Bosnia and Herzegovina, 2021

# Karakteristike epidemije hemoragične groznice za vrijeme COVID-19 pandemije u Bosni i Hercegovini, 2021.

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## ABSTRACT

Introduction: hemorrhagic fever with renal syndrome (HFRS) is an infectious disease caused by hantaviruses which belong to the genus Orthohanta viruses. The presence of hemorrhagic fever was reported in Bosnia and Herzegovina more than 70 years ago, only a few years after first reported cases during the Korean War. Bosnia and Herzegovina is well known for the largest hemorrhagic fever with renal syndrome outbreak described so far in the Southeast Europe. Aim: to present the clinical manifestation, course and outcome of patients with HFRS treated in Clinic for infectious disease Sarajevo during COVID-19 pandemic. Materials and methods: we conducted retrospective analysis of all medical records in Clinical Center University of Sarajevo in 2021. Patients with laboratory confirmed diagnosis of hantavirus infection. Results: in an observed period we had a total of 29 patients hospitalised with clinical or microbiological confirmation of HFRS. Symptoms presented before admission were fever, headache, malaise and vomiting. The parameters that can be considered as possible prognostic factors for hemodialysis during the treatment were levels of BUN ($p<0.001$), and creatinin ($p=0.001$). Conclusion: hemorrhagic fever with renal syndrome still remains a major medical challenge. Quick diagnosis and proper therapy, which in some cases also require hemodialysis, are crucial for favorable outcome.

**Keywords:** HFRS, COVID-19, epidemic, Bosnia and Herzegovina

## SAŽETAK

Uvod: hemoragijska groznica s bubrežnim sindromom (HGBS) je zarazna bolest uzrokovana hantavirusima koji pripadaju rodu Orthohantaviridae. Prisutnost hemoragične groznice u Bosni i Hercegovini zabilježena je prije više od 70 godina, samo nekoliko godina nakon prvih prijavljenih slučajeva tijekom Korejskog rata. Također, Bosna i Hercegovina je poznata po najvećoj do sada opisanoj epidemiji hemoragične groznice s bubrežnim sindromom u jugoistočnoj Europi. Cilj: prikazati kliničke manifestacije, tok i ishod bolesti kod pacijenata liječenih od HGBS u Klinici za infektivne bolesti u Sarajevu u periodu COVID-19 pandemije. Materijal i metode: proveli smo retrospektivnu analizu svih historija bolesti pacijenata liječenih u Kliničkom centru Univerziteta u Sarajevu u 2021. godini s laboratorijski potvrđenom dijagnozom hantavirusne infekcije. Rezultati: u promatranom razdoblju imali smo ukupno 29 pacijenata hospitaliziranih s kliničkom ili mikrobiološkom potvrdom HGBS-a. Simptomi koji su se javili prije prijema bili su vrućica, glavobolja, malaksalost i povraćanje. Parametri koji se mogu smatrati mogućim prognostičkim faktorima za hemodijalizu tijekom liječenja bili su vrijednosti uree ($p<0,001$) i kreatinina ($p=0,001$). Zaključak: hemoragijska groznica sa bubrežnim sindromom i dalje ostaje veliki medicinski izazov. Pravovremena dijagnostika i terapija, koja u pojedinim slučajevima zahtjeva i hemodijalizni tretman, ključni su za pozitivan ishod liječenja.

**Ključne riječi:** HGBS, COVID-19, epidemija, Bosna i Hercegovina

## INTRODUCTION

Hemorrhagic fever with renal syndrome (HFRS) is an infectious disease caused by hantaviruses which belong to the genus Orthohantaviruses. The presence of hemorrhagic fever has been reported in Bosnia and Herzegovina more than 70 years ago, only a few years after the first reported cases during the Korean war (1,2). Bosnia and Herzegovina is well known for the largest hemorrhagic fever outbreak with renal syndrome outbreak described so far in Southeast Europe (3,4). HFRS in the region of Bosnia and Herzegovina is caused by two types of hantaviruses: Dobrava (DOB) and Puumala (PUU) (2,5). Humans are not the natural host of hantavirus, and infection is usually accidental. In most cases, it is caused by contact with aerosolized rodent

urine, feces, or saliva, or during consumption of contaminated food, mostly wild fruits (6). There are no records for human-to-human transmission in Europe. Soldiers, farmers, forest workers, and hikers are at higher risk of contracting infection, and because of that, men get sick more often than women. Hantavirus can cause two forms of disease in humans: hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome (7,8). Symptoms include the acute onset of fever, headache, abdominal pain, hemorrhage, and acute kidney injury presented as oliguria or anuria. HFRS can have a different clinical presentation as a mild, moderate, or even severe life-threatening illness form of the disease. (9). Diagnosis is not based only on clinical presentation but also needs laboratory confirmation with a serology test or PCR (10). Specific therapy for HFRS is not available yet. The treatment is based on supportive therapy and, in some severe cases, haemodialysis. Some studies recommend the use of Ribavirin, which is not widely available (11). The COVID-19 pandemic was declared by WHO in February 2020. The first case of a SARS-COV-2 positive patient in Bosnia and Herzegovina was confirmed in March the same year. In the next months, thousands of patients literally overwhelmed the hospitals in Bosnia and Herzegovina, causing not only different to treat COVID-19 but also left small space to hospitalize and treat other infectious diseases, which have not disappeared during the COVID-19 pandemic. The epidemic of hemorrhagic fever required an extremely additional effort of health workers considering the conditions due to the pandemic of COVID-19.

## AIM

The aim of this work was to present the clinical manifestation, course, and outcome of patients with HFRS treated in the Clinical Center University of Sarajevo during the outbreak of the disease in 2021. in the situation of the present COVID-19 pandemic.

## MATERIALS AND METHODS

We conducted a retrospective analysis of all medical records in the Clinical Center University of Sarajevo in 2021. Patients with laboratory confirmed diagnosis of hantavirus infection. Nextline antibiotics All serum samples were tested in the Clinic for microbiology, Clinical center University of Sarajevo, and RecomLine HantaPlus immuno-line assay (Mikrogen GmbH, Germany) was used as the appropriate test.

## RESULTS

In the observed period we had a total of 29 patients hospitalized with clinical or microbiological confirmation of HFRS. All of them were males. The age of patients ranged from nine to 49 years, witha median value of 34 years. We had positive epidemiological data for 24 (82.2%) patients, and among them 13 had professional exposure, due to their work. The majority of them, 15 (51,7%) came from Central Bosnia, mostly from town Bugojno, 12 (41.4%) from Sarajevo region, and other two (6.9%) came from Goražde and Zenica region each. Symptoms presented before admission were fever in 28 (96.6%) patiens, headache 22 (75.9%), malaise 28 (96.6%), vomiting 19 (65.5%), diarrhea 12 (41.4%), oliguria in 19 (65.5%), manifest bleeding in 5(17.2%), conjunctival bleeding in 13(44.8%) and mucosal hemorrhagic changes in 3 (10.3%) patients. Ultrasound found kidney changes in 25 (86.2%) patients. At admission, we had a wide range of values in laboratory results, as presented in Table 1. The most significant result was elevated creatinin presented in 28 out of 29 patients, with median value of 589.20 umol/l.

Table 1 **Laboratory results at admission.**

| | | Values at admission | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | RBC | Hgb | Plt | WBC | BUN | Creat. | AST | ALT | D-dim. | INR | APTT | Fibr. |
| Mean | | 4.89 | 147.00 | 124 | 10.7 | | | | | 5.58 | | | |
| Std.Dev | | 0.95 | 26.51 | 86 | 3.9 | | | | | 4.321 | | | |
| Minimum | | 3 | 103.00 | 11 | 3 | 3 | 67.00 | 15.00 | 13.00 | 1 | 1 | 24 | 2 |
| Maximum | | 7 | 213.00 | 325 | 22 | 44 | 1253.00 | 933.00 | 929.00 | 15 | 1 | 63 | 37 |
| Percentiles | 25 | | | | | 9.95 | 258.00 | 25.50 | 23.500 | | .90 | 28.65 | 3.70 |
| | M* | | | | | 14.6 | 483.00 | 39.00 | 45.00 | | 1.00 | 32.90 | 4.70 |
| | 75 | | | | | 32.1 | 966.00 | 65.50 | 112.00 | | 1.10 | 35.85 | 6.00 |

*median ( 50$^{th}$ percentil);
Red blood cells - RBC (ref.values 4.3-5.7 1012/L); Hemoglobin - Hgb ( ref.values 119-157 g/L);Platelets - Plt ( ref.values 140-450 109/L); White blood cells WBC (ref.values 3.7-9.3 109/L); Blood urea nitrogen - BUN ( ref .alues 2.0-7.8 mmol/L)
Creat. - Creatinin (ref.values 63-109 umol/L); Aspartat aminotransferase - AST ( ref.values 0-31 U/L); Alanin aminotransferase - ALT ( ref.values 0-36 U/L); D-dimer (ref.values 0-0.55 mg/L); INR ( ref.values 0.8 – 1.2 U)
Activated Partial Thromboplastin Time APTT (ref.values 25.9-36.6 sec); Fibr. - Fibrinogen (ref.values 1.8-3.5 g/L)

Proteinuria was presented in 13 (44.8%), hematuria in 12 (41.4%) and leukocyturia in 9 (31%) of patients. Diagnose was based on positive Hantan virus isolate in 26 (89.7%) patients, while the other three patients had a diagnosis based on clinical and epidemiological criterias. Therapy was combination of antibiotic and symptomatic in 18 (62.1%) of patients, while other patients were treated with symptomatic therapy alone.

The average duration of antibiotic therapy was 10 days (range 4-23 days), and ceftriaxone was the therapy of choice. Hemodialysis was required in 15 (51.7%) patients, with longest duration of 10 days. Oliguric phase lasted 1-7 days and polyuric phase from 3 to 12 days. Hospital stay varied from 5 do 28 days. All patients had favorable outcome. Laboratory results at discharge were as shown in Table 2.

Table 2 **Laboratory results at dischrage.**

| Values at discharge | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | RBC | Hgb | Plt | WBC | BUN | Creat. | D-dim. | INR | APTT | Fibr. |
| Mean | | 4.35 | 126 | 267 | 8.64 | | | 1.73 | | | |
| Std. Dev | | 0.512 | 29.080 | 79.99 | 3.013 | | | 1.46 | | | |
| Minimum | | 3 | 4.00 | 165.00 | 3 | 2 | 32.00 | 1 | 1 | 26 | 4 |
| Maximum | | 5 | 161 | 501.00 | 14 | 14 | 228.00 | 4 | 1 | 33 | 10 |
| Percentiles | 25 | | | | | 4.05 | 78.00 | | .90 | 28.40 | 3.70 |
| | M | | | | | 4.50 | 89.00 | | .90 | 30.60 | 4.50 |
| | 75 | | | | | 6.10 | 106.50 | | 1.00 | 31.98 | 7.25 |

Mean values of RBC, Hgb, WBC, APTT and INR at admission were in normal range, while all other were below or above referal ranges.

At discharge, all mean values except AST and ALT were in normal ranges, even in some of the patients were still above or belowe normal ranges.

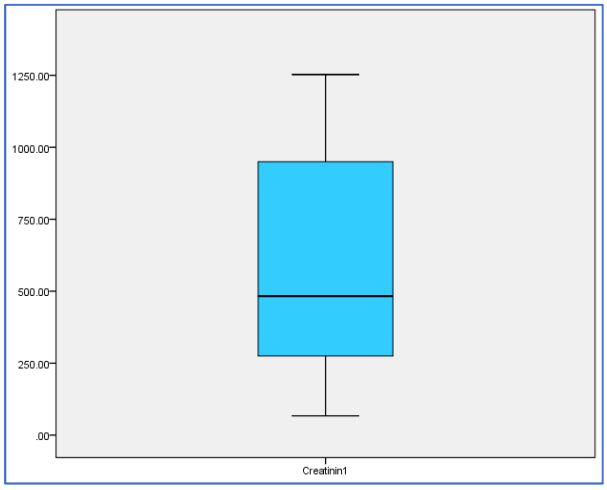


Figure 1 **Creatinin levels in patients at admission in the hospital.**

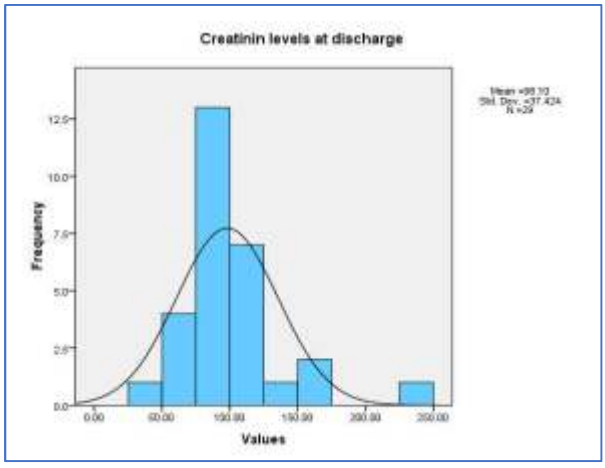


Figure 2 **Creatinin levels in patients at discharge from the hospital.**

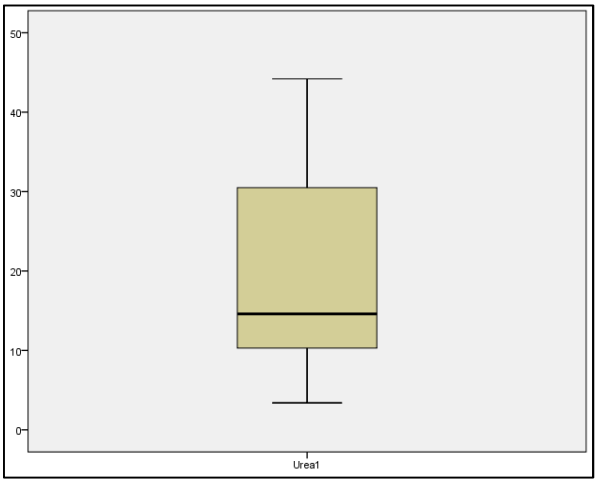


Figure 3 **Urea (BUN) levels in patients at admission in the hospital.**

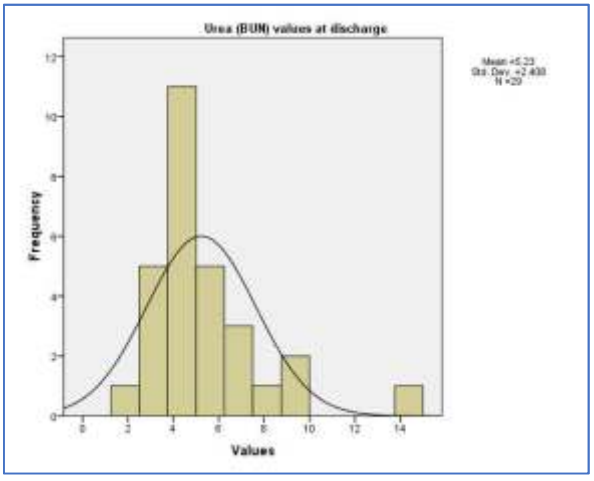


Figure 4 **Urea (BUN) levels in patients at discharge from the hospital.**

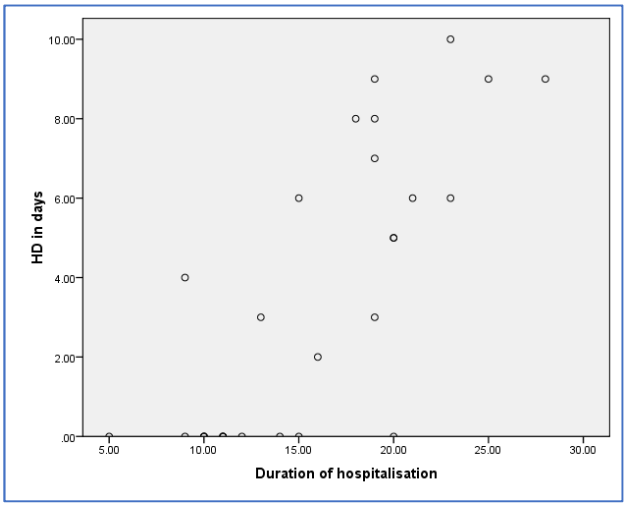


Figure 5 **Correlation between duration of hemodialysis and hospital treatment.**

The parameters that can be considered as possible prognostic factors for hemodialysis during the treatment were levels of urea (BUN) ($p<0.001$), and creatinin ($p=0.001$). The main value that determined the duration of hospital stay was hemodialysis ($p<0.0001$).

## DISCUSSION

COVID-19 pandemic devastated the whole healthcare system in the world, and in that period lots of people with other diagnoses were unable to receive appropriate treatment in healthcare facilities. Patients with chronic diseases were especially affected, while others with acute and urgent needs for medical assistance had possibility to be admitted to the hospital and managed by the protocol. Unfortunately, in some situations they were even sent back and treated as outpatients.

Since there was no decrease in the number of patients with acute infectious disease, clinical healthcare in Sarajevo, Bosnia and Herzegovina, had to find a way to deal with all of these in same time.

During the peak of the pandemic, in 2021, we also dealt with HFRS outbreak that affected patients in different regions of Bosnia and Herzegovina. According to the agreement with other clinics, all of them with moderate or severe forms of the diseases have been sent to Clinic of Infectious Diseases, Clinical Center University of Sarajevo.

Bosnia and Herzegovina has a long history of hemorrhagic fever, and first case was confirmed in 1952 (4). After that, we had a few bigger or smaller outbreaks, and one described in 1967. in Fojnica, a region near Sarajevo, was the largest reported so far in the Southeast Europe. It affected more than 200 people, with mortality rate of almost 10% (8). Almost every year we had sporadic cases, but in the 2021 we experienced large increase of cases, which required strong efforts to deal with it in the situation of actual COVID-19 pandemic.

In 2021 we had 92 cases of HFRS confirmed with ELISA tests, while one year before that number was only two, and in 2019. it was 10 (12).

The total number (92) of hemorrhagic fever cases does not deviate from the incidence of HFRS in the Balkans, with approximately one hundred reported in most years (8). All the patients were men, which is not surprising, first of all, considering the professional exposure (2). Considering the COVID 19 pandemic, we would have expected a smaller number of patients than usual, but this was not the case. This can be explained by the fact that hemorrhagic fever has nothing to do with interhuman transmissions, but with exposure in nature, therefore the measures taken during the pandemic had no impact on the number of people suffering from HFRS. The majority of cases (82.2%) had positive epidemiological data. All the patients were younger people, under 50 years of age, which is common because they are people who are professionally predisposed and engage in jobs that require physical strength (animal trappers, forestry workers, farmers, military personnel) (8), or people who visit recreationally mountains (13). The largest number of patients was from Central Bosnia, which is not surprising considering that this region was previously recognized as endemic for HFRS (2). The symptoms of the patients in our study were not significantly different from the expected symptoms of hemorrhagic fever with renal symptoms. The dominant symptoms were fever, weakness, headaches, vomiting, oliguria, conjunctival suffusion. It is important to note that 15 (51.7%) cases required hemodialysis treatment, which is a significantly higher number compared to other HFRS epidemics (2). This can be explained by the conditions of the COVID pandemic, where other patients were often treated late. The Hantan virus was serologically confirmed in most patients. It is unusual that as many as 18 (62.1%) patients were treated with antibiotics, although the highest recorded CRP was 24. It is understandable that it is often extremely difficult to distinguish the clinical picture of leptospirosis from hemorrhagic fever and that this is probably the reason why such a large number of patients were treated with antibiotics. However, we are of the opinion that a more rational approach should be taken in the future in this matter.

## CONCLUSION

Hemorrhagic fever with renal syndrome still remains a major medical challenge. Quick diagnosis and proper therapy, which in some cases also require hemodialysis, are crucial for clinical course and outcome. Possible prognostic factors, regarding hemodialysis requiurement, remain values of creatinin and BUN.

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**Declaration of patient consent:** the authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in journal

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# Intraoperative neurophysiological monitoring during resection of giant schwannoma of the pontocerebellar angle and paraspinal region: case series and literature review

# Intraoperacijski neurofiziološki monitoring tokom resekcije gigantskih švanoma pontocerebelearnog ugla i paraspinalne regije: serija slučajeva i pregled literature

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## ABSTRACT

Introduction: Intraoperative neurophysiological monitoring (INM) is an important tool in neurosurgery, particularly during the resection of giant schwannomas in the pontocerebellar angle and paraspinal region. Schwannomas are benign tumors that can compress neural structures, causing potential neurological complications. INM is used to monitor nerve function during surgery to minimize the risk of postoperative deficits. Methods: This study combines a case series of three patients and a literature review. The patients underwent resection of giant schwannomas, and intraoperative neurophysiological monitoring, including motor evoked potentials (MEP) and electromyography (EMG). The literature review focused on the role of INM in reducing postoperative neurological deficits in schwannoma surgeries. Results: Three patients were included. Tumor locations included the pontocerebellar angle and paraspinal region. Surgeries were performed using INM to monitor motor and sensory functions, which helped prevent permanent nerve damage. Conclusion: INM significantly reduces the risk of postoperative neurological deficits in schwannoma surgeries. This case series and literature review emphasize the importance of monitoring and multidisciplinary collaboration to ensure optimal patient outcomes.

**Keywords:** intraoperative neurophysiological monitoring (INM), schwannoma, motor evoked potentials (MEP), electromyography (EMG), pontocerebellar angle, paraspinal region, postoperative neurological deficit

## SAŽETAK

Uvod: Intraoperacijski neurofiziološki monitoring (INM) je značajan alat u neurohirurgiji, posebno tokom resekcije gigantskih švanoma u pontocerebelarnom uglu i paraspinalnoj regiji. Švanomi su benigni tumori koji mogu komprimirati nervne strukture, uzrokujući potencijalne neurološke komplikacije. INM se koristi za praćenje funkcije živaca tokom operacije kako bi se minimizirao rizik od postoperativnog deficita. Materijali i metode: Ovaj rad prikazuje seriju slučajeva sa tri pacijenta i pregled literature. Pacijenti su podvrgnuti resekciji gigantskih švanoma, pri čemu je primjenjen intraoperacijski neurofiziološki monitoring, motorni evocirani potencijali (MEP) i elektromiografiju (EMG). Pregled literature je bio fokusiran na ulogu INM-a u smanjenju postoperativnih neurološkog deficita kod operacija švanoma. Rezultati: Uključena su tri pacijenta. Tumori su bili locirani na pontocerebelarnom uglu i paraspinalnoj regiji. Operacije su provedene uz korištenje INM-a radi praćenja motornih i senzornih funkcija, što je pomoglo u sprečavanju trajnih oštećenja nerava Zaključak: INM značajno smanjuje rizik od postoperativnog neurološkog deficita kod operacija švanoma. Ova serija slučajeva i pregled literature naglašavaju važnost monitoringa i multidisciplinarnog pristupa kako bi se osigurali optimalni ishodi za pacijente.

**Ključne riječi:** intraoperacijski neurofiziološki monitoring (INM), švanom, motorno evocirani potencijali (MEP), elektromiografija (EMG), pontocerebelarni ugao, paraspinalna regija, postoperativni neurološki deficit

## INTRODUCTION

Within a decade, intraoperative neuromonitoring has grown from a small new field with a few dedicated practitioners to a neurology subspecialty, specifically neurophysiology. It's exciting to gather functional nervous system data during surgery. In addition to neurosurgical cases, Intraoperative neurophysiological monitoring (INM) is now used in orthopedic, vascular, cardiothoracic, and ENT surgeries. Neuromonitoring has been shown to reduce the morbidity of many procedures that could harm neural structures (1–3).

Neurosurgical procedures can lead to neurological deficits with or without accompanying side effects. During spinal surgery, intraoperative neurophysiological monitoring, such as MEPs, SSEPs, and EMG, helps detect and address signal changes promptly, which can forecast a positive surgical result. Loss or variation of intraoperative neuromonitoring (INM) signals during surgery can predict neural injury and postoperative neurodeficiencies (4). Motor-evoked potential monitoring during surgery showed higher sensitivity (67.9%) and specificity (83.2%) compared to sensory-evoked monitoring in predicting postoperative motor deterioration (5).

First described by Verocay in 1908, schwannomas are the most common peripheral nerve tumors. Schwann cells produce them (5). Because schwannomas are well-encapsulated and displace nerve fibers as they grow, enucleation may not cause neurological deficits. Surgery aims to remove tumors without neural damage. Literary postoperative neurological deficit ranges from 1.5% to 80% (6-9). Short-term observations had more complications. A retrospective study of 76 schwannoma patients found 89% preserved function (10). According to Kline et al., 10.5% of patients developed postoperative motor weakness (11). Multimodal IONM with MEPs, SSEPs, and frEMG may improve clinical outcomes and reduce iatrogenic neural structure injury during EMSCT surgery, though this is still debated (12-15).

## AIM

A case series and literature review evaluate the significance and function of intraoperative neuromonitoring (INM) in pontocerebellar and paraspinal schwannomas surgeries. Neurophysiological monitored surgeries and intraoperative neuromonitoring (INM) were tested for their ability to reduce postoperative neurological deficits. The literature review summarizes schwannoma surgery research and highlights its benefits in improving surgical outcomes.

## MATERIALS AND METHODS

This paper is a combined presentation of a series of cases with a review of the literature to identify the importance of neuromonitoring during operations for pontocerebellar and paraspinal schwannomas. The search was carried out by a systematic search of the Internet search engine PubMed using the following keywords: ("neuromonitoring" OR "Electrophysiologic monitoring") AND ("paraspinal" OR "pontocerebellar") AND ("schwannoma" OR "neurilemomas").

A retrospective analysis of cases of Schwannoma affecting the pontocerebellar and paraspinal regions was conducted between January 2010 and December 2023 and available in English or Bosnian/Croatian/Serbian language, and cases treated at our institution are included. The clinical and demographic data were obtained from the patient's medical records. The research project's protocol received approval from the institutional review board and adhered to the provisions outlined in the Declaration of Helsinki. The patients provided written consent forms.

Entry criteria were as follows:

- all articles that present individual case results of operative treatment of schwannoma,
- systematic reviews show operative treatment of schwannoma.

Exclusion criteria:

- all articles dealing with the construction and validation of questionnaires,
- all studies that have been published more than once
- all articles that were incomplete or data could not be obtained from them
- laboratory research, such as some studies on animal models or bladder cancer cell lines
- all articles that were published as part of the study of specific reforms in a certain country, conferences, dissertations, and master's theses and book chapters

Also, this research paper presents three cases of surgical interventions on pontocerebellar and paraspinal schwannomas, which were performed with the aid of neurophysiological monitoring.

## RESULTS

### Case one

Female, born in 1961, with a giant tumor in the left pontocerebellar angle and interpeduncular fossa (Schwannoma vestibulare, PHD-verified). She underwent retrosigmoid craniectomy with tumor resection (neuromonitoring-assisted) and was presented with left-sided hyperacusis and MRI-confirmed tumor. She reported occasional walking instability, denies headaches or nausea. Upon admission, she couldn't walk or move independently, and had a strong urge to vomit.

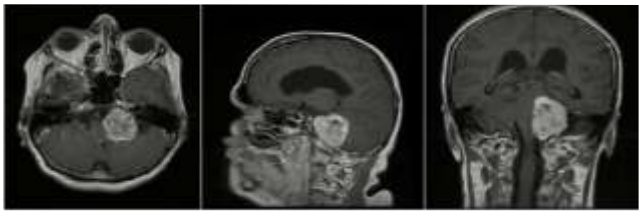

Figure 1 **Preoperative MRI of Patient one. Image 1: A: MRI T1 + contrast demonstrates large tumor in left pontocerebellar angle (T4b Hanover class), B sagittal scan, C coronal scan.**

The surgery involved intraoperative neuromonitoring with electrodes placed in muscles to monitor cranial nerves VII (facial), VI (abducens), and XI (accessory) via motor evoked potentials (MEP). These electrodes were used for monitoring motor evoked potentials (MEP), providing real-time feedback on the functional integrity of these nerves during the procedure.

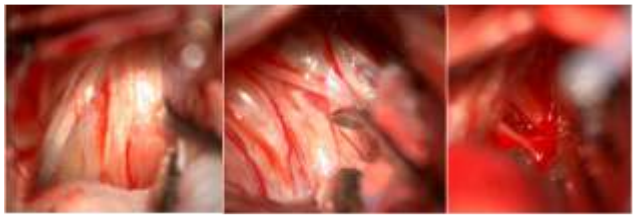

Figure 2 **Image A: Lower floor of the left PCU demonstrates glossopharyngeal branches of stretched over the large tumor mass. B: Upper floor of the left PCU demonstrates trigeminal branch (pulled by the dissector), large tumor mass is shown below. C Vagus and accesorius nerve.**

Postoperatively, the patient was neurologically intact, with preserved facial nerve function. However, she continued experiencing hypersalivation, cough, and difficulty swallowing, suggesting irritation of other cranial nerves.

Figure 3 **Postoperative functional state of the facial nerve.**

Postoperative imaging confirmed the complete resection of the tumor. The initial symptoms of hyperacusis and instability were no longer present.

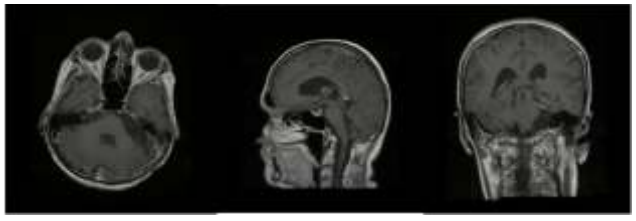

Figure 4 **Postoperative MRI of Case one, which shows the complete resection of the tumor. Image A: axial scan. Image B: sagittal scan. Image C: coronal scan.**

## Case two

Male, born in 1974, diagnosed with a large foraminal and extraforaminal L4/L5 tumor, possibly a left-sided Schwannoma. He reported a long-term lower back pain radiating to the left leg, accompanied by left foot weakness. CT and MRI showed a large tumor at L4/L5 with extension to the left psoas muscle. Neurological status: tense PVM, antalgic posture, positive Lasegue sign on the left at 30 degrees, significant weakness in peroneal dorsiflexion, with sphincter control intact.

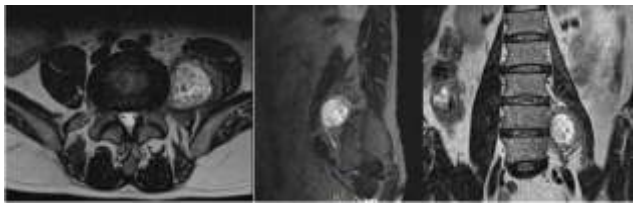

Figure 5 **Preoperative MRI of Case two. Image A: axial scan. Image B: sagittal scan. Image C: coronal scan.**

Based on the positive MRI findings and the existing clinical picture, an operative procedure was indicated, which was performed with neuromonitoring after preoperative internist treatment. The postoperative course was normal.

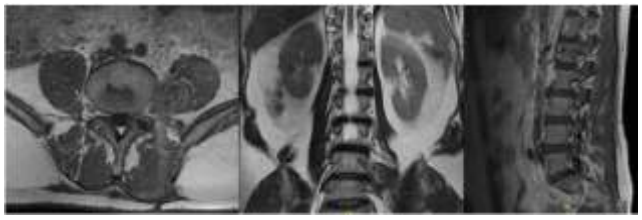

Figure 6 **Postoperative MRI of Case two. Image A: axial scan. Image B: sagittal scan. Image C: coronal scan.**

## Case three

Woman, born in 1951, diagnosed with hydrocephalus and a right-sided APC tumor, likely vestibular Schwannoma (Koss 4; Hannover T4b). She reported gradual hearing loss in the right ear, treated by ENT and neurology. In the past 15 days, she experienced vomiting and unsteady walking. MRI revealed a right PCU tumor with early ventricular system dilation. Neurological status: right ear hearing loss and ataxic gait.

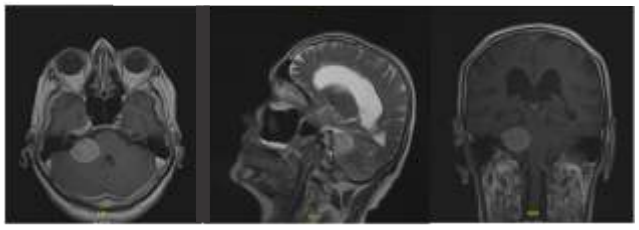

Figure 7 **Preoperative MRI of patient C. Image A: axial scan. Image B: sagittal scan. Image C: coronal scan.**

Intraoperatively without changes in the neuromonitoring potential concerning the arachnoid plan. After the operation, on the extremities, there was no loss, with evident facial paresis on the right (Hosue Breckman 5).

Figure 8 **Preparing the patient for neuromonitoring. Placement of electrodes for neuromonitoring CN IX, CN X, CN XI, CN XII and MEP.**

Electrodes were placed by the neurologist to monitor CN V, VII, and the lower cranial nerves. Intraoperative monitoring of the trigeminal (CN V) and facial (CN VII) nerves was crucial to prevent damage during brainstem or skull base surgeries. Monitoring CN IX, X, XI, and XII ensureed the preservation of swallowing, vocalization, and shoulder movement. Real-time feedback helped the surgical team to minimize the risk of complications.

Figure 9 **Monitoring of MEP and EMG during surgery.**

*Literature review*

Intraoperative Neuromonitoring (INM) is now an essential tool in the surgical treatment of pontocerebellar and paraspinal schwannomas. Multiple studies have emphasized the significance of intraoperative neuromonitoring (INM) in enhancing surgical results and decreasing postoperative neurological deficits (ND).

Table 1 **Summary of Cases and Literature Review on Intraoperative Neuromonitoring in pontocerebellar and paraspinal Schwannomas.**

| Author | INM | Case | Gender | Age | Presenting symptom | Diameter of tumor(cm) | Immediate postoperative ND | Duration of ND recovery (months) |
|---|---|---|---|---|---|---|---|---|
| This series | Yes | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| Lee et al. 2014 (16) | Yes | 1 | Male | 62 | Neck mass | 2 | Minor motor ND | 1 |
| | | 2 | Male | 59 | Neck mass | 1.6 | None | — |
| | | 3 | Male | 53 | Neck mass | 1.8 | None | — |
| | | 4 | Female | 48 | Neck mass | 6 | Minor sensory ND | 2 |
| | | 5 | Male | 56 | Neck mass | 5.5 | None | — |
| Lee et al 2020 (17). | No | 19 cases | 11 females, 8 males | Mean 50.2 | Various | 1.5-11 | Minor sensory ND in 3 patients, and minor motor ND in 2 | 3-10 for sensory ND, 24-60 for motor ND |
| Pace et al 2023(18) | No | 1 | Female | 15 | Various | 16-15 | None | - |
| Shah & Shah 2018 (19) | No | 1 | Male | 45 | Various | 4.6 x 4.5 x 7.3 | None | - |
| Femia et al. 2022 (20) | Yes | 1 | Male | 72 | Various | 5.5 x 5.4 x 5.1 | None | - |
| Bell et al. 2023 (21) | Yes | 1 | Male | 35 | Lower back pain | Multiple | None | - |
| Curry et al. 2022 (22) | Yes | 1 | Female | 48 | Various | 3.9x3.6 | None | - |

Abbreviations: INM, intraoperative neuromonitoring; ND, neurological deficit; –not applicable; y/o years old.

These studies highlight the advantages of INM (Intraoperative Nerve Monitoring) in the surgical treatment of schwannomas, assisting in the prevention and early identification of postoperative nerve deficits. The incorporation of INM into surgical practice has greatly enhanced patient outcomes and decreased the morbidity linked to these tumors.

## DISCUSSION

The cases showcased in this study emphasize the significance of intraoperative neuromonitoring (INM) in the surgical treatment of pontocerebellar and paraspinal schwannomas. Intraoperative neurophysiological monitoring (INM) enables immediate evaluation of neural structures, assisting surgeons in the detection and protection of crucial nerve bundles while removing tumors. Utilizing intraoperative neuromonitoring (INM) has demonstrated

the ability to decrease the likelihood of postoperative neurological deficits (ND) by promptly identifying and addressing signal alterations.

Schwannomas are noncancerous growths that originate from Schwann cells and generally have a slow rate of growth. Nevertheless, the proximity of these tumors to vital neural structures presents a potential danger of neurological complications during the surgical removal process. The analysis of cases presented in this study shows that INM is effective in reducing postoperative neurological deficits, with the majority of patients experiencing no deficits after surgery.

The literature review confirms the advantages of intraoperative nerve monitoring (INM) in schwannoma surgery. The studies conducted by Lee HJ, et al., in 2014 and 2020, Femia F, et al., in 2022, Bell JS, et al., in 2023, and Curry BP, et al., in 2022 consistently demonstrate positive results when using INM, with minimal occurrence of postoperative neurological deficits. Pace et al., (2023) and Shah & Shah (2018), although they did not use INM, also documented positive results without the need for postoperative neurologic deficits, demonstrating the overall efficacy of surgical treatments for schwannomas.

The benefits of various INM modalities, such as SSEP, tcMEP, and EMG, in offering uninterrupted monitoring and identifying motor deficits after surgery, surpass their drawbacks. While certain modalities may have limitations, such as being sensitive to specific anesthetics or producing false-positive alarms, their overall effectiveness in preventing neurological damage during surgery is clear.

## CONCLUSION

Intraoperative neuromonitoring is a valuable tool for surgically managing pontocerebellar and paraspinal schwannomas. The incorporation of intraoperative neuromonitoring (INM) into surgical procedures has greatly enhanced patient outcomes by decreasing the occurrence of postoperative neurological impairments. Future research should prioritize the optimization of INM protocols and the extension of its application to additional neurosurgical procedures to further improve patient care and safety.

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# A rare case of pediatric common variable immunodeficiency with complication of granulomatous lymphocytic interstitial lung disease: our experience

# Rijedak slučaj pedijatrijske uobičajene varijabilne imunodeficijencije sa komplikacijom granulomatozne limfocitne intersticijalne bolesti pluća: naša iskustva

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## ABSTRACT

Introduction: common variable immunodeficiency (CVID) is a heterogeneous primary immunodeficiency characterized by hypogammaglobulinemia and increased susceptibility to infections. Granulomatous lymphocytic interstitial lung disease (GLILD) is a severe complication associated with CVID, leading to chronic lung damage and increased morbidity. Case report: we present a rare case of pediatric CVID complicated by suspected GLILD in a 14-year-old boy, highlighting the diagnostic challenges and specific therapeutic approach. CVID encompasses a spectrum of immunological dysfunctions affecting B and T lymphocytes, predisposing patients to infections, autoimmune phenomena, and lymphoproliferative disorders. GLILD is characterized by granulomatous inflammation and lymphocytic infiltration of lung tissue, posing diagnostic dilemmas due to overlapping clinical features with other pulmonary diseases. The diagnostic workup included chest CT, spirometry, and immunological profiling, confirming radiographic features of ground-glass opacities, restrictive lung function disorder, and interstitial lung disease consistent with GLILD. Data were collected from the patient's medical history. Our patient presented with recurrent respiratory infections since early childhood, progressing to chronic cough and sputum production, initially misdiagnosed as asthma. Initial evaluation revealed hypogammaglobulinemia and decreased switched memory B cells, prompting suspicion of CVID. We ruled out infection, tuberculosis via sputum microbiological analysis, and malignancies such as lymphoma. Radiological findings and pulmonary function tests suggested GLILD. There are no clear guidelines for the diagnosis, treatment, and follow-up. Following initiation of IVIG and corticosteroid therapy, the patient showed significant clinical improvement with resolution of respiratory symptoms and normalization of immunoglobulin levels. Long-term follow-up showed sustained disease remission without relapse, supporting the efficacy of immunomodulatory therapy in pediatric GLILD associated with CVID. Conclusion: this case underscores the importance of early recognition and multidisciplinary management of GLILD in pediatric CVID to reduce disease progression and improve outcomes. Diagnostic challenges include differentiating GLILD from other interstitial lung diseases and optimizing therapeutic strategies tailored to individual patient profiles. Pediatric GLILD complicating CVID requires a high degree of suspicion, comprehensive diagnostic evaluation, and timely initiation of targeted therapies such as IVIG and corticosteroids. Long-term studies are crucial for refining diagnostic criteria, establishing therapeutic algorithms, and improving the prognosis of this complex disease.

**Keywords**: common variable immunodeficiency, granulomatous lymphocytic interstitial lung disease, pediatric immunology, IV immunoglobulin therapy, corticosteroids

## SAŽETAK

Uvod: uobičajena varijabilna imunodeficijencija (CVID) je heterogena primarna imunodeficijencija karakterizirana hipogamaglobulinemijom i povećanom osjetljivošću na infekcije. Granulomatozna limfocitna intersticijalna bolest pluća (GLILD) je teška komplikacija povezana s CVID-om, što dovodi do hroničnog oštećenja pluća i povećanog morbiditeta. Prikaz slučaja: prikazujemo rijedak slučaj pedijatrijske CVID kompliciranе sumnjom na GLILD kod 14-godišnjeg dječaka, ističući dijagnostičke izazove i poseban terapijski pristup. CVID obuhvata spektar imunoloških disfunkcija koje pogađaju B i T limfocite, predisponirajući pacijente na infekcije, autoimune fenomene i limfoproliferativne poremećaje. GLILD je posebna manifestacija bolesti karakterizirana granulomatoznom upalom i limfocitnom infiltracijom plućnog tkiva te postavlja dijagnostičke dileme zbog preklapajućih kliničkih karakteristika s drugim plućnim bolestima. Dijagnostička obrada uključivala je CT grudnog koša, spirometriju i imunološko profiliranje, potvrđujući radiografske značajke staklastih opaciteta, restriktivnog poremećaja plućne funkcije i intersticijske bolesti pluća u skladu s GLILD-om. Podaci su prikupljeni iz medicinske historije pacijenta. Naš pacijent se javio sa ponavljajućim respiratornim infekcijama od ranog djetinjstva, koje su napredovale do hroničnog kašlja i produkcije sputuma te je njegova bolest inicijalno shvaćena kao astma. Početna

evaluacija je otkrila hipogamaglobulinemiju i smanjen broj "shwitched" memorijskih B stanica, što je potaknulo sumnju na CVID. Isključili smo infekciju, tuberkulozu koristeći mikrobiološku analizu ispljuvka, i maligne bolesti kao što je limfom. Radiološki nalazi i funkcionalna plućna dijagnostika su nas naveli da posumnjamo na GLILD. Ne postoje jasne smjernice o provođenju dijagnostike, liječenja i praćenja. Nakon početka terapije IVIG-om i kortikosteroidima, pacijent je pokazao značajno kliničko poboljšanje sa rješavanjem respiratornih simptoma i normalizacijom razina imunoglobulina. Dugoročno praćenje je pokazalo održanu remisiju bolesti bez relapsa, što podupire učinkovitost imunomodulatorne terapije kod pedijatrijskog GLILD-a povezanog s CVID-om. Zaključak: ovaj slučaj naglašava važnost ranog prepoznavanja i multidisciplinarnog liječenja GLILD-a kod pedijatrijskog CVID-a u cilju usporavanja progresije bolesti i poboljšanja ishoda. Izazovi u dijagnostici uključuju razlikovanje GLILD-a od drugih intersticijskih plućnih bolesti te optimiziranje terapijskih strategija prilagođenih individualnim potrebama pacijenata. Pedijatrijski GLILD koji komplicira CVID zahtijeva visok stupanj sumnje, sveobuhvatnu dijagnostičku evaluaciju i pravovremeni početak ciljanih terapija poput IVIG-a i kortikosteroida. Dugoročne studije su ključne za usavršavanje dijagnostičkih kriterija, uspostavu terapijskih algoritama i poboljšanje prognoze ove složene bolesti.

**Ključne riječi**: zajednička varijabilna imunodeficijencija, granulomatozna limfocitna intersticijalna bolest pluća, pedijatrijska imunologija, IV imunoglobulinska terapija, kortikosteroidi

## INTRODUCTION

This case study investigates a patient who developed a severe complication of common variable immunodeficiency (CVID), known as granulomatous lymphocytic interstitial lung disease (GLILD). Globally, primary immunodeficiencies (PIDs) affect roughly 1 in every 10,000 people (1). PIDs are classified as rare diseases that significantly heighten the risk of infections from various pathogens, including bacteria, viruses, fungi, and protozoa. Such infections may become chronic, leading to long-term health complications or even fatality if not treated swiftly and effectively. Moreover, individuals with PIDs are also at an elevated risk for cancer and other immune disorders, such as allergies, autoimmune diseases, and inflammatory conditions (2). Primary antibody deficiencies (PADs) represent the most prevalent and diverse group of inborn errors of immunity, encompassing various disorders characterized by an impaired ability to produce effective antibody responses. Within this group, common variable immunodeficiency (CVID) stands out as the most frequently encountered symptomatic hypogammaglobulinemia, marked by low levels of serum immunoglobulins and an increased susceptibility to infections, autoimmunity, and other immune-related complications. CVID, therefore, represents a significant subset of PADs, often serving as a clinical model for studying the broader implications and management of primary immunodeficiencies (PIDs) (3). CVID is characterized by hypogammaglobulinemia, where serum IgG levels fall more than 2 standard deviations below age-adjusted norms, often accompanied by reduced IgA and/or IgM levels (4). In contrast to X-linked agammaglobulinemia, which primarily affects B cells, common variable immunodeficiency (CVID) also encompasses abnormalities in T-lymphocytes. This dual involvement of B and T cells in CVID potentially contributes to the higher incidence of lymphoproliferative and autoimmune diseases observed in affected individuals (5). The estimated prevalence of CVID ranges from 1 in 10,000 to 1 in 100,000, with the highest proportion among all PIDs reported in the USA at 40.2%, while the lowest rates are observed in the Middle East (2.6%) and Africa (1.3%) (6). The significant regional discrepancies in CVID distribution are closely linked to a country's level of medical advancement, which is largely influenced by its socio-economic status. In regions with higher socio-economic resources, more robust healthcare infrastructure enables better diagnostic capabilities, leading to higher reported rates of CVID. Conversely, limited resources and healthcare access in lower-income areas contribute to underdiagnosis and lower observed prevalence (3). In our country, epidemiological data are scarce, so we do not have accurate information on the incidence of CVID. However, we can say that the patient described below represents the only known case of CVID involving GLILD in our practice.

Primary immune deficiency (PID) frequently manifests with persistent pulmonary symptoms such as recurrent infections, pneumonia, bronchiectasis, and interstitial lung disease (ILD), which may progress to fibrosis. Immune dysregulation is prevalent in many PIDs, contributing to the development of granulomatous lung disease and autoimmune disorders. While considerable effort is directed towards identifying infectious agents responsible for pulmonary manifestations in PIDs, immune dysregulation itself can be the primary determinant of symptoms and disease progression (7). Consequently, treatment strategies often involve immune suppression in conjunction with therapies targeting immune deficiency. Immunoglobulin replacement therapy has been pivotal in reducing the impact of infectious diseases among patients diagnosed with common variable immunodeficiency (CVID). However, the incidence of non-infectious complications, notably granulomatous lymphocytic interstitial lung disease (GLILD), is increasing within the CVID population. GLILD affects approximately 25% of individuals with CVID, contributing to chronic lung damage and an elevated risk of lymphoproliferative disorders (8).

Chronic granulomatous disease and common variable immune deficiency are prominent among PIDs associated with granulomatous lung disease (7). According to the UK-PID Network Consensus, the recommended diagnostic protocol for suspected GLILD involves conducting a chest CT scan, pulmonary function tests (PFTs), and bronchoscopy, with a surgical lung biopsy deemed necessary for definitive diagnosis (9). The diagnosis of GLILD hinges on clinical suspicion, complemented by thorough radiological and histopathological evaluations of lung tissue. Radiographically, typical findings include lung nodules, ground glass opacities, bronchiectasis, reticular patterns, and lymphadenopathy in the thoracic region. Additionally, extrapulmonary manifestations such as generalized lymphadenopathy and splenomegaly are frequently observed.

Treatment strategies for GLILD currently lack consensus. Various immunosuppressive agents, including corticosteroids, are employed based on institutional protocols, but their efficacy varies widely (8). This study presents a case of granulomatous lymphocytic interstitial lung disease (GLILD) as a complication of common variable immunodeficiency (CVID). Through detailed medical history, examination, and laboratory analyses, we outline the patient's disease course and current clinical status. Our aim is to highlight the clinical characteristics of GLILD in the setting of CVID, drawing on our own experience and comparing findings with similar cases reported in other medical centers.

## CASE REPORT

The patient was referred to our clinic for suspected immunodeficiency, supported by immunoglobulin laboratory findings and a history of recurrent severe respiratory infections. This suspicion arose due to low IgG levels for his age 5.3 g/l – ref. 7-14 g/l and IgA levels <0.26 g/l ref. 0.7-2.5 g/l. Laboratory tests initially conducted after he developed fever, cough, and vomiting showed elevated inflammatory parameters (ESR 63 mm/h), CRP 136 mg/L, and leukocytes (Le) at 27 × 10^9/L. Initial chest CT scans raised suspicion of tuberculosis (TB) due to hilar and mediastinal lymphadenopathy. However, subsequent tests including Quantiferon-TB Gold and Lowenstein-Jensen culture were negative for TB, so tuberculosis was ruled out.

The patient is the firstborn from an uncomplicated pregnancy and delivery, with normal birth weight and an uneventful postnatal period. He was immunized according to the standard schedule and was in good health until starting school. Following this, he began experiencing more frequent respiratory infections, particularly in the winter months. Symptoms included occasional dry cough and fever, which progressed to a productive cough. He was diagnosed with childhood asthma and was treated with inhaled bronchodilators and leukotriene inhibitors for 4 to 5 years. He tolerated physical exertion well. Previously, he had pneumonia requiring hospitalization and experienced ear infections 2-3 times in the past year prior to hospitalization. There have been no recurrent episodes of diarrhea. He had no clear history of allergy or atopy.

At the Department of Allergoimmunology and Rheumatology, a 14-year-old male adolescent weighing 68 kg and measuring 1.55 m in height, with a BMI of 31, indicating obesity, was admitted. He was afebrile. Physical examination revealed hyperpigmentation (15x5 cm) on the right forearm and hypopigmentation on the left lower leg, with the rest of the skin normal. Muscles were normal on examination. No enlarged lymph nodes were palpable. The head, eyes, ears, and nose were normal. The lips were pink, the oral mucosa was clean and moist, and the throat was clear. The neck examination was normal with full range of motion. Neurologically, there were no deficits. Lung auscultation revealed diffuse inspiratory crackles and high-pitched wheezes during expiration. A cardiac examination showed rhythmic tachycardia with a systolic murmur along the left sternal edge. The abdomen was soft and non-tender, with no palpable liver or spleen enlargement. Extremities were normal in mobility without edema or deformities. Upon admission, laboratory tests revealed several abnormalities: elevated leukocytes (16.4 × 10^9/L), low mean corpuscular volume (79.9 fL) and mean corpuscular hemoglobin (27.5 pg), decreased segmented and unsegmented neutrophils, and low lymphocytes. Additionally, there were elevated levels of total bilirubin (14.7 µmol/L) and uric acid (472 µmol/L), along with a significantly increased CRP (53.5 mg/L). Urinalysis showed cloudy urine with elevated leukocytes (8-10 per high power field) and the presence of bacteria. Antinuclear antibodies, ENA 6 profile, anti-dsDNA, and hepatitis markers were negative. ASTO was negative, RF <12.5 IU/mL (normal: <20 IU/mL), and IgE <18.8 IU/mL (normal: <100 IU/mL). IgG subtypes were: IgG1 5.45 g/L (normal: 3.0-9.0 g/L), IgG2 0.74 g/L (normal: 0.4-2.2 g/L), IgG3 0.568 g/L (normal: 0.3-1.0 g/L), and IgG4 0.008 g/L (normal: 0.02-1.0 g/L). Microbiological cultures were normal. Allergy tests were normal. Flow cytometry showed 63.7% lymphocyte-sized cells with a CD4/CD8 ratio of 1.6 (normal: 0.9-3.4). Most cell subpopulations were elevated, except activated lymphocytes (CD3+HLA-DR+), which were normal. B lymphocyte analysis revealed increased naive B cells and decreased switched memory B cells.

During hospitalization, a chest CT scan revealed bilateral lower lung field consolidations consistent with ground-glass opacifications (GGO) and smaller plate-like atelectasis near the right lateral chest wall. No bronchiectasis was observed. A sinus X-ray showed hypertrophy of the right frontal sinus and reduced air density in the maxillary sinuses, with a deviated nasal septum to the right.

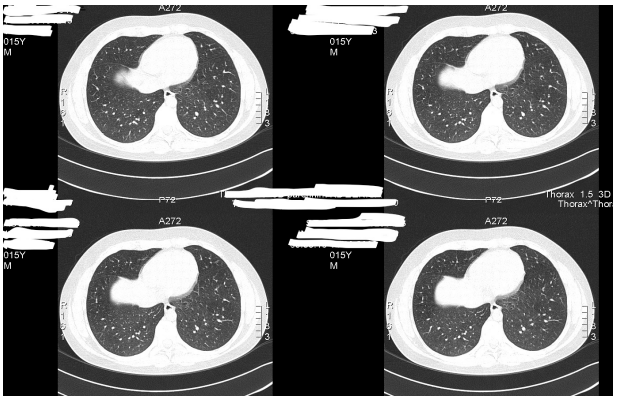


Figure 1 **The chest CT scan showed bilateral lower lung field consolidations with ground-glass opacifications (GGO) and small plate-like atelectasis near the right lateral chest wall, with no evidence of bronchiectasis.**

On the sixth day of hospitalization, a chest X-ray showed normal lung parenchyma transparency. A tracheobronchogram, slightly rotated, displayed well-differentiated and vascularized hilum regions. Linear infiltrations were noted from the right hilum to the basal area, with a suspicious hilar lymph node on the left. Both hemidiaphragms were properly lowered, and the phrenicocostal sinuses were clear. A lung ultrasound showed a normal pulmonary pattern with occasional pleural thickening but missed small invasive changes seen on CT. Parapharyngeal lymph nodes were reactive, with bilateral submandibular and jugulodigastric nodes up to 10 mm, and a 12 mm node in the left axilla. No significant inguinal lymphadenopathy was found. During the diagnostic evaluation of the 14-year-old patient, spirometry indicated a restrictive lung pattern consistent with granulomatous lymphocytic interstitial lung disease (GLILD). The findings suggested a total lung capacity (TLC) of approximately 60% of the predicted value and a forced vital capacity (FVC) of about 65% of the predicted value, while the forced expiratory volume in one second (FEV1) to FVC ratio remained preserved at 80%. These results align with the diagnosis of restrictive pulmonary impairment associated with GLILD. Given elevated inflammatory markers and abnormal lung findings, the patient received parenteral antibiotics (amoxicillin with clavulanic acid, then ceftazidime) and inhaled salmeterol with fluticasone. CVID was confirmed by low IgG levels (5.3 g/L) and reduced "switched B lymphocytes." IV immunoglobulin therapy was recommended. Prophylactic azithromycin and montelukast were also prescribed. CT imaging showed "ground-glass opacities," which, considering the totality of the case, supported the suspicion of GLILD.

During the hospitalization, although some studies and guidelines recommend performing bronchoscopy, we opted against it due to the non-negligible risks associated with the procedure and the limited benefits in this case. All clinical and laboratory findings

strongly suggest the presence of CVID and GLILD, also the patient later showed an adequate response to therapy. It is important to note that other studies also indicate the limited utility of bronchoscopy. The ability to identify clinical, laboratory, and radiological parameters that may pinpoint CVID patients at high risk for developing GLILD or facilitate early diagnosis could reduce the need for lung biopsies and their associated risks, potentially improving the prognosis for affected patients. Given the clinical presentation, lung auscultation findings, negative microbiological results, and spirometry, we suspected GLILD, despite the lack of clear guidelines.

Parents were informed about the chronic nature of the condition and the necessity for long-term immunoglobulin therapy, as well as the respiratory manifestations associated with the underlying disease. During his hospital stay, patient remained afebrile, experienced occasional dyspnea without the need for oxygen, and had stable vital signs. IVIG supplementation was started at 700 mg/kg body weight. Consequently, IVIG therapy was initiated alongside azithromycin prophylaxis (for 6 months) and low-dose oral prednisone (0.2 mg/kg body weight) for the first 2 months. Montelukast and inhaled corticosteroids were also included in the treatment plan.

Three months post-discharge, the patient attended a follow-up visit with no reported symptoms. His IgG level was 14.2 g/L (reference range: 7.0-16.0 g/L). Physical examination revealed he was in good general condition, eupneic, with normal lung sounds and no cardiovascular abnormalities. The abdomen was soft with no palpable liver or spleen.

The patient was advised to continue monthly IV immunoglobulin (IVIg) supplementation at a dose of 0.4 g/kg body weight. IgG levels should be monitored on the day of IVIg administration to allow for necessary dose adjustments. Additionally, the patient was instructed to continue prescribed therapies, including azithromycin prophylaxis, for an additional three months. Microbiological analyses were suggested if any signs of infection arose. Plans were made to initiate the procurement of subcutaneous immunoglobulins. Comprehensive laboratory tests were scheduled for two months for further evaluation. After one year, complete regression of radiological findings on CT scans was observed, with the patient experiencing no respiratory symptoms. Consequently, IVIg therapy continued, followed by the introduction of subcutaneous immunoglobulins (SCIG).

## DISCUSSION

Our case suggests the possibility of Granulomatous-Lymphocytic Interstitial Lung Disease (GLILD) within the context of primary immunodeficiency in a pediatric patient, supported by findings from studies investigating GLILD in children with Common Variable Immunodeficiency (CVID) and syndromic primary immunodeficiencies. These findings underscore the importance of recognizing autoimmune phenomena and immune dysregulation in the diagnosis and management of similar clinical cases. In the study by Szczawinska-Poplonyk A, et al., all children diagnosed with Granulomatous Lymphocytic Interstitial Lung Disease (GLILD) exhibited autoimmune phenomena, organ-specific immunopathology, and immune dysregulation, along with defective B-cell maturation and memory B cell deficiency. Radiological and histopathological features consistent with GLILD, including granulomatous disease and lymphoid hyperplasia, were observed, often accompanied by chronic airway disease with bronchiectasis in patients with Common Variable Immunodeficiency (CVID) and syndromic primary immunodeficiencies (PIDs) (10). GLILD has been described as a primary manifestation of CVID, as confirmed in the study detailing the clinical and radiological characteristics of a 55-year-old woman. The patient exhibited features of small airway lymphoproliferative disorder resembling follicular bronchiolitis or lymphocytic interstitial pneumonitis on histology, prompting the diagnosis of CVID. Treatment with IVIG and corticosteroids significantly improved, followed by maintenance therapy with Mycophenolate mofetil (11). The study by Mannina et al. identified hypersplenism and polyarthritis as significant risk factors for developing GLILD in adults with CVID. Additionally, it found that the percent predicted FVC remained stable over time in patients diagnosed with GLILD (12). These findings can provide valuable insights into potential risk factors and disease progression patterns that may inform the management and prognosis of GLILD in pediatric cases, including our case presentation. In our case, spirometry was performed but not used as a monitoring method, limiting comparison. Additionally, we did not opt for bronchoscopy due to its invasiveness and potential complications, although it could have provided a definitive pathological diagnosis. A multicenter study identified significant predictors for GLILD in CVID patients, including a higher prevalence of splenomegaly, autoimmune cytopenia, and bronchiectasis, along with lower IgA and IgG levels at diagnosis. It also highlighted decreased switched-memory B cells marginal zone B cells, and an elevated percentage of CD21lo B cells. Reduced total lung capacity (TLC) and gas transfer (DLCO) were observed. Univariate logistic regression linked IgG and IgA levels, splenomegaly, autoimmune cytopenia, CD21lo B cells, TLC, and DLCO to GLILD risk. A multiple logistic regression model combining these factors achieved a high AUC of 0.98, suggesting the potential for early identification of interstitial lung disease in CVID patients without invasive procedures (13). The review of 42 studies encompassing 233 patients with GLILD in CVID, conducted by A.C. Lamers et al., highlighted significant variability in treatment response rates across different therapies, including glucocorticoids, rituximab, azathioprine, abatacept, and hematopoietic stem cell transplantation (HSCT). Notably, corticosteroid monotherapy showed higher rates of relapse compared to rituximab-based regimens, albeit qualitative endpoints hindered direct comparisons. HSCT emerged as a potentially effective intervention for managing GLILD, yet it carries substantial mortality risks, especially in immunocompromised cohorts. The lack of quantitative, well-controlled evidence underscores the ambiguity surrounding optimal pharmacological strategies for GLILD in CVID (14). Consequently, inter-institutional collaboration is imperative to establish standardized diagnostic and treatment protocols through international registries, incorporating uniform assessments like pulmonary function tests and high-resolution chest CT, to foster robust comparative analyses and guide future randomized clinical trials. In our case, the patient showed a favorable response to systemic corticosteroid monotherapy, with no relapses during follow-up. Based on these results, there was no need to initiate immunologic therapy or consider hematopoietic stem cell transplantation (HSCT). However, it is important to emphasize that our diagnosis and patient management relied primarily on clinical presentation, medical history, initial CT findings, and ultimately, a favorable therapeutic response. In a multicenter observational study, primary immunodeficiencies (PIDs) were investigated, focusing on their association with interstitial lung disease (ILD), a significant source of morbidity and mortality. This retrospective analysis included eleven children with PID-related ILD, predominantly CVID, where ILD occasionally preceded PID

diagnosis, emphasizing its potential as an initial disease manifestation. Treatment primarily involved corticosteroids, with some patients requiring second-line therapy due to incomplete pulmonary resolution post-treatment. These findings underscore the complexity and management challenges of ILD in PID patients (15). Some studies describe patients initially diagnosed with asthma who were later diagnosed with GLILD or CVID, emphasizing the importance of expanded differential diagnosis in such cases. A 48-year-old active-duty physician initially diagnosed with asthma presented in 2007 with dyspnea and cough, despite optimal therapy. Further evaluation, including chest CT and PET CT, revealed ground-glass nodules, patchy airspace opacities, and thoracic lymphadenopathy with high FDG-18 uptake, consistent with granulomatous-lymphocytic interstitial lung disease (GLILD) secondary to common variable immunodeficiency (CVID). Treatment with IVIG led to significant clinical improvement, highlighting the importance of considering GLILD in cases of refractory respiratory symptoms and radiographic abnormalities (16). The boy described in our case report was treated for many years due to recurrent bronchial obstructions with a suspected diagnosis of asthma and no clear evidence of allergy. His treatment included various medications such as inhaled corticosteroids (ICS), ICS combined with long-acting beta-agonists (LABA), and short-acting beta-agonists (SABA). He experienced frequent exacerbations, particularly after upper respiratory tract infections. Additionally, he had recurrent upper respiratory tract infections (6-9 annually) and 1-2 radiologically confirmed cases of bronchopneumonia per year. This clinical presentation is consistent with the most common findings reported in similar studies.

## CONCLUSION

This case underscores the diagnostic challenges in distinguishing granulomatous-lymphocytic interstitial lung disease (GLILD) from asthma, especially in patients with refractory respiratory symptoms despite optimal therapy. It highlights the critical role of a comprehensive diagnostic evaluation, including laboratory tests, chest CT imaging, and spirometry, in identifying underlying immunodeficiency disorders such as common variable immunodeficiency (CVID) and GLILD. Early initiation of treatment with intravenous immunoglobulin (IVIG) and immunomodulators led to significant clinical improvement. This case emphasizes the importance of considering rare immunologic conditions in the differential diagnosis of persistent respiratory symptoms and underscores the need for clear guidelines for the diagnosis and management of such patients in the future.

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# Psychosis or underrecognized NMDR encephalitis syndrome - case report

# Psihoza ili nedovoljno prepoznat sindrom NMDR encephalitisa - prikaz slučaja

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## ABSTRACT

Introduction: Anti-N-methyl-d-aspartate (NMDAR) encephalitis is relatively common autoimmune encephalitis characterized by complex neuropsychiatric features and the presence of immunoglobulin G (IgG) antibodies against the NR1 subunit of the N-methyl-d-aspartate (NMDR) receptor in the central nervous system. It is the most well-known and also the most common type of immune-mediated limbic encephalitis, affecting 1.5 million people a year. The most common are acute or subacute neuropsychiatric symptoms. Although there is no specific phenotype, variable positive and negative psychiatric symptoms such as visual/auditory hallucinations, depression, mania can appear rapidly within days to weeks in these patients without prior psychiatric diagnoses. The onset is quite rapid in contrast to the slow progression noted in primary psychiatric illnesses. Aim: to present the evaluation and treatment of Anti-NMDR encephalitis. Case report: this paper presents the case of patient AD (1988), who, after her initial admission to the Neurology Clinic, was transferred to the Psychiatry Clinic while on duty. Conclusion: with this paper, we have pointed out the importance of a clinical entity that has a wide differential diagnostic spectrum, and special emphasis is placed on the need to rule out an organic cause of the disease in young patients with predominantly psychiatric signs and symptoms. It is necessary to emphasize the importance of a multidisciplinary approach to this disease, as well as the importance of team work of experts within the health system in improving the care and treatment of patients with this condition.

**Keywords:** psychiatric symptoms, encephalitis, differential diagnosis

## SAŽETAK

Uvod: Anti-N-methyl-d-aspartate (NMDAR) encefalitis relativno je čest autoimuni encefalitis karakteriziran složenim neuropsihijatrijskim obilježjima i prisutnošću imunoglobulina G (IgG) antitijela protiv NR1 podjedinice N-methyl-d-aspartate (NMDR) receptora u centralnom nervnom sistemu. Predstavlja najpoznatiji, ujedno i najčešći tip imunološki posredovanog limbičkog encefalitisa, pogadja 1.5 milion ljudi godišnje. Najčešći su akutni ili subakutni neuropsihijatrijski simptomi. Iako ne postoji specifičan fenotip, varijabilni pozitivni i negativni psihijatrijski simptomi kao što su vizualne/slušne halucinacije, akutne shizoafektivne epizode, depresija, manija i poremećaji ovisnosti/poremećaji prehrane mogu se brzo pojaviti u roku od nekoliko dana do nekoliko sedmica kod ovih pacijenata bez prethodne psihijatrijske dijagnoze. Početak nastupa prilično brzo za razliku od sporog napredovanja zabilježenog kod primarnih psihijatrijskih bolesti. Cilj: nam je prezentirati evaluaciju I tretman Anti-NMDR encefalitisa. Prikaz slučaja: u ovom radu prikazan je slučaj pacijentice A.D. (1988), koja je nakon prvobitnog prijema u Kliniku za neurologiju premještena u toku dežurstva u Kliniku za psihijatriju. Zaključak: ovim radom ukazali smo na važnost kliničkog entiteta koji ima širok diferencijalno dijagnostički spektar, a osobiti naglasak se stavlja na potrebu isključivanja organskog uzroka bolesti u mladih bolesnika s dominantno psihijatrijskim znakovima i simptomima. Neophodno je naglasiti važnost multidisciplinarnog pristupa ovoj bolesti, kao i značaj timskog rada stručnjaka unutar zdravstvenog sistema u poboljšanju brige i liječenja pacijenata sa ovim stanjem.

**Ključne riječi**: psihijatrijski simptomi, enecefalitis, diferenecijalna dijagnoza

## INTRODUCTION

The main role of our immune system is to recognize and eliminate infection. However, sometimes components of the immune system, such as antibodies, can instead – by mistake – react with proteins in our body. This causes an autoimmune disease, and when it is against a protein in the brain we call it "autoimmune encephalitis". If the brain protein is an N-methyl-D-aspartate receptor (NMDAR), the condition is called NMDAR-antibody encephalitis or anti-NMDAR encephalitis (1).

NMDARs help control thought, mood, and movement, and therefore antibodies against NMDA receptors likely alter these functions. This encephalitis affects the brain more broadly than purely the limbic system, and thus is not typically classified as limbic encephalitis (2).

Anti-NMDAR encephalitis is relatively common autoimmune encephalitis characterized by complex neuropsychiatric characteristics and the presence of immunoglobulin G (IgG) antibodies against the NR1 subunit of the NMDA receptor in the central nervous system. It is the best-known and most common type of immune-mediated limbic encephalitis, affecting 1.5 million people a year. The most common are acute or subacute neuropsychiatric symptoms.

Early diagnosis and rapid immunotherapy treatment can be beneficial for the outcome of this disease. The presentation of NMDAR encephalitis is classified into five phases: the prodromal phase, the psychotic phase, the unresponsive phase, the hyperkinetic phase, and the recovery phase (3).

The disease begins with a prodrome that mimics common viral infections. Within a few weeks to a few months (<3 months), the complex neuropsychiatric features of the disease appear rapidly during the subsequent psychotic phase. Clinical characteristics may differ in children and adults. Adults usually have psychiatric symptoms (movement disorders or seizures more common in children). Acute or subacute behavioral symptoms are the most common symptoms in adult patients. Although there is no specific psychiatric phenotype, variable positive and negative psychiatric symptoms such as visual/auditory hallucinations, depression, mania can appear rapidly within days to weeks in these patients without previous psychiatric diagnoses. The onset occurs rather quickly, in contrast to the slow progression noted in primary psychiatric diseases (4).

## AIM

The aim of this paper was to present evaluation and treatment of anti-NMDAR encephalitis.

## CASE REPORT

This paper presents the case of a patient A.D. (1988), who, after her initial admission to the Neurology Clinic, was transferred to the Psychiatry Clinic while on duty.

Information from family members was provided by the husband. AD (1988), has been married, lives with her husband and two children; graduated from high school, unemployed, housewife; psychiatric heredity in the family allegedly negative.

Current illness: due to general weakness that occurred suddenly, the patient was examined in the competent Health Center, the therapy included: Mecobalamin 1000mcg 1x1; Aspirin tbl a 100 mg 1x1; Persen tbl a 40 mg 1x1. Due to occasional agitation, the patient has been taking Lexilium tbl a 3 mg 1x1 on her own initiative 3 days before the examination at the Clinic of Emergency Medicine of the Clinical Centre University of Sarajevo.

The complaints started 7 days before coming to the Clinic of Emergency Medicine in the form of tingling in the first two fingers of the left hand and jaw, difficulty speaking. Disturbances in speech are repeated cyclically during the day, because she used to communicate with her family completely normally for 2-3 hours a day, only to "panic, silence her speech, until it stopped completely" -

The following examination was drafted at the Clinic of Emergency Medicine:

- Examination of urine - no significant changes
- Emergency CT scan of the neurocranium - without visible pathomorphological changes
- Urgent laboratory - without significant deviations

Due to disturbances that persisted for the past seven days prior to admission, the specialist neurologist on duty decided to admit her to the Neurology Clinic.

Heteroanamnesis information was provided by her husband:

On admission she was conscious, oriented to herself and others, weaker temporally, slightly psychomotor disturbed, anxious. The patient had a correct attitude, but at times seemed negative (as she refused or was unable to carry out instructions during cognitive function testing). Speech: dysphatic, intermittent and at times mumbling - limited verbal communication. Basic mood depressed. Delusions were not reached. Neurological status was without outbursts or pathological reflexes.

During her hospitalization at the Neurology Clinic, she was examined several times by a psychiatrist. On two occasions her condition was diagnosed as mixed dissociative-conversion disorder, in th/ diazepam tbl a 5 mg 2x1 tbl. Repeated consultative examination by a Psychiatrist, an organic substrate was suspected due to dysarthric speech, dysgraphia. The patient complained of insomnia, became agitated, tearful, "wandered" around the ward, disturbing other patients during the night.

Due to agitation, unpredictability, and in order to carry out further diagnostics, a transfer to the Clinic of Psychiatry, Department of General Psychiatry was indicated.

Mental status upon admission to the Clinic of Psychiatry:

- (Hospitalized at the clinic in the period from 5 February to 15 February 2021): conscious, moving independently, psychomotor disturbed, sat with closed eyes, then momentarily made eye contact. During the examination, she got up couple of times and tried to leave the room. Verbal contact failed to be established. She tried to offer an answer to the questions asked, but it seemed as if she made effort to do so. She reacted to rough stimuli by moving away and making bizarre movements (as if she was trying to catch something in the air). When asked about perceptual deceptions, she shook her head, but they could not be ruled out with certainty. The neurological status was roughly examined, without manifest pathology. On the second day of her stay in the clinic, the patient becomes extremely agitated, and was transferred to the Emergency Psychiatry Department; verbal contact was still not established, non-verbally adequate answered to questions about husband, children, etc. were obtained.

  Laboratory tests: AST, ALT, CK, LDH (double elevated values compared to reference values), mineralogram normal, afebrile. Ammonia value was normal.

- In the therapy of ordinary infusion solutions; atypical antipsychotic olanzapine in a total dose of 5 mg. Strict monitoring was ordered, vital parameters were monitored. On the third day of her stay in the clinic, the patient was lying in bed staring at the ceiling, did not establish verbal or non-verbal contact. Suddenly, during lunch, she got out of bed, went to the dining room on her own and took a meal, then "sat down staring at one point", and later, with the help of a medic, she was "carried to bed" due to the inability to return

to bed on her own. Due to severe restlessness, the parenteral therapy of the typical antipsychotic haloperidol was prescribed the night before, which was continued the next day in addition to the previously prescribed olanzapine. An examination by a neurologist was carried out, who indicated an MRI.

Liver enzymes were still elevated, but the values were still in a significant decline; CRP neat; coagulation factors normal; elevated D dimer. Also, an X-ray of the lungs as well as an EHO of the abdomen was performed - without any special features.

MRI: the finding indicated the existence of a lesion within the splenium of the corpus callosum that showed signs of restrictive diffusion, which corresponded to a cytotoxic lesion differentially diagnosed in the field of metabolic disorders, a disorder in the direction of drug intoxication, toxins, but also certain infectious conditions. On the tenth day of her stay in the clinic, the patient lied with her eyes closed, hypotensive, triple elevated liver enzymes, total bilirubin in excess, LDH on the rise. Febrile up to 38.2°C.

- A multidisciplinary council was held, consisting of a neurologist, an infectious disease specialist, a neuroradiologist, an endocrinologist, a clinical pharmacologist, and a psychiatrist/ordinary. The patient kept her eyes closed, willingly defending herself by opening her eyes, with the bulbus escaping upwards. On the face without convincing asymmetry, the neck was locked, the head tilted back towards the pillow. In the AG position, when the right arm was raised, with a markedly increased muscle tone, it remained in the same position, but when it changed the position, it stayed in that position. The left hand was in increased tone, significantly less than the right; Babinski negative. Reflexes more alive. MRI findings presented at the Infectology course - necessary analysis of cerebrospinal fluid. In therapy, ampoules of diazepam 3×1, inf solution of Ringer lactate and 500 mg 2x. Placed nasogastric tube by ENT.

  The patient was febrile (prescribed antibiotic therapy by an infectious disease specialist). Realized MRI with contrast, under anesthesia. After the MRI, upon returning to the psychiatry clinic, the patient independently took a glass of water and drank, understood orders, cooperated, carried out orders, sat in bed. A differential diagnosis was made/ Encephalopathy cerebri in obs. Around 8:00 p.m. the same day, the patient was febrile at 38.4° C. The result of the analysis of the cerebrospinal fluid arrived, which showed positive specific IgG antibodies to NMDA receptors in the cerebrospinal fluid (CSL) and in the serum, which in addition clinical picture and other performed tests, will be an indication for transferring the patient to the Clinic of Infectious Diseases for the purpose of more detailed evaluation and therapeutic treatment.

The patient was hospitalized at the Clinic of Psychiatry in the period from 5 to 15 February 2021, when hospital treatment continued at the Clinic of Infectious Diseases, and subsequently at the Clinic of Neurology, from which she was discharged.

During her stay in the aforementioned institutions, the patient was treated by an infectious disease specialist, neurologists and psychiatrists. Following her discharged from the Neurology Clinic, she came for regular follow-up examinations by a neurologist. She functioned without difficulty with persisting headaches.

## DISCUSSION

The identification of anti-NMDA receptor (NMDAR) encephalitis about 12 years ago made it possible to recognize that some patients with rapidly progressive psychiatric symptoms or cognitive impairment, seizures, abnormal movements, or coma of unknown cause have an autoimmune disease. In this disease, autoantibodies serve as a diagnostic marker and alter NMDAR-related synaptic transmission (1). The clinical presentation of anti-NMDA receptor encephalitis varies, with a myriad of neurological and psychiatric symptoms reported. There are also significant differences in the clinical picture between affected adults and young people (5). Most reported cases of adults initially presenting to psychiatric health professionals with symptoms suggestive of mood, anxiety, and/or psychotic disorders, children more often show subtle behavioral and neurological changes.

Most patients with anti-NMDAR encephalitis develop a multistage disease that progresses from initial psychiatric symptoms to memory impairment, seizures, dyskinesia, and catatonia. Psychiatric manifestations include anxiety, mania, social withdrawal, and psychosis (ie, delusions, hallucinations, disorganized behavior) (6). At the onset of symptoms, it is difficult to distinguish the disease from a primary psychiatric disorder. The severity of symptoms often requires intensive care. Apart from clinical assessment, there are no specific prognostic biomarkers. The disease is more common in women (with a ratio of women to men of about 8:2), and about 37% of patients are younger than 18 years old at the time of disease presentation. When faced with a patient such as the patient presented here, there are data to guide the clinical decision-making process; what remains unclear is the targeted treatment of psychiatric symptoms. Psychiatric treatments described in the autoimmune encephalitis literature focus primarily on treating catatonia with electroconvulsive therapy (ECT). The use of multiple classes of psychotropic medications, including conventional and atypical antipsychotics, mood stabilizers, and benzodiazepines, has been detailed in numerous case reports, but concurrent use with other therapeutic modalities makes assessment of clinical outcomes difficult. Despite the severity of symptoms, anti-NMDAR encephalitis has a better prognosis than most other paraneoplastic encephalitis.

Anti-NMDA receptor encephalitis is a relatively newly identified and potentially curable cause of psychiatric symptoms in both adults and children (7). Several hundred cases have been reported since its identification in 2007; however, clinicians may not be aware of developments in this area. It is vital for psychiatrists working in different age groups to be aware of this condition and to cooperate with neurologists in time, thus facilitating early screening and diagnosis (8).

## CONCLUSION

By presenting this case, we tried to emphasize the importance of approaching a psychiatric patient, or a patient who exhibits symptoms that resemble psychiatric illnesses. This clinical entity has a wide differential diagnostic spectrum and special emphasis is placed on the need to rule out an organic cause of the disease in young patients with predominantly psychiatric signs and symptoms. It is necessary to emphasize the importance of a multidisciplinary approach to this disease, as well as the importance of team work of experts within the health system in improving the care and treatment of patients with this condition.

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# Termination of pregnancy after prenatal diagnosis of Spina Bifida Occulta

# Prekid trudnoće nakon prenatalne dijagnoze Spina Bifida Occulta

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## ABSTRACT

Introduction: spina bifida occulta is the mildest form of the neural tube defects (NTD) which involves a hidden vertebral defect and minimal neural involvement. One of the biggest risk factors for delivering a baby with spinal cord defects is insufficient intake of folic acid during pregnancy. Case report: a pregnant woman, 27 years old, 3rd pregnancy. She received a routine prenatal ultrasound examination in our hospital at 15+0. She did not take any medication during pregnancy. Ultrasound examination showed that the deformity size was 10mm x 6mm on the lumbosacral spine. The deformity did not follow the continuity of the bony part of the vertebral column but showed the continuity of skin). Fetal biometry: BPD 20.6 mm, FL 9 mm, CRL 52 mm, FHR positive +, posterior placenta position. She decides to terminate the pregnancy. Medical termination of pregnancy was performed with endocervical gel (PGE2). (Figure 2,3,4) Conclusion: using folic acid before conception and during pregnancy has been shown as a successful method of prevention of spina bifida occulta. Ultrasound examinations should be regularly performed in order to detect anomalies on time. Spina bifida occulta is an anomaly compatible with life. During adolescent development, complications arise that need to be monitored by several different medical specialists. Complications reduce the quality of life, and sometimes require surgical treatment. As a result of the possible complications, women often decide to terminate the pregnancy.

**Keywords**: spina bifida, folic acid

## SAŽETAK

Uvod: spina bifida occulta je najblaži oblik defekta neuralne cijevi (NTD) koji uključuje skriveni vertebralni defekt i minimalno neuralno zahvaćanje. Jedan od najvećih čimbenika rizika za rađanje djeteta s oštećenjima leđne moždine je nedovoljan unos folne kiseline tijekom trudnoće. Prikaz slučaja: trudnica, 27 godina, 3. trudnoća. U našoj je bolnici obavila rutinski prenatalni ultrazvučni pregled u 15+0. Tijekom trudnoće nije uzimala nikakve lijekove. Ultrazvučni pregled je pokazao da je veličina deformiteta 10mm x 6mm na lumbosakralnoj kralježnici. Deformacija nije pratila kontinuitet koštanog dijela kralježnice već je pokazala kontinuitet kože. Fetalna biometrija: BPD 20,6 mm, FL 9 mm, CRL 52 mm, FHR pozitivan +, posteriorni položaj posteljice. Odlučuje prekinuti trudnoću. Medicinski prekid trudnoće izveden je endocervikalnim gelom (PGE2). (Slika 2,3,4) Zaključak: primjena folne kiseline prije začeća i tijekom trudnoće pokazala se kao uspješna metoda prevencije spina bifida occulta. Ultrazvučne preglede potrebno je redovito provoditi kako bi se anomalije otkrile na vrijeme. Spina bifida occulta je anomalija kompatibilna sa životom. Tijekom adolescentnog razvoja nastaju komplikacije koje treba pratiti nekoliko različitih medicinskih stručnjaka. Komplikacije smanjuju kvalitetu života, a ponekad zahtijevaju kirurško liječenje. Zbog mogućih komplikacija žene se često odlučuju na prekid trudnoće.

**Ključne riječi**: spina bifida, folna kiselina

## INTRODUCTION

Spina Bifida is a congenital anomaly that arises from incomplete development of the neural tube. It is commonly used as a nonspecific term referring to any degree of neural tube closure. Spina bifida occulta is the mildest form of the neural tube defects (NTD) which involves a hidden vertebral defect and minimal neural involvement (1).

Typically, the neural tube forms early in pregnancy and closes by the 28th day after conception. In babies with spina bifida, a portion of the neural tube doesn't close all the way. This affects the spinal cord and bones of the spine (2).

Genetic and environmental factors play a central role in neural tube defects. However, there are many other contributing factors like obesity, diabetes, immune dysregulation, folic acid antagonists, dihydrofolate reductase inhibitors, socioeconomic status, geography, ethnicity, etc., that play a vital role as well (3).

Experts are not exactly sure what causes any of the forms of spina bifida, including SBO. One of the biggest risk factors for delivering a baby with spinal cord defects is insufficient intake of folic acid during pregnancy (4).

The most common screening methods to look for spina bifida during pregnancy are maternal serum alpha fetoprotein (MSAFP) screening and fetal ultrasound. Amniocentesis can also be performed. Spina bifida occulta literally means "a hidden spot on

the spine," and for many people with this type of spina bifida, the spot remains hidden (5).

Rarely, spina bifida occulta will cause problems when a child grows to adolescence. By this time in the child's life, the spinal cord has become fastened to the backbone. When the growth spurt of adolescence begins, the nerves of the spinal cord become stretched. The result can be difficulties such as weakness and numbness in the legs, bladder infections and incontinence. The more the spinal cord is stretched, the worse the symptoms become. Surgery to relieve these symptoms by reducing the tension on the spinal cord is simple and often successful (6).

Treatments could include:

- Surgery to close the gap between the vertebrae of the backbone.
- Physical or occupational therapy to improve muscle strength.
- Using mobility equipment such as a back brace, walker or wheelchair.
- Taking drugs to treat bladder or bowel problems. (6)

## CASE REPORT

The patient was a 27 years old on her 3rd pregnancy. She received a routine prenatal ultrasound examination in our hospital at 15 + 0. The patient had regular gynaecological check-ups at that point. A Pap smear was preformed at 3 weeks of pregnancy (CIN I), and the HPV test was positive with type 18.

Menarche: 15 years old, the last menstrual period date: 11.02.2024, previous obstetric history: 1 spontaneous vaginal delivery and 1 ectopic pregnancy. No history of chronic diseases. In 2022 she had a left salpingectomy as a result of ectopic pregnancy. No known drug allergies and blood type of A+. She did not take any medication or vitamin supplementation during pregnancy.

Family history: there was a positive family history of hypertension. Her mother has diabetes mellitus Typ I and the father a history of cardiac disease (MI).

On examination, we found that the patient was conscious, communicative, eupneic, afebrile with normal vital sings. Ultrasound examination showed that the deformity size was 10mm x6mm on the lumbosacral spine. The deformity did not follow the continuity of the bony part of the vertebral column but showed the continuity of skin (Figure 1). Fetal biometry: BPD 20.6 mm, FL 9 mm, CRL 52 mm, FHR positive +, posterior placenta position.

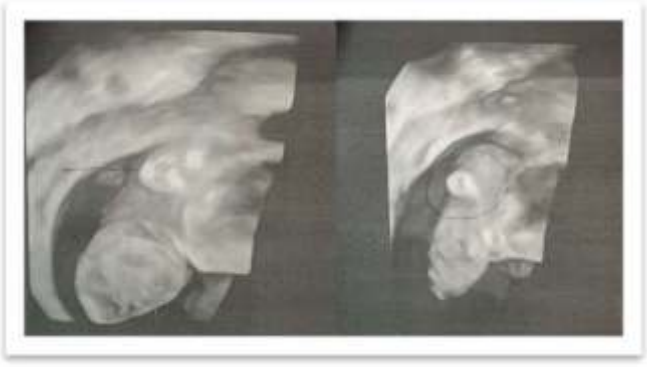

Figure 1 **Ultrasound of the fetus's Spina Bifida Occulta.**

After ultrasound, the diagnosis of spina bifida occulta was established. The diagnosis, cause, frequency, symptoms, prognosis, complications, and treatment options were explained. She received all the information related to the pregnancy and the condition of the fetus.

Subsequently, with her signature, she decided to terminate the pregnancy. Medical termination of pregnancy was performed with endocervical gel (PGE2) (Figure 2,3,4).

*Figure2*

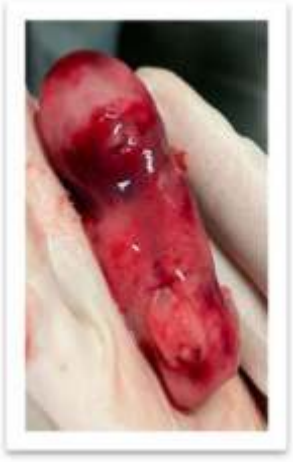

*Figure 3*

*Figure 4*

Figure 2,3,4 **Fetus with Spina Bifida Occulta.**

## DISCUSSION

The primary prevention of spina bifida is vitamin supplementation with folic acid, which has been demonstrated in clinical trials in many countries. Women of reproductive age should supplement before conception with 0.4-1.0 mg of folic acid daily (8).

In the reproductive period between 15 to 45 years of age, women who plan to become pregnant should take 400 micrograms of folic acid on daily basis to prevent spina bifida. If they have diabetes or already have a child with spina bifida, they should take 4,000 micrograms during pregnancy. Folic acid supplementation can reduce spina bifida by 40 to 100 percent (4).

Clinical symptoms of spina bifida occulta are usually the result of neural dysfunction. It can be a result of deformity in the nervous tissue or pressure from adjacent tissues. The most common

symptoms are related to the urinary apparatus. In case when the symptoms become progressive during postnatal life, surgical treatment is recommended.

Open fetal surgery and fetoscopic fetal surgery are two options for prenatal repair. Fetal surgery to repair spina bifida involves a variety of risks, including: preterm labor, loss of pregnancy, need for a cesarean delivery, uterine rupture, and damage to the fetus (10).

In the case of Aguilera S, et al, they analyzed and followed up 74 cases of prenatally diagnosed spina bifida. Termination of pregnancy was chosen in 72% of the cases and 28% were live-born (11).

Of the 21 live births, 3 died in the neonatal period. The other 18 (86%) were all alive after an average follow-up of 3 years and 6 months (range 5 months to 7 years and 4 months). From this group 11% are wheelchair-dependent, 87% of the patients older than 2 years of age are walking, 33% have had cerebral shunting and 72% have normal neurodevelopment. There was a better outcome in patients with closed defects; however, the rates of neuropathic bladder (50%) remain a concern (11).

In the case of Allen R, et al, there were 28,866 terminations of which 4425 (15.33%) had a diagnosis of NTD in the period of 11-years. The number of NTD cases increased over the time period from 2007 to 2017. Termination for NTDs is on the rise in England and Wales. This study shows that pregnant women need further education on the benefit of using folic acid supplementation during pregnancy (12).

## CONCLUSION

Using folic acid before conception and during pregnancy has been shown as a successful method of prevention of spina bifida occulta. Ultrasound examinations should be regularly performed in order to detect anomalies on time. Spina bifida occulta is an anomaly compatible with life. During adolescent development, complications arise that need to be monitored by several different medical specialists. Complications reduce the quality of life, and sometimes require surgical treatment. As a result of the possible complications, women often decide to terminate the pregnancy.

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# Multisystem manifestations in a patient with bilateral bronchopneumonia and Prader-Willi syndrome: a case study

# Multisistemske manifestacije kod pacijenta sa bilateralnom bronhopneumonijom i Prader-Willi sindromom: studija slučaja

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## ABSTRACT

Introduction: Prader-Willi syndrome is a rare genetic disorder characterized by hypotonia, obesity, hypogonadism, and various psychiatric and endocrine abnormalities. Case report: we present a case of an eleven-year-old girl diagnosed with bilateral bronchopneumonia, Prader-Willi syndrome, type 2 diabetes, hypothyroidism, and vitamin D deficiency. The patient underwent clinical examination, laboratory and radiological investigations, and multidisciplinary consultations. Results: complications in respiratory, endocrine, and cardiovascular systems were identified. Conclusion: this case highlights the need for a holistic approach in treating patients with complex comorbidities.

**Keywords**: Bronchopneumonia, Prader-Willi syndrome, type 2 diabetes, hypothyroidism, vitamin D deficiency, pediatrics.

## SAŽETAK

Uvod: Prader-Willijev sindrom je rijedak genetski poremećaj koji karakterišu hipotonija, pretilost, hipogonadizam i razne psihijatrijske i endokrine abnormalnosti. Prikaz slučaja: prikazujemo slučaj jedanaestogodišnje djevojčice s dijagnozom bilateralne bronhopneumonije, Prader-Willi sindroma, dijabetesa tipa 2, hipotireoze i hipovitaminoze D. Pacijentica je podvrgnuta kliničkom pregledu, laboratorijskim i radiološkim pretragama, te multidisciplinarnim konsultacijama. Rezultati: identifikovane su komplikacije u respiratornom, endokrinološkom i kardiovaskularnom sistemu. Zaključak: prikazani slučaj naglašava potrebu za holističkim pristupom u liječenju pacijenata s kompleksnim komorbiditetima kod Prader-Willi sindroma.

**Ključne riječi**: Bronhopneumonija, Prader-Willi sindrom, dijabetes tip 2, hipotireoza, hipovitaminoza D, pedijatrija

## INTRODUCTION

Prader-Willi syndrome (PWS) presents a complex clinical picture that significantly impacts affected individuals' quality of life. PWS is caused by the lack of gene expression from the paternally inherited genes on chromosome 15q11.2-q13. About 70% of cases are due to genomic imprinting errors resulting from a paternal deletion, while maternal uniparental disomy accounts for approximately 25% of cases. A smaller number of cases arise from defects in the imprinting center, such as microdeletions or epimutations on chromosome 15 (1,2). Prader-Willi syndrome is characterized by an overwhelming, uncontrollable appetite and persistent food-seeking behavior. As advancements in genomic medicine continue, identifying risks associated with specific genes and understanding the interaction between genes and environmental factors will become increasingly possible. Environmental influences on gene expression through epigenetic mechanisms may play a role in the development of obesity, especially during fetal development and early childhood (3). Hypotonia is a common feature in infants with Prader-Willi syndrome, leading to feeding difficulties and poor weight gain. This condition often results in diminished muscle mass and strength, which may require specialized feeding methods or prolonged enteral nutrition. Additionally, reduced fetal movement and a delayed perception of fetal movement (quickening) are observed prenatally (4). Managing Prader-Willi syndrome requires age-specific strategies and comprehensive monitoring of various organ systems. Infants with the syndrome often present with muscular hypotonia, feeding difficulties, and inadequate weight gain, which may necessitate a feeding team's evaluation for specialized techniques and high-calorie supplements. As hyperphagia develops in childhood, it becomes crucial to restrict food intake. Most patients have reduced energy needs, consuming about 70% of the calories compared to their peers without Prader-Willi syndrome. While calorie-restricted diets might lack essential vitamins and minerals, supplements should be prescribed to fulfill daily nutritional

requirements, with care taken to avoid gummy vitamins due to their high caloric content and overdose risk (5). The outlook for individuals with Prader-Willi syndrome can vary significantly, depending on the timing of diagnosis and the severity of associated complications. Early intervention and effective management of obesity can improve the chances of reaching a near-average lifespan. Despite this, due to intellectual disabilities, most individuals will need ongoing support and may not achieve complete independence in adulthood. Complications such as obesity, diabetes, and heart failure can reduce life expectancy. Many individuals face premature death in their fourth decade of life if these conditions are not well-managed. However, with effective weight management, individuals with Prader-Willi syndrome have the potential to live into their seventies (2,5,6). Prader-Willi syndrome is a multifaceted and varied condition that profoundly affects both those diagnosed and their families. Significant progress has been made in understanding the genetic mechanisms involved, with promising new insights emerging. Nonetheless, challenges persist in achieving early diagnosis and managing some of the syndrome's most severe symptoms. As knowledge about PWS advances, new therapies and management approaches continue to become available, offering hope for improved care for both clinicians and families (7).

## AIM

The aim of this study is to present a comprehensive case of Prader-Willi syndrome from our institution, highlighting the challenges encountered in the treatment and management of the patient. We seek to provide insights into the complexities of managing this condition, including the practical difficulties and therapeutic approaches used in our setting. By sharing our experiences, we aim to contribute to the broader understanding of Prader-Willi syndrome and offer valuable perspectives for improving patient care and management strategies.

## CASE REPORT

The case involved an 11-year-old female with a multifaceted medical history, including Prader-Willi Syndrome, Type 2 Diabetes Mellitus (DM type 2), hypothyroidism, vitamin D deficiency, and a recent diagnosis of measles. Her complex condition was further complicated by bilateral bronchopneumonia. The patient had a history of multiple admissions to the Pediatric Clinic. She was presented with difficulty breathing, elevated fever up to 38.5°C, and headache, which began two days prior to her admission. Additionally, she experienced intermittent coughing and abdominal pain since the previous day, though her bowel movements and urination were normal.

Her medical regimen included levothyroxine for hypothyroidism, metformin for diabetes, vitamin D supplementation, montelukast for asthma, and cefixime for pneumonia. Born as the second child via cesarean section from a well-managed pregnancy, she faced early difficulties with swallowing and sucking, leading to a 40-day hospitalization in the Neonatology Department. Notably, she was not vaccinated and has a history of Prader-Willi Syndrome, CMV infection at one year, frequent bronchitis, and pneumonia. Family history is non-contributory, and her socio-epidemiological status is considered adequate.

On examination, the patient was febrile and mildly dyspneic, with significant subcutaneous fat accumulation and a "buffalo hump" on her neck. Respiratory assessment revealed diminished breath sounds bilaterally and a decreased oxygen saturation (SpO2 85%) despite oxygen therapy. Her abdomen was soft but tender, especially in the epigastric region, with no palpable enlargement of the liver or spleen. Neurological examination showed no focal deficits, indicating that her general condition required a comprehensive management approach involving endocrinology, pulmonology, and nutritional support.

Serial blood gas analyses demonstrated variable pH levels ranging from 7.29 to 7.38, pCO2 between 7.50 and 11.50 mmHg, pO2 from 5.80 to 14.26 mmHg, and HCO3 levels ranging from 30.8 to 49.7 mmol/L. Other laboratory tests revealed glucose levels between 6.8 and 8.8 mmol/L, C-reactive protein (CRP) from <5 to 7.2 mg/L, and elevated leukocytes (15.1 ×10^9/L), erythrocytes (5.52 ×10^12/L), and hemoglobin (149 g/L). Additional findings included fibrinogen at 2.3 g/L, INR of 0.79, APTT of 24.3 seconds, D-dimer at 1.07 mg/L, urea at 7.9 mmol/L, creatinine at 43 µmol/L, AST at 26 U/L, ALT at 65 U/L, calcium levels between 1.20 and 2.48 mmol/L, sodium ranging from 135 to 140 mmol/L, potassium from 4.8 to 5.4 mmol/L, chloride between 89 and 95 mmol/L, lactate dehydrogenase (LDH) at 267 U/L, and uric acid at 319 µmol/L. Microbiological results included positive serology for measles IgM (>800) and a positive PCR from a nasopharyngeal swab for the measles virus.

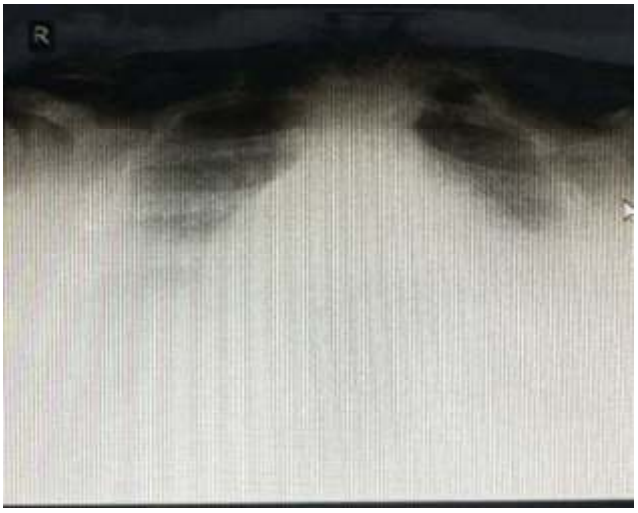


Figure 1 **Chest picture on admission.**

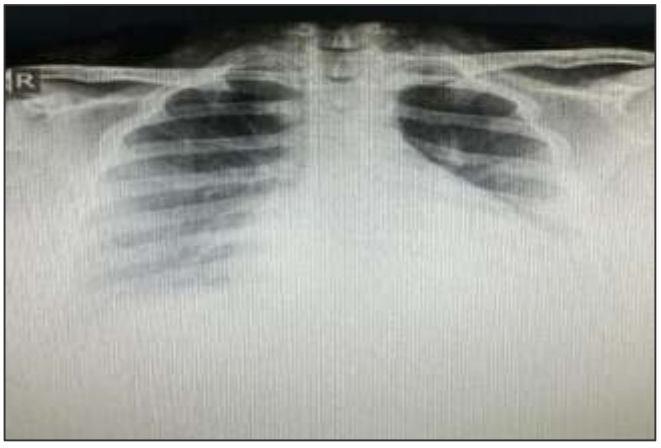


Figure 2 **Chest picture after treatment.**

Initial chest X-rays showed bilateral consolidation in the lower lung fields. Follow-up imaging revealed slight improvement compared to the earlier X-ray, and an ultrasound of the pleura, while technically limited due to the patient's condition, confirmed bilateral consolidation with discrete improvement. Subsequent X-rays showed continued regression of the inflammatory changes over time. The patient initially required oxygen support and was started on parenteral antibiotics, including Cefazolin and Ampicillin, along with corticosteroid therapy and inhalations. On the second day of hospitalization, Azithromycin was added, and the patient was placed on a High Flow oxygen apparatus set at 25L/min. Following the initiation of high-flow therapy, the patient demonstrated significant improvement in both subjective and objective assessments. Over the subsequent days of hospitalization, the patient's oxygen saturation and respiratory rate gradually improved. The flow rate was progressively reduced, and with an FiO2 of 30%, there was a gradual decrease in FiO2 as well. She experienced fever during the first two days but became afebrile thereafter. An endocrinologist was consulted, recommending insulin administration for her diabetes. On the fourth day, the patient developed a rash, leading to a consultation with an infectious disease specialist. PCR and serology tests for measles were conducted, confirming the diagnosis.

Gradually, the patient's condition improved, with a reduction in fever and oxygen support. By the twelfth day of hospitalization, she was off oxygen support, had stable vital signs, and follow-up X-rays showed regression of the initial pulmonary changes. Laboratory results were within normal ranges, and the father expressed a desire to continue treatment at home.

## DISCUSSION

This case demonstrates the complexity of managing patients with multiple comorbidities. Prader-Willi syndrome significantly complicates the management of acute respiratory infections due to obesity, hypothyroidism, and diabetes. The patient required complex therapy including antibiotics, bronchodilators, and specific endocrinological medications. Diagnosis and treatment were further complicated by the presence of cardiomegaly and the risk of respiratory insufficiency. In this case, the critical decision to initiate high-flow therapy was pivotal. This intervention allowed the patient to reduce her respiratory effort and halted the progression of respiratory insufficiency, which, given her underlying condition and morbid obesity, could have been life-threatening. The literature also supports the benefits of non-invasive ventilation for such patients, emphasizing that it should be considered the first-line treatment approach. In a similar case, when CPAP and non-invasive ventilation (NIV) were insufficient, tracheostomy was considered a last-resort treatment option. This case report details a patient with Prader-Willi syndrome, morbid obesity, severe obstructive sleep apnea (OSA), and obesity hypoventilation syndrome (OHS) who was hospitalized due to hypoxemic and hypercapnic respiratory failure. The use of NIV with average volume-assured pressure support and auto-titrating end-expiratory airway pressure (AVAPS-AE), a newer NIV modality, effectively managed the hypoventilation during the hospital stay and continued to be beneficial after discharge. (8) The largest reported pediatric study on AVAPS, published in 2021, involved 19 children suffering from nocturnal hypoventilation due to a range of medical issues, all of whom had experienced inadequate results with bilevel PAP titration because of persistent hypoventilation. The study highlighted that AVAPS titration was more effective than traditional bilevel PAP in reducing nocturnal transcutaneous CO2 levels. Included in the study was a 12-year-old with Prader-Willi syndrome, who was the only participant with morbid obesity in the group. (9) Prader-Willi syndrome, due to its genetic basis on chromosome 15, is associated with several phenotypic features that predispose patients to respiratory issues, such as hypotonia, abnormal ventilatory responses, scoliosis, and obesity. These features can lead to a range of respiratory complications, from sleep-disordered breathing to functional impairment. Growth hormone therapy, while a cornerstone of treatment, has raised concerns due to reported cases of sudden death shortly after initiation. (10) In our patient's case, despite considerable efforts in therapy, including the use of growth hormone and insulin titration managed by an endocrinologist, the lack of caloric intake restriction in an outpatient setting has led to morbid obesity. Additionally, irregular follow-ups have complicated long-term management, often resulting in the patient being admitted to the hospital with exacerbations of chronic respiratory insufficiency. Despite these challenges, non-invasive ventilation, along with other supportive and therapeutic measures, proved to be the appropriate choice in acute treatment. It effectively halted the unfavorable progression of the clinical course, demonstrating its critical role in managing the patient's condition.

## CONCLUSION

This case highlights the need for a multidisciplinary approach in treating patients with Prader-Willi syndrome and comorbid conditions such as bilateral bronchopneumonia, type 2 diabetes, and hypothyroidism. There is a need for control of blood sugar values on a daily basis, regular controls of HbA1c, triglycerides and cholesterol. Also, there is a need for regular weight checkups and dietary regime because of increased body weight. Also, any minor respiratory infection can jeopardize the sick child. The doctor's conversation with parents is important in order for them to understand the seriousness of the disease. With the understanding of the seriousness, life of patients with this syndrome is prolonged and the quality of life is increased. A holistic approach and continuous monitoring are crucial for the successful management of such complex clinical presentations.

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