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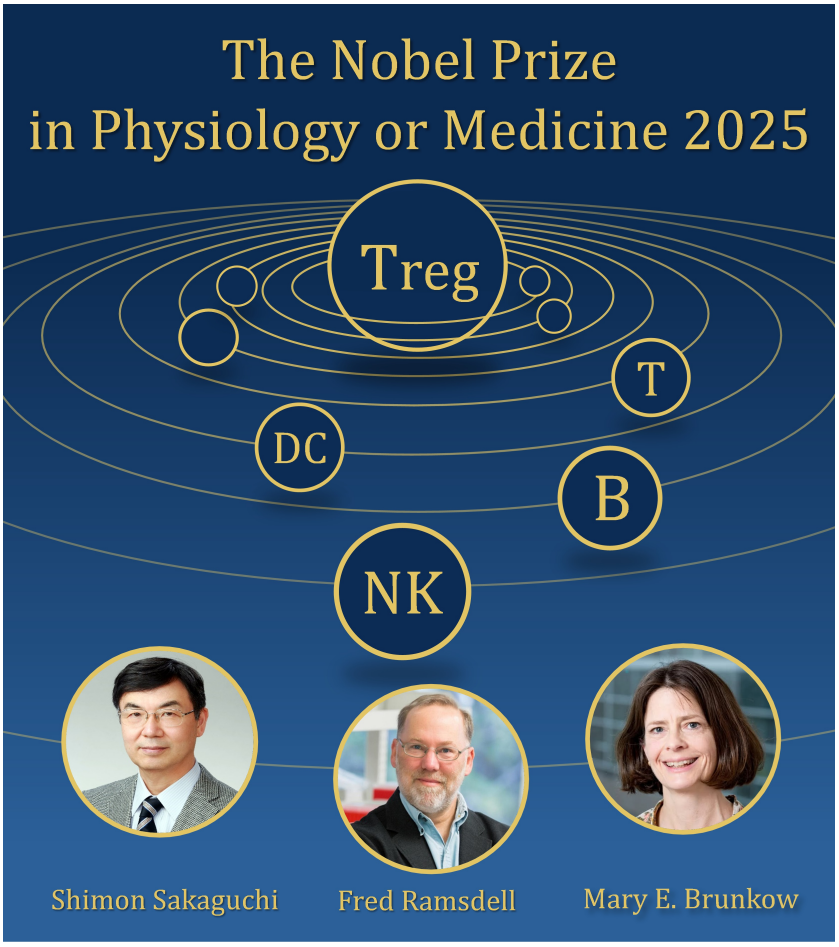

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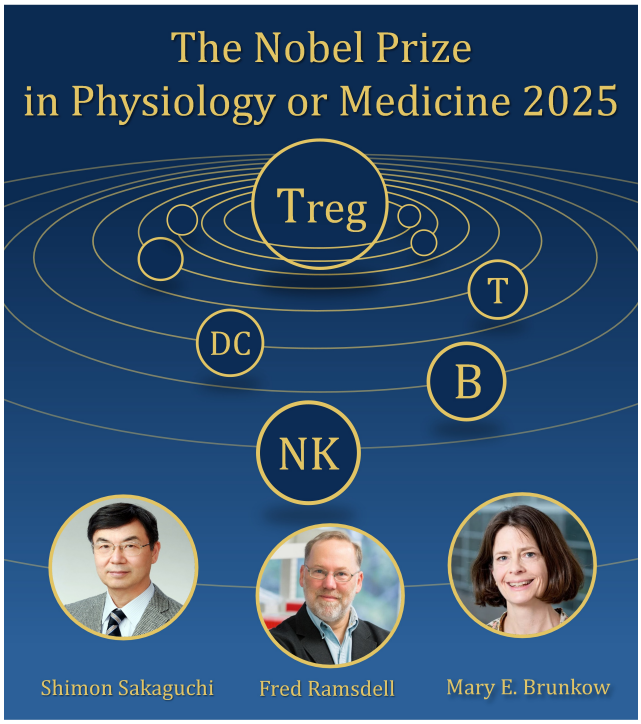

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The immune system, a masterpiece of evolution, is an astonishingly complex system of precisely coordinated regulatory mechanisms. Every day it protects us from infection by killing pathogenic microorganisms while simultaneously, in most cases, refraining from harmful action against its own cells. How does the immune system distinguish between foreign and self? This year's Nobel Prize laureates in Physiology or Medicine are Shimon Sakaguchi (1951, Japan), Fred Ramsdell (1960, USA) and Mary E. Brunkow (1961, USA). They defined $CD4^+CD25^+FOXP3^+$ regulatory T lymphocytes (Treg) and demonstrated their importance in maintaining self-tolerance. The discovery of Treg cells laid the foundation for understanding peripheral immune tolerance. Furthermore, this discovery enabled the initiation of new areas of research whose results could lead to more effective treatment of autoimmune and malignant diseases and the prevention of serious complications after tissue and organ transplantation.

Imunski sistem, remek delo evolucije, je zadivljujuće složen sistem precizno usklađenih regulatornih mehanizama. Svakoga dana nas štiti od infekcije, ubijajući patogene mikroorganizme, dok istovremeno, u većini slučajeva, ne ispoljava štetno delovanje prema sopstvenim ćelijama. Kako imunski sistem razlikuje strano od sopstvenog? Ovogodišnji dobitnici Nobelove nagrade za fiziologiju ili medicinu su Šimon Sakaguči (1951, Japan), Fred Ramzdel (1960, SAD) i Meri E. Brunkov (1961, SAD). Oni su definisali $CD4^+CD25^+FOXP3^+$ regulatorne T limfocite (Treg) i pokazali njihov značaj u održavanju tolerancije prema sopstvenom. Otkrićem Treg ćelija postavljeni su temelji za razumevanje periferne imunske tolerancije. Takođe, ovo otkriće omogućilo je pokretanje novih oblasti istraživanja čiji bi rezultati mogli da dovedu do efikasnijeg lečenja autoimunskih i malignih bolesti i sprečavanja ozbiljnih komplikacija nakon transplantacije tkiva i organa.

M E T A - A N A L Y S I S

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Evaluating the regenerative efficacy of titanium-prepared platelet-rich fibrin in the treatment of gingival recession: a systematic review and meta-analysis

Procena regenerativne efikasnosti titanijumom-pripremljenog fibrina obogaćenog trombocitima u lečenju gingivalne recesije: sistematski pregled i meta-analiza

Shiva Shankar Gummaluri*, Kaarthikeyan Gurumoorthy†, Trinath Kishore Damera*, Sai Karthikeyan SS*, Sandhya Pavan Kumar*, Naveen Vital Kumar Gidijala*

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Abstract

Background/Aim. Titanium-prepared platelet-rich fibrin (PRF) – T-PRF was considered a new platelet concentrate that is now frequently used in dentistry. The aim of this study was to examine T-PRF's regenerative effectiveness in treating gingival recession (GR). **Methods.** The present study is a systematic review and meta-analysis. A comprehensive search was performed in PubMed, Scopus, Embase, Web of Science, Google Scholar, and Cochrane databases. Medical Subject Headings terms like 'platelet-rich fibrin', 'platelets', 'gingival recession', 'titanium', and 'root coverage' were used to identify the final included studies. Review Manager software was used to perform the statistical analysis. The value of $p \leq 0.05$ was considered statistically significant. **Results.** A total of six studies were included in the systematic review, three of which qualified for meta-analysis. The systematic review suggested that T-PRF is a superior biomaterial in the treatment of GR and showed comparable results to those of the gold standard connective tissue graft (CTG). However, in the meta-analysis at six-month follow-up, for mean root coverage width, the combined effect size across three studies with 272 participants was a standardized mean difference of 0.07 (-0.17, 0.31), indicating no significant difference between the interventions. For mean root coverage depth, the combined effect size was 0.50 (-0.71, 1.70), also showing a non-significant trend favoring one intervention over the other. **Conclusion.** Within the limitations, the present systematic review suggests clinically improved outcomes with T-PRF. In contrast, the meta-analysis did not show any significant advantage of T-PRF over CTG or PRF.

Key words:
database; gingival recession; meta-analysis; platelet-rich plasma.

Apstrakt

Uvod/Cilj. Titanijumom-pripremljen fibrin obogaćen trombocitima [*titanium-prepared platelet-rich fibrin* (PRF) – T-PRF] smatran je novim koncentratom trombocita koji se danas često koristi u stomatologiji. Cilj rada bio je da se ispita regenerativna efikasnost T-PRF u lečenju gingivalne recesije (GR). **Metode.** Ovim sistematskim pregledom i meta-analizom izvršena je sveobuhvatna pretraga u bazama podataka *PubMed*, *Scopus*, *Embase*, *Web of Science*, *Google Scholar* i *Cochrane*. Predmetne odrednice iz medicine (*Medical Subject Headings*) kao što su '*platelet-rich fibrin*', '*platelets*', '*gingival recession*', '*titanium*' i '*root coverage*' su korišćene radi utvrđivanja konačnog skupa radova uključenih u studiju. Za statističku analizu korišćen je softver *Review Manager*. Vrednost $p \leq 0,05$ smatrana je statistički značajnom. **Rezultati.** U sistematski pregled ukupno je uključeno šest studija, od kojih su tri ispunjavale kriterijume za meta-analizu. Sistematski pregled ukazao je na to da je T-PRF superioran biomaterijal u lečenju GR i pokazao rezultate koji su bili uporedivi sa zlatnim standardom – transplantatom vezivnog tkiva (TVT). Međutim, u meta-analizi sa praćenjem od šest meseci, za srednju širinu pokrivenosti korena, kombinovana veličina efekta u tri studije sa 272 učesnika iznosila je standardizovanu srednju razliku od 0,07 (-0,17, 0,31), što ukazuje na to da nema značajne razlike između intervencija.

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Za srednju dubinu pokrivenosti korena, kombinovana veličina efekta iznosila je 0,50 (-0,71, 1,70), što takođe pokazuje neznačajan trend u korist jedne intervencije u odnosu na drugu. **Zaključak.** Uzimajući u obzir ograničenja, ovaj sistematski pregled ukazuje na klinički poboljšane ishode primenom T-PRF. S druge strane, meta-analiza nije pokazala bilo kakvu značajnu prednost T-PRF u odnosu na TVT ili PRF.

Ključne reči:
baze podataka; gingiva, povlačenje; meta-analiza; plazma bogata trombocitima.

Introduction

Gingival recession (GR) can be described as an apical shift of the gingival margin in relation to the cement-enamel junction, leading to exposure of the root surface [1, 2]. The management of this condition remains a challenge owing to its multifactorial aetiology. Poor oral hygiene, improper toothbrushing techniques, thin gingival phenotype, and buccal fenestrations are the major etiological factors contributing to the high prevalence of this condition [3]. When left untreated, GR leads to various complications like dentinal hypersensitivity, aesthetic compromise (such as long teeth), cervical abrasions, root caries, bone loss, and eventually loss of teeth [4, 5]. Early intervention not only halts the progression of the disease/condition but also provides excellent regenerative results. Almost 100% root coverage (RC) can be achieved in Miller's class I and II conditions. It also provides the patient with emotional support and confidence in extreme conditions where GR is observed in the front teeth, which affects the aesthetic appearance of patients. Hence, early identification and treatment of this condition is crucial for the success of the therapy [6].

The success of the treatment lies in identifying and understanding the underlying aetiology of the GR condition. Once identified, the etiological factor has to be addressed as necessary. The next step will be to augment the lost tissue [7]. There are various treatment modalities for augmenting GR, which are commonly known as RC procedures. Coronally advanced flap (CAF), semilunar CAF, lateral pedicle flap, guided tissue regeneration techniques involving various biomaterials, free gingival graft, free connective tissue, periosteal pedicle graft, and subepithelial connective tissue graft (CTG) – SCTG have been used with substantial success in terms of recession depth (RD), recession width (RW), keratinized tissue width (KTW), and mean RC (MRC) percentage during the follow-up periods [8]. The application of the CAF alone for RC had presented with limited results. Later, when CAF was used along with SCTG, the results were promising and long-lasting, with greater predictability for RC [9, 10]. A recent systematic review (SR) and meta-analysis (MA) by Carrera et al. [11] stated that the tunneling technique (TT) incorporated with SCTG had greater predictability in clinical and aesthetic results when compared to leukocyte platelet-rich fibrin (PRF) – L-PRF.

Although SCTG is considered the gold standard grafting technique for the treatment of GR, it also presents serious challenges, including the need for a second surgical site, limited graft availability, and reduced patient acceptance [12]. To address these challenges, various materials such as collagen membranes, amnion-chorion membranes [13], and acellular dermal matrix allografts [14] have been combined with CAF to obtain maximum RC with minimal intervention. While these materials have demonstrated efficacy in the treatment of GR, as seen in various studies, they have their own drawbacks, which mainly refer to the high cost of the materials. At this juncture, the introduction of platelet concentrates (PCs) attracted the researchers, since it is an autologous biomaterial that can be easily procured, prepared, and applied without the need for a second surgical site. In addition to being the least expensive of all available biomaterials proposed for RC, PCs are well accepted by patients [3] due to their minimally invasive nature. By providing inherent growth factors (GF), PCs have significantly advanced periodontics and oral surgery through their ability to enhance wound healing [15].

First-generation PCs were fibrin glue and platelet-rich plasma, which were prepared by adding substances such as bovine antithrombin to activate the platelets and polymerize the fibrin. Fibrin glue utilization was restricted due to the increased risk of infection transmission [16]. While coming to platelet-rich plasma, there was a robust release of GF within the first half an hour of its placement at the disease site, and there was the addition of bovine antithrombin for platelet activation with a lengthy two-step protocol [17]. Hence, protocols shifted toward the preparation of a clot or membrane with a three-dimensional fibrin meshwork pattern. Thus, second-generation PCs were developed without the use of additives. L-PRF was introduced by Choukroun et al. [18], where blood was drawn and transferred to sterile silica tubes or silica-coated plastic tubes, then centrifuged at 2,700 rotations *per* minute for 12 min. L-PRF was an autologous concentrate that contains the GF and gradually releases them over time. It has been extensively studied in various treatment entities such as intra-bony defects, GR, sinus augmentation, post-impaction as filler of cavity of third molars, socket preservation, guided tissue, and guided bone regeneration as coverage over the grafts, and has achieved good results [19].

SR and MA conducted by Silva et al. [20] stated that PRF helped in intrabony defect (IBD) regeneration compared to other treatments. Alrayyes and Al-Jasser [21] stated that PRF showed positivity for socket preservation with and without bone grafts in periodontal surgeries. Studies that used L-PRF as a biomaterial for GR and assessed it in MA reported that L-PRF combined with CAF helped in relative RC but did not improve the keratinized mucosa width. These studies also concluded that in the least keratinized mucosa width cases, SCTGs are preferable to PRF [22]. In a recent study, Mancini et al. [22] reported that L-PRF was a better alternative to CAF alone, showing significant improvements in pain perception and discomfort when compared with CTG. They also stated that CTG was still considered the gold standard for the treatment of GR.

Extensive use of L-PRF has been reported in the literature; however, some drawbacks have been noted, including possible silica contamination, a short resorption time of 7–11 days, breakage of silica tubes, a thin and loose fibrin structure, and a thinner border area. These limitations may alter the capacity to retain GF, leading to a search for better biomaterials [23, 24]. In this context, titanium has gained attention due to its favorable properties. It is non-corrosive, non-breakable, and is commonly used in the manufacture of dental implants and other orthopaedic devices such as plates or screws [5]. Titanium, a noble metal, passivates into a titanium dioxide layer on the inner surface of the tube, is highly hemocompatible, and activates platelets similar to silica. These characteristics led to the introduction of titanium-prepared PRF (T-PRF) by Tunali et al. [25]. Histological studies have described T-PRF as having a thicker fibrin meshwork, a well-organized fibrin network pattern and border area, greater cellular entrapment, better retention of GF, and a longer resorption time of 21 days (rabbit study) [26]. In their scanning electron microscopic and immunohistochemical studies, Bhattacharya et al. [27, 28] stated that both L- and T-PRF shared a similar structure, and the mid-area of the T-PRF clot was much thicker. Immunohistochemical analysis revealed a greater distribution of lymphocytes, monocytes, and larger platelets compared with L-PRF, while a similar number of stem cells was observed. With this positivity, studies were performed regarding its usage in intra-bony defects by various authors such as Chatterjee et al. [29], Mitra et al. [30], and Gummaluri et al. [31], and achieved greater to equal amounts of bone fill, decreased probing pocket depth (PD) – PPD, and gain in clinical attachment level (CAL) when compared to L-PRF. A recent narrative review by Gummaluri et al. [32] also stated that T-PRF is a better alternative to L-PRF or advanced PRF, as it eliminates the possible risk of silica cross-contamination. Moreover, titanium tubes are reusable, and T-PRF provides a thickness comparable to that of SCTG, thereby eliminating the need for a second surgical site.

Recently, T-PRF has also been considered a sustained drug delivery system. Ercan et al. [33] incorporated doxycycline in liquid form into T-PRF and checked for the drug release and antimicrobial efficacy. They concluded that there was a gradual release of the drug with antimicrobial activity maintained for seven days against two bacteria (*Streptococcus mutans* and *Pseudomonas aeruginosa*). Furthermore, recent histological studies by Gummaluri et al. [34, 35] reported that T-PRF maintained an intact fibrin structure after being injected with amoxiclav gel, metronidazole, and neem gels. No thinning of the membrane was observed; instead, a thicker fibrin border area with spaces was reported. Under scanning electron microscopy, the injected antibiotics and herbal extracts appeared as a surface coating in the form of haziness, indirectly indicating the holding capacity of T-PRF.

Recent SR and MA by Oza et al. [36] evaluated the use of T-PRF in periodontal regeneration and concluded that T-PRF had superior qualitative and quantitative properties, which were beneficial for the predictable restoration of lost periodontal tissues. Similarly, Manchala et al. [37] conducted an SR on the application of T-PRF in periodontal regeneration and reported improvements in both hard and soft tissue parameters, including intra-bony and recession defects. The use of T-PRF in GR has only recently begun, and the amount of available research remains limited. To the author's knowledge, no SR and MA study has yet been conducted to evaluate the efficacy of T-PRF compared with SCTG/PRF in GR.

The aim of this study was to examine the regenerative efficacy of T-PRF as a biomaterial in the treatment of GR with CAF/modified CAF (mCAF)+PRF/SCTG as a surgical treatment modality.

Methods

Protocol establishment and focused question

The present study was an SR and MA of T-PRF with CAF and CAF alone in the treatment of GR. This study protocol was developed based on the Preferred Reporting Items for SRs and MAs (PRISMA) statement (www.prisma-statement.org) to review the literature of T-PRF+CAF and CAF alone systematically in the treatment of GR. The trial was registered under the International Prospective Register of SRs (PROSPERO) [Center for Reviews and Dissemination (CRD), University of York, the United States] with a number CRD42023467568 (https://www.crd.york.ac.uk/PROSPERO/view/CRD42023467568). The search strategy was established based on the population, index test, comparator, and outcome framing question format. The framing question was: "Can the treatment outcome of GR be enhanced by covering the recession site with T-PRF membrane underneath the CAF surgical technique compared with CAF alone?".

Search strategy

An electronic search was conducted in PubMed/Medline, Scopus, Web of Science, Embase, Google Scholar, and the Cochrane database to identify studies published up to January 31, 2024, for inclusion in this SR and MA. Additional searches were cross-verified to ensure no recent studies were missed. A manual search of available hard-copy journals was also performed to capture any further data. The search strategy used Medical Subject Headings – MeSH terms such as 'platelet-rich fibrin', 'platelets', 'gingival recession', 'titanium', and 'root coverage', combined with Boolean operators (AND/OR). All proper steps were taken to make the searches more authentic with the syntactic rules of all databases.

Inclusion and exclusion criteria

Randomized clinical trials and case series with a minimum follow-up period of six months were included in the study. The considered articles had to be published in English. Case reports, articles without the proper follow-up, incomplete titles, animal studies, and studies with fewer than five patients *per* group were excluded from the study.

Selection of studies

Duplicate articles identified during the search process were excluded. The remaining articles were screened by title and abstract for eligibility, followed by a full-text review to determine inclusion or exclusion. The initial selection of studies was performed by authors Shiva Shankar Gummaluri and Sai Karthikeyan SS, and subsequently cross-verified by Trinath Kishore Damera and Kaarthikeyan Gurumoorthy, with all authors reaching a common agreement.

Risk of bias and synthesis of data

Risk of bias was assessed using Review Manager software 5.4.1. The following data were extracted from the included studies: authors, study design, demographic data, follow-up, number of GR sites, type of surgical technique, smoking status, MRC, and classification of recession defects according to Miller and Cairo. Each of the randomized controlled trials (RCTs) was categorized into TT with PRF vs. TT with T-PRF, mCAF with SCTG vs. mCAF with T-PRF, and CAF with T-PRF vs. CAF with PRF.

Statistical analysis

The mean and standard deviations were used to express the data. Using Review Manager software 5.4.1, risk of bias, odds ratio, forest plots, and MA were calculated. Statistical significance was defined as a significance level of $p \leq 0.05$.

Results

A total of 6,571 searches across several databases were found. Following appropriate screening, 6,518 search duplicates were removed. Later, the remaining 53 articles underwent another step of screening, where 47 articles were removed because they did not match the inclusion criteria. Finally, a total of six publications were finalized for the SR. Further, for the MA, three out of six SR publications were recruited (Figure 1).

All finalized MAs found a low risk of bias for random sequence generation (selection bias). However, the risk was higher for allocation concealment (selection bias), blinding of participants and personnel (performance bias), and blinding of outcome assessment (detection bias) across all three included studies. Further, reporting bias (selective reporting) and attrition bias (incomplete outcome data) were assessed as low risk in the same studies (Figures 2 [38–40] and 3).

This MA comprised three RCTs to assess the effectiveness of various GR treatment approaches. These trials compared T-PRF with conventional CTG at a total of 272 sites across various patient categories.

MAs were conducted for two primary outcomes at the six-month follow-up: MRC width and MRC depth. For MRC, the combined effect size across three studies and 272 participants was a standardized mean difference (IV, random, 95% confidence interval) of 0.07 (-0.17, 0.31), indicating no significant difference between the interventions. For MRC depth, the combined effect size was 0.50 (-0.71, 1.70),

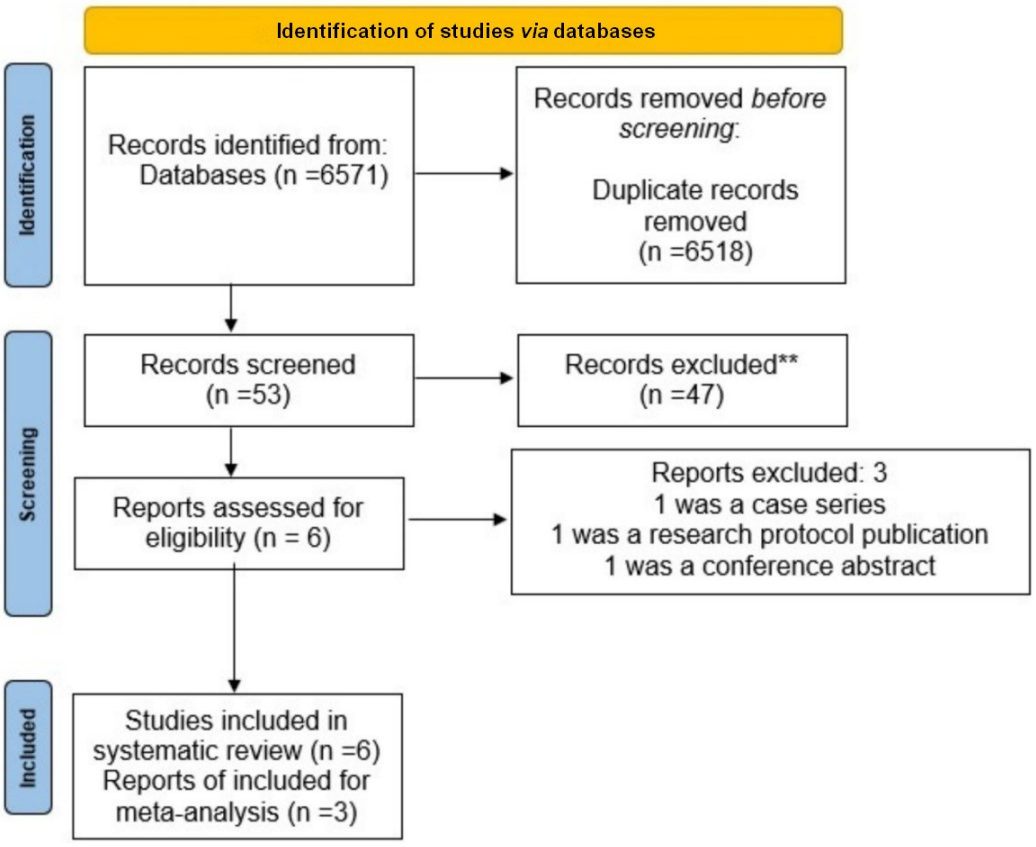

Fig. 1 – PRISMA flow diagram.

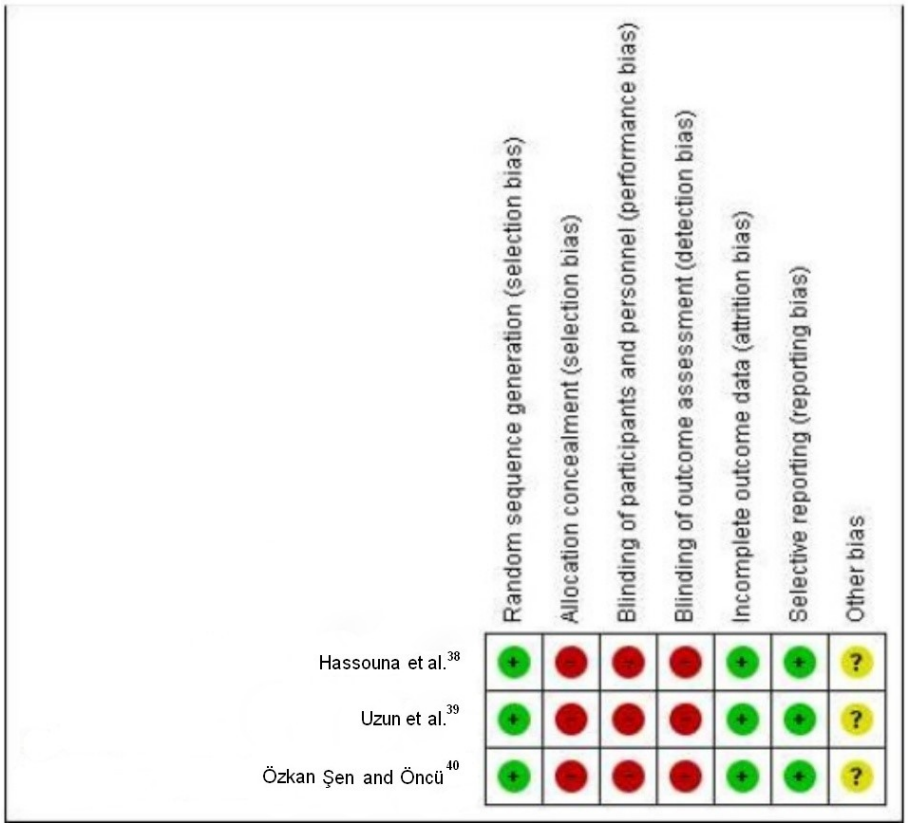

Fig. 2 – Risk of bias graph that shows the bias items of all included studies.

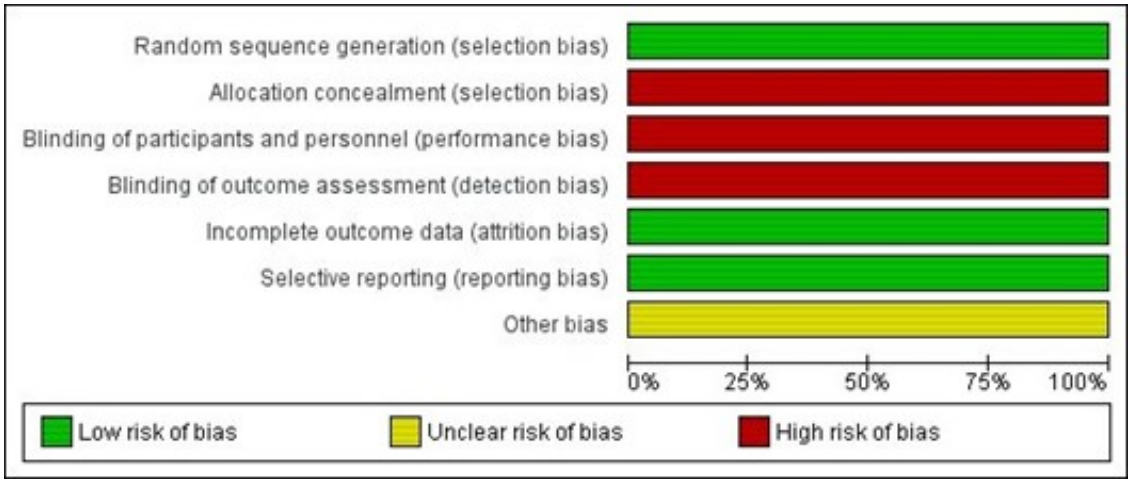

Fig. 3 – Risk of bias summary that shows the bias item for each included study.

also showing a non-significant trend favoring one intervention over the other. Heterogeneity was assessed using the I^2 statistic, with moderate to high levels of heterogeneity observed. This suggests variability in the study outcomes. Specifically, for MRC width and depth, the heterogeneity values were indicative of substantial differences between the studies' results.

Regarding the forest plot analysis for the MRC outcome, there was a favored trend towards the control (CAF alone). For RC depth at six months, two studies (Hassouna et al. [38] and Uzun et al. [39]) showed a neutral pattern, while one study (Özkan Şen and Öncü [40]) favored the control (Figures 4 and 5).

Publication bias was evaluated using funnel plots, which did not indicate significant asymmetry for either MRC width or depth, suggesting minimal publication bias. However, the high risk of bias in several domains across the studies highlights the need for future well-designed RCTs with better blinding and allocation concealment to confirm these findings. Additionally, the moderate to high heterogeneity underscores the necessity for standardized outcome measures in future studies (Figures 6 and 7).

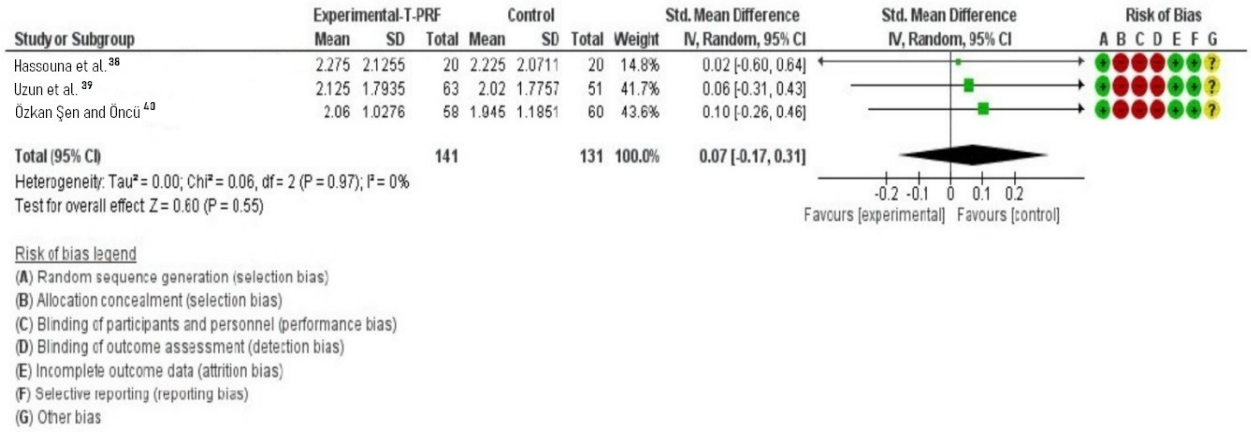

Fig. 4 – Forest plot diagram of mean root coverage outcome width in 6 months.
T-PRF – titanium-prepared platelet-rich fibrin; SD – standard deviation; CI – confidence interval; Std. – standardized.

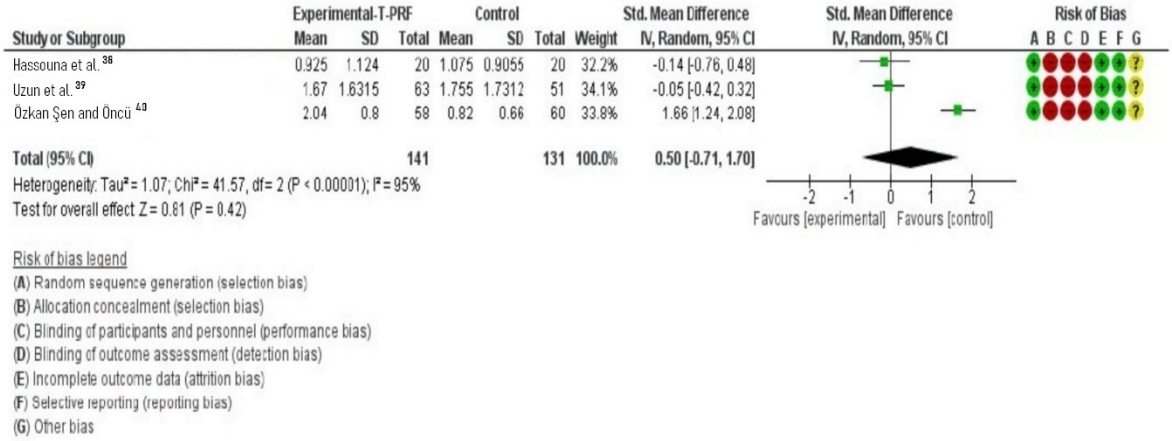

Fig. 5 – Forest plot diagram of the mean root coverage depth outcome in 6 months.
For abbreviations, see Figure 4.

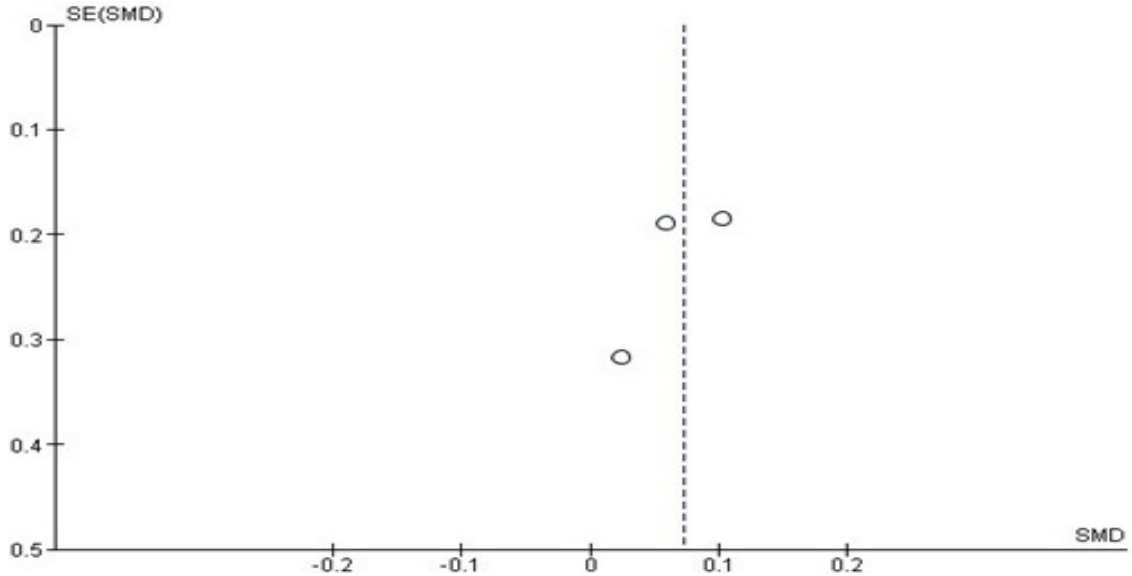

Fig. 6 – Funnel plot diagram of the mean root coverage width outcome in 6 months.
SE – standard error; SMD – standardized mean difference.

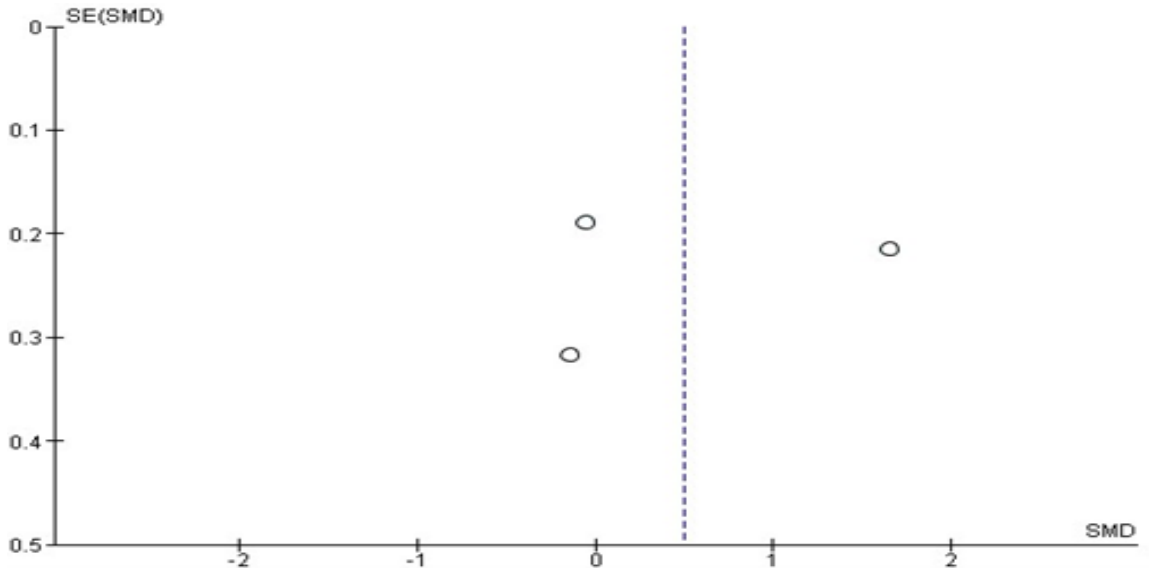

Fig. 7 – Funnel plot diagram of the mean root coverage depth outcome in 6 months. For abbreviations, see Figure 6.

Discussion

The present study was an SR and MA where T-PRF+CAF was compared with CTG/PRF+CAF/tunneling CAF studies. Out of six SR and MA-related articles (Table 1 [38–43]), three were eliminated (one case series, one treatment protocol, and one conference presentation), and three were included in the MA (Table 2 [38–40]). The eliminated studies are summarized below. Bhattacharya et al. [41] reported a case series in which surgeries for GR were performed using T-PRF+CAF as a treatment protocol, with a 6-month follow-up. The outcomes showed improved CAL, reduced PD, and decreased RD and RW. The study by Salian and Dhadse [42] evaluated a treatment protocol comparing T-PRF and L-PRF in the modified vestibular incision subperiosteal tunnel access (M-VISTA) technique. Özdemir et al. [43] presented conference data on the use of T-PRF+CAF for the treatment of Miller's class I and II GR. They concluded that T-PRF had a better treatment outcome for GR by eliminating the second surgical site. However, as this was only a conference presentation, detailed recession parameters were not included. These studies were excluded because they did not meet the inclusion criteria of the present study.

A clinical study by Ustaoğlu et al. [44] utilized T-PRF for palatal wound healing, in which free gingival grafts were harvested from the palate and T-PRF membranes were placed. Epithelialization was subsequently assessed using the hydrogen peroxide bubbling test at 3, 7, 14, and 21 days. These studies were excluded as they did not meet the selection criteria for the present study. Another study by Koyuncuoğlu et al. [45] employed T-PRF as a biomaterial to treat deep GRs and compared it with the CTG group. The surgical technique that was used in this study was modified coronally advanced TT. The authors concluded that T-PRF produced results comparable to CTG and reported a similar complete RC percentage. Further, they also stated that T-PRF can be a safe treatment strategy for Miller's class I and II GR without requiring a second surgical harvesting site.

The study by Uzun et al. [39] included 114 tooth sites in 34 patients, with interventions using T-PRF and CTG for GR. Various clinical parameters were assessed, including plaque index (PI), gingival index (GI), PD, RW, RD, CAL, KTW, gingival thickness (GT), and more. The risk of bias assessment revealed a low risk for random sequence generation and attrition bias, whereas allocation concealment, performance bias, and detection bias were assessed as high risk. In the study by Özkan Şen and Öncü [40], 118 defects in 20 patients with bilateral defects were evaluated. The interventions included an SCTG group and a T-PRF group. Parameters were measured at baseline and six months, including GI, PI, CAL, PD, GT, keratinized gingival width, recession height, and RW. This study, like the previous one, also showed a low risk for random sequence generation and attrition bias, while high risk was recorded for allocation concealment, performance bias, and detection bias. The third study by Hassouna et al. [38] included 40 sites in 24 patients, with treatment interventions using TT with PRF or T-PRF membranes. Clinical parameters were measured at baseline, 3, 6, and 9 months, including PI, GI, PPD, RW, RD, CAL, KTW, GT, and a visual analogue scale for post-operative discomfort. This study demonstrated a low risk for random sequence generation and attrition bias, but a high risk for allocation concealment, performance bias, and detection bias (Tables 1 and 2).

A recent SR and MA on T-PRF usage by Oza et al. [36] for the treatment of IBD reported that T-PRF is a better biomaterial compared with open flap debridement alone, and larger randomized trials with extended follow-ups are needed to confirm these findings. Further MAs conducted by Chambrone et al. [46] and Miron et al. [47] demonstrated

Table 1

Systematic review and meta-analysis included studies comparing TT with PRF vs. TT with T-PRF, mCAF with SCTG vs. mCAF with T-PRF, and CAF with T-PRF vs. CAF with SCTG

Study	Type of research	Type of technique	Type of recession	Total number of defects	Surgical site	Duration of study in months	Age, years (range/ mean)	Mean gingival recession depth (mm)		Mean gingival recession width (mm)		Centrifugation speed (rpm)	Centrifugation time (min)	Blood drawn (mL)
								baseline	after study	baseline	after study			
Hassouna et al. [38]	RCT	TT+PRF (Group I)	Miller's class I and II defects	20	NA	9	23–41	1.9	0.38	4.2	2.4	NA	NA	NA
		TT+T-PRF (Group II)		20	NA			1.85	0.17	4.3	1.6	NA	NA	NA
Uzun et al. [39]	RCT	T-PRF+CAF	Miller's class I (42 teeth) Miller's class II (21 teeth)	63	NA	12	40.3	3.07	0.21	3.47	0.61	3,500	15	10
		CTG+CAF	Miller's class I (37 teeth) Miller's class II (14 teeth)	51	NA			3.25	0.26	3.59	0.56	NA	NA	NA
Özkan Şen and Öncü [40]	RCT	mCAF+SCTG	Cairo RT1 type defects of at least 3 mm	60	Incisors, canines, and premolars of both jaws	6	NA	2.15	0.51	2.63	1.26	NA	NA	NA
		mCAF+T-PRF		58				2.04	0.82	2.6	1.52	3,500	15	10
Bhattacharya et al. [41]	Case series	CAF+T-PRF	Cairo's type 1	34	NA	6	30.3	3.05	0.25	3.55	0.55	3,500	15	10
Salian and Dhadse [42]	Treatment protocol	M-VISTA+T-PRF and M-VISTA+PRF	Miller's class I and II	NA	Maxilla and mandible multiple recession sites	3, 6, and 9	-	-	-	-	-	2,700	12	10
Özdemir et al. [43]	Conference presentation	CAF+T-PRF	Miller's class I and II	12	NA	6	-	4.96	-	-	-	-	-	-
		CAF+free CTG		7	NA		-	5.29	-	-	-	-	-	-

TT – tunnel technique; PRF – platelet-rich fibrin; T-PRF – titanium-prepared PRF; CAF – coronally advanced flap; mCAF – modified CAF; CTG – connective tissue graft; SCTG – subepithelial CTG; rpm – revolutions *per* minute; RCT – randomized controlled trials; M-VISTA – modified vestibular incision subperiosteal tunnel access; NA – not applicable; RT1 – recession type 1.

Table 2

Main characteristics of studies included in the meta-analysis

Study	Study design (follow-up)	Number of treated recessions (*per* group) and number of patients	Age, years (range or mean)	Gender	Smoking status	Miller's class	Recession sites	Author's conclusion
Hassouna et al. [38]	Randomized control trial	n = 40 sites in 24 patients	23–41	NA	Not included	Miller's class I and II	NA	T-PRF procedure is a safe, effective method for localized or multiple-adjacent gingival recessions without additional surgery.
Uzun et al. [39]	Randomized control trial	n = 114 tooth sites in 34 patients [n = 63 (16) in T-PRF group, n = 51 (18) in CTG group]	40.3	15 male, 19 female	Smoking ≤ 5 cigarettes/day was included	Miller's class I and II	NA	T-PRF is an effective treatment option for multiple Miller class I/II GR defects.
Özkan Şeran dÖncü[40]	Randomized split-mouth control trial	n = 118 defects in 20 patients with bilateral defects	NA	7 male, 13 female	Not included	Cairo RT1 type	Incisors, canines, and premolars of both jaws	T-PRF is an alternative to SCTG, considering effective results, patient satisfaction, and rapid recovery

GR – gingival recession; n – number. For other abbreviations, see Table 1.

that CAF with PRF showed better results compared with CAF alone, and SCTG remains a highly effective option for treating GR.

Limitations of this study included a smaller sample size (three studies), the limited number of completed RCTs, ongoing studies that were not yet published, and the relative scarcity of data on GR and CAF. Additionally, the establishment of newer surgical techniques that were not incorporated in the study data because of inclusion criteria constraints might have led to changes in the treatment outcomes.

Conclusion

Within the limitations of this study, clinical findings from the included studies suggest improved outcomes with T-PRF. In contrast, the meta-analysis did not show a statistically significant advantage of T-PRF over connective tissue grafts or platelet-rich fibrin. Further, well-designed randomized controlled trials are necessary to evaluate T-PRF in gingival recession treatment so that a proper conclusion can be provided regarding the efficacy of T-PRF through a highly valued meta-analysis.

R E F E R E N C E S

1. *American Academy of Periodontology*. Glossary of periodontal terms [Internet]. Chicago (IL): AAP; 2001 [cited on 2025 July 18]. Available from: https://members.perio.org/libraries/glossary?ssopc=1
2. *Tróia PM, Spuldaro TR, da Fonseca PA, de Oliveira Fernandes GV*. Presence of gingival recession or noncarious cervical lesions on teeth under occlusal trauma: a systematic review. Eur J Gen Dent 2021; 10(1): 50–9.
3. *Liu XX, Tenenbaum HC, Wilder RS, Quock R, Hewlett ER, Ren YF*. Pathogenesis, diagnosis and management of dentin hypersensitivity: an evidence-based overview for dental practitioners. BMC Oral Health 2020; 20(1): 220.
4. *Lertpimonchai A, Rattanasiri S, Arj-Ong Vallibhakara S, Attia J, Thakkinstian A*. The association between oral hygiene and periodontitis: a systematic review and meta-analysis. Int Dent J 2017; 67(6): 332–43.
5. *Grover V, Kumar A, Jain A, Chatterjee A, Grover HS, Pandit N,* et al. ISP Good Clinical Practice Recommendations for the management of Dentin Hypersensitivity. J Indian Soc Periodontol 2022; 26(4): 307–33.
6. *Sood R, Shergill S, Singh J, Sharma E, Ridhi G*. Treatment of gingival class I or class II recession using subepithelial connective tissue graft and acellular dermal matrix allograft. Bioinformation 2022; 18(9): 801–6.
7. *Imber JC, Kasaj A*. Treatment of Gingival Recession: When and How? Int Dent J 2021; 71(3): 178–87.
8. *Murakami S, Mealey BL, Mariotti A, Chapple ILC*. Dental plaque-induced gingival conditions. J Periodontol 2018; 89(Suppl 1): S17–27.
9. *Mostafa D, Fatima N*. Gingival recession and root coverage up to date, a literature review. Dent Rev 2022; 2(1): 100008.
10. *Pini Prato GP, Franceschi D, Cortellini P, Chambrone L*. Long-term evaluation (20 years) of the outcomes of subepithelial connective tissue graft plus coronally advanced flap in the treatment of maxillary single recession-type defects. J Periodontol 2018; 89(11): 1290–9.
11. *Carrera TMI, Machado LM, Soares MTR, Passos GP, Oliveira GP, Ribeiro Júnior NV,* et al. Root coverage with platelet-rich fibrin or connective tissue graft: a split-mouth randomized trial. Braz Oral Res 2023; 37: e084.
12. *Chambrone L, Chambrone D, Pustiglioni FE, Chambrone LA, Lima LA*. Can subepithelial connective tissue grafts be considered the gold standard procedure in the treatment of Miller Class I and II recession-type defects? J Dent 2008; 36(9): 659–71.
13. *Abdel-Fatah R, Saleh W*. Efficacy of amniotic membrane with coronally advanced flap in the treatment of gingival recession: an updated systematic review and meta-analysis. BMC Oral Health 2024; 24(1): 133.
14. *Balaji VR, Ramakrishnan T, Manikandan D, Lambodharan R, Karthikeyan B, Niazi TM,* et al. Management of gingival recession with acellular dermal matrix graft: A clinical study. J Pharm Bioallied Sci 2016; 8(Suppl 1): S59–64.
15. *Quirynen M, Sculean A, Blanco J, Wang HL, Donos N*. Introduction and overview on Autogenous Platelet Concentrates. Periodontol 2000 2025; 97(1): 7–15.
16. *Potnitz WD*. Fibrin Sealant: The Only Approved Hemostat, Sealant, and Adhesive-a Laboratory and Clinical Perspective. ISRN Surg 2014; 2014: 203943.
17. *Mijiritsky E, Assaf HD, Peleg O, Shacham M, Cerroni L, Mangani L*. Use of PRP, PRF and CGF in Periodontal Regeneration and Facial Rejuvenation-A Narrative Review. Biology (Basel) 2021; 10(4): 317–40.
18. *Choukroun J, Adda F, Schoeffler C, Vervelle A*. An opportunity in perio-implantology: PRF. Implantodontie 2001; 42(55): e55–e62. (French)
19. *Zwittnig K, Mukaddam K, Vegh D, Herber V, Jakse N, Schlenke P,* et al. Platelet-Rich Fibrin in Oral Surgery and Implantology: A Narrative Review. Transfus Med Hemother 2022; 50(4): 348–59.
20. *Silva FFVE, Chauca-Bajaña L, Caponio VCA, Cueva KAS, Velasquez-Ron B, Padín-Iruegas ME,* et al. Regeneration of periodontal intrabony defects using platelet-rich fibrin (PRF): a systematic review and network meta-analysis. Odontology 2024; 112(4): 1047–68.
21. *Alrayyes Y, Al-Jasser R*. Regenerative Potential of Platelet Rich Fibrin (PRF) in Socket Preservation in Comparison with Conventional Treatment Modalities: A Systematic Review and Meta-Analysis. Tissue Eng Regen Med 2022; 19(3): 463–75.
22. *Mancini L, Tarallo F, Quinzi V, Fratini A, Mummolo S, Marchetti E*. Platelet-rich fibrin in single and multiple coronally advanced flap for type 1 recession: An updated systematic review and meta-analysis. Medicina (Kaunas) 2021; 57(2): 144.
23. *Miron RJ, Kawase T, Dham A, Zhang Y, Fujioka-Kobayashi M, Sculean A*. A technical note on contamination from PRF tubes containing silica and silicone. BMC Oral Health 2021; 21(1): 135.
24. *O'Connell SM*. Safety issues associated with platelet-rich fibrin method. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007; 103(5): 587–93.
25. *Tunali M, Özdemir H, Küçükodacı Z, Akman S, Fıratlı E*. In vivo evaluation of titanium-prepared platelet-rich fibrin (T-PRF): a new platelet concentrate. Br J Oral Maxillofac Surg 2013; 51(5): 438–43.
26. *Tunalı M, Özdemir H, Küçükodacı Z, Ezirganlı Ş, Barış E, Akman S,* et al. A novel platelet concentrate for guided bone regeneration: Titanium Prepared Platelet-Rich Fibrin (T-PRF):. Gulhane Med J 2015; 57(2): 102–6.
27. *Bhattacharya HS, Gummaluri SS, Astekar M, Sapra G, Shiva Manjunath RG*. Comparative histological evaluation of L-PRF with T-PRF: A scanning electron microscopic study. J Exp Ther Oncol 2022; 13(3): 207−13.

28. *Bhattacharya HS, Gummaluri SS, Astekar M, Gummaluri RK.* Novel method of determining the periodontal regenerative capacity of T-PRF and L-PRF: An immunohistochemical study. Dent Med Probl 2020; 57(2): 137–44.
29. *Chatterjee A, Pradeep AR, Garg V, Yajamanya S, Ali MM, Priya VS.* Treatment of periodontal intrabony defects using autologous platelet-rich fibrin and titanium platelet-rich fibrin: a randomized, clinical, comparative study. J Investig Clin Dent 2017; 8(3): e12231–6.
30. *Mitra DK, Potdar PN, Prithyani SS, Rodrigues SV, Shetty GP, Talati MA.* Comparative study using autologous platelet-rich fibrin and titanium prepared platelet-rich fibrin in the treatment of infrabony defects: An *in vitro* and *in vivo* study. J Indian Soc Periodontol 2019; 23(6): 554–61.
31. *Gummaluri SS, Bhattacharya HS, Astekar M, Cheruvu S.* Evaluation of titanium-prepared platelet-rich fibrin and leucocyte platelet-rich fibrin in the treatment of intra-bony defects: A randomized clinical trial. J Dent Res Dent Clin Dent Prospects 2020; 14(2): 83–91.
32. *Gummaluri SS, Gurumoorthy K, Kancharla AK, Boyapati R.* Evaluating the Predictability and Regenerative Capacity of Novel Platelet Concentrate (PC)-Titanium Platelet Rich Fibrin (T-PRF) in the field of Dentistry-A Narrative Review. Cumhuriyet Dent J 2023; 26(3): 332–9.
33. *Ercan E, Suner SS, Silan C, Yilmaz S, Siddikoglu D, Sahiner N,* et al. Titanium platelet-rich fibrin (T-PRF) as high-capacity doxycycline delivery system. Clin Oral Investig 2022; 26(8): 5429–38.
34. *Gummaluri SS, Gurumoorthy K, Damera TK, Boddeda A, Kodem T, Lekkala S.* Comparative evaluation of titanium-prepared platelet-rich fibrin with and without herbal extract: a histological study. Vojnosanit Pregl 2024; 81(6): 377–83.
35. *Gummaluri SS, Kaarthikeyan G, Damera TK, Rampalli V, Nagar S, Boyapati R.* Comparative Evaluation of Azadirachtin, Vitamin C and Insulin like Growth Factor 1 release in Titanium Platelet Rich Fibrin infused with Neem and Triphala indica gel extracts: An Invitro Study. JBSMFS 2025; 21(5): 359–68.
36. *Oza DR, Dhadse DP, Bajaj DP, Bhombe DK, Durge DK, Subhadarsanee DC,* et al. Clinical efficacy of titanium prepared platelet rich fibrin in periodontal regeneration: A systematic review and meta-analysis. F1000Res 2024; 12: 393.
37. *Manchala B, Teju A, Pasupuleti MK, Penmetsa GS, Gottumukkala S, Lakshmi V.* Role of Titanium-Reinforced Platelet-Rich Fibrin in Periodontal Tissue Regeneration-A Systematic Review. J Dent Indones 2024; 31(2): 74–80.
38. *Hassouna IA, Mandour HM, El Destawy MT.* Evaluation of clinical effect of titanium-prepared platelet-rich fibrin and platelet-rich fibrin in treatment of gingival recession. Al-Azhar J Dent Sci 2023; 26(3): 345–53.
39. *Uzun BC, Ercan E, Tunalı M.* Effectiveness and predictability of titanium-prepared platelet-rich fibrin for the management of multiple gingival recessions. Clin Oral Investig 2018; 22(3): 1345–54.
40. *Özkan Şen D, Öncü E.* Splith mouth randomized control trial comparison of T-PRF and subepithelial connective tissue graft in the treatment of maxillar multiple gingival recessions. J Esthet Restor Dent 2023; 35(3): 449–56.
41. *Bhattacharya HS, Gummaluri SS, Rani A, Verma S, Bhattacharya P, Rayashettypura Gurushanth SM.* Additional benefits of titanium platelet-rich fibrin (T-PRF) with a coronally advanced flap (CAF) for recession coverage: A case series. Dent Med Probl 2023; 60(2): 279–85.
42. *Salian SS, Dhadse PV.* Effectiveness of Titanium Prepared Platelet Rich Fibrin Membrane vs Platelet Rich Fibrin Membrane in the Treatment of Multiple Gingival Recession Defects using M-VISTA Technique: Protocol for a Randomised Clinical Trial. J Clin Diagnostic Res 2023; 17(1): ZK08–11.
43. *Özdemir H, Tunali M, Akman S, Toker H, Firatli E.* Titanium Prepared Platelet-Rich Fibrin for the Treatment of Gingival Recessions. In: 2013 IADR/AADR/CADR General Session, 2013 March 21; Seattle, Washington.
44. *Ustaoğlu G, Ercan E, Tunali M.* The role of titanium-prepared platelet-rich fibrin in palatal mucosal wound healing and histoconduction. Acta Odontol Scand 2016; 74(7): 558–64.
45. *Koyuncuoğlu CZ, Ercan E, Uzun B, Tunalı M, Firatli E.* Management of deep gingival recessions by modified coronally advanced tunnel technique with titanium platelet rich fibrin membrane or connective tissue graft: 36 months follow-up clinical study. Clin Exp Health Sci 2020; 10(3): 297–303.
46. *Chambrone L, Ortega MAS, Sukekava F, Rotundo R, Kalemaj Z, Buti J,* et al. Root coverage procedures for treating single and multiple recession-type defects: An updated Cochrane systematic review. J Periodontol 2019; 90(12): 1399–422.
47. *Miron RJ, Moraschini V, Del Fabbro M, Piattelli A, Fujioka-Kobayashi M, Zhang Y,* et al. Use of platelet-rich fibrin for the treatment of gingival recessions: a systematic review and meta-analysis. Clin Oral Investig 2020; 24 (8): 2543–57.

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Cognitive status and quality of life of post-stroke patients: evidence from Serbia

Kognitivni status i kvalitet života bolesnika nakon moždanog udara: dokazi iz Srbije

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Abstract

Background/Aim. Stroke is a major global health problem, and more than half of stroke patients suffer from cognitive impairments. The aim of this study was to assess the impact of secondary rehabilitation on cognitive status and to examine its correlation with quality of life in post-stroke patients. **Methods.** A total of 100 patients (average age 66.5 ± 7.3 years) participated in the study, of whom 50 were diagnosed with ischemic stroke (IS) and 50 with intracerebral hemorrhagic stroke (ICH). The Mini-Mental State Examination (MMSE) was utilized to assess cognitive status, while the European Quality of Life (EuroQol) 5-dimensional 3-level (EQ-5D-3L) questionnaire was employed to evaluate quality of life. **Results.** The MMSE test results showed significant differences at three months ($p = 0.037$) and six months ($p = 0.009$) of secondary rehabilitation compared to admission. For the EQ-5D-3L, significant differences were observed at the time of admission ($p < 0.001$), one month ($p = 0.001$), and six months ($p = 0.007$). In addition, the Wilcoxon signed-rank test showed a statistically significant improvement in both MMSE and EQ-5D-3L scores when comparing results from admission to those taken one month ($p < 0.001$), three months ($p < 0.001$), and six months ($p < 0.001$) after secondary rehabilitation for both IS and ICH. **Conclusion.** The results indicate a significant correlation between cognitive status and quality of life, measured at all four time points. Additionally, it was found that a longer duration of secondary rehabilitation leads to improved cognitive status and a higher quality of life for post-stroke patients.

Key words:
cognition disorders; hemorrhagic stroke; ischemic stroke; rehabilitation; quality of life.

Apstrakt

Uvod/Cilj. Moždani udar je veliki globalni zdravstveni problem i više od polovine bolesnika sa moždanim udarom pati od kognitivnih oštećenja. Cilj ove studije bio je da se proceni uticaj sekundarne rehabilitacije na kognitivni status i da se ispita njegova korelacija sa kvalitetom života kod bolesnika nakon moždanog udara. **Metode.** U studiji je učestvovalo ukupno 100 bolesnika (prosečne starosti 66,5 ± 7,3 godine), od kojih je 50 imalo dijagnozu ishemijskog moždanog udara (*ischemic stroke* – IS), a 50 je imalo dijagnozu intracerebralnog hemoragijskog moždanog udara (*intracerebral hemorrhagic stroke* – ICH). Test za procenu mentalnog stanja *Mini-Mental State Examination* (MMSE) korišćen je za procenu kognitivnog statusa, dok je Evropski upitnik za kvalitet života [*European Quality of Life* (*EuroQol*) *5-dimensional 3-level* – EQ-5D-3L] korišćen za procenu kvaliteta života. **Rezultati.** Rezultati MMSE testa pokazali su značajne razlike nakon tri meseca ($p = 0,037$) i šest meseci ($p = 0,009$) trajanja sekundarne rehabilitacije u odnosu na prijem. Za EQ-5D-3L, uočene su značajne razlike u vreme prijema ($p < 0,001$), nakon mesec dana ($p = 0,001$) i šest meseci ($p = 0,007$). Uz to, *Wilcoxon signed-rank test* pokazao je statistički značajno poboljšanje i MMSE i EQ-5D-3L skorova bolesnika i sa IS i sa ICH, kada se uporede rezultati prijema s onima uzetim mesec dana ($p < 0,001$), tri meseca ($p < 0,001$) i šest meseci ($p < 0,001$) nakon sekundarne rehabilitacije. **Zaključak.** Rezultati ukazuju da postoji značajna korelacija između kognitivnog statusa i kvaliteta života merenog u sva četiri momenta. Dodatno, utvrđeno je da duže trajanje sekundarne rehabilitacije dovodi do poboljšanja kognitivnog statusa i višeg kvaliteta života bolesnika nakon moždanog udara.

Ključne reči:
kognicija, poremećaji; moždani udar, hemoragijski; moždani udar, ishemijski; rehabilitacija; kvalitet života.

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Introduction

Acute, focal neurological impairment caused by vascular injury (hemorrhage, infarction) of the central nervous system is known as a stroke. Stroke represents a major and growing global health concern [1]. Stroke is the second leading cause of mortality worldwide and the third leading cause of death and disability combined. Only ten risk factors account for more than 90% of the total modifiable risk for stroke, and they may be responsible for nearly half of all stroke-related deaths. Countries with varying income levels exhibit differences in age-standardized rates of stroke disability and mortality that can be attributed to modifiable risk factors, with higher-income countries being less at risk than lower-income countries [2]. The World Health Organization states that lowering the risk of hypertension (high systolic blood pressure), high lipids, diabetes (high fasting plasma glucose), smoking, inactivity, poor diet, and abdominal obesity (high body mass index) are all effective ways to avoid stroke [3].

The two types of strokes are intracerebral hemorrhagic stroke (ICH) and ischemic stroke (IS) [4]. Differentiating the kind of stroke is important for patient care within a few days after the stroke, but early detection is essential for stroke patients to avoid complications and irreversible damage [5].

There are numerous detrimental effects of a stroke on a person's life. Stroke and cognitive impairment have been strongly associated in numerous studies. The cognitive impairments that stroke patients endure can have a significant effect on their independence, everyday functioning, and general well-being [6].

More than half of stroke patients suffer from cognitive impairments such as memory problems and intellectual disability [7].

Stroke imposes limitations on personal, social, and professional responsibilities, which significantly impacts quality of life (QoL). It also places several restrictions on sensorimotor, cognitive, and behavioral levels, which offers a serious obstacle to functional independence. Evaluating post-stroke patients' QoL is essential for forecasting the imposed illness load and assessing how well treatment is working [8].

The aim of this study was to examine how secondary rehabilitation affects cognitive status and whether there is a correlation between cognitive status and QoL in patients who survived IS and ICH.

Methods

Study design

This was a prospective observational study carried out at the Special Hospital for Progressive Muscular and Neuromuscular Diseases in Novi Pazar, Serbia, from November 1, 2021, to July 1, 2022, designed to evaluate the cognitive status and QoL of post-stroke patients over a six-month period.

The study was approved by the Ethics Committee of the Special Hospital for Progressive Muscular and Neuromuscular Diseases, Novi Pazar (No. 872, from October 20, 2021), and it adhered to the principles of the Declaration of Helsinki [9]. Prior to their recruitment in the study, written informed consent was obtained from each patient. They were also informed that they could withdraw from the study at any time without facing any repercussions. The identities of the participants were concealed in the study report, and all data collected from them were safeguarded, with access restricted solely to the research team.

The respondents were divided into two groups. The first group consisted of patients with IS, and the second group consisted of patients with ICH. Based on neurological examination, computed tomography, or magnetic resonance imaging results, data were gathered by evaluating and monitoring patients who had suffered a stroke. Patients who experienced their first-ever IS or ICH were included no earlier than one month following the acute stroke event, aligning with the start of secondary rehabilitation. Examinations were performed on patients upon admission, and one, three, and six months following secondary rehabilitation.

Study population

Out of the 100 patients who took part in the study, 50% suffered IS, and the other 50% experienced ICH.

Inclusion criteria for the study were as follows: patients 46 years old or above; patients with a National Institutes of Health Stroke Scale (NIHSS) score between 4 and 24; patients who experienced IS or ICH for the first time no earlier than one month after the start of follow-up; patients who could participate in the rehabilitation program; patients able to communicate; those who provided written consent to participate in the study.

The following were exclusion criteria from the study: patients aged below 46 years; an NIHSS score below 4 or above 24; a history of IS or ICH; patients unable to talk; patients reluctant to provide written consent; patients with certain additional neurological conditions that impacted their functional ability.

Measures and procedures

In this study, patients participated in a secondary rehabilitation program that included functional electrostimulation and motor training using kinesitherapy. The program was conducted five days a week. After vital parameters stabilized and with a doctor's approval, rehabilitation began. Individual evaluations and program adaptations were made for each patient. The majority received monitoring and examinations while undergoing treatment in the hospital for three to four weeks, followed by three to four weeks of outpatient care spread out over six months. Patients received psychological support because it is thought to be crucial for both patients and their families to learn to cope with stroke [10].

The total duration of secondary rehabilitation, including inpatient and outpatient care, was approximately six months, with the most intensive phase during the first three months. Psychological support included individual counseling sessions, psychoeducation about stroke recovery, stress management strategies, and emotional support provided both to patients and their families.

The validated Serbian version of the Mini-Mental State Examination (MMSE) instrument was used to assess the patient's cognitive status [11, 12]. The MMSE comprises multiple items assessing cognitive domains, with a maximum score of 30 points. It has eleven items that evaluate linguistic skills: word repetition, recall, orientation, focus, and computation. A score of 24 or higher is considered normal, a score between 19 and 23 is mild, between 10 and 18 is moderate, and a score below 9 represents significant cognitive impairment [11, 12]. To assess the QoL, the European Quality of Life (EuroQol) 5-dimensional 3-level (EQ-5D-3L) questionnaire was employed [13]. It was used in a validated version in the Serbian language that is also free for use in student non-commercial research. It assesses five domains: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression, at three levels of severity (no problem, moderate problem, and severe problem) [13]. Sociodemographic and clinical data relevant to the study's findings were collected using a questionnaire designed specifically for this study.

Statistical analysis

This study used the Kolmogorov-Smirnov test to assess the normality of the data distribution. Statistical significance was evaluated using two-tailed tests at the 0.05 level. We compared the frequency of specific attribute feature groups using the Chi-square test. We employed the analysis of variance (ANOVA) test (non-parametric Friedman) to examine the variance difference before applying the Wilcoxon signed-rank test to ascertain differences in repeated measurements. To examine the relationship between MMSE and EQ-5D-3L, we used Spearman's rank correlation coefficient, as the data were not normally distributed. The delta value (Δ) represents the difference between the MMSE and EQ-5D-3L scores at one, three, and six months of secondary rehabilitation and at the patient's admission. The descriptive statistics are presented either as numbers (n) and frequency (%) or as mean ± standard deviation (SD). SPSS Statistics software (IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY, USA) was used to conduct the statistical analysis.

Results

The research sample consisted of 100 respondents with an average age of 66.5 ± 7.3 years, of whom 48 were male and 52 were female. Among all subjects, 50 had IS (27 men and 23 women), and 50 had ICH (21 men and 29 women). Of the total number, 71 patients had high blood pressure, 46 had high cholesterol, and 39 had diabetes mellitus. Other sociodemographic and clinical characteristics of the patients who participated in the study, which may be important for the outcome of the study, are shown in Table 1.

Descriptive statistical analysis revealed that the mean MMSE score at admission was 12.88 (SD = 9.4), increasing to 16.79 (SD = 9.3) after one month, 21.55 (SD = 8.5) after three months, and 23.34 (SD = 7.5) after six months of secondary rehabilitation. The Kolmogorov-Smirnov test indicated that the distribution of MMSE scores was mixed, necessitating the use of non-parametric tests. Statistically significant improvements in MMSE scores were observed at three months (p = 0.037) and six months (p = 0.009) compared to baseline.

Table 1

Sociodemographic and clinical characteristics of patients

Characteristics	Sample size (n = 100)
Monthly income	
below average	23 (23)
average	67 (67)
above average	10 (10)
Alcohol	
never used	63 (63)
currently using	3 (3)
previously used	34 (34)
Coffee	
never used	7 (7)
currently using	55 (55)
previously used	38 (38)
Cigarettes	
never used	40 (40)
currently using	24 (24)
previously used	36 (36)
Medicaments	
never used	9 (9)
currently using	81 (81)
previously used	10 (10)
Children	
yes	80 (80)
no	20 (20)
Marital status	
not married	11 (11)
married	58 (58)
divorced	11 (11)
widow/widower	20 (20)
Level of education	
primary school	36 (36)
high school	38 (38)
higher education	15 (15)
college	11 (11)
Employment status	
unemployed	20 (20)
employed	19 (19)
housewife	18 (18)
farmer	18 (18)
retired	25 (25)

n – number.

All values are given as numbers (percentages).

Regarding QoL assessed by the EQ-5D-3L, the mean score at admission was 6.2 (SD = 1.9), rising to 7.7 (SD = 2.2) after one month, 9.2 (SD = 2.4) after three months, and reaching 10.9 (SD = 2.4) at the six-month follow-up. Although non-parametric tests were applied due to the distribution of the data, only the three-month follow-up data met the criteria for normal distribution. Statistically significant differences in EQ-5D-3L scores were found at admission ($p < 0.001$), one month (p = 0.001), and six months (p = 0.007), indicating a steady improvement in patients' perceived QoL throughout the rehabilitation period.

MMSE domain values at admission and one, three, and six months after admission were shown to differ statistically significantly ($p < 0.001$) for patients with IS and ICH, according to the Friedman test (Table 2).

Subsequent analysis revealed that both IS and ICH showed statistically significant improvements in MMSE test scores in the Wilcoxon signed-rank test between admission and one ($p < 0.001$), three ($p < 0.001$), and six ($p < 0.001$) months after secondary rehabilitation. The EQ-5D-3L test improved statistically significantly between admission and one ($p < 0.001$), three ($p < 0.001$), and six ($p < 0.001$) months following secondary rehabilitation for both IS and ICH, according to the Wilcoxon signed-rank test (Table 3).

Table 2

Friedman test results for cognitive domains at multiple time points in patients with IS and ICH

MMSE domains	χ^2	*p*
Time orientation		
IS	59.19	< 0.001
ICH	64.45	< 0.001
Spatial orientation		
IS	60.27	< 0.001
ICH	58.03	< 0.001
Verbal memory		
IS	41.65	< 0.001
ICH	50.45	< 0.001
Attention		
IS	60.99	< 0.001
ICH	57.99	< 0.001
Memory recall		
IS	48.41	< 0.001
ICH	53.44	< 0.001
Naming		
IS	28.64	< 0.001
ICH	39.53	< 0.001
Repetition		
IS	30.51	< 0.001
ICH	34.44	< 0.001
Triple order		
IS	53.64	< 0.001
ICH	55.26	< 0.001
Following instructions		
IS	32.66	< 0.001
ICH	27.93	< 0.001
Writing		
IS	29.50	< 0.001
ICH	29.60	< 0.001
Crossing out		
IS	29.80	< 0.001
ICH	30.55	< 0.001

IS – ischemic stroke; ICH – intracerebral hemorrhagic stroke; MMSE – Mini-Mental State Examination.

Table 3

MMSE and EQ-5D-3L scores with changes over time for IS and ICH patients

Stroke type	MMSE (mean ± SD)	Δ MMSE	EQ-5D-3L (mean ± SD)	Δ EQ-5D-3L
IS				
admission	14.4 ± 8.6	-	7.5 ± 2.7	-
1 month	16.4 ± 7.6	2.0	9.4 ± 3.0	1.9
3 months	22.1 ± 6.9	5.6	11.0 ± 2.7	3.5
6 months	24.5 ± 5.1	2.5	11.7 ± 1.9	4.2
ICH				
admission	11.3 ± 7.2	-	5.8 ± 1.7	-
1 month	14.4 ± 6.9	3.1	7.9 ± 2.3	2.1
3 months	21.0 ± 6.8	6.6	9.7 ± 2.5	3.9
6 months	22.2 ± 6.0	1.1	10.9 ± 2.6	5.1

EQ-5D-3L – European Quality of Life 5-dimensional 3-level; SD – standard deviation.
For other abbreviations, see Table 2.

Table 4

Correlation analysis between MMSE and EQ-5D-3L for ischemic stroke

Parameter		EQ-5D-3L			
		admission	1 month	3 months	6 months
MMSE admission	CC	0.747	0.813	0.754	0.504
	p-value	< 0.001	< 0.001	< 0.001	0.010
1 month	CC	0.770	0.836	0.779	0.562
	p-value	< 0.001	< 0.001	< 0.001	0.003
3 months	CC	0.739	0.830	0.799	0.518
	p-value	< 0.001	< 0.001	< 0.001	0.008
6 months	CC	0.444	0.565	0.504	0.496
	p-value	0.026	0.003	< 0.001	0.012

CC – Spearman's correlation coefficient. For other abbreviations, see Tables 2 and 3.

Table 5

Correlation analysis between MMSE and EQ-5D-3L for intracerebral hemorrhagic stroke

Parameter		EQ-5D-3L			
		admission	1 month	3 months	6 months
MMSE					
admission	CC	0.412	0.788	0.791	0.632
	p-value	0.003	< 0.001	< 0.001	0.001
1 month	CC	0.407	0.772	0.794	0.637
	p-value	0.003	0.000	< 0.001	0.001
3 months	CC	0.397	0.794	0.805	0.665
	p-value	0.004	< 0.001	< 0.001	< 0.001
6 months	CC	0.245	0.637	0.610	0.595
	p-value	0.237	0.001	0.000	0.002

CC – Spearman's correlation coefficient. For other abbreviations, see Tables 2 and 3.

The correlation analysis's findings demonstrated a statistically significant association between the MMSE scale scores for both types of stroke and the QoL as assessed at each of the four points in time. There was a high to moderately strong positive correlation (Table 4).

Only in the case of ICH, there was no statistically significant association between EQ-5D-3L values at admission and MMSE scale values after six months (Table 5).

Discussion

Since it has been proven that patients face a series of mental changes after a stroke, we conducted this research with the aim of examining how secondary rehabilitation affects cognitive status and whether there is a correlation between cognitive status and QoL in a group of patients who survived IS and ICH [13].

Given that it has been proven that the ability of patients to communicate (verbally or non-verbally), follow, understand, and carry out orders is essential for a successful outcome of rehabilitation, only patients in whom this ability was preserved were included in our research. It is also important that the patient does not have major memory disorders or psychological changes [14]. Assessment of the impact of the duration of secondary rehabilitation on the cognitive status of our patients was performed using the MMSE instrument, since it represents the gold standard for examining cognitive impairment in hospitalized patients [7].

It was confirmed that the length of secondary rehabilitation significantly improves the cognitive status of stroke patients, with positive correlations between cognitive status and QoL. The MMSE test score at admission and later measurements indicates a positive effect on patients' mental states [15]. Taking this statement into account, and since the aforementioned results were related to the entire sample, the total score of the MMSE test in patients with IS and ICH was shown separately at all four measurement moments. It was observed that the values of the MMSE test increased significantly in both types of stroke, and those changes were statistically significant.

A study involving 218 stroke survivors found that post-stroke cognitive impairment affects 47.7% of participants, with nutrition and social interaction significantly promoting cognitive improvement. The study suggests that maintaining social interaction can lead to improved cognitive function and training effects [16].

Correlation analysis showed that in patients with IS, cognitive status was associated with QoL at all times of the examination. The study found a connection between ICH and secondary rehabilitation in patients at three examination points, but no connection after six months of rehabilitation. Recently published research results by Barbosa et al. [17] at the level of a one-year prospective cohort study of 391 patients with a first stroke, evaluated at the beginning, three, six, and twelve months after the stroke, proved that for a better QoL it is significant that the patients have a higher MMSE score and that the rehabilitation process lasts

as long as possible. These findings are consistent with the findings obtained in our research.

As we have already mentioned, patients with ICH exhibit more severe impairments and slightly lower scores than patients with IS. Therefore, we assume that this is why the results of the correlation analysis suggest that there is no relationship between MMSE scores and QoL after six months of rehabilitation. It has been proven that depression is often present in patients after stroke, and that its occurrence directly affects the QoL [18, 19]. According to research by Capo-Lugo et al. [20], in order to enhance functional recovery and QoL, patients who have had ICH should begin adopting rehabilitation treatments as soon as possible.

All types of stroke affect different aspects of QoL. A study by Katzan et al. [21] with 2,181 patients who had an IS, ICH, subarachnoid hemorrhage, or transient ischemic attack revealed that physical function, social role satisfaction, and executive function were the domains most impacted across all types of these events. This underscores the necessity of creating efficient interventions to enhance these health domains in survivors of these cerebrovascular events.

Research indicates that social interaction is a useful predictor of daily life activities in stroke survivors. It is assumed that this may be a consequence of the beneficial effect of training from good relationships with therapists. Good cognitive function has been shown to lead to better rehabilitation outcomes [22–24].

Certainly, stroke causes a number of mental changes and can sometimes cause serious cognitive impairments that patients face later [25]. Rehabilitation after a stroke requires interdisciplinary cooperation and should begin promptly. Decisions to discharge patients should be individual, and hospital stays should not hinder neurorehabilitation. Knowledge of common complications and early prevention can improve cognitive abilities [26].

As Dimunová et al. [27] demonstrated, through the joint engagement and action of the multidisciplinary team during rehabilitation, significant progress was also achieved in our case in terms of the recovery of patients' mental abilities.

The application of the MMSE scale has fewer limitations and requires minimal patient cooperation for a successful examination. Although the results of this test provide only a rough estimate, it is useful for assessing treatment effectiveness and cognitive status over time [28]. The values of the MMSE scale in our research were additionally analyzed in order to assess whether progress was achieved within all domains.

The analysis of the time orientation domain showed that patients' ability to state the date, year, and time was significantly improved compared to admission, in both IS and ICH patients. In our study, secondary rehabilitation also contributed to higher average values in the spatial orientation domain, underscoring its importance in both types of stroke.

In addition to the results obtained by Bo et al. [29], as well as the findings of our study demonstrating improvements in patients' mental state through exercise and cognitive training, Gamito et al. [30] recommend the use of a virtual reality-based game application incorporating attention and memory tasks, aiming to reduce costs, save time, and offer additional benefits. Within the verbal memory domain, the ability of patients to repeat three words is assessed, and in our sample, significant improvement was achieved over admission in both types of stroke. The study found significant improvements in attention and verbal memory domains at admission in both IS and ICH stroke patients, as well as notable gains in naming and repetition domains, compared to initial assessment.

The values of the three-step command domain, in which patients perform three given actions (following verbal instructions, writing, and crossing), were significantly different at admission in both IS and ICH patients. A recent study suggests that an individual's enriched life experiences, including education and occupation, provide a buffer against stroke-induced cognitive impairment and promote faster cognitive recovery after stroke. In addition, higher education minimizes long-term cognitive decline after stroke, especially in elderly patients [31].

It can be pointed out that clinical measures and secondary rehabilitation care are important predictors of the cognitive status and QoL of stroke survivors, regardless of the sociodemographic and clinical characteristics of the patients and the type of stroke. Our findings offer an evidence base to effectively address the problems that lie ahead while developing suitable ways to reduce disability among post-stroke patients.

In addition to rehabilitation, factors such as social support, mood disorders (especially post-stroke depression), socioeconomic status, and comorbidities such as diabetes or hypertension may also influence cognitive recovery and mental status over the six-month period [32]. These factors warrant further investigation in future studies.

It is clear that after a stroke event, cognitive status and QoL are impaired, and determining which domains are impacted is essential for making plans for future care. Including multiple QoL domains highlights the importance of holistic rehabilitation programs that integrate cognitive, psychosocial, physical, and pharmaceutical factors for stroke survivors [33].

Conclusion

According to our study results, secondary rehabilitation interventions have a substantial impact on stroke patients' cognitive status and quality of life. Six months of follow-up with multiple examinations (at one, three, and six months) showed that patients' cognitive status and quality of life improved when they participated in a secondary rehabilitation program that included cognitive training and psychological support, among other components. The key conclusions of this study are that cognitive status and quality of life are significantly correlated, and that a longer duration of secondary rehabilitation results in better outcomes in both cognitive function and quality of life after stroke.

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Conflict of interest

The authors declare no conflict of interest.

R E F E R E N C E S

1. *Murphy SJ, Werring DJ.* Stroke: causes and clinical features. Medicine (Abingdon) 2020; 48(9): 561–6.
2. *Lindmark A, Eriksson M, Darehed D.* Socioeconomic status and stroke severity: Understanding indirect effects via risk factors and stroke prevention using innovative statistical methods for mediation analysis. PLoS One 2022; 17(6): e0270533.
3. *GBD 2019 Stroke Collaborators.* Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol 2021; 20(10): 795–820.
4. *Ojaghihaghighi S, Vahdati SS, Mikaeilpour A, Ramouz A.* Comparison of neurological clinical manifestation in patients with hemorrhagic and ischemic stroke. World J Emerg Med 2017; 8(1): 34–8.
5. *Bisevac E, Lazovic M, Nikolic D, Mahmutovic E, Dolicanin Z, Jurisic-Skevin A.* Postacute Rehabilitation Impact on Functional Recovery Outcome and Quality of Life in Stroke Survivors: Six Month Follow-Up. Medicina (Kaunas) 2022; 58(9): 1185.
6. *Elendu C, Amaechi DC, Elendu TC, Ibhiedu JO, Egbunu EO, Ndam AR,* et al. Stroke and cognitive impairment: understanding the connection and managing symptoms. Ann Med Surg (Lond) 2023; 85(12): 6057–66.
7. *Bour A, Rasquin S, Boreas A, Limburg M, Verhey F.* How predictive is the MMSE for cognitive performance after stroke? J Neurol 2010; 257(4): 630–7.
8. *Cerniauskaite M, Quintas R, Koutsogeorgou E, Meucci P, Sattin D, Leonardi M,* et al. Quality-of-life and disability in patients with stroke. Am J Phys Med Rehabil 2012; 91(13 Suppl 1): S39–47.
9. *World Medical Association.* World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310(20): 2191–4.
10. *McCurley JL, Funes CJ, Zale EL, Lin A, Jacobo M, Jacobs JM,* et al. Preventing Chronic Emotional Distress in Stroke Survivors and Their Informal Caregivers. Neurocrit Care 2019; 30(3): 581–9.
11. *Bugarski V, Semnic M, Golubović Š.* Quick assessment of cognitive status and presence of depressive symptoms in acute phase of stroke. Psihijatrija danas 2009; 41(1–2): 29–41. (Serbian)
12. *Stojković Ivković M.* Mild cognitive impairment: The importance of early revealing and treatment options. Sestrinska reč 2017; 21(74): 24–6. (Serbian)
13. *EuroQol Group Association.* European Quality of Life-EuroQol EQ-5D [Internet]. Netherlands: EuroQol; 2025 [updated 2025 April 1; cited 2025 July 22]. Available from: https://euroqol.org/register/obtain-eq-5d/available-versions/
14. *Janus-Laszuk B, Mirowska-Guzel D, Sarzynska-Dlugosz I, Czlonkowska A.* Effect of medical complications on the after-stroke rehabilitation outcome. NeuroRehabilitation 2017; 40(2): 223–32.
15. *Isaac V, Stewart R, Krishnamoorthy ES.* Caregiver burden and quality of life of older persons with stroke: A community hospital study in South India. J Appl Gerontol 2011; 30(5): 643–54.
16. *Mori N, Otaka Y, Honaga K, Matsuura D, Kondo K, Liu M,* et al. Factors associated with cognitive improvement in subacute stroke survivors. J Rehabil Med 2021; 53(8): jrm00220.
17. *Barbosa PM, Ferreira LN, Cruz VT, Silva A, Szrek H.* Healthcare, Clinical Factors and Rehabilitation Predicting Quality of Life in First-time Stroke Patients: A 12-month Longitudinal Study. J Stroke Cerebrovasc Dis 2022; 31(4): 106300.
18. *Paolucci S.* Advances in antidepressants for treating post-stroke depression. Expert Opin Pharmacother 2017; 18(10): 1011–7.
19. *Schneider S, Taba N, Saapar M, Vibo R, Kõrv J.* Determinants of Long-Term Health-Related Quality of Life in Young Ischemic Stroke Patients. J Stroke Cerebrovasc Dis 2021; 30(2): 105499.
20. *Capo-Lugo CE, Askew RL, Muldoon K, Maas M, Liotta E, Prabhakaran S,* et al. Longer Time Before Acute Rehabilitation Therapy Worsens Disability After Intracerebral Hemorrhage. Arch Phys Med Rehabil 2020; 101(5): 870–6.
21. *Katzan IL, Schuster A, Newey C, Uchino K, Lapin B.* Patient-reported outcomes across cerebrovascular event types: More similar than different. Neurology 2018; 91(23): e2182–91.
22. *Gialanella B, Santoro R, Ferlucci C.* Predicting outcome after stroke: the role of basic activities of daily living predicting outcome after stroke. Eur J Phys Rehabil Med 2013; 49(5): 629–37.
23. *Ginex V, Vanacore N, Lacorte E, Sozzi M, Pisani L, Corbo M,* et al. General cognition predicts post-stroke recovery defined through minimal clinically important difference (MCID): a cohort study in an Italian rehabilitation clinic. Eur J Phys Rehabil Med 2015; 51(5): 597–606.
24. *Liu H, Lou VWQ.* Functional recovery of older stroke patients discharged from hospital to home: The effects of cognitive status and different levels of therapy intensity. J Clin Nurs 2019; 28(1–2): 47–55.
25. *Seo KD, Kang MJ, Kim GS, Lee JH, Suh SH, Lee KY.* National Trends in Clinical Outcomes of Endovascular Therapy for Ischemic Stroke in South Korea between 2008 and 2016. J Stroke 2020; 22(3): 412–5.
26. *Portegies ML, Bos MJ, Koudstaal PJ, Hofman A, Tiemeier HW, Ikram MA.* Anxiety and the Risk of Stroke: The Rotterdam Study. Stroke 2016; 47(4): 1120–3.
27. *Dimunová L, Soósová MS, Kardosová K, Červený M, Belovičová M.* Quality of life in post-stroke patients. Kontakt 2021; 23(3): 157–61.
28. *Su Y, Dong J, Sun J, Zhang Y, Ma S, Li M,* et al. Cognitive function assessed by Mini-mental state examination and risk of all-cause mortality: a community-based prospective cohort study. BMC Geriatr 2021; 21(1): 524.
29. *Bo W, Lei M, Tao S, Jie LT, Qian L, Lin FQ,* et al. Effects of combined intervention of physical exercise and cognitive training on cognitive function in stroke survivors with vascular cognitive impairment: a randomized controlled trial. Clin Rehabil 2019; 33(1): 54–63.
30. *Gamito P, Oliveira J, Coelho C, Morais D, Lopes P, Pacheco J,* et al. Cognitive training on stroke patients via virtual reality-based serious games. Disabil Rehabil 2017; 39(4): 385–8.
31. *Shin M, Sohn MK, Lee J, Kim DY, Lee SG, Shin YI,* et al. Effect of cognitive reserve on risk of cognitive impairment and re-

covery after stroke: the KOSCO study. Stroke 2020; 51(1): 99–107.
32. *Alawieh A, Zhao J, Feng W*. Factors affecting post-stroke motor recovery: Implications on neurotherapy after brain injury. Behav Brain Res 2018; 340: 94–101.
33. *Dhandapani M, Joseph J, Sharma S, Dabla S, Varkey BP, Narasimha VL,* et al. The Quality of Life of Stroke Survivors in the Indian Setting: A Systematic Review and Meta-Analysis. Ann Indian Acad Neurol 2022; 25(3): 376–82.

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Visceral artery aneurysms, treatment and controversies – 20 years of single-center experience

Aneurizme visceralnih arterija, lečenje i kontroverze – 20 godina iskustva jednog centra

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Abstract

Introduction/Aim. Visceral artery aneurysms (VAAs) are rare diseases most often diagnosed accidentally during diagnostic workups for other diseases or for abdominal pain of unknown etiology. The aim of this study was to present 20 years of single-center experience from the surgical treatment of VAAs. **Methods.** A retrospective study analyzed the outcomes of surgical treatment in 15 patients with VAAs, treated between 2004 and 2024. Both endovascular and classic, open surgical techniques were used, with special emphasis on the histopathological causes of aneurysm formation. Special attention is directed towards symptomatology, preoperative diagnostics, open and endovascular treatment techniques, as well as postoperative follow-up and possible secondary interventions. **Results.** The average age of patients was 56.1 years. There was a total of seven female and eight male patients. The average diameter of the aneurysms was 4.4 cm (ranging from 2.4 to 6 cm). Open surgical operations were performed in 12 patients, while 3 patients underwent endovascular reconstruction. Surgical treatment was performed on 10 patients due to aneurysm of the splenic artery, on 2 patients due to aneurysm of the gastroduodenal artery, on 1 patient due to aneurysm of the common hepatic artery, on 1 patient due to aneurysm of the celiac trunk, and on 1 patient due to aneurysm of the renal artery. Five patients were operated on as emergency cases due to aneurysm rupture and hemorrhagic shock, while the remaining patients were operated on electively. Immediately after surgery, death occurred in three patients, while in the others, the follow-up period lasted from two to ten years. **Conclusion.** VAAs represent a serious vascular disease, which, if not diagnosed and treated in time, can lead to deadly complications due to aneurysm rupture and bleeding. In the era of endovascular surgery, open surgical reconstruction of visceral aneurysms continues to play an important role.

Key words:
aneurysm; arteries; endovascular procedures; treatment outcome; vascular surgical procedures.

Apstrakt

Uvod/Cilj. Aneurizme visceralnih arterija (*visceral artery aneurysms* – VAA) su retka oboljenja koja se najčešće dijagnostikuju slučajno u sklopu dijagnostičkih procedura usled nekog drugog oboljenja, ili zbog abdominalnog bola nepoznate etiologije. Cilj rada bio je da se prikaže 20 godina iskustva jednog centra u hirurškom lečenju VAA. **Metode.** Retrospektivnom studijom analizirani su ishodi hirurškog lečenja 15 obolelih od VAA, lečenih u periodu od 2004. do 2024. godine. Korišćene su i endovaskularne i klasične, otvorene hirurške tehnike, sa posebnim osvrtom na histopatološke uzroke nastanka aneurizmi. Posebna pažnja usmerena je ka simptomatologiji, preoperativnoj dijagnostici, otvorenim i endovaskularnim tehnikama lečenja, kao i postoperativnom praćenju i mogućim sekundarnim intervencijama. **Rezultati.** Prosečna starost bolesnika bila je 56,1 godina. Ukupno je bilo sedam bolesnika ženskog i osam bolesnika muškog pola. Prosečan prečnik aneurizmi bio je 4,4 cm (sa rasponom od 2,4 do 6 cm). Kod 12 bolesnika urađena je otvorena hirurška operacija, dok je kod troje bolesnika urađena endovaskularna rekonstrukcija. Hirurško lečenje sprovedeno je kod deset bolesnika zbog aneurizme lijenalne arterije, kod dva bolesnika zbog aneurizme gastroduodenalne arterije, kod jednog bolesnika zbog aneurizme zajedničke hepatične arterije, jednog zbog aneurizme celijačnog stabla i kod jednog bolesnika zbog aneurizme renalne arterije. Petoro bolesnika operisani su kao hitni slučajevi usled rupture aneurizme i hemoragičkog šoka, dok su preostali bolesnici operisani kao elektivni. Neposredno nakon operacije, smrt je

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nastupila kod tri bolesnika, dok je kod ostalih period praćenja bio od dve do deset godina. **Zaključak.** VAA predstavljaju ozbiljno vaskularno oboljenje, koje ukoliko se na vreme ne dijagnostikuje i ne leči može dovesti do smrtonosnih komplikacija usled rupture aneurizme i krvarenja. U eri endovaskularne hirurgije, otvorena hirurška rekonstrukcija visceralnih aneurizmi i dalje ima važnu ulogu.

Ključne reči:
aneurizma; arterije; endovaskularne procedure; lečenje, ishod; hirurgija, vaskularna, procedure.

Introduction

Aneurysmal disease of the visceral arteries is considered a rare condition, with an incidence ranging from 0.01% to 2.0% in the general population, including findings from autopsies conducted over several decades [1, 2]. With ongoing technological advancements in medicine, particularly in the field of diagnostics, it is likely that the reported incidence rate of visceral artery aneurysms (VAAs) will significantly increase in the near future.

The most common site of VAA occurrence is the splenic artery, accounting for approximately 60% of cases, followed by the hepatic artery in about 20%, while the remaining locations are considerably less frequent (e.g., mesenteric artery, celiac trunk, gastroduodenal artery, renal arteries, and other visceral arteries) [2, 3].

True aneurysms are histopathologically distinguished from pseudoaneurysms by the presence of all three layers of the arterial wall in the aneurysm structure. In contrast, pseudoaneurysms involve a disruption of the vessel's wall integrity. Accordingly, the most frequently encountered types of VAAs are atherosclerotic aneurysms and those associated with congenital structural abnormalities of the arterial wall (e.g., cystic medial degeneration, fibromuscular dysplasia, Marfan syndrome) [4].

Early diagnosis and appropriate treatment of VAAs are of great importance due to the potential complications of this condition. A previous study has shown that VAAs with a diameter of less than 2 cm do not require surgical treatment; periodic monitoring and adequate pharmacologic therapy are sufficient [5]. VAAs larger than 2 cm require surgical intervention, either *via* open surgery or endovascular techniques, to prevent possible complications. Rupture of a VAA is the most common and also the most dangerous complication. Thrombosis, distal embolization of the target organ, and fistulization with surrounding structures are rarer but equally serious complications [5].

The symptomatology of VAAs is highly nonspecific. Symptoms can range from mild, such as occasional dull pain in the epigastrium or back, to severe and dramatic presentations in the case of rupture, when patients experience intense abdominal pain along with signs of hemorrhagic shock. Depending on the location and diameter of the aneurysm, some VAAs can be detected *via* Doppler ultrasonography; however, the gold standard for both diagnosis and treatment planning is still computerized tomography (CT) angiography or nuclear magnetic resonance angiography of the aorta and its visceral branches [6].

Various surgical options are available for the treatment of VAAs. Generally, VAAs can be managed *via* open surgery or endovascular intervention. Open surgical techniques vary depending on the type and location of the aneurysm. They may include aneurysm resection with end-to-end arterial reconstruction, aneurysm resection with venous or synthetic bypass grafting, or aneurysmectomy followed by arterial suturing. Another option includes arterial ligation followed by organ removal if the affected artery supplies a vital organ (e.g., splenectomy or nephrectomy). Endovascular procedures may involve complete exclusion of the aneurysm using an appropriate endograft, coil embolization of the aneurysmal sac, or hybrid procedures (a combination of open and endovascular techniques) [7].

In the event of VAA complications such as rupture or thrombosis with potentially fatal outcomes, emergency surgical intervention is required – most often an open surgical procedure. Reported mortality rates following VAA rupture range from 25% to 75%. Currently, no consensus exists regarding the optimal surgical technique for VAA management, and no randomized controlled trials have been published on this subject [6, 7].

The aim of this study was to present the treatment outcomes of VAAs over a 20-year period.

Methods

This was a retrospective study analyzing the outcomes of surgical treatment for VAAs in patients treated at the Clinic for Vascular and Endovascular Surgery, Military Medical Academy, Belgrade, Serbia. The study covered a 20-year period, from 2004 to 2024, and included both endovascular and classical open surgical techniques, with particular emphasis on the histopathological causes of aneurysm formation. Special attention was also given to symptomatology, preoperative diagnostics, both open and endovascular treatment methods, as well as postoperative follow-up and potential secondary interventions. The primary criterion for elective surgical treatment was a VAA diameter of 2 cm or greater, as diagnosed by CT angiography or magnetic resonance imaging angiography, to prevent severe complications [7, 8]. The choice of treatment technique—either open surgery or an endovascular approach—was made individually, based on the patient's comorbidities and the topographic-anatomical characteristics of the aneurysm. Emergency surgical intervention was required in all patients presenting with clinical signs of VAA rupture and hemorrhagic shock [6, 8].

Results

Between 2004 and 2024, a total of 15 patients were treated for VAAs at our center. All patients received specialized management by vascular surgeons. This included both individuals who underwent conventional open surgical repair and those treated *via* endovascular procedures, following established vascular surgical protocols.

Patient age ranged from 28 to 74 years, with a mean age of 56.1 years. Of the total cohort, seven patients were female and eight were male.

Surgical treatment was performed in ten patients for splenic artery aneurysms (SAA), in two for gastroduodenal artery aneurysms (GDAA), one for a common hepatic artery aneurysm (CHAA), one for a celiac trunk aneurysm (CTA), and in one patient for a renal artery aneurysm (RAA).

The primary indication for elective surgical intervention was a CT angiography-confirmed VAA measuring greater than 2 cm in diameter. Emergent surgical treatment was performed in patients with CT angiography-confirmed symptomatic VAA or ruptured VAA.

Five patients underwent emergency surgery due to aneurysm rupture and hemorrhagic shock, one due to rupture of a GDAA, two due to ruptured SAA, one due to RAA rupture, and one due to CTA rupture (Table 1). The remaining patients underwent elective surgical treatment.

A total of 12 patients were treated with open classical surgical procedures: in 8 cases, aneurysm resection was followed by end-to-end arterial reconstruction, while in 4 cases, arterial ligation was performed. The surgical approach for all patients undergoing conventional open repair involved a standardized transperitoneal route *via* a midline laparotomy, with meticulous dissection and exposure of the abdominal aorta and the involved visceral arterial segment.

In three patients, endovascular procedures were employed. In all patients treated with endovascular repair, vascular access was achieved through a standard transfemoral approach, utilizing the Seldinger technique, which involves percutaneous puncture of one or both common femoral arteries.

The mean aneurysm diameter was 4.4 cm, ranging from 2.4 cm to 6 cm. In the immediate postoperative period, mortality occurred in three patients. For the remaining patients, the follow-up period ranged from 2 to 10 years.

In one case, a secondary intervention was performed one month after an endovascular procedure, involving conversion to open surgical reconstruction.

CT images of a CHAA, treated with an implanted stent graft and an additional stent for ostial occlusion, are shown in Figure 1A (before stenting) and Figure 1B (after stenting).

Etiologically, no clearly defined cause was identified for isolated VAAs. It is considered that all etiological factors contributing to the development of aneurysmal disease may also play a role in VAA formation, including hypertension, chronic obstructive pulmonary disease, smoking, and diabetes mellitus (Table 1).

The most common histopathological substrate in elective male patients operated on for SAA was atherosclerotic disease, whereas in females it was cystic medial degeneration of the arterial wall, with aneurysm localization near the origin of the splenic artery from the celiac trunk. Histopathological analysis of the aneurysm wall specimens was performed using hematoxylin and eosin staining, and the samples were examined under a light microscope (Figure 2). In these cases, aneurysm resection followed by end-to-end arterial anastomosis was performed (three males and five females). These patients were not suitable candidates for endovascular procedures due to a significant diameter discrepancy between the artery proximal and distal to the aneurysm, as well as a wide aneurysmal neck. Two patients who underwent emergency surgery for ruptured VAAs presented with clinical signs of hemorrhagic shock and aneurysm localization near the splenic hilum; they were treated with splenic artery ligation and splenectomy. Postoperative mortality occurred in one elective case and two emergency cases, with causes of death attributed to cardiac failure and pulmonary complications.

A younger male patient with previously diagnosed Marfan syndrome underwent surgery for CHAA. The aneurysm developed as a result of a dissection of the descending thoracic and abdominal aorta, which extended to the hepatic artery. One year after the dissection, due to intermittent right epigastric pain, CT angiography revealed a post-dissection CHAA measuring 6 cm, extending from the hepatic artery

Table 1

Distribution of patients by gender, VAA localization, risk factors, and complications

Parameters	SAA	CHAA	GDAA	RAA	CTA
Gender					
male	3 (20.0)	1 (6.7)	2 (13.3)	1 (6.7)	1 (6.7)
female	7 (46.7)	0	0	0	0
Average aneurysm diameter (cm)	4.2	6.0	4.6	3.0	4.2
Average age, years	48.2	30.0	56.3	74.0	72.0
Smoking	8 (53.3)	0	2 (13.3)	0	1 (6.7)
HTA	5 (33.0)	1 (6.7)	1 (6.7)	1 (6.7)	1 (6.7)
DM	2 (13.3)	0	1 (6.7)	0	1 (6.7)
COPD	2 (13.3)	0	1 (6.7)	0	0
Rupture	2 (13.3)	0	1 (6.7)	1 (6.7)	1 (6.7)

VAA – visceral artery aneurysm; SAA – splenic artery aneurysm; CHAA – common hepatic artery aneurysm; GDAA – gastroduodenal artery aneurysm; RAA – renal artery aneurysm; CTA – celiac trunk aneurysm; HTA – hypertensio arterialis; DM – diabetes mellitus; COPD – chronic obstructive pulmonary disease.
Values are given as numbers (percentages).

Fig. 1 – Common hepatic artery aneurysm (CHAA) with implanted stent graft and stent for ostial occlusion computerized tomography before (A) and after (B) stenting.

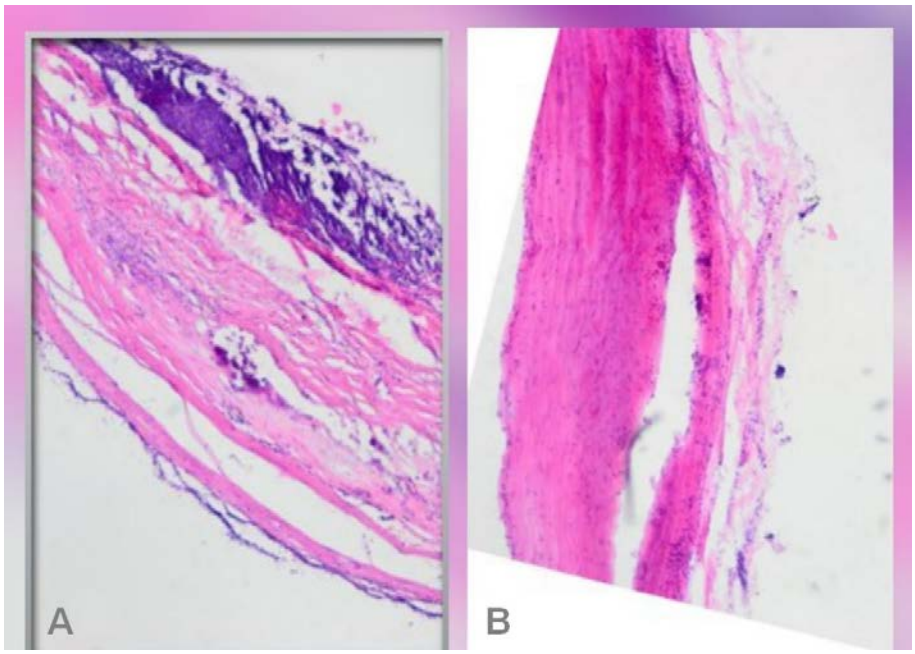

Fig. 2 – Histopathological appearance of the wall of the splenic artery aneurysm: A) severe atherosclerotic changes in the artery wall with calcification; B) mediocystic degeneration with delamination of the artery wall. Hematoxylin and eosin staining, × 20 magnification.

origin to the hepatic hilum. A thoracic stent graft was placed, occluding the celiac trunk. Two months after the endovascular procedure, a fistula developed between the CHAA and the common bile duct, causing hemobilia and cholangitis. An open surgical procedure was then performed with ligation of the hepatic artery; however, the patient succumbed postoperatively due to liver failure.

Two patients underwent surgery for GDAA. Both patients had true GDAA. One patient was electively treated for a 6 cm aneurysm with endovascular exclusion using a stent graft

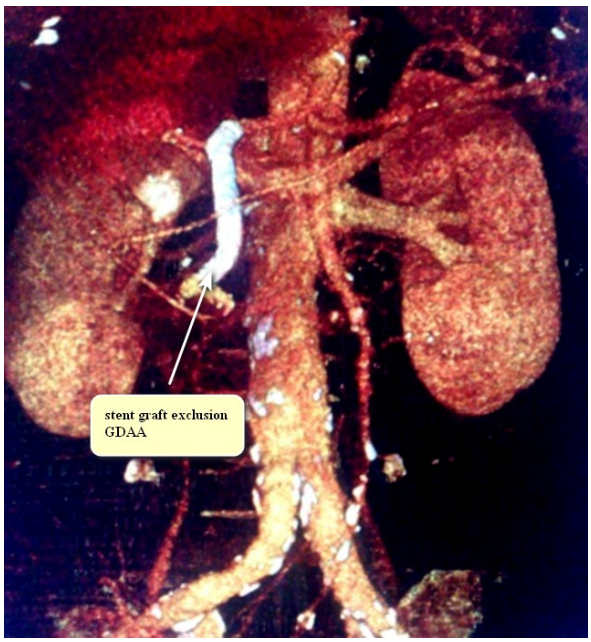

Fig. 3 – Stent graft exclusion of gastroduodenal artery aneurysm (GDAA) – computerized tomography angiography.

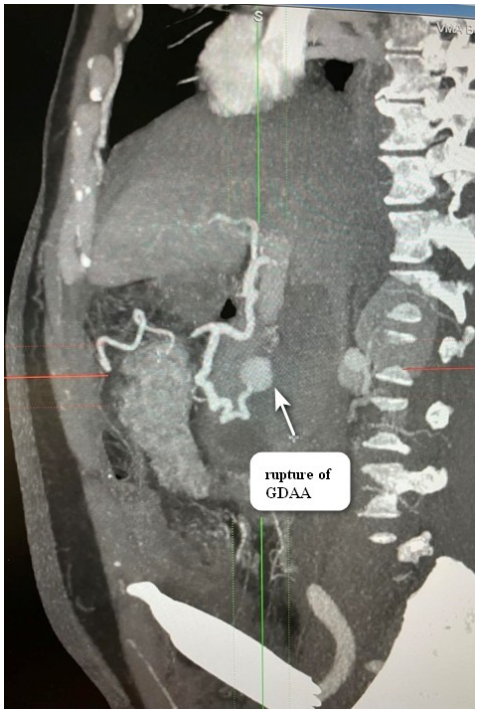

Fig. 4 – Rupture of gastroduodenal artery aneurysm (GDAA) – computerized tomography angiography.

(Viabahn, Gore Medical, USA) (Figure 3). The other patient underwent emergency surgery due to massive intra-abdominal hemorrhage; proximal and distal ligation of the gastroduodenal artery was performed along with aneurysmectomy. Rupture of a GDAA was shown in Figure 4 (CT angiography).

One patient was emergently operated on for CTA, and ligation of the trunk adjacent to the aorta was performed. Unfortunately, the patient died postoperatively due to multiorgan failure.

In one patient with RAA, coil embolization of the aneurysm was performed; however, postoperative renal artery thrombosis necessitated nephrectomy of the infarcted kidney.

Discussion

VAA is a condition characterized by nonspecific symptoms and is often asymptomatic. Diagnosis of this condition is frequently incidental during routine examinations or investigations for other diseases [6–9]. In their 2019 meta-analysis of

studies on the management of true VAAs, Barrionuevo et al. [9] demonstrated that in approximately two-thirds of cases, the most common location of VAAs is the splenic artery, specifically in the segment above the superior border of the pancreas. Their analysis also concluded that the majority of these aneurysms were atherosclerotic in nature (nearly 80% of cases). They found no significant difference in postoperative complication rates between endovascular and open surgical treatments. However, a statistically significant difference in mortality was observed between elective and urgent surgeries in both the endovascular and open surgery groups (mortality for elective patients was approximately 5%, whereas in urgently operated patients, it could reach up to 75%).

Over the 20-year period at our center, most patients treated for VAAs had SAA – 10 patients (67% of all VAA surgeries). Histopathological analysis of the aneurysm wall showed that all patients older than 50 years, regardless of gender, had atherosclerotic aneurysms (five males and three females, totaling 80%). In contrast, two younger female patients exhibited cystic medial degeneration of the aneurysm wall. One patient operated on urgently died in the early postoperative period, and another who underwent elective surgery also died. In both cases, splenic artery ligation combined with splenectomy was performed.

The second most frequent type of VAAs is CHAA. In their 2018 study on the classification, diagnosis, and treatment of CHAA, Piasek et al. [10] reported that these aneurysms are significantly more common in males, are mostly localized in the common hepatic artery, and are almost always atherosclerotic. The main complications of these aneurysms are fistulization with the common bile duct and rupture. There are no reported cases in the global literature of post-dissection CHAA in patients with Marfan syndrome.

True GDAA are extremely rare, while pseudoaneurysms of this artery are significantly more common, as demonstrated by Obara et al. [11] in their 2020 study. They found that only 2% of all VAAs were GDAA, whereas the percentage of pseudoaneurysms in this artery was much higher. This is attributed to the proximity of the pancreas, where inflammatory processes of the pancreas spread to the artery, as well as traumatic injuries to the artery. They also concluded that rupture of these aneurysms is more frequent compared to other VAA locations, with a mortality rate of 21% in ruptures. At our institution, over the past twenty years, one elective endovascular exclusion of a GDAA using a stent graft and one open urgent surgical ligation of a GDAA have been performed. No complications were observed during the ten-year postoperative follow-up for either surgical technique

As shown by Obara et al. [11], CTA and RAA are rarely isolated diseases but are mostly associated with aneurysmal or dissecting aortic disease. Due to their proximity to the aorta, their surgical treatment is complex and often requires simultaneous surgical intervention on both the aorta and VAA. During 20 years of experience at our institution, only one patient with an isolated CTA was treated urgently due to rupture. Ligation of the celiac trunk at its origin from the aorta was performed, but the patient died postoperatively due to multiorgan failure. Additionally, only one patient with an isolated RAA underwent embolization of the aneurysm, considering its location and type (a saccular aneurysm with a narrow neck near the renal hilum). However, due to postoperative renal artery thrombosis and kidney infarction, nephrectomy was necessary.

Conclusion

Visceral artery aneurysms represent a serious vascular disease that, if not diagnosed and treated on time, can lead to fatal complications due to aneurysm rupture and hemorrhage. In the era of endovascular surgery, considering the location of the aneurysms as well as the organ distal to the aneurysm site, open surgical reconstruction of aneurysms still holds an important role whenever possible, involving aneurysm resection and reconstruction either by end-to-end anastomosis or bypass procedure. Whenever possible, ligation of the visceral artery aneurysm should be avoided due to the risk of infarction of the organ supplied by that artery.

REFERENCES

1. *Pulli R, Dorigo W, Troisi N, Pratesi G, Innocenti AA, Pratesi C.* Surgical treatment of visceral artery aneurysms: a 25-year experience. J Vasc Surg 2008; 48(2): 334–42.
2. *Fankhauser GT, Stone WM, Naidu SG, Oderich GS, Ricotta JJ, Bjarnason H,* et al. The minimally invasive management of visceral artery aneurysms and pseudoaneurysms. J Vasc Surg 2011; 53(4): 966–70.
3. *Corey MR, Ergul EA, Cambria RP, English SJ, Patel VI, Lancaster RT,* et al. The natural history of splanchnic artery aneurysms and outcomes after operative intervention. J Vasc Surg 2016; 63(4): 949–57.
4. *Gehlen JM, Heeren PA, Verhagen PF, Peppelenbosch AG.* Visceral artery aneurysms. Vasc Endovascular Surg 2011; 45(8): 681–7.
5. *Berceli SA.* Hepatic and splenic artery aneurysms. Semin Vasc Surg 2005; 18(4): 196−201.
6. *Badea R.* Splanchnic artery aneurysms: the diagnostic contribution of ultrasonography in correlation with other imaging methods. J Gastrointestin Liver Dis 2008; 17(1): 101–5.
7. *Pitton MB, Dappa E, Jungmann F, Kloeckner R, Schotten S, Wirth GM,* et al. Visceral artery aneurysms: Incidence, management, and outcome analysis in a tertiary care center over one decade. Eur Radiol 2015; 25(7): 2004–14.
8. *Abbas MA, Stone WM, Fowl RJ, Gloviczki P, Oldenburg WA, Pairolero PC,* et al. Splenic artery aneurysms: two decades experience at Mayo clinic. Ann Vasc Surg 2002; 16(4): 442–9.
9. *Barrionuevo P, Malas MB, Nejim B, Haddad A, Morrow A, Ponce O,* et al. A systematic review and meta-analysis of the management of visceral artery aneurysms. J Vasc Surg 2019; 70(5): 1694−9.

10. *Piasek E, Sojka M, Kuczyńska M, Światłowski Ł, Drelich-Zbroja A, Furmaga O,* et al. Visceral artery aneurysms – classification, diagnosis and treatment. J Ultrason 2018; 18(73): 148–51.
11. *Obara H, Kentaro M, Inoue M, Kitagawa Y.* Current management strategies for visceral artery aneurysms: an overview. Surg Today 2020; 50(1): 38–49. Erratum in: Surg Today 2020; 50(3): 320.

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Evaluation of Tp-e interval and Tp-e/QTc ratio in crush injury patients

Procena Tp-e intervala i odnosa Tp-e/QTc kod pacijenata sa povredom usled nagnječenja

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Abstract

Background/Aim. While the association between systemic findings and arrhythmia in crush syndrome is well established, limited literature addresses the correlation between the peak and the end of the T wave (Tp-e) interval, Tp-e/QT ratio, and Tp-e/corrected QT (QTc) ratio intervals with crush injury. The aim of this study was to evaluate the potential for arrhythmia in crush injury patients by utilizing the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio. **Methods.** A retrospective study included 42 patients divided into two groups: a group with crush injuries (n = 23) and a control group (n = 19). Demographic data of patients presented with crush injuries were recorded. These details included their age, gender, vital signs, and comorbidities. Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were also recorded for comparison between the two patient groups. **Results.** Parameters derived from the electrocardiogram demonstrated significant differences in Tp-e and Tp-e/QTc values between the group with crush injuries and control group. Tp-e was notably higher in patients with crush injuries in comparison to the control group (94.27 ± 27.90 vs. 73.36 ± 11.25, p = 0.024). Furthermore, it was found that the Tp-e/QTc ratio was markedly elevated among patients with crush injuries compared to the control group (0.223 ± 0.064 vs. 0.180 ± 0.030, p = 0.010). Receiver operating characteristic curve analysis showed that at a Tp-e cut-off value of 79.50, trauma severity could be predicted with 82.6% sensitivity and 73.7% specificity, indicating the prediction capability of Tp-e in trauma severity (area under the curve: 0.805, p < 0.001). **Conclusion.** In patients presenting to the emergency department with crush injuries, we posit that the Tp-e interval and Tp-e/QTc ratio on electrocardiogram may function as markers for potential arrhythmia progression.

Key words:
arrhythmias, cardiac; crush injuries; electrocardiography; emergency medicine.

Apstrakt

Uvod/Cilj. Dok je povezanost između sistemskih nalaza i aritmije kod sindroma nagnječenja dobro poznata, ograničen broj radova se bavi istraživanjem korelacije između intervala *the peak and the end of the T wave* (Tp-e), odnosa Tp-e/QT i odnosa Tp-e/*corrected* QT (QTc) sa povredom usled nagnječenja. Cilj rada bio je da se proceni potencijal za nastanak aritmija kod pacijenata sa povredom usled nagnječenja korišćenjem intervala Tp-e, odnosa Tp-e/QT i odnosa Tp-e/QTc. **Metode.** Retrospektivnom studijom obuhvaćeno je 42 pacijenta podeljena u dve grupe: grupa sa povredama usled nagnječenja (n = 23) i kontrolna grupa (n = 19). Zabeleženi su demografski podaci pacijenata koji su se javili sa povredama usled nagnječenja. Ovi podaci uključivali su starost, pol, vitalne znake i komorbiditete pacijenata. Takođe su zabeleženi interval Tp-e, odnos Tp-e/QT i odnos Tp-e/QTc u cilju poređenja između dve grupe pacijenata. **Rezultati.** Parametri dobijeni elektrokardiogramom pokazali su značajne razlike u vrednostima Tp-e i Tp-e/QTc između grupe povređenih usled nagnječenja i kontrolne grupe. Tp-e je bio znatno viši kod povređenih usled nagnječenja u poređenju sa kontrolnom grupom (94,27 ± 27,90 vs. 73,36 ± 11,25, p = 0,024). Utvrđeno je da je odnos Tp-e/QTc bio značajno povišen kod povređenih usled nagnječenja u poređenju sa kontrolnom grupom (0,223 ± 0,064 vs. 0,180 ± 0,030, p = 0,010). Analiza krive *receiver operating characteristic* pokazala je da se pri graničnoj vrednosti Tp-e intervala od 79,50 težina povrede može predvideti sa osetljivošću od 82,6% i specifičnošću od 73,7%, što ukazuje na mogućnost predviđanja težine povrede pomoću Tp-e intervala (površina ispod krive: 0,805, p < 0,001). **Zaključak.** Kod pacijenata koji se javljaju na odeljenje hitne pomoći zbog povreda usled nagnječenja, pretpostavljamo da interval Tp-e i odnos Tp-e/QTc na elektrokardiogramu mogu služiti kao markeri za potencijalnu progresiju aritmije.

Ključne reči:
aritmija; povrede, kraš; elektrokardiografija; medicina, urgentna.

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Introduction

Earthquakes have led to extensive morbidity and mortality, especially in countries prone to earthquakes, like Turkey. Recently, on February 6, 2023, a severe earthquake with its epicenter in Kahramanmaraş caused widespread problems focused in a specific geographic area [1]. Individuals injured during this earthquake, particularly those trapped under collapsed buildings, have manifested systemic symptoms attributed to crush injuries, leading to direct injury to the muscles and ischemic perfusion injury [2]. Systemic manifestations are common in cases of crush syndrome, which often result in acute renal failure, hemorrhage, sepsis, shock, electrolyte derangement, alongside psychological distress and cardiac arrhythmias [3, 4].

A clinical study has shown that measuring QT prolongation and corrected QT interval on an electrocardiogram (ECG) is an effective method for detecting cardiac arrhythmias in patients [5]. The peak and the end of the T wave (Tp-e) interval are utilized in predicting various cardiovascular diseases such as long QT syndrome, acute myocardial infarction, and hypertrophic cardiomyopathy. It measures the duration between the peak of the T wave and the end of the T wave at the isoelectric line, indicating transmural repolarization [6, 7].

Although the development of arrhythmia after crush injury is a well-established relationship, there is limited literature on the potential correlation between the Tp-e interval, Tp-e/QT ratio, and Tp-e/corrected QT (QTc) ratio intervals and crush injury.

The aim of this study was to examine the potential risk of arrhythmia in crush injury patients using the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio.

Methods

This research is a retrospective study conducted at the Health Science University, Antalya Training and Research Hospital, Department of Emergency Medicine, Antalya, Turkey, examining patients who sought medical help for crush syndrome after an earthquake that occurred in Kahramanmaraş, Turkey, on February 6, 2023.

The study was approved by the Ethics Committee of the Health Science University, Antalya Training and Research Hospital, Antalya (No. 11/22, from August 24, 2023).

Our set of exclusion criteria comprised patients aged below 18 years, individuals with arrhythmias, coronary heart disease, chronic liver and kidney ailments, patients with/possibly having kidney-related pathology from the hospital document system, and previous hospital admissions, as well as pregnant patients and those consuming antiarrhythmic medications such as beta-blockers, calcium channel blockers, digoxin, etc. The study's participants were patients aged 18 years and older who had been diagnosed with crush injury. By this, we mean patients in whom elevated levels of destruction products were found in the blood following muscle destruction. Patients were transported approximately 400–500 km by ship or ambulance. Crush injuries can range in severity from mild to life-threatening. The severity depends on factors like the force of impact, duration of compression, location of the injury, and the extent of tissue damage. Due to the distance of the hospital location from the earthquake zone, only patients with moderate and serious injuries were referred to our hospital, and they were followed up on.

This study included 42 patients divided into two groups: a group with crush injuries (23 patients) and a control group (19 patients). Demographic data regarding patients suffering from crush injuries, encompassing age, gender, vital signs, and accompanying medical conditions, has been compiled. The control group (without any illness) comprised individuals who were admitted to the emergency department due to trauma or non-cardiac pathologies, with comparable age and demographic characteristics established. The control group consisted of patients from regions minimally affected by the earthquake, whose emergency laboratory parameters and ECG findings were unchanged, and who were admitted and discharged from the emergency department with conditions such as vertigo, migraine, or renal colic. Hemogram and biochemical parameters of both patient groups were extracted from their medical files, along with their respective outcomes and trauma-related conditions. The biochemistry parameters of the patients included creatinine [normal range (NR): 0.66–1.09 mg/dL], creatine kinase (NR: 0–172 U/L), calcium (NR: 8.8–10.6 mg/dL), and potassium (NR: 3.50–5.1 mg/dL). ECGs taken upon patients' arrival at the emergency department were recorded at a speed of 50 mm/s and measured for necessary parameters by two senior emergency physicians, whose average was then calculated.

The QT interval was measured and recorded as the time between the onset of the Q wave and the end of the T wave as it returns to the isoelectric line. The QT value was further corrected, using the Bazett formula, and recorded [5, 8]. The Tp-e interval was determined by measuring the duration between the T wave peak and the isoelectric line, which signifies the T wave decline onto the isoelectric line. T wave variables were only assessed in lead V5. The same standard value was asked to be compared in all patient and control groups [5, 8, 9–12]. Additionally, the Tp-e/QTc ratio was recorded to facilitate comparison between the patient and control cohorts.

Statistical analysis

The SPSS software version 25.0 (SPSS Inc., Chicago, IL) was utilized for data analysis of crush syndrome patients. Normality of the data for both groups was assessed using the Kolmogorov-Smirnov test. For variables that followed a normal distribution, comparisons between groups were performed using independent two-sample t-tests. In cases where normal distribution was not observed, the Mann-Whitney *U* test was utilized, while categorical data were assessed using the Chi-square test and Fisher's exact test. A *p*-value of < 0.05 was considered statistically significant.

Results

Age and gender were comparable between the two groups, with no significant differences observed. Upon comparison of vital signs between the groups, the control group showed a marked decrease in systolic and diastolic blood pressures and pulse rate ($p < 0.05$). Significant differences were observed between crush injury and control groups based on the Tp-e and Tp-e/QTc parameters obtained by comparing ECG parameters. The Tp-e parameter for crush injury patients was significantly higher than that for the control group (94.27 ± 27.90 vs. 73.36 ± 11.25, $p = 0.024$). Moreover, the Tp-e/QTc ratio was significantly higher in crush injury patients compared to the control group (0.223 ± 0.064 vs. 0.180 ± 0.030, $p = 0.010$) (Table 1 and Figure 1). Out of the patients with crush injuries, 3 (13.0%) were discharged, 18 (78.3%) were admitted to the ward, and 2 (8.7%) were admitted to the intensive care unit. No deaths occurred during the patients' follow-up (Table 2). Furthermore, the analysis of the receiver operating

Table 1

Statistical analysis of the control and crush injury patients

Parameters	Control group (n = 19)	Crush injury group (n = 23)	*p*-value
Age, years	42.42 ± 19.29	44.6 ± 21.7	0.367
Gender			
male, n(%)	11 (59.7)	13 (56.5)	0.586
Vital sign			
SBP, mmHg	137.91 ± 12.94	141.63 ± 30.21	0.004
DBP, mmHg	81.04 ± 10.21	83.84 ± 20.54	0.003
O_2 saturation, %	96.86 ± 2.92	97.42 ± 1.42	0.039
Pulse, bpm	85.13 ± 10.34	91.26 ± 17.35	0.005
Laboratory			
creatinine, mg/dL	1 ± 0.2	0.79 ± 0.19	0.001
creatine kinase, U/L	69 (29)	1,554 (7,661)	< 0.001
calcium, mg/dL	9.17 ± 0.46	8.33 ± 0.80	0.005
potassium, mg/dL	4.11 ± 0.34	3.80 ± 0.52	0.047
Electrocardiography			
QTc	409.78 ± 24.31	420.52 ± 17.88	0.095
V5 Tp-e	73.36 ± 11.25	94.27 ± 27.90	0.024
V5 Tp-e/QTc	0.180 ± 0.030	0.223 ± 0.064	0.010

SBP – systolic blood pressure; DBP – diastolic blood pressure; bpm – beats *per* minute; Tp-e – peak and the end of the T wave; QTc – corrected QT; n – number.

All values are given as mean ± standard deviation, except for the creatine kinase, which is given as median (interquartile range).

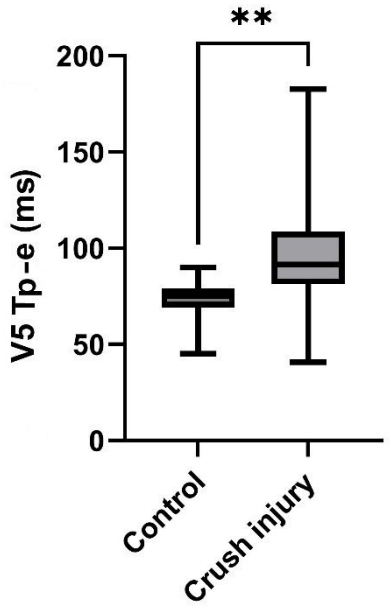

Fig. 1 – Comparison of the Tp-e interval between the crush injury and control groups. Tp-e – peak and the end of the T wave.

***Note*: ** – statistically significant Tp-e interval in crush injury patients compared with control patients ($p = 0.010$).**

Table 2

General demographic data of crush injury patients

Parameters	Crush injury group
Mortality	0 (0)
Length of stay	4 (4)
Hospitalization	
discharged	3 (13.0)
service	18 (78.3)
ICU	2 (8.7)
Diabetes mellitus	2 (8.7)
Hypertension	5 (21.7)
Coronary artery disease	3 (7.1)
Fracture	8 (34.8)

ICU – intensive care unit.
All values are given as numbers (percentages), except for the length of stay parameter, which is given as median (interquartile range).

Table 3

Receiver operating characteristic curves of electrocardiographic parameters between the crush injury and control groups

Variables	AUC	SD	*p*-value	Cut-off	Sensitivity	Specificity
QTc	0.641	0.89	0.114	393.5	95.7	36.8
V5 Tp-e	0.805	0.71	< 0.01	79.50	82.6	73.7
V5 Tp-e/QTc	0.764	0.074	< 0.001	0.219	52.2	100.0

AUC – area under the curve; SD – standard deviation.
For other abbreviations, see Table 1.

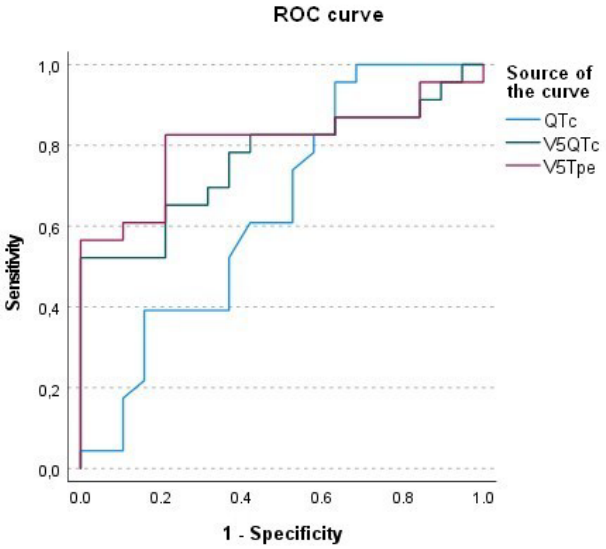

Fig. 2 – Receiver operating characteristic (ROC) curves of electrocardiogram parameters predicted the severity of trauma.
For abbreviations, see Table 1.

characteristic curve indicated that Tp-e accurately predicted the severity of trauma at a cut-off value of 79.50, with a sensitivity of 82.6% and specificity of 73.7% (area under the curve: 0.805, $p < 0.001$) (Table 3 and Figure 2).

Discussion

Chronic fatalities and associated complexities related to heart disease following crush injuries are a well-established phenomenon. A number of cardiovascular conditions emerge as a result of acidosis-induced secondary arrhythmias and electrolyte imbalances [13, 14]. The results of our investigation suggest that Tp-e duration and Tp-e/QTc ratio hold potential as early indicators for detecting arrhythmias after crush injuries.

Numerous studies have emphasized the coexistence of electrolyte imbalances, including hypocalcaemia and hyperphosphataemia, following crush injuries. These have

the potential to cause arrhythmias due to acidosis resulting from the injuries [15]. Additionally, heightened sympathetic activity and overstimulation of cardiac myocytes are recognized factors in trauma patients that may result in arrhythmias [16].

Recently, multiple studies have examined the role of Tp-e interval and Tp-e/QTc ratio as parameters for myocardial repolarization. These studies have revealed associations with cardiovascular and ventricular conditions [17]. Research by Ucar et al. [18] highlighted the potential use of increased Tp-e and Tp-e/QTc values as ventricular repolarization parameters in patients with myocarditis. A recent study conducted by Bilge et al. [19] recommends careful observation of elevated Tp-e and Tp-e/QTc levels on ECG for acute ischemic stroke patients, as they may be at risk of developing arrhythmias. Similarly, Çaltekin and Hidayet [8] found that higher Tp-e and Tp-e/QTc readings may indicate the presence of arrhythmias in blunt chest trauma cases. In a separate study, it was demonstrated that Tp-e interval > 72.5 ms and Tp-e/QT ratio > 0.18 are robust predictors of impaired myocardial reperfusion. The study highlights the ease of applying these parameters [5]. Additionally, ECG changes observed during follow-up appointments of trauma patients were suggested as a useful marker for identifying trauma-associated conditions, such as cardiac contusion [9]. Similarly, a study has demonstrated the usefulness of the Tp-e/QT ratio in predicting significant cardiac incidents after interventional procedures and highlighted its potential role as a marker for coronary ectasia [10]. These parameters have also been found to be valuable as indicators of arrhythmia in medical conditions such as obstructive sleep apnea, ankylosing spondylitis, cardiomyopathy, and hypothyroidism [11, 12].

For the first time in the literature, our study discovered significantly elevated Tp-e and Tp-e/QTc ratios among patients with crush injuries, highlighting the potential utility of these markers as arrhythmogenic indicators. There are several important limitations to this study. First, it is a single-center, retrospective study. Second, the exact duration from the occurrence of the crush injury to the patients' arrival at the emergency department was not precisely determined. Third, ECG monitoring was not conducted after normalization of vital signs, nor during follow-up to assess possible variations in ECG values. Fourth, certain electrolyte and blood gas parameters may have differed between the patient and control groups. Finally, the absence of Holter monitoring limited the ability to fully assess arrhythmia. Therefore, multicenter studies incorporating Holter monitoring and systematic follow-up are needed to address these limitations.

Conclusion

The Tp-e interval and Tp-e/QTc ratio on electrocardiogram could indicate potential arrhythmia in patients with crush injuries who present to the emergency department.

REFERENCES

1. *Hussain E, Kalaycıoğlu S, Milliner CWD, Çakir Z.* Preconditioning the 2023 Kahramanmaraş (Türkiye) earthquake disaster. Nat Rev Earth Environ 2023; 4(5): 287–9.
2. *Ju C, Park E, Kim T, Kim T, Kang M, Lee KS,* et al. Effectiveness of electrical stimulation on nerve regeneration after crush injury: Comparison between invasive and non-invasive stimulation. PLoS One 2020; 15(5): e0233531.
3. *Koyuncu S, Sipahioglu H, Bol O, İlik HKZ, Dilci A, Elmaağaç M,* et al. The Evaluation of Different Treatment Approaches in Patients With Earthquake-Related Crush Syndrome. Cureus 2023; 15(10): e47194.
4. *Ahmad S, Anees M, Elahi I, Fazal-E-Mateen.* Rhabdomyolysis Leading to Acute Kidney Injury. J Coll Physicians Surg Pak 2021; 31(2): 235–7.
5. *Kalantzi K, Gouva C, Letsas KP, Vlachopanou A, Foulidis V, Bechlioulis A,* et al. The impact of hemodialysis on the dispersion of ventricular repolarization. Pacing Clin Electrophysiol 2013; 36(3): 322–7.
6. *Tokatli A, Kiliçaslan F, Alis M, Yiginer O, Uzun M.* Prolonged Tp-e Interval, Tp-e/QT Ratio and Tp-e/QTc Ratio in Patients with Type 2 Diabetes Mellitus. Endocrinol Metab (Seoul) 2016; 31(1): 105–12.
7. *Ucsular F, Karadeniz G, Karadeniz C, Yalnız E, Demir M.* Evaluation of Tpeak-Tend interval and Tpeak-end/QT ratio in patients with Sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2016; 33(2): 151–6.
8. *Çaltekin İ, Hidayet Ş.* Evaluation of Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in blunt chest trauma patients. Ulus Travma Acil Cerrahi Derg 2020; 26(4): 526–30.
9. *Solhpour A, Ananaba-Ekeruo I, Memon NB, Kantharia BK.* Ventricular tachycardia from intracardiac hematoma in the setting of blunt thoracic trauma. Indian Heart J 2014; 66(1): 108–10.
10. *Zhao X, Xie Z, Chu Y, Yang L, Xu W, Yang X,* et al. Association between Tp-e/QT ratio and prognosis in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Clin Cardiol 2012; 35(9): 559–64.
11. *Akboğa MK, Gülcihan Balcı K, Yılmaz S, Aydın S, Yayla Ç, Ertem AG,* et al. Tp-e interval and Tp-e/QTc ratio as novel surrogate markers for prediction of ventricular arrhythmic events in hypertrophic cardiomyopathy. Anatol J Cardiol 2017; 18(1): 48−53.
12. *Gürdal A, Eroğlu H, Helvaci F, Sümerkan MÇ, Kasali K, Çetin Ş,* et al. Evaluation of Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in patients with subclinical hypothyroidism. Ther Adv Endocrinol Metab 2017; 8(3): 25−32.
13. *Long B, Liang SY, Gottlieb M.* Crush injury and syndrome: A review for emergency clinicians. Am J Emerg Med 2023; 69: 180–7.
14. *Anderson JL, Cole M, Pannell D.* Management of Severe Crush Injuries in Austere Environments: A Special Operations Perspective. J Spec Oper Med 2022; 22(2): 43–7.
15. *Matsuda J, Shimizu T, Kittaka T, Fukuda M, Akimoto H.* Cardiopulmonary arrest due to early hyperkalemia after liver injury. Am J Emerg Med 2014; 32(11): 1440.e1–2.
16. *Gupta P, Patel C, Patel H, Narayanaswamy S, Malhotra B, Green JT,* et al. T(p-e)/QT ratio as an index of arrhythmogenesis. J Electrocardiol 2008; 41(6): 567−74.
17. *Koc M, Sumbul HE, Gulumsek E, Koca H, Bulut Y, Karakoc E,* et al. Disease Severity Affects Ventricular Repolarization Parameters in Patients With COVID-19. Arq Bras Cardiol 2020; 115(5): 907–13.

18. *Ucar FM, Ozturk C, Yılmaztepe MA.* Evaluation of Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in patients with acute myocarditis. BMC Cardiovasc Disord 2019; 19(1): 232.
19. *Bılge S, Tezel O, Acar YA, Cüce F, Karadaş Ö, Taşar M.* Investigation of the Value of T peak to T end and QTc Intervals as Electrocardiographic Arrhythmia Susceptibility Markers in Acute Ischemic Stroke. Noro Psikiyatr Ars 2020; 57(3): 171–6.

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Postoperative customary outcomes and complications after extraction of impacted mandibular third molars and influence of surgery on the adjacent second molar

Postoperativni ishodi i komplikacije posle hirurškog vađenja impaktiranih donjih trećih molara i uticaj hirurškog pristupa na susedni drugi molar

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Abstract

Background/Aim. Extraction of impacted mandibular third molars (IMTMs) may be difficult due to a hidden position, anatomical structure, and limited operating space. Therefore, searching for an effective and safe extraction method has always been the focus of research. The aim of this study was to examine postoperative customary outcomes and complications after the extraction of IMTMs and the possible influence of surgery on the adjacent second molar. **Methods.** A total of 86 patients with IMTMs, admitted from March 2022 to March 2024, were randomized into two equal groups: the control group (CG) and the study group (SG), each consisting of 43 patients. Traditional IMTM extraction was performed for CG, while piezosurgery was conducted for SG. Clinical indicators, customary outcomes (pain degree, swelling degree, and degree of mouth opening limitation), and complications were compared between the two groups. **Results.** The pain factor levels and periodontal status of the adjacent second molar were observed pre- and postoperatively. In SG, the operation time was shorter and intraoperative blood loss was less than in CG ($p < 0.05$). After surgery, the Visual Analogue Scale scores were higher in both groups than preoperatively, but they were lower in SG than in CG ($p < 0.05$). The degrees of swelling and mouth opening limitation were lower in SG than in CG ($p < 0.05$). SG had a lower percentage of complications than CG on the 30th day postoperatively ($p < 0.05$). **Conclusion.** For IMTM extraction, patients receiving piezosurgery have satisfactory short-term healing outcomes, accompanied by good long-term outcomes of the adjacent second molar.

Key words:
molar; oral surgical procedures; piezosurgery; tooth extraction; tooth, impacted; treatment outcome.

Apstrakt

Uvod/Cilj. Vađenje impaktiranih donjih (mandibularnih) trećih molara (IMTM) može biti teško zbog skrivenog položaja, anatomske strukture i ograničenog operativnog prostora. Stoga je potraga za efikasnom i bezbednom metodom ekstrakcije uvek bila u fokusu istraživanja. Cilj ovog rada bio je da se ispitaju uobičajeni postoperativni ishodi i komplikacije nakon vađenja IMTM i mogući uticaj operacije na susedni drugi molar. **Metode.** Ukupno 86 pacijenata kojima je izvršena IMTM, primljenih od marta 2022. do marta 2024. godine, randomizovano je u dve jednake grupe: kontrolnu grupu (KG) i ispitivanu grupu (IG), u svakoj po 43 pacijenata. Tradicionalna ekstrakcija IMTM izvršena je u KG, dok je u IG sprovedena piezohirurgija. Između dve grupe upoređeni su klinički indikatori, uobičajeni ishodi (stepen bola, stepen otoka i stepen ograničenja otvaranja usta) i komplikacije. **Rezultati.** Nivoi faktora bola i parodontalni status susednog drugog molara praćeni su pre i posle operacije. U IG, vreme operacije bilo je kraće i intraoperativni gubitak krvi manji nego u KG ($p < 0,05$). Nakon operacije, skorovi na vizuelnoj analognoj skali bili su viši u obe grupe nego pre operacije, ali su bili niži u IG nego u KG ($p < 0,05$). Stepen otoka i stepen ograničenja otvaranja usta bili su niži u IG u poređenju sa KG ($p < 0,05$). IG je imala manji procenat komplikacija nego KG 30. dana nakon operacije ($p < 0,05$). **Zaključak.** Kod vađenja IMTM, pacijenti podvrgnuti piezohirurgiji imaju zadovoljavajuće kratkoročne ishode zarastanja, praćene dobrim dugoročnim ishodima za susedni drugi molar.

Ključne reči:
molari; hirurgija, oralna, procedure; piezohirurgija; zub, ekstrakcija; zub, impakcija; lečenje, ishod.

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Introduction

Impacted teeth are a common finding. Because of their hidden position, impacted and especially semi-impacted mandibular third molars are difficult to clean properly. This allows food residues to accumulate, which can lead to pericoronitis, caries, and periodontal problems [1, 2]. Plaque index (PI), probing depth (PD), and bleeding on probing (BOP) are commonly used indicators for detecting periodontal diseases. PI is mainly based on the thickness of dental plaque, which is directly proportional to plaque thickness [3]. PD is measured as the distance from the upper gingival margin to the bottom of the gingival sulcus, normally ≤ 3 mm [4]. Swelling occurs during gingival inflammation, and in its active stage, this is manifested by sulcus bleeding. Hence, BOP can reflect the degree of gingival inflammation [5]. Impacted mandibular third molar (IMTM) significantly affects the health status of the adjacent second molar, resulting in abnormal increases in PI, PD, and BOP [6]. Therefore, the timely extraction of the IMTM is of great significance.

Extraction of IMTM is a common surgical procedure in stomatology, which aims to remove impacted teeth and restore oral health. Due to the limitations of medical technology, IMTMs were previously often extracted by chisel osteotomy. Despite a high success rate of surgery, this traditional method caused great trauma and obvious postoperative pain, as well as periodontal defects of adjacent second molars. Some patients were unable to tolerate this method [7, 8]. With the continuous development of minimally invasive technology in recent years, the concept of minimal invasion has been gradually applied to stomatology. As a result, various tooth extraction tools, such as air turbine handpieces (ATHs) and ultrasonic bone knives (UBKs), have emerged, gradually replacing traditional extraction techniques [9]. The ATH is characterized by high rotational speed, which helps avoid hammering and chiseling. However, the turbine temperature increases due to high rotational speed, thus damaging the soft tissue [10]. The UBK has the advantages of precise cutting, low heat, and clear surgical fields, but it produces a poor bone cutting effect [11]. For this reason, an ATH and UBK are often combined to further improve the effect of the minimally invasive technique.

The aim of this study was to examine the clinical effects of traditional extraction and piezosurgery of IMTM in patients undergoing extraction. In addition, postoperative customary outcomes, complications, and influence on the adjacent second molar were observed, aiming to provide valuable evidence for better future treatment.

Methods

The study included 86 patients with IMTM admitted to the Beijing Stomatological Hospital, Department of Wangfujing General Dentistry, Beijing, China, from March 2022 to March 2024. The patients were randomized into a control group (CG) and a study group (SG), each comprising 43 patients. This study was approved by the Ethics Committee of the Beijing Stomatological Hospital (approval No. BSH202203006).

Inclusion and exclusion criteria

Inclusion criteria were as follows: patients meeting the diagnostic criteria for IMTMs by imaging examination [12]; lower third molars with total soft tissue retention; lower third molars lack of distal space (Pell-Gregory classification); lower third molars with mesio-angular tilt (Winter's classification) [13]; those with surgical indications, normal coagulation function and good compliance; those who voluntarily signed the informed consent form.

Exclusion criteria included: patients with a history of adjacent tooth extraction; menstruating, lactating, or pregnant women; those complicated with severe infectious diseases; those with recent immune deficiency; chronic smokers and alcoholics; those complicated with hypertension or heart disease; those with loosening of adjacent second molars preoperatively; those with psychosis.

Type of extraction

Extraction of IMTMs was performed in both groups. Coagulation function test, electrocardiogram, and oral examinations were carried out preoperatively. Patients with contraindications to tooth extraction, such as acute inflammatory period, menstrual period, hypertension, and heart disease, and women three months before and after pregnancy were excluded. An X-ray image was taken to identify the position and morphology of the third molar.

Traditional extraction was performed in CG. After anesthesia with local injection of 5 mL of 0.2% lidocaine and 1.7 mL of articaine/epinephrine and disinfection with anerdian, the upper and surrounding soft tissue covering the third molar was incised to expose the third molar fully. Using conventional rotary instruments, the bone tissue was removed to expand the space, and the dental crown and root were separated. Then the tooth tissue was gradually elevated using a dental elevator, and the root was extracted with dental forceps, followed by washing with normal saline. Finally, the wound surface was sutured, and hemostasis by compression was performed with a sterilized cotton sheet.

Piezosurgery was performed in SG [14]. After anesthesia and disinfection in the same way as in CG, a straight-line incision was made on the third molar and flapped with a separator, and the bone tissue was removed using a USI1004 UBK (Shanghai Langyi Medical Equipment Co., Ltd., Shanghai, China) to expose the crown fully. After the resistance of the crown was eliminated, an ATH was used to separate the crown and the root. When approaching the alveolar bone, the tooth tissue was removed using the UBK, the crown was extracted, and the periodontal ligament was separated with a minimally invasive knife. After the root became loose, it was elevated using a minimally invasive dental elevator, and the residual dental sac tissue

was scraped off. Then the UBK was switched to a flush mode to flush the alveolar fossa with hypothermic normal saline. Finally, the wound surface was sutured, and hemostasis by compression was performed with a sterilized cotton sheet.

The patients in both groups were followed up for one week postoperatively. An ice compress was applied intermittently during the first three days. No food was allowed within two hours after surgery, and tooth brushing was prohibited within the first 24 hrs. Meanwhile, prophylactic prescription of antibiotics was given to both groups.

Evaluation of outcomes

To assess clinical indicators, the operation time and intraoperative blood loss were compared between the two groups. In detail, blood from the operative field was suctioned into a calibrated container, and the volume was recorded. Additionally, gauze pads were weighed before and after surgery using a high-precision electronic scale, and the weight difference (1 g approximating 1 mL of blood) was calculated. Total intraoperative blood loss was determined by summing these two measurements.

Customary outcomes include the following: 1) pain degree was evaluated using the Visual Analogue Scale (VAS) preoperatively and 2 and 7 days postoperatively [15], with a maximum score of 10 points. The score was directly proportional to the pain degree. 2) Swelling degree: cheek circumference was measured preoperatively and 2 and 7 days postoperatively. The difference in measurements was used to grade swelling – grade I: ≤ 2 mm; grade II: 2–10 mm; grade III: > 10 mm. 3) To evaluate the degree of mouth opening limitation, the distance between the upper and lower middle teeth was measured with calipers 2 and 7 days postoperatively. Limitation was graded as follows: grade I (> 20 mm), grade II (10–20 mm), grade III (< 10 mm).

For assessing complication, the percentages of dry socket, periodontal defects of adjacent second molars, numbness of lower lip and nerve injury, and delayed infection of the surgery operated area were recorded on the 14th and 30th day postoperatively.

For assessing periodontal status, both groups, both groups were given comprehensive oral examinations preoperatively and 7, 14, and 30 days postoperatively, and the periodontal status of the adjacent second molar was compared from PI, PD, and BOP between the two groups [16].

Statistical analysis

SPSS 23.0 software (IBM, New York, USA) was used for statistical analysis. Measurement data were described by mean ± standard deviation and underwent the independent-samples *t*-test. The count data were described by numbers and percentages. The Chi-square ($\chi 2$) test was used. The rank sum test was performed for ranked data. The value of $p < 0.05$ was considered statistically significant.

Results

In CG, there were 21 males and 22 females aged 22–35 years, with a mean of 26.44 ± 3.33 years. The IMTM was located on the left side in 17 cases and on the right side in 26 cases. The body mass index (BMI) was 20–24 kg/m^2, with a mean of 21.55 ± 1.32 kg/m^2. In SG, there were 24 males and 19 females aged 20–36 years, with a mean of 26.84 ± 3.19 years. The IMTM was located on the left side in 21 cases and on the right side in 22 cases. The BMI was 20–24 kg/m^2, with a mean of 21.89 ± 1.18 kg/m^2. The general data were well balanced between the two groups ($p > 0.05$).

Operation time and intraoperative blood loss

In SG, the operation time was shorter and intraoperative blood loss was less than in CG ($p < 0.05$) (Table 1).

Pain degree

No significant differences were found in the VAS score between the two groups preoperatively ($p > 0.05$). On the first postoperative day, the VAS scores were higher in both groups than preoperatively. However, scores were lower in SG than in CG ($p < 0.05$) (Table 2).

Degrees of swelling and mouth opening limitation

The degrees of swelling and mouth opening limitation were lower in SG than in CG ($p < 0.05$) (Table 3).

Complications in both groups

On the 14th day postoperatively, the two groups had similar percentages of complications. SG had a lower percentage of complications than CG on the 30th day postoperatively ($p < 0.05$) (Table 4).

Table 1

Operation time and intraoperative blood loss

Group	Operation time (min)	Intraoperative blood loss (mL)
Control group (n = 43)	29.76 ± 5.10	6.07 ± 1.14
Study group (n = 43)	26.53 ± 3.47	4.80 ± 1.37
t	3.434	4.673
p	0.001	< 0.001

n – number.
All values are presented as mean ± standard deviation.
Independent-samples *t*-test was used.

Table 2

Pain degree assessed by VAS score

Group	VAS	
	preoperatively	one day postoperatively
Control group (n = 43)	1.35 ± 0.74	4.35 ± 0.54*
Study group (n = 43)	1.36 ± 0.72	2.86 ± 0.64*
t	0.064	11.668
p	0.950	< 0.001

VAS – Visual Analogue Scale; n – number.
All values are presented as mean ± standard deviation.
Independent-samples t-test was used. *$p < 0.05$ vs. the same group preoperatively.

Table 3

Degrees of swelling and mouth opening limitation

Group	Degree of swelling			Degree of mouth opening limitation		
	I	II	III	I	II	III
Control group (n = 43)	9 (20.93)	11 (25.58)	23 (53.49)	3 (6.98)	11 (25.58)	29 (67.44)
Study group (n = 43)	19 (44.19)	17 (39.53)	7 (16.28)	12 (27.91)	21 (48.84)	10 (23.26)
Z		3.408			4.150	
p		0.001			< 0.001	

n – number.
All values are presented as numbers (percentages). The χ^2 test was used.

Table 4

Complications in two groups

Group	Dry socket		Periodontal defects of adjacent second molars		Numbness of the lower lip		Nerve injury		Total	
	days postoperatively									
	14th	30th	14th	30th	14th	30th	14th	30th	14th	30th
Control group (n = 43)	1 (2.33)	1 (2.33)	1 (2.33)	2 (4.65)	2 (4.65)	3 (6.98)	1 (2.33)	2 (4.65)	5 (11.63)	8 (18.60)
Study group (n = 43)	0 (0)	0 (0)	1 (2.33)	1 (2.33)	0 (0)	0 (0)	0 (0)	1 (2.33)	1 (2.33)	2 (4.65)
χ^2									1.613	4.074
p									0.204	0.044

n – number.
All values are presented as numbers (percentages). The χ^2 test was used.

Table 5

Periodontal health

Group	PI, mean ± SD		PD, mean ± SD (mm)		BOP, n (%)	
	days postoperatively					
	14th	30th	14th	30th	14th	30th
Control group (n = 43)	1.15 ± 0.15	0.89 ± 0.08	2.12 ± 0.25	2.03 ± 0.20	11 (25.6)	6 (14.0)
Study group (n = 43)	1.12 ± 0.16	0.91 ± 0.06	2.14 ± 0.22	2.01 ± 0.23	13 (30.2)	9 (20.9)
t/χ^2	0.897	1.312	0.394	0.430	0.839	0.711
p	0.372	0.193	0.695	0.668	0.404	0.479

PI – plaque index; PD – probing depth; BOP – bleeding on probing; n – number; SD – standard deviation.

Periodontal health

On the 14th and 30th day postoperatively, there were no significant differences between PI, PD, and BOP of the two groups ($p > 0.05$) (Table 5).

Discussion

Third molars are the last set of teeth to develop in the mouth and usually emerge at the age of 18–25. As humans evolve, the jaw gradually shrinks, resulting in the dislocation of the third molars, which is clinically known as impacted teeth. Impacted teeth not only fail to achieve normal masticatory function but also cause inflammation of the periodontal tissue. IMTM causes difficulty in eating and mouth opening, gingival swelling and pain, and fever as major clinical symptoms. If left untreated for a long time, this can lead to interdental space infection, which seriously affects patients' daily life [17]. In addition, IMTM can also lead to pathological changes in the adjacent second molars. Therefore, early detection and early treatment are of great significance. Due to a hidden position, complex anatomical structure, and limited

operating space, the extraction of IMTM may be difficult. Therefore, searching for an effective and safe extraction method has always been the focus of research.

Influenced by the available medical devices and prevailing surgical concepts, dental root extraction was previously performed mainly with chisel osteotomy. In this technique, bone tissue was removed and space was expanded through hammering and crown splitting [18]. However, these maneuvers generate strong impact forces that can damage normal periodontal tissues, increase intraoperative blood loss and postoperative complications, and even cause serious injuries such as joint dislocation or fracture. Such outcomes may also heighten the patient's psychological burden and reduce cooperation during surgery [19]. With the advent of minimally invasive surgery, chisel osteotomy has been gradually replaced by piezosurgery. Currently, ATHs and UBKs are commonly used in minimally invasive extraction, and their clinical advantages have been reported [20]. In this study, the results showed that the operation time was shorter and intraoperative blood loss was less in SG than in CG, indicating that the ATH combined with UBK can effectively shorten the operation time and reduce intraoperative blood loss during the extraction of IMTM. The ATH consists of a compressor and a turbine. During surgery, compressed air drives the tur-bine at high speed, enabling efficient separation of the crown and root [21]. By converting electrical energy into mechanical, the UBK gradually removes bone tissue of specific hardness under high-frequency vibration, exhibiting high efficiency and safety when applied to cutting deep alveolar bone tissues [22]. In addition, the cavitation effect produced during the use of the UBK helps prevent blood exudate from the wound surface, eliminates tissue debris, and maintains clear surgical fields [23]. Therefore, the combination of the ATH and the UBK offers the advantages of reduced trauma and minimized mechanical impact compared with chisel osteotomy. This approach can significantly shorten operative time and decrease intraoperative blood loss.

Following the extraction of IMTM, obvious pain, swelling, and mouth opening limitation are often caused, which are closely related to the postoperative natural outcomes. In this study, it was also found that the VAS score was higher in both groups on the first postoperative day than preoperatively, but it was lower in SG compared to CG. The degrees of swelling and mouth opening limitation were also lower in SG than in CG. The ATH can quickly and accurately cut bone tissues, but it is difficult to accurately control the range of cutting deep alveolar bone tissues, and the heat generated may damage soft tissues, causing postoperative pain and swelling [24]. The UBK can automatically distinguish between hard tissues and soft tissues, and selectively cut hard tissues, thereby effectively avoiding damage to soft tissues during bone removal and space expansion. Cooperative use of ATH and UBK can complement each other to further relieve postoperative pain, and reduce the degrees of swelling and mouth opening limitation, achieving good postoperative natural outcomes [25].

In this study, SG had a lower percentage of complications than CG, suggesting that piezosurgery of IMTM can effectively reduce postoperative complications, exhibiting a good safety profile. The reason is mainly related to the less violent operation. In addition, the vibration frequency of the UBK head is 24–30 kHz, which can only damage mineralized tissues. Soft tissues, such as periodontal mucosa and blood vessels, cannot be damaged until the vibration frequency reaches 50 kHz. As a result, the risk of lower lip numbness and nerve injury can be effectively reduced [26]. Moreover, the UBK generates less heat, and the water mist flushing function can reduce thermal damage and prevent dry socket [27]. According to related studies, IMTM can trap dental plaque and food residues in the space between it and the adjacent second molar. This may trigger inflammatory responses and even lead to defects in the second molar, ultimately affecting periodontal health [28]. In this study, there were no significant differences between PI, PD, and BOP of the two groups on the 14th and 30th postoperative days, suggesting that both traditional extraction and piezosurgery can improve periodontal health of adjacent second molars, because oral cleaning becomes simple after the extraction of the third molar. Although the inclusion and exclusion criteria were set up in this prospective randomized controlled study, the influence of individual differences on the study results cannot be completely avoided. In the future, confounding factors should be further reduced, and in-depth analyses are required to provide reliable reference data for clinical practice.

Conclusion

For impacted mandibular third molar extraction, patients receiving piezosurgery have satisfactory short-term healing outcomes, accompanied by good long-term outcomes of the adjacent second molar.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. *Sifuentes-Cervantes JS, Carrillo-Morales F, Castro-Núñez J, Cunningham LL, Van Sickels JE.* Third molar surgery: Past, present, and the future. Oral Surg Oral Med Oral Pathol Oral Radiol 2021; 132(5): 523–31.
2. *Gulnahar Y, Alpan AL.* Comparison of postoperative morbidity between piezoelectric surgery and conventional rotary instruments in mandibular third molar surgery: a split-mouth clinical study. Med Oral Patol Oral Cir Bucal 2021; 26(3): e269–75.
3. *Del Rey YC, Rikvold PD, Johnsen KK, Schlafer S.* A fast and reliable method for semi-automated planimetric quantification of dental plaque in clinical trials. J Clin Periodontol 2023; 50(3): 331–8.
4. *Suryavanshi VG, Tale RK, Aasole AG, Barge AK, Sanikop S, Gopashetti P.* Assessment of IL-8 Levels in Saliva of Healthy and Chronic Periodontitis Individuals. J Pharm Bioallied Sci 2024; 16(Suppl 1): S825–7.

5. *P SM, S S.* Effectiveness of Microneedling Technique Using Olive Oil on the Severity of Gingival Inflammation and Plaque Accumulation: A Randomised Controlled Trial. Cureus 2024; 16(4): e59415.
6. *Canullo L, Rakic M, Corvino E, Burton M, Krumbeck JA, Chittoor Prem A,* et al. Effect of argon plasma pre-treatment of healing abutments on peri-implant microbiome and soft tissue integration: a proof-of-concept randomized study. BMC Oral Health 2023; 23(1): 27.
7. *Chen YW, Chi LY, Lee OK.* Associations between aging and second molar diseases in patients having adjacent impacted third molar extraction. J Formos Med Assoc 2021; 120(1 Pt 2): 380–7.
8. *Patel PS, Shah JS, Dudhia BB, Butala PB, Jani YV, Macwan RS.* Comparison of panoramic radiograph and cone beam computed tomography findings for impacted mandibular third molar root and inferior alveolar nerve canal relation. Indian J Dent Res 2020; 31(1): 91–102.
9. *Mann A, Scott JF.* Coronectomy of mandibular third molars: a systematic literature review and case studies. Aust Dent J 2021; 66(2): 136–49.
10. *Jiang S, Zhou B, Li Z, Gao J, Wang P.* Comparison of the effects of two extraction methods on the alveolar ridge preservation of Maxillary Anterior Teeth. Pak J Med Sci 2023; 39(2): 549–52.
11. *Wang L, Liu Y, Wang S, Li J, Sun Y, Wang J,* et al. Research on ultrasonic bone cutting mechanism based on extended finite element method. Biomech Model Mechan 2024; 23(3): 861–77.
12. *Yang Y, Bao DY, Ni C, Li Z.* Three-dimensional positional relationship between impacted mandibular third molars and the mandibular canal. BMC Oral Health 2023; 23(1): 831.
13. *Kaposvári I, Körmöczi K, Csurgay K, Horváth F, Ashourioun AH, Buglyó A,* et al. Delayed-onset infections after lower third molar surgery: A Hungarian case-control study. Oral Surg Oral Med Oral Pathol Oral Radiol 2021; 132(6): 641–7.
14. *Cicciù M, Stacchi C, Fiorillo L, Cervino G, Troiano G, Vercellotti T,* et al. Piezoelectric bone surgery for impacted lower third molar extraction compared with conventional rotary instruments: a systematic review, meta-analysis, and trial sequential analysis. Int J Oral Maxillofac Surg 2021; 50(1): 121–31.
15. *Hamad SA.* Outcomes of coronectomy and total odontectomy of impacted mandibular third molars. Int Dent J 2024; 74(2): 195–8.
16. *Zhang Y, Chen X, Zhou Z, Hao Y, Li H, Cheng Y,* et al. Effects of impacted lower third molar extraction on periodontal tissue of the adjacent second molar. Ther Clin Risk Manag 2021; 17: 235–47.
17. *Miguel DCN, Oliveira RDS, Panzarella FK.* Postoperative Complications After Extraction of impacted mandibular third molars: A clinical observational study on dental position and risks. J Int Soc Prev Community Dent 2025; 15(2): 155–72.
18. *Genç BGÇ, Orhan K, Or S.* A clinical comparison of Er: YAG Laser, piezosurgery, and conventional bur methods in the impacted third molar surgery. Photobiomodul Photomed Laser Surg 2023; 41(6): 283–90.
19. *Caputo A, Rubino E, Marcianò A, Peditto M, Bellocchio AM, Nucera R,* et al. Three-dimensional facial swelling evaluation of piezoelectric vs conventional drilling bur surgery of impacted lower third molar: a randomized clinical trial. BMC Oral Health 2023; 23(1): 233.
20. *Steel BJ, Surendran KSB, Braithwaite C, Mehta D, Keith DJW.* Current thinking in lower third molar surgery. Br J Oral Maxillofac Surg 2022; 60(3): 257–65.
21. *Civak T, Ustun T, Yilmaz HN, Gursoy B.* Postoperative evaluation of Er: YAG laser, piezosurgery, and rotary systems used for osteotomy in mandibular third-molar extractions. J Craniomaxillofac Surg 2021; 49(1): 64–9.
22. *Nogueira DGM, Leão JC, Sales PHDH, Silva PGB, Gomes ACA.* Piezoelectric surgery is effective in reducing pain, swelling, and trismus after removal of impacted lower third molars: A meta-analysis. J Oral Maxillofac Surg 2023; 81(4): 483–98.
23. *Nehme W, Fares Y, Abou-Abbas L.* Piezo-surgery technique and intramuscular dexamethasone injection to reduce postoperative pain after impacted mandibular third molar surgery: A randomized clinical trial. BMC Oral Health 2021; 21(1): 393.
24. *Alraqibah MA, Rao JKD, Alharbi BM.* Periotome versus piezotome as an aid for atraumatic extraction: A randomized controlled trial. J Korean Assoc Oral Maxillofac Surg 2022; 48(6): 356–62.
25. *Costa SM, Ribeiro BC, Gonçalves AS, Araújo LM, Toledo GL, Amaral MB.* Double blind randomized clinical trial comparing minimally-invasive envelope flap and conventional envelope flap on impacted lower third molar surgery. Med Oral Patol Oral Cir Bucal 2022; 27(6): e518–24.
26. *Wu L, Wang S.* Effect of Ultrasonic Osteotome on therapeutic efficacy and safety of spinal surgery: A system review and meta-analysis. Comput Math Methods Med 2022; 2022: 9548142.
27. *Blagova B, Krastev D, Malinova L.* Conventional drilling versus ultrasound and laser osteotomy in mandibular third molar surgery: A comparative study. Lasers Surg Med 2023; 55(10): 862–70.
28. *Bernabeu-Mira JC, Peñarrocha-Oltra D, Peñarrocha-Diago M.* Coronectomy of impacted mandibular third molars: A clinical and radiological retrospective case series study with 2-9 years of follow-up. Med Oral Patol Oral Cir Bucal 2024; 29(2): e180–6.

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A decade of antibacterial drug consumption for systemic use in Montenegro (2014–2023): trends, patterns, and AWaRe classification insights

Decenija potrošnje antibakterijskih lekova za sistemsku primenu u Crnoj Gori (2014–2023): trendovi, obrasci i uvidi u AWaRe klasifikaciju

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Abstract

Background/Aim. Antimicrobial resistance (AMR) represents an increasing threat to global health, with serious implications for public health and the economy. Monitoring antibiotic consumption is crucial in understanding and addressing AMR. The aim of this study was to analyze trends in the use of antibacterial drugs for systemic use in Montenegro from 2014 to 2023. **Methods.** A ten-year retrospective study was conducted using data collected by the Institute for Medicines and Medical Devices of Montenegro, Podgorica, Montenegro. Antibiotics were classified according to the World Health Organization's (WHO) Anatomical Therapeutic Chemical system, expressed in defined daily doses *per* 1,000 inhabitants *per* day, and categorized by WHO's Access, Watch, Reserve (AWaRe) classification to identify trends and patterns in antibiotic use. **Results.** A gradual decline in antibiotic consumption was observed until 2019, after which a sharp increase in both use and costs occurred during the coronavirus disease 2019 pandemic (2020–2021). Although consumption stabilized after the pandemic, it remained higher compared to pre-pandemic levels. The overall consumption trend showed a tendency to decrease but without statistical significance ($p = 0.291$), while the increase in costs was also not statistically significant ($p = 0.089$). The subgroup analysis revealed no significant changes in the antibiotic consumption of J01C and J01M classes. On the other hand, a statistically significant increase was recorded in the use of antibiotics from classes J01D and P01AB ($p = 0.001$ for both). According to the AWaRe classification, significant positive trends were noted in the consumption of antibiotics from the Access ($p = 0.022$), Watch ($p = 0.006$), and Reserve ($p = 0.026$) categories. **Conclusion.** These results highlight the importance of implementing continuous antibiotic stewardship programs, as well as applying targeted interventions aimed at optimizing their use in Montenegro. Furthermore, these results contribute to global efforts in achieving a reduction in antibiotic consumption.

Key words:
anti-bacterial agents; covid-19; drug resistance, microbial; montenegro.

Apstrakt

Uvod/Cilj. Antimikrobna rezistencija (AMR) predstavlja sve veću pretnju globalnom zdravlju, sa ozbiljnim posledicama po javno zdravlje i ekonomiju. Praćenje potrošnje antibiotika je od ključne važnosti za razumevanje i rešavanje AMR. Cilj rada bio je da se analiziraju promene u upotrebi antibakterijskih lekova za sistemsku primenu u Crnoj Gori u periodu od 2014. do 2023. godine. **Metode.** Sprovedena je desetogodišnja retrospektivna studija u kojoj su korišćeni podaci Instituta za lekove i medicinska sredstva Crne Gore, Podgorica, Crna Gora. Antibiotici su klasifikovani prema Anatomsko-terapijsko-hemijskom sistemu Svetske zdravstvene organizacije (SZO), izraženi u definisanim dnevnim dozama na 1 000 stanovnika na dan i kategorizovani prema *Access, Watch, Reserve* – AWaRe klasifikaciji SZO, kako bi se identifikovali trendovi i obrasci u upotrebi antibiotika. **Rezultati.** Do 2019. godine uočen je postepeni pad u potrošnji antibiotika, nakon čega je tokom pandemije koronavirusne bolesti 2019 (2020–2021) došlo do naglog porasta i u upotrebi i u troškovima. Iako je nakon pandemije došlo do stabilizacije, potrošnja je ostala viša u

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odnosu na nivoe pre pandemije. Ukupni trend potrošnje imao je tendenciju smanjenja, ali bez statističke značajnosti (p = 0,291), dok je porast troškova takođe bio statistički neznačajan (p = 0,089). Analiza po podgrupama nije pokazala značajne promene u potrošnji antibiotika iz klasa J01C i J01M. S druge strane, zabeležen je statistički značajan porast u upotrebi antibiotika iz klasa J01D i P01AB (p = 0,001 za obe). Prema AWaRE klasifikaciji, primećeni su značajni pozitivni trendovi u potrošnji antibiotika iz *Access* (p = 0,022), *Watch* (p = 0,006) i *Reserve* (p = 0,026) kategorija.

Zaključak. Ovi rezultati ističu važnost sprovođenja kontinuiranih programa upravljanja antibioticima, kao i primene ciljanih intervencija usmerenih ka optimizaciji njihove upotrebe u Crnoj Gori. Takođe, ovi rezultati doprinose globalnim naporima u postizanju smanjenja potrošnje antibiotika.

Ključne reči:
antibiotici; covid-19; lekovi, rezistencija mikroorganizama; crna gora.

Introduction

Antimicrobial resistance (AMR) is recognized as one of the top 10 most urgent global health threats, causing approximately 33,000 deaths annually and costing the European healthcare system about €1.1 billion. In the United States of America (USA), AMR-related healthcare expenses are estimated at $4.6 billion *per* year [1]. Moreover, the World Bank estimates AMR could lead to a $1.1 trillion global economic loss by 2030, potentially rising to $2 trillion by 2050 [2]. By 2050, AMR-related infections are expected to cause 10 million deaths annually, with an additional 24 million people projected to fall into extreme poverty [3, 4].

Antibiotic overuse and misuse are major drivers of AMR [5], with strong evidence linking antibiotic consumption to the emergence of resistance [6–10]. Up to 50% of antibiotics in inpatient care and over 50% in outpatient settings are misused or overused [11]. In addition, their widespread use raises healthcare costs, accounting for 20–30% of total drug expenditures [12]. Without effective intervention, global antibiotic consumption is projected to rise by 52.3% by 2030 compared with 2023, and could be nearly 200% higher than 2015 levels, especially in low- and middle-income countries (LMICs) [13, 14]. While high-income countries still have the highest overall use, LMICs are experiencing the fastest growth [15]. If current trends continue, resistance to second-line antibiotics in the European Economic Area (EU/EEA) could increase by 72% from 2005 levels, while resistance to last-line treatments may more than double [1]. These alarming projections highlight the urgent need for global action to limit unnecessary antibiotic use and strengthen antimicrobial stewardship.

Considering that AMR is a public health threat, antimicrobial stewardship programs aim to promote the prudent use of antimicrobials and maintain their effectiveness. Monitoring consumption is central to antimicrobial stewardship programs and national resistance control strategies [16]. Furthermore, surveillance also provides insights into population health, prescribing practices, and factors driving inappropriate use [17].

Quantifying antibiotic consumption is considered a cornerstone in the fight against AMR [18]. While the European Antimicrobial Resistance Surveillance Network covers 29 countries and represents the largest regional surveillance system worldwide, Montenegro is not part of this network. Like many countries in the region, Montenegro faces challenges related to antimicrobial use; however, comprehensive data on consumption patterns are limited. Moreover, as part of the global response to the AMR crisis, the World Health Organization (WHO) developed the Global Antimicrobial Resistance and Use Surveillance System (GLASS) in 2015, within its Global Action Plan to strengthen AMR surveillance. For the first time, data on both AMR and antimicrobial consumption were reported together in the 2022 GLASS report [2].

To help evaluate and monitor the use of antibacterials, the WHO developed a classification system, which includes the Access, Watch, Reserve (AWaRe) categories. Measuring the absolute or relative use of antibiotics in each of the AWaRe categories can provide valuable insights into the overall quality of antibiotic use within a country [2]. Access antibiotics are first-choice antibiotics that are relatively safe and have the lowest potential for resistance. On the other hand, Watch antibiotics are broader-spectrum antibiotics with higher resistance potential and are, therefore, prioritized for monitoring under antimicrobial stewardship programs. Reserve antibiotics, classified as "last resort" options, should only be used when alternatives are ineffective or unsuitable [19, 20].

Despite the widespread issue of AMR, significant gaps remain in understanding antimicrobial consumption, particularly in LMICs, where usage patterns and appropriateness are poorly understood [21]. Montenegro, like many other countries, faces challenges related to antimicrobial use, and there is a need for a comprehensive assessment of its consumption trends.

The aim of this study was to analyze national trends in the consumption of systemic antibacterial drugs in Montenegro over a ten-year period (from 2014 to 2023), with a specific focus on AWaRe classification. By examining antibiotic use patterns, this research seeks to fill an important gap in the European context and provide insights for tailoring future antimicrobial stewardship strategies in Montenegro.

Methods

This study employed a retrospective analysis of antibiotic consumption data provided by the Institute for Medicines and Medical Devices of Montenegro, Podgorica, Montenegro. According to the Medicines Act, this institute is responsible for collecting, processing, and publishing reports on medicine consumption in Montenegro. Data on the overall

pharmaceutical market are based on the values of sales of all medicines, as well as the sales volume for all individual medicines (by packaging) registered by wholesalers in Montenegro. Reports are published for the previous calendar year and provide a comprehensive overview of consumption in both the private and public sectors.

The data covered a ten-year period (from 2014 to 2023) and are classified according to the Anatomical Therapeutic Chemical (ATC) classification system, allowing standardized comparisons. Trends in antibiotic consumption are examined using defined daily doses (DDD) *per* 1,000 inhabitants *per* day as the standard measurement unit. The DDD *per* 1,000 inhabitants *per* day was calculated using the WHO methodology: (total number of DDDs dispensed in a year/population of that year) × 1,000/365.

Annual population estimates were obtained from the Statistical Office of Montenegro and used to adjust for changes over time. While DDD is a standardized and internationally accepted metric, its limitations should be acknowledged. It does not account for individual patient characteristics (e.g., age, weight, comorbidities) or deviations from standard doses in clinical practice. In the Montenegrin context, differences in diagnostic practices, empirical prescribing, or the availability of certain formulations may also lead to discrepancies between DDD values and actual daily doses prescribed or used. Costs of treatment expressed in euros are also presented from the cited agency publications.

To obtain more details on antibiotic consumption, a similar approach was used by authors in a paper that also analyzed the consumption of antibacterials for systemic use [22].

For the analysis of data on medicine consumption, approval was obtained from the Institute for Medicines and Medical Devices of Montenegro (from February 26, 2025).

In addition to ATC classification, antibiotic agents were categorized using the WHO's AWaRe classification to evaluate the balance between essential, broad-spectrum, and last-resort antibiotic use. This framework was chosen because it aligns with global stewardship goals and provides actionable insight into consumption patterns that may contribute to AMR. The classification of each antibiotic into an AWaRe group was based on the most recent WHO Essential Medicines List.

Statistical analysis

To assess temporal trends in antibiotic consumption and cost, linear regression analysis was performed using time (year) as the independent variable. Trends were evaluated for total DDDs, ATC subgroups, and AWaRe categories. The statistical significance of trends was tested using the slope coefficient (β) and corresponding p-values. All analyses were conducted using IBM SPSS Statistics version 24 (IBM Corporation, Armonk, NY, USA), with $p < 0.05$ considered statistically significant.

Results

Trends in the consumption of anti-infective drugs for systemic use

Over the past decade, antibiotic consumption and associated costs in Montenegro experienced notable fluctuations. A general decline was seen until 2019, followed by a sharp increase during the coronavirus disease 2019 (COVID-19) pandemic. This rise was likely due to increased prescribing for suspected bacterial co-infections and COVID-related complications. Although the post-pandemic period brought relative stabilization, both consumption and costs remained above pre-pandemic levels.

Although a negative trend in DDD over time (y = 717.3 - 0.34*x) was observed, this trend was not statistically significant (p = 0.291), indicating that the reduction in consumption was not consistent or strong enough to be considered a meaningful, statistically reliable change over the years (Figure 1).

A positive trend in costs over time (y = -1,420,505,753.9 + 708,344.4*x) was observed, but this trend was not statistically significant (p = 0.089). This implies that while a

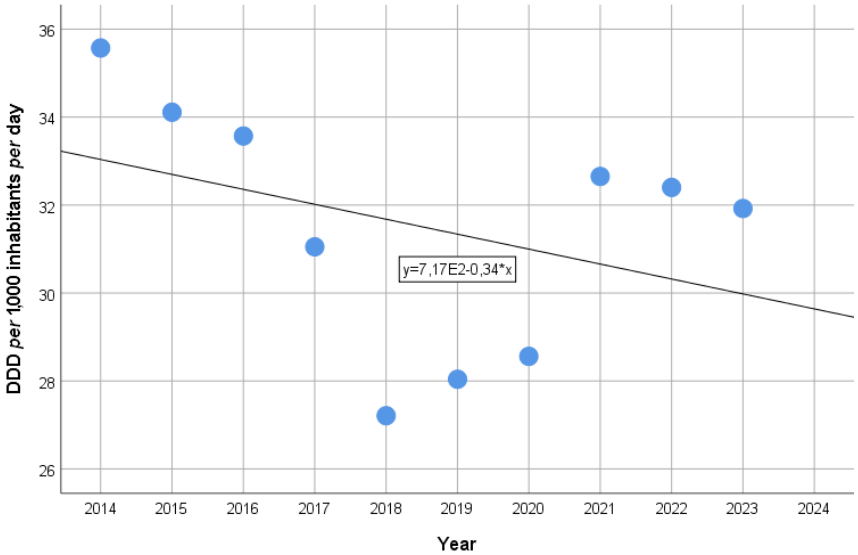

Fig. 1 - Trends in consumption of anti-infective drugs in Montenegro. DDD - defined daily doses.

temporal increase in costs is observed, the trend does not exhibit statistical significance, suggesting that it may not reflect a true underlying pattern. The observed fluctuations may be influenced by external factors, such as the COVID-19 pandemic, which could have contributed to the variability in costs (Table 1).

Consumption of antibacterial drugs for systemic use by subgroups

Table 2 presents antibiotic consumption trends in Montenegro from 2014 to 2023 by ATC code, highlighting shifts in prescribing patterns and changes in the use of various an-

Table 1

Trends in the cost of anti-infective drugs for systemic use in Montenegro over time

Year	Euro
2014	6.973.672,62
2015	6.470.769,16
2016	7.394.161,60
2017	7.599.321,53
2018	7.742.359,68
2019	8.613.069,47
2020	8.569.911,09
2021	19.557.152,93
2022	9.619.360,14
2023	10.333.589,00

Table 2

Annual consumption of antibacterial drugs for systemic use by subgroups expressed in DDD/1,000/day

ATC codes	Antibiotic class	Years									
		2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
J01C	Beta-lactam antibacterials	10.02	9.65	9.97	8.78	9.5	10.15	7.37	7.46	9.57	10.29
J01CA	Penicillins with extended spectrum	7.02	6.89	6.64	6.27	6.35	6.6	5.16	5.16	5.99	5.99
J01CE	Beta-lactamase-sensitive penicillins	1.13	0.64	0.9	0.86	0.91	0.82	0.38	0.09	0.1	0.07
J01CF	Beta-lactamase-resistant penicillins	/	/	0.00	/	/	0.00	0.00	0.00	0.01	0.01
J01CR	Combinations of penicillins, including beta-lactamase inhibitors	1.88	2.12	2.43	1.65	2.25	2.72	1.82	2.21	3.47	4.22
J01D	Other beta-lactam antibacterials	4.12	4.38	4.79	3.95	4.78	5.31	5.84	8.48	7.65	7.55
J01DB	First-generation cephalosporins	1.19	1.1	1.97	1.16	1.86	2.02	1.68	1.38	1.85	2.28
J01DC	Second-generation cephalosporins	0.07	0.07	0.04	0.04	0.03	0.01	0.01	0.01	0.00	0.00
J01DD	Third-generation cephalosporins	2.84	3.17	2.74	2.71	2.84	3.22	4.01	6.84	5.68	5.16
J01DE	Fourth-generation cephalosporins	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00
J01DF	Monobactams	/	/	/	/	/	/	/	/	/	/
J01DI	Other cephalosporins and penems	/	/	/	/	/	/	/	/	0.00	0.00
J01DH	Carbapenems	0.03	0.03	0.04	0.04	0.05	0.06	0.14	0.24	0.1	0.10
J01M	Quinolones	3.70	3.53	3.4	3.16	3.25	1.97	2.48	3.29	2.83	2.62
P01AB	Nitroimidazole derivatives	0.47	0.48	0.46	0.53	0.44	0.45	0.67	0.79	0.83	0.85
J01F	Macrolides	5.32	5.4	5.26	4.72	4.79	5.07	7.9	7.2	7.24	6.61
J01A	Tetracyclines	1.11	1.32	1.37	1.41	1.3	1.5	1.62	2.3	1.74	1.65
J01E	Sulfonamides and trimethoprim	0.12	0.75	0.84	0.81	0.8	1.05	1.05	0.97	0.97	0.96
J01G	Aminoglycosides	0.49	0.12	0.14	0.12	0.13	0.13	0.19	0.49	0.32	0.37
J01B	Amphenicols	/	/	/	/	/	/	/	/	/	/
J01X	Other antibacterials	0.22	0.27	0.29	0.29	0.23	0.21	0.24	0.44	0.41	0.52
Total consumption		25.57	25.90	26.52	23.77	25.22	25.84	27.36	31.42	31.56	31.42

DDD – defined daily doses; ATC – Anatomical Therapeutic Chemical.

***Note*: "/" signifies that the drugs were not commercially available.**

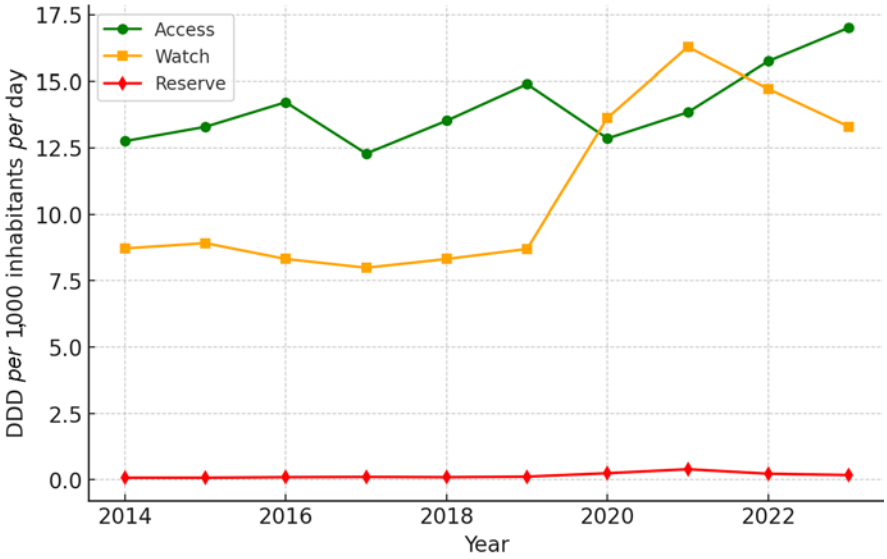

Fig. 2 – Antibiotic consumption by Access, Watch, Reserve (AWaRE) classification in Montenegro. DDD - defined daily doses

tibiotic classes. Among antibiotic subgroups, no significant changes were found in the use of J01C (y = 183.7 - 0.09*x; p = 0.495) and J01M (y = 229.2 - 0.11*x; p = 0.051) classes. These results suggest that the consumption of these classes did not exhibit a consistent or meaningful directional change over the study period. Despite fluctuations in their usage, the absence of statistical significance indicates that these changes were likely due to random variation or external factors, rather than a sustained trend. In contrast, significant positive trends were identified for J01D (y = -953.5 + 0.48*x; p = 0.001) and P01AB (y = -96.7 + 0.05*x; p = 0.001) classes, indicating a consistent increase in the consumption of these antibiotics over time.

Antibiotic consumption by Access, Watch, Reserve classification

From 2014 to 2023, the antibiotic consumption in Montenegro, categorized by the AWaRE classification, displayed distinct trends (Figure 2). A significant positive trend was observed in the consumption of the Access, Watch, and Reserve antibiotics over time (p = 0.022, p = 0.006, p = 0.026, respectively). Antibiotic use increased across all three AWaRe categories. Access and Watch antibiotics showed the most pronounced growth, suggesting their expanding role in empirical treatment. A smaller but significant rise in Reserve antibiotic use highlights a potentially concerning trend that warrants closer monitoring. These trends indicate a consistent increase in the use of antibiotics across all three categories, with the most noticeable rises in the Watch and Access groups, likely due to changes in clinical guidelines, prescribing practices, and the growing need for these antibiotics.

Discussion

This study provides the first comprehensive analysis of long-term outpatient antibiotic consumption trends in Montenegro. The results reveal a slight, non-significant decline in overall use from 2014 to 2019, followed by a sharp increase in 2021, likely influenced by the COVID-19 pandemic and stabilization at elevated levels in 2022 and 2023. A statistically significant upward trend was observed in the consumption of broad-spectrum antibiotics, particularly those from the Watch group, although Access antibiotics remained the most frequently used class.

Antibiotic use in Montenegro showed a slight, non-significant decline from 2014 to 2019, followed by a sharp increase in 2021, likely driven by the COVID-19 pandemic. Although COVID-19 is a disease caused by a viral infection, widespread antibiotic use was reported globally due to concerns about bacterial co-infections, panic, lack of treatment options, and low vaccine trust [23, 24]. This pattern reflects findings from other studies showing disproportionately high antibiotic use during the pandemic, especially in LMICs [3]. Factors such as panic, limited knowledge, lack of treatment options, and low vaccine trust contributed to excessive antibiotic use during this period [24].

In contrast to the declining or stable antibiotic consumption trends observed in many EU/EEA countries, Montenegro experienced an overall increase in outpatient antibiotic use from 2000 to 2022 [25].

This divergence highlights the need to examine factors such as regulatory oversight, prescriber behavior, and public awareness to inform targeted antimicrobial stewardship strategies.

Over a decade ago, Montenegro ranked among the highest consumers of antimicrobial drugs in Europe, with 31.5 DDD/1,000/day recorded in 2011 [26]. In the following years (2014–2019), antimicrobial consumption began to decline, aligning with reductions observed across Europe. However, despite this reduction, Montenegro's consumption levels remained higher than the population-weighted mean in the EU/EEA (19.4 DDD/1,000/day in 2019) [27]. In comparison, Montenegro's antibiotic consumption in 2019 was similar to Romania's (28.8 DDD/1,000/day), but significantly higher than that of its neighboring countries:

Bulgaria (20.7 DDD/1,000/day), Bosnia and Herzegovina, Republic of Srpska (19.4 DDD/1,000/day), Croatia (18.8 DDD/1,000/day), Hungary (14.4 DDD/1,000/day), and Slovenia (13.0 DDD/1,000/day) [24, 27].

The consumption in 2021 was 32.65 DDD/1,000/day, which is almost twice as much as the average consumption in the EU/EEA weighted population for 2021, at 16.4 DDD/1,000/day. After the pandemic-related spike (32.65 DDD/1,000/day), antibacterial consumption slightly declined to 32.40 DDD/1,000/day in 2022 and 31.92 DDD/1,000/day in 2023, indicating that while consumption surged in 2021, it did not continue rising but stabilized at a slightly lower level. For comparison, the EU population-weighted mean for systemic antibacterial drugs was 19.4 DDD/1,000/day in 2022 and 20.0 DDD/1,000/day in 2023 [28]. According to the WHO Regional Office for Europe, in 2023, the total consumption of J01 antibacterials in Montenegro was comparable to that in Serbia (31.4 DDD/1,000/day), while lower levels were reported in Bosnia and Herzegovina (24.7 DDD/1,000/day), Bulgaria (19.8 DDD/1,000/day), and Republic of North Macedonia (16.8 DDD/1,000/day) [29].

A study from Poland reported a slight increase in total antibiotic use between 2007 and 2016, with particular growth in beta-lactamase-sensitive penicillins, reflecting shifting prescribing patterns in Eastern Europe [30]. Similarly, Austria demonstrated relatively low overall antibiotic consumption compared to other European countries, although an increase in the use of fluoroquinolones and beta-lactams was noted over the study period [31]. The European Center for Disease Prevention and Control 2023 report on antimicrobial consumption across the EU/EEA highlighted significant variations between countries and emphasized the impact of the COVID-19 pandemic on antibiotic use trends, underlining the importance of sustained stewardship efforts to control antibiotic consumption and resistance at a regional level [28]. While comparing antibiotic consumption trends across countries provides valuable insights, it is essential to consider differences in data sources, methodologies, healthcare system structures, and prescribing practices. These factors may limit direct comparability and require cautious interpretation of observed similarities or differences.

Implications for policy and stewardship

Although both consumption and expenditure have stabilized, they remain elevated compared to pre-pandemic levels, suggesting a persistent shift in prescribing patterns and financial burden. In comparison, in 2023, Croatia reported €130.5 million in expenditure on systemic antibacterial drugs, reflecting broader regional concerns [32], while Serbia reported an expenditure of approximately €96.8 million for the same category of medications during the same year [33]. These figures underscore the sustained economic burden that antibiotic use continues to impose on national healthcare systems, even as public health efforts aim to promote more rational and targeted prescribing practices. Despite regulations that restrict antibiotics to prescription-only availability, control over the dispensing of antimicrobial drugs remains inadequate in Montenegro. Previous studies have identified inappropriate patient behavior as a major factor contributing to antibiotic misuse. Specifically, a study on antibiotic use in the general population of Montenegro revealed that 60.9% of respondents had used antibiotics in the past 12 months, with 33.4% obtaining them without a prescription or medical supervision [34]. The same issue was reported in Serbia, where approximately a quarter of packages were used for self-medication—purchased at a pharmacy without a prescription (20.65%) [35], and in the Republic of North Macedonia (43.3%) [36]. These findings underscore the urgent need for sustained antimicrobial stewardship efforts and informed policy-making to optimize antibiotic use, curb the rise of resistance, and ultimately protect public health in Montenegro.

The analysis of antibiotic consumption trends revealed differing patterns among the classes studied. Statistically significant increasing trends were observed for J01D and P01AB, reflecting a shift toward broader-spectrum antibiotics. This trend aligns with broader patterns observed across Europe, where countries have shown statistically significant increases in the use of broad-spectrum antibiotics such as penicillins, cephalosporins, and other beta-lactams [28]. Furthermore, the same trend was observed in the USA [37], Africa [38], and Asia [39].

The consumption of AWaRE antibiotics has significantly increased over time, highlighting a growing reliance on these classes of antibiotics. According to Freudenhammer et al. [40], to mitigate the development of AMR, at least 60% of total antibiotic consumption should consist of Access antibiotics. The WHO similarly recommends that Access antibiotics should make up no less than 60% of national consumption [41], which aligns with the prominent use of the Access group observed in this study.

When compared to the WHO's 2015 assessment, which reported 6.3 DDDs for Watch antibiotics and 10.6 DDDs for Access antibiotics [42], Montenegro's consumption levels were slightly higher. Access antibiotics in Montenegro accounted for 13.29 DDDs, while Watch antibiotics reached 8.92 DDDs. This reflects a notable increase in the use of both Access and Watch antibiotics in the country, highlighting changes in prescribing practices and underscoring the need for continuous surveillance and targeted stewardship programs. Access to antibiotic consumption in Montenegro in 2023 is comparable to neighboring countries such as Serbia (16.4 DDD/1,000/day), Bosnia and Herzegovina (15.0 DDD/1,000/day), and Bulgaria (13.7 DDD/1,000/day), while Republic of North Macedonia reports notably lower use (8.3 DDD/1,000/day) [29].

In 2019, comparable consumption levels of Watch group antibiotics were observed among several Balkan countries, including Bosnia and Herzegovina (6.6 DDD/1,000/day), Bulgaria (7.3 DDD/1,000/day), Republic of North Macedonia (7.8 DDD/1,000/day), and Serbia (11.4 DDD/1,000/day) [43]. By 2023, an upward trend was noted, with increased consumption in Bosnia and Herzegovina (9.8 DDD/1,000/day), Republic of North Macedonia (8.0

DDD/1,000/day), and Serbia (15.7 DDD/1,000/day) [29]. However, the increasing use of Watch antibiotics is a significant concern, which may be driven by factors such as economic growth, the affordability of broad-spectrum antibiotics, and market-driven prescribing practices. Weak regulatory frameworks enable over-the-counter antibiotic sales, and diagnostic uncertainty contributes to their overprescription. Physicians may also feel compelled to prescribe "Watch" antibiotics as a precaution due to the lack of resistance data and limited testing. Moreover, antibiotic resistance is often given lower priority in favor of other health issues, while rising rates of resistant infections continue to drive this trend [42, 44].

Based on our findings, we recommend implementing targeted antimicrobial stewardship programs in outpatient care to optimize antibiotic use, particularly broad-spectrum and Watch group antibiotics. Updating national prescribing guidelines, improving provider education on rational use, and strengthening the enforcement of prescription-only antibiotic sales are crucial. Additionally, public awareness campaigns and improved surveillance systems will support efforts to curb antibiotic misuse and resistance.

The observed trends reflect key challenges identified in the WHO Global Action Plan on AMR, particularly in optimizing antimicrobial use and improving surveillance. Strengthening national stewardship efforts will be essential for Montenegro to meet the strategic objectives outlined in both the WHO plan and its national AMR strategy.

Limitations

This study has several limitations that should be taken into account when interpreting the results. The analysis relies on aggregated sales data rather than patient-level prescribing or dispensing records. While sales data provide useful insights into availability and distribution, they may not fully represent actual consumption due to factors such as stockpiling, wastage, or non-adherence. In addition, the study does not incorporate AMR data, which limits the ability to assess direct correlations between antibiotic use and resistance patterns at the national level. Including such data would have strengthened the implications for public health and stewardship strategies. Furthermore, although the use of the DDD metric enables standardized comparisons, it may not accurately reflect local prescribing habits, especially in pediatric or geriatric populations where dosing commonly deviates from the standard DDD. Finally, the retrospective design of the study and reliance on secondary data sources preclude a detailed analysis of contextual factors, such as changes in prescribing practices, regulatory interventions, or public awareness efforts, which may have influenced antibiotic use trends over the study period. Despite these limitations, the findings offer a meaningful overview of long-term antibiotic consumption patterns in Montenegro and can serve as a valuable reference for informing future surveillance efforts and policy development.

Conclusion

This study highlights the surge in outpatient antibiotic use related to the COVID-19 pandemic and its subsequent stabilization in Montenegro, with levels remaining higher than before the pandemic. These trends are concerning and underscore the urgent need for sustained, context-specific stewardship interventions to reduce overuse and mitigate antimicrobial resistance. Tailored strategies should include enhanced surveillance, updates to national prescribing guidelines, and targeted educational campaigns to promote rational antibiotic use. Future research should investigate prescribing behaviors and evaluate the effectiveness of interventions, especially those targeting high-risk antibiotic classes such as the Watch group. Given the global nature of antimicrobial resistance, international collaboration remains essential to support national efforts and align with the goals of the World Health Organization Global Action Plan and regional antimicrobial resistance strategies.

Conflict of interest

The authors declare no conflict of interest.

R E F E R E N C E S

1. *Silva AC, Nogueira PJ, Paiva JA.* Determinants of antimicrobial resistance among the different European countries: more than human and animal antimicrobial consumption. Antibiotics (Basel) 2021; 10(7): 834.
2. *Ajulo S, Awosile B.* Global antimicrobial resistance and use surveillance system (GLASS 2022): Investigating the relationship between antimicrobial resistance and antimicrobial consumption data across the participating countries. PLoS One 2024; 19(2): e0297921.
3. *Khan S, Hasan SS, Bond SE, Conway BR, Aldeyab MA.* Antimicrobial consumption in patients with COVID-19: a systematic review and meta-analysis. Expert Rev Anti Infect Ther 2022; 20(5): 749–72.
4. *Ngoma MT, Sitali D, Mudenda S, Mukuma M, Bumbangi FN, Bunuma E,* et al. Community antibiotic consumption and associated factors in Lusaka district of Zambia: findings and implications for antimicrobial resistance and stewardship. JAC Antimicrob Resist 2024; 6(2): dlae034.
5. *Jiang T, Chen XS.* Outcome impacts due to pathogen-specific antimicrobial resistance: A narrative review of published literature. Int J Environ Res Public Health 2020; 17(4): 1395.
6. *Goossens H, Ferech M, Vander Stichele R, Elseviers M; ESAC Project Group.* Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. The Lancet 2005; 365(9459): 579–87.
7. *Meyer E, Gastmeier P, Deja M, Schwab F.* Antibiotic consumption and resistance: data from Europe and Germany. Int J Med Microbiol 2013; 303(6–7): 388–95.
8. *Pérez-Lazo G, Abarca-Salazar S, Lovón R, Rojas R, Ballena-López J, Morales-Moreno A,* et al. Antibiotic consumption and its relationship with bacterial resistance profiles in ESKAPE pathogens in a Peruvian Hospital. Antibiotics (Basel) 2021; 10(10): 1221.

9. *Barberi G, De Cola MC, Dell'Utri C, Melardi S, Alagna B, Bramanti P,* et al. Antimicrobial consumption and antimicrobial resistance: a snapshot of an Italian neuromuscular rehabilitation center. New Microbiol 2017; 40(2): 119–29.
10. *Guo W, Sun F, Liu F, Cao L, Yang J, Chen Y.* Antimicrobial resistance surveillance and prediction of Gram-negative bacteria based on antimicrobial consumption in a hospital setting: a 15-year retrospective study. Medicine (Baltimore) 2019; 98(37): e17157.
11. *Tsutsui A, Yahara K, Shibayama K.* Trends and patterns of national antimicrobial consumption in Japan from 2004 to 2016. J Infect Chemother 2018; 24(6): 414–21.
12. *Bozkurt F, Kaya S, Tekin R, Gulsun S, Deveci O, Dayan S,* et al. Analysis of antimicrobial consumption and cost in a teaching hospital. J Infect Public Health 2014; 7(2): 161–9.
13. *Klein EY, Impalli I, Poleon S, Denoel P, Cipriano M, Van Boeckel TP,* et al. Global trends in antibiotic consumption during 2016–2023 and future projections through 2030. Proc Natl Acad Sci U S A 2024; 121(49): e2411919121.
14. *Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA,* et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A 2018; 115(15): E3463–70.
15. *Khouja T, Mitsantisuk K, Tadrous M, Suda KJ.* Global consumption of antimicrobials: impact of the WHO Global Action Plan on Antimicrobial Resistance and 2019 coronavirus pandemic (COVID-19). J Antimicrob Chemother 2022; 77(5): 1491–9.
16. *Semenova Y, Kassym L, Kussainova A, Aimurziyeva A, Makalkina L, Avdeyev A,* et al. Knowledge, Attitudes, and Practices towards Antibiotics, Antimicrobial Resistance, and Antibiotic Consumption in the Population of Kazakhstan. Antibiotics (Basel) 2024; 13(8): 718.
17. *The Institute for Medicines and Medical Devices of Montenegro (CInMED).* Consumption of medicines [Internet]. Montenegro: CInMED; 2025 [cited on 2025 July 17]. Available from: https://cinmed.me/en/humane-medicines/consumption-of-medicines/ (Montenegrin)
18. *Barnsteiner S, Baty F, Albrich WC, Babouee Flury B, Gasser M, Plüss-Suard C,* et al. Antimicrobial resistance and antibiotic consumption in intensive care units, Switzerland, 2009 to 2018. Euro Surveill 2021; 26(46): 2001537.
19. *Abu-Ajaleh S, Darwish Elhajji F, Al-Bsoul S, Abu Farha R, Al-Hammouri F, Amer A,* et al. An evaluation of the impact of increasing the awareness of the WHO access, watch, and reserve (AWaRe) antibiotics classification on knowledge, attitudes, and hospital antibiotic prescribing practices. Antibiotics (Basel) 2023; 12(6): 951.
20. *Mudenda S, Nsofu E, Chisha P, Daka V, Chabalenge B, Mufwambi W,* et al. Prescribing patterns of antibiotics according to the WHO AWaRe classification during the COVID-19 pandemic at a teaching hospital in Lusaka, Zambia: implications for strengthening of antimicrobial stewardship programmes. Pharmacoepidemiology 2023; 2(1): 42–53.
21. *Sulis G, Adam P, Nafade V, Gore G, Daniels B, Daftary A,* et al. Antibiotic prescription practices in primary care in low-and middle-income countries: a systematic review and meta-analysis. PLoS Med 2020; 17(6): e1003139.
22. *Perić A, Rančić N, Dragojević-Simić V, Milenković B, Ljubenović N, Rakonjac B,* et al. Association between antibiotic use and hospital-onset Clostridioides difficile infection in University Tertiary Hospital in Serbia, 2011–2021: an ecological analysis. Antibiotics (Basel) 2022; 11(9): 1178.
23. *Sokolović D, Drakul D, Vujić-Aleksić V, Joksimović B, Marić S, Nežić L.* Antibiotic consumption and antimicrobial resistance in the SARS-CoV-2 pandemic: A single-center experience. Front Pharmacol 2023; 14: 1067973.
24. *Sokolović D, Drakul D, Joksimović B, Lalović N, Avram N, Milić M,* et al. Consumption of antibiotics in primary care setting before and during COVID-19 pandemic in Republic of Srpska, Bosnia and Herzegovina. Antibiotics (Basel) 2022; 11(10): 1319.
25. *Duborija-Kovačević N, Djapić-Savelić J, Mijanović A.* Outpatient utilization of antibacterial drugs for systemic use in Montenegro in 2000-2022: how far are we from values and targets of the European Union? Farmacia 2025; 73(1): 140–9.
26. *Versporten A, Bolokhovets G, Ghazaryan L, Abilova V, Pyshnik G, Spasojevic T,* et al. Antibiotic use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe. The Lancet Infect Dis 2014; 14(5): 381–7.
27. *European Centre for Disease Prevention and Control (ECDC).* Antimicrobial consumption - Annual Epidemiological Report for 2019 [Internet]. Stockholm: ECDC; 2020 [cited on 2025 July 17]. Available from: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-consumption-europe-2019
28. *European Centre for Disease Prevention and Control (ECDC).* Antimicrobial consumption in the EU/EEA (ESAC-Net) - Annual Epidemiological Report for 2023 [Internet]. Stockholm: ECDC; 2024 [cited on 2025 July 17]. Available from: https://www.ecdc.europa.eu/en/publications-data/antimicrobial-consumption-eueea-esac-net-annual-epidemiological-report-2023
29. *World Health Organization.* WHO Regional Office for Europe Antimicrobial Medicines Consumption (AMC) Network. AMC data 2023 [Internet]. Copenhagen: WHO Regional Office for Europe; 2025 [cited on 2025 July 17]. Available from: https://iris.who.int/bitstream/handle/10665/380848/9789289061872-eng.pdf?sequence=1
30. *Wojkowska-Mach J, Godman B, Glassman A, Kurdi A, Pilc A, Rozanska A,* et al. Antibiotic consumption and antimicrobial resistance in Poland; findings and implications. Antimicrob Resist Infect Control 2018; 7: 136.
31. *Metz-Gercek S, Maieron A, Strauß R, Wieninger P, Apfalter P, Mittermayer H.* Ten years of antibiotic consumption in ambulatory care: Trends in prescribing practice and antibiotic resistance in Austria. BMC Infect Dis 2009; 9: 61.
32. *The Agency for Medicinal Products and Medical Devices (HALMED).* Annual report on drug utilization for 2023 – Croatian document [Internet]. Croatia: HALMED; 2023 [cited on 2025 July 17]. Available from: https://www.halmed.hr/Novosti-i-edukacije/Publikacije-i-izvjesca/Izvjesca-o-potrosnji-lijekova/ (Croatian)
33. *Medicines and Medical Devices Agency of Serbia (ALIMS*). Drug sales and consumption [Internet]. Belgrade: ALIMS; 2023 [cited on 2025 July 17]. Available from: https://www.alims.gov.rs/humani-lekovi/promet-i-potrosnja-lekova/ (Serbian)
34. *Raicevic M, Labovic Barjaktarovic S, Milic D, Nedovic Vukovic M, Bajceta N.* Public knowledge, attitudes, and practices regarding antibiotics use and resistance in Montenegro. Eur J Public Health 2025; 35(2): 290–4.
35. *Tomas A, Paut Kusturica M, Tomić Z, Horvat O, Djurović Koprivica D, Bukumirić D,* et al. Self-medication with antibiotics in Serbian households: a case for action? Int J Clin Pharm 2017; 39(3): 507–13.
36. *Ivanovska V, Zdravkovska M, Bosevska G, Angelovska B.* Antibiotics for upper respiratory infections: public knowledge, beliefs and self-medication in the Republic of Macedonia. Pril (Makedon Akad Nauk Umet Odd Med Nauki) 2013; 34(2): 59–70.
37. *Goossens H, Ferech M, Coenen S, Stephens P; European Surveillance of Antimicrobial Consumption Project Group.* Comparison of outpatient systemic antibacterial use in 2004 in the United States and

27 European countries. Clin Infect Dis 2007; 44(8): 1091–5. Erratum in: Clin Infect Dis 2007; 44(9): 1259.

38. *Gutema G, Ali S, Suleman S*. Trends of community-based systemic antibiotic consumption: Comparative analyses of data from Ethiopia and Norway calls for public health policy actions. PLoS One 2021; 16(5): e0251400.
39. *Tshering T, Wangda S, Buising K*. Trends in antimicrobial consumption in Bhutan. IJID Reg 2021; 1: 65–71.
40. *Freudenhammer M, Hufnagel M, Steib-Bauert M, Mansmann U, de With K, Fellhauer M,* et al. Antibiotic use in pediatric acute care hospitals: an analysis of antibiotic consumption data from Germany, 2013–2020. Infection 2024; 52(3): 825–37.
41. *World Health Organization*. The WHO AwaRe (Access, Watch, Reserve) antibiotic book [Internet]. Geneva: WHO; 2022 [cited on 2025 July 17]. Available from: https://www.who.int/publications/i/item/9789240062382
42. *Klein EY, Milkowska-Shibata M, Tseng KK, Sharland M, Gandra S, Pulcini C,* et al. Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000–15: an analysis of pharmaceutical sales data. Lancet Infect Dis 2021; 21(1): 107–15.
43. *World Health Organization*. WHO Regional Office for Europe Antimicrobial Medicines Consumption (AMC) Network. AMC data 2019 [Internet]. Copenhagen: WHO Regional Office for Europe; 2022 [cited on 2025 July 17]. Available from: https://www.who.int/europe/publications/i/item/9789289058278
44. *Hoxha I, Godman B, Malaj A, Meyer JC*. 11-Year trend in antibiotic consumption in a south-eastern European country; the situation in Albania and the implications for the future. Antibiotics (Basel) 2023; 12(5): 882.

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SCIENTIFIC MEETING REPORT

First Regional SDIR-HDIR-MOKAD Congress (Belgrade, Serbia, October 8–10, 2025)

Prvi regionalni SDIR-HDIR-MOKAD kongres (Beograd, Srbija, 8–10. oktobar, 2025)

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The Serbian Association for Cancer Research organized the 1st Regional European Congress of Serbian (*Srpsko društvo istraživača raka* – SDIR), Croatian (*Hrvatsko društvo za istraživanje raka* – HDIR), and Turkish (*Moleküler Kanser Araştırma Derneği* – MOKAD) societies for cancer research – SHM1RC. The congress took place at the Nobel Zira hotel in Belgrade on October 8–10, 2025, bringing together around 300 scientists, clinicians, and patient advocates not only from our region, but from 16 countries all over Europe and the USA.

SDIR is a non-profit association, founded to improve conditions for cancer research and the professional development of society members. It also organizes scientific and professional meetings to exchange the latest information in the field of oncology. SDIR, HDIR, and MOKAD belong to the group of national societies affiliated with the European Association for Cancer Research (EACR), which supported all previous SDIR congresses through the auspices of lectures by eminent scientists and traditional EACR awards for the best presentations.

The 1st Regional Congress addressed key topics in current cancer research through the following sessions: Benefits of combination therapies in cancer treatment; Personalized anticancer treatment through targeting signaling pathways; Tumor microenvironment – friend or foe; Immmuno-oncology; Exploring the role of MDR mechanisms and stem cell biology in cancer treatment strategies; Cancer epidemiology – strategies for prevention and early detection; Advancements in molecular diagnostics and cancer biomarkers in oncology; Liquid biopsy (EACR plenary session); Bioinformatics and cancer genomics; Novel cancer therapies and drug development strategies; Toxic triggers – environmental chemicals and cancer risk; Tumor metabolism; Innovative models and approaches in cancer research. A patient–clinician–scientist educational interactive panel took place during the session "Bridging patients and researchers". Patient advocates addressed key concerns related to participation in scientific/clinical research and emphasized the need to strengthen the partnership between patients and researchers. Young scientists had the opportunity to discuss topics on career development in a session called "Meet the Experts". At the very end of the meeting, participants discussed regional collaboration through an interactive panel session. In summary, participants had the opportunity to listen to two plenary lectures, 37 invited lectures, 22 short presentations selected from 106 posters, and six sponsored symposiums. Abstracts from the congress were published in Oncology Insights, the official journal of SDIR (ISSN 3009-3848, 2025, No.3).

During the opening ceremony, SHM1RC participants were welcomed by Dr. Milena Čavić, President of the SDIR, Prof. Engin Ulukaya, President of the MOKAD, Prof. Sonja Levanat, President of the HDIR (Figure 1), Ass. Prof. Milan Žegarac, Acting Director of the Institute for Oncology and Radiology of Serbia, Prof. Nenad Filipović, Director of the Science Fund of the Republic of Serbia, and Dr. Milica Pešić and Dr. Ana Damjanović Veličković as Chairs of the Scientific and Organizing Committees, respectively (Figure 2).

The congress was closed by an Award ceremony supported by the EACR, FebsOpenBio, Molecular

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Fig. 1 – Dr. Milena Čavić, SDIR president, Prof. Engin Ulukaya, MOKAD president, Prof. Sonja Levanat, HDIR president (from left to right).

Fig. 2 – Dr. Ana Damjanović Veličković (left) and Dr. Milica Pešić (right), chairs of the Organizing and Scientific committee.

Fig. 3 – Congress closing and Award ceremony.

Oncology Journal, and the European Liquid Biopsy Society (Figure 3).

The EACR Awards were given to:

1st prize: Beyza Ozturk Sever, Turkey – "Investigation of the effect of exportin-1 gene inhibition with Selinexor on glioma";

2nd prize: Vuk Gordić, Serbia – "The effect of novel diclofenac-based carbon-substituted prodrug on colon cancer cell lines and mouse-derived organoids";

3rd prize: Ivana Banićević, Serbia – "A 3D *in vitro* osteosarcoma model based on porous scaffolds and a perfusion bioreactor for preclinical applications".

Fig. 4 – Congress participants during the guided tour through Belgrade, Serbia.

The Molecular Oncology Award for Best Short Oral Presentation was shared by Muhlis Akman, Turkey, for "TFEB Controls Chemoresistance in NSCLC", and Janja Josić, Croatia, for "Expression profiling of p53 family isoforms in targeted therapy-resistant primary melanoma cell lines".

The FEBSOpenBio Award for Best Young Researcher Abstract was given to Josipa Jelačić, Croatia, for "Estrogen receptor modulation and Hedgehog-GLI crosstalk in head and neck squamous cell carcinoma".

The ELBS Award for the Best Liquid Biopsy Abstract was given to Dr. Bojana Cikota-Aleksić, Serbia, for "The association of baseline concentrations of circulating tumor DNA with the clinical course of advanced melanoma".

On Saturday, October 11, participants of the congress enjoyed a guided tour through the history and streets of our beautiful Belgrade, supported by the National Tourism Organization of Serbia (Figure 4).

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The VSP publishes only papers not published before, nor submitted to any other journals, in the order determined by the Editorial Board. Any attempted plagiarism or self-plagiarism will be punished. When submitting a paper to the VSP electronic editing system **(http://aseestant.ceon.rs/index.php)**, the following should be enclosed: a statement on meeting any technical requirements, a statement signed by all the authors that the paper on the whole and/or partly has not been submitted nor accepted for publication elsewhere, a statement specifying the actual contribution of each author, no conflict of interest statement that make them responsible for meeting any requirements set. What follows subsequently is the acceptance of a paper for further editing procedure. The manuscripts submitted to the VSP pass in-house and external peer review. All authors pay "Article Processing Charge" for coverage all editing and publishing expenses. Domestic authors pay 5,000 RSD, and those from aboard 150 euros. The editing and publishing fee is required for substantive editing, facts and references validations, copy editing, and publishing online and in print by editorial staff of the Journal. No additional fees, other than stated above, are required even if an author who already paid the fee would have more articles accepted for publishing in the year when fee was paid. All authors who pay this fee may, if want, receive printed version of the Journal in year when fee is payed. Please note that the payment of this charge does not guarantee acceptance of the manuscript for publication and does not influence the outcome of the review procedure. The requirement about paying "Article Processing Charge" does not apply to reviewers, members of the Editorial Board and the Publisher's Council of the Journal, young researchers and students, as well as any of the subscribers of the Journal.

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The *Vojnosanitetski pregled* journal fully complies with section II.A.4 of the ICMJE recommendations (update January 2025, **https://www.icmje.org/icmje-recommendations.pdf**), which describes authors' responsibilities and journal requirements regarding the use of artificial intelligence (AI)-assisted technologies in manuscript preparation.

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All measurements should be reported in the metric system of the International System of Units (SI), and the standard internationally accepted terms (except for mmHg and °C).

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Papers are reviewed anonymously by at least two editors and/or invited reviewers. Remarks and suggestions are sent to the author for final composition. Galley proofs are sent to the corresponding author for final agreement.

Preparation of manuscript

Parts of the manuscript are: **Title page; Abstract with Key words; Text; Acknowledgements** (to the authors' desire), **References**, **Enclosures**.

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a) The title should be concise but informative, while subheadings should be avoided;

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c) Exact names and places of department(s) and institution(s) of affiliation where the studies were performed, city and the state for any authors, clearly marked by standard footnote signs;

d) Conclusion could be a separate chapter or the last paragraph of the discussion;

e) Data on the corresponding author.

2. ***Abstract and key words***

The second page should carry a structured abstract (250-300 words for original articles and meta-analyses) with the title of the article. In short, clear sentences the authors should write the **Background**/**Aim**, major procedures – **Methods** (choice of subjects or laboratory animals; methods for observation and analysis), the obtained findings – **Results** (concrete data and their statistical significance), and the **Conclusion**. It should emphasize new and important aspects of the study or observations. A structured abstract for case reports (up to 250 words) should contain subtitles **Introduction, Case report, Conclusion**). Below the abstract **Key words** should provide 3–10 key words or short phrases that indicate the topic of the article.

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The text of the articles includes: **Introduction**, **Methods**, **Results**, and **Discussion**. Long articles may need subheadings within some sections to clarify their content.

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Examples of references:

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DiMaio VJ. Forensic Pathology. 2nd ed. Boca Raton: CRC Press; 2001.

Blinder MA. Anemia and Transfusion Therapy. In: Ahya NS, Flood K, Paranjothi S, editors. The Washington Manual of Medical Therapeutics, 30th edition. Boston: Lippincot, Williams and Wilkins; 2001. p. 413-28.

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: *Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG,* editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

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Primeri referenci:

Đurović BM. Endothelial trauma in the surgery of cataract. Vojnosanit Pregl 2004; 61(5): 491–7. (Serbian)

Balint B. From the haemotherapy to the haemomodulation. Beograd: Zavod za udžbenike i nastavna sredstva; 2001. (Serbian)

Mladenović T, Kandolf L, Mijušković ŽP. Lasers in dermatology. In: *Karadaglić Đ*, editor. Dermatology. Beograd: Vojnoizdavački zavod & Verzal Press; 2000. p. 1437–49. (Serbian)

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: *Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG*, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

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Tabele

Sve tabele pripremaju se sa proredom 1,5 na posebnom listu. Obeležavaju se arapskim brojevima, redosledom pojavljivanja, u levom uglu (**Tabela 1**), a svakoj se daje kratak naslov. Objašnjenja se daju u fus-noti, ne u zaglavlju. Svaka tabela mora da se pomene u tekstu. Ako se koriste tuđi podaci, obavezno ih navesti kao i svaki drugi podatak iz literature.

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