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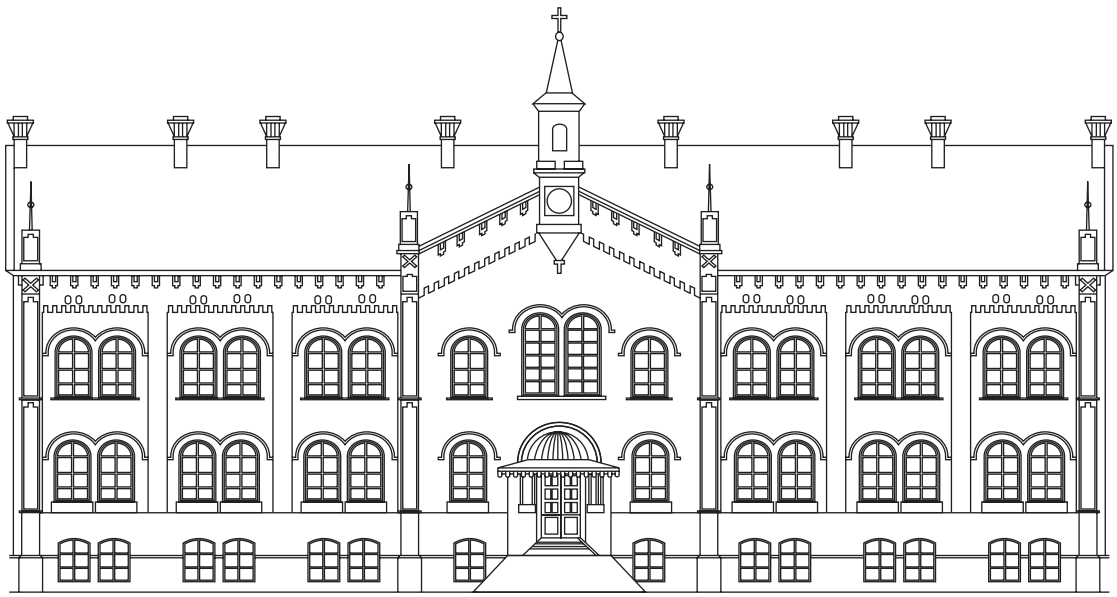

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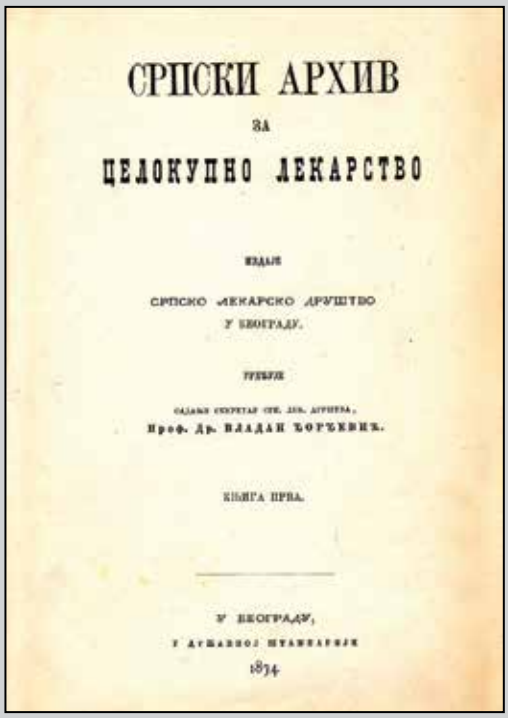

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ЗА

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ИЗДАЈЕ

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У БЕОГРАДУ.

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1874.

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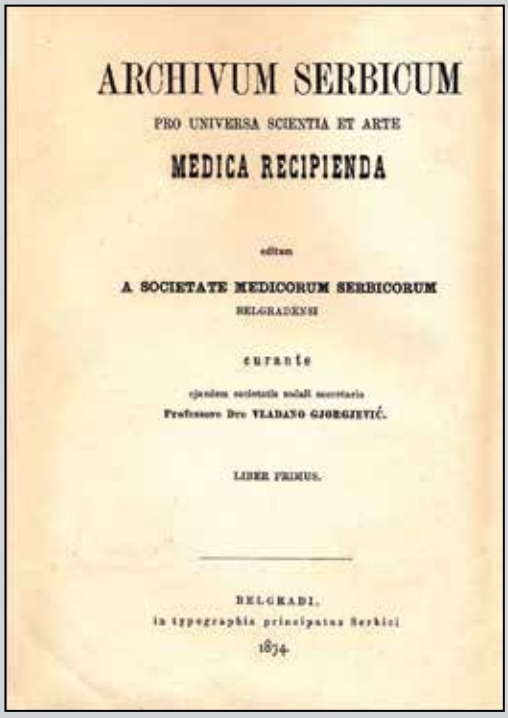

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The amelioration of testicular ischemia-reperfusion injury in rats by oxymatrine

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SUMMARY

Introduction/Objective A crucial factor in testicular damage is the surplus of reactive oxygen species that arises from ischemia-reperfusion. Elevated levels of reactive oxygen species cause critical harm to cells. The present research focused on investigating the role of oxymatrine with antioxidative property in testicular ischemia-reperfusion injury induced by torsion and detorsion in a rat model.

Methods The study utilized a total of 60 rats, which were randomly assigned to one of three groups: a sham group with 20 rats, a testicular ischemia-reperfusion group with 20 rats, and a testicular ischemia-reperfusion group treated with oxymatrine, also consisting of 20 animals. Induction of testicular ischemia-reperfusion involved applying two hours of ischemia via 720° counterclockwise torsion to the left testis, with subsequent reperfusion initiated by detorsion. The activity of neutrophil nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a catalyst for reactive oxygen species production, the concentration of a prevalent reactive oxygen species indicator malondialdehyde, and spermatogenesis were all detected in left testicular tissues collected at the four hours or three months post-detorsion.

Results Testicular ischemia-reperfusion notably elevated NADPH oxidase activity and malondialdehyde content, while it adversely affected spermatogenesis in the testes ($p < 0.001$). Conversely, the administration of oxymatrine significantly lowered both NADPH oxidase activity and malondialdehyde concentration, and it also improved spermatogenic function in the testes ($p < 0.001$).

Conclusion We found that oxymatrine attenuates injury from testicular ischemia-reperfusion, and this effect operates by limiting reactive oxygen species production through NADPH oxidase activity inhibition.

Keywords: oxymatrine; testicular torsion; ischemia-reperfusion

INTRODUCTION

The occurrence of testicular torsion spans all ages, yet it predominantly affects male infants and teenagers in the 12–18 age range, making it a standard emergency seen in urological practice [1]. Testicular torsion occurs when the spermatic cord becomes twisted, leading to a partial or total interruption of blood supply to the testicle. Early detection and quick surgical untwisting must be performed to reinstate testicular blood flow and forestall ischemic necrosis. Although the twisted testicle is surgically untwisted, subsequent atrophy and loss of function afflict 13.5–68% of such cases [2]. Ischemia-reperfusion injury remains the most recognized cause of testicular damage subsequent to testicular torsion and its surgical relief [3]. A crucial factor in testicular damage is the surplus of reactive oxygen species that arises from ischemia-reperfusion [3]. Elevated levels of reactive oxygen species (e.g., hydroxyl radical, superoxide anion, hydrogen peroxide) cause critical harm to cells by oxidizing membrane lipids, altering protein structures, and breaking DNA strands [3].

As of now, patients have no access to clinically utilized drugs that can reduce testicular ischemia-reperfusion injury. Oxymatrine is a type of quinolizidine alkaloid mainly isolated from *Sophora flavescens*, a plant utilized in traditional Chinese herbal practice [4, 5, 6]. $C_{15}H_{24}N_2O_2$ represents its molecular formula, while its weight is calculated as 264.36 g/mol [7, 8]. The antioxidative and anti-inflammatory properties of oxymatrine are among the numerous bioactivities that have been identified through multiple investigations [9, 10, 11]. Studies further report that oxymatrine mitigates damage from ischemia-reperfusion in several areas: the lung, brain, intestine, kidney, and liver [12–17]. Despite this, research has not addressed the therapeutic effect of oxymatrine on testicular ischemia-reperfusion injury. The present research focused on investigating the role of oxymatrine in testicular ischemia-reperfusion injury induced by torsion and detorsion in a rat model.

METHODS

Study subjects

The animals in this study consisted of sixty male Sprague-Dawley rats weighing between 250 and 300 grams, sourced from Shanghai Laboratory Animal Center company, located in Shanghai, China. Their housing consisted of an air-conditioned room with tightly regulated

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conditions: a temperature of 21°C, varying by no more than 1°C, a relative humidity of 55%, varying within 5%, and a standard 12-hour light followed by 12-hour dark schedule. Throughout the experiment, the rats could consume standard food and water at will. The Zhejiang Shuren University Ethics Committee provided ethical approval for all study protocols, which bears the reference number 202309021. The research methods involving animals were designed and executed following universally accepted ethical rules.

Medicinal compound and experimental substances

Sigma-Aldrich (Sigma-Aldrich, St. Louis, MO, USA) was the provider of ketamine, oxymatrine, hematoxylin, and eosin. The Jiancheng Bioengineering Institute (Nanjing, China) supplied the kits for analyzing nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and malondialdehyde. The remaining reagents utilized during the investigation were premium grade and sourced from the market.

Research plan

A random distribution was performed for 60 Sprague-Dawley rats among three groups, namely sham, testicular ischemia-reperfusion, and oxymatrine-treated groups, with 20 animals in each group. The rats received ketamine (50 mg/kg) intraperitoneally for anesthesia and were then positioned on the operating table. Sterility was maintained throughout all experimental manipulations. The left testis was retrieved by a left ilioinguinal surgical approach. To simulate the surgical procedure, an 11-0 atraumatic silk suture was positioned within the tunica albuginea of animals belonging to the sham group [18]. The procedure concluded with the replacement of the testis into the scrotum and the suturing of the skin. Ischemia in the testicular ischemia-reperfusion model was produced through a 720° counterclockwise twist applied to the left testis [18]. An 11-0 silk suture was used to attach the torsioned testis to the scrotum, thereby preserving the ischemic state. At the conclusion of the two-hour interval, restoring the testis to its natural alignment through untwisting enabled reperfusion. In the experimental group receiving oxymatrine, a two-hour period of testicular ischemia preceded reperfusion, at which time a 40 mg/kg dose of oxymatrine was injected intraperitoneally. The justification for the oxymatrine dose employed originated from various prior studies [15, 16, 17]. The rats received nalbuphine (2 mg/kg) subcutaneously for postoperative analgesia. Reperfusion was conducted for four hours, after which 10 rats in each group underwent left orchiectomy with the goal of assessing NADPH oxidase activity and malondialdehyde concentration. The remaining ten animals in each group were subjected to left orchiectomy after three months of reperfusion, allowing for the measurement of testicular spermatogenesis. Once the experimental procedures ended, all animals received a terminal intraperitoneal dose of pentobarbital sodium (200 mg/kg) to ensure a painless death.

Testicular tissue analysis for NADPH oxidase activity

After being homogenized in lysis buffer kept on ice, the samples were centrifuged at 4°C and 10,000 × g for a duration of 10 minutes. To measure NADPH oxidase activity, the supernatant was harvested with care. Assessment of NADPH oxidase activity relied on a kit purchased from a commercial source.

Determining malondialdehyde concentration in tissue from the testis

On ice, testicular tissue underwent homogenization in a buffer designed for lysis with malondialdehyde. The supernatant intended for the malondialdehyde assay was acquired by centrifuging the tissue homogenate at 5000 g for a duration of 15 minutes under 4°C conditions. Measurement of malondialdehyde levels in testicular tissue was performed via the thiobarbituric acid reactive substance assay, following the protocol supplied with a commercial kit.

Evaluation of sperm production within the testicles

Parameters such as seminiferous tubule epithelial layer number, Johnsen score, testicular weight, and seminiferous tubular diameter served as indicators for assessing testicular spermatogenesis [19]. After excision, the testis was placed on a scale for weight measurement. Histopathological examination was facilitated by fixing part of the testis in Bouin's fluid, dehydrating it with increasing ethanol concentrations, and embedding it in paraffin. The paraffin block was sectioned on a rotary microtome to produce slices of 5 μm in thickness. Staining with hematoxylin and eosin was applied to the sections once the routine processes of deparaffinization and hydration were complete. Light microscopic evaluation of the testicular sections was performed by an assessor who was not informed of their origin. The evaluation procedure consisted of selecting 20 seminiferous tubules with circular or near-circular profiles from each histological section and measuring their epithelial layer number, Johnsen score, and diameter. To assess the seminiferous tubule epithelial layers, counts were performed starting at the basement membrane and proceeding inward to the lumen. Histology of the seminiferous tubules was scored in accordance with Johnsen's system, which grades findings based on germinal epithelial maturation [20]. Seminiferous tubules were graded according to Johnsen's criteria, with scores spanning from 1 to 10 [20]. A score of 1 is assigned when the seminiferous tubule is entirely devoid of cells. The highest score of 10 is awarded for complete spermatogenesis accompanied by plentiful spermatozoa, a germinal epithelium of standard thickness, and a patent tubular lumen. Using a microscope that had an ocular micrometer, researcher estimated the diameter of the seminiferous tubules.

Statistical analysis

The GraphPad Prism 4.0 (GraphPad Software, Boston, MA, USA) served as the tool for statistical analysis. Using the Shapiro–Wilk test, we confirmed that the data exhibited a normal distribution. The variance homogeneity was verified by Bartlett's test. Data from the experiments were summarized using means and standard deviations. For intergroup comparisons, we employed one-way analysis of variance and subsequently conducted the Student–Newman–Keuls multiple comparison test. A p-value lower than 0.05 indicated that the differences were statistically significant.

Ethics: The study was approved by the Ethics Committee of the Zhejiang Shuren University (No.:202309021).

RESULTS

NADPH oxidase activity observed in testes

The activity of NADPH oxidase in testes was significantly higher in the ischemia-reperfusion group than in the sham group, a result depicted in Figure 1 ($p < 0.001$). Following testicular ischemia-reperfusion, the observed upregulation of NADPH oxidase activity was significantly decreased by oxymatrine treatment ($p < 0.001$).

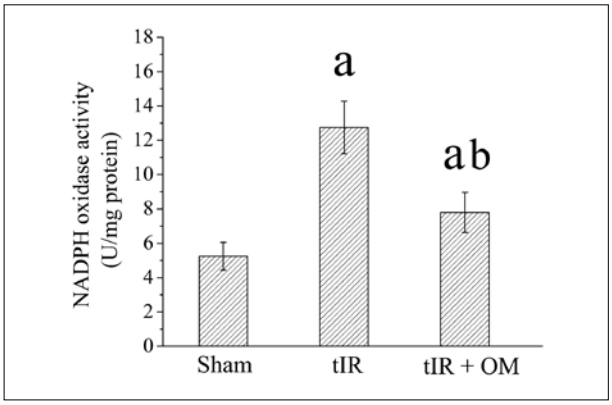

Figure 1. Testicular nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity was analyzed in the following conditions: sham operation, testicular ischemia-reperfusion (tIR), and oxymatrine (OM) treatment; data (n = 10) from the experiments were summarized using means and standard deviations; a – with a p-value of less than 0.001 *vs*. the sham control; b: – with a p-value of less than 0.001 *vs*. the tIR group

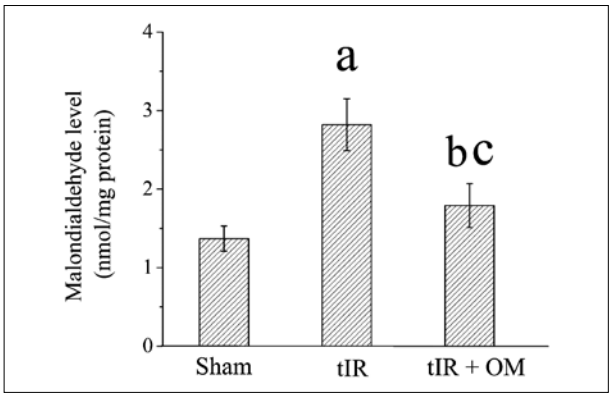

Figure 2. Testicular malondialdehyde level was analyzed in the following conditions: sham operation, testicular ischemia-reperfusion (tIR), and oxymatrine (OM) treatment; data (n = 10) from the experiments were summarized using means and standard deviations; a: with a p-value of less than 0.001 *vs*. the sham control; b: with a p-value of less than 0.01 *vs*. the sham control; c: with a p-value of less than 0.001 *vs*. the tIR group

Testicular tissue levels of malondialdehyde

Figure 2 illustrated a significant elevation in testicular malondialdehyde levels in the ischemia-reperfusion group ($p < 0.001$) relative to the sham-operated controls. Relative to animals subjected to ischemia-reperfusion, those receiving oxymatrine showed significantly ($p < 0.001$) reduced malondialdehyde levels in testicular tissue.

Evidence of spermatogenic activity in testicular tissue

Testicular ischemia-reperfusion injury led to marked declines ($p < 0.001$) in several histological and morphometric parameters, including number of epithelial layers within the tubules, Johnsen scoring, weight of the testes, and diameter of the seminiferous tubules, relative to sham controls (Figures 3 and 4). Oxymatrine-treated animals exhibited significantly ($p < 0.001$) better outcomes for all four testicular parameters compared to those subjected to ischemia-reperfusion injury.

DISCUSSION

In the population of males under 25 years old, testicular torsion arises at a rate of one per 4000 [2]. For the conservation of testicular fertility, early detection and prompt surgical correction of torsion are essential. Testicular infarction occurs if torsion of the testis continues beyond six hours [3]. Timely surgery within a five-hour window of symptom appearance fails to avert testicular atrophy in 27% of affected individuals [21]. The testes in our investigation remained viable after undergoing torsion for two hours and then being surgically restored. Severe impairment of spermatogenesis was observed in the testis three months post-detorsion, a consequence of the initial torsion-detorsion event. Key indicators of this damage, detailed in Figures 3 and 4, included a significantly reduced epithelial layer count in seminiferous tubules, a lower Johnsen score, diminished testicular weight, and narrower seminiferous tubular diameters.

From a pathophysiological perspective, torsion and detorsion of the testis is a quintessential ischemia-reperfusion phenomenon. Reactive oxygen species are produced in excess during ischemia and reperfusion of the testis [22]. The oxidation of proteins, DNA, and membrane lipids by surplus reactive oxygen species is a mechanism capable of initiating cellular damage [3]. The extreme reactivity and fleeting existence of reactive oxygen species make them exceedingly difficult to quantify in a direct manner [18]. Malondialdehyde, produced steadily at the end of lipid

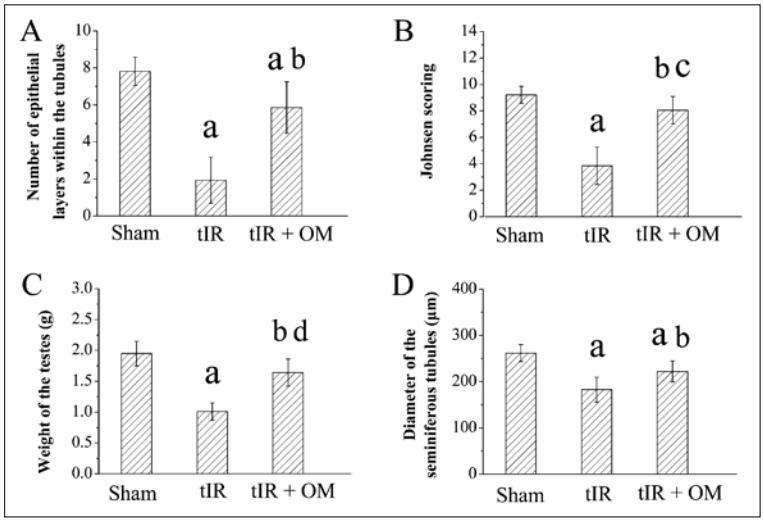

Figure 3. (A) – number of epithelial layers within the tubules; (B) – Johnsen scoring; (C) – weight of the testes; (D) – diameter of the seminiferous tubules were analyzed in the following conditions: sham operation, testicular ischemia-reperfusion (tIR), and oxymatrine (OM) treatment; data (n = 10) from the experiments were summarized using means and standard deviations; a – with a p-value of less than 0.001 vs. the sham control; b – with a p-value of less than 0.001 *vs*. the tIR group; c – with a p-value of less than 0.05 *vs*. the sham control; d – with a p-value of less than 0.01 *vs*. the sham control

hepatitis B, plaque psoriasis, and liver fibrosis from chronic viral hepatitis [23–27]. Therefore, the findings provide a foundation for the potential therapeutic application of oxymatrine in cases of testicular ischemia-reperfusion insult. Yet, the pathways responsible for the decrease in reactive oxygen species induced by oxymatrine are still poorly characterized.

Infiltrating neutrophils represent a primary cause of excessive reactive oxygen species production in tissues undergoing ischemia-reperfusion [28]. In neutrophils, NADPH oxidase is a key contributor to the formation of reactive oxygen species [28]. Ischemia promotes calcium influx into neutrophils, which in turn activates NADPH oxidase [29]. The reperfusion phase is characterized by the restoration of oxygen to previously ischemic tissue. Superoxide anion is generated from oxygen through catalysis by activated NADPH oxidase

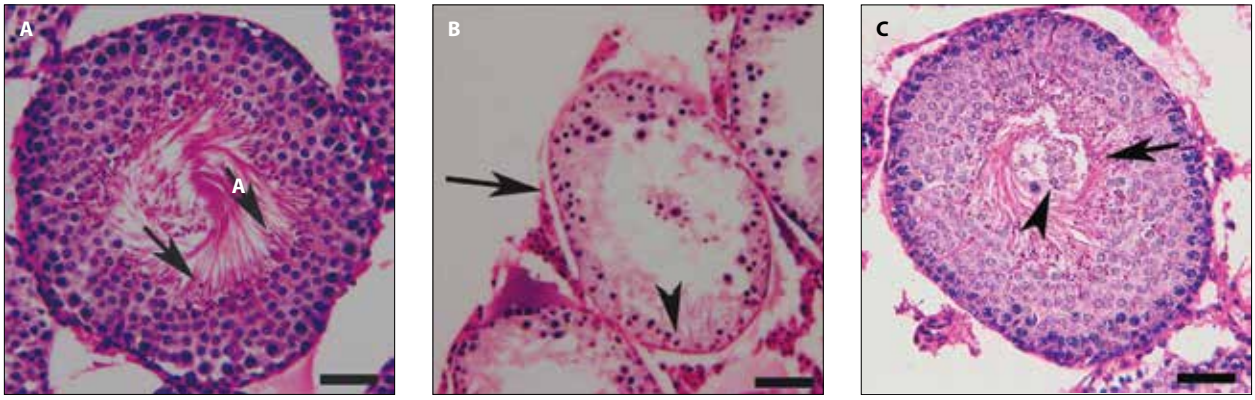

Figure 4. Testis tissue sections were illustrated for the three experimental conditions: sham operation, testicular ischemia-reperfusion, and oxymatrine treatment; at a magnification of × 200, testicular tissue sections underwent microscopic evaluation after being stained with hematoxylin-eosin; (A) – microscopic assessment of sham-operated testes indicated regular layering of the epithelium, full spermatogenic development ranging from early germ cells to spermatozoa (indicated by arrows), and standard tubular diameter; every seminiferous tubule contained a clearly open central lumen; (B) – the ischemia-reperfusion group presented with testicular structural anomalies: seminiferous tubules were atrophic (arrow), their epithelial layers were diminished (arrowhead), and germ cells showed maturation arrest (arrowhead); (C) – the gross morphology of the testes in the oxymatrine-treated group closely matched that of the sham group; inside the tubules, researchers noted numerous mature sperm cells, which are pointed out with an arrow; an arrowhead indicates sloughed germinal cells within the tubular lumen, a condition that often led to blockage; 40 micrometers are the length represented by the scale bar

peroxidation initiated by reactive oxygen species, is largely considered a sensitive sign of their presence and activity [19]. We report here that testicular malondialdehyde levels rose significantly while spermatogenesis was significantly suppressed following ischemia-reperfusion (Figures 2, 3, and 4). The evidence points to overproduction of reactive oxygen species as the underlying cause of testicular ischemia-reperfusion injury. The study demonstrated that oxymatrine supplementation lowered malondialdehyde concentration while boosting testicular spermatogenesis (Figures 2, 3, and 4). According to our results, the antioxidant capacity of oxymatrine underlies its ability to mitigate testicular ischemia-reperfusion injury. Furthermore, the safety and therapeutic effectiveness of oxymatrine have been confirmed in clinical settings for treating chronic [29]. Superoxide anions undergo a self-reaction to generate hydrogen peroxide [30]. The interaction of superoxide anion and hydrogen peroxide yields hydroxyl radical [19]. Thus, reactive oxygen species accumulate in greater amounts following ischemia and subsequent reperfusion. Testicular ischemia-reperfusion in this study produced substantial rises in NADPH oxidase activity and malondialdehyde content, coupled with a pronounced decrease in spermatogenesis within the testes, as illustrated in Figures 1, 2, 3, and 4. The study implies that spermatogenic injury arises from reactive oxygen species overproduction, which itself results from upregulated NADPH oxidase activity in neutrophils following testicular ischemia-reperfusion. Moreover, our results revealed that oxymatrine significantly suppressed NADPH oxidase activity and reduced

malondialdehyde content, while effectively restoring spermatogenesis in testicular tissue (Figures 1, 2, 3, and 4). The data imply that decreased reactive oxygen species production achieved by inhibiting NADPH oxidase activity in neutrophils underlies the protective role of oxymatrine in testicular spermatogenesis.

Khorsand et al. [3] evaluated whether naringin, which is a flavanone glycoside possessing well-documented antioxidant, anti-inflammatory, and anti-apoptotic effects, could prevent testicular ischemia/reperfusion damage induced by torsion/detorsion in mice [3]. Compared to controls, the torsion/detorsion animals exhibited a significant reduction in sperm quality based on concentration, motility, and kinematics, a depletion of antioxidant reserves such as superoxide dismutase, total antioxidant capacity, and glutathione peroxidase, a drop in hormones like follicle-stimulating hormone, testosterone, and luteinizing hormone, a rise in malondialdehyde and apoptosis signals Bax, Bcl-2, and caspase-3, and a loss of fertility. Naringin produced a dose-dependent improvement in sperm indices, antioxidant defense, testicular structure, endocrine parameters, and fertility, particularly when given at 100 or 200 mg/kg. At 50 mg/kg, the treatment exhibited weak effectiveness. Naringin exerted its apoptosis-inhibiting effect via the enhancement of Bcl-2 and the simultaneous reduction of Bax and caspase-3. These findings suggest that testicular ischemia/reperfusion injury is significantly alleviated by naringin, with the 100 to 200 mg/kg doses being especially effective. The comparison reveals that, aside from malondialdehyde and testicular histology, the experimental design of Khorsand et al. [3] was distinct from ours with respect to the other assessed variables and the therapeutic strategies. The next phase of this research will integrate measurements of the other assessed factors, and evaluate the relative potency of oxymatrine *vs*. naringin for treating testicular ischemia-reperfusion damage, identifying the optimal therapeutic candidate.

Several limitations within our research must be thoroughly explored by future studies. Firstly, the impact of unilateral testicular torsion on the contralateral testicle was left unexamined. Secondly, our research only used one oxymatrine dose and lacked dose-response evaluation. Thirdly, our study only used a single animal species and lacked molecular confirmation of the proposed mechanism (e.g., NADPH oxidase isoforms, inflammatory cytokines, antioxidant enzymes, Bax, Bcl-2, and caspase-3).

CONCLUSION

This study presents the first indication that the protection offered by oxymatrine against ischemia/reperfusion-induced testicular injury involves the inhibition of neutrophil NADPH oxidase activity, resulting in reduced generation of reactive oxygen species. According to the results, oxymatrine may function as a viable therapeutic option in cases of testicular torsion-detorsion. The potential clinical usefulness of oxymatrine awaits confirmation from trials conducted in humans.

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Conflict of interest: None declared.

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Ублажавање повреда тестиса услед исхемије-реперфузије код пацова оксиматриному

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САЖЕТАК

Увод/Циљ Кључни фактор оштећења тестиса је вишак реактивних врста кисеоника који настаје услед исхемије-реперфузије. Повишени нивои реактивних врста кисеоника наносе озбиљну штету ћелијама. Ово истраживање било је усмерено на испитивање улоге оксиматрина са антиоксидативним својствима у исхемијско-реперфузијској повреди тестиса изазваној торзијом и деторзијом у моделу пацова.

Методе У студији је коришћено укупно 60 пацова, који су насумично распоређени у једну од три групе: лажно оперисана група са 20 пацова, група са исхемијом-реперфузијом тестиса са 20 пацова и група са исхемијом-реперфузијом тестиса третирана оксиматрином, која се такође састојала од 20 животиња. Индукција исхемије-реперфузије тестиса подразумевала је двочасовну исхемију путем торзије левог тестиса за 720° у смеру супротном од казаљке на сату, а накнадна реперфузија покренута је деторзијом. Активност неутрофилне никотинамид-аденин-динуклеотид-фосфатне (*NADPH*) оксидазе, катализатора за производњу реактивних врста кисеоника, концентрација малондиалдехида, показатеља реактивних врста кисеоника, и сперматогенеза испитивани су у ткивима левог тестиса прикупљеним четири сата или три месеца после деторзије.

Резултати Тестикуларна исхемија-реперфузија значајно је повећала активност *NADPH* оксидазе и садржај малондиалдехида, док је негативно утицала на сперматогенезу у тестисима ($p < 0,001$). Супротно томе, примена оксиматрина значајно је смањила активност *NADPH* оксидазе и концентрацију малондиалдехида, а такође је побољшала сперматогену функцију тестиса ($p < 0,001$).

Закључак Утврђено је да оксиматрин ублажава повреде настале услед исхемије-реперфузије тестиса, а овај ефекат се остварује ограничавањем производње реактивних врста кисеоника инхибицијом активности *NADPH* оксидазе.

Кључне речи: оксиматрин; торзија тестиса; исхемија-реперфузија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Transcatheter aortic valve implantation (TAVI) in the treatment of aortic stenosis – from high-risk to low-risk patients with a presentation of results in Serbia from 2014 to 2025

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Introduction Transcatheter aortic valve implantation (TAVI) is a treatment modality intended for patients with aortic stenosis older than 70 years who also have comorbidities that would make open-heart surgery high risk. The first TAVI procedure was performed on April 16, 2002, in Rouen, France, by Alain Cribier. Since 2008, randomized controlled trials (PARTNER 1B) have been conducted in extremely high-risk patients with a Society of Thoracic Surgeons (STS) score > 15, demonstrating the noninferiority of this method compared with surgical bioprosthetic valve replacement. Subsequent studies (PARTNER 1B and CoreValve HR) in high-risk patients with an STS score > 8 also demonstrated the noninferiority of this method compared with surgical bioprosthetic valve replacement. In intermediate-risk patients with an STS score of 4–8 (PARTNER 2 and SURTAVI), the studies likewise demonstrated the efficacy of this method compared with surgical bioprosthetic valve replacement. The TAVI procedure was also applied in low-risk patients with an STS score < 4 (PARTNER 3, Evolut Low Risk), where the results again confirmed that the TAVI valve was not inferior to surgical bioprosthetic valve replacement. In our country, the first TAVI intervention was performed at the University Clinical Centre of Serbia on April 22, 2014 (Prof. Dr. Milan A. Nedeljković, Prof. Dr. Branko Beleslin).
Methods In our three centers, self-expanding and balloon-expandable TAVI valves were used and implanted via the transfemoral approach (through the femoral artery).
Before the TAVI procedure, we performed a comprehensive assessment of the severity of aortic stenosis, left ventricular function, and the size and type of valve to be implanted. The non-invasive diagnostic evaluation included:
1. Transthoracic echocardiography (TTE);
2. Transesophageal echocardiography (TEE) (when indicated);
3. Computed tomography of the heart and aorta is one of the most important examinations performed before the TAVI procedure. It is used to assess and measure the aortic valve and annulus, as well as the aorta and the blood vessels through which the catheter will be advanced (most commonly the femoral arteries). This examination is essential for selecting the appropriate prosthetic valve and determining the optimal vascular access route;
4. Coronary angiography;
5. Electrocardiogram (ECG);
6. Laboratory tests;
7. Chest X-ray;
8. Assessment of the patient's overall clinical condition.
All of these data were required by the Heart Team to assess the procedural risk for each patient.
Results From 2014 to 2021, a total of 73 TAVI valves were implanted in three centers in Serbia. In 2022, annual procurement of valves by the Health Insurance Fund of Serbia began, and 221 TAVI valves were implanted that year. In 2023, 318 TAVI valves were implanted, and in 2024, 231 TAVI valves. In 2025, 562 TAVI valves were implanted. In Serbia, a total of 1405 TAVI valves were implanted from 2014 up to and including 2025.
These results demonstrate the continuous development of the TAVI program, particularly following the introduction of systematic funding. However, they also indicate that there is still room to improve access to the procedure and to further expand the network of TAVI centers in Serbia.
Conclusion This method has been widely accepted worldwide, and in certain countries it is used to treat more than 50% of patients with aortic stenosis.
Keywords: TAVI; aortic stenosis; STS score

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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is a treatment modality intended for patients with aortic stenosis who are over 70 years old and have significant comorbidities, making conventional open-heart surgery a high-risk procedure. The first TAVI procedure was performed on April 16, 2002, in Rouen, France, by Alain Cribier.

Randomized controlled trials evaluating TAVI began in 2008. The first, PARTNER 1B [1], published in 2010, enrolled patients at extreme surgical risk with a Society of Thoracic Surgeons (STS) Risk Score > 15. The study demonstrated the superiority of TAVI over

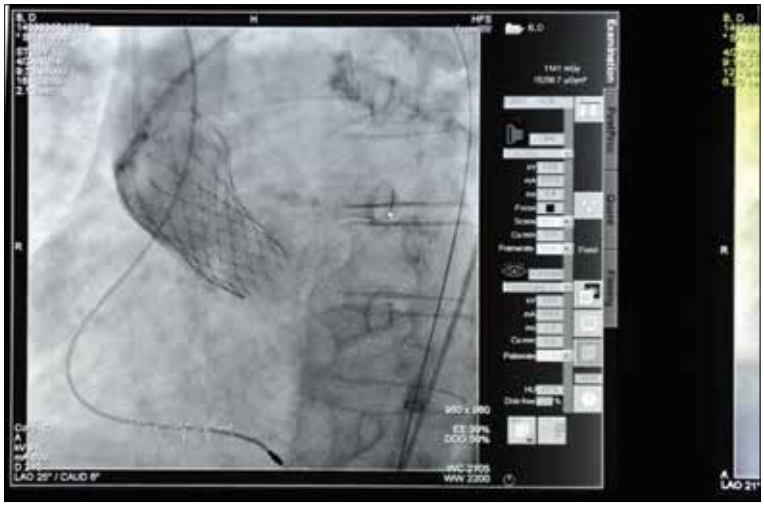

Figure 1. The first CoreValve (Medtronic, Minneapolis, MN, USA) implanted in Serbia in 2014

medical therapy and its non-inferiority compared with surgical aortic valve replacement (SAVR) in the treatment of aortic stenosis.

The PARTNER 1A trial [2], published in 2011, included high-risk patients with an STS score of 8–15 and demonstrated that TAVI was non-inferior to SAVR. Both the PARTNER 1B and PARTNER 1A trials used balloon-expandable intra-annular valves.

In 2014, the US CoreValve High Risk trial [3] was published, enrolling high-risk patients with an STS score of 8–15. In this study, TAVI was shown to be non-inferior, and even superior to SAVR. A self-expanding supra-annular aortic valve prosthesis was used.

The PARTNER 2A trial [4], published in 2016, enrolled patients at intermediate surgical risk (STS score 4–8). The study demonstrated that TAVI was non-inferior to SAVR. A balloon-expandable intra-annular aortic valve prosthesis was used.

One year later, in 2017, the SURTAVI trial [5] was published, also including intermediate-risk surgical patients with an STS score of 4–8. The study demonstrated that TAVI was non-inferior to SAVR with respect to the composite endpoint of all-cause mortality or disabling stroke. A self-expanding supra-annular aortic valve prosthesis was used.

In 2019, two landmark trials were published: PARTNER 3 [6] and Evolut Low Risk [7], both enrolling low-risk surgical patients with an STS score < 4.

In the PARTNER 3 trial, TAVI proved superior to SAVR with respect to early clinical outcomes, whereas in the Evolut Low Risk trial, TAVI was shown to be non-inferior to SAVR in low-risk patients.

The PARTNER 3 trial used a balloon-expandable intra-annular aortic valve prosthesis, while the Evolut Low Risk trial used a self-expanding supra-annular valve prosthesis.

In 2024, the NOTION 10-year study [8], involving low-risk patients (STS score < 4), was published. Its long-term results demonstrated sustained efficacy and durability of TAVI prostheses. A self-expanding supra-annular prosthesis was used.

In Serbia, the first TAVI procedure was performed on April 22, 2014, at the University Clinical Centre of Serbia by Prof. Milan A. Nedeljković and Prof. Branko Beleslin [9–14] (Figure 1).

METHODS

At the four participating centers – the University Clinical Centre of Serbia, Dedinje Institute for Cardiovascular Diseases, and the Institute for Cardiovascular Diseases Sremska Kamenica, the Military Medical Academy (starting with August 18, 2025) – both self-expanding and balloon-expandable TAVI prostheses were used. The valves were implanted predominantly via the transfemoral approach (through the femoral artery).

In addition to the primary vascular access used for valve implantation, a secondary access site (radial or femoral artery) is required for the introduction of a pigtail catheter into the non-coronary cusp to facilitate fluoroscopic guidance and accurate assessment of implantation depth. One of the steps preceding valve implantation is pre-dilation of the aortic valve with a balloon, which is performed with electrical stimulation with a pacemaker (so-called "rapid pacing"), most often via a wire placed in the left ventricle or, less often, via a temporary pacemaker placed in the right ventricle.

Before the TAVI procedure, a comprehensive assessment of the severity of aortic stenosis, left ventricular function, and the size and type of prosthetic valve to be implanted was performed. The pre-procedural non-invasive diagnostic evaluation included:

1. Transthoracic echocardiography (TTE) to confirm the severity of aortic valve stenosis, assess left ventricular function, and evaluate the condition of the remaining heart valves;
2. Transesophageal echocardiography (TEE), when indicated, to provide detailed visualization of the cardiac valves and intracardiac structures;
3. Computed tomography of the heart and aorta, one of the most important investigations before TAVI, used to assess and measure the aortic valve, annulus, aorta, and access vessels (most commonly the femoral arteries) through which the delivery catheter will be advanced. This examination is essential for selecting the appropriate prosthetic valve size and determining the optimal vascular access route. Although the transfemoral approach is preferred, alternative access routes include the axillary, subclavian, carotid, transcaval, and transapical approaches;
4. Coronary angiography;
5. Electrocardiography (ECG);
6. Laboratory investigations;
7. Chest radiography;
8. Assessment of the patient's overall clinical condition.

Table 1. TAVI procedures in Serbia, 2014–2025;

TAVI in Serbia 2014–2025	
• 2014 TAVI = 5 (Clinical Center of Serbia) • 2015 TAVI = 6 (Clinical Center of Serbia – 2, Institute for CVD Dedinje – 2, Institute for CVD Sremska Kamenica – 2) • 2016 TAVI = 1 (Clinical Center of Serbia) • 2017 TAVI = 2 (Military Medical Academy) • 2018 TAVI = 2 (Military Medical Academy) • 2019 TAVI = 1 (Military Medical Academy) • 2019 TAVI = 24 (Institute for CVD Dedinje) • 2020 TAVI = 9 (Institute for CVD Dedinje) • 2021 TAVI = 23 (Institute for CVD Dedinje)	• **2022** TAVI* = 166 (Institute for CVD Dedinje) = 25 (Institute for CVD Sremska Kamenica) = 30 (University Clinical Center of Serbia) **TOTAL = 221** • **2023** TAVI = 167 (Institute for CVD Dedinje) = 80 (Institute for CVD Sremska Kamenica) = 71 (University Clinical Center of Serbia) **TOTAL = 318** • **2024** TAVI = 97 (Institute for CVD Dedinje) = 75 (Institute for CVD Sremska Kamenica) = 53 (University Clinical Centre of Serbia) = 6 (Military Medical Academy) **TOTAL = 231** • **2025** TAVI = 294 (Institute for CVD Dedinje) = 133 (Institute for CVD Sremska Kamenica) = 127 (University Clinical Center of Serbia) = 8 (the Military Medical Academy)** **TOTAL = 562**
TOTAL (2014–2021) = 73	**TOTAL (2022–2025) = 1332**
	TAVI in Serbia (2014–2025) TOTAL = 1405

*In 2022 annual procurement of valves by the Health Insurance Fund of Serbia began;
**The National Health Insurance Fund of Serbia included the Military Medical Academy starting with August 2025

All of these data were reviewed by the multidisciplinary Heart Team, which assessed the procedural risk and determined the most appropriate treatment strategy for each patient [15].

Ethics: This retrospective investigations were carried on in accordance with ethical standards of the Serbian Archives of Medicine and the Declaration of Helsinki.

RESULTS

Between 2014 and 2021, a total of 73 TAVI valves were implanted across the three TAVI centers in Serbia. In 2022, the National Health Insurance Fund of Serbia initiated annual procurement of TAVI valves, resulting in 221 TAVI procedures performed that year. In 2023, 318 TAVI valves were implanted, followed by 231 procedures in 2024. In 2025, the annual number increased to 562 TAVI procedures. Overall, from 2014 through the end of 2025, a total of 1405 TAVI valves were implanted in Serbia (Table 1).

DISCUSSION

First, it is evident that between 2014 and 2021 the number of TAVI procedures performed in Serbia was very low, with only 73 valves implanted across three centers. This limited procedural volume can be attributed to the early stage of the national TAVI program, restricted availability of prosthetic valves, and the fact that the procedure was not yet systematically funded by the National Health Insurance Fund of Serbia during that period [16].

A major turning point occurred in 2022, when the National Health Insurance Fund of Serbia initiated regular procurement of TAVI valves. As a result of this healthcare policy, the number of procedures increased dramatically – from a total of 73 procedures performed during the preceding eight-year period to 221 procedures in 2022 alone. This trend indicates that systematic reimbursement was a key prerequisite for the broader implementation of TAVI and improved access to treatment for patients with severe aortic stenosis.

The upward trend continued in 2023, with 318 procedures performed, reflecting increasing operator experience, further development of the national TAVI program, and expansion of indications in accordance with contemporary European and international guidelines. The lower number of procedures in 2024 (231) most likely reflects organizational factors, the dynamics of valve procurement, or the allocation of healthcare resources rather than a reduced clinical need for this treatment modality. Therefore, this finding should be interpreted with caution in the absence of additional data.

The highest annual procedural volume was recorded in 2025, with 562 TAVI procedures, representing more than a twofold increase compared with the previous year. This substantial growth suggests that TAVI in Serbia has progressed from an initial developmental phase to routine clinical practice, accompanied by a marked expansion of healthcare system capacity and increasing experience of multidisciplinary Heart Teams.

Overall, between 2014 and 2025, a total of 1405 TAVI valves were implanted in Serbia. These findings demonstrate the continuous development of the national TAVI program, which accelerated considerably following the

introduction of systematic reimbursement. Although the number of procedures has increased substantially, it remains lower than that reported in most developed countries, indicating that there is still considerable potential for further expansion of the program, improved patient access, and the establishment of additional TAVI centers throughout the country [17, 18, 19].

CONCLUSION

TAVI represents an effective and safe therapeutic option for the treatment of patients with severe symptomatic aortic stenosis. Advances in technology, improvements in implantation systems, and increasing operator experience have led to a significant reduction in periprocedural complications and improved both short- and long-term outcomes. Results from numerous clinical trials confirm that TAVI provides a high procedural success rate, improvement in functional status and quality of life, with long-term durability of bioprosthetic valves. Individual patient selection, based on the assessment of a multidisciplinary Heart Team, remains crucial for achieving optimal outcomes. Further technological advancements and the availability of long-term outcome data are expected to expand the indications for TAVI in patients with different levels of surgical risk.

This method has been widely adopted worldwide, and in some countries, it is used to treat more than 50% of patients with aortic stenosis.

Conflict of interest: None declared.

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Транскатетерска имплантација аортне валвуле (*TAVI*) у лечењу аортне стенозе – од високоризичних до нискоризичних болесника са приказом резултата у Србији од 2014. до 2025. године

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САЖЕТАК

Увод/Циљ Транскатетерска имплантација аортне валвуле (*TAVI*) метода је лечења предвиђена за болеснике са аортном стенозом који су старији од 70 година и који имају и друга обољења, тако да би сама хирургија на отвореном срцу за њих била високоризична.

Прва *TAVI* метода изведена је 16. априла 2002. године у Руану (Француска), а извршио ју је Алан Крибије (*Alain Cribier*). Од 2008. године почеле су да се спроводе рандомизоване контролисане студије (*PARTNER* 1*B*) код екстремно ризичних болесника чији је скор Друштва торакалних хирурга (*STS*) > 15, које су показале неинфериорност ове методе у односу на хируршку замену биолошком валвулом. Касније спроведене студије (*PARTNER* 1*B* и *CoreValve HR*) код високоризичних болесника чији је *STS* скор > 8 такође су показале неинфериорност ове методе у односу на хируршку замену биолошком валвулом. Код средње ризичних болесника чији је *STS* скор 4–8 (*PARTNER* 2 и *SURTAVI*) студије су такође показале ефикасност ове методе у односу на хируршку замену биолошком валвулом. *TAVI* метода је примењена и код нискоризичних болесника са *STS* скором < 4 (*PARTNER* 3, *Evolut Low Risk*), где су резултати поново потврдили да *TAVI* валвула није инфериорна у односу на хируршку замену биолошком валвулом. У нашој земљи прва *TAVI* интервенција урађена је 22. априла 2014. године у Универзитетском клиничком центру Србије (проф. др Милан А. Недељковић, проф. др Бранко Белеслин).

Методе У наша три центра употребљаване су самоширеће и балон-ширеће *TAVI* валвуле које су пласиране трансфеморалним путем (преко артерије феморалис).

Пре *TAVI* процедуре радили смо детаљну процену тежине аортне стенозе, функције леве срчане коморе и величине и типа залиска који ћемо употребити. Неинвазивне дијагностичке методе укључивале су:

1. трансторакалну ехокардиографију (TTE);
2. трансезофагеалну ехокардиографију (TEE) (по потреби);
3. компјутеризовану томографију срца и аорте, која представља један од најважнијих прегледа пре *TAVI* процедуре, којим се процењују и мере аортни зализак и прстен, као и аорта и крвни судови кроз које ће се уводити катетер (најчешће феморалне артерије). Ово је неопходно за адекватан одабир вештачке валвуле, као и одабир адекватног васкуларног приступа;
4. коронарну ангиографију;
5. електрокардиограм (ЕКГ);
6. лабораторијске анализе;
7. рендген грудног коша;
8. процену општег здравственог стања.

Сви ови подаци били су потребни срчаном тиму (*Heart Team*) ради процене ризика саме процедуре код болесника.

Резултати Од 2014. до 2021. године укупно су у три центра у Србији уграђене 73 *TAVI* валвуле. Од 2022. године почиње годишња набавка валвула од стране Фонда за здравствено осигурање Србије, тако да је те године уграђена 221 *TAVI* валвула. Године 2023. уграђено је 318 *TAVI* валвула, а 2024. године 231 *TAVI* валвула. Године 2025. уграђене су 562 *TAVI* валвуле.

Укупно је у периоду од 2014. до 2025. године имплантирано 1405 *TAVI* валвула. Ови резултати показују континуиран развој *TAVI* програма, посебно након увођења системског финансирања, али и даље указују на простор за повећање доступности процедуре и даљи развој *TAVI* центара у Србији.

Закључак Ова метода је широко прихваћена у свету и у одређеним земљама се њоме лечи више од 50% болесника са аортном стенозом.

Кључне речи: *TAVI*; аортна стеноза; *STS* скор

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Comparison of biparametric and multiparametric magnetic resonance imaging in the detection of clinically significant prostate cancer – a prospective study with prostate-specific antigen density analysis

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SUMMARY

Introduction/Objective Multiparametric MRI (mpMRI) is the standard imaging method for the detection of clinically significant prostate cancer (csPCa). Biparametric MRI (bpMRI), which omits dynamic contrast-enhanced imaging (DCE), may provide a faster and more accessible alternative. The aim of this study was to compare bpMRI and mpMRI in the detection of csPCa and evaluate the role of PSA density (PSAD).

Methods This prospective study included 170 men with suspected prostate cancer. All patients underwent 3-T prostate MRI before biopsy. MRI findings were interpreted according to PI-RADS v2.1, and histopathology served as the reference standard. Diagnostic performance was assessed at PI-RADS thresholds of ≥ 4 and ≥ 3. ROC analysis and logistic regression were used to evaluate PSAD.

Results Agreement between bpMRI and mpMRI was 98.2%. At the PI-RADS ≥ 4 threshold, bpMRI showed sensitivity of 97%, specificity of 77.9%, and accuracy of 85.3%, comparable to mpMRI (97%, 76.9%, and 84.7%). PSAD showed good diagnostic performance (AUC 0.872, 95% CI, 0.813–0.931, $p < 0.001$). The optimal cutoff selected by the Youden index was 0.205 ng/mL/cm^3. Non-inferiority analysis confirmed that bpMRI was non-inferior to mpMRI for overall diagnostic accuracy.

Conclusion Biparametric MRI demonstrated diagnostic performance comparable to that of and non-inferior to mpMRI for detection of csPCa. PI-RADS ≥ 4 was the optimal diagnostic threshold, while PSAD improved risk stratification.

Keywords: prostate cancer; biparametric MRI; multiparametric MRI; PSA density; PI-RADS

INTRODUCTION

Prostate cancer is one of the most frequently diagnosed malignancies in men worldwide and remains a major public health issue [1, 2]. PSA testing has improved early detection, but its limited specificity may lead to unnecessary biopsies and overdiagnosis of clinically insignificant tumors. Current diagnostic pathways therefore aim to improve detection of clinically significant prostate cancer (csPCa) while reducing unnecessary invasive procedures [3].

PSA density (PSAD), calculated as serum PSA divided by prostate volume, has become an important adjunctive parameter in patients with suspected prostate cancer. It improves specificity compared with PSA alone and is particularly useful in men with equivocal MRI findings, especially PI-RADS 3 lesions. Although 0.15 ng/mL/cm^3 is commonly used in clinical practice, recent studies suggest that optimal thresholds may vary according to clinical context and MRI category [4, 5, 6].

Multiparametric MRI (mpMRI) has become central to the diagnostic pathway for suspected prostate cancer. It improves detection of csPCa, enables lesion localization, facilitates targeted biopsy, and reduces unnecessary systematic biopsies [6–11]. The importance of MRI in prostate cancer diagnosis and staging has also been highlighted in regional clinical literature [12, 13]. PI-RADS v2.1 standardized MRI acquisition and interpretation, with the standard mpMRI protocol including T2-weighted imaging, diffusion-weighted imaging (DWI) with ADC mapping, and dynamic contrast-enhanced imaging (DCE) [14, 15].

DCE can be useful in selected cases, particularly for upgrading some PI-RADS 3 peripheral-zone lesions, but it prolongs examination time, increases costs, and requires gadolinium administration [14, 15]. Biparametric MRI (bpMRI), which omits DCE and relies on T2W and DWI, has therefore been proposed as a shorter protocol. Previous systematic reviews and recent prospective studies have reported comparable diagnostic performance of bpMRI and mpMRI for csPCa detection [16–24].

The aim of this study was to compare bpMRI and mpMRI in the detection of csPCa, defined as Gleason score ≥ 3 + 4 / ISUP grade group ≥ 2. We evaluated diagnostic performance, the

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impact of omitting DCE on PI-RADS categorization, and the additional predictive value of PSAD.

METHODS

Study design and study population

This prospective study included patients with suspected prostate cancer based on PSA > 4 ng/mL and/or abnormal digital rectal examination. The study was conducted at the University Clinical Center Niš from January 1, 2021, to December 31, 2025. The protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants.

Of 200 initially evaluated subjects, 170 men met the inclusion criteria and had complete clinical, imaging, and histopathological data. Inclusion criteria were clinical suspicion of prostate cancer, no previous prostate biopsy, and no prior therapy for prostate disease. Exclusion criteria were contraindications to MRI, contraindications to gadolinium administration, insufficient MRI quality, or absence of histopathological verification.

MRI protocol

All examinations were performed before biopsy using a 3.0-T scanner (SIGNA Pioneer, GE Healthcare, Chicago, IL, USA) with a pelvic phased-array surface coil. Two protocols were evaluated: bpMRI (PI-RADS SHORT), consisting of T2W and DWI with ADC maps, and mpMRI (PI-RADS FULL), consisting of T2W, DWI with ADC maps, and DCE.

MRI interpretation

All MRI examinations were interpreted independently by two radiologists (AT and DS) with at least two years of experience in uroradiology. One radiologist interpreted only the bpMRI protocol and was blinded to the DCE sequence, the mpMRI assessment, and the second reader's report. The second radiologist interpreted the complete mpMRI protocol and was blinded to the bpMRI report and the first reader's assessment. Since each protocol was evaluated by a different reader, interobserver agreement was not analyzed; the comparison focused on protocol-level diagnostic performance. Lesions were classified according to PI-RADS v2.1. Positive MRI was defined using two thresholds: PI-RADS ≥ 4 and PI-RADS ≥ 3.

Prostate biopsy and reference standard

Biopsy was performed 1–7 days after MRI. All patients underwent systematic 12-core biopsy, with three additional targeted cores obtained from the MRI-defined suspicious region using cognitive fusion with MR images. Histopathology was classified as malignant (csPCa, Gleason score ≥ 7 / ISUP grade group ≥ 2) or benign/clinically insignificant disease and served as the reference standard.

PSA density assessment

Prostate volume was calculated from MRI measurements using the ellipsoid formula: volume = length × width × height × 0.52. PSAD was calculated as PSA/prostate volume and analyzed both as a continuous variable and at thresholds of 0.15 and 0.2 ng/mL/cm^3. ROC analysis was used to determine the optimal cutoff, selected by the Youden index. AUC values were reported with 95% confidence intervals (CI) and p-values. A subgroup analysis was performed in patients with PI-RADS 3 lesions.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 29 (IBM Corp., Armonk, NY, USA), with additional calculation of confidence intervals for paired diagnostic differences using standard formulas for paired proportions. Agreement between PI-RADS SHORT and PI-RADS FULL was assessed using cross-tabulation and Pearson's χ^2 test. Diagnostic performance was evaluated by sensitivity, specificity, and accuracy. The 95% CI for AUC values was calculated using the nonparametric DeLong method. Logistic regression was used to identify independent predictors of malignancy, with PSAD scaled per 0.1 ng/mL/cm^3 increase. Non-inferiority of bpMRI compared with mpMRI was assessed for overall diagnostic accuracy, with sensitivity and specificity as supportive endpoints. The prespecified non-inferiority margin was -5 percentage points for the paired difference between bpMRI and mpMRI. Confidence intervals for paired differences were calculated using the Wald method based on discordant pairs. Statistical significance was defined as $p < 0.05$.

Ethics: The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the University Clinical Center Niš, Serbia (Decision No. 43428/5, dated December 3, 2019). Written informed consent was obtained from all participants.

RESULTS

Study population

A total of 170 patients were included. Histopathology showed benign or clinically insignificant findings in 104 patients and csPCa in 66 patients (Table 1).

Agreement between PI-RADS SHORT and PI-RADS FULL

Agreement between bpMRI and mpMRI was almost perfect. Identical PI-RADS categories were observed in 167 of 170 patients (98.2%). Three discrepancies were found: two lesions classified as PI-RADS 4 on bpMRI were upgraded to PI-RADS 5 on mpMRI, and one lesion classified as PI-RADS 3 on bpMRI was categorized as PI-RADS 4 on

mpMRI (Table 2). The latter case had a benign or clinically insignificant histopathological finding.

Diagnostic performance of MRI protocols

Diagnostic performance is summarized in Table 3. At the PI-RADS ≥ 4 threshold, bpMRI showed sensitivity of 97%, specificity of 77.9%, and accuracy of 85.3%, while mpMRI showed sensitivity of 97%, specificity of 76.9%, and accuracy of 84.7%. Lowering the threshold to PI-RADS ≥ 3 increased sensitivity to 98.5% but reduced specificity to 47.1%.

Non-inferiority analysis confirmed that bpMRI was non-inferior to mpMRI for overall diagnostic accuracy at the prespecified 5-percentage-point margin (Table 4). The paired accuracy difference was 0.6 percentage points (95% CI, −0.6 to 1.7), and the lower CI bound was above the non-inferiority margin.

Table 1. Patient characteristics and histopathological findings

Variable	Value
Number of patients	170
Patients with complete data	170
Benign findings (B)	104
Malignant findings (M) (csPCa, Gleason ≥ 3 + 4)	66

Table 2. Agreement between PI-RADS SHORT (bpMRI) and PI-RADS FULL (mpMRI) classifications

PI-RADS FULL	PI-RADS SHORT 2	PI-RADS SHORT 3	PI-RADS SHORT 4	PI-RADS SHORT 5	Total
2	50	0	0	0	50
3	0	33	0	0	33
4	0	1	38	0	39
5	0	0	2	46	48
Total	50	34	40	46	170

PI-RADS FULL – mpMRI-based PI-RADS score; PI-RADS SHORT – bpMRI-based PI-RADS score:
Pearson $\chi^2 = 485.76$;
$p < 0.001$

Table 3. Diagnostic performance of bpMRI, mpMRI, and PSA using different diagnostic thresholds

Diagnostic parameter	Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%)
PI-RADS SHORT ≥ 4	97	77.9	85.3
PI-RADS SHORT ≥ 3	98.5	47.1	67.1
PI-RADS FULL ≥ 4	97	76.9	84.7
PI-RADS FULL ≥ 3	98.5	47.1	67.1
PSA ≥ 4 ng/mL	73.5	72.7	73

PI-RADS SHORT – bpMRI-based PI-RADS score threshold for expected malignancy; PI-RADS FULL – mpMRI-based PI-RADS score threshold for expected malignancy; PSA – prostate-specific antigen threshold for expected malignancy

Table 4. Non-inferiority analysis of bpMRI compared with mpMRI at the PI-RADS ≥ 4 threshold

Endpoint	Difference (bpMRI – mpMRI) percentage points	95% CI (percentage points)	Conclusion
Sensitivity	0	No discordant malignant cases	Non-inferior
Specificity	1	-0.9–2.8	Non-inferior
Diagnostic accuracy	0.6	-0.6–1.7	Non-inferior

The prespecified non-inferiority margin was -5 percentage points

PSA alone showed lower diagnostic performance than MRI-based parameters. The relationship between bpMRI findings and histopathology is presented in Table 5.

Using PI-RADS ≥ 4, csPCa was detected in 64 of 87 patients (73.6%) with positive bpMRI findings, compared with 2 of 83 patients (2.4%) with negative bpMRI findings.

Table 5. Association between PI-RADS SHORT (bpMRI) classification (threshold ≥ 4) and histopathological findings

PI-RADS SHORT classification	Benign	Malignant	Total
Negative MRI (PI-RADS ≤ 3)	81	2	83
Positive MRI (PI-RADS ≥ 4)	23	64	87
Total	104	66	170

PI-RADS SHORT – bpMRI-based PI-RADS score; Negative MRI – expected benign; Positive MRI – expected malignancy;
Pearson $\chi^2 = 90.545$;
$p < 0.001$

Multivariate logistic regression analysis

Both PSAD and PI-RADS SHORT score were independent predictors of csPCa (Table 6). PSAD was significant when scaled per 0.1 ng/mL/cm³ increase, and each increase in PI-RADS category was associated with higher malignancy risk.

The unscaled PSAD model produced a very large odds ratio with a wide confidence interval; therefore, the scaled estimate was used and should be interpreted as evidence of association rather than a precise effect-size estimate.

ROC analysis of PSA density

PSAD showed good discriminative ability for csPCa, with an AUC of 0.872 (95% CI, 0.813–0.931, $p < 0.001$). The optimal cutoff selected by the Youden index was 0.205 ng/mL/cm³, with sensitivity of 75% and specificity of 92.7% (Table 7).

Table 6. Multivariate logistic regression analysis for prediction of malignancy

Variable	Odds ratio	95% CI	p-value
PSA density (PSAD) per 0.1 ng/mL/cm³ increase	1.56	1.1–2.21	0.012
PI-RADS SHORT	4.73	2.58–8.65	< 0.001

PSAD – prostate-specific antigen density; PI-RADS SHORT – bpMRI-based PI-RADS score

Table 7. ROC analysis of PSA density (PSAD) for detection of clinically significant prostate cancer

PSAD cutoff	Sensitivity (%)	Specificity (%)
0.1	95.6	52.3
0.15	83.8	75.2
0.2	75	92.7
0.25	58.8	95.4

AUC = 0.872; 95% CI, 0.813–0.931; $p < 0.001$;
Optimal cutoff value: PSAD = 0.205 ng/mL/cm³ (Youden index)

The commonly used threshold of 0.15 ng/mL/cm³ had higher sensitivity but lower specificity. A slightly higher threshold may therefore improve specificity and reduce unnecessary biopsies in selected patients.

Subgroup analysis of PI-RADS 3 lesions

The PI-RADS 3 subgroup included 34 patients, of whom 2 had csPCa and 32 had benign or clinically insignificant findings. In this subgroup, PSAD showed an AUC of 0.969 (95% CI, 0.798–1.000, $p < 0.001$; Figure 1). The optimal cutoff selected by the Youden index was again 0.205 ng/mL/cm^3, achieving 100% sensitivity and 93.8% specificity. Because only two malignant cases were present, these findings should be considered exploratory.

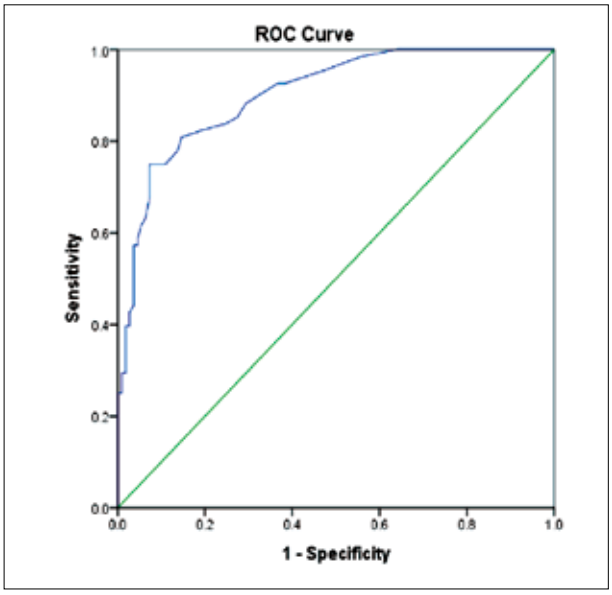

Figure 1. Receiver operating characteristic (ROC) curve of PSA density for detection of clinically significant prostate cancer

DISCUSSION

This prospective study showed that bpMRI was non-inferior to mpMRI for detection of csPCa. Agreement between protocols was 98.2%, with only three discordant cases. Two discrepancies did not affect binary categorization at the PI-RADS ≥ 4 threshold, while one PI-RADS SHORT 3 lesion was upgraded to PI-RADS FULL 4 after DCE but proved benign or clinically insignificant. This suggests that omitting DCE had minimal clinical impact in this cohort.

These findings are consistent with previous studies and meta-analyses reporting comparable diagnostic performance of bpMRI and mpMRI when DWI quality is adequate [16–19]. The prospective PRIME trial also confirmed non-inferiority of bpMRI compared with mpMRI in biopsy-naïve men [20, 21]. Data from PROMIS, PRECISION, STHLM3-MRI, GÖTEBORG-2, and studies on MRI-targeted biopsies support MRI-first diagnostic pathways that improve csPCa detection while reducing unnecessary biopsies [7, 8, 10, 11, 25–27].

In our cohort, PI-RADS ≥ 4 provided the best balance between sensitivity and specificity. Lowering the threshold to PI-RADS ≥ 3 slightly increased sensitivity but markedly reduced specificity, reflecting the heterogeneous nature of PI-RADS 3 lesions [5, 28, 29]. The formal non-inferiority analysis supported this interpretation: the 95% CI for the accuracy difference remained above the −5 percentage-point margin, with no reduction in sensitivity and a small numerical specificity advantage for bpMRI.

PSAD was an important adjunctive parameter. Although PSA alone performed worse than MRI-based assessment, PSAD showed good discrimination, with an AUC of 0.872 and an optimal cutoff of 0.205 ng/mL/cm^3. This threshold was more specific than the commonly used 0.15 ng/mL/cm^3 cutoff and may be useful when the clinical aim is to reduce unnecessary biopsies. Contemporary work from the EAU-YAU collaboration supports our results, emphasizing that biomarker-based, personalized diagnostic strategies, including PSA density, can safely reduce the number of unnecessary MRI examinations and prostate biopsies [30]. Therefore, PSAD thresholds should be interpreted in relation to MRI category and clinical context [4, 29, 31–36].

The PI-RADS 3 subgroup findings are clinically relevant but exploratory. Only two malignant cases were present, so the high AUC and excellent sensitivity at a PSAD of 0.205 ng/mL/cm^3 require validation in larger cohorts. The logistic regression analysis also supports the independent value of PSAD, but the unscaled model produced an unstable estimate; therefore, PSAD was presented per 0.1 ng/mL/cm^3 increase for clearer clinical interpretation.

This study has several limitations. It was single-center, with a moderate sample size and few discordant cases. In addition, bpMRI and mpMRI were interpreted by different readers who were blinded to each other's reports; this design does not permit assessment of interobserver agreement and cannot completely separate protocol effects from reader effects. Finally, PSAD thresholds, especially in PI-RADS 3 lesions, require external validation.

Overall, bpMRI appears to be a reliable and efficient alternative to mpMRI for csPCa detection. It reduces examination time, avoids contrast administration, and may improve accessibility of prostate MRI, while PSAD adds clinically useful risk stratification.

CONCLUSION

Biparametric prostate MRI demonstrated diagnostic performance comparable and non-inferior to mpMRI for detection of clinically significant prostate cancer. PI-RADS ≥ 4 provided the best balance between sensitivity and specificity, while PSAD was an independent predictor of malignancy and improved risk stratification. These findings support further evaluation of bpMRI and PSAD-based decision-making in larger multicenter cohorts.

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Author contributions

Aleksandar Tasić: study conception and design, data collection, MRI interpretation, analysis and interpretation of results, manuscript drafting.

Dragan Stojanov: study supervision, interpretation of imaging findings, critical revision of the manuscript.

Aleksandra Aracki-Trenkić: MRI analysis, methodology development, data interpretation.

Dunja Radovanović: statistical analysis, interpretation of statistical results.

Dragoslav Bašić: urological evaluation, prostate biopsy procedures, clinical interpretation of findings, final revision of the manuscript for publication.

All authors have read and approved the final version of the manuscript.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Компарација бипараметарске и мултипараметарске магнетне резонанце у откривању клинички значајног карцинома простате – проспективна студија са анализом густине простата-специфичног антигена

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САЖЕТАК

Увод/Циљ Мултипараметарска магнетна резонанца (*mpMRI*) представља стандард у дијагностици клинички значајног карцинома простате (*csPCa*). Бипараметарска магнетна резонанца (*bpMRI*), без динамичког постконтрастног снимања (*DCE*), може бити бржа и доступнија алтернатива. Циљ рада био је поређење дијагностичких перформанси *bpMRI* и *mpMRI*, као и процена улоге густине *PSA* (*PSAD*).

Методе У проспективну студију укључено је 170 мушкараца са сумњом на карцином простате. Сви су подвргнути 3-T *MR* пре биопсије. Налази су анализирани према *PI-RADS v2.1*, а хистопатологија је коришћена као референтни стандард. Процена је извршена за прагове *PI-RADS* ≥ 4 и ≥ 3, уз *ROC* анализу и логистичку регресију за *PSAD*.

Резултати Сагласност између *bpMRI* и *mpMRI* износила је 98,2%. За праг *PI-RADS* ≥ 4, *bpMRI* је показао сензитивност 97%, специфичност 77,9% и тачност 85,3%, готово идентично *mpMRI* (97%, 76,9% и 84,7%). *ROC* анализа *PSAD* показала је *AUC* 0,872 (95% *CI* 0,813–0,931, $p < 0,001$). Оптимална гранична вредност, одабрана Јауденовим индексом, износила је 0,205 $ng/mL/cm^3$. Анализа неинфериорности потврдила је неинфериорност *bpMRI* у односу на *mpMRI*.

Закључак Бипараметарска магнетна резонанца показује дијагностичке перформансе упоредиве са *mpMRI* у откривању *csPCa*. Праг *PI-RADS* ≥ 4 представља оптимални дијагностички критеријум, док *PSAD* унапређује стратификацију ризика.

Кључне речи: карцином простате; бипараметарска *MRI*; мултипараметарска *MRI*; густина *PSA*; *PI-RADS*

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Duration of intraoperative fluoroscopy as a determinant of operative time in supracondylar femoral fracture treatment

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SUMMARY

Introduction/Objective Supracondylar femoral fractures are relatively uncommon injuries which, owing to their specific characteristics, present a particular therapeutic challenge. Operative management is the gold standard for treatment. This study aims to analyse operative duration and intraoperative fluoroscopy time in patients treated with a condylar-type self-dynamizable internal fixator compared to a retrograde intramedullary nail for the femur, and to examine the association between these two parameters.

Methods The study included 66 patients, divided into two groups of 33 participants. Patients in the first group underwent treatment with a retrograde intramedullary nail, whereas those in the second group underwent fixation with a condylar-type self-dynamizable internal fixator. In both groups, operative time (in minutes) and fluoroscopy time (in seconds) were recorded.

Results The mean operative time in patients treated with a retrograde intramedullary nail was statistically significantly shorter than in those treated with the self-dynamizable internal fixator. Conversely, the mean fluoroscopy time was statistically significantly longer in the retrograde intramedullary nail group. Radiation exposure time was a significant predictor of operative duration.

Conclusion Operative duration is an important factor in planning the surgical schedule and the type of anaesthesia. As expected, operative time was shorter with a retrograde intramedullary nail than with a self-dynamizable internal fixator. Intraoperative fluoroscopy is standard practice in orthopaedic trauma surgery; therefore, continuous refinement of surgical technique is essential to minimise radiation exposure and protect the health of the surgical team. Intraoperative fluoroscopy time was shorter with the self-dynamizable internal fixator than with the retrograde intramedullary nail.

Keywords: self-dynamizable internal fixator; retrograde intramedullary nail; fluoroscopy; operative duration

INTRODUCTION

Supracondylar fractures of the femur are relatively uncommon injuries, accounting for approximately 1% of all fractures and 3–6% of femoral fractures. Due to their specific characteristics, they present a treatment challenge for both the patient and the surgeon. In younger patients, these fractures most commonly occur as a result of high-energy trauma. In contrast, in the elderly population, often in the context of osteoporosis, they typically result from low-energy trauma [1–5]. Operative treatment is the gold standard when managing this type of fracture. With the development of modern implants and advances in surgical techniques, nonoperative treatment is currently reserved only for patients who refuse surgical treatment or who are deemed unfit for surgery by an anesthesiologist [6, 7].

A wide range of implants can be used to treat supracondylar femoral fractures. External fixators are most commonly used as a temporary solution for early fracture stabilisation and the management of soft-tissue injuries [8–10]. As definitive treatment options, numerous extramedullary and intramedullary fixation systems are currently available. No significant advantages of one implant over another have been demonstrated in terms of final treatment outcomes. The choice of implant depends on the fracture pattern, specific characteristics of each implant, the implantation technique, the postoperative rehabilitation protocol, and is ultimately determined by the surgeon [11–14]. The difference between extramedullary and intramedullary fixation systems primarily reflects the surgical implantation technique and, subsequently, the biomechanics of fracture stabilisation, which play a crucial role in early patient rehabilitation [15].

In this study, we focus on differences between surgical implantation techniques, particularly on how extramedullary *vs.* intramedullary implants influence the operative course, with special emphasis on operative time and intraoperative fluoroscopy time. Operative time is essential for daily operating room scheduling and anaesthetic planning. At the same time, the duration of intraoperative fluoroscopy is relevant to the safety and protection of the surgical

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Figure 1. Retrograde intramedullar nail postoperative image – AP view

Figure 2. Retrograde intramedullar nail postoperative image – lateral view

team from radiation exposure [16, 17, 18]. The advantages of fluoroscopy have led to a significant increase in its use during surgical procedures, resulting in prolonged radiation exposure of the operating staff [19–22].

The literature most commonly compares operative time between retrograde intramedullary nailing (RIMN) and locking anatomical plates, whereas data on intraoperative fluoroscopy time are limited [23, 24, 25]. Two implants are compared in this study: the self-dynamizable internal fixator (SIF) with a condylar unit and the retrograde intramedullary nail (RIMN) for the femur. To the best of our knowledge, no comparative data between these two implants are currently available. The SIF with a condylar unit is an extramedullary fixation system that is anatomically contoured in its distal part to match the distal femur. A special feature of this implant is its ability to undergo a spontaneous, delayed transition from initially rigid to dynamic fixation along the bone's vertical axis, without the need for additional surgical intervention [26].

This study aims to analyse operative time and intraoperative fluoroscopy time during treatment of supracondylar femoral fractures using the condylar-type SIF and the retrograde intramedullary femoral nail, and to examine the relationship between these two parameters.

METHODS

The study included 66 patients, divided into two groups of 33 participants, who underwent surgical treatment between 2022 and 2024. The patients in the first group underwent surgical treatment at the Clinic for Orthopaedics and Traumatology of the University Clinical Centre of Vojvodina, where retrograde intramedullary nailing (RIMN; Expert R/AFN) was the predominant treatment method. The patients in the second group underwent surgical treatment at the Academician Prof. Dr Milorad Mitković Clinic for Orthopaedics and Traumatology of the Niš University Clinical Centre, where the condylar-type self-dynamizable internal fixator (SIF) was the predominant treatment method. Based on the Arbeitsgemeinschaft für Osteosynthesefragen (AO) and the Orthopaedic Trauma Association (OTA) classification, all patients had sustained fractures classified as types 33A2 or 33A3 (Table 1).

Table 1. Fracture type according to Arbeitsgemeinschaft für Osteosynthesefragen (AO) and the Orthopaedic Trauma Association (OTA) classification

Fixation	33A2	33A3			Σ
		33A3.1	33A3.2	33A3.3	
RIMN	6	3	10	14	33
SIF	9	4	11	9	33

RIMN – retrograde intramedullary nail; SIF – self-dynamizable internal fixator

In the first group, 19 patients (58%) were female, and 14 patients (42%) were male. In the second group, 20 patients (61%) were female, and 13 patients (39%) were male. The mean age of patients in the first group was 65.6 years, whereas in the second group it was 73.4 years.

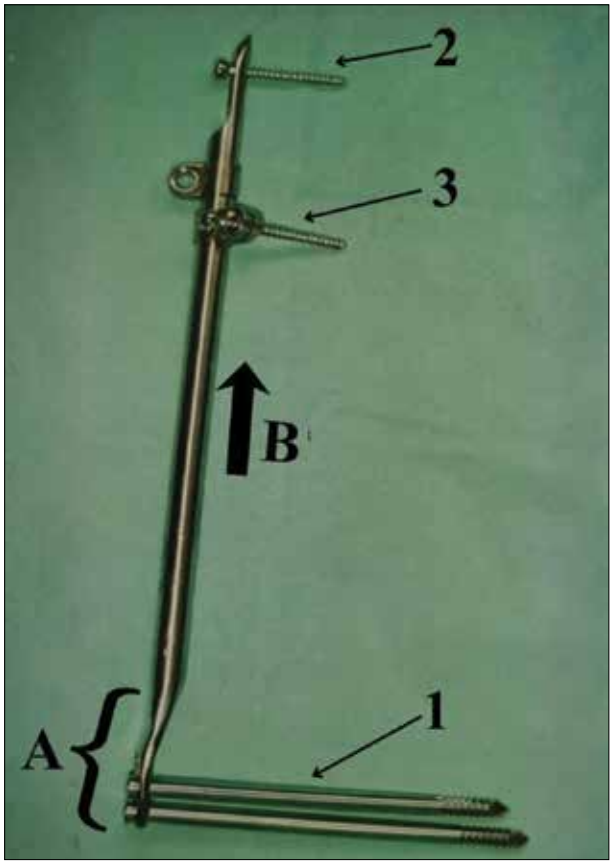

Figure 3. Self-dynamizable internal fixator condylar-type: A – condylar unit; B – dynamisation in the long femoral axis; 1 – locking screw; 2 – cortical anti-rotational screw; 3 – screw with the clamp

Figure 4. Self-dynamizable internal fixator condylar-type – postoperative image

Surgical Technique for Retrograde Intramedullary Nail (RIMN, Expert R/AFN) – All patients were operated on in the supine position on a radiolucent table, with the knee of the injured limb free and flexed up to 90 degrees. Using a standard approach with a longitudinal skin incision and transection of the patellar ligament, the surgeon accessed the intercondylar space. The entry point of the nail was determined by digital palpation and under fluoroscopic control, immediately anterior and lateral to the femoral attachment of the posterior cruciate ligament. Fracture reduction, guidewire insertion, canal reaming, determination of nail dimensions, and nail insertion were all performed and verified under fluoroscopic guidance. The nail was locked distally using a targeting guide and proximally by hand under fluoroscopic control (Figures 1 and 2).

Surgical Technique for Condylar-Type Self-Dynamizable Internal Fixator (SIF) – a standard lateral approach was used to expose the fracture. Fracture reduction was performed under visual control with fluoroscopic assistance. The internal fixator was inserted and temporarily fixed with a Kirschner wire in the condylar region under fluoroscopic guidance. Subsequently, one locking screw was inserted into the condylar region, followed by placement of a cortical anti-rotational screw through the dynamic slot, which allowed for final fracture reduction and stabilisation using bone-holding forceps. After achieving a satisfactory fracture position, a second locking screw was inserted, followed by screw placement through the clamps (Figures 3 and 4). In addition to the open technique, some surgeons employed a mini-incision technique for placement of the self-dynamizable internal fixator, using two incisions – one distal at the level of the condylar region and one proximal to the fracture site. This technique enabled closed indirect fracture reduction but required longer fluoroscopy to confirm adequate fracture reduction and correct implant positioning.

In both groups, operative time (in minutes) and fluoroscopy time (in seconds) were recorded. Operative time was measured from the initial surgical incision to placement of the final suture in the operative wound. Fluoroscopy time was recorded from the C-arm display upon completion of the surgical procedure.

Data were analysed using descriptive and analytical statistical methods. A Student's t-test was used to compare mean values, while Pearson's correlation coefficient (r) was used to assess correlations, along with the coefficient of determination (r^2). Differences between correlation coefficients were tested using Fisher's r-to-z transformation. Linear regression with operative time as the outcome variable was used in the combined data analysis. A p-value < 0.05 was considered to be statistically significant, and a p-value < 0.01 was considered to be highly statistically significant. Data analysis was performed using SPSS Statistics version 26.

Ethics: The study was performed in line with the Declaration of Helsinki and approved by the Ethics Board of the University Clinical Centre Niš (Decision No. 12–6647–2/9).

RESULTS

Comparison of the two surgical techniques in terms of operative time and fluoroscopy duration

During the retrograde intramedullary nailing (RIMN) procedure, the mean operative time was 65.8 ± 19.3 minutes (range: 40–120 minutes), whereas in the self-dynamizable internal fixator (SIF) technique, the mean operative time was 88.3 ± 23.5 minutes (range: 50–150 minutes). This difference was statistically significant, indicating that the RIMN technique was associated with a significantly shorter operative time.

Regarding fluoroscopy duration, the mean exposure time for the RIMN technique was 44.1 ± 10.7 seconds (range: 25–69 seconds), whereas that for the SIF technique was 31 ± 12.2 seconds (range: 11–54 seconds). This difference was highly statistically significant, indicating that the RIMN technique was associated with longer fluoroscopy time.

Analysis of the correlation between operative time and fluoroscopy duration for each surgical technique

Correlation analysis revealed a strong positive association between operative time and fluoroscopy duration for both surgical techniques:

a) In the RIMN group, the correlation coefficient was r = 0.602, and the correlation was highly statistically significant. The coefficient of determination (r^2) was 36%.

b) In the SIF group, the correlation coefficient was r = 0.673, and the correlation was also highly statistically significant. The coefficient of determination (r^2) was 45%.

Comparison of these two correlation coefficients did not demonstrate a statistically significant difference between the correlations (z = -0.47, p = 0.64).

Table 2. Effect analysis of fluoroscopy duration, type of surgical procedure, and their combined effect as independent variables on operative time as the dependent variable

Model	Unstandardised coefficients		95% confidence interval	
	Coefficient ß	p-value	Lower bound	Upper bound
1 (Constant)	43.393	< 0.001	27.385	59.402
Intraop fluorosc sec	1.288	< 0.001	0.807	1.770
Type of surgery	-25.430	0.091	-55.081	4.221
Rad_Tech_Int*	-0.211	0.565	-0.940	0.518

*Interaction between fluoroscopy duration and type of surgical procedure

Effect analysis of fluoroscopy duration, type of surgical procedure, and their combined effect as independent variables on operative time as the dependent variable (Table 2):

Using linear regression analysis that included fluoroscopy duration, surgical technique, and their interaction, fluoroscopy duration was a statistically significant predictor of operative time, with each additional second prolonging operative time by 1.29 minutes (p < 0.001). The interaction between fluoroscopy duration and surgical technique was not statistically significant (p = 0.565), indicating a similar relationship between radiation exposure and operative time across surgical techniques.

DISCUSSION

The longer operative time associated with the SIF technique can be explained by the need for a larger surgical incision through the skin and subcutaneous tissue, then mobilisation of the muscle tissue (primarily the vastus lateralis, which is often associated with significant bleeding), and the need for manual fracture reduction and manual maintenance of the reduction until definitive fixation and stabilisation are achieved. After fracture stabilisation with the fixator, a considerable portion of operative time is devoted to attaining hemostasis, wound irrigation, and wound closure. Due to the deforming effect of muscle forces, particularly those of the gastrocnemius, closed fracture reduction is often challenging to achieve and maintain until final fixation is completed.

In contrast, RIMN is performed through a significantly smaller incision, approximately 4–5 cm in length, and does not require muscle mobilisation. A substantial portion of operative time is devoted to determining the entry point, inserting the guidewire into the proximal fragment, and reaming the intramedullary canal. Fracture reduction is typically indirect and closed, and is achieved through insertion of the intramedullary nail itself. This manoeuvre significantly shortens operative time, as nail insertion neutralises the gastrocnemius muscle's deforming forces and facilitates adequate fracture reduction. Nail locking is performed as with the SIF, with two screws placed distally and then proximally. Proximal locking, however, is performed with a freehand technique under fluoroscopic guidance, which requires more exposure time than the SIF technique, which is performed under direct visual control.

Currently, there is no available literature analysing operative time associated with the use of the SIF. In contrast, data are available for the RIMN and other extramedullary fixation devices, including anatomical locking plates, dynamic condylar screws (DCS), and condylar plates. The mean operative times observed in our study for RIMN are consistent with those reported in the literature. Similarly, operative time with anatomical locking plates is reported to be comparable to or longer than those observed with the SIF [27–30]. The longer operative time associated with anatomical locking plates can be explained by the need to insert more screws, while the implantation technique itself is otherwise similar.

If the time required for wound closure were excluded from the analysis, the difference in the duration of the

fixation technique between the RIMN and the SIF could be expected to be smaller.

Fluoroscopy time is significantly longer in the RIMN group. This can primarily be explained by the more complex technique of RIMN placement compared with the SIF. During RIMN insertion, additional steps must be performed under fluoroscopic guidance, including determining the entry point, inserting the guidewire, selecting nail dimensions, reaming the canal, inserting the nail, and placing proximal locking screws. In contrast, during SIF placement, fluoroscopy is mainly used to position the Kirschner wire and free screws in the condylar region. Subsequent positioning and stabilisation of the fixator can be performed without fluoroscopic assistance.

It is imperative to note that during SIF implantation, the surgeon does not need to remain in proximity to the operative field during fluoroscopy, as the steps requiring fluoroscopy do not require direct hand positioning within the operative field. Conversely, during RIMN placement, numerous steps – including determining the entry point, guidewire insertion, nail insertion, and placement of locking screws – require the surgeon's direct presence within the operative field during fluoroscopy. As a result, during RIMN procedures, the surgeon is directly exposed to radiation and must wear protective equipment. In contrast, during SIF procedures, the surgeon can maintain a safe distance of approximately 2 meters from the radiation source, making protective equipment unnecessary [16–22].

Correlation analysis demonstrates a strong positive association between operative time and fluoroscopy duration for both surgical techniques. The correlation is stronger in the SIF group, which can be explained by fewer fluoroscopy steps, for which repeated use has a more pronounced effect on overall operative time. In the RIMN group, more steps require fluoroscopy. However, these steps typically take less time when repeated and have a less significant impact on total operative time. Nevertheless, operative time is clearly strongly influenced by fluoroscopy duration, with each additional second of radiation exposure prolonging the operation by 1.29 minutes.

When considering cases in which delayed initiation of dynamisation is required to achieve proper fracture healing, the SIF may be regarded as advantageous. In such cases, in addition to shorter fluoroscopy duration, the SIF also reduces the overall operative burden, as its capacity for spontaneous activation of dynamisation eliminates the need for an additional surgical intervention. In contrast, initiation of dynamisation in intramedullary nailing requires a further surgical procedure to remove the static locking screw [26].

CONCLUSION

The duration of the operative procedure is a significant factor when planning the daily surgical schedule and deciding on the type of anaesthesia. As expected, a shorter operative time was observed when using the retrograde intramedullary nail compared with the self-dynamizable internal fixator. Intraoperative fluoroscopy is a standard component of orthopaedic trauma surgery, which is why continuous improvement of surgical techniques is necessary to protect the health of the surgical team. As anticipated, intraoperative fluoroscopy time was shorter with the use of the self-dynamizable internal fixator compared with the retrograde intramedullary nail. The absence of the need for an additional surgical intervention to initiate delayed dynamisation with the SIF may have contributed to a shorter overall cumulative operative time compared with intramedullary nailing in patients who required delayed dynamisation.

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Conflict of interest: None declared.

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Утицај трајања интраоперативне флуороскопије на трајање оперативног захвата код лечења супракондиларних прелома фемура

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САЖЕТАК

Увод/Циљ Супракондиларни преломи фемура су ретке повреде које због својих специфичности представљају посебан изазов за лечење. Оперативно лечење представља златни стандард лечења. Циљ рада је анализа трајања оперативног захвата и интраоперативне флуороскопије код пацијената лечених применом самодинамизирајућег унутрашњег фиксатора кондиларног типа и ретроградног интрамедуларног клина за фемур и испитивање њихове повезаности.

Методе Истраживање је обухватило 66 пацијената, подељених у две групе од по 33 испитаника. Испитаници у првој групи оперисани су применом ретроградног интрамедуларног клина за фемур, док су испитаници друге групе оперисани применом самодинамизирајућег унутрашњег фиксатора кондиларног типа. У обе групе мерено је оперативно време у минутима и време флуороскопије у секундама.

Резултати Просечно трајање операције код пацијената оперисаних ретроградним интрамедуларним клином било је статистички значајно краће него код пацијената оперисаних самодинамизирајућим унутрашњим фиксатором. Насупрот томе, просечно време примене флуороскопије било је статистички значајно дуже код пацијената оперисаних ретроградним интрамедуларним клином. Време изложености зрачењу било је значајан предиктор трајања операције.

Закључак Дужина трајања оперативног захвата је значајан фактор у планирању оперативног програма и врсте анестезије. Као што се и очекивало, време оперативног захвата било је краће код примене ретроградног интрамедуларног клина у односу на самодинамизирајући унутрашњи фиксатор. Интраоперативна флуороскопија је стандард у ортопедској трауми хирургији, због чега је неопходно додатно усавршавати хируршке технике, како би се заштитило здравље хируршке екипе. Време интраоперативне флуороскопије било је краће код примене самодинамизирајућег унутрашњег фиксатора у односу на ретроградни интрамедуларни клин.

Кључне речи: самодинамизирајући унутрашњи фиксатор; ретроградни интрамедуларни клин; флуороскопија; трајање операције

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Clinical, pathological, and molecular predictors of axillary lymph node metastases in young women with breast cancer

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SUMMARY

Introduction/Objective Breast cancer in women shows more aggressive biological characteristics, while the status of axillary lymph nodes remains the most important prognostic factor. The aim of this study was to determine the prevalence of axillary lymph node metastases and to identify histological and immunohistochemical predictors in patients under 40 years of age with breast cancer.

Methods A retrospective cohort study that included patients under 40 years of age with histopathologically confirmed breast cancer who underwent surgical treatment at the Department of Oncological Surgery, Clinical Hospital Center "Bežanijska kosa", between 2014 and 2024.

Results The study included 97 patients under 40 years of age (mean age 34.75 ± 3.74 years). Axillary lymph node metastases were identified in 48.5% of patients, while sentinel lymph node biopsy was positive in 26.8%. The most common molecular subtype was Luminal B (53.6%). Luminal B tumors were associated with younger age (p = 0.031) and higher body mass index (p = 0.007). HER2-positive and triple-negative tumors were more often of high histological grade (p = 0.003) and larger tumor size (p = 0.025), with a higher Ki-67 proliferation index (p = 0.001). Positive axillary lymph node status was significantly associated with Rh-positive blood type (p = 0.004), tumor size (p = 0.001), and mastectomy (p = 0.004).

Conclusion Breast cancer in women under 40 years of age is characterized by marked biological heterogeneity, with axillary lymph node metastases significantly associated with larger tumor size and more aggressive biological characteristics.

Keywords: breast cancer; biopsy; axillary lymph nodes; molecular subtypes

INTRODUCTION

Breast cancer is one of the most common malignancies in women, with an increasing frequency in younger ages, already after the age of 40 [1]. Although the incidence of breast cancer in women under 40 is lower than in older women [2, 3], the disease in this population often has more aggressive biological characteristics, including triple-negative and human epidermal growth factor receptor 2 (HER2)-positive subtypes, later diagnosis, and a poorer prognosis, with a higher risk of local recurrence and distant metastases [4, 5]. Despite the reduction in overall mortality due to advances in early detection and therapy, breast cancer in young women remains a significant clinical and public health challenge [6].

Metastatic disease is the main cause of mortality in breast cancer, responsible for more than 90% of deaths [7]. The metastatic process is complex and includes epithelial-mesenchymal transition, invasion, intravasation, survival in circulation, extravasation, and colonization of target tissues [7]. These processes are influenced by the interaction of tumor cells with the microenvironment, as well as specific signaling pathways that determine the organic tropism of metastases, including frequent dissemination to bones, lungs, liver, and brain [8]. Understanding the mechanisms of metastasis has enabled the identification of biological markers and the development of targeted therapeutic strategies [9].

The status of axillary lymph nodes is the most important independent prognostic factor in breast cancer [10]. Metastasis even in one axillary lymph node significantly increases the risk of distant disease and directly affects decisions on the application of adjuvant therapy [11]. Although the introduction of sentinel lymph node biopsy significantly reduced morbidity compared to classic axillary dissection, this approach carries the risk of false-negative findings [12]. Data show that a significant number of patients with a positive sentinel node do not have additional residual axillary disease, which calls into question the routine application of complete axillary dissection [13].

Recent randomized studies have shown that in selected patients with T1/T2 tumors and limited involvement of sentinel lymph nodes, axillary dissection can be safely omitted with adequate application of radiotherapy and systemic treatment, without jeopardizing

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oncological outcomes [14]. These findings emphasize the need to identify reliable clinical, pathological, and biological predictors of axillary metastases in order to avoid unnecessary surgical interventions.

To date, numerous factors have been identified as independent predictors of axillary lymph node involvement, including tumor size, lymphovascular invasion, histological grade, and molecular characteristics of the tumor [13, 15, 16]. Molecular subtypes of breast cancer further allow for risk stratification, with luminal A tumors having the most favorable prognosis, while luminal B, HER2-positive, and triple-negative cancers show a greater propensity for nodal and distant spread [17, 18]. In addition, radiological methods, especially magnetic resonance imaging (MRI), show potential in predicting axillary metastases, although their diagnostic accuracy is still not sufficient to replace histopathological evaluation [19, 20, 21].

The aim of the study was to determine the frequency of axillary lymph node metastases in women under 40 years of age with breast cancer and to examine the association of these metastases with the histological and immunohistochemical characteristics of the tumor.

METHODS

Type of study, place, and period of research

This study was designed as a retrospective cohort study and included female patients under the age of 40 with a histopathologically confirmed diagnosis of breast cancer who were surgically treated at the Oncology Surgery Department of the "Bežanijska Kosa" Clinical Hospital Center in the period from 2014 to 2024.

All data used in the research were anonymized and encrypted, and the analysis was conducted in accordance with the ethical principles of patient privacy protection. The study was approved by the Ethics Committee and the Expert Council of University Clinical Hospital Center "Bežanijska Kosa." The research did not use personal data that could lead to the identification of female patients.

Source and collection of data

Medical documentation, including electronic medical records from the hospital database used in daily clinical work, was used as a data source. Data on demographic, clinical, surgical, histopathological, and immunohistochemical characteristics of tumors were collected from the available documentation.

The following parameters were analyzed: patient age, body weight (kg), body height (cm), body mass index (BMI), categorized as underweight, normal body weight, overweight, and obesity, blood group and Rhesus factor (Rh factor), affected breast (left/right), type of surgical intervention performed (sparing operation or mastectomy), tumor size, histological type of tumor (ductal, lobular, mucinous, medullary), histological grade (G1, G2, G3), estrogen and progesterone receptor status (positive/negative), HER2 status (positive/negative), Ki-67 proliferative index, and molecular subtype of breast cancer (Luminal A, Luminal B, HER2-positive, and triple negative).

In addition, data on the status of lymph nodes were analyzed, including the performance and results of sentinel lymph node biopsy (not performed/negative/positive), application of axillary lymphadenectomy (not performed/negative/positive), the total number of removed and histopathologically examined lymph nodes, the total number of positive lymph nodes, as well as the number of positive sentinel and axillary lymph nodes.

Statistical analysis

Statistical data processing was performed using the IBM SPSS Statistics for Windows, Version 19.0. (IBM Corp., Armonk, NY, USA). The level of statistical significance was set at $p < 0.05$. Final results are presented as categorical variables (absolute and relative frequencies) and continuous variables (mean ± standard deviation).

Nonparametric tests were used to analyze differences between groups, including the χ^2 test for categorical variables, the Mann–Whitney U test for comparing two independent groups, and the Kruskal–Wallis test for comparing multiple groups.

RESULTS

A total of 97 patients with breast cancer under 40, with an average age of 34.75 ± 3.74 years, were included in the study. Most of the respondents were Rh-positive (81.4%) and blood type A (47.4%). The average BMI was 23.32 ± 4.79, with the largest number of female patients having a normal body weight (62.9%) (Table 1).

The left breast was most often affected (51.5%), and in most patients a sparing surgical intervention was used

Table 1. Sociodemographic and anthropometric characteristics of female patients

Variables		Number	Percentage (%)
Body mass index categories	Malnutrition	9	9.3
	Normal body weight	61	62.9
	Excessive body weight	18	18.6
	Obesity	9	9.3
Rh	Negative	18	18.6
	Positive	79	81.4
Blood type	A	46	47.4
	B	16	16.5
	AB	9	9.3
	O	26	26.8
Parameters	Minimum	Maximum	Mean value ± SD
Age	22	40	34.75 ± 3.74
Body weight (kg)	32	130	65.81 ± 14.3
Body height (cm)	150	185	167.92 ± 6.77
Body mass index	12.04	42.45	23.32 ± 4.79

SD – standard deviation; Rh – Rhesus factor

Table 2. Clinical, surgical, histopathological, and immunohistochemical characteristics of the tumor

Variables		Number	Percentage (%)
Breast	Left	50	51.5
	Right	47	48.5
Operation	Economical	54	55.7
	Mastectomy	43	44.3
Histopathological finding	Ductal	88	90.7
	Mucinous	2	2.1
	Medullary	2	2.1
	Lobular	5	5.2
Gradus of the tumor	First	2	2.1
	Others	74	76.3
	Third	21	21.6
Estrogen receptor	Negative	22	22.7
	Positive	75	77.3
Progesterone receptor	Negative	25	25.8
	Positive	72	74.2
HER2	Negative	62	63.9
	Positive	35	36.1
Luminal category	Luminal A	23	23.7
	Luminal B	52	53.6
	HER2-positive	7	7.2
	Triple negative	15	15.5
Parameters	Minimum	Maximum	Mean value ± SD
Tumor size	4	70	23.9 ± 12.96
Ki_67_percent	1	90	35.22 ± 3.17

SD – standard deviation; HER – human epidermal growth factor receptor; Ki_67 – marker of proliferation Ki-67

(55.7%). Histopathologically, invasive ductal carcinoma predominated (90.7%), with the most common histological grade being II (76.3%). Most tumors were positive for estrogen (77.3%) and progesterone receptors (74.2%), while HER2 positivity was recorded in 36.1% of patients. The most common molecular subtype was Luminal B (53.6%), followed by Luminal A (23.7%), triple-negative (15.5%), and HER2-positive tumors (7.2%) (Table 2).

Table 3. Characteristics of removed sentinel and axillary lymph nodes in women under 40 years of age with breast cancer

Variables		Number	Percentage (%)
Sentinel glands	They were not done	26	26.8
	Done	71	73.2
The result of the sentinel gland examination	It was not done	26	26.8
	Negative	45	46.4
	Positive	26	26.8
Axillary dissection	They were not done	41	42.3
	Done	56	57.7
The result of examination of the axillary glands	It was not done	41	42.3
	Negative	9	9.3
	Positive	47	48.5
Total number of glands examined	Only sentinels removed	41	42.3
	Sentinel and axillary removed	30	30.9
	Only axillary removed	26	26.8
Total positive glands	Negative sentinel and axillary	44	45.4
	Sentinel only positive	6	6.2
	Positive only axillary	27	27.8
	Positive sentinel and axillary	20	20.6

Sentinel lymph node biopsy was performed in 73.2% of patients, with positivity determined in 26.8%. Axillary lymph node dissection was performed in 57.7% of women, and axillary metastases were confirmed in 48.5%. In total, an average of 10.52 ± 9.24 lymph nodes were removed per patient, with an average of 2.16 ± 3.63 positive nodes. Only positive sentinel nodes were present in 6.2% of patients, only axillary nodes in 20.6%, while both sentinel and axillary nodes were positive in 27.8% of subjects (Table 3).

Analysis in relation to molecular subtypes revealed that patients with Luminal B tumors were statistically significantly younger compared to the Luminal A subtype ($p = 0.031$) and had a higher BMI ($p = 0.007$). Luminal A and Luminal B tumors were significantly more often of histological grade II, while HER2-positive and triple-negative tumors were predominantly of high grade ($p = 0.003$). Tumor size was significantly smaller in Luminal A and Luminal B subtypes compared to HER2-positive and triple-negative tumors ($p = 0.025$). The Ki-67 index increased statistically significantly from Luminal A to triple-negative tumors ($p = 0.001$) (Table 4).

When analyzing factors associated with axillary lymph node positivity, it was found that axillary metastases are significantly more common in Rh-positive patients ($p = 0.004$), in larger tumors ($p = 0.001$), and in patients who underwent mastectomy ($p = 0.004$). The number of removed and positive lymph nodes was significantly higher in patients with positive sentinel and axillary lymph nodes ($p = 0.001$) (Table 5).

DISCUSSION

Breast cancer in women under the age of 40 is a distinct clinical entity that differs from the disease in the older population in terms of biological characteristics, patterns of spread, and therapeutic challenges. In our study, the average age of female patients at diagnosis was in the middle of the fourth decade of life, which is in accordance with previously published data indicating that in this age group the disease is often diagnosed during the reproductive period, with significant long-term consequences for quality of life [22].

Anthropometric analysis in our sample showed that most patients had a normal body mass, while significant differences in BMI were observed depending on the molecular subtype of the tumor. In particular, it was observed that patients with Luminal B carcinoma had a higher BMI compared to other subtypes, while patients with triple negative tumors had the lowest BMI values. Although the relationship between body mass and tumor biology is complex and insufficiently elucidated, previous studies indicate that metabolic status may influence the hormonal environment and proliferative potential of tumors, particularly in hormone-dependent subtypes [23].

In terms of localization and histopathological characteristics, in our study the left breast was most

Table 4. Comparison of sociodemographic and clinical-pathological parameters according to molecular (luminal) subtypes of breast cancer in women under 40 years of age

Variables		Luminal A	Luminal B	HER2-enriched	Triple negative	p
Body mass index*		23.1 ± 3.09	24.41 ± 5.31	23.91 ± 4.68	19.64 ± 3.36	0.007
Body mass index categories	Malnutrition	0 (0%)	5 (9.6%)	0 (0%)	4 (26.7%)	0.017
	Normal body weight	15 (65.2%)	30 (57.7%)	5 (71.4%)	11 (73.3%)	
	Excessive body weight	8 (34.8%)	9 (17.3%)	1 (14.3%)	0 (0%)	
	Obesity	0 (0%)	8 (15.4%)	1 (14.3%)	0 (0%)	
Histopathological finding	Ductal	22 (95.7%)	45 (86.5%)	7 (100%)	14 (93.3%)	0.461
	The others	1 (4.3%)	7 (13.5%)	0 (0%)	1 (6.7%)	
Gradus of the tumor	The first	0 (0%)	2 (3.8%)	0 (0%)	0 (0%)	0.003
	Others	21 (91.3%)	43 (82.7%)	3 (42.9%)	7 (46.7%)	
	The third	2 (8.7%)	7 (13.5%)	4 (57.1%)	8 (53.3%)	
Tumor size*		29.61 ± 13.45	20.35 ± 10.32	26 ± 21.09	26.47 ± 13.39	0.025
Ki_67_percent*		14.57 ± 4.24	37.13 ± 21.56	49.29 ± 20.09	53.67 ± 24.67	0.001
The result of the sentinel gland examination	It was not done	6 (26.1%)	15 (28.8%)	3 (42.9%)	2 (13.3%)	0.609
	Negative	11 (47.8%)	22 (42.3%)	4 (57.1%)	8 (53.3%)	
	Positive	6 (26.1%)	15 (28.8%)	0 (0%)	5 (33.3%)	
The result of examination of the axillary glands	It was not done	10 (43.5%)	21 (40.4%)	3 (42.9%)	7 (46.7%)	0.373
	Negative	0 (0%)	5 (9.6%)	2 (28.6%)	2 (33.3%)	
	Positive	13 (56.5%)	26 (50%)	2 (28.6%)	6 (40%)	

*Continuous variable presented as mean ± SD;
HER – human epidermal growth factor receptor; Ki_67 – marker of proliferation Ki-67

Table 5. Comparison of sociodemographic and clinical-pathological parameters in relation to the status of sentinel and axillary lymph nodes in women under 40 years of age with breast cancer

Variables		Sentinel			Axillary		
		Not done/negative	Positive	p	Not done/negative	Positive	p
Rhesus factor	Negative	15 (21.1%)	3 (11.5%)	0.221	15 (30%)	3 (6.4%)	0.004
	Positive	56 (78.8%)	23 (88.5%)		35 (70%)	44 (93.6%)	
Operation	Economical	42 (59.2%)	12 (46.2%)	0.356	35 (70%)	19 (40.4%)	0.004
	Mastectomy	29 (40.85%)	14 (53.8%)		15 (30%)	28 (59.6%)	
Tumor size*		23.31 ± 12.78	25.5 ± 13.58	0.348	19.92 ± 10.24	28.13 ± 14.26	0.001
Ki_67_percent*		33.97 ± 22.82	38.62 ± 24.23	0.381	35.72 ± 23.25	34.68 ± 23.32	0.831
Total glands removed per woman*		8.34 ± 8.54	16.46 ± 18.56	0.001	4.26 ± 5.82	17.17 ± 7.36	0.001
Total positive glands per woman*		1.66 ± 3.84	3.54 ± 32.56	0.001	0.2 ± 0.61	4.26 ± 4.3	0.001

*Continuous variable presented as mean ± SD;
Ki_67 – marker of proliferation Ki-67

often affected, and the dominant histological type was invasive ductal carcinoma, with the predominant histological grade being II. This distribution is consistent with the findings of previous studies examining breast cancer in younger women and confirms that, despite the younger age, the basic histopathological features often follow the patterns seen in the general population [22, 23].

Immunohistochemical analysis in our sample showed a predominance of hormone receptor-positive tumors, with a significant proportion of HER2-positive and triple-negative cancers. According to the molecular classification, Luminal B and Luminal A subtypes were most frequently represented. Recent studies continue to demonstrate that Luminal B remains the predominant molecular subtype among young women with breast cancer, supporting our finding that more than half of the patients belonged to this molecular category [24, 25].

Analysis of molecular subtypes in our work showed clear differences in histological grade, tumor size, and proliferative index. Luminal A and Luminal B tumors were more often in histological grade II and had smaller dimensions compared to HER2-positive and triple-negative tumors, which were predominantly of higher grade. Contemporary studies have confirmed that HER2-positive and triple-negative tumors are characterized by higher histological grade, increased proliferative activity, and more aggressive biological behavior, which is consistent with our findings [25, 26, 27].

The Ki-67 proliferative index in our study showed a statistically significant increase from Luminal A to Luminal B, HER2-positive, and triple-negative tumors. Recent evidence continues to support Ki-67 as an important marker of tumor aggressiveness and treatment response, particularly in biologically heterogeneous breast cancers, which corresponds to the progressive increase observed across molecular subtypes in our cohort [25].

When it comes to surgical treatment, breast-sparing surgery was more often applied in our sample. Modern therapeutic concepts favor breast conservation when it is oncologically safe, especially in younger patients, in whom aesthetic and psychosocial aspects are of particular importance. At the same time, the decision on the scope

of the surgical intervention must be coordinated with the characteristics of the tumor and the status of the axillary lymph nodes. The status of axillary lymph nodes is one of the most important prognostic factors in breast cancer. In our study, sentinel lymph node biopsy was used in most patients, while axillary dissection was performed in part of the subjects, with a high percentage of confirmed axillary metastases in that group. Recent prospective studies suggest that axillary surgery can be safely de-escalated in carefully selected patients; however, the relatively high prevalence of axillary metastases in our cohort indicates that young women still require careful axillary assessment [26, 27, 28].

In our sample, axillary lymph node positivity was significantly associated with larger tumor size and the choice of mastectomy as the surgical method. Several recent predictive models have identified tumor size as one of the strongest predictors of axillary lymph node involvement, which is fully consistent with the results of our study [29].

Literature data additionally indicate that the frequency of lymphatic metastases differs among molecular subtypes of breast cancer. Recent studies continue to demonstrate significant differences in nodal involvement among molecular subtypes, emphasizing the biological heterogeneity of breast cancer and the importance of individualized risk assessment [24]. These data are in agreement with the findings of our study and confirm the heterogeneity of the biological behavior of breast cancer in young women.

Overall, our results confirm that breast cancer in women younger than 40 years is a heterogeneous disease in which molecular subtype, histological characteristics of the tumor and axillary lymph node status play a key role in the assessment of biological behavior and planning of therapy. Similar conclusions have been reported in recent international and regional studies, including data from Serbia, highlighting the persistent prognostic importance of axillary lymph node status despite advances in molecular classification and systemic therapy [30].

CONCLUSION

This retrospective cohort study showed that axillary lymph node metastases are common in women under 40 years with breast cancer and are associated with adverse histopathological and immunohistochemical tumor characteristics. Lymph node involvement was particularly related to larger tumor size and more extensive surgical treatment, supporting its role as an important indicator of local disease progression. These findings emphasize the value of careful preoperative axillary assessment and molecular tumor classification in planning individualized treatment for young women with breast cancer. Further prospective studies with larger patient cohorts are warranted to validate these findings.

Ethical compliance statement: We confirm that we have read the journal's position on issues involving ethical publication and affirm that work is consistent with those guidelines.

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

Conflict of interest: None declared.

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Клинички, патолошки и молекуларни предиктори метастаза у аксиларним лимфним чворовима код младих жена са раком дојке

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САЖЕТАК

Увод/Циљ Рак дојке код жена показује агресивније биолошке карактеристике, док статус аксиларних лимфних чворова остаје најважнији прогностички фактор. Циљ ове студије био је да се утврди преваленција метастаза у аксиларним лимфним чворовима и да се идентификују хистолошки и имунохистохемијски предиктори код болесница млађих од 40 година са раком дојке.

Методе Ретроспективна кохортна студија обухватила је болеснице млађе од 40 година са хистопатолошки потврђеним раком дојке које су подвргнуте хируршком лечењу на Одељењу за онколошку хирургију Клиничко-болничког центра „Бежанијска коса", између 2014. и 2024. године.

Резултати Студија је обухватила 97 болесница млађих од 40 година (просечна старост 34,75 ± 3,74 године). Метастазе у аксиларним лимфним чворовима идентификоване су код 48,5% болесница, док је биопсија сентинел лимфних чворова била позитивна код 26,8%. Најчешћи молекуларни подтип био је Луминал Б (53,6%). Луминални Б тумори били су повезани са млађом животном доби ($p = 0,031$) и вишим индексом телесне масе ($p = 0,007$). *HER*2-позитивни и троструко негативни тумори су чешће били високог хистолошког степена ($p = 0,003$) и веће величине тумора ($p = 0,025$), са вишим *Ki*-67 индексом пролиферације ($p = 0,001$). Позитиван статус аксиларних лимфних чворова био је значајно повезан са *Rh*-позитивном крвном групом ($p = 0,004$), величином тумора ($p = 0,001$) и мастектомијом ($p = 0,004$).

Закључак Рак дојке код жена млађих од 40 година карактерише изражена биолошка хетерогеност, при чему су метастазе у аксиларним лимфним чворовима значајно повезане са већом величином тумора и агресивнијим биолошким карактеристикама.

Кључне речи: рак дојке; биопсија; аксиларни лимфни чворови; молекуларни подтипови

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Constructing a prolonged field care echeloned system for interrupted casualty evacuation chains

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SUMMARY

Introduction/Objective The aim was to analyze the evolution of modern combat casualty care from the Golden Hour and Tactical Combat Casualty Care (TCCC) to Prolonged Field Care (PFC) and Prolonged Casualty Care (PCC), and to construct an Echelon P model for situations in which casualty evacuation is delayed or interrupted.

Methods A structured literature analysis, conceptual differentiation, and model-construction approach was used. Foreign military guidelines, position statements, operational reports, and peer-reviewed studies on PCC were reviewed, with priority given to literature from 2022 to 2026. PFC and PCC were compared by origin, target users, operational scenario, capability requirements, time frame, and interface with traditional echelons of care.

Results The evidence indicates a shift from evacuation-dependent care toward sustained forward care under contested conditions. PFC is primarily a clinical continuation of TCCC by advanced-trained personnel, whereas PCC is a system-level framework for all Role 1 responders when timely evacuation is limited or denied. The proposed Echelon P model includes activation triggers, P0-P3 capability tiers, and medical, blood/resuscitation, data, and command interfaces.

Conclusion Institutionalizing prolonged care as an independent capability layer may improve medical resilience in future high-intensity operations. Implementation should focus on doctrine, training, equipment modularization, telemedicine-enabled support, documentation, and quality assessment.

Keywords: combat casualty care; golden hour; tactical combat casualty care; prolonged field care; prolonged casualty care; military medical resilience

INTRODUCTION

Traditional combat casualty care has been organized around echeloned care and the Golden Hour. In this model, life-threatening problems are controlled at or near the point of injury, the casualty is moved rapidly through Role 1 and Role 2 care, and progressively more specialized treatment is provided at rear facilities. The model achieved major success when tactical conditions, transport assets, air superiority, and medical infrastructure enabled rapid evacuation. Its hidden assumption, however, is that the evacuation chain remains available and predictable. Once this assumption fails, the clinical burden carried by forward providers expands from short stabilization to sustained monitoring, resuscitation, and decision-making [1, 2].

Tactical Combat Casualty Care (TCCC) was developed to reduce preventable deaths before hospital arrival by integrating medical interventions with tactical realities. Its emphasis on massive hemorrhage control, airway support, respiration, circulation, hypothermia prevention, and documentation made forward care more executable under fire. The institutional mechanism of the Committee on TCCC also allowed the guidelines to be updated as battlefield evidence changed, including recent updates to casualty care and resuscitation recommendations [3–7]. Nevertheless, TCCC was designed primarily for the acute phase and cannot by itself define how to maintain a casualty for many hours or days when evacuation is delayed.

Future large-scale combat operations challenge the evacuation-dependent model. Long-range fires, contested airspace, drone surveillance, electronic warfare, difficult terrain, limited communications, and mass casualty surges can delay or deny movement to higher roles of care. Reports from the Russia–Ukraine conflict describe relocation of field hospitals farther from the front, delayed movement windows, severe fragmentation injuries, and

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rapid degradation of Role 2+ capabilities under sustained pressure [8, 9, 10]. These conditions create a practical gap between completing TCCC interventions and reaching definitive care.

This gap has both clinical and organizational consequences. Clinically, the casualty may require repeated assessment, blood or fluid decisions, analgesia adjustment, infection prevention, hypothermia control, respiratory monitoring, and preparation for deterioration rather than simple packaging for transport. Organizationally, the forward team must decide how long available supplies will last, how to divide personnel across casualties, when to request remote consultation, and how to communicate medical risk to commanders. Therefore, prolonged care should be regarded as a planned capability with defined boundaries rather than an accidental waiting period.

Prolonged Field Care (PFC) and Prolonged Casualty Care (PCC), emerged to address this gap, but the two terms are often used interchangeably, which can obscure the difference between a clinical practice package and a system capability. PFC was initially shaped by special operations and austere medicine experience, where small teams in remote areas expected delayed but eventual evacuation. PCC has evolved into a broader system-level concept for conventional forces operating when timely evacuation cannot be assumed. This distinction is important because the solution cannot be limited to teaching individual procedures; it must also define triggers, equipment, documentation, authority, consultation pathways, and quality assessment.

The present study restructures this topic as an original article using a literature-based model-construction approach. Its objectives are to distinguish PFC from PCC, identify the operational logic behind prolonged care, and propose an Echelon P model that can be inserted into traditional echeloned care without treating prolonged care as an improvised extension of TCCC alone. The intended contribution is not to replace the traditional Role system, but to make the prolonged interval between Role 1 and higher echelons visible, trainable, resourced, and assessable.

METHODS

This study used a structured narrative review and conceptual model-construction method. The source pool included military medical guidelines, position statements, clinical practice guidelines, operational reports, and peer-reviewed studies related to TCCC, PFC, PCC, delayed evacuation, far-forward resuscitation, austere wound care, prolonged monitoring, training, equipment configuration, documentation, and team resilience. Priority was given to sources published from 2022 to 2026, while foundational publications were retained when they introduced concepts that remain central to the development of the Golden Hour, TCCC, PFC, or PCC.

Documents were selected when they met at least one of the four criteria: they defined TCCC, PFC, or PCC; described delayed or disrupted evacuation in combat or austere environments; provided clinical or system requirements for prolonged care; or offered evidence relevant to training, equipment, data capture, telemedicine, ethics, or resilience. Sources focused only on routine civilian trauma systems were excluded unless they informed the military prolonged-care problem. Serbian military medical literature was also checked, and a Serbian-authored source relevant to military medical evacuation and deployment stress was retained where appropriate [11].

Conceptual differentiation was performed by comparing PFC and PCC across six dimensions: origin, intended users, typical scenario, clinical and system capabilities, duration, and relationship to traditional echelons of care. This comparison was used to clarify whether prolonged care should be treated as a temporal delay, a clinical skill set, or a system layer. The Echelon P model was then developed by answering two implementation questions: when prolonged care should be activated, and how prolonged care should interface with higher medical, logistic, data, and command systems.

Data extraction focused on recurring operational and clinical requirements rather than on pooled statistical estimation. For each source, relevant information was grouped into the following categories: evacuation assumptions, care duration, provider level, resuscitation needs, wound and infection management, equipment burden, documentation, telemedicine, command decision support, and resilience or ethical concerns. This approach was selected because the available literature is heterogeneous, combining guidelines, reports, reviews, qualitative studies, and model papers. The goal was therefore to synthesize an implementable framework rather than to calculate a single effect size.

Model construction followed a pragmatic logic. First, operational triggers were identified from delayed evacuation, mission constraints, environmental limitations, and casualty-volume mismatch. Second, the minimum–better–best concept used in prolonged-care guidance was translated into a P0-P3 stratification that links time after injury with resource density and clinical complexity. Third, interface mechanisms were defined so that prolonged care would not become an open-ended responsibility isolated from the evacuation, resuscitation, documentation, and command chain. The resulting model was checked against recent guideline and operational evidence for conceptual consistency.

Ethics: An ethics statement was not required for this study type; no human or animal subjects or materials were used. The authors declare that the article was written in accordance with ethical standards of the Serbian Archives of Medicine as well as ethical standards of medical facilities for each author involved.

RESULTS

The first finding is that the evolution from the Golden Hour to TCCC and then to PFC/PCC reflects a shift in the dominant assumption of battlefield medicine. The Golden

Hour and traditional echeloned care assume that rapid movement to more capable facilities is normally available. TCCC improved survival within this framework by reducing preventable death during the immediate tactical phase. In contrast, PFC and PCC begin from the opposite premise: evacuation may be delayed, denied, or interrupted for reasons beyond the control of medical personnel. The problem is therefore not only how to perform early lifesaving interventions, but how to sustain a casualty when the system that usually removes that casualty from the forward area is no longer reliable.

The second finding is that PFC and PCC have overlapping but distinct meanings. PFC originated in special operations and remote austere settings. It emphasizes advanced clinical tasks after TCCC has been completed, including serial reassessment, airway and respiratory support, circulation management, analgesia and sedation, infection prevention, hypothermia control, wound monitoring, nursing care, and preparation for delayed evacuation [1, 12]. PFC is usually delivered by advanced-trained personnel and is therefore close to a clinical module or practice set. PCC, by contrast, is broader. The recent Joint Trauma System and Committee on TCCC materials position PCC as a Role 1 system capability for all responders when timely or optimal medical care is limited by the tactical situation [13, 14, 15]. It includes clinical skills but also doctrine, training, equipment, capacity planning, telemedicine, documentation, ethical decision-making, and command integration.

The distinction between capability and capacity is central to PCC. Capability refers to what a team can do, such as start antibiotics, maintain an airway, monitor vital signs, perform wound care, or request teleconsultation. Capacity refers to how many casualties can be supported, for how long, and under what resource constraints. A team may have the capability to monitor one casualty for 24 hours but lack the capacity to care for several casualties during a mass casualty event. PCC therefore requires planners to connect clinical tasks with supply depth, manpower, rest cycles, communication reliability, and evacuation probability.

The third finding is that prolonged care is increasingly relevant to conventional operations, not only special operations. Evidence from Ukraine indicates that pre-hospital and forward care can be extended by battlefield geometry, drone threat, nighttime movement requirements, limited routes, damage to facilities, and attrition of Role 2+ capabilities [8, 9, 10]. In such circumstances, the forward echelon may face patients with severe blast or fragmentation injuries, ongoing hemorrhage risk, infection risk, hypothermia, pain, psychological distress, and delayed surgical access. The medical task therefore migrates from a short TCCC episode to a prolonged period of physiologic maintenance and resource management. This migration also increases the importance of blood availability, antibiotic timing, nursing tasks, communication, documentation, and triage decisions.

Based on these findings, this study proposes Echelon P as an independent capability layer rather than a new fixed facility. Echelon P is activated when specific triggers are met and then provides a structured pathway for sustained care until transfer to an appropriate level of care becomes possible. The first category of triggers is evacuation delay beyond doctrinal or operational thresholds, for example more than two hours, more than six hours, or more than 24 hours. The second category is mission constraint, such as concealment requirements, ongoing contact, electronic suppression, inability to move during daylight, or lack of secure transport. The third category is capability or capacity mismatch, such as mass casualty events, extreme cold or altitude, depletion of blood or oxygen, limited communications, or simultaneous care for multiple unstable casualties.

The proposed P0-P3 stratification translates the time dimension into capability requirements. P0 – from injury to approximately two hours, remains the acute preventable-death phase. Its core is TCCC execution: hemorrhage control, airway positioning or adjuncts, chest injury management, circulation assessment, hypothermia prevention, analgesia when appropriate, and rapid documentation. The expected output of P0 is not definitive recovery but stabilization, prioritization, and transport readiness.

P1 – approximately 2–6 hours, is the sustained resuscitation and monitoring phase. At this point, the provider must repeat examinations, track vital signs, reassess tourniquets and dressings, continue hypothermia prevention, maintain analgesia and sedation safety, and determine whether the casualty is improving, deteriorating, or consuming resources faster than anticipated. P1 also requires an early estimate of available consumables, blood, oxygen, battery power, and personnel endurance. Failure at this level often occurs not because a single procedure is unknown, but because reassessment, documentation, and handover discipline decline under fatigue.

P2 – approximately 6–24 hours, is the multidimensional management phase. Infection prevention, wound care, sepsis awareness, pressure injury prevention, nutrition and hydration decisions, pain and anxiety control, urine output or perfusion monitoring, and communication with remote consultants become increasingly important [12, 14, 16]. If telemedicine is available, the forward team should transmit structured information rather than informal impressions. If evacuation remains uncertain, the team must also update triage categories and explain resource implications to commanders.

P3 – approximately 24–72 hours, is the systematic maintenance phase. It requires a more formal rhythm of care, including shift organization, medication and supply accounting, serial documentation, remote consultation, end-of-life decision preparation, and team resilience management. Prolonged Field Care Kit (PFAK) studies are particularly relevant at this level because they attempt to define a portable package capable of supporting prolonged objectives under weight and volume constraints [17, 18, 19]. The function of P3 is to prevent prolonged care from degrading into unmeasured improvisation; it turns sustained management into a documented, supervised, and logistically supported activity.

The P0-P3 structure should not be interpreted as rigid time compartments. A casualty can enter P2-level complexity before six hours if severe shock, sepsis concern, airway compromise, or environmental exposure develops

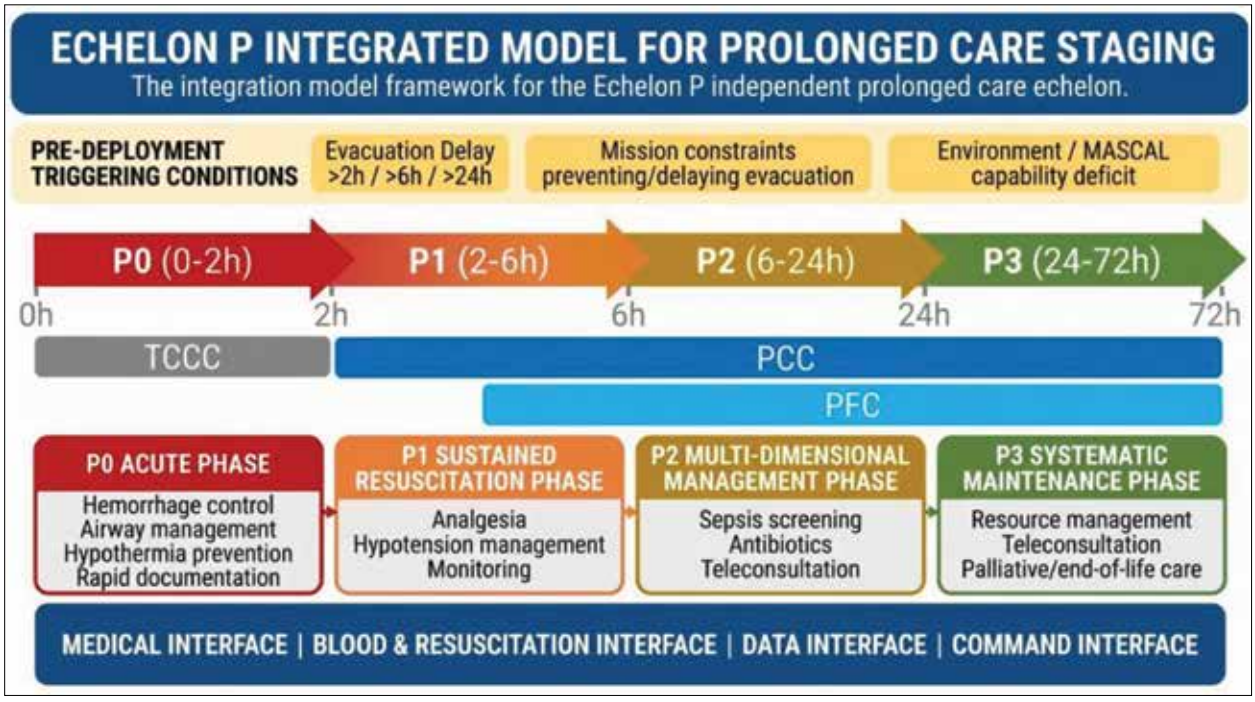

Figure 1. The Echelon P integrated model for prolonged care staging; the model links activation triggers, P0-P3 capability tiers, and four interface mechanisms; TCCC covers the immediate P0 phase, PCC covers the broader Role 1 prolonged-care framework, and PFC represents the continuation of PCC by advanced-trained personnel until transfer to an appropriate level of care becomes possible; MASCAL – mass casualty; h – hours; TCCC – tactical combat casualty care; PCC – prolonged casualty care; PFC – prolonged field care; P0 – acute phase (0–2 hours); P1 – sustained resuscitation phase (2–6 hours); P2 – multidimensional management phase (6–24 hours); P3 – systematic maintenance phase (24–72 hours)

early. Conversely, a stable casualty may remain within a lower capability demand for longer. The practical value of the stratification lies in its forcing function: as time passes, teams are reminded to reassess whether their clinical tasks, supplies, documentation, and consultation mechanisms have kept pace with the increasing risk profile.

Echelon P must also define interfaces. The medical interface determines which clinical findings require urgent evacuation or higher-level consultation, such as suspected sepsis, uncontrolled hemorrhage, airway failure, shock requiring blood products, or deterioration despite initial stabilization. The blood and resuscitation interface links forward providers to whole blood, component therapy, walking blood bank procedures, calcium replacement, and resuscitation priorities. The data interface uses TCCC cards, after-action review, registry-compatible documentation, and automated or simplified records to support quality improvement. The command interface translates medical risk into operational language, including expected resource consumption, likelihood of deterioration, evacuation priority, and ethical constraints. These interfaces are essential because prolonged care without defined boundaries can create unlimited expectations for forward teams.

Finally, the model highlights four support conditions. Equipment support should be modular, portable, environment-resistant, and aligned with P0-P3 needs. Training support should move beyond individual procedures toward scenario-based management, communication, team leadership, documentation, and resource allocation [20, 21]. Technical support should include remote consultation, decision prompts, and documentation tools that reduce cognitive burden during long care intervals. Resilience support should address fatigue, moral injury, grief, team cohesion, and end-of-life care, because prolonged casualty holding may expose small teams to repeated loss and ethically difficult decisions [22, 23, 24]. The integrated relationships among activation triggers, P0-P3 capability tiers, prolonged-care concepts, and the four interface mechanisms are summarized in Figure 1.

DISCUSSION

This study makes three contributions. First, it separates PFC and PCC in a way that is useful for implementation. PFC should be understood as the advanced clinical continuation of care under austere conditions, whereas PCC should be understood as the broader capability framework that prepares the force for delayed or denied evacuation. This distinction matters because a military medical system can possess several PFC-trained providers and still lack a PCC capability if doctrine, equipment, blood supply, communication, documentation, and command interfaces are absent.

Second, the proposed Echelon P model converts prolonged care from a vague duration into an operational structure. The P0-P3 sequence shows that time itself changes the task. During the first minutes and hours, failure is dominated by preventable death and transport readiness. As the delay lengthens, the dominant risks shift toward physiologic deterioration, infection, hypothermia, pain, resource exhaustion, documentation loss, team fatigue, and ethical complexity. This view helps explain why

simply adding more supplies or teaching more procedures is not enough. A prolonged-care system must know when to activate, what capability to bring forward, what information to record, and when to request help.

Third, Echelon P offers a way to connect prolonged care with the traditional role system. It does not propose a separate hospital echelon or a replacement for evacuation. Instead, it formalizes the interval in which evacuation is not yet possible and prevents this interval from being invisible in planning. The model therefore supports resilience: it allows forward teams to continue care in a structured way, while still treating evacuation and definitive care as the final objective. This is especially important in high-intensity conflicts, where forward facilities may need to displace frequently and casualty movement may be governed by enemy fires rather than medical preference.

The model also has implications for training. TCCC training should remain the foundation, but prolonged-care training should start after TCCC mastery and should use longer scenarios that force teams to reassess, document, communicate, ration, hand over, and explain medical risk to commanders. Existing data on incomplete adherence to analgesia and tranexamic acid guidelines suggest that even relatively defined TCCC tasks are difficult to execute consistently [25, 26]. PCC tasks are more complex and therefore require repeated simulation, checklists, and objective assessment rather than lectures alone.

Equipment planning should also follow the P0-P3 logic. A first-line kit optimized for P0 cannot support P3 care by itself, while a full prolonged-care package may be too heavy for dismounted teams. PFAK development studies show the need to balance portability with meaningful capability, including medication, monitoring, wound care, documentation, and environmental protection [17, 18, 19]. The correct solution may be layered: individual TCCC equipment for P0, team-level modules for P1-P2, and mission-specific augmentation for P3 or extreme environments.

Implementation should be incremental. A practical starting point is to define activation thresholds and minimum documentation standards, because these two elements require relatively little equipment but immediately change behavior. The next step is to build modular equipment lists for likely missions and to train teams in prolonged scenarios that last long enough to expose fatigue, communication gaps, and supply depletion. Higher-level medical authorities should then review after-action data to refine triggers, revise kits, and identify training deficiencies. This cycle would turn Echelon P from a theoretical construct into a quality-improvement mechanism.

This study has limitations. It is primarily based on foreign military guidelines, published studies, and operational reports, especially from the US- and Ukraine-related sources. Applicability to another military medical system depends on differences in doctrine, equipment, evacuation assets, command relationships, personnel structure, and operating environment. The Echelon P model is also conceptual and has not yet been validated in field exercises or real operations. In addition, ethical issues such as end-of-life care, resource allocation, and communication with commanders require local cultural and institutional adaptation.

Future research should test the model through tabletop exercises, simulation, and field training. Evaluation indicators could include time to activation, documentation completeness, appropriateness of evacuation requests, ability to maintain vital sign monitoring, blood and medication use, team fatigue, and casualty outcomes. Equipment studies should compare PFAK configurations under weight and volume constraints. Training studies should determine whether P0-P3 scenarios improve performance compared with TCCC-only instruction. Finally, registry-compatible documentation should be designed before implementation so that prolonged care can be measured and improved rather than remembered only through anecdote.

Local adaptation will be necessary before direct application. Different forces may have different evacuation platforms, blood-product policies, telemedicine access, and training pipelines. Therefore, the model should be used as a framework rather than a fixed checklist. Units can map their current assets against P0-P3 requirements, identify the point at which care becomes unsafe, and then decide whether the gap should be closed through additional supplies, training, communication support, or changes in evacuation planning. This mapping process may be the most immediate practical use of Echelon P.

CONCLUSION

Modern combat casualty care is entering a phase in which rapid evacuation can no longer be assumed. TCCC remains the foundation for preventable death control, but prolonged evacuation demands additional clinical, logistical, ethical, and command capabilities. PFC provides the clinical continuation of care by advanced-trained personnel, whereas PCC provides the broader system framework for all Role 1 responders when evacuation is delayed or denied.

The proposed Echelon P model translates prolonged care into an operational structure built on activation triggers, P0-P3 capability tiers, and medical, blood/resuscitation, data, and command interfaces. This model can help prevent prolonged care from being treated as an improvised exception and instead make it a planned, trainable, assessable, and resource-supported part of military medical resilience. Future implementation should proceed through doctrine refinement, modular equipment design, scenario-based training, telemedicine and documentation support, and standardized quality assessment.

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Изградња ешелонираног система продуженог збрињавања на терену за прекинуте ланце евакуације повређених

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САЖЕТАК

Увод/Циљ Циљ рада је анализирати еволуцију савременог збрињавања повређених у борбеним условима – од концепта Златног сата и тактичког збрињавања повређених у борбеним условима (*Tactical Combat Casualty Care – TCCC*) до продуженог збрињавања на терену (*Prolonged Field Care – PFC*) и продуженог збрињавања повређених (*Prolonged Casualty Care – PCC*), као и конструисати модел „Echelon P" за ситуације у којима је евакуација повређених одложена или прекинута.

Методе Примењени су структурирана анализа литературе, концептуално разграничење и приступ конструкцији модела. Анализиране су иностране војномедицинске смернице, званични ставови, оперативни извештаји и рецензиране студије о продуженом збрињавању повређених, уз давање приоритета литератури објављеној у периоду од 2022. до 2026. године. Извршено је поређење концепата *PFC* и *PCC* према пореклу, циљним корисницима, оперативном сценарију, захтеваним способностима, временском оквиру и повезаности са традиционалним ешелонима медицинског збрињавања.

Резултати Докази указују на померање тежишта са збрињавања које зависи од брзе евакуације ка одрживом збрињавању на предњим положајима у оспораваним борбеним условима. Концепт *PFC* представља првенствено клинички наставак *TCCC*-а који спроводи додатно обучено медицинско особље, док *PCC* представља системски оквир за све пружаоце медицинске помоћи на првом нивоу (енгл. *Role 1*) у ситуацијама када је благовремена евакуација ограничена или онемогућена. Предложени модел „Echelon P" обухвата услове за активацију, нивое способности *P0–P3*, као и интерфејсе са медицинским, трансфузиолошким/ресусцитационим, информационим и командним системима.

Закључак Увођење продуженог збрињавања као независног нивоа способности може унапредити отпорност војномедицинске подршке у будућим операцијама високог интензитета. Примену овог концепта треба усмерити на развој доктрине, обуку, модуларизацију опреме, подршку путем телемедицине, документацију и процену квалитета.

Кључне речи: збрињавање повређених у борбеним условима; Златни сат; тактичко збрињавање повређених у борбеним условима; продужено збрињавање на терену; продужено збрињавање повређених; отпорност војномедицинске подршке

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

A study on the improvement of gastrointestinal function and quality of life in patients with lung cancer after chemotherapy by combining traditional Chinese medicine acupoint moxibustion and psychological nursing

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SUMMARY

Introduction/Objective The aim was to investigate the effects of combined Chinese medicine acupoint moxibustion and psychological nursing on the gastrointestinal function and quality of life (QoL) of patients with lung cancer undergoing chemotherapy.

Methods A total of 120 lung cancer patients were randomly divided into two groups. The control group received conventional care, while the observation group was administered combined traditional Chinese medicine acupoint moxibustion and emotional nursing. The observation indicators included serum acetylcholinesterase activity, plasma inhibin B, gastrin, motilin, dopamine, 5-hydroxytryptamine levels, incidence and duration of nausea/vomiting, Self-rating anxiety scale and Self-rating depression scale scores, and World Health Organization QoL-BREF scores.

Results Before intervention, no significant differences were observed between groups ($p > 0.05$). Post-intervention, the observation group showed significantly higher acetylcholinesterase activity (7.64 ± 1.17 U/mL *vs*. 6.96 ± 1.11 U/mL, $p < 0.001$) and inhibin B levels (193.52 ± 15.72 pg/mL *vs*. 166.77 ± 20.36 pg/mL, $p < 0.001$), lower gastrin (146.7 ± 13.02 ng/L *vs*. 157.35 ± 14.4 ng/L, $p < 0.001$) and motilin levels (151.55 ± 9.99 pmol/L *vs*. 158.22 ± 8.37 pmol/L, $p < 0.001$), reduced incidence (2.83 ± 0.64 times/day *vs*. 3.12 ± 0.67 times/day, $p < 0.001$) and duration (1.7 ± 0.5 d *vs*. 2.97 ± 0.64 d, $p < 0.001$) of nausea/vomiting, lower Self-rating anxiety scale (40.55 ± 2.79 *vs*. 47.06 ± 4.12, $p < 0.001$) and Self-rating depression scale (39.82 ± 2.81 *vs*. 47.25 ± 4.5, $p < 0.001$) scores, and higher QoL total scores (309.44 ± 9.11 *vs*. 294.56 ± 8.45, $p < 0.001$) than the control group.

Conclusion The combined use of Chinese medicine acupoint moxibustion and traditional Chinese medicine emotional care for patients with lung cancer undergoing chemotherapy has significant effects, which can significantly improve their gastrointestinal function and effectively improve their anxiety and depression symptoms, and improve their QoL.

Keywords: lung cancer; traditional Chinese medicine acupoint moxibustion; emotional care; gastrointestinal function; quality of life

INTRODUCTION

Lung cancer is the leading malignant tumor, significantly affecting the physical and mental health of patients [1]. Non-small cell lung cancer is the most common type of lung cancer [1]. Currently, treatment strategies include surgical resection, chemotherapy, targeted therapy, and radiotherapy [2]. Chemotherapy is a common treatment option for lung cancer patients, but chemotherapeutic agents often exhibit cytotoxic effects, leading to adverse reactions. Gastrointestinal side effects, primarily nausea and vomiting, are the most common during chemotherapy. Studies have shown that the overall incidence of gastrointestinal symptoms in patients reaches 97.9%, with the most severe and intolerable being gastrointestinal reactions. During the chemotherapy period for lung cancer patients, nausea is the most common symptom (incidence rate of 89.2%), followed by constipation (68.3%) and vomiting (53.3%) [3]. Decreased appetite is one of the most severe symptoms in the diagnosis and treatment of the disease. Patients often refuse chemotherapy due to severe gastrointestinal reactions, delaying treatment and impacting their quality of life (QoL) [4]. The underlying mechanism is that most chemotherapeutic agents do not specifically kill tumor cells but merely inhibit cell proliferation, which, while blocking tumor cells, also causes toxic damage to the epithelial cells

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of the gastrointestinal mucosa, leading to gastrointestinal symptoms.

Research on the QoL of cancer patients is receiving increasing attention. It can assess the impact of the disease and treatment on patients from a professional perspective, thereby guiding the selection of treatment plans and predicting patient survival, enhancing biomedical understanding [5]. Therefore, to ensure the effectiveness of chemotherapy in lung cancer patients, it is essential to actively prevent and manage gastrointestinal adverse reactions during chemotherapy.

Currently, commonly used Western medicines include 5-HT3 receptor antagonists, NK-1 receptor antagonists, hormones, dopamine antagonists, sedatives, and acid-suppressing gastrointestinal protectants. For chemotherapy-related constipation, the main approaches used domestically involve oral prokinetic agents, laxatives, and enemas, such as the use of glycerin suppositories, lactulose, and magnesium oxide [6]. Although these medications are effective for preventing nausea and vomiting, they can cause adverse reactions such as headaches, dry mouth, rashes, and constipation. They are also expensive and do not provide significant relief for other gastrointestinal symptoms such as decreased appetite and constipation, presenting numerous drawbacks.

Traditional Chinese medicine (TCM) emphasizes a "holistic perspective and syndrome differentiation treatment" in addressing gastrointestinal symptoms related to spleen and stomach deficiency in lung cancer chemotherapy. Currently, the main approaches include traditional Chinese nursing techniques and herbal decoctions. Among the treatment methods for gastrointestinal reactions after chemotherapy, acupoint moxibustion has gained attention due to its cost-effectiveness, simplicity, ease of operation, and minimal side effects.

Acupoint moxibustion has shown good effects on gastrointestinal adverse reactions during chemotherapy in patients with malignant tumors. By allowing the absorption of medication through acupoints [7, 8], it helps to alleviate nausea and regulate the stomach, as well as to soothe the liver and promote the flow of Qi. This approach aids in the regular peristalsis of the gastrointestinal tract, enhances digestion and absorption, and can also reduce gastrointestinal symptoms by stimulating vagus nerve activity and promoting the secretion of gastrointestinal neuropeptides [9, 10]. The biological connection between meridians/acupoints and internal organs has been increasingly recognized, and gastrointestinal diseases can trigger specific characterization phenomena on the body surface, providing a scientific basis for acupoint-based therapies [11].

Patients with tumors often experience a range of negative emotions, such as irritability, anger, pessimism, and disappointment, after undergoing chemotherapy and radiotherapy. These emotions can negatively impact their QoL and exacerbate their condition [12]. Anxiety and depression are classified as emotional disorders in TCM. Emotional care in TCM is implemented based on syndrome differentiation. For example, for patients with sadness (grief injuring the lung), nurses use the "joy overcomes grief" principle by providing cheerful media and encouraging pleasant activities. For those with fear (fear injuring the kidney), reassurance about medical measures and relaxation techniques like foot bathing are employed. For anxious patients (thought injuring the spleen), distraction through hobbies and entertainment is encouraged. For those prone to anger (anger injuring the liver), breathing exercises and muscle relaxation are taught to soothe liver Qi stagnation. Additionally, five-element music therapy is utilized based on the correspondence between the five notes (Jue, Zhi, Gong, Shang, Yu) and the five internal organs to regulate emotional imbalances [13, 14]. Research shows that TCM emotional care can alleviate patients' negative psychological states, enabling them to face their illness and treatment positively, thereby improving their QoL [15, 16].

Currently, there have been studies exploring the effects of acupoint moxibustion and TCM emotional care on gastrointestinal function and QoL, but research on their application in lung cancer patients is limited. Therefore, this study aims to investigate the effects of acupoint moxibustion combined with emotional care on the adverse gastrointestinal reactions and QoL in lung cancer patients after chemotherapy, providing new methods for improving gastrointestinal function and QoL in these patients.

METHODS

General information

A total of 120 lung cancer patients undergoing chemotherapy at Hebei University of Chinese Medicine from September 2020 to July 2024 were selected. They were randomly divided into a control group and a study group, with 60 cases in each group, using a random number table method. The acetylcholinesterase (AChE) assay kit was purchased from Suzhou Geruis Biotechnology Co., Ltd. (Suzhou City, Jiangsu Province, China); the human inhibin B enzyme-linked immunosorbent assay (ELISA) kit, human gastrin (GAS) ELISA kit, human motilin (MTL) ELISA kit, and dopamine ELISA kit were all purchased from Wuhan Erylate Biotechnology Co., Ltd. (Wuhan, Hubei, China).

Inclusion and exclusion criteria

Inclusion criteria:

1. Patients who met the diagnostic criteria for lung cancer according to the Chinese Society of Clinical Oncology Guidelines for Diagnosis and Treatment of Primary Lung Cancer 2024 [17] and have developed gastrointestinal dysfunction after chemotherapy.
2. Patients who meet the diagnostic criteria for gastrointestinal dysfunction defined as nausea, vomiting, constipation, or diarrhea ≥ grade 1 according to the Common Terminology Criteria for Adverse Events Version 5.0 [18].
3. Age > 18 years, regardless of gender.

4. Patients who provide informed consent.
5. Patients with Self-rating anxiety scale (SAS) score > 50 and/or Self-rating depression scale (SDS) score > 53, but excluding those with severe mental disorders (defined as SAS ≥ 70 or SDS ≥ 73 or pre-existing diagnosis of major depressive disorder or generalized anxiety disorder prior to cancer diagnosis).

Exclusion criteria:
1. History of allergies to related treatment drugs;
2. Skin inflammation at the application site that prevents treatment;
3. Severe upper gastrointestinal bleeding;
4. Complete mechanical intestinal obstruction;
5. History of mental illness, intellectual disability, and poor compliance.

Intervention methods

Control group

At the beginning of chemotherapy, conventional treatment and nursing intervention were adopted. Patients were given symptomatic treatment, orally Ondansetron tablets (Qilu Pharmaceutical Co., Ltd., National Drug Approval Number H10970062, specification: 8 mg/tablet), 8 mg each time, twice a day. At the same time, routine chemotherapy nursing intervention was carried out:

1. All patients were warmly welcomed upon admission. In order to reduce the patients' unfamiliarity with the hospital and help them better adapt to the hospital, the nurses introduced the patients to their attending doctors and the basic environment of the hospital. Basic nursing care for respiratory medicine was provided to better cooperate with hospital's treatment.
2. Health education: After admission, nurses fully informed patients about the disease, including the relevant pathogenesis of lung cancer clinical manifestations, and treatment methods for lung cancer, as well as precautions for lung cancer chemotherapy. This increased the patient's understanding of their own disease and enhanced their compliance with treatment.
3. Psychological care: The staff communicated with patients, promptly understood the psychological problems they faced, answered their doubts, enhanced their confidence, and helped them maintain a good attitude towards treatment.
4. Infection prevention: Appropriate preventive measures prevented the further aggravation of cancer, prevented patients from getting infections and avoided worsening of their condition, which could affect their recovery.
5. Dietary guidance: Appropriate dietary care was provided to patients, guiding them to eat reasonably and balance their nutrition. Smoking, alcohol, and spicy foods should be avoided, and instead frequent, light meals were consumed, and plenty of water was drunk.

Observation group

On the basis of the control group, TCM acupoint moxibustion was added and combined with TCM care.

1. Acupoint moxibustion: The operation procedure of acupoint moxibustion is based on the Manual of Traditional Chinese Techniques for Nurses issued by the National Administration of TCM: patients were given Wu Zhu Yu plaster, mixed cloves, processed *Pinellia*, and *Evodia* fruit in equal proportions, ground into powder, mixed with vinegar to form a paste, wrapped in gauze to make a ball, and applied on both sides of Zusanli (ST36) and Neiguan (PC6) with adhesive tape. They were applied before bedtime and removed the next morning. The treatment lasted 10 days.
2. TCM emotional care measures refer to relevant literature and are formulated in combination with our own practice: The patients were engaged in detailed communication, and the effects of the seven emotions – joy, anger, sorrow, thought, sadness, fear, and fright – on physical health were patiently explained. Targeted care was then provided according to the patients' individual emotional states and based on individualized care principles.
   – For patients experiencing sadness: Patients were provided with cheerful and pleasant video materials in a comfortable environment. An optimistic attitude and positive mood were fostered using an emotion-regulation approach based on the principle of overcoming emotions.
   – For patients experiencing fear: Patients and their family members were provided with detailed information regarding the hospital's medical and emergency procedures to alleviate doubts and concerns. Patients were also guided to soak their feet and perform foot-point massage before bedtime to promote relaxation and improve sleep.
   – For patients experiencing anxiety: Patients were encouraged to engage in activities of personal interest, and their attention was diverted from the disease through comedies and other forms of entertainment.
   – For patients who were prone to anger: Patients were guided to relieve emotional distress and psychological tension through progressive muscle relaxation and controlled breathing exercises. The effects of anger on their condition were explained patiently, and they were encouraged to maintain a calm and peaceful state of mind. In addition, five-sound therapy was administered. Patients were assisted in selecting relaxing music according to their emotional state and individual musical preferences. Music therapy was provided twice daily (e.g., at 10:00 a.m. and 3:00 p.m.) for 30 minutes per session. Both groups received the intervention continuously for three months.

Observation indicators and statistical methods

Observation indicators

1. Compare the changes in serum AChE activity, plasma inhibin B, GAS, MTL, dopamine, and 5-hydroxytryptamine before and after the intervention between the two groups. Venous blood (6 mL) was collected in the morning after an overnight fast on the day before the study and on the day after the study. The blood was centrifuged at 2000 r/min for 10 minutes (centrifuge radius of 15 cm) two hours later. The upper serum and lower plasma were taken by laboratory personnel for separate detection.
2. Nausea and vomiting episodes and duration: Professional medical staff observed and recorded in detail the episodes and duration of nausea and vomiting in the two groups during the study period. The frequency of nausea and vomiting in this study was expressed in "times/day", calculated as the total number of nausea and vomiting episodes in all patients divided by the total number of intervention days; the duration was the time it took for the nausea and vomiting to subside, defined as no vomiting and no use of rescue drugs, and a Multinational Association of Supportive Care in Cancer Antiemesis Tool nausea severity score < 2 for both, indicating relief of nausea and vomiting.
3. Compare the changes in SAS [19] and SDS [20] scores before and after the intervention between the two groups. The Chinese versions of SAS and SDS have been validated with Cronbach's α coefficients of 0.849 and 0.79, respectively, indicating good reliability and validity for Chinese populations [20, 21]. A SAS score > 50 was considered anxiety; an SDS score > 53 was considered depression, with higher scores indicating severe anxiety and depression.
4. QoL scoring. The World Health Organization QoL-BREF (WHOQOL-BREF) developed by the WHO was chosen [22]. The Chinese version of WHOQOL-BREF has demonstrated good reliability and validity, with Cronbach's α coefficient ranging from 0.763 to 0.91 across different studies in Chinese populations [23, 24]. The scale includes physical, psychological, environmental, and social relationships. Each item is scored from 0 to 100, with higher scores being better.

The survey was conducted on-site, where investigators distributed the questionnaires and organized the subjects to fill them out. During the filling process, each subject was required to complete it alone, and discussion among subjects was prohibited. After the completion, all questionnaires were collected, and a dedicated person managed them to ensure validity of the questionnaires. While filling out the questionnaire, the investigators followed the entire process, identified problems encountered by the subjects or unclear parts, and provided on-site answers to ensure quality.

Statistical methods

All data were statistically analyzed using IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp., Armonk, NY, USA), with the results of normal measurement data expressed as ($\bar{x} \pm s$). Intergroup differences were compared using t-tests, and sample rates were compared using χ^2 tests. A p-value of less than 0.05 was considered significant.

Table 1. Comparison of general information

Project	Observation group (n = 60)	Control group (n = 60)	p
Gender (male/female)	38/22	35/25	0.575
Age (years)	61.7 ± 9.2	62.2 ± 8.19	0.730
Pathological type			0.522
Squamous cell carcinoma	16	13	
Adenocarcinoma	44	47	
Tumor location (left/right)	23/37	31/29	0.142
Tumor staging			0.653
I stage	4	7	
II stage	10	13	
III stage	31	27	
IV stage	15	13	
Chemotherapy regimen			0.859
Gemcitabine and platinum based	5	6	
Etoposide and platinum based	19	16	
Pemetrexed and platinum-based	26	25	
Paclitaxel platinum-based	10	13	
Number of chemotherapy sessions	3 (2, 6)	3 (2, 5)	0.849
Serum total protein (g/L)	67.1 (63.3, 70)	66.2 (62.3, 69)	0.502
Serum albumin (g/L)	41 (37.7, 44.55)	42 (38.9, 44.7)	0.145
Hemoglobin (g/L)	116.11 (106.6, 128)	115 (103.5, 125)	0.502
Lymphocyte count (10^9/L)	1.31 (0.85, 1.69)	1.29 (0.87, 1.68)	0.140
White blood cell count (10^9/L)	5.76 (4.38, 7.37)	5.97 (4.15, 7.89)	0.622
Platelet count (10^9/L)	233 (181.2, 315.5)	240 (185, 318.5)	0.972

Intervention outcomes

General information comparison

Table 1 presents the detailed baseline characteristics of the two groups. In the control group, there were 35 males and 25 females; the age range was 40 to 83 years (62.2 ± 8.19 years). In the observation group, there were 38 males and 22 females; the age range was 40 to 76 years (61.7 ± 9.2 years). No significant differences were found between the two groups regarding gender, age, pathological type, tumor location, tumor staging, chemotherapy regimen, number of chemotherapy sessions, or baseline laboratory indices including serum total protein, serum albumin, hemoglobin, lymphocyte count, white blood cell count, and platelet count (all p > 0.05), indicating comparability of the two groups at baseline. (The specific data are shown in Table 1)

Table 2. Comparison of laboratory parameters before and after intervention

Project	Time	Observation group (n = 60)	Control group (n = 60)	p
Acetylcholinesterase (U/mL)	Before intervention	5.38 ± 1.39	5.33 ± 1.32	0.065
	After intervention	7.64 ± 1.17*	6.96 ± 1.11*	< 0.001
Plasma inhibitor (pg/ mL)	Before intervention	119.51 ± 15.98	120.17 ± 15.32	0.331
	After intervention	193.52 ± 15.72*	166.77 ± 20.36*	< 0.001
Gastrin (ng/L)	Before intervention	161.72 ± 13.07	162.47 ± 13.75	0.138
	After intervention	146.7 ± 13.02*	157.35 ± 14.4*	< 0.001
Gastromotin (pmol/L)	Before intervention	171.05 ± 12	170.83 ± 11.36	0.774
	After intervention	151.55 ± 9.99*	158.22 ± 8.37*	< 0.001
Dopamine (mmol/L)	Before intervention	519.92 ± 24.21	518.83 ± 24.78	0.139
	After intervention	437.93 ± 20.55*	450.83 ± 17.87*	< 0.001
5-hydroxytryptamine (mmol/L)	Before intervention	1508.5 ± 16.11	1507.33 ± 24.78	0.778
	After intervention	1531.73 ± 31.58*	1522.12 ± 26.59*	< 0.001

*significant difference compared to before the intervention

Table 3. Comparison of nausea and vomiting episodes and duration

Project	Time	Observation group (n = 60)	Control group (n = 60)	p
Nausea and vomiting (times/day)	Before intervention	4.33 ± 0.73	4.32 ± 0.75	0.321
	After intervention	2.83 ± 0.64*	3.12 ± 0.67*	< 0.001
Duration (d)	Before intervention	3.88 ± 0.72	3.85 ± 0.73	0.159
	After intervention	1.7 ± 0.5*	2.97 ± 0.64*	< 0.001

*significant difference compared to before the intervention

Table 4. Comparison of SAS and SDS scores before and after intervention

Project	Time	Observation group (n = 60)	Control group (n = 60)	p
SAS	Before intervention	53.15 ± 4.96	53.25 ± 4.94	0.370
	After intervention	40.55 ± 2.79*	47.06 ± 4.12*	< 0.001
SDS	Before intervention	54.11 ± 5.47	54.25 ± 5.52	0.088
	After intervention	39.82 ± 2.81*	47.25 ± 4.5*	< 0.001

SAS – Self-rating anxiety scale; SDS – Self-rating depression scale;
*significant difference compared to before the intervention

Comparison of laboratory-related indicators

The results showed that there were no significant differences in AChE, plasma inhibin B, GAS, MTL, dopamine, and 5-hydroxytryptamine between the two groups before intervention ($p > 0.05$). Compared with before intervention, the levels of AChE, plasma inhibin B, and 5-hydroxytryptamine increased in both groups, while the levels of GAS, MTL, and dopamine decreased ($p < 0.05$). After intervention, the levels of AChE, plasma inhibin B, and 5-hydroxytryptamine in the observation group were higher than those in the control group, while the levels of GAS, MTL, and dopamine were lower ($p < 0.05$), as shown in Table 2.

Comparison of nausea and vomiting episodes and duration

Both groups showed improvement in the number of nausea and vomiting episodes and duration compared to before intervention ($p < 0.05$); The number of nausea and vomiting episodes and duration in the observation group were lower than those in the control group after the intervention, with statistically significant differences ($p < 0.05$), as shown in Table 3.

Comparison of SAS and SDS scores

Before the intervention, there were no significant differences in SAS and SDS scores between the two groups ($p > 0.05$). After the intervention, the SAS and SDS scores of both groups were lower than those before the intervention ($p < 0.05$); the SAS and SDS scores of the observation group after the intervention were lower than those of the control group after the intervention, and the differences were statistically significant ($p < 0.05$), as shown in Table 4.

Comparison of QoL scores

The QoL scores of the two groups were significantly higher after the intervention than before the intervention ($p < 0.05$). After the intervention, the total score, physical function, psychological, environmental, and social relationship scores of the observation group were higher than those of the control group, and the differences were statistically significant ($p < 0.05$) (presented in Table 5).

DISCUSSION

This study demonstrates that combined TCM acupoint moxibustion and emotional nursing significantly ameliorate chemotherapy-induced gastrointestinal adverse reactions and improve psychological status and overall QoL in lung cancer patients. Specifically, the intervention group exhibited enhanced serum AChE activity and 5-HT levels, reduced MTL and GAS levels, lower frequency and duration of nausea and vomiting, decreased anxiety and depression scores, and higher WHOQOL-BREF scores compared to the control group. Acupoint moxibustion mainly employs the theory of TCM meridians. The heat generated by the application of drugs on acupoints can stimulate blood circulation under the acupoints, relieve

Table 5. Comparison of quality-of-life scores

Project	Time	Observation group (n = 60)	Control group (n = 60)	p
Total score	Before intervention	284.22 ± 6.33	283.34 ± 4.56	0.065
	After intervention	309.44 ± 9.11*	294.56 ± 8.45*	< 0.001
Physiology	Before intervention	71.33 ± 1.73	71.2 ± 1.61	0.073
	After intervention	74.77 ± 1.91*	73.07 ± 2.22*	< 0.001
Psychology	Before intervention	69.23 ± 2.05	69.5 ± 1.72	0.103
	After intervention	73.27 ± 1.72*	72.05 ± 1.93*	< 0.001
Environment	Before intervention	72.95 ± 3.38	72.92 ± 3.4	0.159
	After intervention	76.05 ± 1.82*	75.2 ± 2.29*	< 0.001
Social relationships	Before intervention	70.58 ± 1.31	70.53 ± 1.38	0.182
	After intervention	74.75 ± 1.99*	73.02 ± 2.1*	< 0.001

*significant difference compared to before the intervention

meridian stasis, and unblock meridians [25]. It can also absorb the body's biological energy to produce a resonance effect, causing vasodilation and improving microcirculation [26]. Chemotherapy-induced adverse reactions in the digestive system are mainly related to gastric disharmony and upward Qi inversion [27]. Based on this pathogenesis, acupoints related to gastric Qi and blood, such as Neiguan (PC6), Tiantu (CV22), Yongquan (KI1), Zhongwan (CV12), and Zusanli (ST36), can be selected. By applying patches on these acupoints, the gastric Qi and blood can be effectively improved. Among them, Zusanli (ST36) is the lower confluent point of the foot-Yangming stomach Meridian, and its role in regulating gastrointestinal function has been confirmed in animal experiments and clinical practice [28]. *Evodia rutaecarpa* tastes bitter and is warm in nature, belonging to the liver, stomach, and kidney meridians. It has the effect of dispelling cold and relieving pain, descending Qi to stop vomiting, and regulating the liver and descending Qi; its main components are alkaloids, which have a bidirectional regulatory effect on the gastrointestinal tract [29].

The results of this study show that after the intervention, the activity of AChE and inhibin B in the observation group were higher than those in the control group, while GAS and MTL were lower than those in the control group. After the intervention, the serum dopamine level in the observation group was lower than that in the control group, and the serum 5-hydroxytryptamine level was higher than that in the control group. This is mainly because acupoint moxibustion can stimulate blood vessels to absorb drugs, stimulate nerve endings, and regulate the secretion of dopamine and 5-hydroxytryptamine in the patient's body. MTL and GAS are gastrointestinal excitatory hormones, MTL is an orexigenic peptide produced by gastrointestinal endocrine cells, which regulates food intake, gastrointestinal motility, digestion and absorption, proliferation and differentiation of adipocytes and lipid storage. The interdigestive phase (i.e., the fasting phase) hormone control-mediated phase III migrating motor complex is mainly accomplished by MTL, which can cause strong gastric contractions and obvious segmentation movements in the small intestine. GAS is a peptide hormone secreted by human G cells, which can promote gastric emptying by increasing gastric contractions and accelerating intestinal peristalsis. The mechanism of chemotherapy-induced gastrointestinal reactions is mainly due to the fact that chemotherapeutic drugs kill tumor cells while also destroying normal human cells to some extent, most commonly cells in the blood and lymphatic tissues, inhibiting the proliferation of gastrointestinal mucosal epithelial cells, leading to gastric mucosal damage, reduced intestinal cell division, and thus causing reactions such as nausea, vomiting, loss of appetite, constipation, and diarrhea [30].

Among them, modern medicine proposes that chemotherapy-induced vomiting is achieved through peripheral and central mechanisms. The peripheral mechanism refers to the damage caused by chemotherapeutic drugs to the gastrointestinal mucosa, which stimulates chromaffin cells to release large amounts of neurotransmitters 5-HT, substance P, and binds to 5-HT3 receptors, causing nerve impulses to be transmitted to the vomiting center, leading to vomiting [31]; The central mechanism refers to the stimulation of the chemoreceptor trigger zone located in the medulla oblongata by chemotherapeutic drugs, which sends impulses to the vomiting center, causing vomiting. Nausea, vomiting, and other gastrointestinal reactions after chemotherapy have a significant impact on patients. A study noted that while the histological damage in the gut may subside within days after chemotherapy treatment, long-term gastrointestinal dysfunction can persist for up to 10 years after chemotherapy [32]. Gastrointestinal symptoms are a lifelong issue for patients as a side effect of chemotherapy, so gastrointestinal reactions must be better managed.

The number of episodes and duration of nausea and vomiting in the observation group were lower than those in the control group after intervention, and the difference was statistically significant. This indicates that acupoint moxibustion combined with emotional care can improve these indicators in lung cancer patients undergoing chemotherapy. *Evodia* fruit has the effects of dispelling cold and relieving pain, and using *Evodia* fruit patches for acupoint moxibustion can achieve the function of dredging meridians and regulating the Qi and blood of internal organs. Applying on Neiguan (PC6) acupoint can harmonize the stomach and reduce nausea, soothe the liver and regulate Qi, and achieve an excellent antiemetic effect; Applying on Zusanli (ST36) acupoint can regulate the spleen and stomach, promote digestion and absorption, improve immune function, and alleviate various gastrointestinal discomforts caused by chemotherapy. Furthermore, the improvement in QoL scores observed in the observation group is not solely due to emotional changes. By significantly reducing gastrointestinal symptoms such as nausea, vomiting, and dyspepsia, acupoint moxibustion directly alleviates physical discomfort, thereby enhancing physical function and social engagement. Improved nutritional status resulting from reduced vomiting also contributes to better physical health, which is reflected in the higher physiology and environment domain scores of WHOQOL-BREF.

Another result of this study shows that the SAS and SDS scores of the observation group after intervention were lower than those of the control group and the QoL scores of the observation group were higher than those of the control group after intervention, with statistically significant differences. TCM believes that "thought hurts the spleen, worry hurts the lungs, and fear hurts the kidneys". Chemotherapy patients, due to their concerns about their condition and lack of understanding of treatment methods, are prone to anxiety, depression, and fear, which affects the treatment effect. In the process of TCM emotional care, attention is paid to the relationship between the development of the patient's condition and psychological activities, and individualized emotional care is provided through detailed communication and interaction with the patient. Additionally, the liver facilitates excretion and regulates the flow of Qi, disliking depression and preferring smoothness, which is closely related to the patient's mental state. The five musical notes (Jue, Zhi, Gong, Shang, Yu) correspond to the five elements (wood, fire, earth, metal, water) and the five internal organs (liver, heart, spleen, lung, kidney) of the body. According to TCM theory, listening to specific types of music can regulate the corresponding organs, treat diseases, and relieve liver Qi stagnation, thereby alleviating negative emotions such as anxiety and depression [14].

This study has certain limitations. The patients included were all from a single hospital, with limitations in terms of region and personnel. There are issues such as small sample size, short study duration, and limited personnel, which need to be addressed by increasing the number and scope of samples and extending the study duration for deeper observation. Due to restrictions on funding and time, animal experiments related to the research were not conducted. Therefore, studies on the mechanism of action could not be carried out, and further exploration is needed.

CONCLUSION

The combination of acupoint moxibustion and emotional care for lung cancer patients undergoing chemotherapy has significantly improved gastrointestinal function, significantly alleviated anxiety and depression, reduced gastrointestinal reactions, and improved QoL.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Hebei University of Chinese Medicine (Approval No: YXLL202307001). Written informed consent was obtained from all participants.

Availability of data and materials

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Authors' contributions

Wang Y and Wang SY conceived of the study, and Liu L, Wang CJ and Wang ZY participated in its design and data analysis and statistics and Liu H and Liu W helped to draft the manuscript. All authors read and approved the final manuscript.

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Студија о побољшању гастроинтестиналне функције и квалитета живота код болесника са карциномом плућа након хемотерапије комбинацијом моксибустије акупунктурних тачака традиционалне кинеске медицине и психолошке неге

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САЖЕТАК

Увод/Циљ Циљ овог рада је истражити ефекат комбиноване примене моксибустије акупунктурних тачака традиционалне кинеске медицине и психолошке неге на гастроинтестиналну функцију и квалитет живота болесника са карциномом плућа који су подвргнути хемотерапији.

Методе Укупно 120 болесника са карциномом плућа насумично је подељено у две групе. Контролној групи је пружана конвенционална нега, док је испитивана група примала комбиновану терапију моксибустијом акупунктурних тачака традиционалне кинеске медицине и психолошком негом. Праћени индикатори укључивали су активност серумске ацетилхолинестеразе (*AChE*), нивое инхибина Б, гастрина, мотилина, допамина, 5-хидрокситриптамина у плазми, учесталост и трајање мучнине и повраћања, резултате на Скали за самопроцену анксиозности и Скали за самопроцену депресије, као и резултате Упитника Светске здравствене организације за процену квалитета живота.

Резултати Пре интервенције нису уочене статистички значајне разлике између група ($p > 0,05$). После интервенције, испитивана група показала је значајно већу активност *AChE* (7,64 ± 1,17 *U/mL* према 6,96 ± 1,11 *U/mL*, $p < 0,001$) и виши ниво инхибина Б (193,52 ± 15,72 *pg/mL* према 166,77 ± 20,36 *pg/mL*, $p < 0,001$), нижи ниво гастрина (146,7 ± 13,02 *ng/L* према 157,35 ± 14,4 *ng/L*, $p < 0,001$) и мотилина (151,55 ± 9,99 *pmol/L* према 158,22 ± 8,37 *pmol/L*, $p < 0,001$), смањену учесталост (2,83 ± 0,64 пута/дан према 3,12 ± 0,67 пута/дан, $p < 0,001$) и трајање (1,7 ± 0,5 дана према 2,97 ± 0,64 дана, $p < 0,001$) мучнине и повраћања, нижи скор на Скали за самопроцену анксиозности (40,55 ± 2,79 према 47,06 ± 4,12, $p < 0,001$) и Скали за самопроцену депресије (39,82 ± 2,81 према 47,25 ± 4,5, $p < 0,001$), као и виши укупан скор за процењени квалитет живота (309,44 ± 9,11 према 294,56 ± 8,45, $p < 0,001$) у односу на контролну групу.

Закључак Комбинована примена моксибустије акупунктурних тачака и психолошке неге у оквиру традиционалне кинеске медицине код болесника са карциномом плућа који се подвргавају хемотерапији показује значајне резултате; она може значајно да побољша њихову гастроинтестиналну функцију, ефикасно ублажи симптоме анксиозности и депресије и унапреди квалитет њиховог живота.

Кључне речи: карцином плућа; моксибустија акупунктурних тачака традиционалне кинеске медицине; психолошка нега; функција гастроинтестиналног тракта; квалитет живота

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Personality and burnout among medical doctors in the Republic of Serbia

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SUMMARY

Introduction/Objective Burnout is a multidimensional syndrome that disproportionately affects healthcare professionals. While organizational and occupational factors have been extensively studied, the role of individual traits, such as personality, remains underexplored. This study aimed to examine the relationship between specific personality traits, sociodemographic variables, and occupational burnout among medical doctors in the Republic of Serbia.

Methods A cross-sectional, correlational study was conducted in 2024 using an online survey completed by 304 medical doctors. The instruments included a sociodemographic questionnaire, a shortened Big Five Plus Two personality inventory, and the Copenhagen Burnout Inventory (work-related scale). Data were analyzed using descriptive statistics, t-tests, and linear regression.

Results There were no significant gender differences in burnout levels ($p = 0.958$), nor differences based on communication skills training ($p = 0.214$). However, participants who reported insufficient time for patient care had significantly higher burnout levels ($p < 0.001$). Linear regression analysis indicated that extraversion negatively predicted burnout ($\beta = -0.24$, $p = 0.003$), while conscientiousness ($\beta = 0.21$, $p = 0.002$) and openness ($\beta = 0.12$, $p = 0.024$) were positive predictors. The model was significant ($R = 0.307$, $F(5, 298) = 6.18$, $p < 0.001$), explaining 9.4% of the variance in burnout.

Conclusion Extraversion appears to serve as a protective factor against burnout, whereas higher levels of conscientiousness and openness are associated with increased burnout. These findings highlight the relevance of personality traits in burnout susceptibility and suggest the potential for targeted interventions in physician support programs.

Keywords: occupational stress; personality traits; health personnel; psychological resilience

INTRODUCTION

Burnout is commonly described as an "occupational phenomenon," although it lacks a single definition [1, 2]. Maslach and Jackson [3] categorized burnout as comprising emotional exhaustion, depersonalization, and reduced personal accomplishment, the latter referring to a diminished sense of competence and achievement at work. While people in nearly all professions can experience burnout due to continuous exposure to job-related stress, "helping" professions such as healthcare workers, lawyers, teachers, and social workers are more likely to experience burnout [4]. Numerous studies have shown that burnout affects various healthcare workers, negatively impacting their physical and mental health [4, 5]. Undesirable effects can include stress-related psychiatric and somatic complaints such as depression, anxiety, memory problems, sleep disturbance, and cardiovascular disorders [6]. Medical errors, reduced productivity, early retirement, and a disrupted work-life balance are common consequences of these negative impacts [7, 8]. Given its prevalence and potentially harmful effects, understanding the underlying causes of burnout is crucial.

When examining the etiology of burnout, opinions vary. Many believe that the nature of the job and the circumstances in which the job is performed are the main triggers for the development of burnout [9–12]. While there has been considerable focus on studying how sociodemographic, organizational, and occupational factors relate to burnout, the connection between burnout and individual factors, such as personality traits, has been relatively underexplored [13].

The question arises as to why some people who do the same job under the same conditions experience burnout while others do not exhibit such symptoms. Researchers have often concluded that, alongside the nature of the job, personality traits play a crucial role in the development of burnout. Personal characteristics have been shown to contribute to burnout [13–16]. A study in Serbia that examined burnout syndrome in the academic population obtained the following results:

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most participants (85.6%) expressed a moderate degree of burnout. Emotional exhaustion and depersonalization were linked to traits such as aggressiveness, neuroticism, and negative valence, whereas personal accomplishment showed a positive correlation with traits such as extraversion, conscientiousness, openness, and positive valence [17]. Numerous studies conducted in the past decade have emphasized the importance of psychological factors and identified specific personality traits that either facilitate or act as barriers to burnout development [13–16]. Recent studies and reviews have confirmed that personality traits, particularly neuroticism, extraversion, conscientiousness, agreeableness, and openness, are relevant to burnout susceptibility in healthcare professionals [13–16]. The Big Five theory, which breaks down personality into five basic components, is a widely accepted framework for measuring personality traits. The Big Five model is considered the most reliable and cost-effective model for analyzing relationships between personality traits and behavior [18]. The model classifies personality into five broad dimensions: neuroticism, extraversion, conscientiousness, agreeableness, and openness. The Big Five theory is a widely accepted framework for measuring personality traits [18]. In the Serbian context, the Big Five Plus Two model was developed from lexical descriptions of personality and subsequently validated in a shortened version [19, 20]. Most reviewed studies indicate that individuals with higher levels of neuroticism and lower levels of extraversion, agreeableness, conscientiousness, and openness are more prone to burnout [13]. Neuroticism, in particular, can contribute to burnout due to difficulties in managing emotions and impulses. Neurotic individuals often experience insecurity, anxiety, anger, and symptoms of depression, which hinder their ability to meet work demands and act as an amplifying "filter" for negative events, increasing the risk of burnout [13, 16, 21, 22, 23]. On the other hand, agreeableness, which enables warm interpersonal interactions, can have a protective effect against burnout, preventing individuals from experiencing depersonalization [13, 16, 21, 22, 23]. However, the results are not entirely consistent. Some studies have reported positive correlations between openness and burnout, whereas most others found a negative relationship between these two constructs. For example, a negative relationship was observed between openness and personal/professional achievement, as well as positive correlations between openness and emotional exhaustion and depersonalization [13, 16, 21–24]. Furthermore, while certain studies found a positive relationship between burnout and extraversion, the reasons for this contradictory finding remain unexplained [13, 16, 24]. Given these discrepancies, further clarification of the links between the Big Five personality traits and burnout is needed.

This study aimed to examine the relationships between specific personality traits, sociodemographic characteristics, and burnout among medical doctors employed in the Republic of Serbia. Specifically, we explored associations between each Big Five personality trait, selected sociodemographic characteristics, and components of burnout. Understanding these relationships may help identify physicians at greater risk of burnout and implement targeted preventive measures.

METHODS

Research design

A cross-sectional, comparative, and correlational design using an online self-assessment survey was applied to a sample of medical doctors employed in the Republic of Serbia.

Sample and setting

The cross-sectional study was conducted in 2024 among medical doctors. It included 304 physicians of different genders and specialties employed in the Republic of Serbia. Data were collected through an online questionnaire distributed to this group. The inclusion criteria were being a medical doctor employed in Serbia, providing consent to participate, and completing the questionnaire. There were no exclusion criteria.

Instruments

Sociodemographic questionnaire

The demographic variables included gender, age, years of undergraduate study, place of employment (primary, secondary, or tertiary healthcare institution), employment sector (public and/or private), presence and type of medical specialization, and average number of on-call shifts per month. The questionnaire also covered marital status, need for psychological or psychotherapeutic support, communication-skills training, and perceived adequacy of the time available for diagnosing and/or treating patients. It consisted of 16 mostly mixed-format questions, including dichotomous, multiple-choice, and open-ended items.

Personality traits

For the assessment of personality traits, a shortened version of the Big Five Plus Two questionnaire was used [19, 20]. Specifically, the Big Five Inventory (BFI), developed by John, Donahue, and Kentle in 1991, is an instrument consisting of five scales used to assess the key characteristics of the Big Five personality dimensions, including neuroticism, extraversion, conscientiousness, agreeableness, and openness [18]. This shortened version of the Big Five Plus Two questionnaire, created by Serbian psychologists, was constructed from lexical descriptions of personality in the Serbian language. The questionnaire measures seven personality dimensions: neuroticism, extraversion, openness, conscientiousness, aggressiveness, positive valence, and negative valence [19]. The questionnaire is publicly available, and no license is required for its use. It was subsequently validated in 2014, demonstrating satisfactory reliability, convergent validity, and predictive validity [20]

Table 1. Sociodemographic characteristics of the sample

Variable	Category	N	%
Marital status	Divorced	15	4.9
	Single	53	17.4
	Married	149	49
	In a relationship	86	28.3
	Widowed	1	0.3
Number of children	Three or more children	7	2.3
	Two children	67	22
	One child	59	19.4
	No children	171	56.3
Place of employment	Primary healthcare institution	70	23
	Secondary healthcare institution	60	19.7
	Tertiary healthcare institution	174	57.2
Sector of employment	Public sector	252	82.9
	Private sector	26	8.6
	Public and private sector	26	8.6
Employment in the territory	Republic of Serbia	289	95.1
	Bosnia and Herzegovina	8	2.6
	Montenegro	2	0.7
	Croatia	1	0.3
	Germany	4	1.3
Specialization	No specialization (general practitioner)	42	13.8
	Currently undergoing specialization	149	49
	Completed specialization	113	37.2
Communication skills training	Yes	86	28.3
	No	218	71.7
Do you feel you have enough time for reliable diagnosis and/or treatment of patients	Yes	134	44.1
	No	170	55.9
Personal psychotherapy in the last 6 months	Yes	47	15.5
	No	257	84.5

Burnout syndrome

The Copenhagen Burnout Inventory was used to assess burnout syndrome, which consists of 19 questions that examine exhaustion and fatigue related to burnout in three domains: personal burnout (six questions), work-related burnout (seven questions), and client-related burnout (six questions) [25]. The questionnaire is designed to be applicable to all groups of people, regardless of their employment status. For this study, only the work-related burnout subscale was used. This subscale was selected because the primary aim of the study was to examine occupational burnout specifically associated with professional demands and workplace functioning among medical doctors. Given the study's focus on work environment characteristics and occupational stressors, the work-related dimension of the Copenhagen Burnout Inventory was considered the most directly relevant for the research objectives. Responses on the work-related subscale are rated on a five-point Likert scale, ranging 0–5, where 0 represents "never" and 5 represents "always." The questionnaire was translated and adapted to the Serbian language by a multidisciplinary team using standard translation methods (forward translation, back-translation, and pre-testing) following the World Health Organization's recommendations. Previous Serbian-language applications of the Copenhagen Burnout Inventory have reported satisfactory psychometric properties in local samples [26, 27]. Recent validation work in physicians has also supported the psychometric adequacy of the Copenhagen Burnout Inventory [28]. Pilot testing was conducted with 20 participants to assess the clarity and comprehensibility of the items, the correctness of their order, and to determine the time required for completion.

Ethical considerations

The study was approved by the competent ethics committee (decision No. 01–39/93/1) and was conducted in accordance with the Declaration of Helsinki and applicable legal standards. Participation was voluntary, and all participants were informed of the study's objectives. Anonymous responses ensured data confidentiality.

RESULTS

Sample

The study involved 304 physicians, of whom 114 (37.5%) were male and 190 (62.5%) were female. The participants' ages ranged 25–66 years, with a mean of 37.38 years. Table 1 presents additional sociodemographic characteristics of the participants.

The sociodemographic data in Table 1 show that most respondents were married or in a relationship and had no children. Most were employed in tertiary healthcare institutions and in the public sector, worked in the Republic of Serbia, and were either undergoing or had completed specialization. Table 2 displays the distribution of respondents according to ongoing or completed specializations.

Out of the total number of respondents, only 86 (28.3%) reported having received some form of communication skills training during their education. When asked whether they believe they have enough time for reliable diagnosis and/or treatment of patients, 134 (44.1%) respondents answered affirmatively. Of the total number of respondents, 47 (15.5%) had attended psychotherapy or sought some form of psychological assistance in the previous six months (Table 1).

Results

Before conducting the main analyses, descriptive statistics of the variables used in the study, as shown in Figure 1, were examined. The skewness and kurtosis values indicated that the variables were approximately normally distributed, satisfying the prerequisite for further analyses.

Independent-samples t-tests were used to compare occupational burnout by gender, prior communication-skills

Table 2. Medical specialties of participants

Specialty	N	%
Anesthesiology, reanimatology, and intensive care	26	10
Anesthesiology, reanimatology, and intensive care, clinical pharmacology	1	0.4
Dermatovenereology	4	1.5
Pediatric surgery	4	1.5
Child and adolescent psychiatry	1	0.4
Pediatric neurology	1	0.4
Epidemiology	5	1.9
Physical medicine and rehabilitation	16	6.2
Gynecology and obstetrics	5	1.9
Hygiene	4	1.5
Infectious diseases	2	0.8
Internal medicine	58	22.3
Internal oncology	1	0.4
Public health	1	0.4
Clinical biochemistry	5	1.9
Clinical pharmacology	2	0.8
Medical microbiology	1	0.4
Neurosurgery	1	0.4
Neurology	5	1.9

Specialty	N	%
Ophthalmology	11	4.2
General surgery	1	0.4
General surgery, abdominal surgery	1	0.4
General medicine	7	2.7
Orthopedic surgery and traumatology	4	1.5
Orthopedic surgery and traumatology, pediatric surgery	1	0.4
Otorhinolaryngology	5	1.9
Pathology	1	0.4
Pediatrics	31	11.9
Pediatrics, pediatric neurology	1	0.4
Plastic, reconstructive, and aesthetic surgery	3	1.2
Psychiatry	28	10.8
Radiation oncology	7	2.7
Radiology	6	2.3
Social medicine	2	0.8
Sports medicine	1	0.4
Emergency medicine	3	1.2
Urology	3	1.2
Vascular surgery	1	0.4

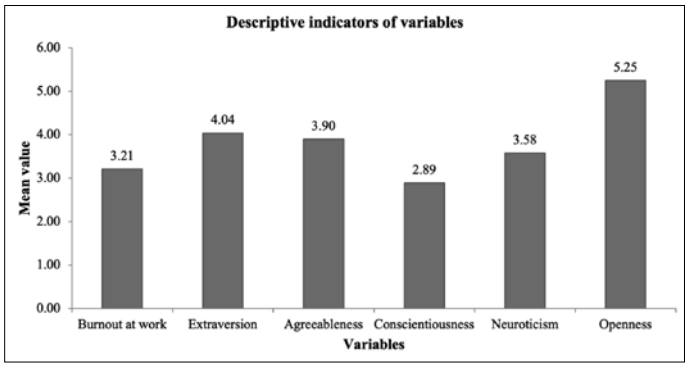

Figure 1. Descriptive indicators of variables

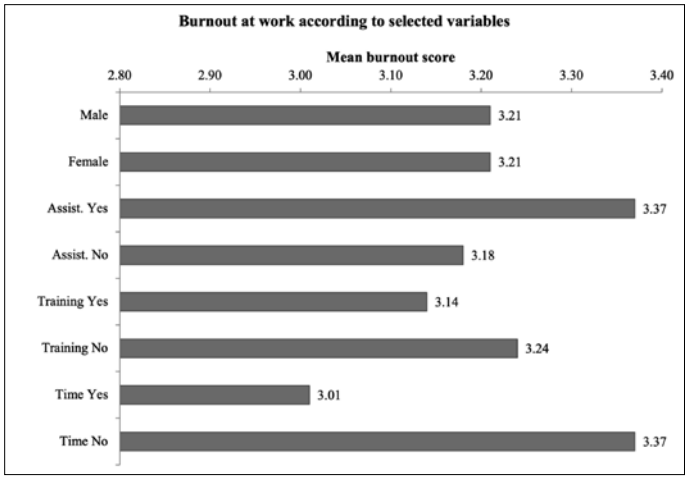

Figure 2. Burnout at work according to selected variables (t-test);

Assist – seeking psychological assistance; Training – communication skills training; Time – perception of having enough time for patients

Table 3. Multiple regression analysis predicting burnout at work

Predictor	B	β	p
Extraversion	-0.2285	-0.2433	0.003
Agreeableness	0.0475	0.0531	0.498
Conscientiousness	0.1892	0.2146	0.002
Neuroticism	-0.0216	-0.0269	0.747
Openness	0.1401	0.1222	0.024

B – unstandardized regression coefficient;
β – standardized regression coefficient

training, perceived sufficiency of time for patient care, and previous psychological assistance (Figure 2). The results showed no gender differences in occupational burnout and no difference between participants who had received communication-skills training and those who had not. A significant difference was found according to perceived time available for patients: participants who felt that they lacked enough time for each patient had a higher level of occupational burnout. The difference according to whether participants had sought psychological assistance was borderline but not statistically significant. Participants with higher occupational burnout appeared more likely to seek psychological assistance, although the difference did not reach statistical significance.

To examine the contribution of personality traits to occupational burnout, a linear regression analysis was conducted, with personality traits as predictors and burnout at work as the criterion variable. The regression model ($R = 0.307$, $F(5, 298) = 6.18$, $p < 0.001$) was statistically significant. The model explained 9.4% of the variance. Individual contributions of variables to explaining the criterion are shown in Table 3. Extraversion was a significant

negative predictor (β = −0.24), whereas conscientiousness (β = 0.21) and openness (β = 0.12) were significant positive predictors.

DISCUSSION

This study sought to investigate the relationship between personality traits, sociodemographic parameters, and the development of burnout syndrome among medical doctors in Serbia. To our knowledge, this is among the first studies in Serbia to include physicians from various healthcare facilities.

Previous studies have reported inconsistent findings regarding gender differences in burnout, suggesting that gender effects may vary depending on occupational context, workload, and organizational conditions [4, 5, 8].

However, our results suggest that within the Serbian medical context, burnout transcends gender lines, indicating that occupational stressors may outweigh gender-specific factors. The findings highlight the importance of considering both occupational conditions and broader psychosocial circumstances when addressing burnout prevention among healthcare professionals. It is advised to launch stress management and resilience programs specifically designed for healthcare workers to effectively navigate workplace stressors. Moreover, the introduction of flexible working conditions is recommended to support professionals across different personal circumstances, potentially including part-time roles and adaptable schedules. There is also a call for specialized support for those in high-stress areas or at greater risk of burnout, possibly through peer support, mentorship, and mental health resources. Conducting regular evaluations of burnout levels will help in identifying and addressing trends and at-risk groups, ensuring a healthier work environment.

The relationship between workload, specifically the perception of insufficient time for patient care, and burnout cannot be overstated. Participants reporting inadequate time allocation for patients exhibited higher burnout levels, underscoring the critical impact of workload management on healthcare professionals' well-being [9–12]. This finding is particularly relevant in the context of Serbia's healthcare system, which, like many others, is grappling with resource constraints and staffing shortages. Enhancing workforce management strategies to better allocate time for patient care is paramount. This could include adopting more efficient patient scheduling systems, increasing the healthcare workforce to reduce individual workload, and implementing time management training for staff. These measures could improve healthcare professionals' well-being and the overall quality of patient care within the constraints of Serbia's healthcare system.

Taken together, these findings support the view that burnout among physicians cannot be explained solely by either organizational or individual factors. While workplace conditions such as workload and insufficient time for patient care represent important external stressors, individual personality characteristics appear to influence how physicians perceive, process, and cope with these demands. Our results, therefore, suggest that burnout develops through the interaction between organizational pressures and individual vulnerability factors.

Our findings underscore the multifaceted nature of burnout, revealing that personality traits significantly contribute to the syndrome's development, consistent with prior research indicating the role of individual differences in susceptibility to burnout [13–16, 21–24, 29]. Although the regression model was statistically significant, the relatively modest proportion of explained variance suggests that burnout is a multifactorial phenomenon influenced by numerous additional organizational, occupational, interpersonal, and psychological factors that were not included in the present model.

Furthermore, personality traits such as extraversion, conscientiousness, and openness were found to be significant predictors of burnout at work, highlighting the role of individual differences in coping with occupational stress. Interestingly, extraversion appeared to serve as a protective factor against burnout [13, 16, 24, 29], which aligns with previous studies suggesting that extraverted individuals may possess better coping strategies and social support mechanisms [13, 16, 30]. The finding that conscientiousness and openness positively predicted burnout differs from part of the existing literature and may reflect specific characteristics of the medical profession. Highly conscientious physicians may demonstrate excessive responsibility, perfectionism, and increased emotional investment in patient care, which can contribute to chronic occupational stress and exhaustion. Similarly, individuals with higher openness may exhibit greater emotional sensitivity, stronger engagement with complex interpersonal situations, and heightened awareness of workplace difficulties, potentially increasing vulnerability to burnout under prolonged occupational strain. Recognizing and utilizing the inherent strengths associated with these personality traits in the workplace can foster a more supportive and adaptive environment, reducing the risk of burnout among employees.

Limitations

The cross-sectional design limits our ability to infer causality between personality traits and burnout. Furthermore, our reliance on self-report measures may introduce bias. Future longitudinal studies are needed to explore these relationships over time and to assess the impact of interventions aimed at reducing burnout among medical doctors. Additionally, the use of online data collection may have influenced sample representativeness, as participation depended on voluntary response and access to digital platforms, introducing the possibility of selection bias.

CONCLUSION

This study contributes to our understanding of burnout among physicians and underscores the multifaceted nature

of this phenomenon. Addressing burnout requires a holistic approach that considers not only work-related factors but also individual characteristics and psychosocial support systems. Future research could explore additional factors contributing to burnout and evaluate the effectiveness of targeted interventions in mitigating burnout risk among healthcare professionals.

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Conflict of interest: None declared.

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Карактеристике личности и синдром изгарања код лекара у Републици Србији

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САЖЕТАК

Увод/Циљ Синдром изгарања је вишедимензионални поремећај који нарочито погађа здравствене раднике. Како улога индивидуалних карактеристика, попут особина личности, није довољно истражена, циљ истраживања био је да испита повезаност карактеристика личности, социодемографских одредница и синдрома изгарања међу лекарима запосленим у Републици Србији.

Методе Спроведена је студија пресека, односно корелационо истраживање, 2024. године на узорку од 304 лекара путем онлајн упитника. Примењени су социодемографски упитник, скраћена верзија инструмента „Великих пет плус два" и радна подскала Копенхагенског упитника изгарања. Подаци су анализирани применом дескриптивне статистике, *t*-теста и линеарне регресије.

Резултати Није утврђена статистички значајна разлика у нивоу изгарања између мушкараца и жена ($p = 0,958$), нити у зависности од обуке из комуникационих вештина ($p = 0,214$). Ипак, учесници који су изјавили да немају довољно времена за рад са болесницима имали су значајно виши ниво изгарања ($p < 0,001$). Анализа линеарне регресије показала је да екстраверзија негативно предвиђа изгарање ($\beta = -0,24$, $p = 0,003$), док су савесност ($\beta = 0,21$, $p = 0,002$) и отвореност ($\beta = 0,12$, $p = 0,024$) позитивни предиктори. Модел је био статистички значајан ($R = 0,307$, $F(5, 298) = 6,18$, $p < 0,001$) и објашњавао је 9,4% варијансе изгарања.

Закључак Екстраверзија се показала као заштитни фактор од синдрома изгарања, док су више вредности савесности и отворености повезане са израженијим изгарањем. Ови налази указују на значај особина личности као вулнерабилног фактора за изгарање и наглашавају потребу за циљаном подршком лекарима кроз специфичне интервенцијске програме.

Кључне речи: професионални стрес; карактеристике личности; здравствени радници; психолошка отпорност

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Factor structure of job satisfaction among healthcare professionals in public hospitals in Belgrade, Serbia

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SUMMARY

Introduction/Objective This study aimed to examine job satisfaction among healthcare professionals in public hospitals in Belgrade, Serbia, and to identify its underlying dimensions using exploratory factor analysis.

Methods A cross-sectional study was conducted using a standardized job satisfaction questionnaire developed according to the methodology of the Institute of Public Health of Serbia. The analysis included 6899 healthcare professionals, categorized into two groups according to educational level: those with a university degree and those with secondary school or college education. Descriptive statistics, Student's t-test, χ^2 test, and exploratory factor analysis were applied.

Results Healthcare professionals with a university degree reported significantly higher satisfaction than those with secondary school or college education across the analyzed domains. The highest satisfaction scores were observed for collaboration with colleagues and superiors, whereas salary was the lowest-rated item in both groups. Exploratory factor analysis identified three dimensions of job satisfaction: "Organizational Culture and Personal Development", "Working Conditions," and "Workplace Change Intention."

Conclusion Job satisfaction among healthcare professionals in Belgrade public hospitals was multidimensional and differed according to educational background. The findings indicate that interpersonal collaboration was among the most positively evaluated aspects of work, whereas salary and other working conditions represented important sources of dissatisfaction. The identified factor structure provides exploratory evidence for further research and more detailed organizational assessment of job satisfaction in healthcare settings.

Keywords: professional satisfaction; professional development; professional communication

INTRODUCTION

Over the past three decades, research has consistently shown that employees represent one of the most important resources in any organization, and that their job satisfaction directly affects performance, motivation, and commitment to meeting organizational expectations. Motivated and satisfied employees contribute to continuous quality improvement, make better use of their knowledge and skills, share expertise with colleagues, and actively participate in improving the quality of their work [1–4].

In healthcare institutions, healthcare professionals play a particularly important role, as they are a key determinant of patients' perceptions of the quality of care received and of the extent to which services meet their expectations [5].

Previous studies have shown that job satisfaction and motivation among healthcare professionals are influenced by a wide range of individual (gender, age, marital status, occupation, level of education, years of work experience, managerial position), organizational (autonomy at work, opportunities for career advancement, interpersonal relationships), and external factors (economic conditions, broader social circumstances, and family obligations). Healthcare managers should recognize and understand these factors in order to manage human resources effectively [6–10].

Several recent studies have examined the dimensionality of job satisfaction instruments using exploratory factor analysis in the context of healthcare professionals' job satisfaction [10–12]. Munir and Rahman found that job satisfaction consisted of four factors: salary, coworker support, managerial support, and career development [11]. Another study identified six factors: benefits and salary, management attitude, supervision, communication, nature of work, and colleagues' support [12]. These findings suggest that financial compensation may represent an independent dimension of job satisfaction among healthcare professionals. In contrast, Lorber and Skela Savič reported that salary was not an independent factor, but rather a component of a broader motivational factor [10]. These inconsistent findings indicate that

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the structure of job satisfaction may vary across healthcare systems, professional groups, and organizational contexts.

Physicians have a particularly important role in healthcare management because they directly influence patient care, clinical decision-making, and team dynamics [13]. Given the increasing complexity of healthcare environments and changing workforce expectations, it is important to understand differences in job satisfaction across professional roles, leadership responsibilities, and educational backgrounds.

Therefore, the aim of this study was to examine the multidimensional structure of job satisfaction among healthcare professionals in public hospitals in Belgrade, Serbia, using exploratory factor analysis and to analyze differences in job satisfaction according to professional role and educational level.

METHODS

This study was based on a secondary analysis of data obtained from a job satisfaction survey conducted according to the methodology of the Institute of Public Health of Serbia [14]. A cross-sectional study design was used, and employee satisfaction was assessed at a single point in time on the survey day. Data entry from the completed survey forms was performed at the Institute of Public Health in Belgrade [15]. For the purposes of the present study, only questionnaires completed and returned by healthcare professionals were included in the analysis.

Healthcare professionals were divided into two groups according to their educational level. The first group consisted of healthcare professionals with a university degree, including doctors, dentists, and pharmacists, hereinafter referred to as HPUD. The second group consisted of healthcare professionals with secondary school or college education, including nurses and healthcare technicians, hereinafter referred to as HPSEC.

The questionnaire consisted of 24 closed-ended questions covering the general characteristics of healthcare professionals, including gender, age group, occupation, managerial position, participation in teaching, and engagement in private practice. The questionnaire also assessed working conditions, opportunities for professional development, relationships with superiors, collaboration with colleagues, perceived patient attitudes toward employees, overall job satisfaction, and intention to change jobs.

Respondents rated their satisfaction on a five-point Likert scale, where 1 indicated "very dissatisfied," 2 "dissatisfied," 3 "neither satisfied nor dissatisfied," 4 "satisfied," and 5 "very satisfied." In the analysis, responses rated 4 or 5 were considered to indicate satisfaction with the investigated variable, whereas responses rated 1 or 2 were considered to indicate dissatisfaction. Responses rated 3 were treated as neutral, indicating neither satisfaction nor dissatisfaction.

Descriptive statistics were used to describe the study population. Differences between groups were analyzed using Student's t-test for continuous variables and the chi-square test for categorical variables. Exploratory factor analysis was performed to identify the underlying dimensions of job satisfaction. Items with negative loadings were interpreted according to the direction of the original coding. Prior to factor extraction, the suitability of the data for factor analysis was assessed using the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity.

Principal component analysis was used as the extraction method, followed by Varimax rotation with Kaiser normalization. Factors were retained based on eigenvalues greater than 1 and the interpretability of the extracted factor structure. For each retained factor, the eigenvalue, percentage of explained variance, and cumulative percentage of explained variance were reported. For all statistical tests, the level of significance was set at $\alpha = 0.05$. Statistical analysis was performed using IBM SPSS Statistics, Version 21.0 (IBM Corp., Armonk, NY, USA).

Ethics: The study protocol was approved by the Ethics Committee of the City Institute for Public Health, Belgrade (No. 59/1 V-2, January 26, 2026).

RESULTS

On the day of the survey, 13,384 employees were present at work, and 11,689 questionnaires were distributed. A total of 9,236 questionnaires were completed and returned, corresponding to a response rate of 79%. The present study included 6,899 healthcare professionals, representing 74.7% of all respondents who returned completed questionnaires in the participating healthcare institutions [15].

Among the 6,899 healthcare professionals included in the analysis, 5,202 were nurses and healthcare technicians, 1,568 were doctors, 68 were pharmacists, and 63 were dentists. The characteristics of healthcare professionals according to educational level and gender are presented in Table 1.

Among HPUD, no statistically significant gender differences were observed in age distribution or managerial position. However, male HPUD were significantly more likely to be involved in academic teaching and to have an additional healthcare job in the private sector. Among HPSEC, statistically significant gender differences were observed for age distribution, managerial position, participation in teaching, and additional work in the private sector.

Mean satisfaction scores related to professional relationships, communication, and career development opportunities are presented in Table 2.

HPUD reported significantly higher satisfaction scores than HPSEC for all analyzed items. These included the ability to apply knowledge and skills at work, recognition and evaluation of work, collaboration with colleagues, collaboration with superiors, opportunities for professional development and continuing medical education, receiving clear instructions regarding job expectations, and the ability to present ideas to superiors.

Mean satisfaction scores related to organization and working conditions are presented in Table 3.

Table 1. Characteristics of healthcare professionals according to educational level and gender (percentages)

Variable		Male	Female	Total	χ^2	p
Healthcare professionals with a university degree						
Age	Less than 35	17.7%	17.5%	17.6%	0.009	p ≥ 0.05
	35–54	57.7%	58%	57.9%		
	More than 55	24.6%	24.5%	24.5%		
Managerial position	Yes	32%	27.5%	29.2%	3.8	p ≥ 0.05
	No	68%	72.5%	70.8%		
Academic career	Yes	36.5%	26.1%	30.3%	11.9	p ≤ 0.01
	No	63.5%	73.9%	69.7%		
Additional healthcare job in the private sector	Yes	44.5%	35.5%	39%	7.9	p ≤ 0.05
	No	55.5%	64.5%	61%		
Health professionals with secondary education and college degree						
Healthcare						
Age	Less than 35	42.7%	25.9%	28.2%	93.1	p ≤ 0.05
	35–54	46.1%	60.6%	58.6%		
	More than 55	11.2%	13.5%	13.2%		
Managerial position	Yes	10.3%	13.4%	12.8%	7.9	p ≤ 0.01
	No	89.7%	86.6%	87.2%		
Academic career	Yes	4.8%	2.6%	2.9%	4.8	p ≤ 0.05
	No	95.2%	97.4%	97.1%		
Additional healthcare job in the private sector	Yes	30%	16.1%	18%	37.5	p ≤ 0.05
	No	70%	83.9%	82%		

χ^2 test value, p value

HPUD reported significantly higher satisfaction scores for equipment, available time for job tasks, time available for patient interaction, autonomy in job performance, salary, and management quality and organizational work structure. The largest difference between the two groups was observed for autonomy in job performance.

Exploratory factor analysis was conducted separately for healthcare professionals with a university degree and those with secondary school or college education. The analysis identified three factors in both groups: "Organizational Culture and Personal Development", "Working Conditions", and "Workplace Change Intention" (Tables 4 and 5).

Overall, the factor structure was broadly similar in the two educational groups, although some differences were observed in the loading of individual items. In particular, patient perception of the employee appeared to be more closely related to working conditions among HPUD, whereas in the HPSEC group it showed a weaker and more complex association with the first factor, "Organizational Culture and Personal Development."

Table 2. Satisfaction with professional relationships, communication, and career development opportunities among healthcare professionals in Belgrade public hospitals

Variable	Education	N	Mean	SD	t, p
q5	HPUD	1665	3.7	1.1	10.1*
	HPSEC	5088	3.4	1.1	
q6	HPUD	1674	3.4	1.3	11.2*
	HPSEC	5128	3	1.2	
q7	HPUD	1676	4	1	6.5*
	HPSEC	5123	3.8	1	
q8	HPUD	1669	3.9	1.1	9.5*
	HPSEC	5113	3.6	1.1	
q10	HPUD	1666	3.5	1.2	8.4*
	HPSEC	5080	3.2	1.2	
q13	HPUD	1675	3.6	1.1	8.9*
	HPSEC	5133	3.3	1.1	
q14	HPUD	1675	3.7	1.2	13.2*
	HPSEC	5131	3.2	1.2	

HPUD – healthcare professionals with a university degree; HPSEC – healthcare professionals with secondary education or college degree; q5 – ability to apply knowledge and skills at work; q6 – recognition and evaluation of work; q7 – collaboration with colleagues; q8 – collaboration with superiors; q10 – opportunities for professional development/continuing education (CME); q13 – receiving clear instructions regarding job expectations; q14 – ability to express ideas to superiors; t – Student's t-test value; SD – standard deviation;
*p < 0.001

DISCUSSION

Healthcare professionals in public hospitals in Belgrade are most satisfied with direct collaboration with colleagues and superiors, which is a critical motivational factor influencing the quality of services and patient safety [16]. However, work motivation can be adversely affected by conflicts among colleagues. Studies from Australia, Canada, and New Zealand highlight increasing conflict among nursing staff, particularly new nurses, which often leads to higher turnover rates and a willingness to leave the job [17].

Assertive communication training has been shown to improve communication skills, enhance mutual respect, and mitigate conflicts. Assertiveness involves honest, direct communication that respects the rights and feelings of others, which is crucial in minimizing workplace conflicts and fostering a positive work environment [17]. Nurses, compared to doctors, often face less autonomy, receive less support, and are more frequently exposed to workplace violence and injuries [18].

In our study, nurses and healthcare technicians were particularly less satisfied with opportunities for professional

Table 3. Satisfaction with organization and working conditions among healthcare professionals in Belgrade public hospitals

Variable	Education	N	Mean	SD	t, p
q1	HPUD	1685	3.3	1.2	4.3*
	HPSEC	5146	3.1	1.1	
q2	HPUD	1685	3.4	1.1	7.4*
	HPSEC	5141	3.2	1.1	
q3	HPUD	1587	3.3	1.2	6.5*
	HPSEC	4824	3.1	1.1	
q4	HPUD	1662	3.8	1.1	19.9*
	HPSEC	5039	3.2	1.1	
q11	HPUD	1675	2.7	1.2	11.3*
	HPSEC	5121	2.3	1.1	
q12	HPUD	1659	3.4	1.2	9.9*
	HPSEC	5087	3.1	1.2	

q1 – equipment; q2 – available time for job tasks; q3 – time available for patient interaction; q4 – autonomy in job performance; q11 – salary; q12 – management quality and organizational work structure; t – Student's t-test value; SD – standard deviation; *p < 0.01

Table 4. Factor analysis of responses among healthcare professionals with a university degree

Item	Factor loading		
	Organizational culture and personal development	Working conditions	Workplace change intention
q14	**0.814**	0.218	-0.14
q5	**0.803**	0.366	
q8	**0.8**	0.137	-0.14
q13	**0.755**	0.405	
q4	**0.745**	0.202	0.287
q12	**0.74**	0.366	-0.21
q6	**0.711**	0.466	
q7	**0.688**		
q10	**0.621**	0.464	
q2	0.201	**0.789**	0.178
q3	0.266	**0.763**	0.191
q15		**-0.663**	0.272
q9	0.183	**0.619**	
q16	-0.16	**-0.558**	0.468
q11	0.385	**0.51**	-0.187
q1	0.367	**0.501**	
q17			**0.767**
Factor	Eigenvalue	% of variance explained	Cumulative %
Organizational culture and personal development	7.44	43.81	43.81
Working conditions	1.8	10.61	54.43
Workplace change intention	1.16	6.83	61.25

KMO = 0.866; Bartlett's test of sphericity: $\chi^2 = 3157$, df = 231, $p \leq 0.001$;
Extraction Method: Principal Component Analysis;
Rotation Method: Varimax with Kaiser Normalization;

q1 – equipment; q2 – available time for job tasks; q3 – time available for patient interaction; q4 – autonomy in job performance; q5 – ability to apply knowledge and skills at work; q6 – recognition and evaluation of work; q7 – collaboration with colleagues; q8 – collaboration with superiors; q9 – patient perception of the employee; q10 – opportunities for professional development/continuing education (CME); q11 – salary; q12 – management quality and organizational work structure; q13 – receiving clear instructions regarding job expectations; q14 – ability to express ideas to superiors; q15 – stress level during work; q16 – satisfaction with the job compared with five years earlier; q17 – workplace change intention

advancement, which suggests that career development policies should be more clearly defined for this group. Only 27% of doctors, dentists, and pharmacists and 16.9% of nurses and healthcare technicians expressed satisfaction with their income. These findings indicate that financial compensation remains an important source of dissatisfaction among healthcare professionals. However, the factor analysis showed that salary did not emerge as an independent dimension of job satisfaction, but was instead included within the broader "Working Conditions" factor. This finding is consistent with the results reported by Lorber and Skela Savič, who found that salary was part of a broader motivational factor rather than an independent determinant of job satisfaction [10]. The factor analysis provides additional insight into the structure of job satisfaction. The first factor, "Organizational Culture and Personal Development," reflects higher-order aspects of work, including respect, professional identity, communication, participation, and personal growth. In this sense, the findings are compatible with Maslow's hierarchy of needs, as they suggest that healthcare professionals' job satisfaction is determined not only by material conditions but also by recognition, belonging, self-esteem, and opportunities for self-actualization [19]. Nevertheless, the present study did not test Maslow's theory directly; rather, the theory may provide one possible interpretative perspective for understanding why non-material aspects of work are important for healthcare professionals' job satisfaction.

The second factor, "Working Conditions," reflects the practical and organizational conditions under which healthcare professionals perform their daily work. The results suggest that dissatisfaction with salary should be interpreted together with other aspects of working conditions, rather than as an isolated problem. Therefore, managerial interventions should not focus solely on financial incentives, but should also address workload, staffing, equipment, time pressure, stress, and work organization. The third factor, "Workplace Change Intention," was related to the intention to change jobs. This dimension is particularly important from the perspective of workforce planning and retention. Previous findings have shown that a considerable proportion of healthcare professionals consider changing their workplace, moving to the private sector, leaving healthcare, or working abroad [20, 21]. Such intentions may reflect accumulated dissatisfaction with working conditions, career opportunities, salary, and organizational support. In this context, systematic monitoring of health workforce mobility, timely replacement of personnel, and institutionalized transfer of knowledge and skills from experienced workers to younger colleagues are essential components of strategic health workforce management [20, 21]. Compared with findings from other settings, our results show both similarities and differences. For example, a study conducted in Chhattisgarh, India, also reported dissatisfaction with salary among healthcare professionals, but unlike our study, it also found dissatisfaction with interpersonal communication [22]. In contrast, healthcare professionals in Belgrade hospitals reported relatively high satisfaction with collaboration with colleagues and superiors. Previous research has also emphasized that working conditions and contextual factors are important determinants of job satisfaction and willingness to remain in the profession [23].

The findings of this study suggest several practical implications that are directly related to the observed dimensions of job satisfaction. First, the results indicate that healthcare institutions and relevant authorities should systematically monitor job satisfaction among healthcare professionals and use these data to identify areas requiring organizational improvement.

Second, healthcare professionals with secondary school or college education reported lower satisfaction than healthcare professionals with a university degree across several analyzed domains. Improving their job satisfaction may require stronger support systems in the workplace, clearer job descriptions, recognition of educational level

Table 5. Factor analysis of responses among healthcare professionals with secondary school or college education

Item	Factor Loading		
	Organizational culture and personal development	Working conditions	Workplace change intention
q8	**0.839**	0.166	
q14	**0.829**	0.307	
q4	**0.723**	0.393	
q7	0.716		
q5	**0.712**	0.366	
q13	**0.701**	0.401	
q6	**0.693**	0.498	
q12	**0.618**	0.53	
q10	**0.573**	0.5	
q9	**0.406**	0.308	-0.302
q2	0.218	**0.822**	
q3	0.194	**0.792**	
q1	0.317	**0.675**	
q11	0.27	**0.641**	
q16	-0.279	**-0.528**	0.282
q15	-0.294	**-0.514**	0.248
q17			**0.941**
Factor	Eigenvalue	% of variance explained	Cumulative %
Organizational culture and personal development	8.13	47.83	47.83
Working conditions	1.23	7.25	55.08
Workplace change intention	1.02	6.02	61.1

KMO = 0.868; Bartlett's test of sphericity: $\chi^2 = 8613$, df = 231, $p \leq 0.001$;
Extraction Method: Principal Component Analysis;
Rotation Method: Varimax with Kaiser Normalization;
q1 – equipment; q2 – available time for job tasks; q3 – time available for patient interaction; q4 – autonomy in job performance; q5 – ability to apply knowledge and skills at work; q6 – recognition and evaluation of work; q7 – collaboration with colleagues; q8 – collaboration with superiors; q9 – patient perception of the employee; q10 – opportunities for professional development/continuing education (CME); q11 – salary; q12 – management quality and organizational work structure; q13 – receiving clear instructions regarding job expectations; q14 – ability to express ideas to superiors; q15 – stress level during work; q16 – satisfaction with the job compared with five years earlier; q17 – workplace change intention

and professional competencies, opportunities for career development, autonomy within the scope of practice, and support in demanding clinical settings (such as intensive care, transplant units, geriatric departments, emergency departments). Third, the identification of "Workplace Change Intention" as a separate factor suggests that the intention to change workplaces should be monitored as an important indicator of potential workforce instability.

Limitations and future research

Several limitations of this study should be acknowledged. First, the cross-sectional design does not allow causal relationships to be established between the analyzed factors and job satisfaction. Second, the study was based on self-reported questionnaire data, which may be influenced by subjective interpretation, response bias, and social desirability bias. Third, participation in the survey was voluntary; therefore, the views of healthcare professionals who did not participate could not be assessed, and non-response bias cannot be excluded.

Another limitation is that the analysis was based on an existing job satisfaction questionnaire developed for institutional monitoring purposes. Although this enabled the analysis of a large sample of healthcare professionals, the questionnaire was not specifically designed to examine all potential determinants of job satisfaction in detail. For example, the present study could not fully assess the effects of workload intensity, administrative burden, private-sector engagement, family obligations, exposure to workplace violence, or specific sources of occupational stress.

Future research should use more detailed and specifically designed instruments to examine how workload, stress, additional private work, work-life balance, and organizational support influence job satisfaction and motivation among healthcare professionals. Longitudinal studies would be particularly useful for assessing changes in job satisfaction over time and for examining whether dissatisfaction with working conditions, salary, or career development predicts the intention to change workplaces or to leave the healthcare system. Additional research should also focus on nurses and healthcare technicians, given that this group reported lower satisfaction across several domains.

CONCLUSION

Healthcare professionals reported the highest levels of satisfaction with collaboration with colleagues and superiors, suggesting that interpersonal relationships represent an important strength of the hospital work environment. In contrast, salary was the lowest-rated aspect of job satisfaction in both educational groups. However, factor analysis showed that salary was part of the broader "Working Conditions" factor rather than an independent dimension, indicating that financial dissatisfaction should be interpreted together with other aspects of the work environment, such as workload, equipment, available time for patient care, stress, and work organization.

The identification of "Workplace Change Intention" as a separate factor indicates that the intention to change workplaces represents a distinct aspect of job satisfaction in this sample. The findings provide descriptive and exploratory evidence on the structure of job satisfaction among healthcare professionals in Belgrade public hospitals and may serve as a basis for further research and more targeted organizational assessment.

Overall, the findings suggest that improving job satisfaction in hospital settings requires a multidimensional approach that addresses working conditions, professional development, recognition, communication, and retention, while preserving the positive aspects of organizational culture and interpersonal collaboration.

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Структура фактора задовољства послом међу здравственим радницима у државним болницама у Београду, Србија

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САЖЕТАК

Увод/Циљ Циљ студије био је да испита задовољство послом међу здравственим професионалцима у државним болницама у Београду, у Србији, и да идентификује основне димензије задовољства коришћењем експлоративне факторске анализе.

Методе Спроведена је студија пресека коришћењем стандардизованог упитника Института за јавно здравље Србије. Узорак је обухватио 6899 здравствених професионалаца из државних болница у Београду, категорисаних у две групе на основу нивоа образовања, и то: са универзитетским образовањем, и са средњом и високом струковном школом. Примењене су дескриптивне статистичке анализе, Студентов *t*-тест, тест χ^2, као и експлоративна факторска анализа.

Резултати Уочене су значајне разлике у задовољству послом између две групе, при чему су здравствени професионалци са универзитетским образовањем били задовољнији у свим анализираним доменима. Испитаници су били најзадовољнији међуљудским односима, сарадњом са колегама и претпостављенима, док су плата и услови рада били главни разлози незадовољства у обе групе. Експлоративна факторска анализа је идентификовала три димензије задовољства послом: (1) организациону културу и лични развој, (2) услове рада и (3) намеру за промену посла.

Закључак Задовољство послом међу здравственим професионалцима у државним болницама у Београду било је вишедимензионално и разликовало се у зависности од нивоа образовања. Резултати показују да су сарадња са колегама и претпостављенима, као и међуљудски односи, били најпозитивније оцењени аспекти задовољства послом, док су плата и други услови рада представљали важне изворе незадовољства. Идентификована факторска структура пружа истраживачке доказе за даља истраживања и детаљнију организациону процену задовољства послом у здравственим установама.

Кључне речи: задовољство послом; професионални развој; професионална комуникација

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

A case report of successful pregnancy after radical trachelectomy

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SUMMARY

Introduction Cervical cancer, as a global health problem, is most commonly associated with HPV infection. The incidence is rising among women of reproductive age. The challenge is that standard treatment is radical hysterectomy that remains a serious problem for women who still wish to conceive. Fertility-sparing surgery is possible in strictly controlled cases, but pregnancy afterwards is still an issue.

Case outline A 32-year-old, nulliparous patient with a diagnosis of early-stage invasive squamous cell cervical cancer is presented. After evaluation and only after selection criteria were met, radical abdominal trachelectomy with pelvic lymph node dissection was performed. Final histological diagnosis revealed that cancer infiltrated the entire depth of the specimen, with malignant cells present at the lateral resection margin. Radical hysterectomy was indicated, but the patient refused. After a year, the patient conceived spontaneously and had a successful pregnancy.

Conclusion The fertility-sparing treatment for early-stage cervical cancer is an oncologically safe option in carefully selected patients. The pregnancy afterwards remains high risk and needs close follow-up to optimize both maternal and fetal outcomes.

Keywords: cervical cancer; fertility-sparing treatment; pregnancy

INTRODUCTION

Cervical cancer is a global health problem, and although the incidence varies across the world, it is the most common cause of death in this part of Europe [1]. It is primarily associated with HPV infection and its global burden arises from differences in prevalence of oncogenic subtypes and inequalities in screening and treatment [2]. Standard treatment for early-stage disease is radical hysterectomy that remains a serious problem for women of reproductive age who still wish to conceive. Given the issues of rising incidence of cervical cancer among younger women, delayed childbearing, and declining quality of life after radical surgery, in recent years, a few fertility-sparing guidelines, by relevant gynecological and oncological societies, have been published [3, 4, 5]. Fertility-sparing treatments for gynecological malignancies are possible in selected cases, enabling women to keep reproductive organs and their function with no reduction in survival rate compared with standard radical treatment [3]. Depending on clinical and radiological staging, possible conservative options for cervical cancer treatment are cold-knife conization, simple and radical trachelectomy.

However, pregnancy afterwards is still an issue. The rate of successful pregnancies after fertility-sparing treatment is lower than in the general population [6]. Studies show promising rates of spontaneous conception, but due to complications of surgical treatment, as well as patient's characteristics, assisted reproductive treatments may be indicated [7]. Even after successful conception, common adverse events after fertility-sparing treatment for cervical cancer are first- and second-trimester miscarriage, preterm labor and prematurity [8].

Managing malignancy while considering the patient's future reproductive wishes and possible pregnancy after cancer treatment requires a meticulous, multidisciplinary approach to provide comprehensive oncological, obstetric, neonatal, and psychological care.

CASE REPORT

A 32-year-old nulliparous patient was initially evaluated by the Clinic's Cancer Board with a diagnosis of squamous-cell invasive cervical cancer (G2, NG2, without lymphovascular invasion) after a cold-knife conization with a positive apical margin. Further standard evaluation for staging included abdominal and pelvic MRI and chest X-ray. Also, expert histological revision was performed, confirming the previous histological diagnosis. Based on the radiological imaging and histological report, the disease was staged IB1. Taking into consideration the young age of the patient, previous reproductive history, desire to conceive, and only after the selection criteria were met, the final decision of the Board was to perform radical abdominal trachelectomy

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with pelvic lymph node dissection. During the operation, so-called *ex tempore* biopsies of the apical portion of the cervix, a slice biopsy of the isthmic portion, and the pelvic lymph nodes had to be examined and found negative for malignancy before the operation could proceed. In this case, *ex tempore* analysis reported free margins, so radical trachelectomy with pelvic lymphadenectomy was done. However, final histological diagnosis revealed moderately differentiated (G2) squamous-cell cervical cancer with 10 mm of stromal infiltration and positive lymphovascular invasion. The final report stated that squamous-cell cervical cancer was present at the lateral resection margin of the cervix. There was no infiltration of the parametria and pelvic lymph nodes were negative. Considering the negative prognostic parameters (depth of infiltration, lymphovascular invasion, and positive resection margins), the Board suggested simple hysterectomy, which the patient refused. First pelvic MRI at six months after surgery did not show any signs of disease progression. The patient conceived spontaneously one year after the surgery. Except for gestational diabetes, the pregnancy was otherwise unremarkable. The patient delivered a healthy term infant weighing 3200 g by Cesarean section, with an Apgar score of 9/10. At one and six months after delivery, no progression of disease was noted.

Ethics: According to the journal's position on issues involving ethical publication, the written consent for publication of this article has been obtained from the patient.

DISCUSSION

Fertility-sparing surgery is nowadays an important strategy in cancer treatment because an increasing number of women under 45 years of age survive malignancy [9]. One-fifth of diagnosed cases occur among young adults under 39 years [10]. This case of a 32-year-old nulliparous woman draws attention to the rising incidence of cervical cancer among young women who have not completed childbearing. Hence, regular Papanicolaou screening gives the opportunity to diagnose the disease in early stages when fertility-sparing treatment is possible. According to the guidelines, preserving fertility is recommended in young patients up to 45 years of age and up to the FIGO stage IB1 [5]. Certain selection criteria are to be fulfilled for fertility-sparing management, including tumor size, depth of invasion, distance between cranial edge of tumor and internal cervical orifice, as well as local spread and lymph node involvement [3].

Only stage IA1 is treated with less invasive surgery – conization of the cervix. Radical trachelectomy, which includes removal of the cervix with surrounding parametrium and upper vagina, as well as pelvic lymphadenectomy, is reserved for FIGO stages IA2–IB1 [3]. Fertility-sparing treatment could be considered in stage IB2 in selected cases [4]. The reason why trachelectomy is acceptable in young women under strict conditions is because it is oncologically safe, meaning that the oncological outcome is similar to the standard radical treatment in which the entire uterus is removed [3, 4]. Results from the study by Siegler et al. [11] that analyzed 36 patients after simple trachelectomy showed no recurrence of disease after a mean follow-up of 7.5 years. The systematic review by Morice et al. [12] showed that the recurrence rate after abdominal radical trachelectomy was 2.4%. Another systematic review including 29 studies on cervical cancer involving 2432 patients showed that 28 (3.6%) patients had recurrent disease and six (0.8%) died of disease during a median follow-up of 53 months [9]. More recurrences occurred in patients with FIGO stage IB1 (3.1%) and IB2 (5.6%) disease than in patients with FIGO stage IA1 (0.2%) and IA2 (0.7%) disease [9]. In stage IB2 disease, the lower rate of recurrence is observed after radical trachelectomy via an abdominal approach and the highest recurrence rate is observed after neoadjuvant chemotherapy and conservative surgery [12]. These promising results in terms of disease-free survival rates are shifting the perspective from oncologic treatment toward quality of life and pregnancy [9, 13]. The short follow-up period represents a limitation of this case, as longer surveillance is required for definitive evaluation of oncological outcome.

Oncological outcomes are well reported, and fertility-sparing surgery is clearly recommended in selected patients, but the data on pregnancy outcomes are limited and inconsistently reported [9]. This highlights the importance of reporting a term pregnancy after trachelectomy.

As mentioned, the reason why trachelectomy is performed in the first place is to preserve the uterus and reproductive function in order to enable an uncomplicated term pregnancy [14]. Unfortunately, the rate of pregnancy is lower than in the general population. A possible medical reason is that the procedure can leave scarring in the uterine isthmus, which may impede sperm passage into the uterine cavity. In addition, malignancy may affect the woman's mental health, her fertility and desire for offspring. Moreover, adjuvant chemotherapy and radiotherapy affect ovarian reserve. Most studies show that few patients attempted to conceive [15].

An additional reason for the lower rate of pregnancy could be the age of these patients. The fertility rate declines with age, especially after the age of 35. One systematic review showed that 45.4% required infertility treatment after surgery, emphasizing the importance of IVF procedures [15]. The reported pregnancy rates after ART ranged 36–42% [15]. According to Okugawa et al. [16], 49% (112/230) of the patients attempted to conceive after trachelectomy, with a pregnancy rate of 41%. Twenty percent of those patients conceived spontaneously [16]. In the study analyzing oncological and reproductive outcomes in 471 patients with radical vaginal trachelectomy, the fertility rate was higher, at 73% [17]. In our case, the 32-year-old patient conceived spontaneously only one year after the operation.

After successful conception, these pregnancies are at risk of miscarriage and second-trimester pregnancy loss [18]. According to data, the incidence of first-trimester miscarriage, which is 16%, is no different from that in the general population. In contrast, second-trimester pregnancy loss is almost twice as high as in the general population, 7% *vs*. 4%, due to incompetence of the lower uterine

segment, infection, and premature prelabor rupture of membranes. The difference in risk between the trimesters could be explained by the fact that second-trimester loss is more strongly influenced by cervical factors and infection than first-trimester loss.

Preterm labor and intensive care unit stays are also more frequent among pregnant women with previous trachelectomy [19]. Even in the study by Kohler et al. [18], which reported a high pregnancy rate, 43% of pregnancies were preterm. On the other hand, some studies show an exceptional term-pregnancy rate, such as the results from two oncological centers where 16/36 (44.5%) patients achieved pregnancy and all pregnancies reached term [11]. Prematurity is a major problem mainly because of sequelae that can lead to lifelong disability. There is no strict recommendation in terms of prevention of infection and preterm delivery. In this case, the patient delivered a healthy term infant.

According to the Serbian national guideline for normal pregnancy, urinalysis is routinely performed in each trimester, and urine culture is done at the first visit to screen for asymptomatic bacteriuria [20]. A vaginal swab is taken at the first visit in the first trimester and again in the second trimester, and a cervical swab is recommended in the third trimester with GBS screening [20]. Since the permanent cervical cerclage placed during trachelectomy could be a source of infection, pregnancies after fertility-sparing treatment are high risk, and these patients require closer follow-up and infection screening to avoid complications.

This case demonstrates an example of successful term pregnancy after radical trachelectomy with a favorable outcome. Fertility-sparing treatment for early-stage cervical cancer is an oncologically safe option in carefully selected patients. Pregnancy afterwards remains high risk, and management in specialized tertiary centers with close follow-up is crucial. A multidisciplinary approach optimizes both maternal and fetal outcomes.

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Трудноћа након радикалне трахелектомије – приказ болесника

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САЖЕТАК

Увод Карцином грлића материце, као глобални здравствени проблем, најчешће је повезан са инфекцијом хуманим папилома вирусом (ХПВ). С обзиром на то да његова учесталост расте међу женама репродуктивног доба, проблем представља стандардни вид лечења који подразумева радикалну хистеректомију. То остаје озбиљан проблем за жене које и даље желе да остваре трудноћу. Поштедно хируршко лечење је могуће у строго контролисаним условима, али трудноћа након тога и даље представља изазов.

Приказ болесника Представљен је случај 32-годишње болеснице, која до тада није рађала, са дијагнозом инвазивног сквамоцелуларног карцинома грлића материце. Након пажљиве евалуације испуњени су критеријуми за поштедни третман те је урађена радикална абдоминална трахелектомија са пелвичном лимфонодектомијом. Коначна хистолошка дијагноза је показала да је карцином инфилтрисао целу дебљину грлића и да су малигне ћелије присутне на латералној ивици ресекције, те је индикована радикална хистеректомија, коју је болесница одбила. Након годину дана, болесница је спонтано затруднела и уследила је успешна трудноћа.

Закључак Лечење карцинома грлића материце у раном стадијуму уз очување плодности представља онколошки безбедну опцију код пажљиво одабраних болесница. Трудноћа након тога остаје високог ризика и захтева пажљиво праћење како би се оптимизовали исходи и за мајку и за фетус.

Кључне речи: рак грлића материце; лечење које штеди плодност; трудноћа

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Superior vena cava syndrome associated with alveolar soft part sarcoma – a possible paraneoplastic mechanism

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SUMMARY

Introduction Alveolar soft part sarcoma (ASPS) is an exceptionally rare soft tissue sarcoma, accounting for less than 1% of all cases. It typically presents as an indolent, slow-growing, painless mass. Superior vena cava (SVC) syndrome is usually caused by extraluminal compression from intrathoracic malignancies.
Case outline We report the case of a 53-year-old male who developed acute symptoms of SVC thrombosis. Imaging revealed extensive venous thrombosis without significant extrinsic venous compression. The clinical findings mimicked classic SVC syndrome, yet the underlying mechanism was intraluminal obstruction caused by thrombus formation. Histopathological evaluation confirmed the diagnosis of ASPS.
Conclusion To our knowledge, this is the first reported case of ASPS presenting with SVC syndrome secondary to extensive thrombosis rather than compression. Although the underlying mechanism remains uncertain, this case raises the possibility of a paraneoplastic mechanism. Awareness of this atypical manifestation may facilitate earlier recognition and timely management in similar presentations.
Keywords: alveolar soft part sarcoma; superior vena cava syndrome; thrombosis; paraneoplastic; chemotherapy

INTRODUCTION

Alveolar soft part sarcoma (ASPS) is a rare subtype of soft tissue sarcoma, constituting less than 1% of all soft tissue sarcomas. It typically occurs in the lower extremities, head, and neck, affecting mostly adolescents and young adults aged 15–35 [1]. ASPS often metastasizes late, primarily to the lungs, bones, and brain. Despite its slow growth, prognosis is poor unless complete surgical resection is achieved. The standard treatment is wide surgical excision, and adjuvant radiotherapy is used if negative margins are not possible. Systemic chemotherapy has limited effectiveness in managing ASPS [1].

The aim of this report is to describe a rare presentation of ASPS manifesting with superior vena cava (SVC) secondary to extensive thrombosis and to discuss the possibility of an underlying paraneoplastic mechanism.

CASE REPORT

We present the case of a 53-year-old male who experienced sudden swelling of the face, neck, and upper limbs, along with dyspnea. He had no cough, hemoptysis, chest pain, or wheezing but reported erythema and pruritus on his forehead, cheeks, and upper chest (Figure 1). One week later, his symptoms progressed to dyspnea and dysphagia, with no fever, weight loss, or night sweats. Physical examination revealed suffusion of the right conjunctiva but no signs of icterus or clubbing. A firm, palpable right axillary lymph node was identified. The patient was diagnosed with SVC syndrome (SVCS) and positioned with head elevation while receiving supplemental oxygen.

On admission, orthostatic changes were observed (supine blood pressure (BP): 130/80 mmHg, heart rate: 60–80 bpm; sitting BP: 85/55 mmHg, heart rate: 135 bpm). Oxygen saturation was 86% on room air, improving to over 95% with two liters of oxygen. Despite cyanosis and facial plethora (Figure 1), cardiovascular and respiratory examinations were otherwise unremarkable. Laboratory tests showed hemoglobin at 7.3 g/dL, platelets at 70×10^9/L, and white blood cells at 5.8×10^9/L. Ultrasonography revealed an extensive thrombus in the right jugular vein. Contrast-enhanced computed tomography of the chest confirmed a thrombus in the right brachiocephalic and internal jugular veins, and a 6 cm hematoma with ecchymosis within the sternocleidomastoid muscle (Figure 2). The patient was started on intravenous fluids and low-molecular-weight heparin. Due to ongoing bleeding, a core needle biopsy was performed, confirming sarcoma via immunohistochemistry (Figure 3).

Based on clinical presentation, imaging findings, and histopathological confirmation, a diagnosis of ASPS-associated SVCS secondary to

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Figure 1. Thrombosis-associated superior vena cava syndrome in a 53-year-old man; A – facial and neck plethora due to venous congestion; B – swelling of the right upper limb, a result of impaired venous return

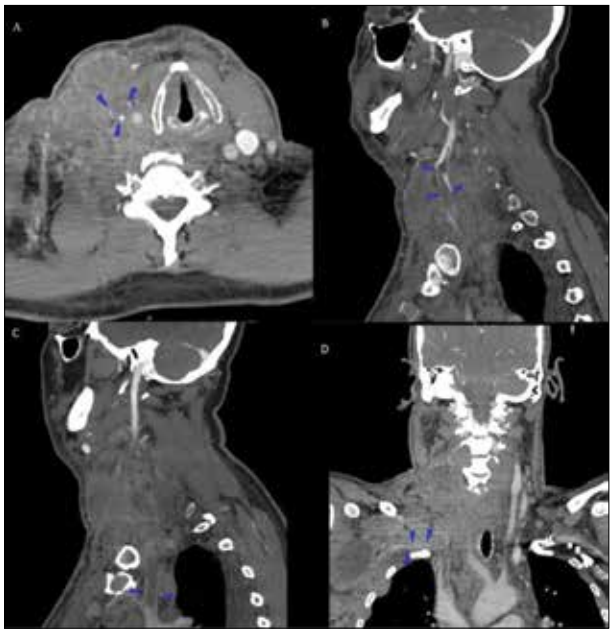

Figure 2. Computed tomography images; A – axial view shows right jugular vein obstruction by thrombus (arrow); B – sagittal view reveals jugular vein thrombus (arrow); C – sagittal view shows brachiocephalic vein thrombus (arrow); D – coronal view demonstrates mild extrinsic compression of the subclavian vein by the adjacent mass (arrow)

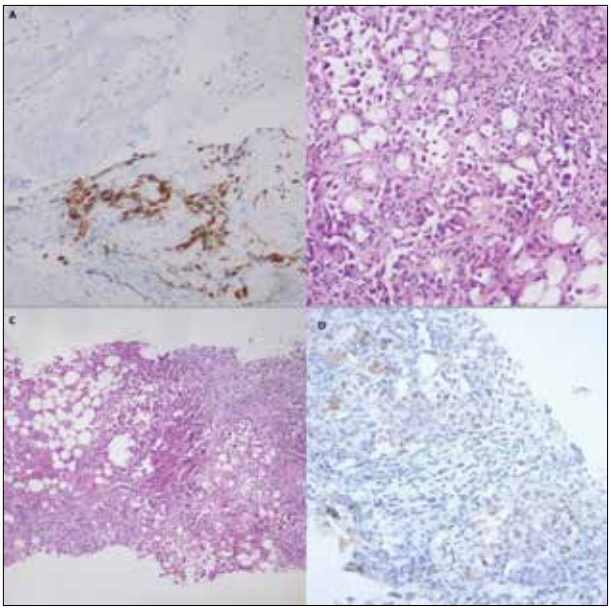

Figure 3. Histopathological and immunohistochemical findings; A – cytokeratin-7 positivity in tumor cells near bone trabeculae (× 40); B – atypical tumor cells in an alveolar pattern in soft tissue (H&E, × 40); C – similar pattern in tru-cut biopsy (H&E, × 20); D – TFE3 positivity in tumor (× 40)

extensive venous thrombosis was established. This presentation is highly atypical, as SVCS in malignancy most commonly results from extrinsic compression rather than intraluminal thrombosis. At the time of diagnosis, the patient was initiated on targeted systemic therapy for ASPS and continues on long-term anticoagulation.

Ethics: The patient agreed to have his photos and medical information published in the journal. He was aware that his name will not be revealed and that every effort will be made to maintain his anonymity.

DISCUSSION

ASPS is a rare soft tissue neoplasm characterized by historically uncertain histogenesis and an overall poor prognosis [1]. It predominantly affects females, usually involving the head and neck in children and the extremities in adults. Typically, tumor progression is slow, with symptoms developing over months to years; however, in our case, the presentation was acute and potentially fatal. ASPS has a notable metastatic potential, commonly spreading to the lungs, bones, and brain [2]. Tumors in the extremities show

metastases in approximately 20–40% of cases at diagnosis [3]. ASPS is highly vascular, as reflected in its imaging findings. Hypervascularity with prominent draining veins and prolonged capillary staining is not exclusive to ASPS; it can also occur in hemangiomas or vascular malformations. In contrast to typical arteriovenous malformations, which demonstrate rapid contrast washout, ASPS is characterized by delayed contrast clearance and intense, persistent tumor enhancement. On magnetic resonance imaging, ASPS typically presents a substantial solid component, whereas vascular malformations are composed entirely of vascular elements [2, 3]. However, this distinction was not clear in our case.

SVC syndrome affects an estimated 15,000 patients annually in the United States [4], with around 70% of cases linked to malignancies, while the remainder is mostly associated with medical devices. Accurate diagnosis is essential for selecting appropriate treatment, which may include radiotherapy, chemotherapy, surgery, or glucocorticoids, depending on the clinical scenario [4]. Among malignancies causing SVC syndrome, non-small cell lung cancer accounts for 50%, small cell lung cancer for 25%, and lymphomas for 10% [4]. Sarcomas, including ASPSs, are rare, with ASPS comprising about 1% of all soft tissue sarcomas [2]. Rare mesenchymal tumors of the thorax may present with unusual clinical syndromes and pose significant diagnostic challenges, as previously reported in rare intrapulmonary soft tissue tumors [5].

Paraneoplastic syndromes are distant effects of cancer, often unrelated to direct tumor invasion or obstruction, and typically manifest as neurological, hormonal, or hematologic symptoms. To our knowledge, this phenomenon has not been previously documented in ASPS. Cancer-associated hypercoagulability represents an important alternative explanation for the extensive venous thrombosis observed in our patient. Previous studies have demonstrated that tumor-associated thrombosis may result from multiple mechanisms, including tissue factor expression, thrombin generation, platelet activation, extracellular vesicles, and inflammatory cytokines, all of which contribute to a prothrombotic state [6]. However, the clinical presentation in our patient was unusual. ASPS is generally characterized by an indolent clinical course, whereas our patient presented with rapidly progressive SVCS as the initial manifestation of the disease in the absence of significant extrinsic venous compression. Although malignancy-associated thrombosis remains the most plausible explanation, the atypical presentation raises the possibility of a paraneoplastic mechanism. Nevertheless, in the absence of molecular, hormonal, or immunological evidence, a definite paraneoplastic syndrome cannot be established. The severity of these syndromes may not correlate with tumor size and can precede cancer diagnosis. In our case, SVCS was the initial presentation, despite the tumor being less than 4 cm at diagnosis. Although curative surgery was not an option for this patient due to the advanced stage of ASPS, early suspicion of such syndromes may facilitate the detection of malignancy at an earlier stage.

Currently, the most commonly described paraneoplastic syndromes are associated with the secretion of functional peptides and hormones by the tumor, as seen in endocrine manifestations, or with immunological cross-reactions between normal host tissue and the tumor, as observed in neurological manifestations. In addition to these, venous thromboembolism (VTE) is also frequently reported in patients with malignancies. The incidence of VTE is relatively common in patients with sarcoma, reported in approximately 5–10% of cases [7]. Few studies have examined VTE in patients with sarcoma. For example, a SEER-Medicare data retrospective study focused on older patients (aged over 65) reported a total VTE rate of approximately 16%, likely influenced by the advanced age of the cohort [8]. Another study reported a clinically relevant risk of VTE in patients undergoing surgery for bone or soft-tissue sarcomas, particularly in the absence of thromboprophylaxis, with a non-statistically significant trend toward risk reduction when prophylaxis was used [9]. These findings, along with our results, indicate that VTE is not uncommon in patients with sarcoma and that both chemotherapy administration and the postoperative setting are significant risk factors.

This case highlights an unusual presentation of ASPS presenting with SVCS due to thrombosis, raising the possibility of a paraneoplastic mechanism. Awareness of such atypical thrombotic events may facilitate earlier diagnosis and improve timely management.

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Availability of data and materials: Data supporting the findings of this case report are available from the corresponding author upon reasonable request.

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Синдром горње шупље вене повезан са алвеоларним саркомом меког ткива – могући паранеопластични механизам

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САЖЕТАК

Увод Алвеоларни сарком меког ткива је изузетно редак малигни тумор меког ткива, који чини мање од 1% свих саркома. Обично се манифестује спорим, индолентним растом и безболном масом. Синдром горње шупље вене најчешће настаје услед екстралуминалне компресије интраторакалним малигнитетима.

Приказ болесника Приказујемо случај мушкарца старог 53 године који је развио акутне симптоме тромбозе горње шупље вене. Радиолошке методе откриле су опсежну венску тромбозу без знакова спољашње компресије. Клиничка слика је опонашала класични синдром горње шупље вене, али је основни механизам била интралуминална опструкција услед формирања тромба. Хистопатолошка анализа потврдила је дијагнозу алвеоларног саркома меког ткива.

Закључак Колико нам је познато, ово је први описани случај алвеоларног саркома меког ткива који се презентује синдромом горње шупље вене секундарним опсежној тромбози, а не компресији. Иако основни механизам остаје неизвестан, овај случај указује на могући паранеопластични механизам. Препознавање ове атипичне манифестације може допринети ранијој дијагностици и правовременом лечењу сличних стања.

Кључне речи: алвеоларни сарком меког ткива; синдром горње шупље вене; тромбоза; паранеопластички; хемиотерапија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Atypical neuroleptic malignant syndrome associated with clozapine therapy – case report with literature review

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SUMMARY

Introduction Neuroleptic malignant syndrome (NMS) is a potentially fatal complication of neuroleptic drugs. Over the past few decades, it has been mostly considered as idiosyncratic reaction. The aim of this report is to present the case of an atypical NMS associated with clozapine treatment.

Case outline We describe a case of a young male patient treated with clozapine (400 mg), who developed NMS for the first time during the third relapse of schizoaffective disorder. The patient rapidly developed hyperthermia (40°C), tachycardia, labile blood pressure, confusion, elevated creatine phosphokinase, leukocytosis, and rhabdomyolysis, without muscle rigidity or other extrapyramidal signs. Extensive investigations excluded infectious, neurological, endocrine, and metabolic causes. Antipsychotics were discontinued, and treatment with lorazepam, intravenous hydration, and supportive care resulted in complete somatic recovery. Olanzapine was successfully reintroduced after stabilization.

Conclusion Specific pharmacodynamic profile of clozapine hampers early detection of NMS, since muscular rigidity is rare. Therefore, the presentation of NMS in this case is atypical. Atypical development of NMS during clozapine therapy imposes increased clinical attention.

Keywords: neuroleptic malignant syndrome; diagnostic criteria; clozapine; generic

INTRODUCTION

Neuroleptic malignant syndrome (NMS) was first described by Delay et al. [1] more than 50 years ago, during the treatment with first-generation antipsychotics (FGA). Since then, a growing body of literature demonstrated an incidence range from 0.01% to 3.2% of patients exposed to antipsychotics [2].

Reported mortality from NMS has declined from approximately 27% to 5.6%. This improvement in NMS outcome is due to better recognition of the syndrome and early intervention [3].

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for the diagnosis of NMS consist of major criteria (which are all required) and other criteria (at least two required). Major criteria include: exposure to dopamine-blocking agent, severe muscle rigidity and fever. Other criteria are diaphoresis, dysphagia, tremor, incontinence, altered level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, elevated creatine phosphokinase (CPK) [2].

Nierenberg et al. [4] proposed hierarchical organization of symptoms, emphasizing severe muscle rigidity and elevated temperature associated with antipsychotic medication use as cardinal features of NMS, while other criteria include tachycardia, excessive sweating, fluctuating blood pressure, leukocytosis and changes in level of consciousness. However, some researchers consider that autonomic dysfunction also represents one of the key features of NMS [5]. Likewise, altered mental status has also been proposed as one of the main criteria of NMS [6]. Moreover, recent research suggests that clozapine-induced NMS may have an atypical presentation, which implies the absence of muscular rigidity with all other criteria being fulfilled [7]. Also, complicating diagnosis even further is the fact that certain signs and symptoms found in NMS could be observed in other disorders (Table 1) [8].

Several risk factors for NMS have been reported, including older age, dehydration, dementia, parenteral therapy, rapid neuroleptic loading, polypharmacy and adjunctive psychotropics (e.g. lithium) [9].

Although NMS is less common with second-generation antipsychotics (SGA), it has been reported with all antipsychotics in this group, including those with weak D2 effects such as clozapine and quetiapine [5]. To date, extensive research has reported relatively frequent occurrence of NMS during clozapine treatment [10].

The aim of the present case report is to describe atypical NMS during clozapine treatment.

CASE REPORT

A 30-year-old man, high-school graduate, employed, was admitted to our clinic due to the

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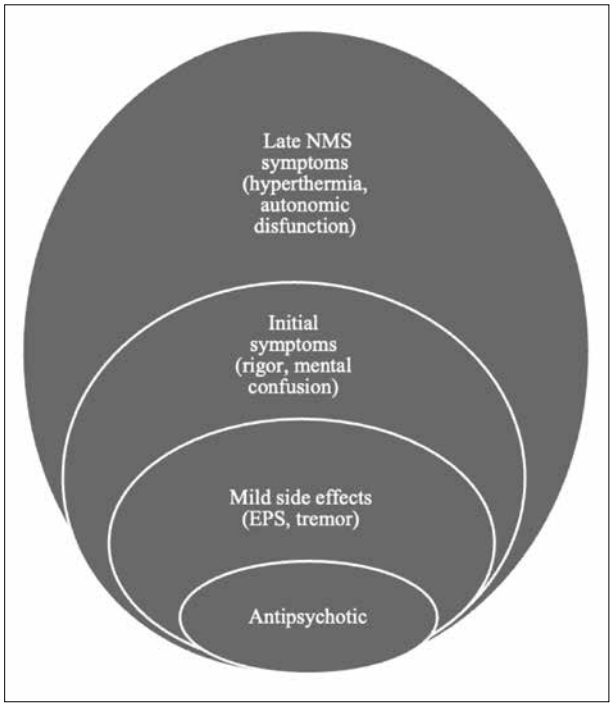

Figure 1. The continuum of neuroleptic malignant syndrome (NMS) and antipsychotic side effects (adapted from Velamoor et al. [20]); EPS – extrapyramidal symptoms

Table 1. Differential diagnosis of neuroleptic malignant syndrome (adapted from Orsolini and Volpe [8])

Infectious
Meningitis or encephalitis
Postinfectious encephalomyelitis syndrome
Sepsis
Psychiatric or neurological
Idiopathic malignant catatonia
Agitated delirium
Nonconvulsive status epilepticus
Toxic or pharmacological
Anticholinergic delirium
Malignant hyperthermia
Serotonin syndrome
Substances of abuse
Endocrine
Thyrotoxicosis
Pheochromocytoma

Table 2. Criteria of the neuroleptic malignant syndrome and clinical signs of the patient

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria		Patient
Major criteria (all required)	Exposure to dopamine-blocking agent	X
	Rigidity	
	Hyperthermia	X
Two or more of the following symptoms/signs	Diaphoresis	X
	Dysphagia	
	Tremor	
	Incontinence	
	Changes in the level of consciousness	X
	Mutism	
	Tachycardia	X
	Elevated or labile arterial blood pressure	X
	Leukocytosis	X
	Laboratory evidence of muscle injury (elevated creatine phosphokinase level)	X

exacerbation of Schizoaffective psychosis – F25. The patient has been treated since the age of 19, at the following maximum daily doses:

- Haloperidol 15 mg in combination with levomepromasine 100 mg – insufficient efficacy;
- Clozapine 200 mg (original formulation) – after achieving stable remission, the patient received maintenance dose of 50 mg daily.

Due to the acute exacerbation of his primary condition – schizoaffective disorder, manic type, the patient was hospitalized at the Clinic for Psychiatry. Clozapine dosage (generic formulation) was gradually increased to 400 mg, in the combination with benzodiazepine in the dosage of 10–30 mg daily.

Owing to the further worsening of the patient's condition (high agitation with impulsivity, insomnia, delusions and hallucinatory behavior, with normal somatic and laboratory findings), the patient was treated with a first generation antipsychotic (haloperidol ≤ 5 mg for two days and chlorpromazine ≤ 200 mg for four days) during the episodes of psychomotor agitation, as augmentation therapy. Despite these measures, the patient's condition worsened, primarily due to the altered mental status.

Since the aforementioned augmentation strategies were unsuccessful, we included lithium carbonate, which was proven to be effective in the combination with clozapine in the treatment of schizoaffective disorder [11]. Two hours after receiving a single 300 mg dose of lithium-carbonate (300 mg) with clozapine (400 mg, generic compound) the patient exhibited: hyperthermia (40°C), a rise in the CPK levels (1639 U/L), neutrophilia (85.3%) and lymphopenia (7%), accompanied by increased total white blood cell count (10.2×10^9/l). Physical examination revealed tachycardia (120 beats per minute) and a labile blood pressure (ranging from 120/80 mmHg to 150/100 mmHg), without muscle rigidity and extrapyramidal symptoms. Differential diagnosis was considered according to the criteria presented in Table 1. Viral disease was dismissed after immunological analyses were negative. Computed tomography scan of the brain was normal, as well as the electroencephalography and the endocrine status (levels of thyroxine, thyroid-stimulating hormone and cortisol were within reference ranges). Although the patient did not fulfill the full DSM-5 diagnostic criteria because severe rigidity was absent, the overall presentation was highly suggestive of atypical NMS associated with clozapine therapy (Table 2). Malignant catatonia, which can also manifest by hyperthermia, was considered. Although in 20% of cases NMS and malignant catatonia cannot be distinguished [8], temporal relationship of the onset of symptoms and the use of antipsychotics is suggestive of NMS. Laboratory values are typically normal. In both cases the treatment strategy involves the discontinuation of antipsychotics and the benzodiazepine initiation.

Consequently, an antipsychotic drug was discontinued, and the patient was treated with benzodiazepine therapy (lorazepam 12.5 mg/day), accompanied by intravenous rehydration. In the following seven days the patient's temperature was between 36.5–37.5°C. We did not observe extrapyramidal symptoms, however, laboratory parameters remained elevated: CPK up to 2000 U/L, alanine aminotransferase up to 228 U/L, aspartate aminotransferase up to 160 U/L, gamma glutamyl aminotransferase up to 66 U/L, erythrocyte sedimentation up to 56 mm/hour, accompanied by mild leukocytosis.

In the following seven days, psychomotor agitation, confusion, and hallucinatory behavior remained prominent in the patient's status. The trend of somatic stabilization was observed during the second week of intensive care. On day 10, the laboratory findings were in reference ranges. Psychomotor agitation was reduced; however, confusion remained for the following few weeks (the score on the Mini Mental State Examination was 20/30 in the first week, and 23/30 in the third week). Antipsychotic therapy was reintroduced with olanzapine, administered at an initial low dose and titrated gradually to achieve clinical stabilization. The patient was discharged five weeks after the beginning of the NMS, in partial remission of primary psychiatric disorder and in stable somatic state. A year later, the patient was mostly stable, working and on continuous treatment with moderate dosages of olanzapine.

Ethics: All procedures were carried out in compliance with the institutional and/or national research committees' ethical standards (No.920/5, 08.05.2025), as well as the 1964 Helsinki Declaration and its revisions or similar ethical standards.

DISCUSSION

This case illustrates an atypical presentation of NMS, characterized by hyperthermia, rhabdomyolysis, significant autonomic dysfunction, mental confusion, and agitation, notably without extrapyramidal symptoms such as muscle rigidity.

Regarding the fulfillment of the major DSM-5 criteria, exposure to dopamine antagonists and hyperthermia were present. Severe muscle rigidity was not present in our patient. Of the additional criteria where a minimum of two are required, all were present: diaphoresis, disturbed state of consciousness, variable blood pressure, tachycardia, leukocytosis, elevated CPK up to 2000 U/L. Although one major criterion (rigidity) is absent, the combination of required exposure and fever with all additional diagnostic features and the exclusion of infectious and metabolic mimics makes the diagnosis of NMS in this patient.

Therefore, NMS should be considered as a consequence of: 1) effects of clozapine; 2) effects of lithium; and 3) effects of both clozapine and haloperidol/chlorpromazine.

In this case, clozapine is the most likely primary factor, given the titration up to 400 mg and the recognized ability of clozapine to cause atypical forms of NMS, often with mental status disturbance and autonomic dysfunction [12]. Recent reports have further demonstrated that clozapine itself may induce atypical NMS even in the absence of concomitant treatment with high-potency FGA [13]. Recent pharmacovigilance analyses additionally suggest that multiple neurochemical pathways, including dopaminergic, serotonergic and cholinergic signaling, contribute to the development and progression of NMS, supporting the atypical clinical presentation observed with clozapine therapy [14]. Therefore, early signs – particularly sudden confusion, blood pressure lability, and tachycardia – should raise the suspicion of NMS in patients on clozapine, even when rigidity is absent.

The addition of lithium to antipsychotics has occasionally been associated with the occurrence of NMS. Pope et al. [15] first described NMS associated with clozapine-lithium therapy in a man with past history of NMS with fluphenazine-lithium therapy. Tomcuk et al. [16] recently reported a case where a patient developed NMS after receiving clozapine and lithium, indicating that clozapine, though usually considered safer alternative following NMS can still lead to the syndrome when combined with lithium.

The likely temporal sequence of events in this case – the onset of severe hyperthermia and elevated CPK shortly after the first dose of lithium suggests that lithium acted as an accelerant in an already sensitive system, but does not prove singular causation; which is consistent with the recent report [16].

In polypharmacy, the use of haloperidol and chlorpromazine may contribute to cumulative dopaminergic imbalance; however, in the absence of prolonged exposure or high-dose FGA therapy, they are less likely to represent the sole trigger of NMS [5, 14]. The augmentation with moderate dose of haloperidol in short-time period, without muscle rigidity and other extrapyramidal symptoms is less likely to be the cause of NMS. We have to note that patient had already received haloperidol during the first episode of his mental illness (long-term and in a higher doses) without any complications.

The unique receptor profile of clozapine, characterized by relatively weak D2 receptor antagonism together with potent antimuscarinic and antihistaminergic activity, may explain the atypical presentation of NMS, particularly the reduced incidence of muscle rigidity [17]. The distinctive receptor pharmacology that underlies clozapine's superior efficacy in treatment-resistant schizophrenia may likewise contribute to the atypical clinical phenotype of clozapine-associated NMS [17, 18]. The atypical presentation observed in our patient may also have resulted from synergistic pharmacodynamic interactions between clozapine and chlorpromazine. Nevertheless, chlorpromazine alone has rarely been implicated in NMS, with the available literature limited to isolated case reports.

Rare studies showed that generic clozapine compared to the original formulation causes altered mental symptoms more frequently [19]. This could be the case in our patient, but the data about adverse effects of generic form of clozapine are limited and inconclusive.

In the present case, the clinical course was followed, as shown in the scheme of Velamoor et al. [20]. The patient's condition is worsening through exacerbation of schizoaffective psychosis and despite treatment, it complicated with mental confusion and agitation followed by hyperthermia, autonomic dysfunction and biochemical disorders, which all are signs of late phase of NMS. Namely, dopamine depletion in the mid-brain–cortex–limbic system pathways may be the cause of changes in mental status. Blockade of dopamine receptors in the hypothalamus causes impaired heat dissipation, resulting in hyperthermia [21]. Thus, timely recognition of NMS during the clozapine therapy is hindered by the absence of rigidity, because of clozapine receptor profile.

Our case highlights that the early emergence of changes in mental status such as mental confusion, should cause suspicion of NMS in a patient treated with clozapine, despite the absence of muscle rigidity. Thus, whenever clozapine is administered, regardless of the length of previous treatment and drug tolerability, patients should be carefully monitored in order to detect aforementioned early signs, because that is the only way to act promptly and prevent late complications.

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Атипични неуролептички малигни синдром повезан са терапијом клозапином – приказ случаја са прегледом литературе

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САЖЕТАК

Увод Неуролептички малигни синдром (НМС) јесте потенцијално фатална компликација лечења антипсихотицима која се последњих пет деценија схвата углавном као идиосинкратска реакција. Овај приказ случаја има за циљ да укаже на могућност настанка атипичног НМС-а током терапије клозапином.

Приказ болесника Описан је развој НМС-а код младића леченог клозапином (400 *mg*), који је први пут настао током треће епизоде основне болести (шизоафективна психоза). Код болесника су се брзо развили хипертермија (40° C), тахикардија, нестабилан крвни притисак, ментална конфузија, повишен ниво креатин-фосфокиназе, леукоцитоза и рабдомиолиза, без мишићне ригидности или других екстрапирамидалних знакова. Детаљна испитивања искључила су инфективне, неуролошке, ендокрине и метаболичке узроке. Примена антипсихотика је обустављена, а лечење лоразепамом, интравенском хидратацијом и супортивним мерама довело је до потпуног соматског опоравка. Након стабилизације стања, поново је успешно уведена терапија оланзапином.

Закључак Специфичан фармакодинамски профил клозапина отежава рано препознавање НМС-а, јер је појава мишићне ригидности ретка. Стога овај случај представља атипичну форму НМС-а. Атипичност развоја приликом примене клозапина налаже повишену пажњу клиничара.

Кључне речи: неуролептички малигни синдром; дијагностички критеријуми; клозапин; генерички лекови

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PRELIMINARY AND SHORT COMMUNICATION
/ ПРЕТХОДНО И КРАТКО САОПШТЕЊЕ

The significance of systemic inflammatory markers in differentiating benign from malignant parotid gland tumors – a pilot study

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SUMMARY

Introduction/Objective This study aimed to assess the diagnostic value and explore the potential role of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) in distinguishing benign from malignant parotid gland tumors.

Methods Clinical data from 129 patients who underwent parotid surgery between 2014 and 2024 were evaluated retrospectively. Demographic characteristics, preoperative complete blood count parameters, and histopathological findings were compared. Patients were categorized into benign and malignant tumor groups based on histopathological diagnosis.

Results No significant difference was found in sex distribution between the groups ($p > 0.05$). Patients with malignant tumors were significantly older than those with benign tumors ($p = 0.038$). Lymphocyte and platelet counts were significantly higher in the benign tumor group ($p = 0.008$ and $p = 0.029$, respectively). In contrast, mean NLR values were significantly higher in patients with malignant tumors ($p = 0.016$). Although PLR and SII values were also higher in the malignant tumor group, the differences were not statistically significant ($p > 0.05$).

Conclusion NLR may serve as a supportive and adjunctive marker rather than a standalone diagnostic tool for differentiating between benign and malignant parotid gland tumors. This study should be considered a pilot study, and larger, controlled studies are required.

Keywords: parotid tumors; parotidectomy; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; systemic immune-inflammation index

INTRODUCTION

Major salivary gland tumors constitute approximately 3–10% of head and neck neoplasms, with nearly 80% originating from the parotid gland [1, 2, 3]. Parotid masses may arise from primary neoplasms or reflect inflammatory diseases, metastatic malignancies, or lymphomas [2, 4]. Clinical evaluation relies on physical examination and imaging methods for diagnosis and treatment planning. Features such as pain, rapid growth, fixation to surrounding tissues, and cervical lymphadenopathy suggest malignancy; evaluation commonly includes fine-needle aspiration biopsy (FNAB), ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) [1, 5, 6]. Differentiating non-neoplastic from neoplastic lesions, benign from malignant tumors, and low-grade from high-grade malignancies is essential for appropriate treatment planning and surgical management. Although MRI and CT are valuable for evaluating large or deep-lobe masses with suspected malignancy, FNAB remains the first-line diagnostic method because of its simplicity, low cost, and rapid results [1, 6]. However, intratumoral heterogeneity, morphological overlap, and the histological diversity of salivary gland tumors often hinder a definitive preoperative cytological diagnosis, and diagnostic accuracy largely depends on the cytopathologist's experience [1, 2, 6].

The interaction between cancer and the immune system has become an important focus of recent research. While immune surveillance mediated by lymphocytes and natural killer (NK) cells provides protection against transformed cells, chronic inflammation is recognized as a major contributor to carcinogenesis. The tumor microenvironment contains various immune cell populations that influence tumor progression through complex interactions between tumor cells and the host [5–8].

Chronic inflammation contributes to multiple stages of tumor development, including cellular transformation, proliferation, angiogenesis, invasion, and metastasis [3, 5, 9]. Cytokines such as IL-6 and TNF-α, released by tumor cells and the tumor microenvironment, may promote oxidative stress, genomic instability, and tumor progression [9–11]. In addition, inflammatory mediators may enhance tumor invasiveness through pathways involving vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) [9–11].

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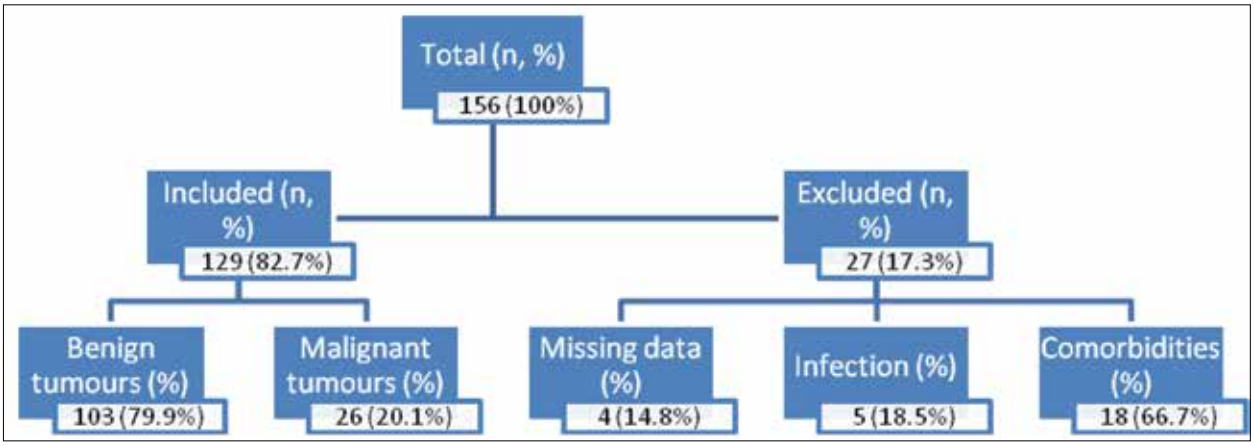

Figure 1. Flow diagram of patient selection and grouping

Conversely, lymphopenia reflects impaired host immune surveillance, facilitating tumor immune escape [5].

Peripheral blood inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have emerged as accessible indicators of the balance between tumor-associated inflammation and the host immune response [3, 6]. Cytokines released by tumor cells and the tumor microenvironment may trigger systemic inflammation by altering circulating neutrophil, lymphocyte, platelet, and monocyte levels [10]. This inflammatory response may further promote tumor progression and suppress host immune activity [1, 5, 7, 8]. Therefore, peripheral blood inflammatory cells are considered important mediators of carcinogenesis and tumor progression. A complete blood count (CBC) is a routine, cost-effective preoperative test that allows these markers to be readily calculated from neutrophil, lymphocyte, and platelet counts [1, 6].

This pilot study aimed to evaluate the potential role of preoperative inflammatory markers (NLR, PLR, and SII) in differentiating benign from malignant parotid gland tumors.

METHODS

Patients

Clinical data from 156 patients who underwent surgery for parotid masses at the Department of Otorhinolaryngology, Medipol Mega University Hospital, between January 2014 and December 2024 were retrospectively reviewed. All consecutive patients meeting the study criteria were screened. Patients aged 10–83 years were included, and no specific age cut-off was applied; therefore, both pediatric and adult patients were evaluated. To minimize potential inflammatory confounders, patients with acute infection, diabetes, heart failure, autoimmune or hematological diseases, chronic renal failure, corticosteroid use, obesity (BMI > 30), or missing preoperative CBC data were excluded. Some patients had overlapping exclusion criteria. After exclusions, 129 patients were included in the final analysis. A flow diagram of the patient selection process is presented in Figure 1.

Demographic characteristics, medical history, preoperative hemogram findings, and postoperative histopathological diagnoses were obtained from hospital records. Sex data referred to biological sex. Only primary parotid gland neoplasms confirmed by final pathology reports were included. Patients were classified into benign and malignant tumor groups according to their postoperative histopathological diagnoses.

Venous blood samples were collected between 09:00 and 11:00 within one week before surgery. Preoperative CBC data were used to determine neutrophil, lymphocyte, and platelet counts. NLR (N/L), PLR (P/L), and SII (N × P/L) were calculated. All measurements were performed using the same automated hematology analyzer.

Statistical analysis

Data were analyzed using the SPSS Statistics, Version 17.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to summarize the data: quantitative variables were expressed as mean ± standard deviation, median, minimum, and maximum, while qualitative variables were presented as frequency and percentage. Normality was assessed using the Shapiro–Wilk test. The Student's t-test was used for normally distributed quantitative variables, and the χ^2 test was used for categorical comparisons. Risk factors for malignancy were evaluated using binary logistic regression (enter method). Logistic regression analysis included NLR, PLR, SII, and age as potential predictors. The pseudo-R^2 value (Nagelkerke R^2) was used to assess model fit. Diagnostic performance was assessed using receiver operating characteristic (ROC) curve analysis. A p-value < 0.05 was considered statistically significant at a 95% confidence level.

Ethics: For this retrospective study, ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Istanbul Medipol University (registration number: E-10840098–202.3.02–575, decision no.: 09.01.2025/40), and the study was conducted in accordance with the Declaration of Helsinki.

Table 1. Comparison of demographic and hematological parameters between benign and malignant parotid tumors

Parameter	Value	Benign (n = 103)	Malignant (n = 26)	[a]p
Sex	Male	64 (62.1)	14 (53.8)	[a]0.440
	Female	39 (37.9)	12 (46.2)	
Age (years)	Mean ± SD	44.39 ± 15.36	51.88 ± 19.79	[b]0.038*
	Median (min–max)	45 (10–83)	50 (15–79)	
Neutrophils	Mean ± SD	4.91 ± 1.99	4.9 ± 2.21	[b]0.999
	Median (min–max)	4.6 (2.2–15.2)	4.5 (0.4–10)	
Lymphocytes	Mean ± SD	2.53 ± 0.78	2.08 ± 0.68	[b]0.008**
	Median (min–max)	2.4 (0.8–4.6)	2 (0.9–3.8)	
Platelets	Mean ± SD	268.18 ± 66.13	236.65 ± 59.44	[b]0.029*
	Median (min–max)	261 (104–443)	223 (167–442)	
NLR	Mean ± SD	2.05 ± 0.89	2.65 ± 1.74	[b]0.016*
	Median (min–max)	1.8 (0.9–5.9)	2.4 (0.2–8.2)	
PLR	Mean ± SD	112.83 ± 35.03	126.47 ± 55.95	[b]0.123
	Median (min–max)	106 (46.6–246.3)	112.5 (63.6–298.9)	
SII	Mean ± SD	543.37 ± 246.38	617.71 ± 392.09	[b]0.160
	Median (min–max)	506.4 (198.6–1374.1)	514.4 (63.6–1750.5)	

NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio;
SII – systemic immune-inflammation index;
[a]Pearson χ^2 test;
[b]Student's t-test;
*p < 0.05;
**p < 0.01

Table 2. Logistic regression analysis of risk factors affecting malignancy

	p	Odds ratio	95% CI	
Constant	0.001**	0.072	Lower	Upper
NLR	0.013*	2.965	1.260	6.976
PLR	0.199	1.009	0.995	1.022
SII	0.049*	0.996	0.992	1.000

NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio;
SII – systemic immune-inflammation index;
Method – enter logistic regression;
*p < 0.05;
**p < 0.01

RESULTS

A total of 129 patients were included, comprising 78 males (60.5%) and 51 females (39.5%). The benign tumor group included 103 patients aged 10–83 years (mean age: 44.39 ± 15.36 years, median age: 45 years), whereas the malignant group consisted of 26 patients aged 15–79 years (mean age: 51.88 ± 19.79 years, median age: 50 years). Histopathological evaluation revealed 103 benign (79.8%) and 26 malignant (20.2%) lesions (Table 1). Pleomorphic adenoma (n = 51, 49.5%) and Warthin tumor (n = 30, 29.1%) were the most common benign tumors, whereas squamous cell carcinoma (n = 6, 23.1%), low-grade mucoepidermoid carcinoma (n = 4, 15.4%), and adenoid cystic carcinoma (n = 3, 11.5%) were the most frequent malignant tumors. The benign group included 64 males (62.1%) and 39 females (37.9%), while the malignant group included 14 males (53.8%) and 12 females (46.2%). Sex distribution did not differ significantly between the groups (p > 0.05). However, mean age was significantly higher in the malignant group than in the benign group (51.88 ± 19.79 *vs.* 44.39 ± 15.36 years, p = 0.038) (Table 1).

Mean hematological parameters and inflammatory markers are presented in Table 1. Neutrophil counts did not differ significantly between the groups (p > 0.05), whereas lymphocyte and platelet counts were significantly higher in the benign group (p = 0.008 and p = 0.029, respectively). The mean NLR was significantly higher in the malignant group (2.65 ± 1.74) than in the benign group (2.05 ± 0.89) (p = 0.016). Although PLR and SII values were also higher in the malignant group, these differences were not statistically significant (p > 0.05) (Table 1).

Logistic regression analysis using the enter method included NLR, PLR, and SII. NLR and SII were identified as predictors of malignancy (p = 0.022), and the Nagelkerke R^2 value of the model was 0.806. A one-unit increase in NLR was associated with an odds ratio of 2.965 for malignancy (95% CI: 1.260–6.976, p = 0.013), whereas a one-unit increase in SII corresponded to an odds ratio of 0.996 (95% CI: 0.992–1.000, p = 0.049). Although NLR showed a statistically significant association with malignancy, the significance of SII was borderline and should be interpreted cautiously (Table 2).

Receiver operating characteristic (ROC) curve analysis demonstrated an optimal cut-off value of 2.199 for NLR (AUC: 0.615, p = 0.068) and 716.447 for SII (AUC: 0.522, p = 0.073). However, neither marker demonstrated statistically significant diagnostic performance, limiting their clinical applicability (Figure 2, Table 3).

DISCUSSION

The discovery of leukocytes within tumor tissue has strengthened the evidence linking chronic inflammation to carcinogenesis. Numerous studies have shown that chronic inflammation in the tumor microenvironment influences tumor initiation, metastasis, prognosis, and treatment response [5, 6, 10, 12, 13]. Systemic inflammatory markers such as NLR, PLR, and SII have similarly been associated with tumor progression and prognosis in various malignancies. Neutrophils and platelets may promote angiogenesis, DNA damage, and tumor proliferation, whereas lymphocytes contribute to antitumor immunity by suppressing tumor growth and metastasis. Consequently, alterations in neutrophil, platelet, and lymphocyte counts have been recognized as independent prognostic indicators in many cancers [1, 2, 6, 12–17]. Lymphopenia reflects impaired cellular immunity and has

Table 3. Diagnostic performance and ROC analysis for predicting malignancy using NLR and SII

	Diagnostic scan					ROC curve		p
	Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	AUC	95% confidence interval	
NLR	**≥ 2.199**	57.69	69.9	32.6	86.7	0.615	0.481–0.749	**0.068**
SII	**≥ 716.447**	38.46	84.47	38.5	84.5	0.522	0.378–0.665	**0.073**

NLR – neutrophil-to-lymphocyte ratio; SII – systemic immune-inflammation index; AUC – area under the curve

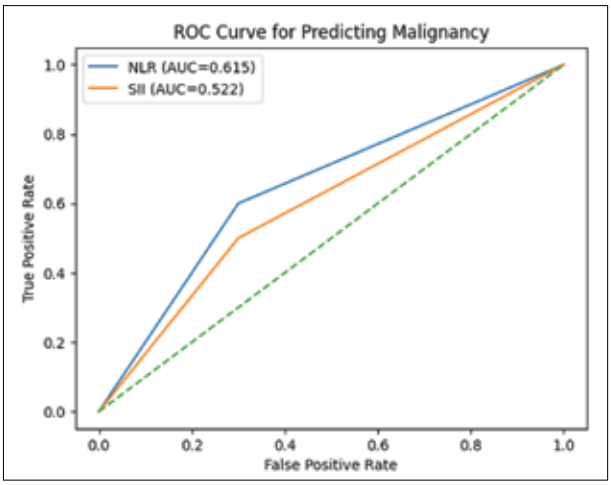

Figure 2. ROC curves demonstrating the diagnostic performance of NLR and SII in distinguishing benign and malignant parotid tumors

been associated with poorer prognosis and cancer-related immunosuppression, partly through elevated interleukin-6 (IL-6) and tumor necrosis factor receptor levels [1, 6, 18]. Reduced lymphocyte counts together with elevated neutrophil and platelet counts may lead to increased NLR, PLR, and SII values [1, 3, 18, 19]. A meta-analysis of 33 studies demonstrated that elevated SII values are associated with increased risks of all-cause, cardiovascular, and cancer-related mortality [20]. Similarly, elevated NLR has been identified as a prognostic marker in various head and neck malignancies [14, 21, 22]. In addition, high SII values have been associated with aggressive pathological features such as perineural invasion, lymphovascular invasion, and extranodal spread [3, 15]. The diagnostic value of inflammatory markers has also been investigated in submandibular and thyroid gland lesions. Bora [23] reported significantly higher preoperative NLR values in malignant submandibular gland tumors compared with benign lesions. Likewise, NLR and PLR have been proposed as supportive markers for differentiating benign from malignant thyroid nodules [5, 23, 24], and Atak et al. [24] demonstrated that elevated PLR values may have moderate diagnostic utility in thyroid malignancies. Parotid gland tumors account for most major salivary gland neoplasms and pose significant diagnostic challenges due to their marked histological heterogeneity and overlapping clinical presentations [10, 15]. Our finding that NLR was independently associated with malignancy risk is consistent with previous studies investigating inflammatory markers in salivary gland tumors [1, 2, 15]. Recent evidence, including the study by Ozcelik Erdem et al. [25], has further supported the potential clinical relevance of inflammatory biomarkers in the preoperative evaluation of salivary gland malignancies. This association may reflect a biological imbalance in which an intensified neutrophil-associated inflammatory response contributes to a tumor-promoting microenvironment, while concomitant lymphopenia reflects impaired host immune surveillance [1, 5, 7, 8]. Our findings are also consistent with previous reports demonstrating higher NLR levels in malignant salivary gland lesions compared with benign lesions [23].

Although SII demonstrated borderline statistical significance in our cohort ($p = 0.049$), this finding reflects the ongoing debate in the literature regarding the diagnostic value of composite inflammatory indices. Sahin et al. [3] reported significantly higher SII values in malignant parotid tumors, whereas Ikinciogullari et al. [26] did not observe a statistically significant difference in this parameter between the benign and malignant groups. In our ROC analysis, neither NLR nor SII demonstrated statistically significant diagnostic performance, suggesting that these markers should be interpreted cautiously and primarily as supportive rather than standalone diagnostic tools. The variability among studies may partly be explained by the marked histopathological heterogeneity of parotid gland tumors, differences in study design, and the relatively limited number of malignant cases in single-center cohorts, which may have reduced the statistical power of subgroup analyses.

Although PLR is frequently discussed as a negative prognostic factor in several malignancies, our findings suggest that its diagnostic contribution in parotid gland tumors may be more limited and should be interpreted as an adjunctive parameter rather than a primary predictor [16, 19]. The sensitivity and specificity of PLR may vary substantially depending on tumor subtype, tumor burden, and accompanying inflammatory conditions.

Preoperative assessment of parotid masses continues to rely mainly on imaging methods and FNAB; however, the diagnostic accuracy of FNAB may be limited in cystic, heterogeneous, or low-grade lesions [1, 6, 15]. Recent studies by Abbate et al. [27] and Committeri et al. [28] emphasized that inflammatory biomarkers may serve as useful supportive tools, particularly in indeterminate or suspicious cytological cases. In this context, inflammatory markers such as NLR, PLR, and SII may provide clinicians with easily accessible and cost-effective adjunctive information that can support preoperative risk stratification and surgical planning without disrupting routine clinical workflows. The biological interaction underlying these observations may also be associated with chronic inflammation-related cytokine activity, including IL-6 and TNF-α pathways,

which contribute to tumor progression and suppression of antitumor immunity [9, 10, 11].

This study has several limitations that should be considered when interpreting the findings. As a retrospective, single-center study, the generalizability of the results may be limited. In addition, some baseline characteristics differed between the benign and malignant groups, particularly age distribution, which may have affected the direct comparability of the groups. Another important limitation is the relatively small number of malignant cases compared with benign cases, which may have reduced the statistical power and robustness of the analyses. Moreover, the imbalance between the benign and malignant groups may have further limited the ability to draw definitive conclusions regarding differences between tumor subtypes. Although strict inclusion and exclusion criteria were used to minimize the influence of inflammatory comorbidities, these criteria may also have introduced selection bias and may not fully reflect the broader patient population encountered in daily clinical practice. Therefore, the results should be interpreted with caution. Future large-scale, prospective, multicenter studies with more balanced study groups are needed to further clarify the diagnostic value and clinical utility of systemic inflammatory markers in parotid gland tumors. In this context, the present study should be considered a pilot study.

CONCLUSION

NLR, PLR, and SII may provide preliminary and supportive information in distinguishing malignant from benign parotid tumors. These findings are exploratory and should not be used alone for diagnostic decision-making. Further large-scale, prospective, multicenter studies are needed to validate these results. This study should be considered a pilot study, and its findings should be interpreted with caution. Future research should prioritize the integration of systemic inflammatory markers with specific molecular profiles, including PD-L1 status, TP53 mutations, and DNA damage response pathways (e.g., ATM/CHK2), to enhance preoperative risk stratification and better define the immune-inflammatory crosstalk in parotid carcinogenesis.

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Conflict of interest: None declared.

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Значај системских инфламаторних маркера у разликовању бенигних од малигних тумора паротидних жлезда – пилот-студија

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САЖЕТАК

Увод/Циљ Циљ ове студије је процена дијагностичке вредности односа неутрофила и лимфоцита (*NLR*), односа тромбоцита и лимфоцита (*PLR*) и индекса системске имуноинфламације (*SII*) у разликовању бенигних од малигних тумора паротидне жлезде.

Методе Ретроспективно су процењени клинички подаци 129 болесника који су имали операцију паротидне жлезде између 2014. и 2024. године. Упоређени су демографски подаци, резултати преоперативне крвне слике и хистолошки резултати. Болесници су категорисани у групе бенигних и малигних тумора на основу хистопатолошке дијагнозе.

Резултати Није пронађена значајна разлика у расподели полова између група (p > 0,05). Болесници са малигним туморима били су значајно старији од оних са бенигним туморима ($p = 0,038$). Број лимфоцита и тромбоцита био је значајно већи у групи са бенигним туморима ($p = 0,008$ и $p = 0,029$, респективно). Насупрот томе, средње вредности *NLR* биле су значајно веће код болесника са малигним туморима ($p = 0,016$). Иако су вредности *PLR* и *SII* такође биле веће у групи са малигним туморима, разлике нису биле статистички значајне ($p > 0,05$).

Закључак *NLR* може послужити као помоћни и додатни маркер, а не као самостални дијагностички алат за разликовање бенигних и малигних тумора паротидне жлезде. Ову студију треба сматрати пилот-студијом и потребне су веће контролисане студије.

Кључне речи: паротидни тумори; паротидектомија; однос неутрофила и лимфоцита; однос тромбоцита и лимфоцита; индекс системске инфламације

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HISTORY OF MEDICINE / ИСТОРИЈА МЕДИЦИНЕ

Development of hematopoietic stem cell transplantation at the Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia

Dragana Vujić

University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia, Belgrade, Serbia;
Euromedik, Belgrade, Serbia

SUMMARY
The first allogeneic hematopoietic stem cell transplantation in children in Serbia was performed in the 1970s at the Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia. In December 1990, a haploidentical hematopoietic stem cell transplantation was performed on a nine-month-old infant suffering from X-linked severe combined immunodeficiency. Seven years later, a Bone Marrow Transplantation Department was established at the Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia. Thanks to the members of the transplantation team, with the help and support of the Ministry of Health of the Republic of Serbia and the Republic Fund of Health Insurance, as well as assistance from several centers in Italy and England, significant success was achieved in the development of transplantation medicine. Each year, the members of the transplantation team at the Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia perform 18–26 hematopoietic stem cell transplantations, both autologous and allogeneic (from an identical related donor, unrelated matched donor, related partially matched donor, related and unrelated cord blood).
Keywords: children; hematopoietic stem cell transplantation; Serbia

INTRODUCTION

Nearly seven decades ago, in 1957, Thomas et al. [1] performed the first hematopoietic stem cell transplantations (HSCT) in patients suffering from leukemia. Two years later, Mathe et al. [2] applied this form of treatment to six patients who had been irradiated in an accident at the Vinča Institute of Nuclear Sciences near Belgrade. Mathe et al. [2] became the most active group in this field during the following years, and in 1968 they reported the first results of the treatment of patients with leukemia. They were also the first to provide a clinical description and the basis for the pathology of graft-versus-host disease, and emphasized the importance of viral and fungal infections in patients after HSCT. The first HSCT in children were performed in 1968, on two boys suffering from primary immunodeficiency [one with severe combined immunodeficiency and the other with Wiskott–Aldrich syndrome] [1–7].

In the 1970s, Dr. Jovan Kezić, founder and first head of the Hematology and Oncology Department, and Dr. Mirko Mikuška, founder and first head of the Immunology Department, performed the first allogeneic HSCT at the Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia (DVCIHPMCS) in a child suffering from severe acquired aplastic anemia. Nearly two decades later, in December 1990, Dr. Mario Abinun and Dr. Dragana Vujić (born Makić), with the great help and support from Prof. Dr. Miomir Malešević and Prof. Dr. Dese Lilić from the Military Medical Academy in Belgrade, performed the first HSCT from a related partially matched donor (haploidentical HSCT) in a nine-month-old boy suffering from severe combined immunodeficiency. Monoclonal antibody "Campath-1M" (anti-CD52), necessary for bone marrow processing, which was used as the source of hematopoietic stem cells, were obtained as a donation from colleagues in London, Prof. Roland Levinsky and Dr. Gareth Morgan (Institute of Child Health, Great Ormond Street Hospital, Department of Paediatric Immunology, London, UK), thanks to the private contacts of Dr. Mario Abinun. The complicated process of bone marrow processing (removal of T lymphocytes – T-cell depletion) was performed by Prof. Dr. Desa Lilić with her team at the Institute for Experimental Medicine, the Military Medical Academy. This was the first haploidentical HSCT not only in Serbia and the former Yugoslavia, but in the region. Except for a mild chronic form of graft-versus-host disease on the skin, the patient did not have other post-transplant complications [8–12] (Figures 1 and 2).

Recognizing the importance of HSCT in the treatment of congenital and acquired diseases of the lymphohematopoietic system in children, the doctors of the Hematology and Oncology Department (Dr. Jovan Kezić, Dr. Sofija Aleksandrović-Boberić, Dr. Nada

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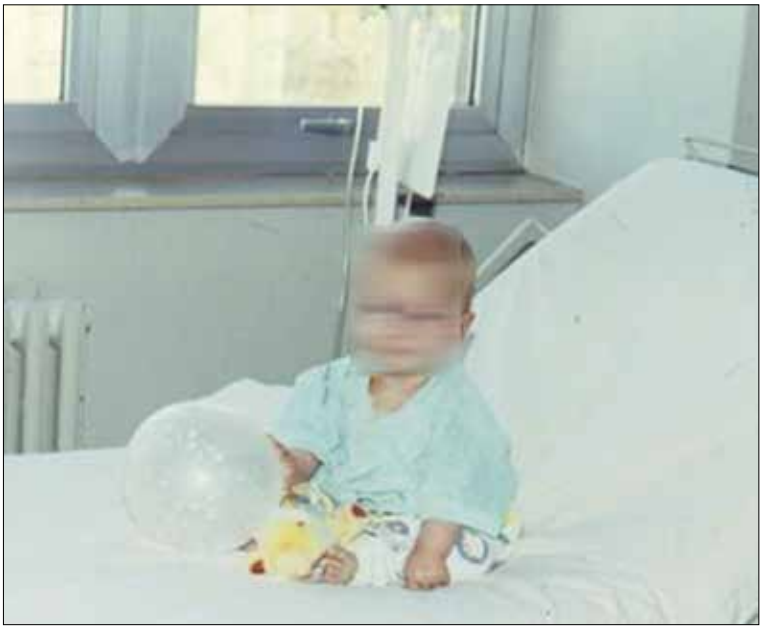


Figure 1. Photograph of M.A. in 1990 at the age of nine months (photograph obtained from Prof. Dr. Mario Abinun)

Figure 2. M.A. with family and Prof. Dr. Dragana Vujić, in 2024

Rašović-Gvozdenović, and Dr. Petar Ivanovski) and the doctors of the Immunology Department (Dr. Mirko Mikuška and Dr. Mario Abinun) of the DVCIHPMCS, supported by the director Dr. Božidar Vlajić, in 1986 sent a letter to the Republic Fund of Health Insurance requesting the formation of a Bone Marrow Transplant Unit. Virtually, from 1986, an effort to establish the Bone Marrow Transplantation Unit began. The first "sterile unit" was donated by Prof. Wilhelm Friedrich, the Ulm transplantation team, thanks to the private contacts of Dr. Mario Abinun. In October 1991, a letter was sent to the Republic Health and Health Insurance Fund of Serbia with a proposal to establish a Bone Marrow Transplant Unit for children at the DVCIHPMCS. A new letter to the Republican Fund of Health Insurance requesting the establishment of a Bone Marrow Transplant Unit was submitted on December 16, 1993. The following year, in March 1994, the director of the DVCIHPMCS, Prof. Dr. Miloš Banićević, and the head of the Hematology and Oncology Department, Prof. Dr. Gordana Bunjevački, have prepared the "Program for the Establishment and Operation of the Intensive Care Unit and Treatment Department in the Department of Hematology" and submitted it to the City Fund for Health Insurance. After receiving all necessary approvals and required funds, at the end of 1994, the construction of the future Bone Marrow Transplantation Unit began at the start of 1995, and opened and put into operation on April 18, 1997. On the day the Bone Marrow Transplantation Unit

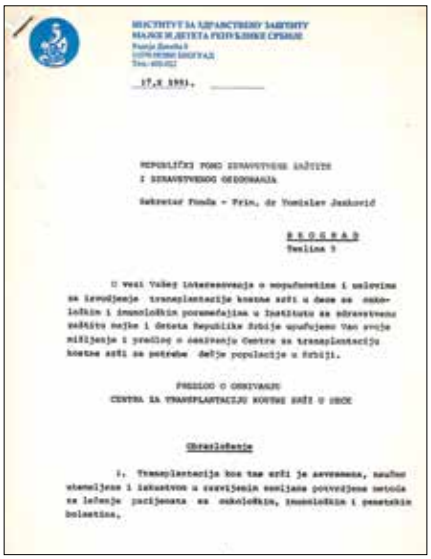


Figure 3. Letter to the Republic Health Insurance Fund dated October 17, 1991

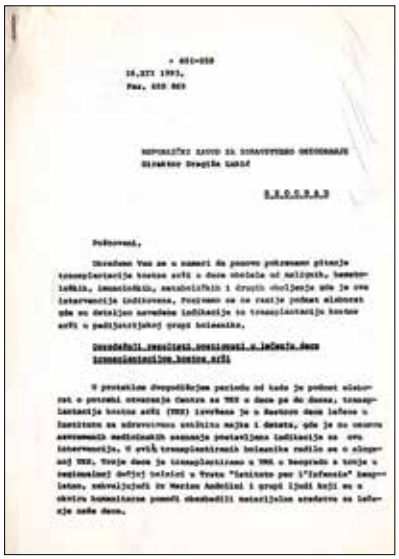


Figure 4. Letter to the Republican Health Insurance Institute on December 16, 1993

P R O G R A M

OSNIVANJA I RADA ODELJENJA ZA INTENZIVNU TERAPIJU I NEGU U SLUŽBI ZA HEMATOLOGIJU INSTITUTA ZA ZDRAVSTVENU ZAŠTITU MAJKE I DETETA SRBIJE

Obrađivač: Gradski zavod za zaštitu zdravlja - Beograd

Beograd, mart 1994.godine

Figure 5. Program for the establishment and operation of the Intensive Care and Therapy Department at the Hematology Department

Figure 6. Health workers and associates who on April 18, 1997, performed the first allogeneic bone marrow transplant in the newly opened sterile unit (from left to right stand Prof. Dr. Srđan Pašić, Prof. Dr. Dragana Vujić)

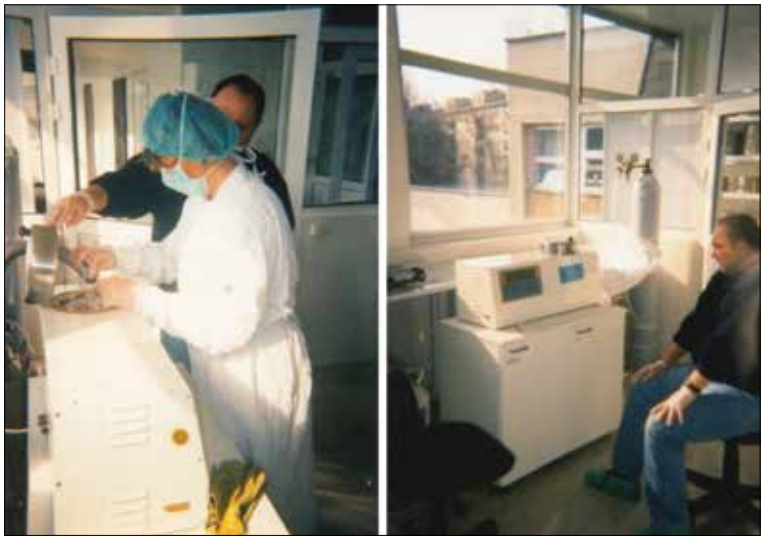


Figure 7. Danko Đurić MSc. and Prof. Dr. Dragana Vujić, 1997, freezing of hematopoietic stem cells

was opened, a HSCT was performed on a six-month-old infant suffering from severe combined immunodeficiency. The bone marrow donor was an older brother. Prof. Dr. Dragana Vujić and Prof. Dr. Srđan Pašić led the transplant team that successfully performed this transplantation. That same year, in August, the first autologous transplantation was performed in a girl who had a relapse of rhabdomyosarcoma. This was also the first autologous HSCT in a child in Serbia where control rate freezing of hematopoietic stem cells was used. The head of the transplantation team was Prof. Dr. Dragana Vujić. From the opening of the Bone Marrow Transplantation Unit until 2004, the transplantation team of the DVCIHPMCS performed 1–3 transplants per year. Thanks to the fact that in 2004 the Ministry of Health of the Republic of Serbia and the Republic Fund of Health Insurance recognized transplantation medicine as one of the priorities, the transplantation team became increasingly active and in 2005 performed eight HSCT. From 2005 to the present the transplantation team performs between 18 and 26 HSCT per year [8, 13] (Figures 3–6).

Educating the members of the future transplantation team began in 1993 at centers in Italy (Trieste, Perugia, Genoa, Monza, Brescia, and Pavia) and in England (Newcastle upon Tyne). We owe great gratitude to Dr. Marino Andolina (Burlo Garofolo Children's hospital, Trieste, Italy), Dr. Augusto Amici (University of Perugia, Clinic of Pediatrics, Perugia, Italy), Dr. Momčilo Janković (San Gerardo Hospital, Monza, Italy), Dr. Bruno De Bernardi (Giannina Gaslini Institute, Genoa, Italy), Dr. Luigi D Notarangelo (Azienda Ospedaliera Spedali Civili di Brescia, Brescia, Italy) and Dr. Marco Zecca (La Fondazione IRCCS Policlinico "San Matteo," Pavia, Italy), as well as Dr. Mario Abinun (North Children's Hospital, Newcastle upon Tyne, England). The funds for the education of the transplantation team members were provided by colleagues from centers in Italy and England, partly through the project "Creating Conditions for HSCT in Children in Serbia," which has been financed from the budget since 2008 through the Ministry of Health of the Republic of Serbia [13].

Prof. Dr. Dragana Vujić, Prof. Dr. Vujo Drndarević (University of Belgrade, Faculty of Electrical Engineering, Vinča Institute of Nuclear Sciences), Danko Đurić, MSc (Vinča Institute of Nuclear Sciences), Miroljub Aranđelović (Vinča Institute of Nuclear Sciences), as well as numerous associates from the Vinča Institute of Nuclear Sciences, in October 1994 started the implementation of a project for the development of a microprocessor for the programmed freezing of hematopoietic stem cells. The first testing of the microprocessor took place in 1995, when hematopoietic stem cells from laboratory animals were used, and a year later, in 1996, Dr. Dobrila Veljković, the head of the Transfusion Department at the DVCIHPMCS performed the first isolation of human hematopoietic stem cells from peripheral blood, and the obtained cells were used for testing the microprocessor. The donor of the hematopoietic stem cells from peripheral blood was Prof. Dr. Dragana Vujić. The obtained test results confirmed the reliability of the microprocessor, which was successfully used in the period from August 1997 to 2002 [14, 15] (Figure 7).

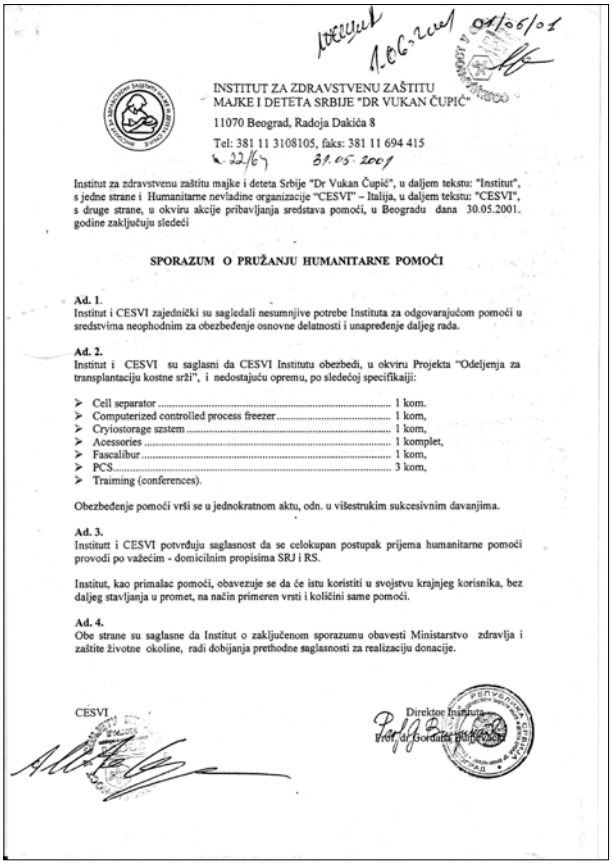
During 1996 and 1997, Prof. Dr. Dragana Vujić and the head of the Transfusion Department of the DVCIHPMCS, Dr. Sci. Med. Dobrila Veljković, prepared the "Standards for Bone Marrow Transplantation in Children", which were submitted to the Ministry of Health of the Republic of Serbia and the Republic Fund for Health Insurance. A year later, in December 1998, the Ministry of Health made a decision to establish the Republic Center for Bone Marrow

TRANSPLANTACIJA MATIČNIM ĆELIJAMA HEMATOPOEZE IZ KOSTNE SRŽI I PERIFERNE KRVI

SPECIFIKACIJA USLUGA, POTROŠNOG MATERIJALA I LEKOVA

predlog sačinile: Dr Dragana Makić, Mr Sc.
Dr Dobrila Veljković, Mr Sc.

Figure 8. Standards for bone marrow transplantation in children



INSTITUT ZA ZDRAVSTVENU ZAŠTITU
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Institut za zdravstvenu zaštitu majke i deteta Srbije "Dr Vukan Čupić", u daljem tekstu: "Institut", s jedne strane i Humanitarne nevladine organizacije "CESVI" – Italija, u daljem tekstu: "CESVI", s druge strane, u okviru akcije pribavljanja sredstava pomoći, u Beogradu dana 30.05.2001. godine zaključuju sledeći

SPORAZUM O PRUŽANJU HUMANITARNE POMOĆI

Ad. 1.
Institut i CESVI zajednički su sagledali nesumnjive potrebe Instituta za odgovarajućom pomoći u sredstvima neophodnim za obezbeđenje osnovne delatnosti i unapređenje daljeg rada.

Ad. 2.
Institut i CESVI su saglasni da CESVI Institutu obezbedi, u okviru Projekta "Odeljenja za transplantaciju kostne srži", i nedostajuću opremu, po sledećoj specifikaiji:

- Cell separator ..... 1 kom.
- Computerized controlled process freezer ..... 1 kom,
- Cryiostorage szstem ..... 1 kom,
- Acessories ..... 1 komplet,
- Fascalibur ..... 1 kom,
- PCS ..... 3 kom,
- Traiming (conferences).

Obezbeđenje pomoći vrši se u jednokratnom aktu, odn. u višestrukim sukcesivnim davanjima.

Ad. 3.
Institutt i CESVI potvrđuju saglasnost da se celokupan postupak prijema humanitarne pomoći provodi po važećim - domicilnim propisima SRJ i RS.

Institut, kao primalac pomoći, obavezuje se da će istu koristiti u svojstvu krajnjeg korisnika, bez daljeg stavljanja u promet, na način primeren vrsti i količini same pomoći.

Ad. 4.
Obe strane su saglasne da Institut o zaključenom sporazumu obavesti Ministarstvo zdravlja i zaštite životne okoline, radi dobijanja prethodne saglasnosti za realizaciju donacije.

CESVI

Direktor Instituta
Prof. dr Gordana [illegible]

Figure 9. Contract with Gruppo Cesvi L´Espresso

Transplantation in Children at the DVCIHPMCS. In the same year, we became members of the European Group for Blood and Marrow Transplantation [8, 13] (Figure 8).

The Laboratory for Cryobiology at the Bone Marrow Transplantation Unit was established in 2001 thanks to a donation from the government of the Republic of Italy and the Italian non-governmental organization "Nuova frontier alisei." A year later, the non-governmental organization "Gruppo Cesvi L´Espresso" from Italy provided the funds necessary for the acquisition of equipment for the Transfusion Department, the Flow Cytometry Laboratory, and the Cryobiology Laboratory. These two significant donations enabled the further development of HSCT at the DVCIHPMCS [8, 13] (Figure 9).

The project proposal "Creating Conditions for HSCT in Children in Serbia" was prepared in 2007 and submitted to the Ministry of Health of the Republic of Serbia. The project was approved and its implementation began in 2008. The project was prepared by Prof. Dr. Dragana Vujić in collaboration with healthcare workers and associates from the Bone Marrow Transplantation Unit and the Cryobiology Laboratory of the DVCIHPMCS, and from 2008 to 2025 she was the coordinator of the project. The implementation of the project enabled the procurement of the necessary equipment for the successful implementation of the HSCT program at the DVCIHPMCS the preparation of the conceptual, technological, and main project for a new bone marrow transplantation unit and public/family cord blood bank, the construction and equipping of the public/family cord blood bank, and the procurement of necessary consumable materials for hematopoietic stem cells processing, as well as the preparation of guides for patients, parents, hematopoietic stem cell donors, and healthcare workers and collaborators [8, 13] (Figure 10).

After obtaining the necessary permits, the construction of a public/family umbilical cord blood bank began in April 2013. While the necessary equipment for the future bank was being acquired and team members were undergoing training, the construction of the public/family cord blood bank proceeded in phases. Architectural and construction work was completed in 2020, when, due to changes in legal regulations, the struggle for the legalization of the public/family cord blood bank building began. The public/family cord blood bank building was legalized in September 2023, and in September 2025, with the relocation of the cryobiology laboratory, the public/family cord blood bank building was put into operation [16, 17, 18] (Figure 11).

The first sample of related cord blood was collected, processed, and cryopreserved in 2002 in the newly established cryobiology laboratory. Seven years later, in November 2009, approval was obtained from the Commission for New Technologies of the Ministry of Health of the Republic of Serbia for the establishment of a family cord blood bank, and by 2025, 117 samples had been processed and stored. The procedure for obtaining

Figure 10. Guides created by the transplantation team of Dr. Vukan Čupić Mother and Child Health Care Institute of Serbia (taken from: https://www.zdravlje.gov.rs/tekst/429156/vodici-dobre-klinicke-prakse-iz-oblasti-transplantacije.php)

the necessary approvals to operate a public cord blood bank is currently underway [16, 17, 18].

The transplantation team of the DVCIHPMCS provided assistance and support to the transplantation team of the Clinic for Hematology of the University Clinical Center of Serbia from 2008 to 2020 by collecting, processing, and storing patients' hematopoietic stem cells for autologous transplantation [13].

Significant progress has been achieved thanks to the collaboration with the Institute for Medical Research, where the viability of collected and cryopreserved hematopoietic stem cells was assessed, as well as monitoring of Toxoplasma reactivation in the post-transplant period. Prof. Dr. Tanja Jovanović and Prof. Dr. Valentina Arsić Arsenijević from the University of Belgrade, Faculty of Medicine, Institute of Microbiology and Immunology, along with their teams, enabled the monitoring of the virological and mycological status of patients in the peri-transplant period. Thanks to the establishment of the National Registry of Voluntary Hematopoietic Stem Cell Donors at the Institute for Blood Transfusion of Serbia and the special involvement of Dr. Zorana Andrić, PhD, and Dr. Gloria Blagojević, it became possible to find unrelated voluntary hematopoietic stem cell donors not only in the Serbian registry but also in the worldwide registry [13, 18–21] (Figure 12).

During 2009–2010, the Zvončica Parents' House was built as part of the DVCIHPMCS, intended for the accommodation of children after leaving the Bone Marrow Transplantation Unit, as well as for children from the Hematology and Oncology Department, to ensure adequate monitoring. This significant project was realized through the substantial involvement of the then Director of the Republic Fund of Health Insurance, Mrs. Svetlana Vukajlović [13] (Figure 13).

Significant events for HSCT in children in Serbia are: the first bone marrow transplantation at the DVCIHPMCS, the first haploidentical transplantation with T-cell

Figure 11. Construction of a public/family umbilical cord blood bank; in the photograph, from left to right: Prof. Dr. Dragana Vujić and Emilija Lazić (molecular biologist)

Figure 12. Part of the team that participated in processing the first unrelated bone marrow sample; the donor is from the National Registry of Voluntary Hematopoietic Stem Cell Donors of Serbia, November 2009 (from left to right: Dr. Olivera Šerbić, Dr. Marino Andolina, Prof. Dr. Dragana Vujić, Dr. Dobrila Veljković, Dr. Zorana Andrić)

depletion in December 1990, the opening of the Bone Marrow Transplantation Unit and the first transplantation in the newly opened Unit in April 1997, the first autologous HSCT in August 1997, the first haploidentical transplantation with *ex vivo* treatment of stem cells using vincristine and methylprednisolone in March 2006, the first transplantation from an unrelated matched donor from the Serbian registry in November 2009, approval by the Commission for New Technologies of the Ministry of Health of the Republic of Serbia for the formation of a family cord blood bank in November 2009, processing of haploidentical graft using the alpha/beta TCR/CD19 depletion method in November 2012, the first CD34+ selection in February 2013, the first transplantation from an unrelated donor from the global registry in April 2013, the first transplant with identical related cord blood in May 2017, the first transplant from unrelated cord blood from the world registry in December 2017, administration of



Figure 13. Construction of the Zvončica Parents' House

donor lymphocyte infusion in February 2022, use of extracorporeal photopheresis in 2023 [10, 13, 14, 16, 22–25].

Since the establishment of the sterile unit, members of the transplantation team have introduced new forms of transplantation, immunomodulation, methods for processing hematopoietic stem cells, diagnostic procedures for early recognition, and reduction of the incidence of acute and chronic transplantation complications. Better survival, improved quality of life after HSCT were achieved, and projects and programs were developed aimed at creating a center capable of gaining international accreditation. This significant achievement could not be reached without close cooperation of all members of the transplantation team of the DVCIHPMCS, the Institute of Microbiology of the Faculty of Medicine of the University of Belgrade, the Laboratory for Human Leukocyte Antigen Typing, and the National Register of Voluntary Hematopoietic Stem Cell Donors of the Institute for Blood Transfusion of Serbia, the Institute for Medical Research of the University of Belgrade, as well as the assistance and support of the Ministry of Health and the Republic Fund of Health Insurance, colleagues from foreign centers who helped in the education of members of the transplantation team and in providing the necessary equipment, and people of good will who provided significant donations.

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I owe special thanks to Dr. Mario Abinun for the support and help he provided me during the preparation of this work. Without the help of the members of the transplantation team from the DVCIHPMCS, members of the team outside the Institute, as well as the support of the Ministry of Health of the Republic of Serbia and the Republic Fund of Health Insurance, colleagues from foreign centers, and people of good will, this great task would have been only in its beginning.

Ethics: The author declares that the article was written according to the ethical standards of the Serbian Archives of Medicine as well as the ethical standards of its institution.

Conflict of interest: None declared.

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Развој трансплантације матичних ћелија хематопоезе у Институту за здравствену заштиту мајке и детета Србије „Др Вукан Чупић“

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САЖЕТАК

Прва алогена трансплантација матичних ћелија хематопоезе код деце у Србији урађена је седамдесетих година 20. века у Институту за здравствену заштиту мајке и детета Србије „Др Вукан Чупић“. У децембру 1990. године урађена је хаплоидентична трансплантација матичних ћелија хематопоезе код деветомесечног одојчета које је боловало од *X*-везане тешке комбиноване имунодефицијенције. Седам година касније отворено је Одељење за трансплантацију коштане сржи у Институту за здравствену заштиту мајке и детета Србије „Др Вукан Чупић“. Захваљујући члановима трансплантационог тима, уз помоћ и подршку Министарства здравља Републике Србије и Републичког фонда за здравствено осигурање, као и помоћ неколико центара из Италије и Енглеске, постигнут је значајан успех у развоју трансплантационе медицине. Чланови трансплантационог тима Института за здравствену заштиту мајке и детета Србије „Др Вукан Чупић“ годишње изведу 18–26 трансплантација матичних ћелија хематопоезе, како аутологних, тако и алогених (од идентичног сродног даваоца, несродног подударног даваоца, сродног делимично подударног даваоца, сродне и несродне крви пупчаника).

Кључне речи: деца; трансплантација матичних ћелија хематопоезе; Србија

Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ (СА) сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво ће одложити или одбити његово публиковање. Радови објављени у СА се не хонорарашу. За чланке који ће се објавити у СА, самом понудом рада Српском архиву сви аутори рада преносе своја ауторска права на издавача часописа – Српско лекарско друштво.

ОПШТА УПУТСТВА. СА објављује радове који до сада нису нигде објављени, у целости или делом, нити прихваћени за објављивање. СА објављује радове на енглеском и српском језику. Због боље доступности и веће цитираности препоручује се ауторима да радове свих облика предају на енглеском језику. У СА се објављују следеће категорије радова: уводници, оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови, актуелне теме, радови за праксу, радови из историје медицине и језика медицине, медицинске етике, регулаторних стандарда у медицини, извештаји са конгреса и научних скупова, лични ставови, коментари по позиви, писма уреднику, прикази књига, стручне вести, *In memoriam* и други прилози. Оригинални радови, претходна и кратка саопштења, прикази болесника и случајева, видео-чланци, слике из клиничке медицине, прегледни радови и актуелне теме, публикују се искључиво на енглеском језику, а остале врсте радова се могу публиковати и на српском језику само по одлуци Уредништва. Радови се увек достављају са сажетком на енглеском и српском језику (у склопу самог рукописа). Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 *pt*). Све четири маргине подесити на 25 *mm*, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 *mm*, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лењиру и *Toolbars*. За прелазак на нову страну документа не користити низ „ентера“, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користити кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ^{99}Tc, *IL*-6, O_2, *CD*8). Уколико се нешто уобичајено пише курзивом (*italic*), тако се и наводи, нпр. гени (*BRCA1*).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања, да ли је рад и како публикован (нпр. исти или другачији наслов или сажетак).

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања утицаја једног или више средстава или мера на исход здравља. Регистарски број истраживања се наводи у последњем реду сажетка.

ЕТИЧКА САГЛАСНОСТ. Рукописи о истраживањима на људима треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншком декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME; http://www.wame.org*) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало би да буду наведени у Захвалници с описом њиховог доприноса раду, наравно, уз писани пристанак.

ПЛАГИЈАРИЗАМ. Од 1. јануара 2019. године сви рукописи подвргавају се провери на плагијаризам/аутоплагијаризам преко *SCIndeks Assistant – Cross Check* (*iThenticate*). Радови код којих се докаже плагијаризам/ аутоплагијаризам биће одбијени, а аутори санкционисани.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; предлог кратког наслова рада, пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установа у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

САЖЕТАК. Уз оригинални рад, претходно и кратко саопштење, преглед литературе, приказ случаја (болесника), рад из историје медицине, актуелну тему, рад за рубрику језик медицине и рад за праксу, на другој по реду страници документа треба приложити сажетак рада обима 100–250 речи. За оригиналне радове, претходно и кратко саопштење сажетак треба да има следећу структуру: Увод/Циљ рада, Методе рада, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. Закључак не сме бити уопштен, већ мора бити директно повезан са резултатима рада. За приказе болесника сажетак треба да има следеће делове: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Сажетка навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH (https://www.nlm.nih.gov/mesh/meshhome.html)*.

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установа у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити сажетак (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан сажетак на енглеском језику. Превод појмова из стране литературе треба да буде у духу српског језика. Све стране речи или синтагме за које постоји одговарајуће име у нашем језику заменити тим називом. Уколико је рад у целости на српском језику, потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад и претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навести као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе и актуелну тему чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. 12,5 ± 3,8). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса (*°C*), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада који чине – насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, рад из историје медицине и преглед литературе до 5000 речи, а за претходно и кратко саопштење, приказ болесника, актуелну тему, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3000 речи; радови за остале рубрике могу имати највише 1500 речи.

Видео-радови могу трајати 5–7 минута и бити у формату *avi, mp4* (*flv*). У првом кадру филма мора се навести: у

наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле. Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

Слике су сви облици графичких прилога и као „слике" у СА се објављују фотографије, цртежи, схеме и графикони. Слике се означавају арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватати за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини. Уколико је рад неопходно илустровати са више слика, у раду ће их бити објављено неколико, а остале ће бити у е-верзији чланка као *PowerPoint* презентација (свака слика мора бити нумерисана и имати легенду).

Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видео-приказа у е-издању и објављена у штампаном издању. Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Слике се у свесци могу штампати у боји, али додатне трошкове штампе сносе аутори.

Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикона. У штампаној верзији чланка вероватније је да графикон неће бити штампан у боји, те је боље избегавати коришћење боја у графиконима, или их користити различитог интензитета. Уколико је рукопис на српском језику, приложити називе графикона и легенду на оба језика.

Цртежи и схеме се достављају у *jpg* или *tiff* формату. Схеме се могу цртати и у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме. Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести *DOI* број чланка (јединствену ниску карактера која му је додељена) и *PMID* број уколико је чланак индексиран у бази *PubMed/MEDLINE*.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50, и у метаанализи, где их је дозвољено до 100. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публикације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не би требало да буде старија од пет година. Није дозвољено цитирање апстраката. Уколико је битно коментарисати резултате који су публиковани само у виду апстракта, неопходно је то навести у самом тексту рада. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (*http://www.icmje.org*), чији формат користе *U.S. National Library of Medicine* и базе научних публикација. Примери навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници *https://www.nlm.*

nih.gov/bsd/uniform_requirements.html. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (*SUBMISSION LETTER*). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (*http://www.srpskiarhiv.rs/en/submission-letter/SubmissionLetterForm2023.pdf*).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА И НАКНАДЕ ЗА ОБРАДУ И ОБЈАВЉИВАЊЕ ЧЛАНКА. Да би рад био разматран за објављивање у часопису *Српски архив за целокупно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 9 Статута Друштва) у години у којој рад предају на разматрање.

Следеће накнаде су обавезне како би рад био прегледан, обрађен и потенцијално објављен у *Српском архиву за целокупно лекарство*:

- накнада за преглед сваког примљеног рада домаћих аутора: 6.000 динара по раду;
- накнада за прихваћен рад, односно накнада за објављивање рада домаћих аутора: 12.000 динара по раду;
- накнада за преглед сваког примљеног рада страних аутора: 75 евра (или 9000 динара) по раду;
- накнада за прихваћен рад, односно накнада за објављивање рада страних аутора: 150 евра (или 18000 динара) по раду.

Накнаде се плаћају пре прегледања, односно пре објављивања рада. Радови за које нису плаћене накнаде неће бити прегледани, односно објављени.

Треба напоменути да уплата накнаде за преглед рада није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокупно лекарство*.

Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и накнаду за преглед чланка, као доказ о уплатама. Часопис прихвата донације од спонзора који сносе део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за преглед чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

СЛАЊЕ РУКОПИСА. Онлајн систем за подношење радова водиће вас кроз поступак уноса података о чланку и отпремања ваших датотека. Рукопис рада и сви прилози уз рад достављају се искључиво електронски преко система за пријављивање на интернет-страници часописа: *http://www.srpskiarhiv.rs*

НАПОМЕНА. Рад који не испуњава услове овог упутства не може бити упућен на рецензију и биће враћен ауторима да га допуне и исправе. Придржавањем упутства за припрему рада знатно ће се скратити време целокупног процеса до објављивања рада у часопису, што ће позитивно утицати на квалитет чланака и редовност излажења часописа.

За све додатне информације, молимо да се обратите на доле наведене адресе и бројеве телефона.

АДРЕСА:
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The papers are always submitted with Summary in both English and Serbian, included in the manuscript file. The text of the manuscript should be typed in *MS Word* using the *Times New Roman* typeface, and font size 12 pt. The text should be prepared with margins set to 25 mm and onto A4 paper size, with double line spacing, aligned left and the initial lines of all paragraphs indented 10 mm, without hyphenation. Tabs and successive blank spaces are not to be used for text alignment; instead, ruler alignment control tool and *Toolbars* are suggested. In order to start a new page within the document, *Page Break* option should be used instead of consecutive enters. Only one space follows after any punctuation mark. If special signs (symbols) are used in the text, use the *Symbol* font. References cited in the text are numbered with Arabic numerals within parenthesis (for example: [1, 2]), in order of appearance in the text. Pages are numbered consecutively in the right bottom corner, beginning from the title page.

When writing text in English, linguistic standard American English should be observed. Write short and clear sentences. Generic names should be exclusively used for the names of drugs. Devices (apparatuses, instruments) are termed by trade names, while their name and place of production should be indicated in the brackets. If a letter-number combination is used, the number should be precisely designated in superscript or subscript (i.e., ^{99}Tc, IL-6, O_2, CD8). If something is commonly written in italics, such as genes (e.g. *BRCA1*), it should be written in this manner in the paper as well.

If a paper is a part of a master's or doctoral thesis, or a research project, that should be designated in a separate note at the end of the text. Also, if the article was previously presented at any scientific meeting, the name, venue and time of the meeting should be stated, as well as the manner in which the paper had been published (e.g. changed title or abstract).

CLINICAL TRIALS. Clinical trial is defined as any research related to one or more health related interventions in order to evaluate the effects on health outcomes. The trial registration number should be included as the last line of the Summary.

ETHICAL APPROVAL. Manuscripts with human medical research should contain a statement that the subjects' written consent was obtained, according to the Declaration of Helsinki, the study has been approved by competent ethics committee, and conforms to the legal standards. Experimental studies with human material and animal studies should contain statement of the institutional ethics committee and meet legal standards.

CONFLICT OF INTEREST STATEMENT. The manuscript must be accompanied by a disclosure statement from all authors (contained within the Submission Letter) declaring any potential interest or stating that the authors have no conflict of interest. For additional information on different types of conflict of interest, please see World Association of Medical Editors (WAME, *www.wame.org*) policy statement on conflict of interest.

AUTHORSHIP. All individuals listed as authors should be qualified for authorship. Every author should have participated sufficiently in writing the article in order to take responsibility for the whole article and results presented in the text. Authorship is based only on: crucial contribution to the article conception, obtaining of results or analysis and interpretation of results; design of manuscript or its critical review of significant intellectual value; final revision of the manuscript being prepared for publication.

The authors should enclose the description of contribution to the article of every co-author individually (within the Submission Letter). Funding, collection of data or general supervision of the research group alone cannot justify authorship. All other individuals having contributed to the preparation of the article should be mentioned in the *Acknowledgment* section, with description of their contribution to the paper, with their written consent.

PLAGIARISM. Since January 1, 2019 all manuscripts have been submitted via SCIndeks Assistant to Cross Check (software iThenticate) for plagiarism and auto-plagiarism control. The manuscripts with approved plagiarism/auto-plagiarism will be rejected and authors will not be welcome to publish in Serbian Achieves of Medicine.

TITLE PAGE. The first page of the manuscript (cover sheet) should include the following: title of the paper without any abbreviations; suggested running title; each author's full names and family names (no titles), indexed by numbers; official name, place and country of the institution in which authors work (in order corresponding to the indexed numbers of the authors); at the bottom of the page: name and family name, address, phone and fax number, and e-mail address of a corresponding author.

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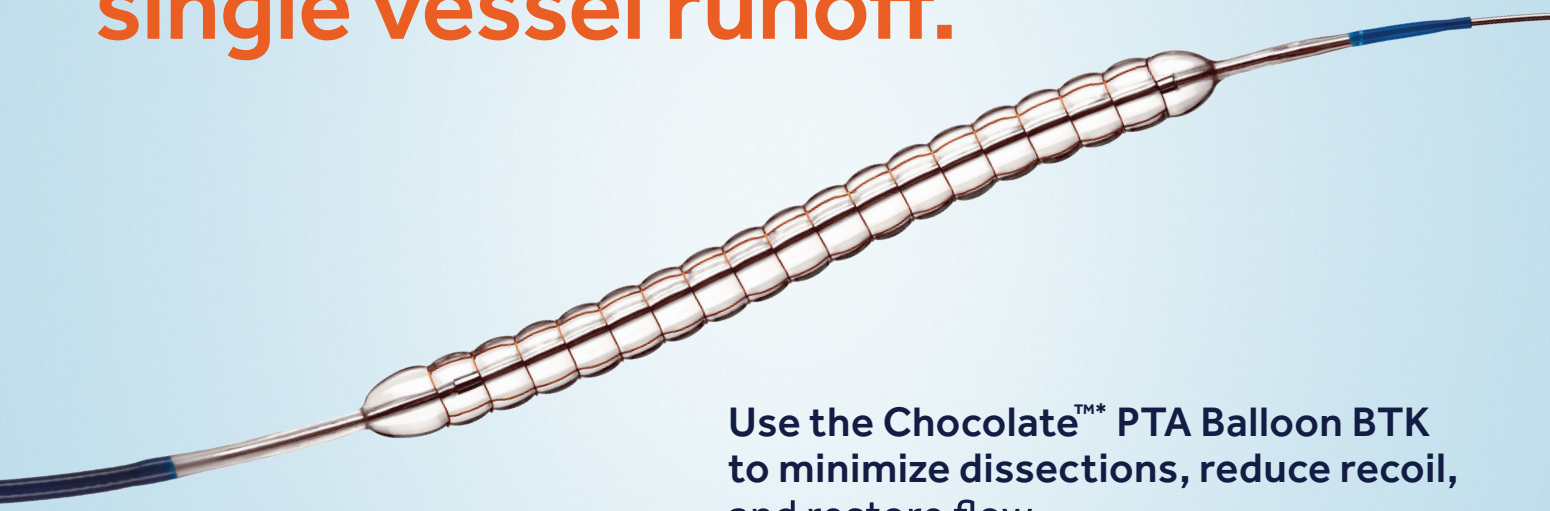

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