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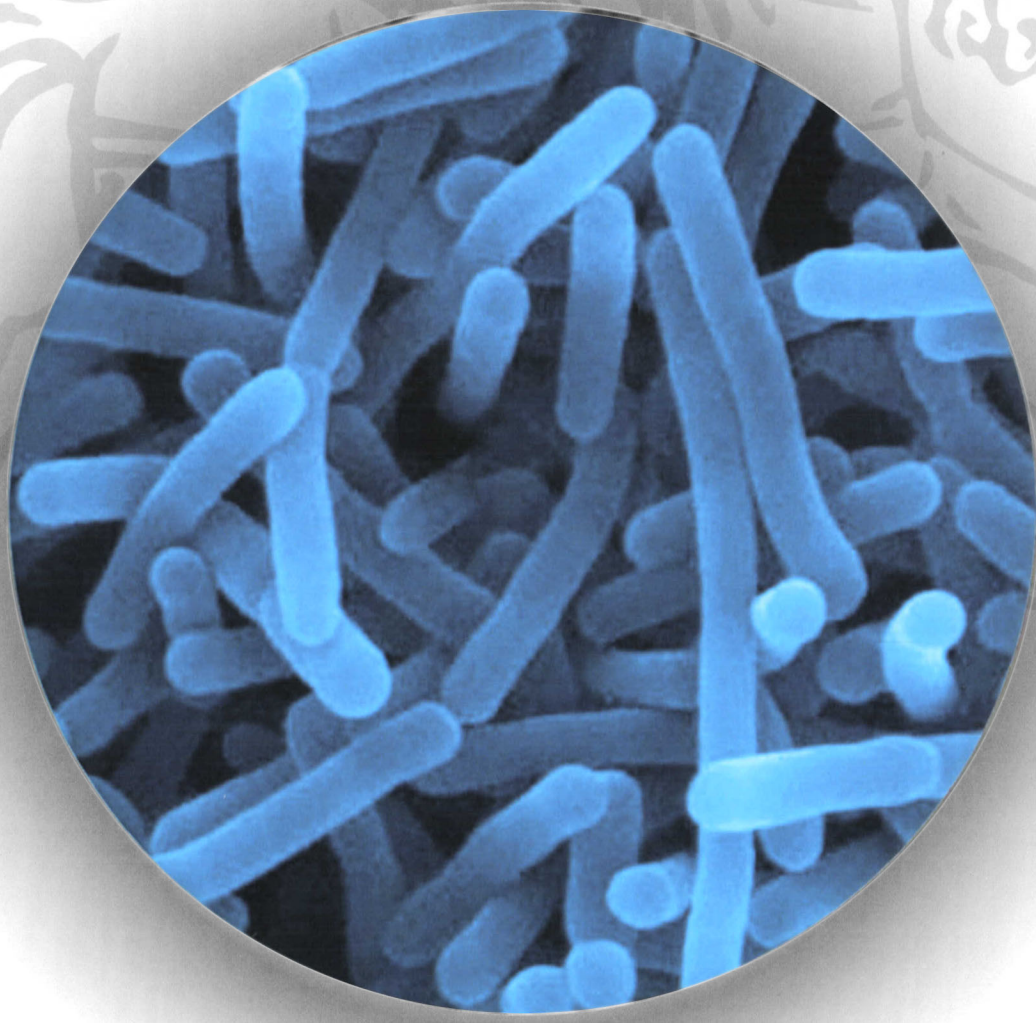

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Contents

STRUČNI ČLANCI
Professional papers

Editorial
Uvodnik

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Far-echoing Voice - Documenting the Consequences of the War in Ukraine in Medical Journals

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The Russian aggression against Ukraine began in 2014 with the Russian annexation of Crimea and escalated into a full-scale invasion on February 24, 2022. The war taking place on the territory of Ukraine is still raging mercilessly two and a half years after its beginning. According to the estimation of the Office of the United Nations High Commissioner for Human Rights, it has claimed over 30,000 Ukrainian civilian casualties so far. There are no reliable data on Ukrainian military losses, with the estimates varying between 30 and 50 thousand lost lives.[1–3] To better understand the devastating and far-reaching consequences of the current war in Europe, we have to know that in the first 17 months of the war, almost 50,000 Ukrainians underwent amputations due to injuries from land mines and other heavy artillery. That is a scale only comparable to the number of amputations during brutal World War I.[4] The consequences of severe injuries will be permanently suffered by over 200,000 Ukrainians who have been injured so far, but also by their families and society in general.

The experience of the Croatian War of Independence makes us especially sensitive to the suffering of the Ukrainian people. The best way for scientists to fight the war is to continue their research and produce scientific papers. To systematically and objectively document war injuries and the consequences of destruction is invaluable. In the early 1990s, Professor Matko Marušić showed the suitable model by founding the renowned Croatian Medical Journal. He also educated many Croatian scientists who published over 360 scientific articles in English on the Croatian War of Independence, mostly in high-rank international medical journals.[5]

Encouraged by the example mentioned above, Professor Damir Sapunar, Head of the Translational Research in Medicine PhD Program at the University of Split, and Professor Livia Puljak, Head of the Center for Evidence-Based Medicine and Healthcare at the Catholic University of Croatia, decided to help Ukrainian colleagues and scientists with what they knew the best, which was teaching methodology and writing scientific papers. Two altruistic Croatian scientists visited Ukraine in March 2024, where they held a series of lectures and workshops on planning research and writing articles. The cooperation continued even after their return to Croatia. Professors Sapunar and Puljak consider assistance in translating, editing, and publishing papers in English on the suffering of the Ukrainian people to be a social responsibility. To date, ten scientific papers have been published within this noble project called "Giving Voice".[6]

Zadar and its surroundings suffered great destruction during the Croatian War of Independence, and most of the wounded civilians and soldiers were treated in Zadar General Hospital. The doctors who participated in the treatment of complex injuries in wounded civilians and soldiers also contributed through the production of scientific papers, congress abstracts, and reviews. The most comprehensive report on the situation in the war-affected hospital in Zadar was published by Professor Neven Skitarelić in the Proceedings on the Croatian War of Independence.[7,8] There is still a lot of data in the hospital archive available to enthusiastic young doctors to discover. More research could produce

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papers describing surgical endeavors that older surgeons anecdotally recount to residents.

Publishing the consequences of war destruction is a social responsibility. Therefore, our duty as doctors is to document the spectrum of war injuries and treatment in the same way as continuing professional medical education. The journal Medica Jadertina supports the publication of peer-reviewed scientific papers so that the truth reaches as broad as possible an audience. Thus, the war-affected Ukrainian doctors can disseminate their papers in international, indexed medical journals.

We are proud to publish a retrospective study from Ukraine by Horoshko and colleagues in this issue. The study explores the high incidence of chronic pain after a combat injury, the profound impact of acute stress reaction, and post-traumatic stress disorder on the perception of pain, recovery, and quality of life of soldiers after the treatment.[9]

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Chronic pain and psychological well-being in soldiers wounded during Russo-Ukrainian war: a retrospective study

Kronična bol i psihološka dobrobit u vojnika ranjenih tijekom rusko-ukrajinkog rata: retrospektivna studija

Vasyl Horoshko[1], Iurii Kuchyn[1], Kateryna Bielka[1], Damir Sapunar[2]

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Summary

Background: Chronic pain is highly prevalent among Ukrainian soldiers with gunshot and mine-explosive injuries. Our study examines the impact of acute stress reaction (ASR) and post-traumatic stress disorder (PTSD) on chronic pain development and its effect on soldiers' quality of life post-treatment.

Methods: In this retrospective study, we analyzed data from 1,166 wounded soldiers diagnosed with PTSD following ASR. We assessed pain intensity, anxiety/depression, quality of life, and PTSD presence at hospital discharge, one and three months later.

Results: We identified significant predictors of chronic pain in wounded soldiers, emphasizing the role of psychological factors and the quality of life. High levels of anxiety and depression, PTSD symptoms, and low quality of life scores were strongly associated with chronic pain, even after adjusting for injury type and initial pain intensity. The presence of an ASR, high Hospital Anxiety and Depression Scale scores (HADS), and low scores on the Chaban Quality of Life Questionnaire (CQLS) were identified as predictors of chronic pain, with a notably high risk (95.6%) for patients meeting these criteria. Our findings suggest a significant association between the risk of chronic pain and ASR, with quality of life scores at discharge, one month, and three months post-treatment, indicating a high predictive accuracy. Moreover, ineffective pain treatment correlated with ineffective PTSD treatment.

Conclusion: Soldiers' diminished psychological well-being post-gunshot and mine-explosive injuries significantly increase chronic pain risk. Addressing anxiety, depression, and PTSD symptoms, alongside improving quality of life, could reduce the likelihood of chronic pain and other negative health outcomes in soldiers with combat injuries.

Keywords: Ukraine; War-Related Injuries; Chronic Pain; Acute Stress Reaction; Post-Traumatic Stress Disorder

Sažetak

Pozadina: Kronična bol vrlo je česta među ukrajinskim vojnicima s prostrijelnim i minsko-eksplozivnim ozljedama. Naša studija ispituje utjecaj akutne stresne reakcije (ASR) i posttraumatskog stresnog poremećaja (PTSP) na razvoj kronične boli i njezin utjecaj na kvalitetu

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života vojnika nakon liječenja.

Metode: U ovoj retrospektivnoj studiji analizirali smo podatke 1.166 ranjenih vojnika kojima je dijagnosticiran PTSP nakon ASR-a. Procijenili smo intenzitet boli, anksioznost/depresiju, kvalitetu života i prisutnost PTSP-a pri otpustu iz bolnice, te mjesec i tri mjeseca kasnije.

Rezultati: Identificirali smo značajne prediktore kronične boli u ranjenih vojnika, naglašavajući ulogu psiholoških čimbenika i kvalitete života. Visoke razine anksioznosti i depresije, simptomi PTSP-a i niske ocjene kvalitete života bili su snažno povezani s kroničnom boli, čak i nakon prilagodbe za tip ozljede i početni intenzitet boli. Prisutnost ASR-a, visoke ocjene na Bolničkoj ljestvici anksioznosti i depresije (HADS) i niske ocjene na Chabanovom upitniku kvalitete života (CQLS) identificirani su kao prediktori kronične boli, s posebno visokim rizikom (95,6%) za bolesnike koji zadovoljavaju ove kriterije. Naši rezultati ukazuju na značajnu povezanost između rizika od kronične boli i ASR-a, s ocjenama kvalitete života pri otpustu, mjesec i tri mjeseca nakon liječenja, što potvrđuje visoku prediktivnu točnost. Štoviše, neučinkovito liječenje boli korelira s neučinkovitim liječenjem PTSP-a.

Zaključak: Smanjena psihološka dobrobit vojnika nakon prostrijelnih i minsko-eksplozivnih ozljeda značajno povećava rizik od kronične boli. Rješavanje problema anksioznosti, depresije i simptoma PTSP-a, uz poboljšanje kvalitete života, moglo bi smanjiti vjerojatnost kronične boli i drugih negativnih zdravstvenih ishoda u vojnika s ratnim ozljedama.

Ključne riječi: Ukrajina; ratne ozljede; kronična bol; akutna stresna reakcija; posttraumatski stresni poremećaj

Background

Pain management on the battlefield has changed markedly in recent times and has become an essential component of treatment for the wounded in combat.[1,2] Most soldiers wounded on the battlefield experience pain, and more of them require analgesics for pain management than life-saving interventions.[3] Kuchyn et al. demonstrated that 70% of patients experience chronic pain following gunshot wounds, which impairs functionality and diminishes the quality of life.[4]

Mills et al. revealed the bidirectional relationship between chronic pain and negative emotional states, such as depression and anxiety, suggesting that chronic pain can both cause and result from poor mental health.[5] Furthermore, anxiety and fear related to pain are associated with a higher likelihood of developing chronic pain and experiencing poorer recovery outcomes.[5] Fear-avoidance behaviors and a lack of movement are also identified as independent risk factors for developing chronic pain.[5]

Recently, Kuchyn et al. demonstrated that acute stress reactions (ASR) increase the risk of developing chronic pain.[4] ASR is characterized by a prompt and diverse array of psychological and physiological symptoms in response to severe stress. The impact of this reaction varies in terms of the functional capabilities of individuals exposed to high-stress situations. While a person might recover swiftly, for professions demanding high performance under pressure, even a brief disruptions in functionality can heighten risks for the individual, their colleagues, and the overall mission.[6] After gunshot wounds, civilian patients are diagnosed with ASR in 75% of cases.[7] Additionally, evidence indicates that 56% of children are diagnosed with ASR following gunshot wounds.[7] Adler et al. reported that during combat-related events, ASR was observed in 51.7% of cases.[8]

Considering that ASR can disrupt the operations of a military unit, posing a risk to the combat team,[9] the investigation of ASR among soldiers during the war in Ukraine holds significant importance for the future treatment of such conditions. This issue may evolve into a broader concern with national implications over time. Furthermore, symptoms of ASR were strongly associated with a positive screening result for post-traumatic stress disorder (PTSD) in long-term treatment.[8]

Our studies on soldiers wounded during the war in Ukraine show that high postoperative pain intensity is associated with a higher risk of PTSD treatment failure among patients with gunshot wounds.[10] Among soldiers who sustained gunshot injuries during combat, 82.1% of PTSD treatment cases are complicated by chronic pain and treatment resistance.[10] Early pain treatment improves post-injury outcomes, whereas inadequate treatment contributes to higher rates of PTSD.[11] This link is also evident from data on the civilian population, where 82.5% of patients who endured a traumatic event were diagnosed with PTSD.[12] This proves that prompt and effective pain management enhances post-injury recovery, whereas inadequate pain treatment leads to elevated PTSD incidence.[11]

Our study aimed to analyze whether anxiety and

depression symptoms, PTSD, and quality of life affect the risk of chronic pain in soldiers with gunshot and mine explosive injuries sustained during combat tasks in the war in Ukraine. We hypothesized that severe anxiety, depression, PTSD, and poor quality of life would predict chronic pain in these injured military personnel.

Methods

The setting and the participants

This retrospective study was conducted at the National Military Medical Clinical Center "Main Military Clinical Hospital" in Kyiv, Ukraine. It analyzed medical records of soldiers wounded during the Anti-Terrorist Operation/Operation of the United Forces (ATO/OJF) in Eastern Ukraine from 2014 to 2021 (n=550) and the defense of Kyiv from February 24 to May 24, 2022, amid the full-scale Russian invasion (n=616).

Inclusion criteria were soldiers with gunshot or mine-explosive injuries, diagnosed with PTSD one month post-discharge, which was preceded by a diagnosis of ASR. Exclusion criteria were individuals with an ASR diagnosis without subsequent PTSD, those showing isolated symptoms of ASR/PTSD, those with a history of craniocerebral trauma before or during hostilities, and those enrolled in another study.

Ethics

The study was approved by the Bioethical Expertise and Ethics of Scientific Research Committee of the O. Bogomolets National Medical University (protocol #158 of May 23, 2022).

Procedures

After sustaining battlefield injuries, wounded soldiers were initially evacuated to a field medical team, which included at least one anaesthesiologist, one surgeon, one nurse anesthetist, and one operating room nurse strategically positioned near the front lines. The team's responsibility was to stabilize the patients' general condition before evacuating them to a military mobile hospital and, subsequently, to a military medical clinical center, a larger facility with advanced treatment and diagnostic capabilities. During the defense of Kyiv, all wounded soldiers were evacuated to the National Military Medical Clinical Center "Main Military Clinical Hospital" for treatment. In contrast, only a portion of the wounded soldiers from the Anti-Terrorist Operation/Operation of the United Forces (ATO/OJF) received treatment at this hospital. Following treatment completion, injured soldiers underwent rehabilitation (Figure 1).

Anesthetic support for surgical operations was provided through either general anesthesia or regional anesthesia, with some patients receiving sedation during regional anesthesia via a continuous infusion of 1% propofol at a rate of 1-4 mg/kg/h. Fentanyl solution (0.005%) was used for analgesia, with dosages varying during induction and maintenance. Regional anesthesia was conducted under ultrasound guidance, injecting 20-30 ml of 0.5% bupivacaine near the nerve roots. Postoperative analgesia included paracetamol, nonsteroidal anti-inflammatory drugs, opioids, and, if necessary, repeated peripheral blockades or catheterization for prolonged regional anesthesia using 0.25% bupivacaine solution (20-30 ml). Patients were evaluated by a psychiatrist at admission, discharge, and 1 and 3 months post-admission.

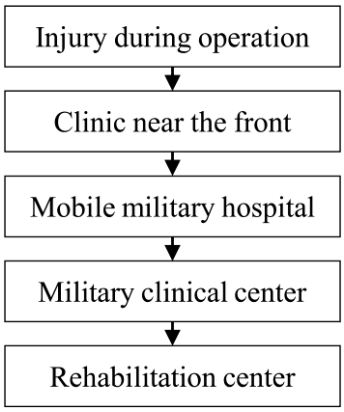

Figure 1 Roadmap of wounded Ukrainian military soldiers' treatment
Slika 1. Shema protokola liječenja ranjenih ukrajinskih vojnika

Data collection

All study data were derived from the patients' medical histories stored at the National Military Medical Clinical Center "Main Military Clinical Hospital" in Kyiv, Ukraine. The study's outcomes were pain intensity, anxiety and depression scores, and the quality of life of soldiers through psychometric assessments conducted at four different times, as depicted in Figure 2.

Prior to surgery, the anaesthetic risk was assessed in all soldiers according to the American Society of Anaesthesiologists (ASA) scale during admission to all stages of treatment.

A Numerical Rating Scale (NRS) was utilized upon admission and at 1 and 3 months post-discharge

to assess pain intensity. Pain intensity categories on a scale of 0 to 10 are 0 for no pain, 1-3 for mild pain, 4-6 for moderate pain, and 7-10 for severe pain.[13]

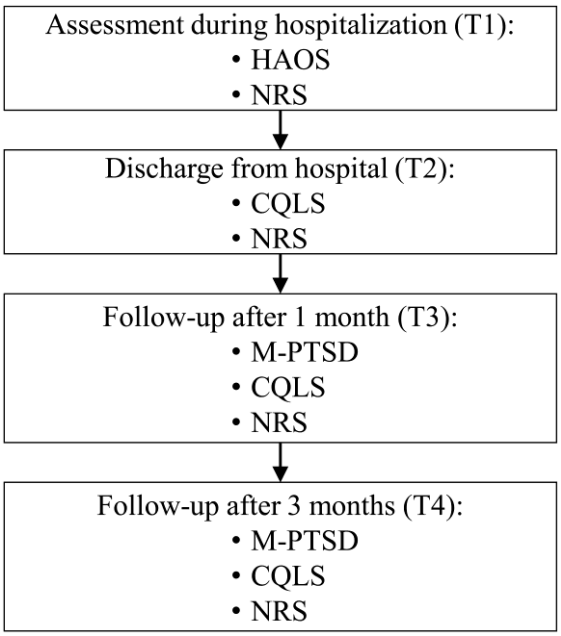

Figure 2 Assessment points. Abbreviations: HADS - Hospital Anxiety and Depression Scale; NRS – Numerical Rating Scale; M-PTSD - Mississippi Scale for Combat-Related Post-traumatic Stress Disorder; CQLS - Chaban Quality of Life Questionnaire

Slika 2. Vremenske točke mjerenja. Kratice: HADS - Bolnička skala anksioznosti i depresije; NRS – Numerička ocjenska skala; M-PTSD - Mississippi skala za posttraumatski stresni poremećaj povezan s borbenim djelovanjima; CQLS - Chaban upitnik kvalitete života

A psychiatrist made the diagnosis of Acute Stress Reaction (ASR) upon the admission of wounded soldiers to a military mobile hospital, based on clinical symptoms.

The Hospital Anxiety and Depression Scale (HADS) was used to quantify anxiety and depression, key components of the psycho-emotional state during an ASR.[14] The HADS, a validated instrument (α=0.94), comprises of 14 items divided into two subscales for anxiety (odd-numbered items) and depression (even-numbered items), with each item scored from 0 to 3. Scores range from 0 to 21 for each subscale, where higher scores indicate more severe symptoms.[15]

Post-Traumatic Stress Disorder (PTSD) was diagnosed by a psychiatrist one month following release from hospital and confirmed after 3 and 6 months, following standard procedures. To objectively assess PTSD severity, the Mississippi Scale for Combat-Related Post-traumatic Stress Disorder (M-PTSD), a 35-item screening tool for combat-related PTSD, was used.[10,16] M-PTSD demonstrates high internal consistency (α = .92), and its sensitivity (68% to 81%) and specificity (61% to 70%) render it a valuable screening tool for combat-related PTSD.[17] Scores range from 58-94, indicating good adaptability; 95-112, suggesting the presence of mental disorders; and 113-148, indicating PTSD.

The Chaban Quality of Life Questionnaire (CQLS)[18] was used to assess soldiers' quality of life at hospital discharge and 1 and 3 months post-discharge. This self-administered questionnaire consistsed of 10 items, each rated on an 11-point scale from 0 (not at all satisfied) to 10 (extremely satisfied), leading to a total score range from 0 to 100 points. The scoring criteria range from very low to very high quality of life, with the questionnaire demonstrating high internal consistency, reliability, and validity.[18]

Statistical analysis

The sample size calculation was performed using G*Power v.3.1.9.6 (19), while subsequent analyses were conducted using the EZR v.1.35 package, which is based on R statistical software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) (20). The distribution of data was assessed for normality using the Kolmogorov-Smirnov tests. Group comparisons were made using the Mann-Whitney U test. To explore the association between the risk of chronic pain (NRS > 0 after 3 months) and observed outcomes, both univariate and multivariate logistic regression models were utilized. These models were also applied to examine the relationship between the risk of not achieving the desired treatment effect and factor characteristics. The quality of these models was evaluated by the area under the ROC curve (AUC), and the 95% confidence interval (CI) for this measure was calculated.[21] The odds ratio (OR) and its 95% CI were determined using a direct selection method at an alpha level of 5% to quantify the impact of factor characteristics. The significance level was set at 0.05.

Results

A total of 2,000 medical records were initially pre-screened for compliance with the study's inclusion criteria. Of these, 1,166 records met the inclusion criteria. The remaining 834 records were excluded during the pre-screening process due to failure to meet the inclusion criteria or the presence of exclusion criteria, as illustrated in Figure 3.

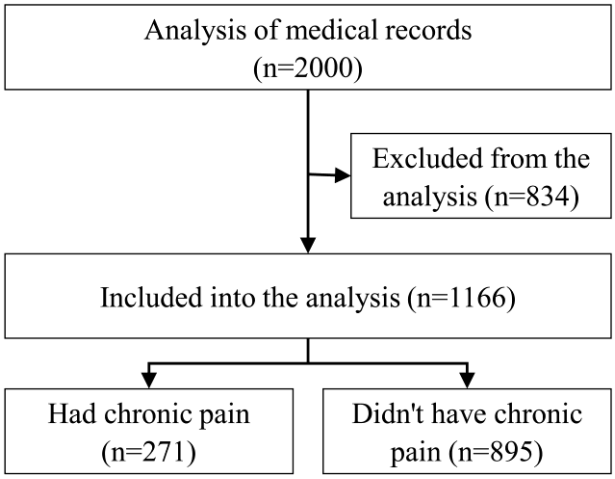

Figure 3 Flow diagram of medical records' selection
Slika 3. Dijagram tijeka odabira povijesti bolesti

All participants were males, with an average age of 32 years (range 25-39 years), an average height of 178 cm (range 176-182 cm), and an average weight of 78 kg (range 75-84 kg). Each underwent surgical procedures, with an average of 5 (range 4-7) procedures. The average number of wounds per soldier was 2 (range 1-3) across different anatomical body parts. The mean anesthetic risk, as assessed by the ASA score, was 3. The average duration of the surgical procedures was 115 minutes (range 105-130 minutes), and the average anesthesia duration was 125 minutes (range 110-150 minutes). Soldiers from both groups, i.e., those with or without chronic pain, showed no significant differences in socio-demographic characteristics or the diagnosis and treatment received (Table 1).

Table 1 General characteristics of patients with gunshot and mine-explosive injuries; median (Me), and interquartile range (QI-QIII) are presented.
Tablica 1. Opće karakteristike ranjenika s prostrijelnim i minsko-eksplozivnim ozljedama; prikazani su medijan (Me) i interkvartilni raspon (QI-QIII).

Variables / *Varijable*	Soldiers with gunshot wounds (n=786) *Vojnici s prostrijelnim ranama*	Soldiers with mine blast wounds (n=380) *Vojnici s ranama od eksplozije mina*	P value *P vrijednost*
Age (years)/*starost (godine)*	32 (25-39)	32 (26-39)	0.791
Height (cm) / *visina*	178 (176-182)	178.5 (176-182)	0.29
Weight (kg) /*težina*	78 (75-84)	79.5 (75-84)	0.148
No. of surgical operations *Broj opertivnih zahvata*	5 (5-7)	5 (4-7)	0.349
No. of injuries /*broj ozljeda*	2 (2-2)	2 (1-3)	0.767
ASA	3 (3-3)	3 (3-3)	0.563
Duration of anesthesia (min.) *Trajanje anestezije (min)*	125 (110-145)	125 (110-150)	0.786
Duration of surgical operations (min.) *Trajanje operativnih zahvata (min)*	115 (105-130)	115 (105-130)	0.369
NRS score upon admission *NRS uspjeh kod prijema*	7 (7-7)	7 (7-7)	0.106

Abbreviations: ASA - American Society of Anesthesiologists Classification; NRS - Numerical Rating Scale
Skraćenice: ASA -Američko društvo klasifikacije anesteziologa; NRS - Numerička skala ocjenjivanja

When the NRS score was above 0 after three months, it indicated that a positive effect had not been achieved (n=271 cases). Conversely, if the NRS score was 0 after three months, this denoted that a positive effect was achieved (n=895 cases).

The risk of chronic pain was reported as 23.2%, with a 95% confidence interval of 20.8%-25.8%. For factorial analysis, we utilized HADS scores from patients diagnosed with ASR by a psychiatrist upon admission to a military mobile hospital. Additionally, we included M-PTSD scores at 1 and 3 months post-discharge, as well as CQLS data at discharge and at 1 and 3 months after treatment.

Due to the significant correlation between the subscales of the HADS indicating a high probability of multicollinearity in the regression analysis, the scores of both HADS subscales were aggregated to form a single HADS variable for use in the regression analysis. No other variables were transformed. The outcomes of this analytical approach are presented in Table 2.

The analysis of univariate logistic regression

models for predicting the risk of chronic pain in wounded soldiers revealed several significant predictors. The HADA coefficient (the change in the log odds of the outcome for a one-unit increase in the predictor variable) was 1.69±0.34, indicating a strong association with chronic pain, with a significance level of <0.001 and an odds ratio (OR) of 5.41 (95% CI: 2.77-10.6). The M-PTSD showed a significant association at 3 months post-injury (0.085±0.013, significance: p<0.001, OR: 1.09, 95% CI: 1.06-1.12), but not at 1 month. The CQLS at discharge and 1 and 3 months post-injury were strongly inversely associated with chronic pain, showing coefficients of –2.45±0.28, –1.63±0.11, and –1.64±0.11 respectively, all with significance levels of <0.001. These results suggest that higher levels of anxiety, depression, and PTSD symptoms, along with lower quality of life, are significant predictors of chronic pain in this population. Figure 4 illustrates the receiver operating characteristic (ROC) curve for predicting chronic pain risk based on M-PTSD data 3 months after treatment.

Table 2 Coefficients of univariate logistic regression models for predicting the risk of pain chronicity in soldiers with gunshot and mine-explosive injuries.
Tablica 2. Koeficijenti univarijatnih logističkih regresijskih modela za predviđanje rizika od kroničnosti boli u vojnika s prostrijelnim i minsko-eksplozivnim ozljedama.

Factor variable ***Faktorska varijabla***	**Coefficient, b±m** ***koeficijent***	**Significance level** ***Razina značaja***	**OR (95% CI)**	**AUC (95% CI)**
HADS	1.69±0.34	**<0.001**	5.41 (2.77-10.6)	0.98 (0.97-0.99)
M-PTSD after 1 month *Nakon 1 mjeseca*	0.006±0.011	0.579	–	–
M-PTSD after 3 months *Nakon 3 mjeseci*	0.085±0.013	**<0.001**	1.09 (1.06-1.12)	0.65 (0.62-0.68)
CQLS at discharge *Kod otpusta*	–2.45±0.28	**<0.001**	0.09 (0.05-0.15)	0.98 (0.97-0.99)
CQLS after 1 month *Nakon 1 mjeseca*	–1.63±0.11	**<0.001**	0.20 (0.16-0.25)	0.98 (0.97-0.99)
CQLS after 3 months *Nakon 3 mjeseci*	–1.64±0.11	**<0.001**	0.19 (0.16-0.24)	0.98 (0.97-0.99)

Abbreviations: HADS - Hospital Anxiety and Depression Scale; M-PTSD - Mississippi Scale for Combat-Related Post-traumatic Stress Disorder; CQLS - Chaban Quality of Life scale; OR – Odds Ratio; AUC – area under curve.
Skraćenice: HADS – *skala bolničke napetosti i depresije:* M-PTSD – *Mississippi skala za Posttraumatski stresni poremećaj povezan s borbom; CQLS – Chaban skala kvalitete života; OR – Odds Ratio*; *AUC – područje ispod krivulje.*

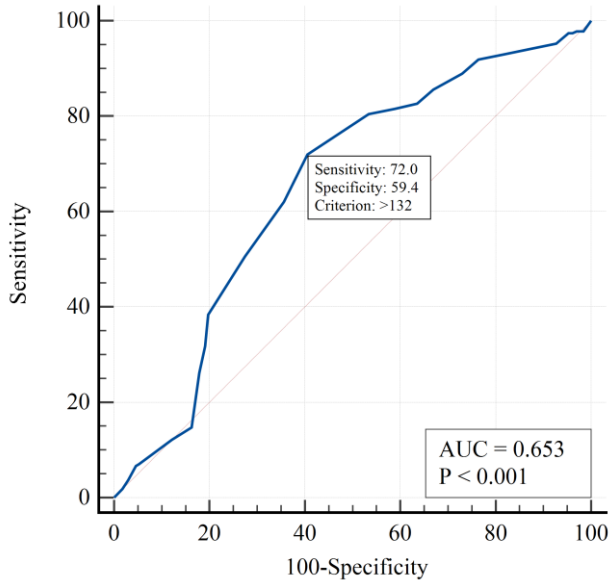

Figure 4 Receiver Operating Characteristic (ROC) curve predicts pain chronicity risk according to M-PTSD 3 months after inpatient treatment in the military medical clinical center. Abbreviation: AUC – Area under curve.
Slika 4. ROC krivulja predviđa rizik kroničnosti boli prema M-PTSP-u 3 mjeseca nakon bolničkog liječenja u vojnom medicinskom kliničkom centru. Kratica: AUC – Površina ispod krivulje.

When the analysis was adjusted for the NRS pain intensity at admission and the type of injury (gunshot and mine-explosive injuries), similar trends were observed. The HADS coefficient increased slightly to 1.81±0.36 with a significance level of <0.001 and an OR of 6.10 (95% CI: 3.03–12.3). The M-PTSD at 3 months remained significant with a similar coefficient (0.086±0.013, significance: <0.001, OR: 1.09, 95% CI: 1.06–1.12). The CQLS scores at discharge, 1 month, and 3 months post-injury showed even stronger inverse associations with coefficients of –2.52±0.29, –1.71±0.13, and –1.73±0.13 respectively, all with significance levels of <0.001. For each model, an increase in the risk of pain chronicity was found regardless of the injury type. These adjusted models reinforce the importance of

psychological factors and quality of life in predicting chronic pain, highlighting the potential benefits of targeted interventions in these areas for wounded soldiers. The results of this analysis are presented in Table 3.

Table 3 Coefficients of logistic regression models predicting the risk of pain chronicity when standardized by Numerical Rating Scale (NRS) pain intensity at admission and type of injury in soldiers with gunshot and mine-explosive injuries.
Tablica 3. Koeficijenti logističkih regresijskih modela za predviđanje rizika od kroničnosti boli kada se standardiziraju prema intenzitetu boli na Numeričkoj ocjenskoj skali (NRS) pri prijmu i vrsti ozljede u vojnika s prostrijelnim i minsko-eksplozivnim ozljedama.

Factor variable ***Faktorska varijabla***	**Coefficient, b±m** ***koeficijent***	**Significance level** ***Razina značaja***	**OR (95% CI)**	**AUC (95% CI)**
HADS	1.81±0.36	**<0.001**	6.10 (3.03–12.3)	0.99 (0.99–1.00)
M-PTSD after 1 month *Nakon 1 mjeseca*	0.005±0.012	0.652	–	0.55 (0.52–0.58)
M-PTSD after 3 months *Nakon 3 mjeseci*	0.086±0.013	**<0.001**	1.09 (1.06–1.12)	0.65 (0.62–0.68)
CQLS at discharge *Kod otpusta*	–2.52±0.29	**<0.001**	0.08 (0.05–0.14)	0.98 (0.97–0.99)
CQLS after 1 month *Nakon 1 mjeseca*	–1.71±0.13	**<0.001**	0.18 (0.14–0.23)	0.98 (0.97–0.99)
CQLS after 3 months *Nakon 3 mjeseci*	–1.73±0.13	**<0.001**	0.18 (0.14–0.23)	0.98 (0.97–0.99)

Abbreviations: HADS - Hospital Anxiety and Depression Scale; M-PTSD - Mississippi Scale for Combat-Related Post-traumatic Stress Disorder; CQLS - Chaban Quality of Life scale; OR – Odds Ratio; AUC – area under curve.
Skraćenice: HADS *– skala bolničke napetosti i depresije:* M-PTSD *– Mississippi skala za posttraumatski stresni poremećaj povezan s borbom; CQLS – Chaban skala kvalitete života; OR – Odds Ratio*; *AUC – područje ispod krivulje.*

Discussion

Our analysis emphasizes the impact of psychological distress, as measured by HADS, and the presence of PTSD symptoms in patients previously diagnosed with ASD, particularly three months post-injury, on the likelihood of the chronic pain outcome. Additionally, the significant negative relationship between the quality of life measures (CQLS) at discharge and subsequent evaluations with chronic pain emphasizes the importance of addressing psychological well-being and enhancing quality of life as pivotal components of post-injury care. These findings suggest that interventions aimed at reducing anxiety, depression, and PTSD symptoms, along with efforts to improve quality of life, could be crucial in mitigating the risk of adverse outcomes in affected populations regardless of the type of sustained injury.

Life-saving measures greatly increase survival rates and decrease complications in injured soldiers. Although pain management is essential for improving results, the frequent under-treatment of pain and its effect on the effectiveness of these life-saving interventions is not well-studied.[22]

Chronic pain significantly impacts the readiness for return to duty among soldiers following rehabilitation. Only 75% of these soldiers reported feeling fully mission-capable.[23] Also, nearly 38% experienced a time-loss injury within one year of returning to duty.[23] Moreover, nearly all soldiers demonstrated at least one dysfunctional movement pattern.[23] These findings underscore the urgent need for enhanced rehabilitation strategies to improve mission readiness and minimize the risk of future injuries in soldiers.[23]

Engagement in jobs with high risks may lead to the development of ASR. ASR can interfere with the functioning of a military unit and pose a danger to the team in the context of a combat mission,[9] so studying this issue in soldiers during the war in Ukraine was a priority for us.

We know that the early treatment of pain following trauma improves long-term outcomes, whereas inadequately managed pain can lead to a higher incidence of PTSD (1) and poorer outcomes in PTSD treatment.[11]

The most commonly reported mental health issues among US military veterans were PTSD and depression. Studies focusing on soldiers deployed to Iraq and Afghanistan have highlighted issues within the military healthcare system regarding the management of chronic pain, which is associated with adverse outcomes following transitions to subsequent treatment stages. Identified issues included alcohol and drug use, suicidal ideation, intentional self-harm,

and all-cause mortality. Additionally, research suggests that a multimodal approach to treating chronic pain, which includes the use of opioids, may mitigate the risk of severe adverse outcomes linked to chronic pain and opioid utilization.[24-26]

It was estimated that between 14% and 16% of service members who had served in non-combat roles in Afghanistan or Iraq suffered from PTSD or depression.[27] Therefore, understanding the relationship between military service and a patient's physical and mental health is crucial for improving the quality of care and could potentially save lives.[27]

Some studies indicate that group psychotherapy has an impact on the treatment of PTSD in patients with combat trauma.[28] There is also evidence of a genetic predisposition to PTSD in Vietnam War veterans.[29] However, we were unable to find published studies that demonstrate the association of chronic pain with ASR and PTSD.

In soldiers who sustained gunshot wounds during combat operations, 82.1% of treatment cases of PTSD are associated with chronic pain and treatment resistance.[10] The results of another study[12] show that among civilian patients who have experienced a traumatic event, PTSD is diagnosed in 82.5% of cases. It is necessary to continue researching the issue of chronic pain in soldiers after injuries, as this can improve the long-term outcomes of PTSD treatment and improve the quality of life of soldiers after hospitalization.

While the study highlights important predictors of chronic pain in wounded soldiers, it is essential to acknowledge its limitations. Firstly, the retrospective nature of the study design introduces inherent biases and limitations in data collection. Secondly, the diagnosis of conditions such as PTSD and ASR presents challenges, which were addressed through efforts to standardize diagnostic procedures as much as possible. Despite these efforts, variability in diagnosis may still affect the study's outcomes. Lastly, the findings' applicability is primarily within the context of military medicine, limiting their generalizability. However, it is speculated that the results could extend to professions requiring high performance under pressure, suggesting potential broader implications.

Chronic pain, ASR, and PTSD significantly reduce soldiers' quality of life, posing a complex challenge in military medicine. Despite the high expertise of military physicians, especially noted during the Russian aggression in Ukraine, pain management outcomes are unsatisfactory, signaling a potential national healthcare crisis. This crisis stems not only from the high prevalence of chronic pain among veterans but also from the co-occurrence of PTSD, worsening their well-being.

Observations indicate that soldiers with severe anxiety and depression after ASR are more likely to develop chronic pain, with the transition possibly beginning at the injury's onset. This suggests a direct link between initial trauma and chronic pain, underscoring the need for in-depth research into how different types of injuries affect pain's chronicity.

Data shows an inverse relationship between chronic pain severity and soldiers' quality of life, with PTSD's association with chronic pain highlighting the need for integrated treatment approaches. Therefore, it is crucial to focus research on improving pain management and PTSD interventions, addressing both symptoms and their root causes to enhance soldiers' lives and address wider health and security issues.

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Prehrambeni unos i koncentracija joda u urinu kod trudnica s područja istočne Hrvatske

Dietary and urinary iodine in pregnant women from Eastern Croatia

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Sažetak

Uvod: Jod je mikronutrijent neophodan za održanje zdravlja, a štitnjača ima ključnu ulogu u metabolizmu joda. Prenizak i previsok unos joda imaju negativan utjecaj na funkciju štitnjače, te je adekvatan prehrambeni unos joda iznimno važan u kritičnim razdobljima života, među kojima se ističe trudnoća.

Cilj i metode: Cilj ovoga presječnog opažajnog istraživanja bio je analizirati prehrambeni unos joda i koncentraciju joda u urinu, koja je najbolji indikator prehrambenog unosa joda, kod trudnica s područja istočne Hrvatske pred termin poroda. Istraživanje je obuhvatilo 24 trudnice koje su zaprimljene na Kliniku za ginekologiju i opstetriciju Kliničkog bolničkog centra Osijek do poroda.

Rezultati: Medijan prehrambenog unosa joda procijenjen je na 569,94 µg/dan, što je 2,8 puta više od preporučenog unosa od 200 µg/dan, a kod 10/24 trudnice (42 %) procijenjen je prehrambeni unos joda viši od maksimalno preporučenih 600 µg/dan. Osim soli, najveći doprinos dnevnom unosu joda potječe iz jogurta, kravljeg mlijeka, suhomesnatih proizvoda, jaja, bijelog kruha i oslića, što je očekivano obzirom na tradicionalne prehrambene obrasce istočne Hrvatske. Medijan koncentracije joda u urinu je 134,63 µg/L, a čak je 75 % trudnica imalo koncentraciju joda u urinu ispod minimalno preporučenih 150 µg/L. Prehrambeni unos joda i koncentracija joda u urinu nisu statistički značajno korelirali, no prehrambeni unos joda je bio viši kod mlađih trudnica (ρ=-0,490), te kod pretilih, u odnosu na trudnice povećane tjelesne mase (p=0,022) i normalne tjelesne mase (p=0,037) koje su imale najvišu koncentraciju joda u urinu.

Zaključak: Prevalencija bolesti štitnjače je u porastu u svim fazama života, a trudnoća je kritično razdoblje kada je uloga joda još izraženija. Rezultati ovoga istraživanja ukazuju na raskorak između statusa joda (promatranog kroz koncentraciju joda u urinu) i prehrambenog unosa joda; unatoč visokom prehrambenom unosu joda, koncentracija joda u urinu većine trudnica je ispod minimalno preporučene. Potrebno je provesti analize sadržaja joda u hrani, posebice različitih tipova soli s ciljem kreiranja baze podataka s točnim podacima o sadržaju joda, što bi omogućilo točniju procjenu prehrambenog unosa joda. To je preduvjet za osmišljavanje javnozdravstvenih aktivnosti usmjerenih na unos joda prehranom i zdravlje štitnjače.

Ključne riječi: jod; trudnoća; prehrana

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Summary

Introduction: Iodine is a micronutrient critical for health, and the thyroid gland plays a key role in iodine metabolism. Too low and too high intake negatively impact the functioning of the thyroid, making adequate dietary iodine during critical life stages especially important, particularly during pregnancy.

Aim and Methods: This cross-sectional observational study aimed to analyze dietary and urinary iodine in pregnant women at term from Eastern Croatia. The research encompassed 24 pregnant women admitted to the Department of Gynecology and Obstetrics, Osijek University Hospital Centre, until delivery.

Results: Median estimated dietary iodine was 569.94 µg/day and was 2.8 times higher than the recommended 200 µg/day consumption. Ten pregnant women (42 %) had an estimated dietary iodine consumption higher than the maximum recommended 600 µg of iodine per day. Besides salt, the biggest contribution to the daily iodine came from yogurt, cow's milk, dry meat, eggs, white bread, and hake, which was expected due to traditional dietary patterns in Eastern Croatia. Median urinary iodine was 134.63 µg/L, and 75 % of pregnant women had urinary iodine below the minimum recommended value of 150 µg/L. Dietary and urinary iodine did not correlate statistically significantly. Still, dietary iodine was higher in younger women (ρ=-0.490), while obese pregnant women had the highest urinary iodine in comparison to overweight (p=0.022) and normal-weighted (p=0.037) pregnant women.

Conclusion: The prevalence of thyroid disease is rising in all life stages, and pregnancy is the critical period when iodine's importance is even more emphasized. The results of this research show discrepancy between iodine status (urinary iodine) and dietary iodine consumption. Despite high dietary iodine consumption, the majority of pregnant women had urinary iodine values below the minimum recommended. It is necessary to conduct a chemical analysis of foods rich in iodine, especially various types of salt, to create a database with the exact iodine content, which is a prerequisite for a more precise estimation of dietary iodine consumption. This is imperative for all future public health actions focused on dietary iodine and thyroid health.

Key words: Iodine; Pregnancy; Diet

Uvod

Jod je mikronutrijent i element u tragovima od ključne važnosti za zdravlje i dobrobit svih ljudi. U metabolizmu joda središnju ulogu ima štitnjača.[1] Hormoni štitnjače tiroksin (T_4) i trijodtironin (T_3), čiji je jod sastavni dio, reguliraju važne biokemijske reakcije, uključujući sintezu proteina i enzimsku aktivnost, a neophodni su za pravilan razvoj kostura i središnjeg živčanog sustava fetusa i dojenčadi. Unos dovoljne količine joda važan je za sve dobne skupine, ali posebno za dojenčad i trudnice.[2,3]

Potrebe za jodom u trudnoći povećavaju se za otprilike 50 %, što ovu populaciju potencijalno dovodi do stanja nedostatka joda.[4] Nedostatak joda u trudnoći vodeći je uzrok mentalne retardacije[4]i učestalijih poremećaja pažnje i hiperaktivnosti[5] u djece u cijelom svijetu. Učinci ozbiljnog nedostatka joda na razvoj fetusa dobro su poznati, dok to nije slučaj s učincima blagog do umjerenog nedostatka joda. Pretpostavlja se da blagi nedostatak joda u trudnoći može rezultirati nižim kvocijentom inteligencije kod djece, ali i povećanjem rizika od perinatalnih komplikacija.[4]

Teški nedostatak joda danas je rijedak zbog jodiranja soli koje je široko rasprostranjeno, ali blagi do umjereni nedostatak joda zabilježen je u velikom broju razvijenih zemalja. Procjenjuje se da je više od trećine svjetske populacije izloženo nedostatnom unosu joda.[6] Upravo je sol najvažniji izvor joda u svakodnevnoj prehrani,[7] no s ciljem prevencije kardiovaskularnih bolesti preporučuje se ograničenje unosa soli, što može rezultirati disbalansom u metabolizmu joda.[4,8] Morska riba, školjke i morske alge najbogatije su jodom,[9] potom jaja, mlijeko i mliječni proizvodi, žitarice, zeleno lisnato povrće, soja, sezam, češnjak i repa.[10-12] Jodiranje soli pokazalo se najisplativijom javnozdravstvenom intervencijom kojom se poboljšavaju zdravstveni ishodi trudnica, te dojenčadi i svih populacijskih skupina.[13]

Cilj ovoga istraživanja bio je usporediti prehrambeni unos joda s koncentracijom joda u urinu trudnica pred termin poroda, uzimajući u obzir dob, status, uhranjenosti i funkciju štitnjače.

Ispitanici i metode

Provedeno je presječno opažajno istraživanje koje je odobrilo Etičko povjerenstvo Kliničkog bolničkog centra Osijek (Broj: R1/13151/2021 od 6. 10. 2021. godine). Odabrane su trudnice koje su zaprimljene na Kliniku za ginekologiju i opstetriciju Kliničkog bolničkog centra Osijek do poroda. Od ukupno 27 trudnica koje su potpisale suglasnost za sudjelovanje, tri su zbog nepotpunog popunjavanja upitnika

isključene iz konačne analize.

Antropometrijska mjerenja

Po prijamu na Kliniku, trudnicama su izmjerene tjelesna masa i visina (medicinska vaga s integriranim stadiometrom, Seca, UK), na osnovu čega je izračunat indeks tjelesne mase (ITM) koji je potom uspoređen s kategorijama stanja uhranjenosti.[14]

Upitnici i izračun prehrambenog unosa joda

Trudnice su ispunile opći upitnik o sociodemografskim karakteristikama i semikvantitativni upitnik o učestalosti konzumacije hrane koja je najvažniji prehrambeni izvor joda, uključujući tip(ove) soli.

Upitnik o sociodemografskim karakteristikama uključivao je opća pitanja (godina rođenja, bračni status, stručna sprema, zaposlenje, prihodi i sl.), kao i pitanja o zdravstvenom stanju, te općim prehrambenim i životnim navikama.

Semikvantitativnim upitnikom koji se odnosio na razdoblje od zadnjih mjesec dana ispitana je konzumacija ukupno 49 namirnica, među kojima su bile kuhinjska i/ili morska sol, morske ribe i morski plodovi, različiti mesni proizvodi, jaja, mlijeko i mliječni proizvodi. Ponuđena učestalost konzumacije bila je: dva i više puta na dan, jednom na dan, tri do pet puta tjedno, dva do tri puta tjedno, jednom tjedno, dva do tri puta mjesečno, jednom mjesečno i rjeđe. Bile su ponuđene srednje veličine porcija (npr. šalica, kriška, žlica i/ili grami, ovisno o hrani), a one su na temelju njih procjenjivale jesu li konzumirale malu, srednju ili veliku porciju ponuđenih namirnica. Na osnovi procjene učestalosti konzumacije i veličine porcije izračunata je dnevna konzumacija ponuđenih namirnica na osnovu koje se potom računao prehrambeni unos joda. Dobivena vrijednost odgovara procijenjenom prehrambenom unosu joda. Sadržaj joda u pojedinim namirnicama preuzet je iz Frida tablica.[15]

Mjerenje koncentracije joda u urinu

U uzorcima jutarnjeg urina, koji je prikupljen dan nakon zaprimanja na Kliniku od trudnica koje su potpisale informirani pristanak, određena je koncentracija joda spektrofotometrijskom metodom.[16] Koncentracija joda u urinu smatra se dobrim biomarkerom prehrambenog unosa joda s obzirom na to da se gotovo 90 % svog joda unesenog prehranom izlučuje urinom. Urin se kuha s amonijevim persulfatom, nakon čega nastali jodid reducira amonij cerijev sulfat od žutog obojenja do obezbojenja, ovisno o količini prisutnog jodida. Koncentracija joda izražava se u µg/L urina, a izračunava se preko standardne krivulje koja se radi u rasponu od 0 do 300 µg I_2/L. Očitanje apsorbancije radi se na valnoj dužini od 420 nm.

Metoda je provedena po sljedećem postupku: otpipetira se 250 µL urina u epruvetu, te doda 1 mL 1 M otopine amonij persulfata, zatvori se epruveta i stavi kuhati 60 minuta na 100 °C na vodenoj kupelji. Nakon toga se ohladi i u epruvetu se doda 2,5 mL reagensa arsenske kiseline, te se ostavi stajati 15 minuta. Potom se doda 300 µL otopine cerij amonij sulfata i ostavi stajati 30 minuta, nakon čega se očita apsorbancija na 420 nm. Uzorci se analiziraju u paraleli.

Isti postupak se primjenjuje i kod izrade kalibracijske krivulje, ali se uzima 250 µL otopine svakog razrjeđenja. Štok otopina za izradu razrjeđenja za kalibracijsku krivulju sadrži 16,8 mg KIO_3/L vode, te se naprave razrjeđenja u rasponu od 0 do 300 µg/L.

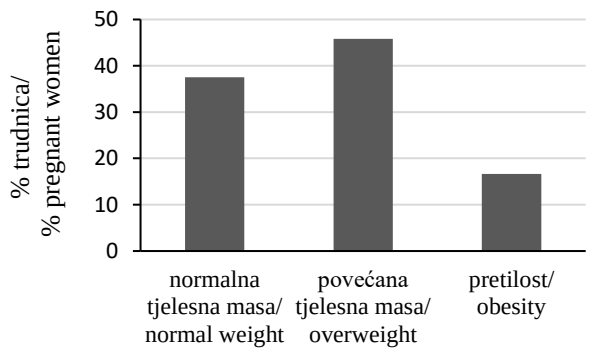
Obrada rezultata

Statistička analiza provedena je pomoću programskog sustava Statistica, inačice 14 (StatSoft), dok je grafička obrada podataka odrađena pomoću MS Office Excel tablice (Microsoft).

Zbog malog broja ispitanika korišteni su neparametrijski statistički testovi uz odabranu razinu statističke značajnosti $\alpha = 0,05$. Numeričke varijable prikazane su kao medijan i interkvartilni raspon, uz prikaz raspona minimalne i maksimalne vrijednosti, osim ako nije drugačije navedeno. Kategoričke varijable prikazane su kao apsolutne frekvencije. Za ispitivanje korelacija numeričkih varijabli korišten je Spearmanov test, dok je za usporedbu numeričkih varijabli između nezavisnih skupina korišten Mann-Whitneyev U test.

Rezultati

Prosječna dob trudnica bila je 33,0 ± 4,6 godina (27 do 44 godine). Ukupno je 13 prvorotkinja, a kod devet trudnica se radilo o drugoj dvije o trećoj trudnoći. Kod šest trudnica, trudnoća je ostvarena postupcima medicinski pomognute oplodnje. Prosječan ITM trudnica prije poroda iznosio je 27,5 ± 5,2 kg/m^2 (20,4 do 45,2 kg/m^2), a sve su navele kako su se udebljale tijekom trudnoće. Najviše ih spada u kategoriju povećane tjelesne mase (45,8 %), a dodatno ih je 16,6 % pretilo u trenutku poroda (jedna trudnica je imala treći stupanj, a tri trudnice prvi stupanj pretilosti) (Slika 1.).



Slika 1. Status uhranjenosti trudnica
Figure 1 Nourishment status of pregnant women

Ukupno pet trudnica ima bolest štitnjače (20,8 %), dvije autoimunu bolest štitnjače (Hashimotov tireoiditis) koji je bio prisutan i prije trudnoće, dok je trima dijagnosticirana hipotireoza u trudnoći. Vrijednosti hormona štitnjače prikazane su u Tablici 1. Medijan vrijednosti TSH iznosi 1,92 mU/L, što je unutar referentnog raspona (0,27 – 4,20 mU/L), dok je vrijednost T_3 iznad referentnog raspona (1,3 – 3,1 nmol/L), a T_4 značajno ispod referentnog raspona (66 – 181 nmol/L).

Tablica 1. Vrijednosti hormona štitnjače kod trudnica
Table 1 Thyroid hormone values in pregnant women

	n	Sr. vrij. ±SD *Mean ±SD*	Medijan (25 % - 75 %) *Median (25 % - 75 %)*	Raspon *Range*
TSH (mU/L)	13	1,78 ±0,6	1,92 (1,38–2,3)	0,74 – 2,59
T_3 (nmol/L)	12	4,01 0,5	3,88 (3,66–4,27)	3,34 – 5,00
T_4 (nmol/L)	13	12,04 ±1,9	11,77 (10,28–13,41)	9,62 – 15,3

TSH – tiroidni stimulirajući hormon; T_3 – trijodtironin; T_4 – tiroksin/*TSH – thyroid stimulating hormone; T3 – triiodothyronine; T4 – thyroxine*

Prehrambeni unos joda trudnica iznosio je 569,94 µg/dan (Tablica 2.). Najniži prehrambeni unos zabilježen je kod tr18 161,39 µg/dan, dok je tr27 prehranom unosila čak 1865,46 µg/dan. Treba napomenuti kako niti jedna od trudnica koje su sudjelovale u ovom istraživanju nije koristila dodatke prehrani koji sadrže jod.

Morsku sol konzumira 58 % trudnica (42 % ne konzumira), dok kuhinjsku (kamenu) sol koristi polovina trudnica (50 % ih ne konzumira). Doprinos pojedine hrane dnevnom unosu joda prikazan je na Slici 2. Najveći doprinos dnevnom unosu joda je iz jogurta (107,7 µg), kravljeg mlijeka (75,5 µg), suhomesnatih proizvoda (42,7 µg), jaja (18 µg), bijelog kruha (16,8 µg) i oslića (16,6 µg).

Tablica 2. Dnevni unos joda i koncentracija joda u urinu trudnica
Table 2 Daily dietary intake of iodine and urinary iodine concentrations in pregnant women

Trudnica *Pregnant woman*	Jod (µg) *Dietary iodine (µg)*/ Urinarni jod (µg/L) *Urinary iodine (µg/L)*	Trudnica *Pregnant woman*	Jod (µg) *Dietary iodine (µg)*/ Urinarni jod (µg/L) *Urinary iodine (µg/L)*
tr1	632,61/ 109,82	tr13	342,29/ 99,6
tr2	207,70/ 153,38	tr14	764,30/ 173,77
tr3	610,54/ 170,04	tr15	576,40/ 139,04
tr4	418,51/ 66,43	tr16	621,83/ 145,16
tr5	525,61/ 124,04	tr17	1228,91/ 121,82
tr6	341,53/ 126,77	tr18	161,39/ 136,49
tr7	1007,56/ 105,38	tr19	563,48/ 31,08
tr8	835,83/ 107,21	tr20	248,17/ 170,27
tr9	242,32/ 143,10	tr24	778,27/ 133,99
tr10	601,71/ 66,27	tr25	462,90/ 106,71
tr11	587,63/ 186,66	tr26	429,43/ 135,27
tr12	521,70/ 163,43	tr27	1865,46/ 139,93
Medijan/ *Median*	25% – 75%	Min	Max
569,94/ 134,63	380,40 – 698,45/ 106,96 – 149,27	161,39/ 31,08	1865,46/ 186,66

Koncentracija joda u urinu trudnica iznosila je 134,63 µg/L (Tablica 2.). Najnižu vrijednost imala je tr19, samo 31,08 µg/L a najvišu tr11 186,66 µg/L.

Nije utvrđena statistički značajna korelacija između koncentracije joda u urinu i prehrambenog unosa joda. Ove dvije varijable nisu se razlikovale s obzirom na dijagnozu bolesti štitnjače, naviku pušenja, pijenje alkohola ili korištenje dodataka prehrani. Također, nije utvrđena razlika s obzirom na porod, no trudnice kod kojih je trudnoća ostvarena postupcima medicinski pomognute oplodnje imale su

statistički značajno veću koncentraciju joda u urinu u usporedbi s trudnicama koje su spontano začele (p=0,0069).

Statistički značajna negativna korelacija utvrđena je između koncentracije joda u urinu i vrijednosti TSH (ρ=-0,637), dok prehrambeni unos joda negativno korelira s dobi ispitanica (ρ=-0,490) (Tablica 3.).

Utvrđena je statistički značajna razlika u koncentraciji joda u urinu s obzirom na kategoriju stanja uhranjenosti (Tablica 4.). Pretile trudnice imale su najvišu koncentraciju joda u urinu u usporedbi s onima povećane tjelesne mase (p=0,022) i onima koje su normalnog statusa uhranjenosti (p=0,037).

Tablica 3. Spearmanovi rangovi korelacija između koncentracije joda u urinu, prehrambenog unosa joda, dobi, indeksa tjelesne mase i hormona štitnjače
Table 3 Spearman's correlation coefficients between urinary iodine, dietary iodine, age, BMI and thyroid hormones

	Urinarni jod (μg/L) *Urinary iodine (μg/L)*	Prehrambeni unos joda (μg/dan) *Dietary iodine (μg/day)*
Dob (godine)/ *Age (years)*	0,231	-0,490*
ITM (kg/m^2)/ *BMI (kg/m^2)*	0,268	0,005
TSH (mU/L)	-0,637*	-0,165
T_3 (nmol/L)	0,011	-0,406
T_4 (nmol/L)	0,143	-0,374

ITM – indeks tjelesne mase; TSH – tiroidni stimulirajući hormon; T_3 – trijodtironin; T_4 - tiroksin
BMI – Body Mass Index; TSH – thyroid stimulating hormone; T3 – triiodothyronine; T4 – thyroxine
*statistički značajno kod p<0,05/ **statistically significant at p<0.05*

Tablica 4. Koncentracija joda u urinu s obzirom na kategoriju stanja uhranjenosti trudnica
Table 4 Urinary iodine concentrations in pregnant women according to their nourishment status

Kategorija stanja uhranjenosti *Nourishment status*	Urinarni jod (μg/L)/ *Urinary iodine (μg/L)*		
	Medijan/ *Median*	25% - 75%	Min - Maks
Normalno uhranjene/ *Normal weight*	135,27	106,71 – 139,93	66,27 – 163,43
Povećana tjelesna masa/ *Overweight*	121,82	99,60 – 139,04	31,08 – 170,27
Pretile /*Obese*	150,46	144,13 – 180,21	143,10 – 186,66

Rasprava

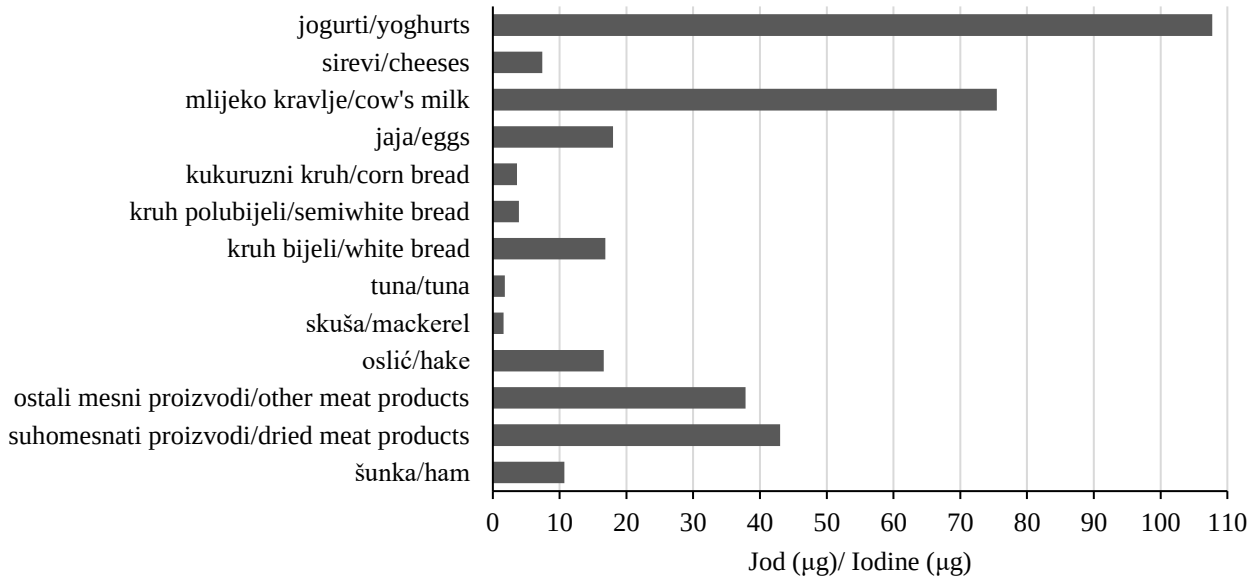
Nedostatak joda globalni je problem, a kao jedno od najučinkovitijih rješenja pokazalo se jodiranje soli koja se koristi u kućanstvima.[13] Odnos između funkcije štitnjače i unosa joda u obliku je slova U, pa disfunkciju štitnjače mogu jednako izazvati i neadekvatan i prekomjeran unos joda.[17] Mentalna retardacija djeteta, bolesti štitnjače, povećana smrtnost novorođenčadi i dojenčadi, usporavanje razvoja središnjeg živčanog sustava u djece i neplodnost odrasle populacije, proporcionalni su nedostatnom unosu joda.[18] Kada se tome doda i problem pretilosti u trudnoći koji je danas u ginekologiji i opstetriciji jedan od najvećih izazova, jasno je da se radi o problemu od javnozdravstvenog interesa. Pretilost, ne samo da je sama za sebe problem, već je često praćena drugim kroničnim bolestima s kojima danas, zbog sve više starosne dobi u trenutku začeća, žene sve češće započinju trudnoću.[19,20] Povišen ITM majke u trenutku poroda povezan je s brojnim nepovoljnim ishodima poput preeklampsije, eklampsije, prijevremenog i kasnog poroda, induciranog poroda, makrosomije, poroda carskim rezom i produljenim postporođajnim krvarenjem. Osim toga, djeca rođena od majki koje su u trudnoći imale povišen ITM imaju veći rizik od pretilosti u djetinjstvu, kao i rizik od koronarnih bolesti srca, dijabetesa tipa 2 i astme.[21] Unatoč malom broju trudnica, rezultati ovoga istraživanja potvrđuju sve višu starosnu dob trudnica, problem povećane tjelesne mase i pretilosti, kao i prisutnost drugih komorbiditeta, u ovom slučaju bolesti štitnjače.

Prema dostupnim rezultatima istraživanja, do sada u Hrvatskoj nije provedeno istraživanje koje je istovremeno analiziralo prehrambeni unos i koncentraciju joda u urinu trudnica.

Prosječan prehrambeni unos joda u trudnica (Tablica 2.) koje su sudjelovale u ovom istraživanju je 2,8 puta viši od preporučenog.[10] Kada se uzme u obzir maksimalno dopušteni unos joda za trudnice i dojilje koji iznosi 600 μg/dan,[22] čak 10/24 (42 %) trudnica premašuje taj unos. Ipak, treba uzeti u obzir kako je za procjenu prehrambenog unosa joda korištena dijetetička metoda koja se oslanja na prisjećanje i moguće je da je dio ispitanica precijenio svoj unos hrane koja je značajan izvor joda. Treba napomenuti kako ovaj prehrambeni unos joda uključuje doprinos kuhinjske i/ili morske soli, te govori u prilog visokoj konzumaciji soli u populaciji. Prema podacima za Hrvatsku, žene unose 10,2 g, a muškarci 13,3 g soli u danu.[23]

Konzumacija jaja, mlijeka i mliječnih proizvoda uvelike može doprinijeti statusu joda u organizmu, unatoč varijabilnom sadržaju joda zbog geografskog

područja u kojemu životinje obitavaju, načinu proizvodnje različitih mliječnih proizvoda, pa i o načinu konzumacije istih.[12,24] Doprinos mlijeka i mliječnih proizvoda i jaja dnevnom unosu joda prednjači doprinosu iz morske ribe i morskih plodova (Slika 2.), što se može pripisati tradicionalnim prehrambenim navikama istočne Hrvatske, gdje su morska riba i morski plodovi sporadično zastupljeni u prehrani. Istraživanjem kojem je ispitivano znanje 378 žena reproduktivne dobi (15 do 49 godina) o jodu, uključujući izvore u prehrani, obogaćivanje soli jodom, utjecaj niskih i visokih koncentracija joda na zdravlje, došlo se do poražavajućih rezultata.[25]



Slika 2. Doprinos pojedinih skupina namirnica dnevnom unosu joda u trudnica
Figure 2 Contribution of selected foods to the daily iodine consumption among pregnant women

Posebno nisku razinu znanja imale su mlađe žene i žene nižeg stupnja obrazovanja, a veći je broj žena bio upoznat s negativnim učincima nedovoljnog unosa joda u odnosu na dostatan unos joda.[25] Mandatorno obogaćivanje kuhinjske soli jodom je većini ispitanica nepoznato (62 % ispitanica), a posebno zabrinjava kako čak ni žene koje imaju neku bolest štitnjače ne pokazuju bolje znanje o jodu.[25]

U Hrvatskoj je trenutno na snazi zakon kojim se propisuje obvezno obogaćivanje kamene soli s 25 mg kalij jodida po kilogramu soli. Koncentracija joda u urinu u klinički zdravih trudnica trebala bi se kretati od 150 do 249 µg/L.[26] S obzirom na referentni raspon, 75 % trudnica ima nisku koncentraciju joda u urinu, dok je 25 % trudnica unutar referentnog intervala (Tablica 2.). Unatoč velikom broju trudnica s niskom koncentracijom joda u urinu, rezultati su u skladu s prethodno provedenim istraživanjima,[27-29] ali bi istraživanje trebalo provesti na većem broju trudnica, kako bi se dobio bolji uvid u stanje. Istraživanje koje su 2012. godine proveli Kusić i sur.[27] na 103 trudnice s područja grada Zagreba pokazalo je kako je medijan koncentracije joda u urinu kod trudnica iznosio 159 µg/L, od čega ih je polovina imala koncentraciju nižu od preporučenih 150 µg/L. Istraživanje[28] koje je provedeno u Tuzli, Bosna i Hercegovina na 300 trudnica kroz sva tri tromjesečja, utvrdilo je medijane koncentracije joda u urinu od 151 µg/L u prvom, 146 µg/L u drugom i 126 µg u trećem tromjesečju. Udio trudnica koje su imale koncentraciju joda u urinu < 150 µg/L bio je 46,0 % u prvom, 55,0 % u drugom i 64 % u trećem tromjesečju[28]. Značajno više koncentracije joda u urinu (≥ 250 µg/L) utvrđene su kod 18,0 % u prvom, 12,0 % u drugom i 7,0 % u trećem tromjesečju[28]. Prpić i sur.[29] analizirali su status joda u 133 parova dojilja-dojenče s područja Hrvatske. Medijan koncentracije joda u urinu dojilja iznosio je 75 µg/L (19,0-180,5 µg/L) i 234 µg/L (151,0-367,5 µg/L) kod dojenčadi, dok je u majčinom mlijeku utvrđeno 121 µg joda/kg (87,8-170,8 µg/kg)[29]. Potvrdili su kako je sadržaj joda u majčinom mlijeku u korelaciji s dojenačkim statusom joda, a majčin status joda s dojenačkom funkcijom štitnjače.[29]

Iako su prehrambeni unos joda i koncentracija joda u urinu bili visoki kod značajnog broja trudnica (17/24, podebljane vrijednosti prikazane u Tablici 2.), nije utvrđena statistički značajna povezanost između njih, što je vjerojatno zbog malog broja trudnica. Ovome u prilog govori i činjenica kako je kod pretilih

trudnica utvrđena najviša koncentracija joda u urinu (Tablica 4.), što je vjerojatno rezultat konzumacije veće količine hrane i/ili hrane koja je bogata solju. Ipak, ne treba odbaciti i činjenicu mogućeg precjenjivanja i/ili podcjenjivanja konzumacije hrane bogate jodom, a što je potrebno ispitati opsežnijim istraživanjem na većem broju trudnica, kao i drugih populacijskih skupina, koristeći i druge dijetetičke metode za analizu prehrambenog unosa joda. Osim toga, potrebno je utvrditi gubitak joda iz soli, koji se prema prethodno provedenim istraživanjima, ovisno o uvjetima čuvanja, kreće između 30% i 40%[30-32]. Upravo bi ovo moglo biti razlog zbog kojeg je došlo do precjenjivanja unosa joda s obzirom na to da baze podataka koje se koriste za izračune nutritivnih vrijednosti koriste fiksne vrijednosti joda.

Viša koncentracija joda u urinu povezana je s nižim TSH (Tablica 3.), što je prethodno zabilježeno u istraživanju provedenom na 180 trudnica pred termin poroda u Turskoj.[33] Treba napomenuti kako niti jedna trudnica nije imala vrijednost TSH ispod ili iznad referentnog raspona (Tablica 2.), što potvrđuje dobru funkciju štitnjače. S druge strane, istraživanje provedeno na 1844 trudnice s područja Španjolske u razdoblju od 2004. do 2008. godine, pokazalo je kako su najviši rizik od visokih vrijednosti TSH (karakteristično za hipotiroidizam) imale žene koje su uzimale jod kroz dodatke prehrani.[34] Prehrambeni unos joda viši je kod mlađih trudnica (Tablica 3.), što se može objasniti lošijim prehrambenim navikama mlađih trudnica koje manje paze na prehranu, unatoč trudnoći i često posežu za hranom koja je bogata solju.

Zaključak

Rezultati ovoga opažajnog istraživanja ukazuju na raskorak između statusa joda promatranog kroz koncentraciju joda u urinu i prehrambenog unosa joda. Koncentracija joda u urinu je kod 2/3 trudnica bila ispod minimalnih 150 µg/L, dok je procijenjeni prehrambeni unos joda bio višestruko iznad preporučenoga, pa čak i maksimalno dopuštenog unosa. Rezultati pokazuju kako je potrebno provesti analizu sadržaja joda u hrani, prvenstveno u soli i utvrditi koliki je gubitak joda u soli koja je dostupna na tržištu Republike Hrvatske, uzimajući u obzir uobičajene uvjete u kućanstvu (načine čuvanja soli). Na osnovu tih rezultata potrebno je potom ponoviti istraživanje o odnosu prehrambenog i urinarnog joda na trudnicama, kao i drugim populacijskim skupinama, kako bi se dobili temelji za buduće javnozdravstvene akcije.

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The contemporary approach to chylothorax – Single-center experience with the proposal of a management algorithm

Suvremeno liječenje hilotoraksa – iskustva naše bolnice s prijedlogom postupnika liječenja

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Summary

Objectives*:* Chylothorax is a relatively rare condition of lymphatic fluid accumulation in the thoracic cavity due to a leakage from the thoracic duct or its tributaries. Patients present with dyspnea, malnutrition, and immunosuppression. Treatment can be conservative or surgical, depending on etiology and clinical course. The optimal management algorithm for chylothorax is still controversial.

Methods*:* This is a ten-year period retrospective study of all patients with chylothorax treated at our Department of Thoracic Surgery.

Results*:* A total of 14 patients were identified for the study. Nine patients had chylothorax after lung or esophageal cancer surgery. Four patients had chylothorax in advanced lymphoma. One patient had chylothorax after blunt chest trauma. A conservative approach was initiated in most patients (92%), including pleural drainage, nil per mouth, total parenteral nutrition, and somatostatin 0.1 mg bid subcutaneously. Surgical treatment was indicated in patients with thoracic drain production >800 mL per day beyond the fifth day of treatment and those with blunt thoracic trauma. Two patients had thoracic duct ligation via right-sided thoracotomy, and five patients had video-assisted thoracoscopic thoracic duct ligation with the immediate arrest of chylous leakage.

Conclusion*:* Chylothorax should be treated conservatively initially. Surgical treatment should not be delayed beyond the fifth day in case of failure. In our series of patients, a video-assisted thoracoscopic approach for thoracic duct ligation proved to be minimally invasive, highly efficient, and well tolerated. Therefore, it should be the preferable route of surgical treatment.

Key Words: Chylothorax; Thoracic Duct; Video-Assisted Thoracoscopic Surgery

Sažetak

Cilj: Hilotoraks je relativno rijetko stanje nakupljanja limfne tekućine u prsnoj šupljini zbog curenja iz prsnog limfovoda (lat. ductus thoracicus) ili njegovih pritoka. Bolesnici se prezentiraju dispnejom, pothranjenošću i imunosupresijom. Liječenje može biti konzervativno ili kirurško, ovisno o etiologiji i kliničkom tijeku. Optimalni postupnik liječenja hilotoraksa još uvijek je diskutabilan.

Metode: Ovo je retrospektivna studija svih bolesnika s hilotoraksom liječenih na našem Odjelu za torakalnu kirurgiju tijekom 10-godišnjeg razdoblja.

Rezultati: U istraživanju je identificirano ukupno 14 bolesnika. Devet bolesnika imalo je hilotoraks nakon operacije karcinoma pluća ili jednjaka, četiri bolesnika imala su hilotoraks zbog uznapredovalog

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limfoma, dok je jedan bolesnik imao hilotoraks nakon tupe ozljede prsnog koša. Konzervativni pristup liječenju započet je kod većine bolesnika (92%), što podrazumijeva pleuralnu drenažu, ukidanje peroralne prehrane, uvođenje totalne parenteralne prehrane i terapiju somatostatinom 0,1 mg dva puta dnevno supkutano. Kirurško liječenje indicirano je u bolesnika s produkcijom pleuralne drenaže >800 mL na dan nakon petog dana od početka liječenja, kao i kod bolesnika s hilotoraksom uzrokovanog tupom ozljedom prsnog koša. Dva bolesnika podvrgnuta su ligaciji prsnog limfovoda kroz desnu torakotomiju, a kod pet bolesnika učinjena je video-asistirana torakoskopska (VATS) ligacija prsnog limfovoda, što je kod svih bolesnika dovelo do brzog zaustavljanja limforeje.

Zaključak: Hilotoraks treba u početku liječiti konzervativno. U slučaju neuspjeha kirurški zahvat ne treba odgađati dulje od petog dana od početka konzervativnog liječenja. U našoj seriji video-asistirani torakoskopski pristup za ligaciju prsnog limfovoda pokazao se minimalno invazivan, visoko učinkovit i dobro podnošljiv za bolesnike, te bi stoga VATS trebao biti preporučeni način kirurškoga liječenja.

Ključne riječi: hilotoraks; prsni limfovod; video-asistirana torakoskopska kirurgija

Introduction

The thoracic duct originates in the abdomen from the cisterna chyli sac, which confluences the right and left lumbar trunks and the intestinal trunk, collecting lipid products of digestion. It courses cranially, entering the right chest cavity through the aortic aperture in the diaphragm between the azygos vein, esophagus, and aorta. It drains into the posterior confluence of the left subclavian and internal jugular veins. The thoracic duct is typically 35–45 cm long and has an average diameter of about 2-3 mm.[1] It collects most of the lymph in the body other than from the right thorax, right arm, right part of the head, and neck, as well as liver convexity. The above-described course is found in 65% of the population. Variations are common, consisting mainly of duplications of the duct, left-sided course, and bilateral course.[2] The primary function of the thoracic duct is the transport of chyle, a liquid containing both lymph and emulsified fats, from the intestines into the venous circulation.

Chylothorax is an accumulation of lymph in the thoracic cavity commonly due to loss of thoracic duct integrity. The most common reason is iatrogenic thoracic duct injury during thoracic surgical procedures. It typically occurs during esophageal resection. Chylothorax incidence after esophageal surgery is 4 - 10%.[3,4] The intimate relation of the esophagus and thoracic duct, the presence of collateral lymphatic ducts, and the variable course of the thoracic duct are the main reasons for a high incidence of injuries during surgery. Prophylactic ligation of the thoracic duct during esophagectomy should be considered an effective preventative measure to reduce the incidence of postoperative chylothorax.[5] Radical mediastinal lymphadenectomy results in chylothorax in 3-5% of patients. Other surgical procedures potentially causing chylothorax are aortic surgery, pneumonectomy, and removal of posterior mediastinal tumors.[6]

Even non-surgical procedures like subclavian vein catheterization can cause vein thrombosis and bilateral chylothorax with chylopericardium.[7] Chylothorax occurs after penetrating, rarely after blunt thoracic injuries. The mechanism of blunt injury is spine hyperextension with thoracic duct overstretching over vertebral bodies, leading to duct rupture, usually just above the diaphragm. The dislocation of costovertebral joints of lower ribs and their anterior migration can also damage the thoracic duct.[8] Chylothorax can rarely occur as a result of birth trauma.[9] Nontraumatic chylothorax occurs in only 20% of cases. The most common cause is malignant thoracic duct obstruction, with lymphoma as a leading malignancy in 70% of patients.[10]

Leakage of lymphatic fluid into the chest leads to severe depletion of proteins, immunoglobulins, fats, vitamins, electrolytes, and water. Massive chylothorax can cause hypovolemia due to extensive circulation volume loss.[1,4,6] The dynamics of decompensation depend on the amount, speed, and duration of leakage. In the early period, patients might be symptom-free. In the advanced stage, malnutrition, hyponatremia, hypocalcemia, and acidosis occur.

Patients and methods

We have conducted a retrospective study of all consecutive patients treated at the Department of Thoracic Surgery at Zadar General Hospital over a ten-year period. Our hospital is a secondary to tertiary referring and teaching center, providing elective and emergency thoracic surgery services to an estimated population of 200,000, which rises during the summer season to half a million due to a marked tourist influx.

The Hospital's Ethics Committee approved our study (No. 02-7908/20-2/20).

Between January 2010 and December 2019, all patients with chylothorax records were reviewed. The patients' age, gender, history, the underlying cause of

the chylous effusion, treatment outcome, and complications were collected retrospectively using operations logs and electronic and paper medical records. The collected data were analyzed using descriptive statistical methods.

All patients were diagnosed after pleural fluid sampling obtained by insertion of a thoracic drain. The milky appearance of the pleural effusion was usually macroscopically evident. Still, all the samples were sent for biochemical analysis of the triglyceride level and the comparison of the serum triglyceride levels, which can help determine the diagnosis of chylothorax. All patients in our series had pathognomonic triglyceride levels >1.24 mmol/L (110 mg/dL). All patients had imaging with a contrast-enhanced thorax CT to confirm the pleural effusion and rule out other pathology that may interfere with the treatment plan.

Results

During ten years (January 2010 to December 2019), a total of 14 patients with chylothorax were treated at our Department of Thoracic Surgery. There were five women (35%) and nine men (65%). The age span was from 23 to 81 years (mean 65 years).

Five patients developed chylothorax after lung cancer surgery and mediastinal lymph node dissection. Four patients had chylothorax after radical resection of esophageal cancer. One patient had chylothorax after blunt chest trauma. Malignant chylothorax was noticed in four patients caused by advanced lymphoma.

Ten patients (71%) had right-sided chylothorax, two patients (14.5%) had left-sided, and two patients (14.5 %) had bilateral chylothorax.

A conservative approach was initiated in most patients (13 patients, 92%), including pleural drainage, a nil-per-mouth regime, total parenteral nutrition, and octreotide 0.1 mg bid subcutaneously. Although treatment with octreotide, a somatostatin analog, is of unproven value, its use was described in the successful treatment of several off-label indications, including chylothorax.[11,12]

Surgical treatment was indicated relatively early in patients with thoracic drain production >800 mL per day beyond the fifth day of treatment and in a patient with blunt thoracic trauma.

All patients had surgery under endotracheal bi-luminal intubation, allowing selective lung ventilation. Two earlier patients had an open right-sided thoracotomy, while more recent five patients had a video-assisted thoracoscopic surgical approach (VATS). This important shift in the surgical approach is related to our growing experience using VATS for various thoracic pathology, including lung resections. We have used the EndoCAMeleon™, Karl Storz, 10-mm thoracoscope with the variable direction of view (0° - 90^0) for a minimally invasive approach to thoracic duct identification and ligation.[13]

The distribution and characteristics of 14 analyzed patients are presented in Table 1.

Table 1 Distribution and characteristics of 14 consecutive patients with chylothorax.
Tablica 1. Distribucija i karakteristike 14 uzastopnih bolesnika s hilotoraksom.

Patient No. *Br. pacijenta*	**Age** *Dob*	**Gender** *Spol*	**Etiology**	**Side** *Strana*	**Management** *Upravljanje*
1	72	M	Postoperative	Right/*desna*	Conservative
2	61	F	Postoperative	Left/*lijeva*	Conservative
3	53	M	Postoperative	Bilateral/*obje*	Conservative
4	67	M	Lymphoma	Right/*desna*	VATS
5	58	M	Postoperative	Right/*desna*	Thoracotomy
6	81	F	Lymphoma	Right/*desna*	Conservative
7	74	M	Postoperative	Right/*desna*	VATS
8	60	F	Postoperative	Right/*desna*	Conservative
9	65	M	Postoperative	Left/*lijeva*	Conservative
10	58	F	Postoperative	Right/*desna*	Thoracotomy
11	74	M	Lymphoma	Bilateral/*obje*	Conservative
12	68	M	Postoperative	Right/*desna*	VATS
13	72	F	Lymphoma	Right/*desna*	VATS
14	23	M	Blunt injury *Tupa ozljeda*	Right/*desna*	VATS

Conservative treatment was successful in seven patients (50%). The rest had a daily production of >800 mL of fluid beyond the fifth day of conservative treatment, which was the threshold for the surgical approach. It is significant that in all patients with malignant etiology of chylothorax, conservative

therapy failed, and they all had to be operated on. The patient with blunt thoracic trauma developed chylothorax on the second day after the injury and had a high daily lymph production of more than 1,500 mL. Considering the mechanism of injury and high output leakage, early surgery was indicated three days after the injury.

VATS approach was successfully used for thoracic duct identification and ligation using Weck® Hem-o-Lok® non-absorbable polymer locking clips (Video 1). Resected proximal and distal thoracic duct ends were routinely sent for pathology verification. A total of seven patients underwent surgical therapy. Two of them had massive ligation of tissue between the aorta, azygos vein, esophagus, and spine approached through right thoracotomy. Five patients had video-assisted thoracoscopic precise ligation of the thoracic duct through the right chest. None of the patients required parietal pleurectomy. All operated patients stopped leaking chyle within the 24 hours following surgery, contrary to the results of the literature review conducted by Kakamad et al. on 39 published case reports.[14] Exact thoracic duct ligation facilitated with the thoracoscopy might provide another reason for the immediate stoppage of chylous leakage.

Oral nutrition was introduced on postoperative day one and advanced as tolerated. Based on our experience and along with the reviewed literature, we propose an algorithm for chylothorax management, as shown in Figure 1.

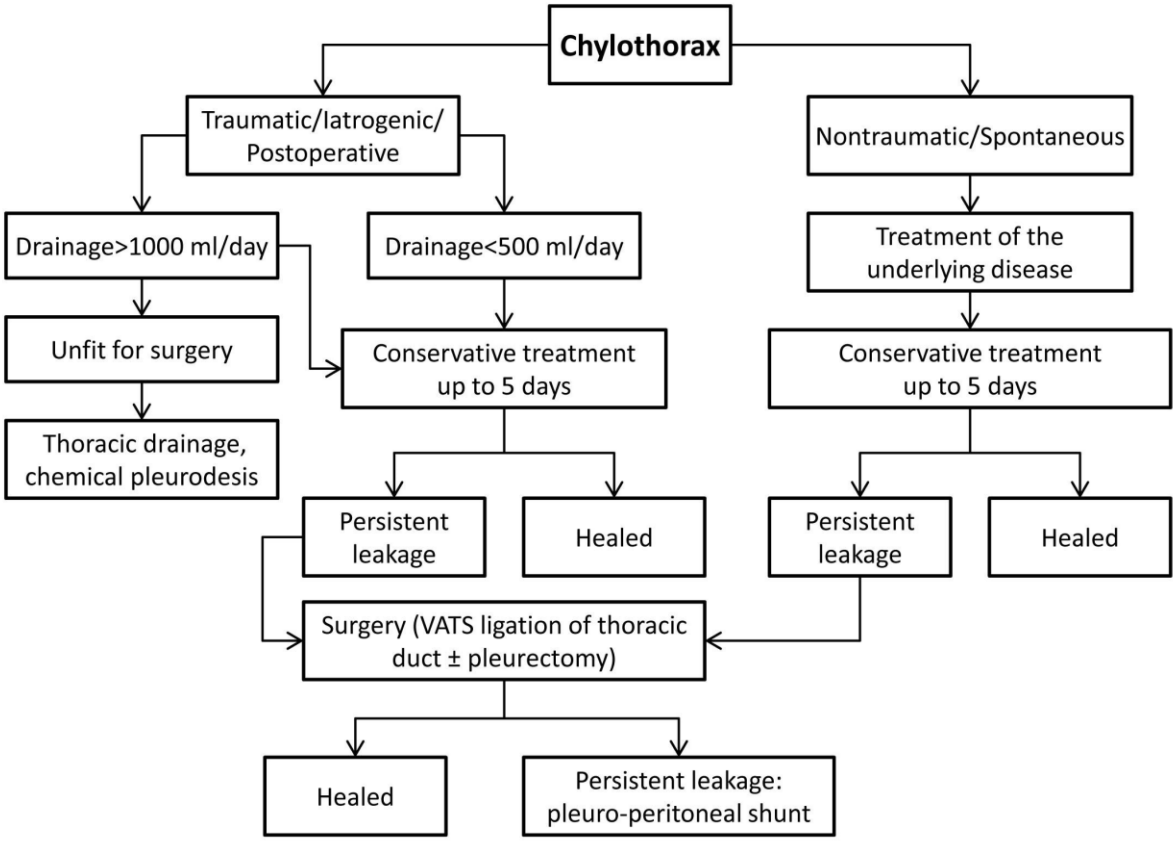

Figure 1 Algorithm of chylothorax management.
Slika 1. Algoritam upravljanja hilotoraksom

Discussion

Before Lampson reported thoracic duct ligation in 1948, the standard of care in the treatment of traumatic chylothorax was conservative, including nil per mouth, parenteral nutrition, and repeated thoracentesis, which was burdened with devastating 50% mortality.[13] Nontraumatic (malignant) chylothorax at the time had a mortality of 100%.[1,6] Introducing thoracic duct ligation lowered mortality towards a contemporary rate of 7 - 10%. Bilateral and malignant chylothorax harbor the highest mortality rate even today.

The case of death in untreated or inappropriately treated patients is mainly wasting due to malnutrition, gradual immunodeficiency, and sometimes heart failure because of fluid accumulation and compression. Mortality is increased when the condition is unrecognized or treated inappropriately. High output depletion of proteins, immunoglobulins,

fats, vitamins, electrolytes, and water leads to rapid malnutrition and immunodeficiency. Therefore, early recognition of this subgroup of patients and timely indication for surgery is essential to prevent the irreversible phase of metabolic and immunologic demise. Continuous loss of immunoglobulins and lymphocytes induces severe immunosuppression with opportunistic infections.[6] Nevertheless, infection of pleural fluid is rare due to the bacteriostatic properties of lymphatic fluid.[1]

Early diagnosis and appropriate management increase the chances for successful treatment and decrease the complication rate. The milky or murky macroscopic appearance of pleural effusion should raise suspicion of chylothorax.[7] Clear pleural effusion is expected in the early postoperative period because patients traditionally have reduced oral intake or are fasting. Daily return of the chyle via the thoracic duct is estimated at 1.5 - 2.5 liters. Drainage of more than 400 mL of pleural fluid per day deserves further work-up. Biochemical analysis of pleural fluid in chylothorax is positive if it shows a high triglyceride content. Triglyceride level >1.24 mmol/L (110 mg/dL) is pathognomonic for chylous effusion. Triglyceride level <0.56 mmol/L (50 mg/dL) rules out chylothorax.[1,15] The levels in between the upper and lower range might present diagnostic challenges, but the serum triglyceride level might help confirm or exclude the diagnosis. Also, the cholesterol level in the pleural effusion should be lower than the serum cholesterol value, which is also a prerequisite for a positive diagnosis of chylothorax.

Non-traumatic chylothorax is more challenging to diagnose, sometimes needing magnetic resonance lymphangiography (MRL), which allows noninvasive detection of the source of the chylous leak and selection of the appropriate management approach.

Chylothorax can be treated conservatively, using thoracic duct embolization or with surgery. Medical care aims to lower chyle production through dietetic measures and drainage of pleural space, hopefully leading to the spontaneous occlusion of the leaking site. Symptomatic patients need tube thoracostomy, which alleviates respiratory distress caused by excessive fluid accumulation and lung and heart compression. Drainage allows lung re-expansion, which reduces available space for fluid accumulation. The apposition of the pleurae also contributes to the compression of the leaking site, thus reducing the flow and fluid accumulation.

The patient refrains from eating and receives a total parenteral replacement of calories, proteins, fluid, and electrolytes. Several authors reported successful off-label treatment with somatostatin or its synthetic analog octreotide, which inhibits the synthesis of growth hormone, glucagon, and insulin and decreases lymphatic production.[11,18,19]

Chemical pleurodesis with bleomycin, minocycline, tetracycline, or, most often, talk, is another therapeutic option aiming to obliterate pleural space, thus preventing fluid accumulation. Pleurodesis can be combined with thoracic duct ligation or as a stand-alone procedure.[19,20] When daily fluid production is <500 mL, the reported success rate of conservative treatment is 70 - 90%.

Itkin and colleagues report a series of 109 patients successfully treated with thoracic duct catheter embolization after traumatic thoracic duct leakage. They conclude that this novel approach is a safe, feasible, and minimally invasive method for treating traumatic chylothorax. Nevertheless, this is a technically challenging procedure that needs appropriate facilities and highly trained interventional radiologists, which might be reserved for selected tertiary trauma centers or large teaching hospitals.[21]

Persistent leakage of more than 1000 mL per day indicates a high-output of chylothorax with poor chances for a spontaneous resolution, especially if the etiology is iatrogenic (postoperative). Indications for surgical treatment of chylothorax are daily production of >1000 mL in adults or >600 mL in children for four days; persistent leakage for more than two weeks despite conservative treatment; metabolic complications such as electrolyte or immunologic disbalance.[1,4,10,15] Surgical options are direct ligation of the thoracic duct approached through thoracotomy or VATS; mass ligation of the thoracic duct through thoracotomy or VATS; pleurectomy with pleurodesis or implantation of a pleuro-peritoneal shunt. If the patient has already had thoracic surgery, the approach through the postoperative wound is reasonable. Still, depending on local expertise and the thoracic surgeon's discretion, it does not preclude the minimally invasive (VATS) approach. The placement of pledgeted sutures or local sealants such as fibrin glue or blood patch was not necessary in our series of patients, although advocated by some as an ancillary means of stopping the leakage.[22,23]

Intraoperative identification of a leaking spot might be challenging despite a clear anatomical position. Several techniques help surgeons identify the site of injury. Administration of olive oil or full-fat milk one hour before surgery per os or via a nasogastric tube can help visualize the leaking spot due to enhanced production of milky effusion.[4,6] If it cannot be identified, the thoracic duct should be ligated directly or *en masse* above the diaphragm. The right pleural space is approached through

thoracotomy or VATS. *En masse* ligation encompasses a bundle of tissue between the aorta, azygos vein, esophagus, and spine.[22,25,26] Isolated ligature requires precise identification and thoracic duct ligation. Traditional suture ligature is usually replaced with titanium or polymeric clips, especially in the era of VATS.[27-29] Parietal pleurectomy might be added after the ligation when lymph leakage control is uncertain.[1,6] If thoracic duct ligation remains unsuccessful with persistent symptomatic chylothorax, the ultimate option in recurring cases is a pleuro-peritoneal shunt with the rationale that the peritoneum will absorb the excessive fluid.[30,31] The method should be used only as a last resort because of the high complication rate, such as catheter obstruction with fibrin, infection, and pneumoperitoneum.[32]

Conclusion

In our experience, chylothorax should be initially treated conservatively. However, the indication for surgery should not be delayed for more than five days, especially in non-traumatic (malignant) chylothorax and in postoperative (iatrogenic) cases of chylothorax. Due to the advantages of a minimally invasive thoracoscopic approach, high success rate of operative treatment, and low morbidity and mortality after surgical ligation of the thoracic duct, the threshold for surgery seems to be lower than ever before.

In our series of patients, the VATS approach for thoracic duct ligation proved to be minimally invasive, highly efficient, and well tolerated. It confirms the golden standard in treating chylothorax with a high success rate. Alternative options, such as thoracic duct embolization, might need dedicated staff and available facilities, precluding the broader use of this exciting but demanding technique. Although recommended by several authors, the need for parietal pleurectomy was not encountered since the therapeutic goal was achieved with thoracic duct ligation only.

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Pregledni članak
Review

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Usporedba učinkovitosti neoperacijskog i operacijskog liječenja akutne rupture ahilove tetive

Comparison of the effectiveness of conservative and surgical treatment of acute Achilles tendon rupture

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Sažetak

Cilj rada: Usporediti učinkovitost neoperacijskog i operacijskog liječenja akutne rupture Ahilove tetive obzirom na razlike u ishodu liječenja.

Metode i materijali:Pretražene su baze medicinskih podataka MEDLINE, Web of Science i Cochrane Library za razdoblje od siječnja 2012. godine do prosinca 2022. godine korištenjem ključnih riječi "rupture", "Achilles tendon", "conservative treatment", "operative treatment" i "rehabilitation". Obuhvaćena su randomizirana istraživanja, pregledni i sistematski pregledni radovi, te metaanalize objavljeni na engleskom jeziku.

Rezultati: Analizirano je ukupno 12 radova koji su se bavili problematikom liječenja potpune akutne rupture Ahilove tetive. Neoperacijskim liječenjem uz korištenje protokola funkcionalne rehabilitacije ne postoji veća razlika u ishodu liječenja u usporedbi s operacijskim liječenjem u vidu učestalosti ponovne rupture, povratku mišićne snage i opsega pokreta u gležnju, a bol je manja. Ostale komplikacije liječenja (infekcije rane, nekroza kože i tetiva, fistule, adhezija ožiljka, oštećenje suralnog živca, duboka venska tromboza, plućna embolija) su općenito učestalije i povezane s operativnim liječenjem.

Zaključak: Akutna ruptura Ahilove tetive može se neoperacijski i operacijski uspješno liječiti. Rezultati većine radova ukazuju na to da je neoperacijsko liječenje uz protokol funkcionalne rehabilitacije učinkovito, pri čemu su stopa ponovne rupture i funkcionalni oporavak usporedivi s onime u operativnom liječenju, ali uz manje popratnih komplikacija.

Ključne riječi: Ahilova tetiva, ruptura, konzervativno liječenje, operativno liječenje, rehabilitacija

Summary

Objective: The aim was to compare the effectiveness of conservative and surgical treatment of acute Achilles tendon rupture regarding outcome differences.

Methods and materials: An extensive literature search of MEDLINE, Web of Science, and Cochrane Library was conducted from January 2012 to December 2022 using the following keywords: "rupture", "Achilles tendon", "conservative treatment", "operative treatment" and "rehabilitation". Randomized controlled trials, literature reviews, and systematic literature reviews as well as meta-analyses published in English were included.

Results:12 studies were analyzed focusing on the treatment of complete Achilles tendon rupture. Conservative treatment with a functional rehabilitation protocol has no major outcome differences regarding the frequency of rerupture, return of muscle strength, and range of motion in the ankle compared to the operative treatment, with milder pain reported. Other treatment complications (wound infections, skin and tendon necrosis, fistulas, scar adhesion, sural nerve damage, overlengthening of the tendon, deep

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venous thrombosis, pulmonary embolus) are generally more frequent and associated with operative treatment.

Conclusion: Acute Achilles tendon rupture can be successfully treated both conservatively and surgically. Results indicate that a complete acute Achilles tendon rupture can be successfully treated conservatively with a functional rehabilitation protocol, with comparable rates of rerupture and functional recovery to those treated operatively, while having less complications.

Key words: Achilles Tendon, Rupture, Conservative Treatment, Operative treatment, Rehabilitation

Uvod

Ahilova tetiva najsnažnija je tetiva u ljudskom tijelu.[1,2] Nastaje spajanjem stražnje površinske skupine mišića potkoljenice m. soleusa i m. gastrocnemiusa, dužine je pet do šest centimetara, debljine pet do šest milimetara, šira u proksimalnom dijelu i obavijena elastičnom, tankom opnom, paratenonijem.[3] Opskrba krvlju vrlo je oskudna, osobito u području dva do šest centimetara iznad hvatišta za petnu kost.[1,2] Ruptura Ahilove tetive relativno je česta sportska, rekreacijska i radna ozljeda, a češće se javlja u muškaraca u odnosu na žene (10:1) s bimodalnom distribucijom.[1,2,4,5] Prvi vrhunac pojavnosti je u osoba između 25 i 40 godina, kada je najčešće ruptura posljedica sportskih visokoenergetskih ozljeda, dok se drugi vrhunac javlja u osoba starijih od 60 godina, kada se najčešće radi o rupturi degenerativno promijenjene tetive.[2]

Ruptura Ahilove tetive može biti akutna i zastarjela, a može se previdjeti u do čak 25% slučajeva.[6,7] Zastarjela ruptura definira se kao kašnjenje u postavljanju dijagnoze rupture od četiri do šest tjedana od ozljede,[6,7,8] a često se pogrešno dijagnosticira kao uganuće gležnja.[9] Tipični glavni simptom akutne rupture nagla je i jaka bol u donjem dijelu m. tricepsa surae, koja onemogućava daljnje kretanje, a često je praćena karakterističnim zvučnim fenomenom. U području rupture mogu biti vidljivi oteklina i hematom. Pri pregledu bolesnika s potpunom rupturom tetive u potrbušnom ležećem položaju sa stopalima koja vise preko ruba kreveta, može se palpirati mjesto razdora tetive, a testom stiskanja potkoljenice (engl. *the calf squeeze test*) pri pritisku na m. triceps surae ne dolazi do plantarne fleksije stopala.[5,10,11] U našoj kliničkoj praksi, te na sjevernoameričkom području, test je poznat pod imenom Thompsonov test, dok je na britanskim otocima poznat kao Simmondsov test.[11] Pri potpunoj rupturi, bolesnik se često ne može odići na prste ozlijeđene noge.[5,10] Međutim, kod četvrtine bolesnika aktivna plantarna fleksija stopala bude očuvana zbog djelovanja m. tibialis posterior, mm. peronei i m. flexor digitorum longus.[11] Diferencijalna dijagnoza rupture Ahilove tetive obuhvaća peritendinitis Ahilove tetive, rupturu m. gastrocnemiusa, istegnuće ili rupturu mišića potkoljenice, ozljedu ligamenta, ozljedu n. peroneusa i prijelom potkoljenice.[9] Ultrazvučni (UZV) pregled smatra se zlatnim standardom u dijagnostici akutnih ruptura Ahilove tetive.[1] Pri potpunoj rupturi uočava se prekid kontinuiteta tetive, što se osobito dobro može detektirati prilikom dinamičkog pregleda.[10,12] Dinamičkim pregledom može se utvrditi postoji li kontakt, odnosno kolika je udaljenost između rupturiranih dijelova tetive u plantarnoj fleksiji, o čemu ovisi daljnje liječenje.[7,13,14,15] Magnetska rezonancija (MR) u dijagnostici akutnih ruptura najčešće nije potrebna, dok indikacije za MR mogu biti uredan ili dvosmislen Simmonds-Thompsonov test, nejasan UZV nalaz, normalna napetost tetive u mirovanju u usporedbi s neozlijeđenom stranom, neopipljiv razmak između rubova tetiva, zastarjela, djelomična ili ponovna ruptura, prethodna operacija Ahilove tetive, anamneza kronične tendinoze, te klinička sumnja na rupturu kod atraumatskog mehanizma ozljede.[16,17,18,19,20] Liječenje akutne rupture Ahilove tetive može biti neoperacijsko i operacijsko, a izbor ovisi o UZV nalazu, dobi bolesnika, sportskoj aktivnosti, te prisutnim komorbiditetima.[1,4,7,13,14,15,21] Ukoliko prilikom UZV dijagnostike, pri 20° plantarne fleksije, dolazi do apozicije rupturiranih dijelova tetive ili je razmak manji od pet milimetara, u obzir dolazi neoperacijsko liječenje.[14,15]

Cilj ovoga preglednoga rada je usporediti učinkovitost neoperacijskog i operacijskog pristupa u liječenju rupture Ahilove tetive.

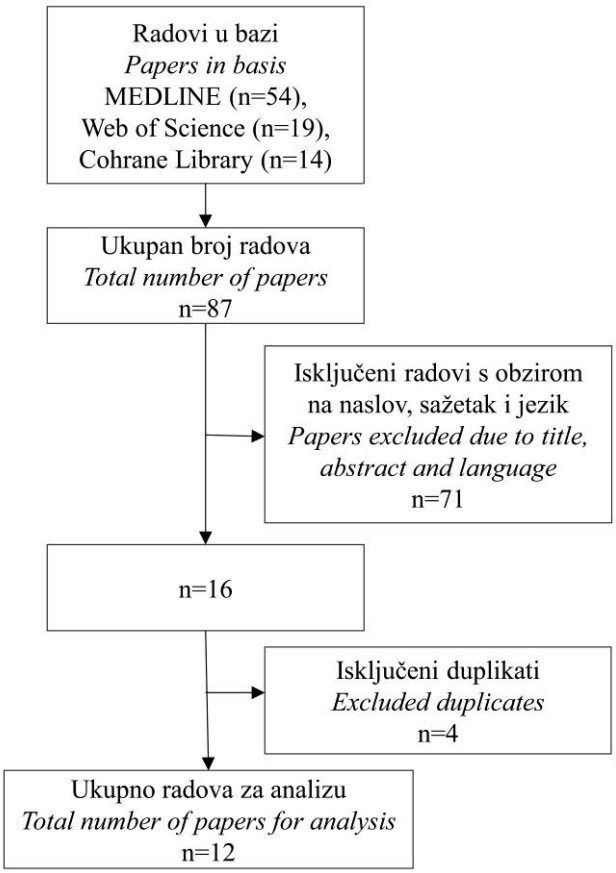
Metode i materijali

Pretražene su baze medicinskih podataka MEDLINE, Web of Science i Cochrane Library za razdoblje od siječnja 2012. godine do prosinca 2022. godine, korištenjem ključnih riječi "ruptura","Ahilova tetiva", "konzervativno liječenje", "operativno liječenje" i "rehabilitacija" (engl. "rupture", "Achilles tendon", "conservative treatment", "operative treatment" and "rehabilitation"), uz korištenje AND operatora, objavljeni na engleskom jeziku, te dostupni u cijelosti. Obuhvaćena su randomizirana istraživanja, pregledni i sistematski pregledni radovi, te metaanalize koji su uspoređivali neoperacijsko i operacijsko liječenje akutne rupture Ahilove tetive.

Isključeni su radovi koji su uspoređivali samo različite tehnike neoperacijskog ili samo različite tehnike operacijskoga liječenja.Uspoređivani ishodi liječenja uključuju usporedbu učestalosti ponovne rupture, povratka mišićne snage i opsega pokreta, smanjenja boli, te pojavnosti drugih komplikacija (infekcija rane, nekroza kože i tetiva, fistule, adhezija ožiljka, oštećenje suralnog živca, prekomjerno produljenje tetive, duboka venska tromboza (DVT) i plućna embolija).

Rezultati

Pretraživanjem literature nađeno je 87 radova, a nakon pregleda naslova i sažetaka isključeno je njih 71 koji nisu odgovarali zadanim kriterijima, te dodatno četiri duplikata (Slika 1). U konačnu analizu uključeno je ukupno 12 radova (Tablica 1) koji su uspoređivali neoperacijsko i operacijsko liječenje akutne rupture Ahilove tetive.



Slika 1. Proces strategije pretraživanja
Figure 1 Flowchart of research strategy

Neoperacijsko liječenje može biti konvencionalno i s funkcionalnom rehabilitacijom. Konvencionalno neoperacijsko liječenje uključuje mirovanje u imobilizaciji sa stopalom u plantarnoj fleksiji bez opterećenja noge, tijekom deset tjedana, nakon čega slijedi rehabilitacija.[1] Iako postoje različiti protokoli, generalno neoperacijsko liječenje s funkcionalnom rehabilitacijom obuhvaća ranu mobilizaciju i djelomično opterećenje težinom tijela između nultog i 14. dana od postavljanja imobilizacije. Postavlja se ortoza za stopalo u položaju plantarne fleksije od 30°, koja se od drugog do šestog tjedna postupno smanjuje do neutralnog položaja. Između šestog i osmog tjedna započinje se s rehabilitacijom. Isti principi funkcionalne rehabilitacije koriste se i nakon operacijskoga liječenja.[2,9,22,23,24,25] Operacijsko liječenje može biti otvorenim pristupom, te perkutanom i endoskopskom metodom.[2,9,21,22,23] Konvencionalno neoperacijsko liječenje pokazuje veću stopu ponovne rupture u odnosu na operacijsko liječenje.[2,9,22,23,26,27,28,29] Neoperacijsko liječenje s funkcionalnom rehabilitacijom pokazuje manju stopu ponovne rupture koja je usporediva sa stopom ponovne rupture u operacijski liječenih bolesnika.[2,9,22,23,26,27,28,29]

U analiziranim studijama stopa ponovne rupture nakon neoperacijskoga liječenja kreće se od 0 do 13%, a nakon operacijskoga liječenja od 0 do 8%,[2,9,22,23,24,25,26,27,28,29,30,31] dok jedna studija navodi mogućnost ponovne rupture nakon operacijskog liječenja i do 16% u osoba mlađih od 30 godina, što povezuju s agresivnijim pristupom rehabilitaciji.[2] U analiziranim studijama korištene su različite metode neoperacijskoga i operacijskoga liječenja. Tri od četiri metaanalize randomiziranih kliničkih studija pokazuju kako nema statistički značajne razlike u stopi ponovne rupture između neoperacijskoga i operacijskoga liječenja, ukoliko se koriste protokoli funkcionalne rehabilitacije.[26,27,30] Istraživanje Denga i sur. iz 2017. godine pokazuje učestalost ponovne rupture u neoperacijski liječenih bolesnika od 9,71%, te operacijski liječenih od 4,31%.[31]

U metaanalizama i preglednim radovima nema statistički značajne razlike u povratku snage mišića potkoljenice,[2,9,23,27,28,29,30,31] dok jedno randomizirano kliničko istraživanje pokazuje 10-18% veću snagu mišića potkoljenice nakon operacijskoga liječenja,[25] a drugo 13% manju snagu.[24] U studiji Manenta i sur. opseg pokreta plantarne fleksije smanjen je za četiri stupnja u odnosu na zdravu nogu kod neoperacijski liječenih, a pet do deset stupnjeva kod operacijski liječenih bolesnika.[24] Metaanaliza Soroceanu i sur pokazuje smanjenu plantarnu fleksiju kod neoperacijski liječenih bolesnika, koja je statistički značajna, ali klinički nema značaja jer iznosi 1,07°.[29] Ostale studije ne pokazuju statistički značajnu razliku u opsegu pokreta.[26,27,28,31] Bol je zasebno analizirana u jednoj studiji koja se javila u operiranih bolesnika u 7,4%, te je povezana s poslijeoperacijskim ožiljkom.[24]

Tablica 1. Obilježja analiziranih radova
Table 1 Characteristics of the analyzed papers

Prvi autor, godina/ *First author, year*	**Manent, 2019.**[24]
Vrsta studije/ *Type of study*	Prospektivno randomizirano kontrolirano kliničko istraživanje/ *Prospective randomized controlled trial*
Demografski podaci/ podaci o istraživanjima/ *Demographic data/research data*	Srednja dob 41 (18 do 59) godina, 32 muškarca, 2 žene / *Median age 41 (18 to 59) years, 32 men, 2 women*
Vrsta rupture, opis intervencije, kontrolna skupina, trajanje liječenja/ *Type of rupture, intervention description, control group, duration of intervention*	Potpuna akutna ruptura Neoperacijski liječeni n=11 Operacijski liječeni perkutanom tehnikom n=11 Operacijski liječeni otvorenom tehnikom n=12 1 godina/ *Total acute rupture Conservative treatment n=11 Percutaneous surgery n=11 Open surgery n=12 1 year*
Ishodi liječenja/*Treatment outcomes*	Sposobnost stajanja s podignutim petama mono- i bipodalno 3 sekunde, ocjena boli ≤2 nakon hodanja, povratak u aktivni prethodni život/ *Ability to stand with heels raised mono- and bipodally for 3 seconds, pain score ≤2 after walking, return to active previous life*
Slaba točka i ograničenja/*The weak point and limitations*	Mali broj ispitanika/ *Small sample size*
Opažanje i zaključak/*Observation and conclusion*	Konzervativno liječenje jednako je učinkovito kao i operativno liječenje, uz protokol rehabilitacije s ranim opterećenjem težinom./*Conservative treatment is as effective as operative treatment with an early weight-bearing rehabilitation protocol.*
Prvi autor, godina/*First author, year*	**Heikkinen, 2017.**[25]
Vrsta studije/*Type of study*	Prospektivno randomizirano kontrolirano istraživanje / *Prospective randomized controlled trial*
Demografski podaci/podaci o istraživanjima/ *Demographic data/research data*	Srednja dob 39,3 godina (27 do 60), 55 muškaraca, 5 žena/ *Median age 39.3 (27 to 60) years, 55 men, 5 women*
Vrsta rupture, opis intervencije, kontrolna skupina, trajanje liječenja/ *Type of rupture, intervention description, control group, duration of intervention*	Potpuna akutna ruptura Neoperacijski liječeni n=28 Operacijski liječeni n=32 18 mjeseci / *Total acute rupture Conservative treatment n=28 Surgical treatment n=32 18 months*
Ishodi liječenja/*Treatment outcomes*	Volumen mišića potkoljenice, masna degeneracija mišića potkoljenice, duljina zahvaćene Ahilove tetive, izokinetička snaga plantarne fleksije/ *Calf muscle volume, muscle fatty infiltration, Achilles tendon length, isokinetic strength of plantar flexion*
Slaba točka i ograničenja/*The weak point and limitations*	Nije snimljena nezahvaćena Ahilova tetiva; metoda za mjerenje duljine Ahilove tetive nije validirana za MR/ *The unaffected Achilles tendon was not imaged; the method for measuring the length of the Achilles tendon has not been validated for MR*
Opažanje i zaključak/*Observation and conclusion*	Konzervativno liječenje rezultiralo je većom atrofijom mišića soleusa, prosječna duljina Ahilove tetive bila je 19 mm duža nakon konzervativnog liječenja. 10% do 18% veća snagu mišića bila je kod operativno liječenih bolesnika./ *Conservative treatment resulted in greater soleus muscle atrophy, the average length of the Achilles tendon was 19 mm longer after conservative treatment. 10% to 18% greater muscle strength was observed in operative treated patients.*

Prvi autor, godina/*First author, year*	**Buddecke, 2021.**[22]
Vrsta studije/ *Type of study*	Pregledni rad *Review*
Demografski podaci/ podaci o istraživanjima/ *Demographic data/research data*	
Vrsta rupture, opis intervencije, kontrolna skupina, trajanje liječenja/ *Type of rupture, intervention description, control group, duration of intervention*	Potpuna akutna ruptura/*Total acute rupture*
Ishodi liječenja/ *Treatment outcomes*	
Slaba točka i ograničenja/ *The weak point and limitations*	
Opažanje i zaključak/*Observation and conclusion*	Operativno liječenje je metoda izbora za vrhunske sportaše, dok je za opću populaciju individualni izbor između bolesnika i liječnika./*Operative treatment is the treatment of choice for elite-level athletes, while for the general population it is an individual choice between the patient and physician.*
Prvi autor, godina/*First author, year*	**Park, 2020.**[2]
Vrsta studije/*Type of study*	Pregledni rad /*Review*
Demografski podaci/ podaci o istraživanjima/ *Demographic data/research data*	
Vrsta rupture, opis intervencije, kontrolna skupina, trajanje liječenja/ *Type of rupture, intervention description, control group, duration of intervention*	Potpuna akutna ruptura/*Total acute rupture*
Ishodi liječenja/*Treatment outcomes*	
Slaba točka i ograničenja/*The weak point and limitations*	
Opažanje i zaključak/*Observation and conclusion*	Akutna ruptura zdrave tetive može se uspješno liječiti konzervativno i operativno./*Acute rupture of a healthy tendon can be successfully treated conservatively and operatively.*
Prvi autor, godina/ *First author, year*	**Kauwe, 2017.**[9]
Vrsta studije/*Type of study*	Pregledni rad /*Review*
Demografski podaci/ podaci o istraživanjima/ *Demographic data/research data*	
Vrsta rupture, opis intervencije, kontrolna skupina, trajanje liječenja/ *Type of rupture, intervention description, control group, duration of intervention*	Potpuna akutna ruptura/ *Total acute rupture*
Ishodi liječenja/*Treatment outcomes*	
Slaba točka i ograničenja/*The weak point and limitations*	

Opažanje i zaključak/ *Observation and conclusion*	Konzervativno i operativno liječenje daju dobar funkcionalni ishod uz protokol funkcionalne rehabilitacije./ *Conservative and operative treatment give a good functional outcome with a functional rehabilitation protocol.*
Prvi autor, godina/*First author, year*	**Nandra 2012.**[23]
Vrsta studije/*Type of study*	Pregledni rad /*Review*
Demografski podaci/ podaci o istraživanjima/ *Demographic data/research data*	
Vrsta rupture, opis intervencije, kontrolna skupina, trajanje liječenja/ *Type of rupture, intervention description, control group, duration of intervention*	Potpuna akutna ruptura/ *Total acute rupture*
Ishodi liječenja/*Treatment* outcomes	
Slaba točka i ograničenja/*The weak point and limitations*	
Opažanje i zaključak/*Observation and conclusion*	Programi rane mobilizacije i rehabilitacije učinkoviti su tijekom konzervativnog i operativnog liječenja, te su stope ponovne rupture usporedive. / *Early mobilization and rehabilitation programs are effective during conservative and operative treatment and re-rupture rates are comparable.*
Prvi autor, godina/*First author, year*	**Holm, 2015.**[26]
Vrsta studije/*Type of study*	Sustavni pregledni rad /*Systematic Review*
Demografski podaci/ podaci o istraživanjima/ *Demographic data/research data*	7 randomiziranih prospektivnih kontroliranih ispitivanja na ljudima s ukupnim brojem ispitanika n=577/ *7 randomized prospective controlled trials on humans with a total number of subjects n=577*
Vrsta rupture, opis intervencije, kontrolna skupina, trajanje liječenja/*Type of rupture, intervention description, control group, duration of intervention*	Potpuna akutna ruptura; Usporedba neoperacijski i operacijski liječenih bolesnika / *Total acute rupture / Comparison of conservatively and surgicaly treated patients*
Ishodi liječenja/*Treatment* outcomes	Ponovna ruptura, druge komplikacije, funkcionalni ishodi/ *Rerupture, other complications, functional outcomes*
Slaba točka i ograničenja/*The weak point and limitations*	Različiti rehabilitacijski protokoli/ *Different rehabilitation protocols*
Opažanje i zaključak/*Observation and conclusion*	Razlike između konzervativnog i operativnog liječenja su suptilne, što bi moglo značiti da je rehabilitacija važnija od stvarnog početnog liječenja. / *The differences between conservative and operative treatment are subtle and this could mean that rehabilitation is more important than the actual initial treatment*.
Prvi autor, godina/*First author, year*	**Zhang, 2015.**[27]
Vrsta studije/*Type of study*	Sustavni pregledni rad /*Systematic Review*
Demografski podaci/ podaci o istraživanjima/ *Demographic data/research data*	9 meta-analiza koje su uključivale samo randomizirana kontrolirana ispitivanja objavljena između 2002. i 2013./ *9 meta-analyses that included only randomized controlled trials published between 2002 and 2013.*
Vrsta rupture, opis intervencije, kontrolna skupina, trajanje liječenja/*Type of rupture, intervention description, control group, duration of intervention*	Potpuna akutna ruptura; Usporedba neoperacijski i operacijski liječenih bolesnika / *Total acute rupture Comparison of conservatively and surgicaly treated patients*

Ishodi liječenja/*Treatment outcomes*	Stopa ponovne rupture i funkcionalni ishod/*Rerupture rate and functional out come*
Slaba točka i ograničenja/*The weak point and limitations*	Članci na engleskom jeziku / *Articles in English*
Opažanje i zaključak/*Observation and conclusion*	Konzervativno liječenje bilo je jednako operativnom liječenju u pogledu učestalosti ponovne rupture, opsega pokreta, opsega potkoljenice i funkcionalnih ishoda, dok je smanjena učestalost drugih komplikacija./ *Conservative treatment was equivalent to operative treatment in terms of rerupture rate, range of motion, lower leg circumference, and functional outcomes, while the incidence of other complications was reduced.*
Prvi autor, godina/*First author, year*	**Deng, 2017.**[31]
Vrsta studije/*Type of study*	Metaanaliza/ *Meta-Analysis*
Demografski podaci/ podaci o istraživanjima/ *Demographic data/research data*	8 randomiziranih kontroliranih istraživanja koja su uključivala 762 bolesnika/ *8 randomized controlled trials involving 762 patients*
Vrsta rupture, opis intervencije, kontrolna skupina, trajanje liječenja/*Type of rupture, intervention description, control group, duration of intervention*	Potpuna akutna ruptura; Neoperacijski liječeni n=377; Operacijski liječeni n=381 / *Total acute rupture Conservative treatment n=377 Surgicaly treated n=381,*
Ishodi liječenja/*Treatment outcomes*	Stopa ponovne rupture, učestalost DVT-a, bolesnici koji se vraćaju sportu, opseg pokreta gležnja, funkcionalni rezultati/ *Rerupture rate, incidence of DVT, patients returning to sport, ankle range of motion, functional outcomes*
Slaba točka i ograničenja/*The weak point and limitations*	Relativno male studije s relativno malim brojem ciljanih bolesnika, kratko prosječno razdoblje praćenja, različite varijable / *Relatively small studies with a relatively small number of target patients, short average follow-up period, different variables*
Opažanje i zaključak/*Observation and conclusion*	Operativno liječenje može učinkovito smanjiti stopu ponovne rupture i moglo bi biti bolji izbor za liječenje akutne rupture Ahilove tetive/ *Operative treatment can effectively reduce the rate of re-rupture and may be a better choice for the treatment of acute Achilles tendon rupture*.
Prvi autor, godina/*First author, year*	**van der Eng, 2013.**[28]
Vrsta studije/*Type of study*	Metaanaliza/ *Meta-Analysis*
Demografski podaci/ podaci o istraživanjima/ *Demographic data/research data*	7 randomiziranih kontroliranih istraživanja objavljenih od 2001. do 2012. s uključenih 576 odraslih bolesnika/ *7 randomized controlled trials published from 2001 to 2012 with included 576 adult patients*
Vrsta rupture, opis intervencije, kontrolna skupina, trajanje liječenja/*Type of rupture, intervention description, control group, duration of intervention*	Potpuna akutna ruptura; Neoperacijski liječeni n=286; Operacijski liječeni n=290 / *Total acute rupture Conservative treatment n=286 Surgicaltreatment n=290*
Ishodi liječenja/*Treatment outcomes*	Stopa ponovne rupture, stopa drugih komplikacija/ *Rerupture rate, rate of other complications*
Slaba točka i ograničenja/*The weak point and limitations*	Heterogenost prisutna pri analizi komplikacija, razlika u rehabilitacijskim protokolima / *Heterogeneity present when analyzing complications, difference in the rehabilitation protocols*
Opažanje i zaključak/*Observation and conclusion*	Nema razlike u stopi ponovne rupture između konzervativno i operativno liječenih bolesnika. Operativno liječenje bilo je povezano s dvostruko većom stopom komplikacija od konzervativnog liječenja./ *There is no difference in rerupture rate between conservatively and operatively treated patients. Operative treatment was associated with twice the complication rate of conservative treatment.*

Prvi autor, godina/*First author, year*	**Soroceanu, 2012.**[29]
Vrsta studije/*Type of study*	Metaanaliza/ *Meta-Analysis*
Demografski podaci/ podaci o istraživanjima/ *Demographic data/research data*	10 randomiziranih kontroliranih istraživanja koja su uspoređivala konzervativno i operativno liječenje od 2005. do 2011./ *10 randomized controlled trials comparing conservative and operative treatment from 2005 to 2011*
Vrsta rupture, opis intervencije, kontrolna skupina, trajanje liječenja/*Type of rupture, intervention description, control group, duration of intervention*	Potpuna akutna ruptura; Neoperacijski liječeni n=408; Operacijski liječeni n=418 / *Total acute rupture Conservative treatment n=408 Surgical treatment n=418*
Ishodi liječenja/*Treatment outcomes*	Stopa ponovne rupture, stopa drugih komplikacija, snaga, opseg pokreta, vrijeme do povratka na posao, opseg potkoljenice i funkcionalni ishodi/ *Rerupture rate, rate of other complications, strength, range of motion, time to return to work, calf circumference, and functional outcomes*
Slaba točka i ograničenja/*The weak point and limitations*	Značajna heterogenost između istraživanja/ *significant heterogeneity among the studies*
Opažanje i zaključak/*Observation and conclusion*	Konzervativno liječenje je razuman izbor liječenja u centrima koji koriste funkcionalnu rehabilitaciju. */ Conservative treatment represents a reasonable treatment choice at centers that use functional rehabilitation.*
Prvi autor, godina/*First author, year*	**Jiang, 2012.**[30]
Vrsta studije/*Type of study*	Metaanaliza/ *Meta-Analysis*
Demografski podaci/ podaci o istraživanjima/ *Demographic data/research data*	10 randomiziranih kontroliranih istraživanja koja su uspoređivala konzervativno i operativno liječenje od 1980. do 2011. s ukupno 894 bolesnika/ *10 randomized controlled trials comparing conservative and operative treatment from 1980 to 2011. a total of 894 patients*
Vrsta rupture, opis intervencije, kontrolna skupina, trajanje liječenja/*Type of rupture, intervention description, control group, duration of intervention*	Potpuna akutna ruptura; Neoperacijski liječeni n=453; Operacijski liječeni n=441 / *Total acute rupture Conservative treatment n=453 Surgical tretment n=441*
Ishodi liječenja/*Treatment outcomes*	Ponovna ruptura, vrijeme bolovanja, povratak sportu, adhezija ožiljka, površinska infekcija, poremećaj senzibiliteta, duboka infekcija, DVT, ekstremno produljenje Ahilove tetive/ *Rerupture, sick leave, returned to sports, scar adhesion, superficial infection, sensitivity disorder, deep infection, DVT, extreme lengthening of the Achilles tendon*
Slaba točka i ograničenja/*The weak point and limitations*	Visoka heterogenost među istraživanjima, nedostatak odgovarajućih istraživanja i dosljednog sustava funkcionalne procjene/ *High heterogeneity among studies, lack of appropriate studies and a consistent system of functional assessment.*
Opažanje i zaključak/*Observation and conclusion*	Operativno liječenje može učinkovito smanjiti rizik od ponovne rupture, ali i povećati vjerojatnost ostalih komplikacija. Iz trenutačnih studija nema dovoljno dokaza koji bi poduprli uvjerenje da operacija može dovesti do boljeg funkcionalnog oporavka./ *Operative treatment can effectively reduce the risk of re-rupture, but increase the likelihood of other complications. There is insufficient evidence from current studies to support the belief that surgery can lead to better functional recovery.*

Ukupne stope komplikacija, isključujući ponovnu rupturu, kreću se od 2,7 do 8% kod neoperacijski liječenih, dok se kod operacijski liječenih bolesnika pojavljuju u 26,6 do 34,1%.[22,23,26,28,29] Kod operiranih bolesnika infekcija se pojavljuje od 0 do 13%,[2,22,31,32] ozljeda n. suralisa od 0,42 do 19%,[22,23,30,31] a češća je kod perkutane tehnike operacije.[22,23] DVT se kod neoperiranih bolesnika pojavljuje u 0 do 39% slučajeva, a kod operiranih u 0 do 29%. U metaanalizama učestalost DVT je bez statistički značajne razlike između neoperacijskog i operacijskoga liječenja.[22,26,30,31]

Rasprava

Akutna ruptura Ahilove tetive može se uspješno liječiti neoperacijski i operacijski, posebice ukoliko je neoperacijsko liječenje praćeno funkcionalnom rehabilitacijom koja obuhvaća rano opterećenje težinom.[2,9,22,23,26,27,28,29] Neoperacijsko liječenje prikladna je opcija izbora u liječenju osoba starije životne dobi, sportski neaktivnih osoba, te u bolesnika u kojih postoji povećani rizik od operativnog zahvata, poput težih srčanih bolesti, lošeg općeg stanja bolesnika, u bolesnika s transplantiranim organom, bubrežnom insuficijencijom, sustavnim bolestima, težim oblikom dijabetesa ili terapije glukokortikoidima.[1] Konvencionalno neoperacijsko liječenje podrazumijeva mirovanje u sadrenoj imobilizaciji sa stopalom u položaju plantarne fleksije tijekom šest do osam tjedana, nakon čega se postavlja ortoza sa stopalom u neutralnom položaju kroz dva tjedna, a fizikalna terapija i opterećenje noge započinju od desetoga tjedna. Komplikacije koje se javljaju u konvencionalnom neoperacijskom liječenju su: ponovna ruptura (do15%), izražena atrofija potkoljenične muskulature (do 30%), ukočenost gornjeg nožnog zgloba (neizvediva plantarna i dorzalna fleksija stopala; do 15%), te smanjena gruba snaga ozlijeđenog ekstremiteta (do 40%).[1,2] Za uspjeh neoperacijskoga liječenja ključna je adekvatna funkcionalna rehabilitacija koja obuhvaća rano opterećenje težinom i ranu aktivnu rehabilitaciju uz nošenje funkcionalne ortoze. U dosadašnjim istraživanjima opisani su različiti protokoli funkcionalne rehabilitacije, te još uvijek ne postoji konsenzus o tome koji je protokol najbolji.[2,9] Općeniti pristup temelji se na što ranijem početku rehabilitacije nakon postavljanja dijagnoze potpune akutne rupture Ahilove tetive. Bitno je da UZV nalaz u plantarnoj fleksiji stopala pokazuje kontakt krajeva rupturirane tetive, odnosno da udaljenost nije veća od pet milimetara.[14,15] Inicijalno se postavlja sadrena imobilizacija ili ortoza uz stopalo u plantarnoj fleksiji, od 25° do 30°. Ukoliko stopalo nije postavljeno u adekvatan stupanj plantarne fleksije, razmak između krajeva tetive će i dalje postojati, a ukoliko se postavljanje stopala u plantarnu fleksiju odgađa, za jedan do dva tjedna dolazi do ispunjavanja praznine fibroznim tkivom koje posljedično onemogućava odgovarajuću apoziciju tetivnih krajeva i cijeljenje tetive.[16] Između sedmog i 14. dana,[22,24,25] a prema nekim autorima čak i od prvog dana[9] nakon postavljanja imobilizacije, potrebno je započeti s opterećenjem težinom. Nakon 10 do 14 dana od početka liječenja postavlja se funkcionalna ortoza koja kontrolira opseg pokreta u gležnju. Između drugog i šestog tjedna plantarna fleksija se postupno smanjuje do nultog položaja. Tijekom sedmog i osmog tjedna stopalo se nastavlja progresivno opterećivati težinom u nultom položaju, uz vježbe opsega pokreta od 0° do 30° plantarne fleksije. Nakon osam tjedana skida se ortoza, te se započinje s individualiziranom fizikalnom terapijom koja uključuje terapijske vježbe (opsega pokreta, snaženja mišića potkoljenice i propriocepcije, s postupnim povećanjem opterećenja).[22,24,25] Nakon 12 tjedana započinje se s pravocrtnim trčanjem, vožnjom bicikla i plivanjem, dok se skokovi, ubrzanja i sportski elementi uvode nakon šest mjeseci.[2,25]

Novija istraživanja ukazuju na to da mehaničko opterećenje tijekom funkcionalne rehabilitacije stimulira cijeljenje tetive jer se povećava proizvodnja čimbenika rasta unutar tetive i proizvodnja kolagena.[9,24,26] Patohistološkim pretragama na životinjskom modelu uočeno je kako neoperacijski liječena potpuna akutna ruptura Ahilove tetive pokazuje gotovo normalan histološki uzorak, dok operativno liječena sadrži ožiljno tkivo i manje organizirana kolagena vlakna tijekom prvih osam tjedana.[32] Glavni ciljevi rehabilitacije su povratak anatomske duljine i fiziološke napetosti tetive, te povratak snage i funkcionalni oporavak uz smanjenje boli.[7,9] Važno je spriječiti ponovnu rupturu i poboljšati snagu mišića potkoljenice tijekom prva tri mjeseca rehabilitacije. Kako bi se isto postiglo, rehabilitacijski protokol u prvoj godini nakon ozljede, a osobito unutar prvih šest mjeseci mora biti razumno agresivan, obzirom na to da je potrebna i godina dana bez obzira na modalitet liječenja (neoperacijski ili operacijski) kako bi se funkcionalna snaga mišića potkoljenice vratila na razinu od prije ozljede.[2]

Operacijsko liječenje rupture Ahilove tetive može se izvesti otvorenom, perkutanom i endoskopskom tehnikom.[1,4,21] Jedan od operacijskih načina liječenja je transpozicija tetive m. flexor hallucis longus koja se može učiniti različitim tehnikama, od kojih je sve

popularnija endoskopska tehnika. Prednosti transpozicije m. flexor hallucis longus pred drugim tetivama koje je moguće koristiti u rekonstrukciji poput tetive m. peroneus brevis i m. flexor digitorum longus, je to što je ona izdržljiva tetiva s jačim mišićem od ostalih, ima isti smjer djelovanja i pokreće se u istoj fazi s m. triceps surae.[33,34,35] Ciljevi nakon operacijskoga liječenja su smanjenje trajanja kontinuirane postoperacijske imobilizacije, rana mobilizacija gležnja, te rani početak opterećenja ekstremiteta uz nošenje funkcionalne ortoze.[36] Komplikacije operacijskoga liječenja su ponovna ruptura (do16,6%), DVT (do 27,2%), infekcija rane (do 12,5 %), bol (do 17,5%), ozljede suralnog živca (4,1-18%) i komplikacije ožiljka (1,4-27%).[2,22,24,26]

Prospektivno, randomizirano, kontrolirano istraživanje Manenta i sur. (2019. godina) o liječenju potpune akutne rupture Ahilove tetive obuhvatilo je 11 neoperacijski liječenih bolesnika, 11 bolesnika liječenih operacijski perkutanom tehnikom i 12 bolesnika liječenih operacijski otvorenom tehnikom s jednakim protokolom funkcionalne rehabilitacije. Rezultati su pokazali sličnu učinkovitost sva tri oblika liječenja nakon jednogodišnjeg praćenja, koja je definirana kao sposobnost podizanja na prste jedne i obje noge tijekom tri sekunde, bol nakon hoda ≤2 na skali boli, te povratak aktivnom prijašnjem životu. Nakon jednogodišnjeg praćenja, udio onih koji su uspješno izliječeni bio je 100% u neoperacijski liječenoj skupini, 82% u skupini operiranih perkutanom tehnikom i 83% u skupini operiranih otvorenom tehnikom. Intenzitet bola ≤2 u 52. tjednu bio je 100% u neoperacijskoj skupini, 82% u skupini operiranih perkutanom tehnikom i 83% u skupini operiranih otvorenom tehnikom. Bol je bila povezana s induracijom ožiljka. Aktivnom prijašnjem životu vratilo se 90,9% neoperacijski liječenih bolesnika, 81,8% operiranih perkutanom tehnikom i 91,6% bolesnika operiranih otvorenom tehnikom. Svi neoperacijski liječeni bolesnici imali su postignutu maksimalnu mišićnu snagu potkoljenice, dok se snaga jednog bolesnika operiranog perkutanom tehnikom i dva bolesnika operirana otvorenom tehnikom smanjila za 20 N. Srednja vrijednost plantarne fleksije u mirovanju nakon 52 tjedna u neoperacijski liječenoj skupini bila je 26°, u skupini liječenih operativno perkutanom tehnikom 20°, dok je u skupini liječenih operativno otvorenom tehnikom bila 15°.[24] Suprotne rezultate dobili su Heikkinen i sur. (2017 godine) u svojem randomiziranom kontroliranom istraživanju neoperacijskog i operacijskog liječenja rupture Ahilove tetive u 60 bolesnika s identičnim rehabilitacijskim protokolom. Zaključili su kako je neoperacijsko liječenje rezultiralo većom atrofijom m. soleusa u usporedbi s operativnim, dok je prosječna duljina Ahilove tetive bila 19 mm veća. Ove strukturne promjene djelomično objašnjavaju 10-18% veću mišićnu snagu potkoljenice primijećenu kod operacijski liječenih bolesnika. Također su dokazali kako m. fleksor hallucis longus i duboki fleksori pokazuju jasnu hipertrofiju bez obzira na metodu liječenja. Ovaj nalaz pokazao je da je slabost m. tricepsa surae kompenzirana drugim fleksorima.[25] Krapf i sur. proveli su randomizirano istraživanje na animalnom modelu štakora tijekom osam tjedana. Od ukupno 80 štakora kojima su presječene Ahilove tetive, polovini su operacijski zašivene, a polovina je puštena na slobodan režim. Presječene Ahilove tetive zacijelile su u svih životinja tijekom rane mobilizacije s opterećenjem punom težinom. Nakon četiri tjedna nije bilo razlike u čvrstoći tetive između skupina. Neoperacijsko liječenje pokazalo je pozitivne učinke na remodeliranje s višim stupanjem organizacije kolagenih vlakana. Međutim, uočeno je značajno produljenje tetive u ranoj fazi cijeljenja. U operacijski liječenoj skupini tetive su oko šavova imale ožiljno tkivo, te su se mogli vidjeti samo djelomično organizirani snopovi vlakana.[32]

Park i sur. zaključili su da se akutna ruptura može uspješno liječiti operacijski i neoperacijski, te da je rehabilitacija ključna komponenta liječenja. Kao komplikacije neoperacijskoga liječenja naveli su ponovnu rupturu Ahilove tetive i slabost mišića potkoljenice, a operacijskoga liječenja infekciju, ponovnu rupturu, DVT, hipertrofiju ožiljka i ozljedu suralnog živca.[2] Kauwe je u svom preglednom radu zaključio da funkcionalna rehabilitacija smanjuje rizik ponovne rupture tijekom neoperacijskoga liječenja do mjere da ne postoji značajna razlika u stopi rupture u usporedbi s operacijskim liječenjem. Uzevši u obzir relativno visok rizik komplikacija operacijskoga zahvata, navodi kako najnovija istraživanja prednost daju neoperacijskom liječenju.[9] Nandra i sur. Istaknuli su da se liječenje akutne rupture Ahilove tetive mora individualno procijeniti, ovisno o razini aktivnosti bolesnika prije ozljede i prisutnosti komorbiditeta. Navode da kirurška intervencija smanjuje stopu ponovne rupture, ali uz veći rizik infekcije i postoperativnog morbiditeta. Zaključili su da je program rane mobilizacije i rehabilitacije učinkovit i u operacijskom i u neoperacijskom pristupu, uz usporedive stope ponovne rupture.[23] Holm i sur. su u sustavnom pregledu literature analizirali sedam randomiziranih studija koje su usporedile neoperacijsko i operacijsko liječenje akutne rupture Ahilove tetive sa zaključkom kako su razlike u ishodu minimalne, te da nije utvrđena značajna razlika u učestalosti ponovne rupture ili DVT-a.[26] Sustavni pregledni rad Zhanga i

sur. u kojem je analizirano devet metaanaliza pokazao je da je neoperacijsko liječenje s funkcionalnom rehabilitacijom bilo usporedivo s operacijskim liječenjem u pogledu učestalosti ponovne rupture, postignutog opsega pokreta, opsega potkoljenice i funkcionalnog ishoda, dok je smanjena učestalost drugih komplikacija. U neoperacijski liječenih bolesnika u kojih nije provedena funkcionalna rehabilitacija, zabilježena je povećana stopa rupture.[27]

Deng i sur. su u svojoj metaanalizi zaključili da je kod operacijski liječenih bolesnika smanjena učestalost rupture (3,7% kod operativno, te 9,8% kod konzervativno liječenih bolesnika), no praćeno je povećanim rizikom infekcije rane (5%). Međutim, bitno je istaknuti da je u pet od osam analiziranih radova neoperacijsko liječenje uključivalo dugotrajnu imobilizaciju bez opterećenja težinom. Nije utvrđena značajna razlika između neoperacijski i operacijski liječenih bolesnika u učestalosti DVT-a, broju bolesnika koji su se uspješno vratili sportskim aktivnostima, postignutom stupnju dorzalne fleksije, plantarne fleksije i funkcionalnog ishoda.[31] Van der Eng i sur. u svojoj metaanalizi nisu utvrdili značajnu razliku u stopi ponovne rupture između neoperacijski i operacijski liječenih bolesnika, no neoperacijsko liječenje bilo je povezano s dvostruko većom stopom komplikacija.[28] Soroceanu i sur. su u svojoj metaanalizi zaključili da je korištenjem funkcionalne rehabilitacije stopa rupture bila jednaka i u neoperacijski i u operacijski liječenoj skupini bolesnika, a ukoliko nije korištena funkcionalna rehabilitacija, povećana je stopa rupture u neoperacijski liječenih. Operacijsko liječenje bilo je povezano s apsolutnim povećanjem rizika od 15,8% za ostale komplikacije (duboka i površinska infekcija rane, nekroza kože i tetiva, fistule, adhezija ožiljaka, oštećenje suralnog živca, smanjena pokretljivost gležnja, prekomjerno produljenje tetive, DVT, plućna embolija). Operacijski liječeni bolesnici vratili su se na posao 19 dana prije neoperacijski liječenih. Nije bilo značajne razlike između dvije vrste liječenja s obzirom na postignuti opseg potkoljenice, mišićnu snagu i funkcionalni ishod.[29] Rezultati metaanalize Jianga i sur. pokazali su da je operacijsko liječenje bilo superiorno u odnosu na neoperacijsko u pogledu nižeg rizika rupture i kraćeg vremena bolovanja, ali inferiorno u pogledu rizika od komplikacija. Nije utvrđena značajna razlika između dvije vrste liječenja u pogledu broja bolesnika koji su se uspješno vratili sportu prije ozljede. Analize podskupina pokazale su značajne razlike u odnosu na adheziju ožiljka, površinsku infekciju i poremećaj senzibiliteta koji se javljaju u operacijski liječenih bolesnika. Obzirom na to da nisu utvrđene značajne razlike u pojavi infekcije, DVT-a i ekstremnog produljenja Ahilove tetive, zaključili su kako temeljem dostupnih istraživanja nema dovoljno dokaza koji bi podržali uvjerenje da operacijsko liječenje dovodi do boljeg funkcionalnog oporavka.[30]

Zaključak

Rezultati istraživanja objavljenih u posljednjih deset godina ukazuju na to da se akutna ruptura Ahilove tetive može uspješno liječiti i neoperacijski i operacijski, naročito ukoliko je neoperacijsko liječenje praćeno funkcionalnom rehabilitacijom koja obuhvaća rano opterećenje težinom. Korištenjem takvog protokola liječenja pokazalo se da je učestalost ponovne rupture gotovo jednaka kao i kod operacijski liječenih bolesnika. Rezultati također pokazuju da ne postoji veća razlika između dva načina liječenja vezano za povratak mišićne snage i opsega pokreta u gležnju. Što se tiče boli, ona je manja kod neoperacijski liječenih bolesnika, jer se bol u operiranih bolesnika javlja i zbog induracije ožiljka. Ostale komplikacije liječenja odnose se na infekciju rane, nekrozu kože i tetiva, fistule, adheziju ožiljka, oštećenje suralnog živca, prekomjerno produljenje tetive, DVT i plućnu emboliju, te su općenito učestalije i povezane s operacijskim liječenjem. Funkcionalna rehabilitacija ističe se kao neizostavni dio liječenja rupture Ahilove tetive, bilo neoperacijskim bilo operacijskim načinom. Opća načela rehabilitacije obuhvaćaju rano opterećenje tjelesnom težinom tijekom hoda i ranu kontroliranu mobilizaciju, što dovodi do boljeg funkcionalnog oporavka i zadovoljstva bolesnika.

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Pregledni članak
Review

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Prevencija padova starijih osoba

Prevention of falls of the elderly

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Sažetak

Uvod i cilj istraživanja: U Europi i svijetu broj ljudi starijih od 65 godina kontinuirano i ubrzano raste, što smatramo jednim od značajnih javnozdravstvenih izazova današnjice. Starije osobe često doživljavaju padove koji mogu dovesti do prijeloma, ozljeda glave, smanjene pokretljivosti i dugotrajne hospitalizacije i smrti. Cilj ovoga rada bio je utvrditi rizične čimbenike i prikazati načine prevencije padova starijih osoba kako bi se spriječila invalidnost, smrtnost, te troškovi zdravstvenih ustanova koje iste izdvajaju pri padovima i posljedičnim prijelomima starijih osoba.

Metode: Pregledano je i analizirano 116 članaka iz baze podataka PubMed i 60 članaka iz baze podataka Google Schoolar koje su sadržavale neke ili sve ključne riječi za pretraživanje, za razdoblje od 2017.- 2022. godine.

Od toga je iskorišteno 33 članka iz obje baza podataka koji su sadržavali sve ključne riječi. Ključne riječi bile su: rizični čimbenici za padove, sprječavanje padova, starije osobe, zajednica.

Isključni kriteriji bili su članci stariji od 2017.godine, osobe mlađe od 65 godina, institucionalizirani bolesnici i članci koji nisu bili na engleskom jeziku.

Rezultati: Utvrđeno je da se jednokratni padovi uglavnom pripisuju vanjskim čimbenicima, dok se ponavljajući padovi javljaju zbog unutarnjih čimbenika (kuće, stanovi).

Tijekom promatranog razdoblja rezultati brojnih studija potvrdili su da su programi vježbanja snage i ravnoteže tijela kod kuće značajno smanjili broj padova starijih osoba. Plesne aktivnosti bile su povezane s manjim rizikom od pada (37%) i smanjenom stopom pada (31%). Imale su povoljne ishode na tjelesnim funkcijama i pokazalo se da su učinkovita intervencija prevencije pada.

Rezultati studija pokazuju da je potrebno poboljšati suradnju između multidisciplinarnih zdravstvenih timova na svim razinama zdravstvene zaštite, a posebno primarne zdravstvene zaštite, kako bi se pratile starije osobe s potencijalnim rizicima od pada i s prethodnim padovima, te smanjila njihova pojava. Time će se izbjeći potreba za hospitalizacijom i potrebom rehabilitacije u bolnicama pri zadobivanju težih tjelesnih ozljeda uslijed padova.

Zaključak: Brojne studije utvrdile su da specifični programi vježbanja smanjuju rizik i stopu padova kod starijih ljudi koji žive u zajednici. Zdravstveni djelatnici trebali bi biti uključeni u planiranje programa prevencije pada. Robotski omogućena podrška za dnevne aktivnosti u okruženju pametnog doma može se koristiti za istraživanje pomoćnih tehnologija za skrb o starijim osobama. To je obećavajuće područje koje detektira padove starijih osoba.

Ključne riječi: rizični čimbenici za padove, sprječavanje padova, starije osobe, zajednica

Summary

Objectives: In Europe and the world, the number of older people is continuously and rapidly growing which we consider one of the most significant public health-challenge of today. Seniors of ten experience falls that can lead to fractures, head injuries, reduced mobility, and long-term hospitalization and death.

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The aim of this paper was to determine risk factors and show ways of preventing falls of the elderly in order to prevent disability, mortality and the costs of health institutions that allocate them in such events.

Methods: 116 articles from the Pub Med database and 60 articles from the Google Scholar database that contained some or all of the search key words for the period 2017-2022 were reviewed and analyzed.

Thirty three of these articles from both databases were used, which contained all the key words. The key words were: risk factors for falls, prevention of falls, elderly, community.

The exclusive criteria were articles older than 2017, people younger than 65, institutionalized patients and articles that were not in English.

Results: It was found that one of the falls was mainly attributed to external factors, while repetitive declines occur due to internal factors (houses, apartments). During the observed period, the results of numerous studies confirmed that strength and balance exercise programs at home significantly reduced the number of falls of the elderly. Dance interventions were associated with a lower risk of falling (37%) and a reduced rate of decline (31%). Dance mind-motor activities had favorable outcomes on bodily functions and were shown to be an effective fall prevention intervention.

The results of the studies show that collaboration between multidisciplinary health teams at all levels of health care, especially primary care, needs to be improved to follow older people with potential risks of falling and with previous falls and reduce their occurrence. This will avoid the need for medium and high-complexity emergency procedures in hospital units.

Conclusion: Specific exercise programs have been found to reduce the risk and rate of falls in older people living in the community. Health professionals should be involved in planning a fall prevention program. Robotically integrated smart homes can be used to explore assistive technologies for senior care. It is a promising area, especially for long-term care and prevention of falls of the elderly.

Key words: risk factors for falls, prevention of falls, elderly people, community

Uvod

Europska i svjetska populacija stari.[1]Svaka treća osoba starija od 65 godina i svaka druga osoba starija od 80 godina doživi barem jedan pad tijekom godine dana.[2]Starenje povećava rizik od pada, kao i rizik od ozljeda zbog pada, što zahtijeva dugotrajnu njegu i skrb. Dugotrajna skrb je financijski teret za zdravstveni sustav jer uslijed padova često dolazi do težih tjelesnih ozljeda i prijeloma koje iziskuju hospitalizaciju i potrebu za rehabilitacijom.[3]

Nenamjerni pad smatra se događajem koji rezultira nenamjernim zaustavljanjem osobe na tlu. Ako osoba pretrpi težak udarac, gubitak svijesti ili paralizu tijekom moždanog udara ili epileptičkog napadaja i padne, takav se događaj ne smatra nenamjernim padom.[2]U 30% slučajeva dolazi do ponovljenih padova. Ponavljajući padovi definiraju se kao više od dva pada godišnje i često su povezani s čimbenicima rizika za pad, uključujući kronične bolesti. Padovi često rezultiraju prijelomima, ozljedama glave, poteškoćama s pokretljivošću, dugotrajnom hospitalizacijom, potrebom rehabilitacije, te mogućim smrtnim ishodom.[4]

Smanjenje rizika od padova ključni je fokus preventivnih napora za poboljšanje kvalitete života starijih osoba.[5]

Cilj ovoga rada bio je utvrditi rizične čimbenike i prikazati načine prevencije padova starijih osoba, kako bismo spriječili invalidnost, smrtnost, te troškove zdravstvenih ustanova koje iste izdvajaju pri ovakvim događajima.

Metode

Pregledano je i analizirano 116 članaka iz baze podataka PubMed i 60 članaka iz baze podataka Google Schoolar koje su sadržavale neke ili sve ključne riječi za pretraživanje za razdoblje od 2017.-2022. godine.

Od toga je iskorišteno 33 članka iz obje baza podataka koji su sadržavali sve ključne riječi. Ključne riječi bile su: rizični čimbenici za padove, sprječavanje padova, starije osobe, zajednica.

Isključni kriteriji bili su članci stariji od 2017. godine, osobe mlađe od 65 godina, institucionalizirani bolesnici i članci koji nisu bili na engleskom jeziku.

Rezultati

Čimbenici rizika za pad podijeljeni su na unutarnje i vanjske. Unutarnji čimbenici rizika su starija dob, ortostatska hipotenzija, smanjena pokretljivost, nestabilan hod ili poremećaj ravnoteže, ograničena fizička izdržljivost, problemi sa stopalima, oslabljen vid i sluh, poliurija, promijenjeno mentalno stanje, kronične bolesti poput dijabetes melitusa, neurološke, koštane i mišićno-koštane bolesti.[6] Vanjski čimbenici rizika za pad uključuju okolišne uvjete kao što su slabo osvjetljenje, neodgovarajuća obuća i odjeća koja utječe na pokretljivost osobe, skliska podna prostirka, skliske kade, kabeli, podaci o prethodnom padu, polifarmacija i uporaba određenih lijekova. Rizik od

pada povećava se s povećanjem broja čimbenika rizika.[6]

Jedan od rizika da starije osobe padnu u kućnom okruženju je nedostatak pomagala za kretanje (invalidska kolica, štake, pomagala za hodanje).[7]Namještaj koji predstavlja rizik od pada za starije osobe uključuje mekane fotelje s niskim rukohvatima, te stolove ili sjedala s oštrim rubovima za koje se teško uhvatiti ili držati pri kretanju.[7]

U domovima starijih osoba često nema protu-kliznih pločica, protukliznih traka i protu klizne zaštite na rukohvatima i podovima u kupaonici.[7] Niski kreveti povećavaju rizik od pada zbog poteškoća pri ustajanju ili spoticanja prilikom ležanja na krevetu.[7] Rasvjeta u dnevnoj sobi često je neprikladna i slaba, pa se pri hodanju starija osoba može spotaknuti i pasti.[7] Izrazito rizične su stepenice i kupaonice. [7,8]

U Hrvatskoj se Morseova ljestvica koristi za procjenu rizika od pada, a kao sastavni dio dokumentacije za njegu definirane Pravilnikom o dokumentaciji za njegu. Morseova ljestvica procjenjuje šest čimbenika rizika: povijest padova, sekundarne dijagnoze, korištenje pomagala za kretanje, primjenu intravenske terapije, pokretljivost i mentalno stanje bolesnika. Svaki od šest čimbenika rizika procjenjuje se kroz dvije ili tri ponuđene stavke sa zbrojem brojčane vrijednosti odgovora. Mogući raspon bodova je od 0 do 125. Ovisno o konačnom rezultatu, bolesnici se kategoriziraju kao niski (0-24 boda), umjereni (25-44 boda) ili visoki rizik od pada (45 ili više bodova).[9]

Intervencije za prevenciju padova mogu biti jedno komponentne i višekomponentne. Jedno komponentne intervencije uključuju vježbanje, dok višekomponentne intervencije mogu uključivati grupno ili individualno vježbanje, psihološke intervencije (kognitivno-bihevioralna terapija), nutritivnu terapiju, edukaciju, liječenje lijekovima, liječenje urinarne inkontinencije, promjene u okolišu, fizikalnu ili radnu terapiju, socijalne usluge ili usluge u zajednici i upućivanje specijalistima (npr. oftalmolog, neurolog ili kardiolog).[10]

Tijekom promatranog razdoblja rezultati brojnih studija potvrdili su da su programi s fokusom na vježbe jačanja snage i ravnoteže tijela od kuće značajno smanjili broj padova starijih osoba. Plesne intervencije bile su povezane s manjim rizikom od pada (37%) i smanjenim brojem padova (31%).

Longitudinalna studija A. K. de Souze koja je uključivala 345 starijih odraslih osoba koje su ostale u klinici za prevenciju pada, otkrila je da program vježbanja snage i ravnoteže kod kuće značajno smanjuje rizik za pad u usporedbi s uobičajenom njegom u samoj klinici. (1,4 naspram 2,1 pada po osobi godišnje).[9]

Rezultati studije autora T. Liu - Ambrosea podržavaju korištenje programa vježbanja kod kuće za sekundarnu prevenciju pada, ali zahtijevaju ponavljanje u drugim kliničkim okruženjima.[11]

Pregledni članak autora E. Gambare opisuje da se jednokratni padovi uglavnom pripisuju vanjskim čimbenicima, dok se ponavljajući padovi javljaju zbog unutarnjih čimbenika (unutar stambenih objekata). [11]

Tablica 1. Čimbenici rizika za padove
Table 1 Risk factors for falls

Vanjski: slabo osvjetljenje/ ***External*** *low lighting*
neodgovarajuća obuća i odjeća/ *inappropriate footwear and clothing*
s kliska podna prostirka/ *slippery floor mat*
skliske kade/ *bathtubs*
kabeli/ *cables*
podaci o anamnestičnom padu/ *data on anamnestic falls*
polifarmacija/ *polypharmacy*
upotreba određenih lijekova/ *use of certain medications*
Unutarnji: starija dob/ ***Interior:*** *older age*
Ortostatska hipotenzija/ *Orthostatich potension*
smanjena pokretljivost/ *reduced mobility*
nestabilan hod ili poremećaj ravnoteže/ *unstable gaitor balance disorder*
ograničena fizička izdržljivost/ *limited physical endurance*
problemi sa stopalima/ *foot problems*
oslabljen vid i sluh/ *impaired vision and hearing*
poliurija/ *polyuria*
promijenjeno mentalno stanje/ *altered mental state*
kronične bolesti/ chronic diseases

Tablica 2. Intervencije za prevenciju padova
Table 2 Interventions for the prevention of falls

Jednokomponentne:vježbanje/ *Single-component training*
Višekomponentne: vježbanje/ *Multi-component: training*
probir lijekova/

drug screening
kognitivno-bihevioralna terapija/ *cognitive-behavioral therapy*
*n*utritivna terapija/ *nutritional therapy*
*e*dukacija/ *education*
liječenje urinarne inkontinecije *treatment of urinary incontinence*
promjene u okolišu/ *changes in the environment*
fizikalna i radna terapija/ *physical and occupational therapy*
upućivanje specijalistima/ *referral to specialists*

Rasprava

Starije osobe sklone su padovima koji rezultiraju ozljedama i invaliditetom, zbog čega je prevencija pada nacionalni interes. Prevencijom padova i posljedičnih ozljeda smanjujemo troškove zdravstvenih ustanova koji se izdvajaju pri hospitalizaciji i rehabilitaciji starijih osoba.[12]

Slučajni pad među starijim osobama koje žive u zajednici povećava rizik od morbiditeta, hospitalizacije i posljedične institucionalizacije i može se spriječiti.[12]

Procjene kućnog okruženja često se koriste za usmjeravanje intervencija za sprječavanje padova.[8]

Ženski spol, starije osobe (starije od 80 godina), osobe sa smanjenim kognitivnim statusom, oštećenja vida, osobe s reumatološkim bolestima i pojava prethodnih padova u posljednjih šest mjeseci, čimbenici su koji povećavaju učestalost padova.[4] Čimbenici rizika za padove na koje ne utječemo kako bismo smanjili rizik od padova dovode do opetovanih padova koji narušavaju kvalitetu života starijih osoba.[13]

Čimbenici rizika za padove kod starijih ljudi su brojni, a uključuju kućno okruženje, prethodne padove, socijalni status pojedinca, mobilnost i farmakoterapiju.[14]Starenje je ključni čimbenik povezan s padom. Stopa smrtnosti povezana s padom raste s godinama, s najvišom nakon 80. godine života.[14] Starenje dovodi do fizičke slabosti, smanjene pokretljivosti ili nepokretnosti, smanjene funkcionalne sposobnosti i pojave kroničnih bolesti. Brojna kronična stanja i bolesti isprepliću se kod starijih osoba, što otežava procjenu točne identifikacije određenog čimbenika rizika.[14]

Padovi muškaraca često su povezani s vanjskim okruženjem, dok su padovi žena povezani s unutarnjim okruženjem. Vjerojatnije je da će na starije muškarce utjecati vanjsko okruženje, dok se, primjerice, vraćaju kući neravnim pločnikom.[15] Stariji ljudi koji žive u urbanim sredinama često padaju pri hodu uz cestu, dok stariji ljudi koji žive u selu češće padaju u dvorištu. Stariji ljudi koji žive u gradovima nakon pada imaju veću vjerojatnost da će biti hospitalizirani od starijih ljudi koji žive na selu. Žene s kroničnim bolestima imaju veću vjerojatnost pada u kućnom okruženju, te se predlaže i procjena opasnosti kod kuće. Tijekom odijevanja, kuhanja, odlaska u nužnik, često se javljaju padovi starijih osoba. [15]

Stariji ljudi koji su doživjeli padove mogu imati strah od pada, anksioznosti nakon pada, depresiju i smanjenje tjelesne aktivnosti, što negativno utječe na njihovu dobrobit.[2]

Iako su brojna istraživanja pronašla niz čimbenika rizika za padove u starijih osoba, jedan od važnih čimbenika rizika je depresija. Depresija dovodi do kognitivnog oštećenja, poteškoća u svakodnevnom funkcioniranju, smanjene kvalitete života i rizika od samoubojstva. Simptomi mogu trajati godinama ako nije postavljena dijagnoza i nije propisana terapija.[11]

Tijekom depresije dolazi do psihomotorne sporosti, usporavanja hoda, smanjene razine energije i smanjene tjelesne aktivnosti. Ovo stanje povećava rizik od pada i dovodi do samog pada.

Budući da su posljedice padova često ozbiljne, iznimno je važno identificirati čimbenike rizika i promijeniti ih. Na temelju kriterija Bradford Hilla utvrđeno je da je bolji način rješavanja simptoma depresije provođenje nefarmakoloških mjera (psihoterapija, radna terapija), te se na taj način smanjuje rizik od pada koji može biti povezan s psihotropnim lijekovima – selektivnim inhibitorima ponovne pohrane serotonina (SIPPS).[16]

Često se javlja i strah od pada (SOP).[11] Iako su brojne studije zabilježile veliki broj čimbenika rizika za padove u starijih osoba, prisutnost barem jednog pada u prethodnoj godini najjači je prediktor pojave novih padova. SOP je opisan kao zabrinutost zbog pada koji može rezultirati ograničenjima aktivnosti ljudi, što smanjuje kvalitetu života. Trenutno je SOP dio rutinske procjene i skrbi za starije osobe.[17,18]Za svaku stariju osobu treba utvrditi promjenjive čimbenike rizika za padove na temelju početne procjene i potrebnih intervencija. Stoga je važno da zdravstveni djelatnici mogu točno utvrditi je li došlo do prethodnog pada.[17]

Kod socijalno aktivnih starijih stanovnika zajednice čimbenici rizika za pad su prethodni pad, niža razina obrazovanja, starenje, blaga demencija i određena ograničenja mobilnosti. Te rezultate treba integrirati u programe za sprječavanje padova.[14]

Kardiovaskularne zdravstvene studije i pokazatelji prijeloma osteoporoze učinkoviti su za predviđanje rizika od padova kod starijih ljudi. Starije odrasle

osobe s krhkom osteomuskularnom građom imale su veću vjerojatnost da će doživjeti ponovljene padove.[18]Padovi često uzrokuju velike ozljede (prijelome kuka i intrakranijalna krvarenja) koje zahtijevaju hospitalizaciju i rehabilitaciju. Stoga su preventivne intervencije od iznimne važnosti.[19]

Ljudi koji su bili pothranjeni ili su imali rizik od pothranjenosti, imali su 45% veću vjerojatnost da će doživjeti barem jedan pad od onih koji su bili dobro hranjeni, iako nije uočena povezanost između indeksa tjelesne mase (ITM) i ponovljenih padova.[20]

Intervencije za prevenciju padova mogu biti jedno komponentne i višekomponentne. Jedno komponentne intervencije uključuju vježbanje, dok višekomponentne intervencije mogu uključivati vježbanje i npr. probir lijekova. Višekomponentne intervencije mogu smanjiti stopu padova i rizik od pada više od adekvatne zdravstvene njege.[21]Intervencije vježbanja su učinkovite kada se provode i u skupinama i pojedinačno. Posebno su učinkoviti programi mišićne snage i ravnoteže, te programi koji uključuju trening ravnoteže. Vježbe za gornje i donje udove koje se mogu izvoditi kod kuće i primijeniti na veći broj starijih ljudi koji žive u zajednici, izuzetno su učinkovite.[22]Brojne studije potvrđuju kako vježbanje sprječava padove u starijih osoba.[23]

Kako se broj starijih ljudi u Europi i svijetu svakodnevno povećava, a time i rizik od padova i ozljeda, Britanski nacionalni institut za zdravlje i njegu uveo je smjernice za prevenciju padova. Smjernice uključuju: vježbe snage i ravnoteže, procjenu opasnosti fizičkog okruženja, procjenu vida i upućivanje oftalmologu, pregled lijekova sa smanjenjem doze lijeka ili prekid uzimanja određenog lijeka.[2]Višekomponentne intervencije smanjuju stopu padova i rizik od ponavljajućih padova.[24]

Potrebne intervencije mogu uključivati grupno ili individualno vježbanje, psihološke intervencije (kognitivno-bihevioralna terapija), nutritivnu terapiju, edukaciju, liječenje lijekovima, upravljanje urinarnom inkontinencijom, promjene u okolišu, fizikalnu ili radnu terapiju, socijalne usluge ili usluge u zajednici i upućivanje specijalistima (npr. oftalmologu, neurologu ili kardiologu).[25]

Zdravstveni djelatnici, uključujući medicinske sestre, trebali bi biti uključeni u planiranje programa prevencije pada jer svakodnevno pružaju skrb i njegu starijim osobama.[19]Potrebno je da medicinske sestre uz pomoć standardiziranih testova za procjenu rizika za pad utvrde vjerojatnost pada starijih osoba.[26]

Pokazalo se da su preventivne intervencije, poput kombiniranih intervencija vježbanja i medicinske skrbi, učinkovite jer smanjuju rizik od pada starijih osoba. Više se primjenjuju u urbanim sredinama, a teže im je pristupiti u ruralnim zajednicama.[27]

Dokazi naglašavaju da programi vježbanja mogu spriječiti padove kod starijih odraslih osoba, a mogu imati i blagotvoran učinak na depresivnu simptomatologiju.[16]

Longitudinalna studija A. K. de Souze, koja je uključivala 345 starijih odraslih osoba koje su ostale u klinici za prevenciju pada, otkrila je da program vježbanja snage i ravnoteže kod kuće značajno smanjuje rizik za pad u usporedbi s uobičajenom njegom u samoj klinici. (1,4 naspram 2,1 pada po osobi godišnje).[9]Rezultati studije pokazuju da je potrebno poboljšati suradnju između primarne i sekundarne zdravstvene zaštite, posebno primarne zdravstvene zaštite, kako bi se otkrile starije osobe s potencijalnim rizicima od pada i s prethodnim padovima, te smanjila njihova pojava. Time će se pri težim tjelesnim ozljedama uslijed padova izbjeći potreba za hospitalizacijom.[9]

Rezultati studije autora T. Liu - Ambrosea podržavaju korištenje programa vježbanja kod kuće za sekundarnu prevenciju pada, ali zahtijevaju ponavljanje u drugim kliničkim okruženjima.[10]

Pregledni članak autora E. Gambare opisuje da se jednokratni padovi uglavnom pripisuju vanjskim čimbenicima, dok se ponavljajući padovi javljaju zbog unutarnjih čimbenika (stambeni objekti).[11]

Uvidom u metaanalizu 29 randomiziranih kliničkih ispitivanja koja su proveli M. Mattle i sur. pokazuju da su plesne intervencije povezane s manjim rizikom od pada (37%) i smanjenom stopom pada (31%). Plesne aktivnosti imale su povoljne ishode na tjelesnim funkcijama, a pokazalo se da su učinkovita intervencija prevencije pada.[12]

Plesne intervencije poboljšavaju ravnotežu i pokretljivost i ne zahtijevaju veće fizičke napore. Zbog toga ova aktivnost može biti korisna u sprječavanju padova starijih ljudi.[12]

Tjelesna aktivnost, strah od pada i kvaliteta života vrlo su važne sastavnice gerijatrije. Interakcija između ovih sastavnica može varirati između starijih odraslih osoba koje žive u zajednici i ljudi koji žive u ustanovi (starački domovi). Trenutni rezultati sugeriraju da starenje u vlastitom domu osigurava bolje zdravstvene ishode od institucionaliziranog starenja.[25]Adaptacija prostora stanovanja, poput kupaonica, mijenja se tek nakon višestrukih padova. Čini se da samo jedan pad ne dovodi do adaptacije životnog prostora.[28] Potrebno je odrediti rizične čimbenike za pad u vlastitom domu, te ga izmijeniti.[29]Štoviše, neophodno je razviti preventivni rad koji uključuje cijelu zajednicu, kako bi se podigla svijest o ovom ponavljajućem događaju među starijim osobama.[9]

Kuće s ugrađenom pametnom tehnikom i robotikom mogu se koristiti za istraživanje pomoćnih tehnologija za njegu i otkrivanje padova starijih osoba. Pametne kuće imaju robota za kućne usluge, mrežu kućnih senzora, mrežu senzora za tijelo i mobilne uređaje. Razvijene su pametne pomoćne tehnike koje omogućuju prepoznavanje aktivnosti kretanja tijela pomoću senzora i kućnih robota putem audio signala.[30] Proizvedene su aplikacije na visokoj razini koje otkrivaju i reagiraju na ljudske padove i ozljede.[30]Pametne kuće su obećavajuće područje, posebno za dugotrajnu skrb za starije osobe. [30] Međutim, tehnologije praćenja treba podići na višu razinu. Potrebne su detaljnije studije kako bi se procijenio i pokazao njihov potencijal za produljenje neovisnog života starijih osoba.[30,31]Zbog brzog napretka tehnologije i interneta, povezanost čovjeka i računala pomoću senzora smatra se učinkovitom metodom za rješavanje problema otkrivanja pada.[32]

Zaključak

Starije osobe sklone su padovima koji rezultiraju ozljedama i invaliditetom, zbog čega je prevencija pada nacionalni interes. Prevencijom padova i posljedičnih ozljeda smanjujemo troškove zdravstvenih ustanova koji se izdvajaju pri hospitalizaciji i rehabilitaciji starijih osoba. Specifični programi vježbanja smanjuju rizik i stopu padova kod starijih ljudi koji žive u zajednici. Aktivne višekomponentne intervencije imale su pozitivne učinke na smanjenje stope pada i broja ljudi koji su doživjeli padove. Zdravstveni djelatnici trebali bi biti uključeni u planiranje programa prevencije pada (vježbanje, zdravstvena zaštita i njega). Pametne kuće mogu se koristiti za istraživanje pomoćnih tehnologija za skrb o starijim osobama.To je obećavajuće područje, posebno za dugotrajnu njegu i prevenciju padova starijih osoba. Međutim, tehnologije praćenja treba podići na višu razinu. Potrebne su detaljnije studije kako bi se procijenio i pokazao njihov potencijal i doprinos produljenju neovisnog života starijih osoba. Budući da smo populacija koja stari, te broj starijih ljudi svakodnevno raste, postoji hitna potreba za razvojem sustava za otkrivanje padova.

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Review
Pregledni članak

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The role of Toll-like receptors in the etiopathogenesis and treatment of schizophrenia: a literature review

Uloga Toll-like receptora u etiopatogenezi i liječenju shizofrenije: pregled literature

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Summary

In this review paper, we present current theories about the inflammatory etiopathogenesis of schizophrenia. We mentioned the biopsychosocial etiological model of the disease and stressed the importance of neuroinflammation and neurodegeneration in its biological basis.

We searched the literature about innate immunity, Toll-like receptors, inflammation, and neurodegeneration, and we summarized their role in the etiopathogenetic mechanisms of schizophrenia. We also found studies on available antipsychotics that can regulate the expression of Toll-like receptors and modulate innate inflammatory mechanisms. Despite the effective properties of antipsychotics in reducing psychotic symptoms, their role in inflammatory mechanisms remains imprecise and under-researched.

More specific information about how antipsychotics affect neuroinflammation could lead to the development of a wider range of possible drugs that could keep inflammatory processes working properly and improve mental abilities and, ultimately, the quality of life.

Key words: anti-psychotics, immunity, inflammation, neurodegeneration, schizophrenia

Sažetak

U ovom preglednom radu predstavili smo aktualne teorije o upalnoj etiopatogenezi shizofrenije. Spomenuli smo biopsihosocijalni etiološki model bolesti i naglasili važnost neuroinflamacije i neurodegeneracije u njezinoj biološkoj osnovi.

Pretražili smo literaturu o urođenoj imunosti, Toll-like receptorima, upali i neurodegeneraciji, te smo saželi njihovu uloga u etiopatogenetskim mehanizmima shizofrenije. Također smo pronašli i studije o dostupnim antipsihoticima koji mogu regulirati ekspresiju Toll-like receptora i modulirati urođene upalne mehanizme. Unatoč učinkovitim svojstvima antipsihotika u smanjenju psihotičnih simptoma, njihova uloga u upalnim mehanizmima ostaje neprecizna i nedovoljno istražena.

Specifičnije informacije o tome kako antipsihotici utječu na neuroinflamaciju mogu dovesti do razvoja šireg raspona mogućih lijekova koji bi mogli održati ispravnima upalne procese, poboljšati mentalne sposobnosti, a u konačnici i kvalitetu života.

Ključne riječi: antipsihotici, imunitet, upala, neurodegeneracija, shizofrenija

Introduction

Schizophrenia is a severe mental disease that affects a large number of people around the world. According to the World Health Organization, about 24 million people worldwide have this disease, which

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is about 0.32% of the total world population.[1] The etiology of schizophrenia has not been clarified at the moment. However, many studies show a possibility of multiple factors that confirm the biopsychosocial etiopathogenetic model presented as a combination of genetic vulnerability, impacts from the environment, and various psychological factors.[2] It is assumed that the beginning of this disease dates back to the fetal period. Exposure to infectious diseases, traumas, or dangerous substances during pregnancy can trigger inflammatory reactions that alter fetal brain development, which continues later through synaptogenesis and a flawed disorder of neural connections.[3]

There are many descriptions of a connection between infection, long-term inflammation of the central nervous system (CNS), and schizophrenia. For example, signs of schizophrenia have been observed in cases of encephalitic, viral central nervous system infections caused by the herpes simplex virus, measles, and autoimmune disorders such as lupus erythematosus and scleroderma.[4] The immune system plays a significant role in brain development and the pathophysiology of neurodegenerative diseases such as Alzheimer's, Parkinson's, and multiple sclerosis, as well as in the etiopathogenesis of psychiatric disorders such as schizophrenia, depression, and bipolar affective disorder. Neuroinflammation in neurodegenerative disorders is a pathophysiological mechanism that could explain the pathophysiology of schizophrenia, which involves an innate immune response through the Toll-like receptors (TLRs).[5]

The etiology and pathophysiology of schizophrenia

Schizophrenia seems to be not a single disease but a whole spectrum of disorders with abnormalities in perception of reality, opinion, emotions, and behavior. Although the exact cause of this disorder is unknown, various studies show that it is a state of complex etiology and pathophysiology depending on many psychological, biological, and environmental factors.[6] Various psychological factors, including stress, trauma, and addiction, have been associated with the onset and worsening of schizophrenia symptoms. Much genetic research has resulted in evidence to suggest that individuals with a family predisposition to schizophrenia are at greater risk of developing psychotic disorders.[7]

The environment can also have a significant impact. Various environmental factors have been found to contribute to the prenatal risk of schizophrenia, including viral, bacterial, and parasitic infections; complications during fetal and perinatal development; exposure to stress or trauma; and the misuse of various psychoactive substances.[8] Consequently, these harmful factors can cause changes in neural connections with the manifestation of symptoms of schizophrenia, which are clinically seen in impaired abilities of perception, thought, and behavior.[9] The anti-inflammatory properties of antipsychotics, the therapeutic effects of anti-inflammatory substances, and the genetic, biochemical, and immunological discoveries indicate that inflammation plays a significant role in schizophrenia.[4] Activation of microglia, production of inflammatory factors, and damage to neural connections are associated with the onset and development of psychotic symptoms. TLRs could be involved in these complex processes as part of the innate immune response, which triggers neuroinflammation.[5]

Toll-like receptors

The host's innate immune system is the primary defense against infectious antigens, but tissue damage from noninfectious etiology factors can also trigger an inflammatory response. This system is evolutionarily preserved in various species, from the wine fly to mammals. Compared to the acquired immunity that develops specifically against each infection, the innate immune system's response is considered stereotypical and nonspecific. TLRs play a crucial role in this type of immunity.[10] TLRs belong to the group of pattern recognition receptors (PRRs). They are responsible for detecting molecular samples associated with pathogens, known as pathogen-associated molecular patterns (PAMPs), or with molecular patterns related to tissue damage, known as damage-associated molecular patterns (DAMPs).[11] So far, 13 species of Toll-like receptors have been found in mammals, and 10 have a functional role in humans. The first member of this receptor family, which was discovered in humans, is TLR4. It can recognize lipopolysaccharide (LPS) obtained from the outer membrane of Gram-negative bacteria as a ligand, and its role so far has been most explored in the pathophysiology of schizophrenia.[12] Some TLRs are located on the cell surface, and some are on the endosomal surface within the cell. The cell membranes contain TLR1, 2, 4, 5, and 6. The remaining receptors, TLR3, 7, 8, 9, and 10, are on the endosomal membrane.[13,14] In Table 1, we summarized their characteristics.

In tissue damage,the primary role of TLRs is to initiate the inflammatory process, manage the pain system, preserve the central nervous system, and

Table 1 Toll-like receptors and their characteristics
Tablica 1. Toll-like receptori i njihove karakteristike

Receptor	**Location** *Lokacija*	**Ligand**		**Main role** *Glavna uloga*
		Pathogen-associated molecular pattern *Molekularni uzorak povezan s patogenima*	**Damage-associated molecular pattern** *Molekularni uzorak povezan s oštećenjem*	
TLR1	Cell surface *Površina stanice*	Peptidoglycan *Peptidoglikan* Lipopolysaccharide *Lipopolisaharid*	Unknown *Nepoznat*	Bacterial infection recognition *Prepoznavanje bakterijske infekcije*
TLR2	Cell surface *Površina stanice*	Lipoproteins *Lipoproteini*	Hyaluronic acid *Hijaluronska kiselina* High-mobility group box 1 protein *Grupa 1 proteina visoke mobilnosti* S100 proteins *S100 proteini* Heat shock proteins *Proteini toplinskog šoka*	Immune activation and inflammation *Imunološka aktivacija i upala*
TLR3	Endosomes *Endosomi*	Double-strained DNA from viruses *Dvostruka DNA iz virusa*	Double-strained DNA from damaged cells *Dvostruka DNA iz oštećenih stanica* Mitochondrial DNA *Mitohondrijska DNA*	Viral infection recognition *Prepoznavanje virusne infekcije*
TLR4	Cell surface *Površina stanice*	Lipopolysaccharide *Lipopolisaharid*	Heat shock proteins *Proteini toplinskog šoka* S100 proteins *S100 proteini* Fibrinogen Hyaluronic acid *Hijaluronska kiselina*	Bacterial infection recognition *Prepoznavanje bakterijske infekcije* Tissue damage recognition *Prepoznavanje oštećenja tkiva* Pain modulation *Modulacija boli*
TLR5	Cell surface *Površina stanice*	Flagellin *Flagelin*	Unknown *Nepoznat*	Bacterial infection recognition *Prepoznavanje bakterijske infekcije*
TLR6	Cell surface *Površina stanice*	Diacyl lipoprotein *Diacil-lipoprotein*	Unknown *Nepoznat*	Bacterial infection recognition *Prepoznavanje bakterijske infekcije*
TLR7	Endosomes *Endosomi*	Single-strained RNA from viruses *Jednostruka RNA iz virusa*	Endogenous RNA *Endogena RNA*	Viral infection recognition *Prepoznavanje virusne infekcije*

Receptor	Location *Lokacija*	Ligand: Pathogen-associated molecular pattern *Molekularni uzorak povezan s patogenima*	Ligand: Damage-associated molecular pattern *Molekularni uzorak povezan s oštećenjem*	Main role *Glavna uloga*
				Neurodegeneration *Neurodegeneracija*
TLR8	Endosomes *Endosomi*	Single-strained RNA from viruses and bacteria *Jednostruka RNA iz virusa i bakterija*	Endogenous RNA *Endogena RNA*	Bacterial and viral infection recognition *Prepoznavanje bakterijske i virusne infekcije* Neurodevelopment *Neurorazvoj* Neurodegeneration *Neurodegeneracija*
TLR9	Endosomes *Endosomi*	CpG-DNA fragments from viruses, bacteria, and protozoa *CpG-DNA fragmenti iz virusa, bakterija i praživotinja*	Genomic DNA from necrotic and apoptotic cells *Genomska DNA iz nekrotičnih i apoptotskih stanica*	Infection recognition *Prepoznavanje infekcije* Neuroplasticity *Neuroplastičnost*
TLR10	Endosomes *Endosomi*	Unknown *Nepoznat*	Unknown *Nepoznat*	Anti-inflammatory *Protuupalni*

maintain the organism's internal stability, whether the stimulus is caused by molecular samples associated with damage or exogenous ligands associated with pathogens.[15] They trigger an inflammatory response through the synthesis of cytokines, interferon, and chemokines such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α).[16] TLRs can recognize different PAMPs. TLR4 specifically recognizes ligands derived from gram-negative bacteria. TLR1, 2, 5, and 6 can identify specific regions of other bacterial species, while TLR3, 7, 8, and 9 specifically recognize genetic material from the viruses.[14] The ligand of TLR10 is unknown, and this type of receptor is different from other TLRs in its function because it has anti-inflammatory effects.[13] In addition to PAMPs, TLRs can also recognize DAMPs, which are naturally found in the body during tissue damage,such as heat shock proteins (HSPs), high-mobility group box 1 protein (HMBG1), S100 proteins, hyaluronic acid, fibrinogen, and broken parts of genetic materials.[5,17]

Toll-like receptor expression in schizophrenia

The potential immunological mechanisms in the etiopathogenesis of schizophrenia were observed in the 1920s after the pandemic of Spanish flu. Some patients showed symptoms of psychosis after the flu, although they had been mentally healthy before the pandemic.[18] Subsequently, the notion of virus-induced psychosis became widely accepted, along with a multitude of additional diseases caused by bacteria and parasites that have the possibility of causing psychotic symptoms, especially after fetal infection during pregnancy. Examples of infectious agents associated with the development of schizophrenia are the herpes simplex virus (HSV), the Epstein-Barr virus (EBV),[19]*Treponema pallidum*,[20] and *Toxoplasma gondii*.[21] Recent research shows that the immune system and its various components, including cytokines, C-reactive protein, chemokines, and antibodies, may play a role in determining vulnerability to schizophrenia.[22] Studies have identified different features of Toll-like receptors in patients with schizophrenia compared to healthy control groups. In Table 2, we summarized the features of TLRs in patients with schizophrenia.

Individuals diagnosed with schizophrenia showed increased inflammatory reactions to peripheral stimulation of TLRs. IL-6 and TNF-α were released in large quantities when the blood of schizophrenia patients was exposed to TLR2 and TLR4 agonists *in vitro* relative to the control healthy group.[23]

Table 2 Features of Toll-like receptors in schizophrenia
Tablica 2. Značajke Toll-like receptora u shizofreniji

Reference/*Izvor*	**ExaminedToll-like receptors** *Istraženi Toll-like receptori*	**Features**/*Značajke*
Mantovani et al. 2019 *Mantovani i sur. 2019.*	TLR2 and 4 *TLR2 i 4*	Proinflammatory cytokines were released in high amounts in schizophrenia patients' blood when exposed to agonists of Toll-like receptors in vitro compared to healthy controls. *Proupalni citokini otpuštani su u velikim količinama u krvi bolesnika sa shizofrenijom kada su bili izloženi agonistima Toll-like receptora in vitro, u usporedbi sa zdravim kontrolnim ispitanicima.*
Muller et al. 2012 *Muller i sur. 2012.*	TLR4	Schizophrenia patients' monocytes expressed more Toll-like receptors than those of the healthy control group. *Monociti bolesnika sa shizofrenijom izražavaju više Toll-like receptora od monocita u zdravih kontrolnih skupina.*
Murphy et al. 2021 *Murphy i sur. 2021.*	TLR4	Schizophrenia patients exhibit higher levels of Toll-like receptors and proinflammatory cytokines in the prefrontal cortex. *Bolesnici sa shizofrenijom pokazuju više razine Toll-like receptora i proupalnih citokina u prefrontalnom korteksu.*
McKernan et al. 2011 *McKernan i sur. 2011.*	TLR2,4 and 8 *TLR2,4 i 8*	Stimulating the entire blood with ligands for Toll-like receptors in schizophrenia patients led to more increase of proinflammatory cytokines than in the healthy control group. *Stimuliranje cijele krvi ligandima za Toll-like receptore u bolesnika sa shizofrenijom dovelo je do većeg povećanja proupalnih citokina nego u zdravoj kontrolnoj skupini*.
Zhu et al. 2010 *Zhu i sur. 2010.*	TLR4	The lack of Toll-like receptor 4 in rats increased hippocampal nerve stem and progenitor cell proliferation and differentiation. *Nedostatak Toll-like receptora 4 u štakora povećao je proliferaciju i diferencijaciju hipokampalnih živčanih ogranaka i progenitorskih stanica.*
Prata et al. 2017 *Prata i sur. 2017.*	TLR2	Neonatal mice with Toll-like receptor stimulation had less gray and white matter, fewer hippocampus neurons, and more microglial cells. *Neonatalni miševi sa stimulacijom Toll-like receptora imali su manje sive i bijele tvari, manje neurona hipokampusa i više mikroglijalnih stanica.*
Kozlowska et al. 2019 *Kozlowska i sur. 2019.*	TLR1,2,3,4,5,6,7,8 and 9 *TLR1,2,3,4,5,6,7,8 i 9*	Schizophrenia patients express different amounts of Toll-like receptors than healthy people. *U bolesnika sa shizofrenijom eksprimiraju se različite količine Toll-like receptora nego u zdravih osoba.*
Juncal-Ruiz et al. 2020 *Juncal-Ruiz i sur. 2020.*	TLR5 and 8 *TLR5 i 8*	Decreased expression of Toll-like receptors 5 and 8 in persons with the first episode of psychosis compared to healthy control group. *Smanjena ekspresija Toll-like receptora 5 i 8 u osoba s prvom epizodom psihoze u usporedbi sa zdravom kontrolnom skupinom.*
Ademe et al. 2022 *Ademe i sur. 2022.*	TLR4	Schizophrenia patients have elevated peripheral immune system Toll-like receptor 4 expression and activity and often have gastrointestinal problems. *Bolesnici sa shizofrenijom imaju povišenu ekspresiju i aktivnost perifernog imunološkog sustava Toll-like 4 receptora i često imaju gastrointestinalne probleme.*
Kéri et al. 2017 *Kéri i sur. 2017.*	TLR2,4 and 5 *TLR2,4 i 5*	Toll-like receptor expression is increased in both unmedicated and treated patients with schizophrenia. Antipsychotic therapy upregulates Toll-like receptor 2 but downregulates Toll-like receptor 4 expression. *Ekspresija Toll-like receptora povećana je i u neliječenih i u liječenih bolesnika sa shizofrenijom. Antipsihotici povećavaju Toll-like receptor 2, a smanjuju Toll-like receptor 4 ekspresiju.*

A study conducted by Muller et al. 2012 found that the monocytes of patients diagnosed with schizophrenia showed increased levels of TLR4 expression compared to the control group.[24] Several studies have shown that patients with schizophrenia show altered levels of proteins and mRNA for TLRs compared to people without mental disorders. The researchers studied the brains of people who died and found that mRNA levels were altered due to genes involved in innate immunity. For example, tlr4 mRNA, as well as il6, il10, and tnf-α mRNA, are increased in the prefrontal region of the brain by people with schizophrenia.[25] On the other hand, some studies confirm increased levels of DAMPs in patients with schizophrenia,as they areS100 proteins and extracellular double-strand DNA from apoptotic cells.[26,27] A study by McKernan et al. 2011 observedan increased level of IL-1, IL-6, and TNF-α when ligands for TLR2 stimulate the whole blood of people with schizophrenia than in the healthy control group. However, only the level of IL-1 was increased after the TLR4 and TLR8 stimulation. They concluded that there is a difference in the manifestation of TLRs in people with schizophrenia and the healthy population, as well as in the response of TLRs to different ligands. They supposed that immune response could vary during the various stages of the disease, and for now, there is insufficient data to determine its exact function in the etiopathogenesis of schizophrenia.[12]

Several studies have shown that TLRs are present during brain development, affecting neurons' growth and establishing synapses. Certain types of TLRs can stop the process of cortical neurogenesis and the creation of neural connections, which can lead to behavioral problems in children and the consequent development of psychotic symptoms.[28] In addition, the absence of TLR4 in rats increased the proliferation and differentiation of the nerve stem and progenitor cells in the hippocampus.[12] The stimulation of TLR2 led to a decrease in gray and white matter, a decrease in hippocampal neuronal concentrations, and an increase in the number of microglial cells in the brains of neonatal mice. Similar pathological characteristics of the brain may be observed in patients with schizophrenia.[29] The study conducted by Kozlowska et al. in 2019 concluded that individuals with schizophrenia exhibit distinct levels of peripheral blood mononuclear cell (PBMC) expression for most of the examined TLRs compared to healthy individuals. In patients with schizophrenia, TLR1,2,4,6, and 9 expressions were decreased, while TLR3 and 7 showed increased expression. The mRNA levels for TLR5 and 8 were similar in both groups and showed no significant differences.[30]

The study by Juncal-Ruiz in 2020 examined the PBMCs of people with first-episode psychosis without psychiatric medicines in therapy and compared them to those of healthy volunteers. At the beginning of the trial and after three months of antipsychotic treatment, the findings emphasized the potential involvement of TLR5 and TLR8 in the pathophysiology of psychosis. It was observed that a decreased expression of these receptors in persons with the first episode of psychosis compared to healthy volunteers, both at the beginning and after three months of therapy. Most TLRs exhibited diminished functionality, as seen by dramatically decreased intracellular levels of TNF-α in patients with schizophrenia compared to healthy volunteers. The results of this study indicate that persons with psychosis may exhibit a distinct pattern of TLR expression compared to healthy volunteers, which could vary depending on the degree of the immune/inflammatory response.[31]

Studies in animal models show that infections that occur before and during birth significantly affect the activation of the mother's immune system and oxidative stress. The activation of TLRs through infection affects the immune response in the mother and fetus and can damage brain development. These disorders can result in behavioral problems in offsprings.[15]

The inflammatory etiopathogenetic theories of schizophrenia also fit the concept of "increased digestive permeability" in neuropsychiatric diseases, which is based on elevated intestinal permeability, leading to the entry of bacteria into the blood and activation of TLR4.[17,32] Patients with schizophrenia have shown increased expression and activity of TLR4 in their peripheral immune system and often encounter gastrointestinal problems such as hypersensitivity to gluten or casein. In addition, antibodies to *Toxoplasma gondii* are usually present in these patients.[33] Modern theories that connect the digestive system to schizophrenia say that the changes in the microbiome make the intestinal barrier less effective, and that causes microorganisms or their components, such as LPS, to move from the intestines to other parts of the body, triggering the immune system's response and causing schizophrenia symptoms.[34]

Toll-like receptor expression in response to antipsychotics

Antipsychotics work by modulating the activities of neurotransmitters in the brain.[35] However, some of them may also affect the immune system by altering the activity of TLRs,[36] as we summarized in Table 3.

Table 3 Antipsychotics that can change the expression of Toll-like receptors
Tablica 3. Antipsihotici koji mogu promijeniti ekspresiju Toll-like receptora

Receptor	**Inflammation modulating agent** **Modulirajući agent upale**	**Reference/Izvor**
TLR1	No data/*Nema podataka*	No data/*Nema podataka*
TLR2	Chlorpromazine↑ *Klorpromazin↑*	Gandhi et al.2012 *Gandhi i sur.2012.*
	Clozapine↓ *Klozapin↓*	Park et al. 2015 *Park i sur. 2015.*
	Olanzapine ↑ *Olanzapin↑*	Kéri et al.2016;Da Silva et al.2017 *Kéri i sur.2016;Da Silva i sur.2017.*
	Risperidone↑ *Risperidone↑*	Kéri et al. 2016 *Kéri i sur. 2016.*
TLR3	Fluphenazine↓ *Flufenazin↓*	Zhu et al. 2010 *Zhu i sur. 2010.*
	Paliperidone↓ *Paliperidon↓*	MacDowell et al.2016 *MacDowell i sur. 2016.*
	Clozapine↓ *Klozapin ↓*	Reisinger et al. 2015/ *Reisinger i sur. 2015.*
	Olanzapine ↓ *Olanzapin↓*	Li et al. 2021 *Li i sur. 2021.*
TLR4	Paliperidone ↓ *Paliperidon↓*	MacDowell et al. 2014 *MacDowell i sur. 2014.*
	Risperidone↓ *Risperidon↓*	Kéri et al. 2016; Feiner et al. 2019 *Kéri i sur. 2016;* *Feiner i sur. 2019.*
	Olanzapine↓ *Olanzapin↓*	Kéri et al. 2016 *Kéri i sur. 2016.*
	Olanzapine↑ *Olanzapin↑*	He et al. 2020 *He i sur. 2020.*
	Fluphenazine↓ *Flufenazin↓*	Zhu et al. 2010 *Zhu i sur. 2010.*
	Chlorpromazine↑ *Klorpromazin↑*	Gandhi et al. 2012 *Gandhi i sur. 2012.*
	Clozapine↓ *Klozapin↓*	Jeon et al. 2017 *Jeon i sur. 2017.*
TLR5	No data/*Nema podataka*	No data/ *Nema podataka*
TLR6	No data/*Nema podataka*	No data/ *Nema podataka*
TLR7	Fluphenazine↓ *Flufenazin↓*	Zhu et al. 2010 Zhu i sur. 2010.
TLR8	Fluphenazine↓ *Flufenazin↓*	Zhu et al. 2010 Zhu i sur. 2010.
TLR9	Olanzapine↑ *Olanzapin↑*	Zuo et al. 2023 Zuo i sur.2023.
TLR10	No data/*Nema podataka*	No data/ *Nema podataka*

↑=Increases expression of Toll-like receptors/ ↑=*Povećava ekspresiju Toll-like receptora*
↓=Decreases expression of Toll-like receptors/↓=*Snižava ekspresiju Toll-like receptora*

In a study by McDowell et al. from 2014, TLR4 was associated with the pharmacological processes involved in the treatment of schizophrenia. Studies have shown that the antipsychotic paliperidone controls TLR4 activation in rats by reducing blood LPS levels, relieving schizophrenia symptoms, and thus stopping the presence of molecular samples associated with TLR4 activation.[37] In 2016, McDowall et al. conducted a new study that demonstrated how the immune system can be triggered before birth to induce brain damage in mice, similar to in patients with schizophrenia. They activated TLR3 using viral mimic samples injected into pregnant mice. Both adult mothers and their

infants had an activated innate signaling pathway through TLR3, proinflammatory mediators, and increased oxidative stress levels. Prolonged paliperidone injections effectively suppressed the neuroinflammatory system and oxidative stress. Furthermore, paliperidone successfully reduced the spatial working memory loss shown in this animal model of schizophrenia. Researchers found that giving young adult mice paliperidone regularly, while they were still developing and exposed to immune stimulants during pregnancy, protected them against inflammation and oxidative damage.[38]

In support of these studies, there is also a study on human liposarcoma cells that express TLR4. When stimulated by LPS, there was an increase in the level of proinflammatory cytokines, but when the antipsychotic risperidone was added, a minor expression of proinflammatory cytokines mRNA was observed. Similar effects risperidone could have on neuroinflammation are not surprising because the risperidone metabolite paliperidone is known to reduce neuroinflammation.[39] The study conducted by Kéri et al. in 2016 found that alterations in TLRs in individuals with schizophrenia are not specific to particular cell types. The study found that TLR5 expression went up in both untreated and treated cases of the disease, and TLR2 expression went up in response to antipsychotic treatment. No significant differences were observed between olanzapine and risperidone regarding TLR2 expression. The down-regulation of TLR4, which is connected to antipsychotic medication, exhibited an opposite change in direction compared to TLR2.[36]

Olanzapine inhibits the activation of TLR3, which is known to play a crucial role in the development of inflammatory disorders such as sepsis and rheumatoid arthritis. Thus, inhibition of TLR3 activation may have beneficial effects in preventing the development of these disorders, but it may impair the immune response to viral infections.[40] In the central nervous system, olanzapine, through TLR4, is thought to activate astrocytes in the hypothalamus and thus trigger an inflammatory cascade that increases hunger sensation and food intake, which is a widespread side effect of this very effective antipsychotic.[41] In addition to the activation of TLR4, olanzapine may also affect the activity of TLR2 and 9. The activation of TLR2 may promote a dipogenesis and insulin resistance, while TLR9 has been shown to promote inflammation and insulin resistance.[42] Chlorpromazine has also been found to stimulate an inflammatory response in peripheral cells through TLR2 and 4.[43]

A study by Zhu et al. in 2010 observed that fluphenazine directly inhibits the innate immune signaling system and the induction of neuroinflammatory processes through TLR3, 4, 7, and 8. As TLR3,7, and 8 are endosomal receptors, they stop the neuroinflammatory process; however, they go through different pathways compared to the TLR4 found on the cell surface.[10]

Some studies have shown that clozapine can inhibit the activation of TLR2, 3, and 4, reducing the production of proinflammatory cytokines.[44] Inhibition of TLR4 activation leads to both beneficial and harmful consequences. The modulation of TLR activity by clozapine has implications for the immune response to infections and inflammatory disorders. At the same time, the inhibition of TLR activation may have beneficial effects in preventing the development of sepsis and other inflammatory and neuroinflammatory disorders such as schizophrenia and Alzheimer's disease. On the other hand, it may also increase the risk of chronic inflammatory disorders by impairing tissue repair and the clearance of damaged cells. It may increase the risk of infections and malignancies associated with the long-term use of clozapine.[45,46]

The expression and activity of TLRs may vary depending on the stage of the disease and the use of antipsychoticsthat can modulate inflammatory processes. For now, we can suppose that higher cytokine levels in patients with schizophrenia are a result of changes in TLR function, which may start with damage during neurodevelopment.

Conclusion

The neurodevelopmental and neuroinflammatory theories of schizophrenia are currently an important area in the pathophysiology of mental disorders. Numerous studies have found that the expression of TLRs is associated with neurodegenerative diseases in which inflammation plays a significant role. Some studies have been conducted on the role of the immune response in schizophrenia and the association of TLRs with neuroinflammatory processes. Some of them could be more consistent and clear, possibly due to the many different tissues and parts of the body in which they were investigated. For now, the importance of TLR2 and 4 in schizophrenia is particularly emphasized, as they have been more clearly researched than other TLRs. Available evidence presenting the involvement of TLRs in the etiopathogenesis of schizophrenia remains limited and requires further research. Antipsychotics may inhibit the activity of TLRs, reducing the production of proinflammatory cytokines and improving the quality of life. However, long-term use of antipsychotics can inhibit TLR

activation and change the innate immune response. Obtaining more concrete results could increase the range of potential pharmacological approaches to maintaining the proper functioning of the inflammatory processes for optimal mental capacities and improve the overall quality of life of patients with schizophrenia.

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Splenic infarction in patients with Epstein-Barr virus infectious mononucleosis-case reports and literature review

Infarkt slezene u bolesnika s Epstein-Barr virusnom mononukleozom – prikaz slučajeva i pregled literature

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Summary

Introduction: Epstein-Barr virus (EBV) is one of the most common herpes viruses in humans with over 90% of adults demonstrating antibodies to EBV. Infectious mononucleosis (IM) is the most frequently occurring clinical presentation of EBV infection and typically presents with fever, tonsillitis/pharyngitis, cervical lymph node enlargement and tenderness and fatigue. Splenomegaly is also part of the clinical presentation. Splenic infarction (SI) due to IM is rare but its exact frequency is unknown.

Methods: We present two cases of SI accompanying IM caused by EBV in young adults without underlying comorbidities together with a literature review of this topic. Literature search included journal articles describing splenic infarctions confirmed by CT or MRI associated with IM due to EBV infection published in English between 2005 and 2024 in PubMed. A total of 32 case reports presenting 34 patients were selected for detailed analysis.

Results: Among 34 patients, 58,8% were males and the median age was 20.97 years. Only 26.5% of patients had some chronic disease, the most common one being hereditary spherocytosis present in four patients. The most common symptoms were: fever (82.4%), abdominal pain (88.2%) localized mostly in the left upper abdomen and splenomegaly (50%).

Conclusion: Our overall conclusion is that establishing the diagnosis of SI does not change the therapeutic approach in most cases and that symptomatic treatment is sufficient.

In the future, greater availability of abdominal imagining methods and a higher index of suspicion will lead to more accurate data about SI.

Keywords: splenic infarction; Epstein-Barr virus; infectious mononucleosis; case reports; literature review

Sažetak

Uvod: Epstein-Barr virus (EBV) jedna je od najčešćih herpes virusnih infekcija u ljudi, a više od 90% odraslih ima prisutna protutijela na EBV. Infektivna mononukleoza (IM) najčešća je klinička manifestacija EBV infekcije koja se obično manifestira vrućicom, tonzilitisom/faringitisom, povećanim i bolnim cervikalnim limfnim čvorovima, te umorom. Splenomegalija je također dio kliničke slike. Infarkti slezene (IS) tijekom IM pojavljuju se rijetko, a stvarna učestalost nije poznata.

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Metode: U ovom radu prikazana su dva slučaja IS tijekom IM uzrokovan EBV-om u mladih odraslih osoba bez komorbiditeta, zajedno s pregledom literature o ovoj temi. U pretraživanje literature uključeni su članci iz časopisa koji opisuju infarkte slezene potvrđene CT-om ili MRI-om, povezane s IM-om, uzrokovane EBV-om, te objavljene na engleskom jeziku između 2005. i 2024. u PubMed-u. Za detaljnu analizu odabrana su ukupno 32 prikaza slučaja s 34 bolesnika.

Rezultati: Od 34 bolesnika, 58,8% njih bili su muškarci, a medijan dobi bio je 20,97 godina. Samo 26,5% bolesnika imalo je neku kroničnu bolest, a najčešća je bila nasljedna sferocitoza prisutna u četiri bolesnika. Najčešći simptomi bili su: povišena tjelesna temperatura (82,4%), bolovi u trbuhu (88,2%) lokalizirani pretežno u lijevom gornjem dijelu trbuha i splenomegalija (50%).

Zaključak: Postavljanje dijagnoze IS u većini slučajeva ne mijenja terapijski pristup, te je dovoljno simptomatsko liječenje. U budućnosti će sve veća dostupnost slikovnih pretraga abdomena i veća svijest o postojanju te bolesti sigurno dovesti do točnijih podataka o IS.

Ključne riječi: infarkt slezene; Virus Epstein-Barr; infektivna mononukleoza; prikazi slučajeva; pregled literature

Introduction

Epstein-Barr virus (EBV) is one of the most common herpes viruses in humans. It is spread through intimate contact between asymptomatic or symptomatic EBV shedders and susceptible persons. Antibodies to EBV have been demonstrated in over 90% of adults worldwide [1,2]. Most primary EBV infections that occur during childhood are subclinical. Infectious mononucleosis (IM) is the most common clinical presentation of EBV infection and usually occurs in adolescents and adults. After primary infection, both asymptomatic and symptomatic, EBV persists asymptomatically for life by establishing latent infection of B lymphocytes.[1,3,4]

A typical clinical presentation of IM includes fever, tonsillitis/pharyngitis, cervical lymph node enlargement and tenderness and fatigue.[1,3,5]

However, EBV can affect any organ system and has been associated with a variety of clinical presentations, some of which are present more often than others.

Splenomegaly is also part of the clinical presentation of IM, but the frequency of its occurrence is reported unevenly. For example, Rea TD et al. reported that only 8% of observed patients with IM had splenomegaly.[5] In contrast, earlier studies of Domerby H et al. demonstrated that all patients had an enlarged spleen but palpable in only a few [6]. Hosey RG et al. also reported an enlarged spleen in all participants of their study which included young athletes with IM.[7] Somewhere in between are the data published by Hoagland RJ in which splenomegaly was present in about one half of all analysed cases (52%) over the course of the illness.[8]

Splenic infarction (SI) due to IM is rare and its exact frequency is unknown due to underreporting or underdiagnosing.

Clinical manifestation of SI includes abdominal pain, fever, and tachycardia but even abdominal pain as the most consistent symptom is present in only half of the cases.[9] Therefore, a high index of suspicion is needed to confirm this diagnosis.

As abdominal pain is uncommon in IM, splenic rupture, which is also a rare but possibly lethal complication of IM, must be strongly considered whenever abdominal pain occurs.[10]

To establish the diagnosis of IM, routine laboratory tests are used together with specific tests for EBV.

In laboratory findings, peripheral blood lymphocytosis with atypical lymphocytes (defined as more than 10% of total lymphocytes), together with elevated aminotransferases (seen in the vast majority of patients), are present.[11]

The detection of EBV-specific antibodies is the gold standard for the diagnosis of IM. EBV serostatus can be defined by the presence of IgM and IgG antibodies against EBV viral capsid antigen (VCA), IgG against early antigen-diffuse (EA-(D)) and IgG against EBV nuclear antigen (EBNA). Acute infection is characterized by the presence of IgM anti-VCA and anti-EA(D) IgG without antibodies against EBNA.[12] EBV deoxyribonucleic acid (DNA) can be detected and quantified by polymerase chain reaction (PCR) assays on blood or plasma [13,14] which is positive in 40-70% of patients at symptom onset and in up to 90% of patients two weeks after disease onset.[15]

If splenic involvement is suspected, abdominal ultrasound should be performed, but to confirm the diagnosis of SI, a computed tomography (CT) or magnetic resonance imaging (MRI) is indicated [9].

We present two cases of SI accompanying IM caused by EBV in young adults without underlying comorbidities together with a literature review of this topic.

Case presentations

Case 1

A 34-year-old male presented with fever of up to 38.5°C starting 11 days prior to admission, accompanied with chills and malaise. He also reported lower back pain and flatulence with loose stools, and two days prior to admission he noticed dark urine and developed scleral icterus.

His past medical history was unremarkable except for obesity, with BMI at admission of 40.6 kg/m^2, and he was smoking up to 40 cigarettes per day.

The physical examination revealed icterus of the sclera and skin as well as hepatos plenomegaly without palpatory tenderness of the abdomen.

Laboratory tests on admission showed elevated acute phase reactants with erythrocyte sedimentation rate of 30 mm/h and C-reactive protein (CRP) of 107.3 mg/L. The white blood cell count (WBC) was 11.6 ×10^9/L with 24% of lymphocytes and 18% of atypical lymphocytes on peripheral blood smear, with red blood cell and thrombocyte counts within normal ranges. Clotting profile showed elevated fibrinogen of 4.4 g/L and D-dimers of >4.30 mg/L with normal values of prothrombin time, activated partial thromboplastin time and thrombin time. Bilirubin was elevated (96 µmol/L, direct 53 µmol/L, indirect 43 µmol/L) along with liver function tests (aspartate aminotransferase (AST) 164 U/L, alanine aminotransferase (ALT) 235 U/L, gamma-glutamyl transferase 478 U/L, alkaline phosphatase (AP) 165 U/L) and elevated lactate dehydrogenase (LDH) of 994 U/L.

A CT scan of the abdomen and pelvis with contrast revealed as teatotic, enlarged liver with a diameter of 25 cm in the medial clavicular line and splenomegaly with a sagittal diameter of 16.5 cm, with multiple subcapsular infarctions ranging from 2 to 4 cm as shown in Figure 1.

Blood cultures were negative while transthoracic and transoesophageal cardiac ultrasound revealed no signs of infective endocarditis.

Extensive screening for infectious diseases was negative for HIV and viral hepatitis, leptospirosis, tularemia, haemorrhagic fever with renal syndrome, bartonellosis, SARS CoV-2 and CMV but revealed an acute EBV infection with positive VCA IgM and IgG and borderline result of EA IgG. Acute EBV infection was confirmed by PCR of blood and 17 300 copies of viral DNA/mL were detected.

Flow cytometry of peripheral blood showed an elevated T lymphocyte count of7219/µL or 93.8% with elevated CD8+ T lymphocytes and lowered B lymphocyte count of 27 or 0.4%, which was consistent with the diagnosis of IM. The screen for thrombophilia was negative. All relevant laboratory findings are listed in Table 1.

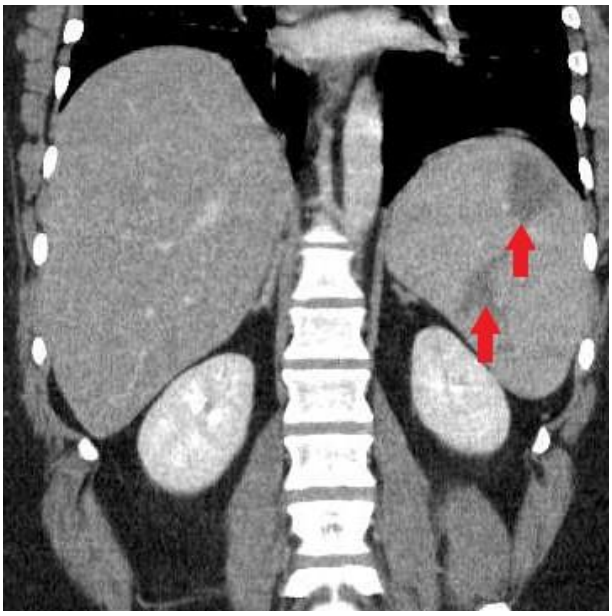

Figure 1 The coronal view of contrast enhanced abdominal CT in a 34-year-old male, demonstrated two well-demarcated wedge shape (arrows) and several small round shape low-density areas (arrowheads) in the spleen, consistent with splenic infarctions.
Slika 1. Koronarni prikaz CT-a abdomena s kontrastom u 34-godišnjeg muškarca pokazuje dvije dobro omeđene klinaste promjene (strelice) i nekoliko malih okruglih područja niske gustoće (vrhovi strelica) u slezeni, koji odgovaraju infarktima slezene.

The patient received empirical parenteral antibiotic treatment with ceftriaxone and metronidazole because intrabdominal infection was suspected, along with thromboprophylaxis with enoxaparin subcutaneously and other supportive measures. He was discharged after 13 days with the recommendation to continue anticoagulant therapy with rivaroxaban for three months and strict bed rest.

On follow-up, three weeks after discharge, the patient was afebrile and feeling better with a decrease in liver function tests and lactate dehydrogenase levels accompanied with a slight decrease of splenomegaly (14 cm) on abdominal ultrasound, but with still visible multiple hypoechogenic infarctions. After six months, the control abdominal ultrasound was normal.

Table 1 Selected laboratory findings of patients
Tablica 1. Odabrani laboratorijski nalazi prikazanih bolesnika

	Case 1 *Bolesnik 1*	**Case 2** *Bolesnik 2*	**Normal range** *Referentne vrijednosti*
C-reactive protein *C-reaktivni protein*	107.3	13.0	<5.0 mg/L
Leukocytes *Leukociti*	11.6	9.3	3.4-9-7 x10^9/L
Lymphocytes *Limfociti*	46 %	38%	20-46 %
Reactive lymphocytes *Reaktivni limfociti*	24%	28%	
Haemoglobin *Hemoglobin*	133	122	119-157 g/L
Platelets *Trombociti*	172	91	158-424 x10^9/L
Bilirubin *Bilirubin*	96	131	3-20 µmol/L
AST *AST*	164	630	11-38 U/L
ALT *ALT*	235	792	12-48 U/L
GGT *GGT*	478	405	11-55 U/L
AP *AF*	165	251	60-142 U/L
LDH *LDH*	994	896	> 241 U/L
PT / INR *PV/INR*	0.75/1.17	0.83/1.12	>0.70
APTT *APTV*	26.1	27.6	23-36 s
TT *TV*	16.6	/	16-21 s
Fibrinogen *Fibrinogen*	4.4	2.4	1.8-3.5 g/L
D-dimers *D-dimeri*	>4.30	>4.28	<0.55 mg/L
EBV VCA IgM	+	+	
EBV VCA IgG	-	+	
EA IgG	Borderline *Graničan*	+	
EBNA IgG	-	-	
EBV DNA PCR blood *EBV DNA PCR krv*	17 300	22 800	<1000 copies/mL of blood *<1000 kopija/mL krvi*

AST- aspartate aminotransferase; ALT- alanine aminotransferase; GGT- gamma-glutamyl transferase; ALP- alkaline phosphatase; LDH- lactate dehydrogenase; PT- prothrombin time; APTT- activated partial thromboplastin time; TT- thromboplastin time; EA – early antigen; EBNA – Epstein Barr nuclear antigen; VCA – viral capsid antigen
AST- aspartatam inotransferaza; ALT- alaninam inotransferaza; GGT- gamma-glutamil transferaza; AF- alkalna fosfataza; LDH- laktat dehidrogenaza; PV- protrombinsko vrijeme; APTV- aktivno parcijalno tromboplastinsko vrijeme; TV- tromboplastinsko vrijeme;EA – rani antigen; EBNA – Epstein Barr nuklearni antigen, VCA – virusni kapsidni antigen

Case 2

A 36-year-old female was admitted on the 9th day of illness which presented with fever of up to 39°C accompanied with sore throat and abdominal pain in the upper left and right quadrant worsening on inspiration. The day before hospital admission, she noticed scleral icterus along with dark urine and

reported several episodes of vomiting.

Except for being a smoker (10 cigarettes per day) and a tonsillectomy in childhood, she had no significant prior illnesses.

On physical examination, she was afebrile, with scleral icterus, pharyngeal injection without exudate and tender, mildly enlarged cervical lymph nodes up to 1.5 cm. Spleen was palpable but without abdominal tenderness.

Routine laboratory tests revealed a CRP of 13.0 mg/L, a WBC of 9.3×10^9/L with 38% of lymphocytes and 28% of reactive lymphocytes on peripheral blood smear. The red blood cell count was normal with thrombocytopenia of 91×10^9/L. The clotting profile showed elevated D-dimers of >4.28 mg/L while fibrinogen, prothrombin time, activated partial thromboplastin time and thrombin time were within normal ranges. The patient also had elevated serum bilirubin of 131 µmol/L (direct 83, indirect 48 µmol/L) and hepatic lesion with AST 630 U/L, ALT 792 U/L, GGT 405 U/L, AP 251 U/L and LDG 896 U/L. All relevant laboratory findings are listed in Table 1.

A CT scan of the abdomen with contrast revealed hepatomegaly with craniocaudal diameter of 20 cm, without parenchymal lesions and splenomegaly of 18×10.5×7.5 cm with multiple hypovascular and avascular subcapsular zones, the largest of which measured 2x3 cm as shown in Figure 2.

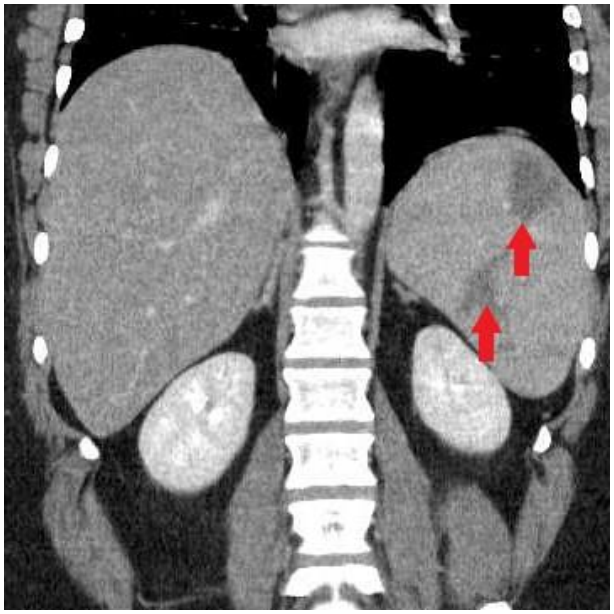

Figure 2 The coronal view of contrast enhanced abdominal CT in a 36-year-old female, demonstrated two well-demarcated triangular hypodense areas in the spleen (arrows), representing splenic infarction.

Slika 2. Koronarni prikaz CT-a abdomena s kontrastom u 36-godišnje žene, pokazuje dva dobro omeđena trokutasta hipodenzna područja u slezeni (strelice), što predstavlja infarkt slezene.

Blood cultures were negative as well as testing for HIV, viral hepatitis viruses and leptospirosis.

Serological testing for CMV and EBV virus revealed borderline IgM for CMV and positive VCA IgM and IgG together with positive EA IgG and negative EBNA IgG which suggested acute EBV infection.

The diagnosis was further confirmed with PCR of blood which revealed 22 800 copies of EBV DNA per ml of blood. The flow cytometry of peripheral blood was also consistent with infectious mononucleosis. The screen for thrombophilia was negative. The patient received only symptomatic treatment and was discharged after six days. After six months, the control abdominal ultrasound was normal.

Literature review

A review of the literature was conducted by searching English articles on splenic infarction confirmed by CT or MRI associated with IM due to EBV infection, published between 2005 and 2024 in PubMed. The keywords „Epstein-Barr virus AND splenic infarction "OR „Infectious mononucleosis AND splenic infarction" were used. A total of32 case reports that presented 34 patients were selected for detailed analysis.[16-47] Characteristics of patients presented in these articles are listed in Table 2.

Among 34 patients, there were 20 males (58.8%) and the median age was 20.97 years (range, 7-40 years). Only nine patients had some chronic diseases (26.5%) with the most common one being hereditary spherocytosis present in four patients. The most common symptoms that were highly suggestive for splenic involvement in EBV IM were as follows: fever in 28 (82.4%) patients; abdominal pain in 30 (88.2%) patients (left upper abdominal pain or tenderness in 22 (64.7%); unspecified abdominal pain in three; epigastric pain in two; right upper abdominal pain in two and upper abdominal pain in one patient); splenomegaly in 17 (50%) patients; nausea/vomiting in five (14.7%); fatigue in eight (23.5%) and general symptoms in four (11.8%) patients.

In all but one patient EBV infection was confirmed by serological testing, and in eight (23.5%) patients also by positive PCR DNA blood test.

The final diagnosis was made by CT in 29 (85.3%) patients and by MRI in five patients.

Only one patient underwent splenectomy, others were only treated using conservative methods and symptomatic treatment.

Table 2 Characteristics of patients with splenic infarction in EBV infectious mononucleosis
Tablica 2. Karakteristike bolesnika s infarktom slezene tijekom EBV infektivne mononukleoze

Reference *Referenca*	**No. of Cases** *Broj bolesnika*	**Age/Sex/Race** Dob/Spol/Rasa	**Symptoms/ Signs of Splenic Involvement** *Simptomi/znakovi zahvaćenosti jetre*	**Chronic Disease/ Concomitant Infection** *Kronične bolesti/konkomitantne infekcije*	**Serology** *Serologija*	**PCR Copies/Ml PCR Kopije/Ml**	**Method of Confirmation of SI** *Dijagnostička metoda za IS*	**Treatment Method** *Način liječenja*
Ma Z et al. (2016)	1	19/F/Chinese *19/Ž/Kineskinja*	Fever, splenomegaly, tenderness in LUA *Temperatura, splenomegalija, osjetljivost u LGA*	Hereditary spherocytosis *Hereditarna sferocitoza*	EBV VCA IgM + EBV VCA IgG + EA IgG + EBNA IgG +	NP *NU*	CT *CT*	Splenectomy *Splenektomija*
Wang XL et al. (2023)	1	8/F/Chinese *8/Ž/Kineskinja*	Fever, splenomegaly, UA pain *Temperatura, splenomegalija, bol u GA*	None *Ništa*	EBV VCA IgM + EBV VCA IgG + EA IgG - EBNA IgG -	281	MRI *NMR*	Conservative *Konzervativno*
Kana T et al. (2023)	1	29/M/NA *29/M/NP*	Fever, general symptoms, fatigue, splenomegaly, LUA pain *Temperatura, opći simptomi, umor, splenomegalija, bol u LGA*	Morbid obesity Acute CMV infection *Morbidna pretilost Akutna CMV infekcija*	EBV VCA IgM + EBV VCA IgG + EA IgG NA/*NP* EBNA IgG +	NP *NU*	CT *CT*	Conservative *Konzervativno*
Jeong JE et al. (2018)	1	16/F/NA *16/Ž/NP*	Fever, fatigue, epigastric pain, splenomegaly *Temperatura, umor, bol u epigastriju, splenomegalija*	None *Ništa*	EBV VCA IgM + EBV VCA IgG NA EA IgG NA/*NP* EBNA IgG NA/*NP*	10828	CT *CT*	Conservative *Konzervativno*
Nishioka H et al. (2021)	1	19/M/Japanese *19/M/Japanac*	Fever, LUA and epigastric pain *Tempertura, bol u LGA iepigastriju*	None *Ništa*	EBV VCA IgM + EBV VCA IgG + EA IgG NA/*NP* EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*

Reference *Referenca*	**No. of Cases** *Broj bolesnika*	**Age/Sex/Race** Dob/Spol/Rasa	**Symptoms/ Signs of Splenic Involvement** *Simptomi/znakovi zahvaćenosti jetre*	**Chronic Disease/ Concomitant Infection** *Kronične bolesti/konkomitantne infekcije*	**Serology** *Serologija*	**PCR Copies/Ml PCR Kopije/Ml**	**Method of Confirmation of SI** *Dijagnostička metoda za IS*	**Treatment Method** *Način liječenja*
Heo DH et al. (2017)	1	20/F/NA *20/F/NP*	Fever, abdominal pain *Temperatura, bol u abdomenu*	None *Ništa*	EBV VCA IgM + EBV VCA IgG - EA IgG NA/*NP* EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*
Kobayashi K et al. (2023)	1	31/M/NA *31/M/NP*	Fever, RUA pain *Temperatura, bol u DGA*	None *Ništa*	EBV VCA IgM + EBV VCA IgG - EA IgG NA/*NP* EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*
Gavriilaki E et al. (2013)	1	17/M/NA *17/M/NP*	Fever, LUA pain, splenomegaly *Temperatura, bol u LGA, splenomegalija*	None *Ništa*	EBV VCA IgM + EBV VCA IgG NA/*NP* EA IgG NA/*NP* EBNA IgG NA/*NP*	NP *NU*	MRI *NMR*	Conservative *Konzervativno*
Gang MH et al. (2013)	1	7/F/NA *7/Ž/NP*	Fever, RUA and periumbilical pain, splenomegaly *Temperatura, bol u DGA iperiumbilikalno, splenomegalija*	None *Ništa*	EBV VCA IgM + EBV VCA IgG - EA IgG NA/*NP* EBNA IgG -	Positive *Pozitivno*	CT *CT*	Conservative *Konzervativno*
Li Y et al. (2014)	1	19/F/Hispanic *19/Ž/Latinoamerikanka*	Fever, general symptoms, severe abdominal pain, vomiting, splenomegaly *Temperatura, opći simptomi, izražena bol u abdomenu, povraćanje, splenomegalija*	Coinfection CMV and *My. pneumoniae* *Koinfekcija CMV i My. pneumoniae*	EBV VCA IgM + EBV VCA IgG NA/*NP* EA IgG + EBNA IgG NA/*NP*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Kobayashi T et al. (2024)	1	17/F/NA *17/Ž/NP*	Fever, fatigue, epigastric pain, splenomegaly	None *Ništa*	EBV VCA IgM + EBV VCA IgG NA/*NP*	NP *NU*	CT *CT*	Conservative *Konzervativno*

Reference *Referenca*	**No. of Cases** *Broj bolesnika*	**Age/Sex/Race** Dob/Spol/Rasa	**Symptoms/ Signs of Splenic Involvement** *Simptomi/znakovi zahvaćenosti jetre*	**Chronic Disease/ Concomitant Infection** *Kronične bolesti/konkomitantne infekcije*	**Serology** *Serologija*	**PCR Copies/Ml PCR Kopije/Ml**	**Method of Confirmation of SI** *Dijagnostička metoda za IS*	**Treatment Method** *Način liječenja*
			Temperatura, umor, bol u epigastriju, splenomegalija		EA IgG NA/*NP* EBNA IgG NA/*NP*			
Suzuki Y et al (2007)	1	18/M/Japanese *18/M/Japanac*	Fever, splenomegaly *Temperatura, splenomegalija*	Hereditary spherocytosis *Hereditarna sferocitoza*	EBV VCA IgM + EBV VCA IgG + EA IgG + EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*
Hasibi M et al. (2021)	1	28/M/NA *28/M/NP*	Fever, splenomegaly *Temperatura, splenomegalija*	None *Ništa*	EBV VCA IgM + EBV VCA IgG NA/*NP* EA IgG NA/*NP* EBNA IgG NA/*NP*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Nofal R et al. (2019)	1	7/M/African American *7/M/Afroamerikanac*	Fever, LUA pain, splenomegaly *Temperatura, bol u LGA, splenomegalija*	Sickle cell trait *Bolest srpastih stanica*	EBV VCA IgM + EBV VCA IgG + EA IgG NA/*NP* EBNA IgG NA/*NP*	NP *NU*	MRI *NMR*	Conservative *Konzervativno*
Li Y et al. (2018)	3	24/F/NA *24/Ž/NP*	Fever, severe LUA pain, nausea *Temperatura, jaka bol u LGA, mučnina*	Crohn's disease, Hashimoto's thyroiditis, sacroiliitis *Chronova bolest, Hashimoto tireoiditis, sakroileitis*	EBV VCA IgM + EBV VCA IgG + EA IgG NA/*NP* EBNA IgG-	NP *NU*	CT *CT*	Conservative *Konzervativno*
		20/M/NA *20/M/NP*	LUA pain, nausea *Bol u LGA, mučnina*	None *Ništa*	Positive heterophile antibody *Pozitivna heterofilna protutijela*	NP *NU*	CT *CT*	Conservative *Konzervativno*
		27/M/NA *27/M/NP*	Fever, LUA pain, general symptoms, nausea, splenomegaly *Temperatura, bol u LGA, opći simptomi,*	None *Ništa*	Positive heterophile antibody *Pozitivna heterofilna protutijela*	NP *NU*	CT *CT*	Conservative *Konzervativno*

Reference *Referenca*	**No. of Cases** *Broj bolesnika*	**Age/Sex/Race** Dob/Spol/Rasa	**Symptoms/ Signs of Splenic Involvement** *Simptomi/znakovi zahvaćenosti jetre*	**Chronic Disease/ Concomitant Infection** *Kronične bolesti/konkomitantne infekcije*	**Serology** *Serologija*	**PCR Copies/Ml PCR Kopije/Ml**	**Method of Confirmation of SI** *Dijagnostička metoda za IS*	**Treatment Method** *Način liječenja*
			mučnina, splenomegalija					
van Hal S et al. (2005)	1	35/F/Caucasian *35/Ž/Bjelkinja*	Fever, LUA tenderness *Temperatura, osjetljivost u LGA*	None *Ništa*	EBV VCA IgM + EBV VCA IgG + EA IgG NA/*NP* EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*
Khan S et al. (2019)	1	30/M/NA *30/M/NP*	Fatigue, abdominal pain *Umor, bol u abdomenu*	None *Ništa*	EBV VCA IgM + EBV VCA IgG - EA IgG - EBNA IgG -	Positive *Pozitivno*	CT *CT*	Conservative *Konzervativno*
Machado C et al. (2015)	1	24/M/NA *24/M/NP*	Fever, general symptoms, LUA pain *Temperatura, opći simptomi, bol u LGA*	None *Ništa*	EBV VCA IgM + EBV VCA IgG - EA IgG NA/*NP* EBNA IgG NA/*NP*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Thida AM et al. (2020)	1	19/F/African American *19/Ž/Afroamerikanka*	LUA pain, malaise, nausea, splenomegaly *Bol u LGA, slabost, mučnina, splenomegalija*	Hereditary spherocytosis *Hereditarna sferocitoza*	EBV VCA IgM + EBV VCA IgG + EA IgG + EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*
Batista M et al. (2023)	1	20/M/NA *20/M/NP*	Fever, general symptoms *Temperatura, opći simptomi*	None *Ništa*	EBV VCA IgM + EBV VCA IgG + EA IgG NA/*NP* EBNA IgG NA/*NP*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Naviglio S et al. (2016)	1	14/M/NA *14/M/NP*	Fever, LUA pain, splenomegaly *Temperatura, bol u LGA, splenomegalija*	None *Ništa*	NA (Serologic tests confirmed the diagnose) *NP (dijagnoza je potvrđena serološkim testovima)*	19956	MRI *NMR*	Conservative *Konzervativno*

Reference *Referenca*	**No. of Cases** *Broj bolesnika*	**Age/Sex/Race** Dob/Spol/Rasa	**Symptoms/ Signs of Splenic Involvement** *Simptomi/znakovi zahvaćenosti jetre*	**Chronic Disease/ Concomitant Infection** *Kronične bolesti/konkomitantne infekcije*	**Serology** *Serologija*	**PCR Copies/Ml PCR Kopije/Ml**	**Method of Confirmation of SI** *Dijagnostička metoda za IS*	**Treatment Method** *Način liječenja*
Breuer C et al. (2008)	1	13/M/Caucasian *13/M/Bjelac*	Fever, LUA pain, splenomegaly *Temperatura, bol u LGA, splenomegalija*	Hereditary spherocytosis *Hereditarna sferocitoza*	EBV VCA IgM + EBV VCA IgG NA/*NP* EA IgG NA/*NP* EBNA IgG NA/*NP*	Positive *Pozitivno*	MRI *NMR*	Conservative *Konzervativno*
Reichlin M et al. (2022)	1	17/M/NA *17/M/NP*	LUA pain, diarrheal *Bol u LGA, proljev*	None *Ništa*	EBV VCA IgM + EBV VCA IgG - EA IgG NA/*NP* EBNA IgG NA/*NP*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Mamo G et al. (2023)	1	32/M/NA *32/M/NP*	Fever, fatigue, LUA pain *Temperatura, umor, bol u LGA*	Obesity, depression, PTSD, migraine *Debljina, PTSP, migrena*	EBV VCA IgM + EBV VCA IgG - EA IgG - EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*
Pervez H et al. (2020)	1	20/M/NA *20/M/NP*	Fever, LUA pain, malaise *Temperatura, bol u LGA, slabost*	None *Ništa*	EBV VCA IgM + EBV VCA IgG NA/*NP* EA IgG NA/*NP* EBNA IgG NA/*NP*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Kensey NL et al. (2023)	1	36/M/NA *36/M/NP*	Fever, LUA pain *Temperatura, bol u LGA*	None *Ništa*	Positive heterophile antibody *Pozitivna heterofilna protutijela*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Suzuki Y et al. (2018)	1	22/M/NA *22/M/NP*	Fever, fatigue, LUA pain *Temperatura, umor, bol u LGA*	None *Ništa*	NP *NU*	Positive *Pozitivno*	CT *CT*	Conservative *Konzervativno*
Bhattarai P et al. (2014)	1	16/M/NA *16/M/NP*	Epigastric pain *Bol u epigastriju*	None *Ništa*	Positive heterophile antibody *Pozitivna heterofilna protutijela*	NP *NU*	CT *CT*	Conservative *Konzervativno*

Reference *Referenca*	**No. of Cases** *Broj bolesnika*	**Age/Sex/Race** Dob/Spol/Rasa	**Symptoms/ Signs of Splenic Involvement** *Simptomi/znakovi zahvaćenosti jetre*	**Chronic Disease/ Concomitant Infection** *Kronične bolesti/konkomitantne infekcije*	**Serology** *Serologija*	**PCR Copies/Ml PCR Kopije/Ml**	**Method of Confirmation of SI** *Dijagnostička metoda za IS*	**Treatment Method** *Način liječenja*
Benz R et al. (2007)	1	19/F/NA *19/Ž/NP*	Fever, LUA pain, splenomegaly *Temperatura, bol u LGA, splenomegalija*	None *Ništa*	Positive heterophile antibody *Pozitivna heterofilna protutijela*	NP *NU*	CT *CT*	Conservative *Konzervativno*
Cull E et al. (2012)	1	18/F/NA *18/Ž/NP*	Fatigue, LUA pain *Umor, bol u LGA*	None *Ništa*	Positive heterophile antibody *Pozitivna heterofilna protutijela*	NP *NU*	CT *CT*	Conservative *Konzervativno*
García-Vázquez J et al. (2017)	1	12/M/NA *12/M/NP*	Fever, LUA pain, splenomegaly *Temperatura, bol u LGA, splenomegalija*	None *Ništa*	EBV VCA IgM + EBV VCA IgG + EA IgG NA/*NP* EBNA IgG -	NP *NU*	CT *CT*	Conservative *Konzervativno*
Kim KM et al. (2005)	1	40/M/NA *40/M/NP*	Fever, fatigue, LUA pain *Temperatura, umor, bol u LGA*	None *Ništa*	Positive heterophile antibody *Pozitivna heterofilna protutijela*	Positive *Pozitivno*	CT *CT*	Conservative *Konzervativno*

Only one systemic literature review which investigated SI association with EBV was published in 2023 [48] and included articles published between 1970 and 2022. SI was described in 29 patients, predominantly young males (70%) and underlying haematological disease (hereditary spherocytosis and sickle cell trait) was observed in 21% of patients.

Discussion

EBV infection is one of the most common infections in humans. In IM, which is the most common clinical manifestation of primary EBV infection, the spleen, as the largest lymphatic organ in the body, is always involved. Although the spleen is not always palpable, splenomegaly can be detected by ultrasound. Complications affecting the spleen during IM, such as splenic rupture or SI, are extremely rare.[48]

SI occurs when splenic circulation (arterial and venous) is compromised, causing tissue ischemia. The vessel occlusion is usually caused by emboli as well as venous congestion by abnormal cells. The anatomic structure of the distal branches of the splenic artery which are noncommunicating end arteries leads to development of spleen infarcts when these distal branches occlude.

In IM, SI is caused by the infiltration of splenic parenchyma with lymphocytes and rapidly enlarging spleen with structural changes.[48] IM is among the causes of non-iatrogenic SI. The size and distribution of SI in patients with IM are variable, from small, focal infarcts to complete SI.

SI can be also associated with other infectious diseases, but studies are limited. In the retrospective study made by Im JH et al. (2020) that included 101 patients in a 10-year period, the most common causes of SI were: bacteremia (in 26 patients), malaria (in 12 patients), respiratory tract infections (in 11 patients), infective endocarditis (in 10 patients) and EBV infection confirmed in only one patient.[49]

SI is in general a very rare disease. The exact prevalence is unknown and a high index of suspicion is needed during the diagnostic process. The diagnosis of SI starts either with symptoms that indicate splenic involvement (usually abdominal pain), or the diagnosis of underlying diseases (cardioembolism, hypercoagulable state, hematologic disease). Due to increased availability of abdominal imaging, such as CT and MRI, SI is being diagnosed more frequently in patients with less specific symptoms, sometimes even in patients without symptoms. To illustrate this shift from symptomatic to asymptomatic SI, the results of two studies published with a gap of 11 years can be used. In a large multicentric study published in 2009, Antopolsky M et al.[50] reported that 80% of patients with SI during a 10-year period had characteristic symptoms such as abdominal pain, while in a retrospective observational study published in 2020, Brett AS et al.[51] reported that 33% of patients with SI presented without abdominal pain in a five-year period.

Imaging has a very important role in the diagnostics of SI. In our clinical settings, usually, the first routine diagnostic method in abdominal examination in patients with IM is ultrasound. This method has limited sensitivity and is operator-dependent, so very often splenic lesions are not detected. When they are visible and reported, they present as ill-defined, nodular, or wedge-shaped hypoechoic areas. Contrast-enhanced CT is the preferable diagnostic method, because of its high sensitivity. In the acute phase, the SI appears as a wedge shaped, hypodense area with no enhancement or poor enhancement. In the subacute phase, it may look like a cystic lesion, if liquefaction occurs. In the chronic phase infarct may completely disappear, or the involution of the non-functional parenchyma may be seen with fibrotic contraction of the infarct and progressive volume loss.[52] A MRI is not often used as an initial diagnostic method of SI. The infarcted area is usually wedge-shaped. The signal intensity is varying, according to the phase of the infarct.[52]

The treatment approach to SI depends on the underlying causative disease.[53] Since there is no specific treatment for EBV infection, patients can only be treated with symptomatic measures and means of supportive care.

The necessity of anticoagulant therapy in SI patients is still questionable due to the difference in pathogenic mechanisms. This therapy aims to achieve vessel recanalization and decrease mortality by preventing subsequent thromboembolic complications. Wand O et al.[54] demonstrated in their study that anticoagulant therapy in patients with SI was associated with decreased long-term mortality, but patients with active non-hematologic malignancy, hematologic disease and infective endocarditis were excluded. The use of anticoagulant therapy is even more questionable in patients with SI and EBV infection since there is no available data on the subject. One of our patients was treated with anticoagulant therapy and one was not, and the final result in both patients was the same in six months follow up-disappearance of the lesions.

The results of our literature review are similar to the results of other researchers; the majority of cases were young males, the most common underlying disease was hereditary spherocytosis and the most frequent symptoms indicating splenic involvement during IM were diffuse or left upper abdominal pain, splenomegaly and fever.[21,48]

Conclusion

SI in EBV infections is an uncommon and rare complication of IM and the available knowledge is mainly based on case reports. We describe two patients; one without characteristic symptoms of IM or splenic affection and one with classical symptoms of IM and left upper abdominal pain. The literature review indicated that fever, left upper abdominal pain and splenomegaly together with other symptoms of IM must arouse suspicion of a SI. Establishing the diagnosis of SI does not change the therapeutic approach in the majority of SI cases in EBV infection and symptomatic treatment is sufficient.

In the future, greater availability of abdominal imagining methods and a higher index of suspicion will lead to more accurate data about SI including underlying conditions/diseases, symptoms, diagnostic methods, treatment and prognosis.

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Data Availability Statement: We used institutional data that is not available for sharing.

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Izolacija plućnih vena kao metoda liječenja fibrilacije atrija u Općoj bolnici Zadar od 2018. - 2022. godine

Pulmonary vein isolation as a treatment method for atrial fibrillation in Zadar General Hospital from 2018 to 2022

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Sažetak

Uvod: fibrilacija atrija (FA) predstavlja najčešći poremećaj srčanoga ritma u općoj populaciji. Njezina pojavnost raste sa životnom dobi. Ranije smo na raspolaganju za liječenje fibrilacije atrija imali samo antiaritmijske lijekove, no unazad 30 godina u kliničku praksu je uvedena nova metoda liječenja fibrilacije, izolacijom plućnih vena.

Bolesnici i metode: retrospektivno istraživanje provedeno je na bolesnicima liječenima od fibrilacije atrija na Odjelu kardiologije Opće bolnice Zadar od 01. siječnja 2018. do 31. prosinca 2022. godine. Tijekom navedenoga razdoblja liječeno je 746 bolesnika, 523 muškarca i 223 žene. Većina bolesnika bila je u dobnoj skupini od 50-70 godina. Istraživanje je provedeno na temelju podataka pohranjenih u bolničkom informatičkom sustavu (BIS).

Rezultati: u razdoblju od 01. siječnja 2018. do 31. prosinca 2022. godine u Općoj bolnici Zadar liječeno je 746 bolesnika zbog FA, metodom izolacije plućnih vena. Promatrano prema godinama, 2018. godine učinjeno je 156 izolacija plućnih vena, 2019. godine učinjeno je 127, a 2020. godine 128 zahvata, dok se u 2021. godini bilježi povećenje broja zahvata na 143. Najveće povećanje broja zahvata zabilježeno je 2022. godine, tijekom koje je učinjen 191 zahvat izolacija plućnih vena. Od ukupno 746 izolacija plućnih vena, 523 (70%) je provedeno u muškaraca, a 223 (30%) u žena. Izolaciji plućnih vena su najčešće bili podvrgnuti bolesnici u dobi od 50-70 godina. Najčešća metoda izolacije plućnih vena bila je radiofrekventna ablacija. Zahvatu su nešto češće bili podvrgnuti bolesnici s perzistentnom (52%) u odnosu na paroksizmalnu (48%) fibrilaciju.

Zaključak: elektrofiziološki tim Opće bolnice Zadar u liječenju bolesnika s fibrilacijom atrija, uz konzervativne metode liječenja, koristi i invazivnu metodu izolacije plućnih vena. Metoda se najčešće koristi kod bolesnika s perzistentnom atrijskom fibrilacijom i to prvenstveno kod bolesnika mlađe životne dobi.

Ključne riječi: fibrilacija atrija, liječenje, izolacija plućnih vena

Summary

Introduction: Atrial fibrillation (AF) is the most common arrhythmiain in the general population. Its incidence increases with age. Previously, only antiarrhythmic drugs were available for the treatment of atrial fibrillation, but 30 years ago a new method of AF treatment was introduced into clinical practice - pulmonary vein isolation.

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Patients and methods: A retrospective study was conducted on patients treated with pulmonary vein isolation in Zadar General Hospital, Cardiology Department from January 1, 2018 to December 31, 2022. During the mentioned period, 746 patients were included of which 523 men and 223 women. Most of the patients were in the age group of 50-70 years. The research was conducted on the data stored in the hospital information system.

Results: In the period between January 1, 2018 and December 31, 2022, over the course of five years, 746 patients were treated for AF using the method of pulmonary vein isolation at Zadar General Hospital. Observed according to age, in 2018, 156 isolations of pulmonary veins were performed, in 2019, 127 were performed, and in 2020, 128 procedures were performed. In 2021, an increase in the number of procedures was noticed to 143. The largest increase in the number was observed in 2022, during which 191 pulmonary vein isolation procedures were performed. Out of 746 pulmonary vein isolations, 523 (70%) were performed in men, and 223 (30%) in women. Pulmonary vein isolations were most often performed on patients aged 50-70 years. The most common method of pulmonary vein isolation was with radiofrequency energy. Patients with persistent (52%) rather than paroxysmal (48%) atrial fibrillation underwent the procedure somewhat more often.

Conclusion: The electrophysiology team of Zadar General Hospital follows world trends in the treatment of patients with AF, with a note that in our center, ablation methods are used more often in patients with persistent AF than in other centers, especially if the patients are of younger age.

Keywords: atrial fibrillation, pulmonary vein isolation, treatment

Uvod

Fibrilacija atrija (FA) najčešća je srčana aritmija u općoj populaciji. Globalna prevalencija FA procjenjuje se na 2% do 4%, s očekivanim daljnjim porastom broja oboljelih.[1]Procijenjeno je da je 2016. godine u Hrvatskoj od FA bolovalo između 40 i 50 tisuća bolesnika.[2] Prevalencija je veća u muškoj populaciji s omjerom 1,2:1.[3]

U mehanizmu nastanka FA izrazito važnu ulogu ima dilatacija atrija.[4,5]Patološki električni impulsi nastaju u plućnim venama ili dilatiranom atriju.[4-6]Samom dilatacijom, atrij postaje podložniji nastanku i provođenju patoloških električnih impulsa. Dilatacija atrija facilitira nastanak FA, dok nekoordinirane i nepravilne kontrakcije atrija pogoduju daljnjoj dilataciji. Navedeni proces naziva se električno remodeliranje atrija. Strukturno i električno remodeliranje pogoduje nastanku, ali i daljnjoj progresiji FA.[4-6] Prema European Society of Cardiology (ESC) smjernicama FA se dijeli na: prvu dijagnosticiranu FA (FA koja nije ranije dijagnosticirana), paroksizmalnu (epizode FA koje prestaju unutar sedam dana od nastupa), perzistentnu (epizode FA koje traju dulje od sedam dana), dugotrajnu perzistentnu (FA koja je prisutna dulje od 12 mjeseci), te permanentnu (FA kod koje je u dogovoru liječnika i bolesnika odlučeno da se kontrola srčanoga ritma ne provodi).[1]

Liječenje FA obuhvaća više mogućnosti, a to su: kontrola ritma, kontrola frekvencije, antikoagulacija, te ablacijske procedure.[7]Zlatni standard u liječenju FA je kateterska izolacija plućnih vena.[8]Trenutno su raspoložive tri metode izolacije plućnih vena: radiofrekventna izolacija plućnih vena, krioablacija, te najnovija metoda ablacije pulsnog polja (engl. *Pulsed field ablation*). [9-11] Meta analize su pokazale da je uspješnost jednokratne izolacije plućnih vena između 43 i 67 %, pri čemu je uspješnost veća u bolesnika s paroksizmalnom, nego perzistentnom FA.[12]

Bolesnici i metode

Retrospektivno istraživanje provedeno je na bolesnicima liječenima od fibrilacije atrija na Odjelu kardiologije Opće bolnice Zadar od 01. siječnja 2018. do 31. prosinca 2022. godine. Tijekom navedenoga razdoblja liječeno je 746 bolesnika ablacijskom procedurom, od toga 523 (70%) muškarca i 223 (30%) žene. Bolesnici su, osim po spolu, podijeljeni prema dobnim kategorijama: 1. mlađi od 30 godina, 2. od 31- 50 godina, 3. od 51 - 70 godina i 4. stariji od 70 godina. S obzirom na vrstu FA, bolesnici su podijeljeni na skupinu s paroksizmalnom fibrilacijom i skupinu bolesnika s perzistentnom fibrilacijom, u koju su bili uključeni bolesnici s dugotrajnom perzistentnom fibrilacijom.

Postupak izolacije plućnih vena provodi kardiolog - elektrofiziolog u interventnoj elektrofiziološkoj dvorani, u strogim aseptičnim uvjetima. Kod svih bolesnika provedena je prijeoperativno odgovarajuća antikoagulantna terapija, najmanje tijekom tri tjedna prije operativnog zahvata. Na početku zahvata se, u cilju smanjenja bolnih senzacija bolesnika, u preponsku regiju ubrizgavao lokalni anestetik, potom se punktira femoralna vena i u nju ubrizgava heparin u dozi od 200 IU/kg. U svih bolesnika, lijevom atriju se pristupalo putem femoralne vene, dok je transeptalna punkcija rađena primjenom duge uvodnice SL-1 i igle za transeptalnu punciju BRK-1.

Od interventnih metoda ablacije korištena je

metoda krioablacije (CRYO), te radiofrekventna ablacija.

Istraživanje je provedeno na temelju podataka pohranjenih u bolničkom informatičkom sustavu (BIS). Dobiveni rezultati prikazani su grafički.

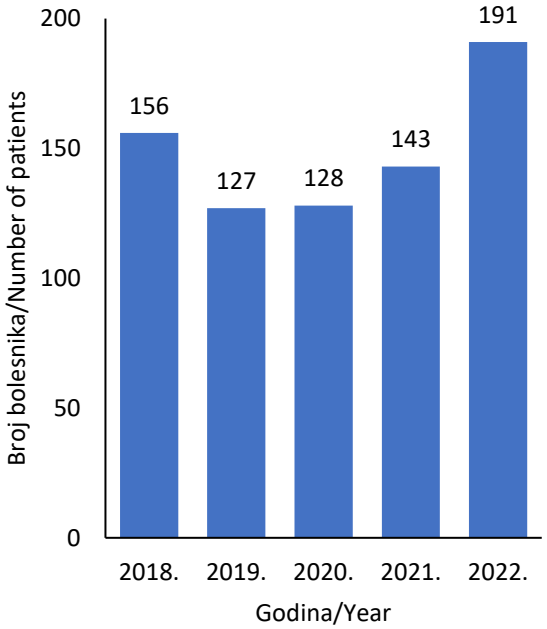
Rezultati

U razdoblju od 01. siječnja 2018. do 31. prosinca 2022. godine (tijekom pet godina) , u Općoj bolnici Zadar liječeno je 746 bolesnika zbog FA, metodom izolacije plućnih vena.

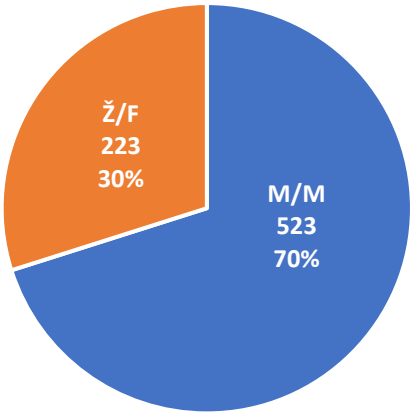
Prema godinama ispitivanja, 2018. godine učinjeno je 156 izolacija plućnih vena, a tijekom 2019.godine i 2020.godine bilježi se smanjenje broja postupaka. Tijekom 2019.godine učinjeno je 127, a 2020. godine 128 zahvata. U 2021. godini bilježi se povećanje broja zahvata na 143. Povećanje broja izvršenih zahvata zabilježeno je i 2022.godine, tijekom koje je učinjen 191 postupak izolacija plućnih vena (Slika 1).

Od ukupno 746 izolacija plućnih vena, 523 (70%) je provedeno u muškaraca, a 223 (30%) u žena (Slika 2).

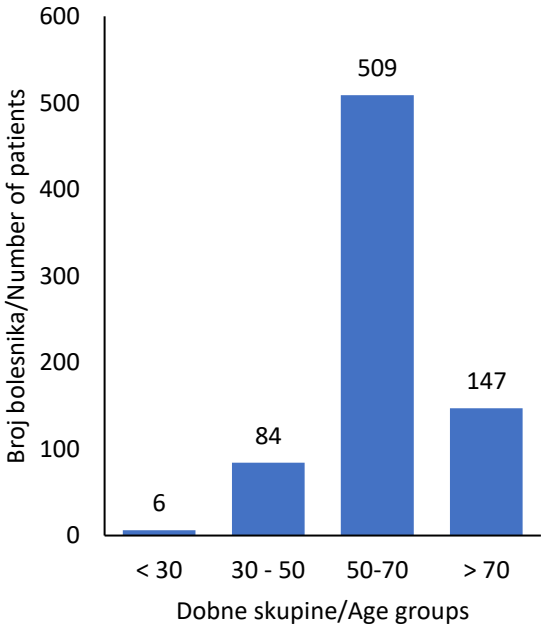
Izolaciji plućnih vena najčešće su bili podvrgnuti bolesnici u dobi od 50-70 godina (Slika 3).



Slika 1. Na slici je prikazan broj bolesnika liječenih ablacijom plućnih vena po godinama ispitivanoga razdoblja.
Figure 1 shows the number of patients treated with isolation of the pulmonary veins (ablation) by years of the examined period.



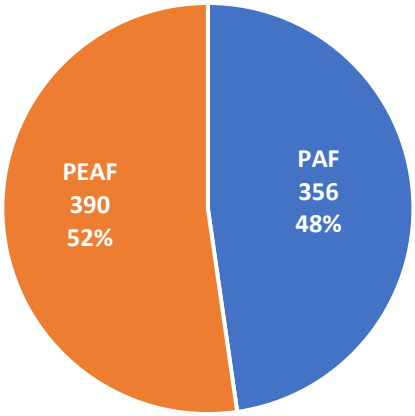
Slika 2.Slika prikazuje distribuciju bolesnika po spolu (ž-žene, m- muškarci).
Figure 2 Distribution by gender in the period 2018-2022.



Slika3.Distribucija bolesnika po dobi tijekom ispitivanoga razdoblja 2018.-2022.god.
Figure 3 Distribution by age during the examined period 2018-2022

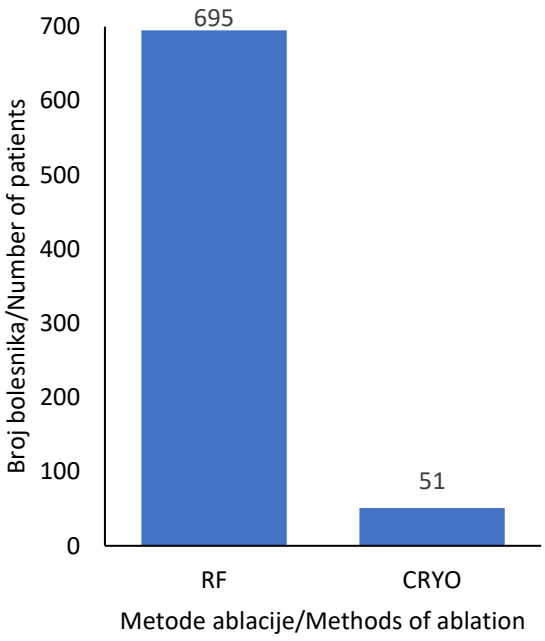
Postupku izolacije plućnih vena nešto su više bili podvrgnuti bolesnici s perzistentnom fibrilacijom, u odnosu na bolesnike s paroksksizmalnom fibrilacijom (Slika 4).

Od invazivnih metoda primijenjenih u ablaciji plućnih vena, krioablacija je primjenjena u 51 (7%), a radiofrekventna ablacija u 695 (93%) bolesnika s FA (Slika 5).



Slika 4.Vrsta fibrilacije atrija kod bolesnika podvrgnutih invazivnom zahvatu u razdoblju 2018.-2022., PAF- paroksizmalna fibrilacija atrija, PEAF- perzistentna fibrilacija atrija

Figure 4 Type of atrial fibrillation in patients undergoing invasive procedures in the period 2018-2022 PAF- paroxysmal atrial fibrillation, PEAF- persistent atrial fibrillation



Slika 5. Slika prikazuje metode ablacije plućnih vena kod oboljelih. Krioablacija (CRYO) je primijenjena kod 51 oboljelog (7%), a radiofrekventna ablacija (RF) kod 695 (93%) oboljelih.

Figure 5 The Figure shows methods of ablation in patients. Cryoablation(CRYO) was used in 51 patients (7%), and radiofrequency ablation(RF) in 695 (93%) patients.

Uspješnost terapijskoga zahvata bila je 68% u ispitivanoj grupi bolesnika.

Rasprava

Izolacija plućnih vena je tijekom posljednjih 20 godina postala standard u liječenju bolesnika s paroksizmalnom i perzistentnom FA. Navedeni zahvat prvi je put u Republici Hrvatskoj učinjen 2009. godine upravo u Općoj bolnici Zadar u kojoj nakon toga postaje standardna metoda liječenja bolesnika s FA. Kontinuiranim povećanjem broja zahvata povećala se njihova učinkovitost uz istodobno minimaliziranje broja komplikacija.

Ovo istraživanje obuhvatilo je bolesnike kojima je izolacija (ablacija) plućnih vena u Općoj bolnici Zadar učinjena tijekom pet godina, u razdoblju od 01. siječnja 2018. do 31. prosinca 2022. god. U navedenom razdoblju zabilježili smo kontinuirano povećanje broja postupaka uz prolazan pad tijekom 2019. i 2020. godine, što je posljedica poremećaja u radu zdravstvene službe uzrokovanog pandemijom COVID-19. Prestankom pandemije, već 2021. godine, broj postupaka vraća se na broj zahvata prije pandemijskoga razdoblja.

Raspodjela bolesnika podvrgnutih izolaciji plućnih vena prema dobnim skupinama u cijelosti je podudarna s rezultatima drugih elektrofizioloških centara. Naime, u našem, a i u drugim centrima, zahvatu se najčešće podvrgavaju bolesnici u dobi od 51 do 70 godine života.[13,14]Naime, zbog činjenice da je FA bolest starije dobi, očekivalo bi se da je najveći broj bolesnika koji se podvrgavaju ablaciji upravo u najstarijoj dobnoj skupini (iznad 70 godina), ali metodama ablacije češće se podvrgavaju osobe u dobi ispod 60 godina života. Razlog tome je u činjenici da je uspjeh postizanja i održavanja sinusnog ritma nakon interventnog zahvata izgledniji zbog manjih strukturnih oštećenja srca. Takva su oštećenja u starijih osoba znatno češća i teža jer starije osobe imaju brojna i dugotrajna srčana oštećenja, kao i više pridruženih bolesti i čimbenika srčanožilnoga rizika.[15,16]

U odnosu na podatke iz literature prema kojima se ablaciji češće podvrgavaju bolesnici s paroksizmalnom FA, u našem istraživanju bilježimo gotovo jednaki broj ablacija u bolesnika s paroksizmalnom i perzistentnom FA.[17]Naime, stav je našega elektrofiziološkog tima da se svim simptomatskim bolesnicima, napose onima mlađe životne dobi, neovisno o tipu FA, ablacija ponudi kao trenutno najbolja dostupna metoda liječenja ove aritmije. [18]Liječenje FA usmjereno je primarno prema smanjenju rizika od moždanoga udara i smrtnosti, te redukcije simptoma u bolesnika.

Tijekom ispitivanog razdoblja kod 51 (6,8%) bolesnika učinjena je izolacija plućnih vena primjenom krioablacije. Razlog ovako maloga broja

krioablacija ekonomske je naravi jer je krioablacija značajno skuplja u odnosu na radiofrekventnu ablaciju. Ipak, zadnjih nekoliko godina pri Hrvatskom zavodu za zdravstveno osiguranje (HZZO) djeluje Fond za posebno skupe materijale iz kojega se elektrofiziološkim centrima odobravaju sredstva sukladno broju učinjenih postupaka. Ovakva pomoć HZZO-a omogućila je uvođenje i sve češću primjenu novijih, složenijih i skupljih medicinskih postupaka. Stoga se u RH bilježi povećanje broja zahvata učinjenih tzv. *„single shot“* tehnologijom krioablacije. Istodobno u zapadnim se sustavima sve više koristi najnovija tehnika tzv. PFA, pa se u budućnosti očekuje porast broja postupaka izvršenih ovom tehnikom.[11]Trenutno je PFA metodom u Općoj bolnici Zadar liječeno oko 70 bolesnika koji nisu uključeni u ovo istraživanje.

Nastavljajući tradiciju interventnoga liječenja bolesnika s FA u Općoj bolnici Zadar i dalje ćemo težiti uvođenju modernih tehnika ablacijskog liječenja, sukladno ekonomskim mogućnostima hrvatskoga zdravstvenog sustava.

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Tablice treba izraditi na zasebnoj stranici s rednim brojem i naslovom. Riječi u tablicama ne smiju se kratiti. Naslovi i tekstualni sadržaj tablice moraju biti dvojezični, na hrvatskom i engleskom jeziku. Svaka tablica mora imati redni broj. Naslov i redni broj pišu se iznad tablice. Izbjegavati korištenje vertikalnih linija u tablici. Legende tablica pisati ispod tablice.

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Novinski članak

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Poglavlje u knjizi

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