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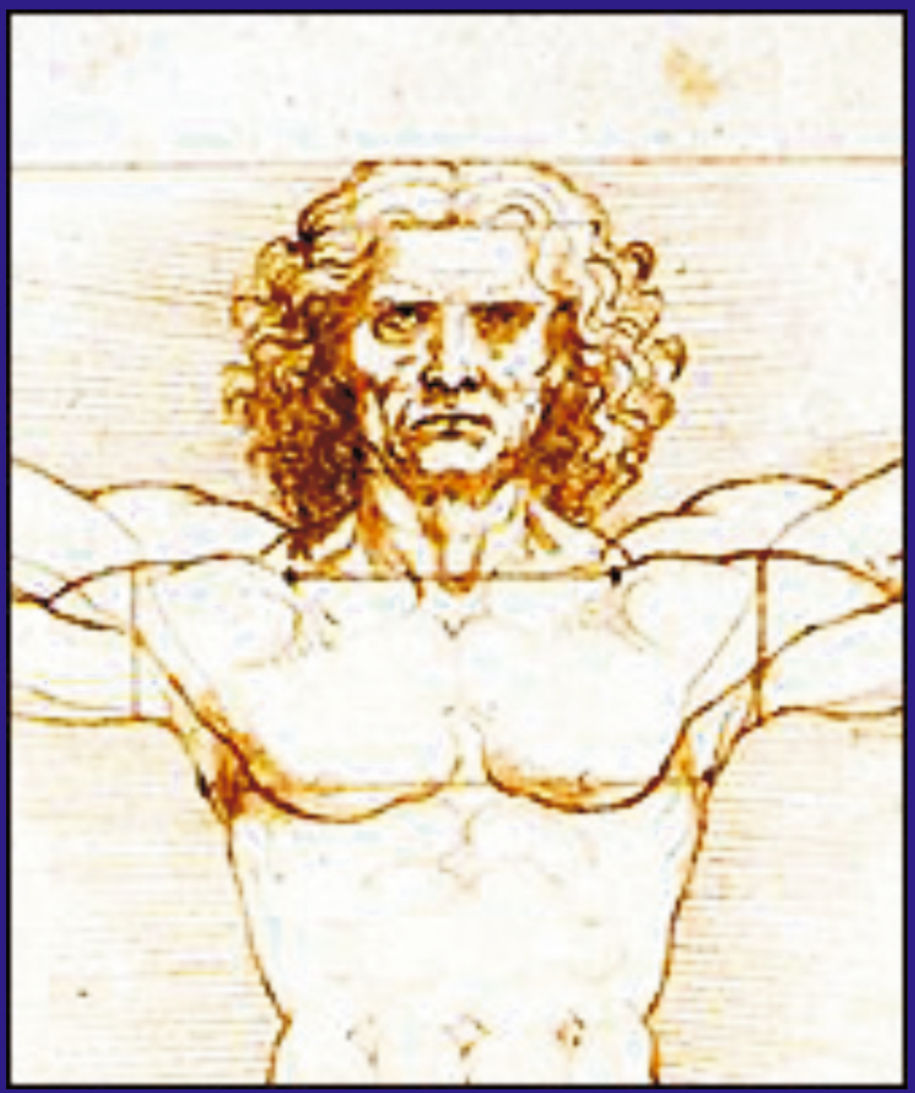

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Letter to editor

TREND IN THE PLACEMENT OF PERMANENT AND TEMPORARY CENTRAL VENOUS CATHETERS FOR HEMODIALYSIS

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Dear Editor

Chronic kidney disease (CKD) is one of the fastest-growing diseases worldwide (1). As the world population ages, the incidence of renal failure is increasing globally, along with the prevalence of people receiving chronic dialysis. There are three renal replacement modalities: peritoneal dialysis (PD), transplantation (Tx), and hemodialysis (HD), HD being the most common form of dialysis, with a worldwide prevalence of 89%, with PD accounting for the remaining 11%. The standard approach for HD is the arteriovenous fistula (AVF), while an alternative vascular access device for HD, still the tunneled central venous catheter (CVC) (1,2), is a salvage vascular access option for HD, but it is still used in approximately one-quarter of prevalent patients worldwide, although it is associated with poor performance and higher risks (2).

The literature suggests that CVC remains the most commonly used vascular access option for HD, despite guidelines advising that AVFs should be used whenever possible. The risk of CVC has mostly focused on catheter-related bacteremia and/or has only evaluated tunneled CVCs (TCVKs) (3). CVCs were first used in a patient in 1969. Over time, indications for their use have become more numerous, such as parenteral nutrition, chemotherapy, and situations where peripheral venous access is not possible in patients in intensive care units. CVC placement involves the placement of a catheter in a large-lumen venous system, most commonly the internal jugular, subclavian, or femoral vein. Complications associated with CVC placement occur in 2–26% of cases, so its use is rare and is most often in acute renal failure (4).

Globally, almost three-quarters of patients on HD require a CVC (5, 6). CVCs provide immediate access to hemodialysis in cases where high nitrogenous wastes, hyperkalemia, and anuria require urgent HD, but the use of a catheter is thought to increase the risk of complications associated with placement and long-term use (7).

In patients on HD, CVCs are used when other vascular access options are not available (8–11). Since the introduction of CVCs, catheters have been coated with heparin or antibiotics, and catheter-related complications are less common (12, 13).

The literature suggests that CVC-associated bloodstream infections in patients on HD are an important cause of hospitalization, morbidity, and mortality. Eliminating bloodstream infections in the hemodialysis setting has been a focus of the Centers for Disease Control and Prevention (CDC) Coalition (14, 15 ,16).

General preventive measures, including the use of asepsis and antisepsis, play a key role in the prevention and early detection of CVC-associated infections in patients on HD. Infection control surveillance, together with a team approach to care (doctor–nurse), significantly contributes to the reduction of CVC-related morbidity and mortality (4).

Our data from the Nephrology Clinic show that in 2025, out of approximately eighty patients on HD, 14 had a temporary or permanent CVC. Our HD center does not differ significantly from other centers in terms of the trend of CVC placement and the occurrence of complications, which can be explained by the correct placement and monitoring of therapeutic guidelines by anesthesiologists and nephrologists, and the correct maintenance and hygiene of CVCs by educated nurses in the dialysis center, Nephrology Clinic, Clinical Center of Montenegro, and the application of asepsis and antisepsis measures. Continuous evaluation, proper care and hygiene of dialysis catheters, and early detection of patients with end-stage renal disease are recommended in order to initiate HD on time and

thereby prevent complications and reduce morbidity and mortality rates, with the aim of extending life expectancy and improving the quality of life of patients on HD.

Abbreviations

AVF – arteriovenous fistula
CDC – Centers for Disease Control and Prevention
CVC – central venous catheter
CKD – chronic kidney disease
HD – hemodialysis
PD – peritoneal dialysis
TCVC – tunneled central venous catheter
Tx – transplantation

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Conflicts of Interest: None declared.

Note: Artificial intelligence was not utilized as a tool in this study.

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Original article

RISK FACTORS FOR POTENTIAL DRUG-DRUG INTERACTIONS OF ANALGESICS IN HOSPITALIZED UROLOGICAL PATIENTS

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Abstract: **Objective:** To evaluate potential drug–drug interactions (pDDIs) involving analgesics in hospitalized urological patients and identify risk factors influencing their number.

Methods: This study involved a post hoc analysis based on data obtained from a retrospective observational cohort clinical study conducted at the Clinic of Urology, University Clinical Centre Kragujevac, Serbia. Of the original 220 patients, 191 who received analgesics were included. Daily pharmacotherapy data, along with demographic and clinical characteristics, were collected, while pDDIs were identified and classified using the Lexicomp Interaction Checker. Descriptive statistics were used to summarize the data. Multiple linear regression with backward elimination was used to identify independent predictors of the number of pDDIs.

Results: Analgesic-related pDDIs were detected in 175 patients (91.6%). Non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed to 173 patients (90.6%), opioids to 53 (27.7%), and paracetamol to 54 (28.3%). The mean number of pDDIs per patient was 5.5 ± 5.5 (range 0–30). Category X interactions most frequently included NSAID combinations (diclofenac + ketorolac, ketorolac + metamizole), while category D interactions frequently involved enoxaparin + ketorolac and opioid–benzodiazepine pairs. Category C interactions were dominated by NSAID + potassium chloride and tramadol + ondansetron or atropine combinations. Multiple regression analysis identified diabetes, a higher number of prescribed drugs, and the use of NSAIDs or opioids as positive predictors of the number of pDDIs, whereas a cancer diagnosis was associated with a lower number.

Conclusion: Analgesic-related pDDIs affect the majority of hospitalized urological patients. Avoiding high-risk combinations, close monitoring, and multidisciplinary medication review in patients with risk factors may help reduce preventable harm.

Keywords: analgesics, drug–drug interactions, urology, hospitalized patients.

INTRODUCTION

The safe and effective use of analgesics remains a major challenge in hospitalized patients, particularly in those with complex comorbidities, polypharmacy, and specialist-care needs (1). Drug–drug interactions (DDIs) occur when the response or exposure to one drug is altered by the concurrent administration of another drug, which may result in a change in the therapeutic effect or the development of adverse drug reactions, while the term potential DDI (pDDI) refers to the "co-prescription of two drugs known to interact" (2).

Within hospital settings, urological patients represent a subset of inpatients who may be particularly vulnerable to analgesic-related interactions (3, 4). These patients frequently undergo surgical procedures, often have renal impairment, and receive analgesics alongside diverse urologic and non-urologic pharmacotherapies (5). A recent retrospective cohort study in a urology clinic reported that 95% of patients had at least one pDDI during hospitalization, while risk factors included duration of hospitalization, surgical interventions, arrhythmias, dementia, renal failure, cancer, number of prescribed drugs, and various pharmacological drug classes, including some analgesics (3). Despite these findings, there is limited published

work focusing specifically on analgesic-related pDDIs in hospitalized urological populations.

Prescribing practices in analgesic therapy can also influence DDI risk (6, 7, 8). In a study from a tertiary hospital in Pakistan, analgesics were often prescribed without formal pain-intensity assessment, and every prescription was found to include at least one pDDI, with 60% of interactions rated as major (6). These findings emphasize that prescribing context, analgesic selection, monitoring, and patient-level characteristics may all contribute to pDDI development (6,7). Comparable patterns have been observed in outpatient settings (9, 10, 11). Several population-based studies conducted in primary care and community pharmacy practice have reported that analgesics are among the drug groups most frequently implicated in pDDIs in ambulatory patients, particularly non-steroidal anti-inflammatory drugs (NSAIDs) co-prescribed with antihypertensives, antithrombotics, or other nephrotoxic agents (9, 10, 11). For example, in a national cohort study from Poland, analgesic-related pDDIs affected 6.47% of the entire population, with the most common combinations involving NSAIDs and antihypertensive therapy (9). In family medicine clinics in Mexico City, approximately 80% of ambulatory adults aged ≥ 50 years receiving non-opioid analgesics had at least one pDDI, while older age, cardiovascular disease, and the use of ≥ 5 medications were significant predictors (10). A more recent community-pharmacy study similarly identified clinically relevant interactions between NSAIDs and antithrombotics, reinforcing that polypharmacy and long-term analgesic use also drive pDDI risk in non-hospital settings (11).

AIM

The aim of this study was to evaluate pDDIs involving analgesics in hospitalized urological patients and to identify independent risk factors influencing their number. By focusing on this specialized inpatient population, we aim to generate evidence to support safer analgesic prescribing, strengthen interdisciplinary collaboration across urology, pharmacy, and pain management, and ultimately reduce preventable harm associated with pDDIs.

MATERIAL AND METHODS

Study design

This study involved a post hoc analysis based on data obtained from a retrospective observational cohort clinical study conducted at the Clinic of Urology of the University Clinical Centre Kragujevac, a public tertiary care hospital in Kragujevac, Serbia (3). The primary aim of the original study was to evaluate pDDIs and the factors influencing their number among hospitalized urological patients (3), while this post hoc analysis focused on pDDIs involving analgesics. Ethical approval was granted by the Ethics Committee of the University Clinical Centre Kragujevac prior to the initiation of the study (3).

Selection criteria and study sample

The original cohort included all consecutive patients admitted to the Clinic of Urology between January 1 and December 28, 2023, who had urological conditions, including but not limited to urinary tract infections, male genital tract infections, urinary tract tumors, male genital tract tumors, benign prostatic hyperplasia, and urinary stones (3). Eligible patients were those aged over 18 years who received at least two medications during a hospital stay lasting at least 48 hours, while patients hospitalized for organizational reasons, pregnant patients, and those with incomplete medical documentation were excluded (3). The original study population consisted of 220 patients (3), and for this post hoc analysis aimed at evaluating pDDIs involving analgesics, 191 patients who received analgesic therapy during hospitalization were identified and included in the analysis.

Data collection

Data were collected from the patients' medical records. Pharmacotherapy data for each day of hospitalization (all drugs prescribed to the patient during each day of hospital treatment), along with demographic and clinical characteristics, were collected. The following variables were considered: age, gender, length of hospital stay (in days), primary urological pathology (reason for admission), comorbidities, Charlson Comorbidity Index, occurrence of infection during hospitalization, surgery during hospitalization, endoscopic procedure during hospitalization, transfusion of blood or blood products during hospitalization, documented drug allergies, pharmacotherapy data (number of prescribed drugs as a continuous variable, number of prescribed therapeutic subgroups [Anatomical Therapeutic Chemical (ATC) Classification level 2], prescribed pharmacological drug classes, and number of physicians prescribing drugs during hospitalization), and interaction-checker data (number and description of pDDIs). The pDDI, which served as the outcome variable, was defined as the co-prescription of two drugs known to interact (2, 3). Identification and classification of pDDIs were performed using the Lexicomp Interaction Checker, a commercial drug-interaction database with a paid subscription, which categorizes interactions according to the following risk

ratings: X (Avoid combination), D (Consider therapy modification), C (Monitor therapy), B (No action needed), and A (No known interaction) (3).

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 18. Descriptive statistics were used to summarize the data. Measures of central tendency (mean, median) and dispersion (standard deviation and range) were calculated for continuous variables, while categorical variables were expressed as frequencies and percentages. The influence of potential risk factors on the number of analgesic-related pDDIs per patient was assessed using univariate linear regression and multiple linear regression with backward elimination, applying a probability of $F \leq 0.1$ for variable removal. In this procedure, all potential predictor variables were initially included in the model and subsequently removed one at a time, beginning with the variable showing the highest p value, until only predictors with $p \leq 0.1$ remained. Dichotomous categorical variables were coded as 0 and 1, where 0 indicated the absence of a qualitative attribute and 1 indicated its presence, except for gender, where 0 represented female and 1 represented male. The statistical validity of the regression model was evaluated using analysis of variance (F value) and the coefficient of determination (R^2), which indicated the percentage of variance in the outcome (number of pDDIs per patient) explained by the model. The effects of individual risk factors were interpreted using their regression coefficients (B) with corresponding 95% confidence intervals. A p value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of the study population are shown in Table 1. Some form of urological cancer was the main pathology in 77 patients (40.3%), including bladder cancer (n = 46; 24.1%), prostate cancer (n = 15; 7.9%), kidney cancer (n = 15; 7.9%), and testicular cancer (n = 3; 1.6%); two patients had cancer in two organs. The remaining urological diagnoses were distributed as follows: benign prostatic hyperplasia (n = 55; 28.8%), infections (n = 32; 16.8%), hematuria (n = 22; 11.5%), calculosis (n = 23; 12.0%), hydronephrosis (n = 17; 8.9%), urinary retention (n = 11; 5.8%), hydrocele (n = 8; 4.2%), urethral stricture (n = 5; 2.6%), renal colic (n = 5; 2.6%), and other diagnoses (n = 8; 4.2%). Additionally, eight patients (4.2%) had non-urological cancers, bringing the total number of patients with any form of cancer to 85 (44.5%).

NSAIDs were prescribed to 173 patients (90.6%), paracetamol to 54 patients (28.3%), and opioid analgesics to 53 patients (27.7%). Analgesic-related pDDIs were detected in 175 patients (91.6%). By category, X pDDIs occurred in 30 patients (15.7%), D in 62 (32.5%), C in 167 (87.4%), and B in 67 (35.1%). The overall mean ± standard deviation (range) number of analgesic-related pDDIs per patient was 5.5 ± 5.5 (0–30), with category-specific means of 0.3 ± 0.6 (0–3) for X, 0.8 ± 1.6 (0–9) for D, 3.7 ± 3.7 (0–21) for C, and 0.6 ± 1.1 (0–9) for B.

Table 1. *Characteristics of the study population (n = 191)*

Variable	Mean ± standard deviation; median (range) or number (%)
Age (years)	65.8 ± 12.4; 68.0 (23–90)
Gender (male/female)	145 (75.9%)/46 (24.1%)
Duration of hospitalization (days)	7.7 ± 6.1; 6.0 (2–31)
Comorbidities	
Charlson Comorbidity Index	1.4 ± 1.3; 2.0 (0–6)
Hypertension	116 (60.7%)
Renal failure	47 (24.6%)
Diabetes	49 (25.7%)
Hyperlipidemia	33 (17.3%)
Arrhythmias	18 (9.4%)
Psychiatric disorders	13 (6.8%)
Ischemic heart disease	13 (6.8%)
Chronic obstructive pulmonary disease	10 (5.2%)
Non-urological cancer	8 (4.2%)

Dementia	3 (1.6%)
Asthma	1 (0.5%)
Cerebrovascular diseases	1 (0.5%)
Heart failure	1 (0.5%)
Development of infection during hospitalization	30 (15.7%)
Endoscopic procedure during hospitalization	10 (5.2%)
Surgery during hospitalization	148 (77.5%)
Transfusion of blood or blood products during hospitalization	52 (27.2%)
Number of physicians prescribing drugs to the patient during hospitalization	2.5 ± 1.1; 2.0 (1–6)
Information about drug allergy in the medical documentation	19 (9.9%)
Number of prescribed drugs	13.1 ± 5.6; 12.0 (3–33)
Number of different therapeutic subgroups prescribed (2^{nd} level of ATC classification)	9.0 ± 3.4; 9.0 (3–20)
Pharmacological drug classes	
5-alpha-reductase inhibitors	9 (4.7%)
Angiotensin-converting enzyme inhibitors	79 (41.4%)
Acetylcholinesterase inhibitors	85 (44.5%)
Alpha-blockers	25 (13.1%)
Antiarrhythmic drugs	17 (8.9%)
Antibiotics	190 (99.5%)
Anticoagulants	61 (31.9%)
Antidepressants	8 (4.2%)
Antidiabetics	59 (30.9%)
Antiemetics	84 (44.0%)
Antiepileptics	6 (3.1%)
Antiplatelets	11 (5.8%)
Antipsychotics	6 (3.1%)
Beta-blockers	88 (46.1%)
Benzodiazepines	34 (17.8%)
Bronchodilators	24 (12.6%)
Calcium channel blockers	45 (23.6%)
Corticosteroids	23 (12.0%)
Diuretics	72 (37.7%)
Hypouricemics	25 (13.1%)
Iron preparations	7 (3.7%)
Nitrates	10 (5.2%)
Proton pump inhibitors	128 (67.0%)
Products containing calcium	55 (28.8%)
Products containing potassium	149 (78.0%)
Statins	31 (16.2%)

Table 2 shows the most frequently detected NSAID-related pDDIs, while Table 3 shows the most frequently detected opioid-related pDDIs. The most common category X NSAID-related pDDIs involved co-administration of NSAIDs, particularly diclofenac + ketorolac and ketorolac + metamizole, both associated with an increased risk of bleeding and serious NSAID-related adverse effects. There were no opioid-related category X pDDIs.

Table 2. *Description and frequency of most frequently detected potential drug-drug interactions of nonsteroidal anti-inflammatory drugs*

Combination	Possible clinical outcome	Number (%)
X (Avoid combination)		
Diclofenac + ketorolac	Enhanced adverse/toxic effects (additive risk of bleeding and serious NSAID-related adverse effects).	20 (10.5%)
Ketorolac + metamizole	Enhanced adverse/toxic effects (additive risk of bleeding and serious NSAID-related adverse effects).	17 (8.9%)
D (Consider therapy modification)		
Enoxaparin + ketorolac	Enhanced anticoagulant effect of enoxaparin.	25 (13.1%)
Furosemide + ketorolac	Reduced diuretic effect of furosemide and enhanced nephrotoxic effect of ketorolac.	17 (8.9%)
C (Monitor therapy)		
Ketorolac + potassium chloride	Enhanced hyperkalemic effect of potassium salts.	81 (42.4%)
Diclofenac + potassium chloride	Enhanced hyperkalemic effect of potassium salts.	44 (23.0%)
B (No action needed)		
Amlodipine + ketorolac	Reduced antihypertensive effect of amlodipine.	24 (12.6%)
Amlodipine + diclofenac	Reduced antihypertensive effect of amlodipine.	13 (6.8%)

Abbreviations*: NSAID – Nonsteroidal anti-inflammatory drug(s)*

Table 3. *Description and frequency of most frequently detected potential drug-drug interactions of opioids*

Combination	Possible clinical outcome	Number (%)
D (Consider therapy modification)		
Diazepam + tramadol	Increased risk of central nervous system depression	3 (1.6%)
Bromazepam + tramadol	Increased risk of central nervous system depression	2 (1.0%)
Lorazepam + tramadol	Increased risk of central nervous system depression	2 (1.0%)
Clobazam + tramadol	Increased risk of central nervous system depression	1 (0.5%)
Diazepam + fentanyl	Increased risk of central nervous system depression	1 (0.5%)
C (Monitor therapy)		
Ondansetron + tramadol	Ondansetron may enhance the serotonergic effect of tramadol (it could result in serotonin syndrome) and may diminish the therapeutic effect of tramadol.	40 (20.9%)
Atropine + tramadol	Enhanced adverse/toxic effect of tramadol (increased risk for constipation and urinary retention).	40 (20.9%)
B (No action needed)		
paracetamol + tramadol	Decreased absorption of paracetamol.	7 (3.7%)

Significant predictors from univariate linear regression and from the final step of multiple linear regression evaluating the number of pDDIs involving analgesics are shown in Table 4. In the multiple linear regression model, positive predictors of the number of analgesic pDDIs, i.e., factors which may increase their rate, were diabetes, number of prescribed drugs, NSAIDs and opioid analgesics. In contrast, cancer was identified as a negative predictor.

Table 4. *Significant predictors from univariate linear regression and from the final step of multiple linear regression evaluating the number of potential drug-drug interactions involving analgesics*

Variable	B	95% CI	*p*
Univariate linear regression			
Charlson Comorbidity Index	0.816	0.230; 1.402	0.007*
Hypertension	3.370	1.850; 4.891	< 0.001*
Diabetes	2.420	0.669; 4.170	0.007*
Length of hospitalization	0.387	0.270; 0.503	< 0.001*
Surgery during hospitalization	3.750	1.963; 5.536	< 0.001*
Number of physicians who prescribed drugs to the patient during hospitalization	1.368	0.682; 2.055	< 0.001*
Number of prescribed drugs	0.687	0.587; 0.787	< 0.001*
Calcium channel blockers	3.055	1.272; 4.838	0.001*
Diuretics	2.919	1.367; 4.471	< 0.001*
Non-steroidal anti-inflammatory drugs	4.156	1.557; 6.756	0.002*
Opioid analgesics	6.664	5.210; 8.118	< 0.001*
Paracetamol	1.929	0.221; 3.637	0.027*
Final step of multiple linear regression			
Constant	–6.742	–8.613; –4.872	<0.001*
Diabetes	1.672	0.573; 2.771	0.003*
Cancer	–1.049	–2.024; –0.073	0.035*
Number of prescribed drugs	0.514	0.416; 0.612	< 0.001*
Non-steroidal anti-inflammatory drugs	4.724	3.100; 6.349	< 0.001*
Opioid analgesics	4.544	3.330; 5.757	< 0.001*
R^2; F (*p*)	0.646; 67.599 (< 0.001*)		

Abbreviations*:* pDDIs – potential drug-drug interactions, B – Unstandardized coefficient; CI – *Confidence interval*; Constant – model intercept (predicted value of the outcome when all predictors equal zero); F (*p*) – F-statistic (test statistic used to assess whether the overall regression model is statistically significant) and the probability value associated with it;*p* – Statistical significance; R^2 – Coefficient of determination (indicates the percentage of variance in the outcome); *Statistically significant ($p < 0.05$). List of variables entered in multiple linear regression analysis: age, gender, drug allergy noted in the medical documentation, Charlson Comorbidity Index, renal colic, hypertension, diabetes, cancer, length of hospitalization, surgery during hospitalization, development of infection during hospitalization, number of physicians who prescribed drugs to the patient during hospitalization, number of prescribed drugs, calcium channel blockers, diuretics, non-steroidal anti-inflammatory drugs, opioid analgesics, paracetamol.

DISCUSSION

Analgesic-related pDDIs occurred in more than 90% of patients, indicating that interaction-relevant co-prescribing is not occasional but rather a routine pharmacotherapeutic reality in this clinical setting. Although most interactions were classified as category C (Monitor therapy), clinically relevant category X (Avoid combination) and category D (Consider therapy modification) interactions were also recorded. These latter categories represent combinations for which therapy modification or complete avoidance is recommended, carrying more direct implications for clinical decision-making. Notably, many of the highest-frequency category X and D pDDIs involved combinations of ketorolac with other NSAIDs or with drugs associated with bleeding risk or nephrotoxicity, while category C interactions were dominated by NSAID–potassium chloride combinations, consistent with potential hyperkalaemia risk. Multiple regression analysis showed that diabetes, a higher number of prescribed drugs, NSAID use, and opioid use independently predicted higher pDDI counts, whereas cancer diagnosis was associated with lower counts.

The findings of this study highlight several critical prescribing considerations that physicians should observe to minimize the risk of clinically significant pDDIs. NSAID co-administration represents the highest-risk interactions (category X) and should be strictly avoided due to the additive potential for gastrointestinal bleeding, renal injury, and other serious NSAID-related adverse effects (12, 13). Concomitant

use of two NSAIDs magnifies cyclooxygenase inhibition, leading to a more profound reduction in protective gastrointestinal prostaglandins, which play a crucial role in maintaining mucosal blood flow, stimulating mucus and bicarbonate secretion, and promoting epithelial repair (14). When prostaglandin synthesis is markedly suppressed by the concurrent use of two NSAIDs, the gastric and duodenal mucosa becomes significantly more susceptible to injury, thereby increasing the risk of serious gastrointestinal complications, including ulceration, bleeding, and perforation (14). Large observational studies and systematic reviews have shown markedly elevated upper gastrointestinal bleeding risk with NSAID exposure, with ketorolac among the agents carrying particularly high gastrotoxicity (15, 16). Furthermore, NSAIDs inhibit cyclooxygenase and reduce the synthesis of key renal prostaglandins, which are essential for maintaining renal blood flow and glomerular filtration (17). By disrupting this prostaglandin-mediated autoregulatory mechanism, NSAIDs diminish the kidney's ability to preserve adequate filtration pressure, thereby increasing susceptibility to reduced renal perfusion and precipitating acute kidney injury (17).

Similarly, combinations of anticoagulants and NSAIDs and loop diuretics, such as enoxaparin + ketorolac and furosemide + ketorolac (category D), warrant careful evaluation and, where possible, therapy modification, given the potential risk of bleeding or nephrotoxicity and reduced diuretic efficacy (18, 19). Concurrent use of anticoagulants and NSAIDs significantly increases bleeding risk because NSAIDs impair gastrointestinal mucosal protection while anticoagulants inhibit clot formation, so even minor mucosal lesions may lead to serious bleeding (18). Loop diuretics such as furosemide reduce intravascular volume by promoting natriuresis and diuresis, rendering the kidney more dependent on prostaglandin-mediated vasodilation to maintain glomerular filtration (20). The addition of ketorolac (or other NSAIDs) removes this compensatory mechanism, increases the risk of renal injury, and compromises diuretic efficacy (20). Beyond that, NSAIDs can decrease the natriuretic and diuretic effects of loop diuretics by reducing renal prostaglandin-mediated afferent arteriolar dilation and impairing sodium and water excretion (21).

Physicians should also monitor for category C interactions, including NSAIDs with potassium chloride, which can exacerbate hyperkalemia (22, 23). NSAIDs reduce renal prostaglandin synthesis, impairing renal blood flow and decreasing potassium excretion in the distal nephron (23). When potassium chloride is administered concurrently, the reduced ability to excrete potassium can amplify potassium accumulation, thereby increasing the risk of hyperkalemia (23). Opioid–benzodiazepine combinations likewise require attention because of the risk of enhanced central nervous system depression (18). Co-administration of these agents can lead to profound sedation, respiratory depression, and impaired cognitive or motor function, increasing the risk of falls, accidents, and other adverse events (24, 25). Overall, these results underscore the importance of avoiding high-risk combinations, adjusting or substituting medications when necessary, and closely monitoring patients for signs of adverse effects, particularly in settings of polypharmacy or coexisting comorbidities.

The identification of diabetes, a higher number of prescribed drugs, NSAID use, and opioid use as independent predictors of higher pDDI counts is consistent with previously published inpatient and outpatient studies (3, 26–30). Diabetes is a multidrug state, and diabetic patients are more frequently prescribed drugs that can alter renal hemodynamic autoregulation, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and diuretics, all of which have well-known interaction potential with NSAIDs (19, 31). The number of prescribed drugs has repeatedly been identified as the strongest predictor of pDDIs across clinical settings, and this was also confirmed here, suggesting that medication burden, rather than any single pharmacological class, remains the core system-level driver of interaction exposure (3, 26, 28, 29). Opioid use as a predictor likely reflects the fact that opioid recipients are those with more severe pain syndromes or postoperative recovery, which is often accompanied by multimodal analgesic strategies and co-prescription of sedatives and antiemetics (7, 8, 30).

Interestingly, cancer diagnosis was a negative predictor. This finding may relate to more standardized analgesic protocols in oncology patients, as well as stricter multidisciplinary pharmacovigilance practices among physicians prescribing drugs to these patients. In the outpatient literature, oncological cohorts show higher pDDI risk in primary care because of polypharmacy (32), but in inpatient surgical oncology cohorts, a more streamlined, protocolized analgesic approach has been reported (33), which may align with our finding. This result suggests that oncology-type prescribing may represent an unintended "best practice" model for safer analgesic stewardship even within general urology.

This study has several limitations. First, it was conducted at a single center, which may limit generalizability and reflect center-specific prescribing practices and training characteristics. Second, we evaluated only pDDIs and did not assess clinical outcomes associated with the identified combinations. This is an

inherent limitation, as attribution of actual DDI events in real-world hospital settings is complex and notoriously difficult to ascertain.

CONCLUSION

In conclusion, analgesic-related pDDIs occurred in the majority of hospitalized urological patients, with NSAIDs and opioids contributing most to clinically relevant interactions. Diabetes, a higher number of prescribed drugs, and the use of NSAIDs or opioids independently increased pDDI risk, whereas cancer diagnosis was associated with lower risk. Careful avoidance of high-risk combinations, regular monitoring, and multidisciplinary medication review may help reduce preventable harm.

Abbreviations

DDI(s) – drug–drug interaction(s)
pDDI(s) – potential drug–drug interaction(s)
NSAID(s) – non-steroidal anti-inflammatory drug(s)

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Data Availability Statement: Requests to access the datasets should be directed to the corresponding author.

Note: Artificial intelligence was not utilized as a tool in this study.

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Sažetak

FAKTORI RIZIKA ZA POTENCIJALNE INTERAKCIJE ANALGETIKA KOD HOSPITALIZOVANIH UROLOŠKIH BOLESNIKA

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Cilj: Izvršiti evaluaciju potencijalnih interakcija između lekova (PIL) koje uključuju analgetike kod hospitalizovanih uroloških bolesnika i identifikovati faktore koji utiču na njihov broj.

Metode: Studija je predstavljala *post hoc* analizu podataka prikupljenih u retrospektivnoj opservacionoj kohortnoj studiji sprovedenoj na Klinici za urologiju Univerzitetskog kliničkog centra Kragujevac, Srbija. Od originalnih 220 bolesnika, u analizu je uključen 191 bolesnik sa propisanim analgeticima. Prikupljeni su podaci o propisanim lekovima, demografskim i kliničkim karakteristikama, dok su PIL identifikovane i klasifikovane pomoću *Lexicomp* baze. Podaci su obrađeni metodama deskriptivne statistike. Nezavisni prediktori broja PIL identifikovani su pomoću multiple linearne regresije koristeći metodu eliminacije varijabli „unazad".

Rezultati: Potencijalne interakcije analgetika identifikovane su kod 175 bolesnika (91,6%). Nesteroidni antiinflamatorni lekovi (NSAIL) su bili propisani kod 173 bolesnika (90,6%), opioidi kod 53 (27,7%), a paracetamol kod 54 (28,3%). Prosečan broj PIL

po bolesniku bio je 5,5 ± 5,5 (opseg 0–30). Najčešće interakcije kategorije X uključivale su kombinacije NSAIL (diklofenak + ketorolak, ketorolak + metamizol), dok su interakcije kategorije D često uključivale enoksaparin + ketorolak i kombinacije opioid + benzodiazepin. Među interakcijama kategorije C dominirale su kombinacije NSAIL + kalijum-hlorid i tramadol + ondansetron ili atropin. Multiplaregresiona analiza je identifikovala dijabetes, veći broj propisanih lekova i upotrebu NSAIL ili opioida kao pozitivne prediktore broja PIL, dok je dijagnoza karcinoma bila povezana sa manjim brojem PIL.

Zaključak: Potencijalne interakcije analgetika javljaju se kod većine hospitalizovanih uroloških bolesnika. Izbegavanje kombinacija visokog rizika, pažljivo praćenje i multidisciplinarni pregled terapije kod pacijenata sa faktorima rizika mogu pomoći u smanjenju preventabilnih neželjenih ishoda.

Ključne reči: analgetici, interakcije između lekova, urologija, hospitalizovani bolesnici.

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HÜRTHLE-CELL CARCINOMA OF THE THYROID: CLINICOPATHOLOGIC FEATURES AND SURGICAL OUTCOMES AT A SINGLE INSTITUTION

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Abstract: **Background:** Hürthle cell carcinoma (HCC) is a rare differentiated thyroid malignancy with variable biological behavior. This study evaluates clinicopathologic features, treatment patterns, and long-term outcomes in patients managed at a single tertiary institution.

Methods: We retrospectively reviewed medical records of patients with histologically confirmed HCC between January 2005 and December 2020. Demographics, tumor characteristics, surgical treatment, adjuvant radioactive iodine (RAI) therapy, recurrence, and survival were analyzed. Outcomes were compared with reported retrospective series and discussed in the context of current ATA guidelines.

Results: Forty-eight patients were identified (mean age, 58.7 ± 11.4 years; female-to-male ratio, 2.2:1). Mean tumor size was 38.5 ± 14.2 mm. Minimally invasive disease was present in 29 patients (60.4%), and widely invasive disease in 19 (39.6%). Total thyroidectomy was performed in 36 patients (75%), and lobectomy in 12 (25%). RAI therapy was administered to 30 patients (62.5%), predominantly in widely invasive cases. Median follow-up was 104 months (range, 24–192 months). Recurrence occurred in 8 patients (16.7%), with a median time to relapse of 78 months. Five- and ten-year overall survival (OS) rates were 91.3% and 81.5%, respectively. Disease-specific survival (DSS) was 95.6% at 5 years and 90.2% at 10 years. Ten-year disease-free survival (DFS) was 82.1%.

Conclusions: Our results support existing evidence that minimally invasive HCC carries an excellent prognosis, while widely invasive tumors have a higher risk of recurrence. Long-term follow-up is essential, given the potential for late recurrence. These findings are consistent with current ATA guidelines recommending risk-tailored treatment and surveillance strategies.

Keywords: Hürthle cell carcinoma, thyroid cancer, minimally invasive, widely invasive, recurrence, survival, ATA guidelines.

INTRODUCTION

Hürthle cell carcinoma (HCC) accounts for approximately 3–10% of differentiated thyroid cancers and is characterized by oncocytic cells with abundant granular cytoplasm rich in mitochondria (1, 2). Historically considered a variant of follicular thyroid carcinoma, HCC is now recognized as a distinct clinicopathologic entity in the WHO classification (3). The diagnosis of malignancy requires histologic demonstration of capsular and/or vascular invasion, with classification into minimally and widely invasive subtypes based on the extent of invasion (4). Widely invasive tumors are associated with worse recurrence-free and disease-specific survival rates (5, 6).

Given the rarity of HCC, most outcome data derive from single-institution retrospective series or population registries. Reported recurrence rates range from 8% to 27% (7–12), with disease-specific survival generally exceeding 85% at 10 years in minimally invasive disease but falling to approximately 60% in widely invasive tumors (9, 11). While Oluic et al. (8) and Chiapponi et al. (9) provide foundational recurrence data, more recent investigations by Kim et al. (13) have emphasized the importance of preoperative clinical and radiologic factors in predicting malignancy and long-term outcomes in Hürthle cell neoplasms. Moreover, incorporating contemporary clinical guidelines—notably the 2015 American Thyroid Association (ATA) recommendations for differentiated thyroid

carcinoma management—is essential for framing therapeutic decisions and surveillance strategies in HCC (12).

This study describes the clinicopathologic features, treatment, and long-term outcomes of HCC patients treated at a single tertiary institution over a 16-year period.

Knowledge Gap: While prior studies report 10-year survival rates, data on very late recurrences (> 15 years) remain scarce. Our study provides long-term outcomes with a median follow-up of 104 months, contextualized within recent literature and ATA guideline recommendations.

MATERIAL AND METHODS

Study design and setting

A retrospective review was conducted of patients diagnosed with Hürthle cell carcinoma (HCC) between January 2005 and December 2020 at Bin Tayyab Medical Complex (BTMC) Hyderabad, Sindh, Pakistan. Patient inclusion spanned 2005–2020, and follow-up extended through 2024, allowing for updated survival outcomes. This retrospective study was approved by the Institutional Review Board. The requirement for informed consent was waived owing to the retrospective nature of the study and anonymization of patient data.

Inclusion criteria were**:** Histopathologic confirmation of HCC**,** primary surgical management at our institution and minimum follow-up of 24 months.

Exclusion criteria were: Hürthle cell adenoma**,** non-oncocytic thyroid malignancies and incomplete medical records.

Data collection

Patient demographics, presenting symptoms, tumor size, histologic subtype (minimally vs. widely invasive), surgical approach, radioactive iodine (RAI) administration, follow-up duration, recurrence type, and survival status were recorded.

Définitions

***Recurrence*:** Recurrence was defined as the reappearance of Hürthle cell carcinoma after achieving an initial complete response following primary surgical management. Recurrence included locoregional disease (thyroid bed or regional lymph nodes) or distant metastasis (lung, bone, or other sites). All recurrences were confirmed either radiologically (contrast-enhanced CT, MRI, or ultrasound) or histologically via biopsy.

***Overall survival (OS)*:** OS was defined as the time interval from the date of initial thyroid surgery to death from any cause, regardless of disease status. Patients alive at the last follow-up were censored.

Disease-specific survival (DSS): DSS was defined as the time interval from surgery to death caused specifically by Hürthle cell carcinoma. Deaths from unrelated causes were censored at the date of death.

Disease-free survival (DFS): DFS was defined as the time interval from surgery to the first documented recurrence (locoregional or distant) or death attributable to Hürthle cell carcinoma, whichever occurred first. Patients without events were censored at the last follow-up.

Statistical analysis

Kaplan–Meier methods were used to estimate OS, DSS, and DFS. Survival comparisons between subgroups were performed using the log-rank test. Cox proportional hazards regression was applied to evaluate prognostic factors, including age, tumor size, and invasion type. A p-value < 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS version 26.

RESULTS

Patient demographics and tumor characteristics

Forty-eight patients were included. Baseline characteristics are summarized in Table 1. The cohort had a mean age of 58.7 ± 11.4 years and a female predominance (68.8%). Mean tumor size was 38.5 ± 14.2 mm. Minimally invasive Hürthle cell carcinoma was observed in 29 patients (60.4%), and widely invasive disease in 19 patients (39.6%). Vascular invasion was present in 21 patients (43.8%). Widely invasive tum-

Table 1. *Patient demographics and tumor characteristics*

Variable	Total (N = 48)	Minimally Invasive (n = 29)	Widely Invasive (n = 19)	P Value
Female Sex, n (%)	33 (68.8%)	21 (72.4%)	12 (63.2%)	0.49
Tumor Size (mm), Mean ± SD	38.5 ± 14.2	32.1 ± 10.5	48.3 ± 12.8	< 0.001*
Vascular Invasion, n (%)	21 (43.8%)	7 (24.1%)	14 (73.7%)	0.002*

*P value for vascular invasion added to clarify subgroup differences.

ors were associated with significantly larger tumor size and a higher rate of vascular invasion, while patient age and sex did not differ between groups.

Treatment details

Total thyroidectomy was performed in 36 patients (75%), while 12 patients (25%) underwent lobectomy. Radioactive iodine (RAI) therapy was administered to 30 patients (62.5%), predominantly in widely invasive cases (84.2% vs. 48.3% in minimally invasive disease; p = 0.02). A summary of patient and treatment characteristics is provided in Table 2.

Recurrence analysis

Eight patients (16.7%) developed recurrence—locoregional in 5 patients and distant (lung or bone) in 3 patients. The median time to recurrence was 78 months (range, 36–144), illustrating the need for extended follow-up (Table 2). Widely invasive tumors had a 3.8-fold higher risk of recurrence (hazard ratio [HR] = 3.8; p = 0.01). Tumor size > 4 cm and vascular invasion showed non-significant trends toward increased recurrence, suggesting limited statistical power to detect significance.

Radioactive iodine (RAI) administration was associated with a lower risk of recurrence (HR = 0.42; p = 0.04); however, its benefit in minimally invasive HCC remains controversial, given reduced RAI avidity in Hürthle cells and differential treatment allocation favoring widely invasive disease (Table 3).

The results of the multivariate analysis for recurrence are shown in Table 3.

Table 2. *Summary of patient and treatment characteristics*

Characteristic	Value
Sample Size	48 Patients
Mean Age (years)	58.7 ± 11.4
Female: Male Ratio	2.2 : 1
Mean Tumor Size (mm)	38.5 ± 14.2
Histologic Subtype	
Minimally Invasive	29 (60.4%)
Widely Invasive	19 (39.6%)
Surgical Procedure	
Total Thyroidectomy	36 (75%)
Lobectomy	12 (25%)
RAI Therapy Administered	30 (62.5%)
Median Follow-up (months)	
Recurrence Rate	8 (16.7%)
Median Time to Relapse (months)	78 (Range: 36–144)

Survival outcomes

The 5- and 10-year survival rates are detailed in Table 4. Widely invasive disease was associated with significantly lower DFS ($p = 0.01$) and DSS ($p = 0.03$) than minimally invasive disease. The disease-specific survival patterns for the two subtypes are illustrated in Figure 1.

Comparative Analysis

Our outcomes were compared with those from prior studies, as shown in Table 5.

Table 3. *Multivariate Cox regression analysis for recurrence*

Variable	Hazard Ratio (HR)	95% Confidence Interval	P Value
Widely Invasive (vs. Minimally Invasive)	3.8	1.4 -10.2	0.01
Tumor Size > 4 cm	2.1	0.9 – 5.0	0.09
Vascular Invasion	1.7	0.7 – 4.3	0.24
RAI Therapy	0.42	0.18 – 0.98	0.04

HR-hazard ratio. Statistically significant p values ($p < 0.05$) are as follows. An HR > 1.0 indicates a higher risk of recurrence, while an HR < 1.0 indicates a lower risk (protective effect). The 95% confidence interval (CI) shows the precision of the estimate. An interval that does not include 1.0 is considered statistically significant.

Table 4. *Long-term survival outcomes*

Outcome	5-Year Rate (%)	10-Year Rate (%)	15-Year Rate (%)
Overall Survival (OS)	91.3	81.5	76.2
Disease-Specificsurvival (DSS)	95.6	90.2	85.7
Disease-FreeSurvival (DFS)	90.5	82.1	78.4

Notes: *OS: Time from surgery to death from any cause; DSS: Time from surgery to death specifically from Hürthle cell carcinoma; DFS: Time from surgery to first recurrence or death from Hürthle cell carcinoma.*

Table 5. *Comparative analysis with prior studies*

Study	Number of Patients	Recurrence Rate (%)	10-Year Disease-Specific Survival (%)	RAI Use (%)
Our Study	48	16.7	90.2	62.5
Oluic et al (8)	182	12.1	92.5	54
Bešić et al. (10)	89	27.0	88.0	70
Kim et al. (13)	112	15.2	89.8	58

Notes: RAI: Radioactive Iodine therapy.

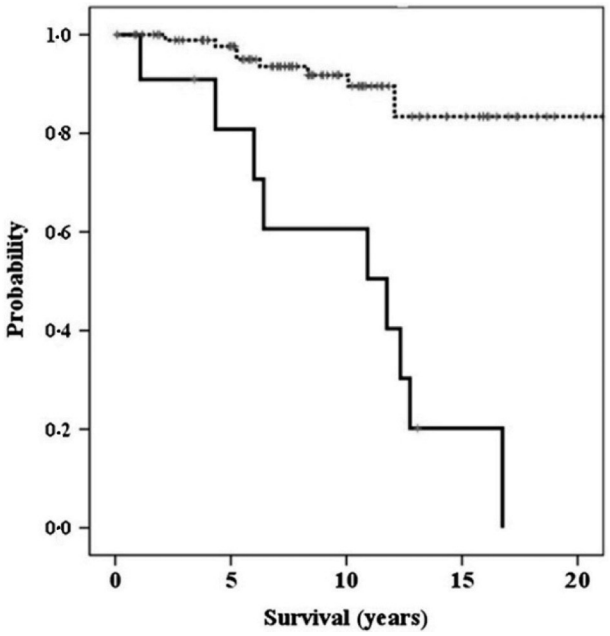

Figure 1. *Disease-specific survival by histologic subtype*
(Image: Kaplan-Meier curve showing two lines, one for minimally invasive HCC with high survival probability, and one for widely invasive HCC with lower survival probability over time.)

DISCUSSION

This study reinforces prior reports that minimally invasive HCC has an excellent prognosis, with rare disease-specific mortality and low recurrence rates (7, 8). Widely invasive disease was associated with higher recurrence and reduced survival, which is consistent with previously published findings (10-year DSS 88%, recurrence 27%) (10) and Oluic et al. (DSS 92.5%, recurrence 12.1%) (8). The mean tumor size in our cohort (38.5 mm) aligns with prior studies, where larger tumors (> 4 cm) have been linked to worse outcomes (5, 10). Our recurrence rate (16.7%) is intermediate between low (12.1% (8) and high (27% (10) published rates, possibly reflecting our higher proportion of widely invasive cases. Late recurrences occurred, emphasizing the need for long-term surveillance—findings echoed by other series reporting relapses beyond 10 years (7, 10).

Incorporation of ATA Guidelines: The 2015 ATA guidelines recommend risk-adapted management for differentiated thyroid carcinoma, including HCC, emphasizing extent of invasion as a key prognostic factor influencing surgical extent, use of RAI, and surveillance intensity (12). Our findings align with these guidelines, supporting more aggressive management and RAI use in widely invasive tumors, while highlighting uncertainty about RAI benefit in minimally invasive disease due to lower RAI avidity of oncocytic cells. The protective association of RAI seen in our analysis may primarily reflect its use among high-risk patients, underscoring the need for further research into selective RAI benefit in minimal disease.

While total thyroidectomy and RAI remain standard for widely invasive tumors, their role in minimally invasive disease remains debated (11, 12). Strengths of this study include detailed histologic classification and a long median follow-up (> 8 years). Limitations include retrospective design, small sample size, and single-center setting.

This single-institution study provides further evidence supporting prior reports that minimally invasive HCC typically has an excellent prognosis, characterized by rare disease-specific mortality and low recurrence rates. Conversely, consistent with findings from other retrospective series, widely invasive tumors are associated with higher recurrence rates and decreased survival (8,10). The mean tumor size observed in our cohort (38.5 mm) is consistent with the literature, which often links larger tumors (exceeding 4 cm) to poorer outcomes. Our observed recurrence rate of 16.7% falls within the intermediate range of published rates, which vary from a low of 12.1% to a high of 27% (Table 6).

Table 6. *Comparison with literature*

Study	Recurrence rate	10-year| DSS
Our study	16.7%	90.2%
Oluic et al[8]	12.1%	92.5%
Besic et al[10]	27%	88%

This variation may partly be attributed to the higher proportion of widely invasive cases included in our study cohort. A critical finding was the occurrence of late recurrences, with a median time to recurrence of 78 months. This observation strongly emphasizes the necessity of long-term surveillance for HCC patients, a finding echoed by other series reporting relapses occurring beyond 10 years. While total thyroidectomy and radioactive iodine (RAI) therapy are considered standard treatments for widely invasive tumors, their precise role and benefit in minimally invasive HCC remain a subject of debate. This debate is further complicated by the potentially reduced avidity of Hürthle cells to RAI.

Strengths of this study include its detailed histologic classification of HCC into minimally and widely invasive subtypes and a long median follow-up period of over 8 years.

Limitations

This study is limited by its single-center retrospective design and small sample size, which may restrict statistical power and generalizability. Larger multicenter prospective studies, as advocated by the ATA, are needed to refine prognostic models and therapeutic guidelines.

CONCLUSION

In conclusion, Hürthle cell carcinoma demonstrates favorable outcomes in its minimally invasive form, with high survival rates and low recurrence. Conversely, widely invasive tumors are associated with a significantly higher risk of recurrence and decreased survival. The potential for late recurrence, as evidenced by our data and illustrated in the survival curves (Figure 1), necessitates prolonged and diligent long-term follow-up for all HCC patients. To further refine current treatment algorithms and establish more definitive guidelines, larger-scale multicenter prospective studies are urgently needed.

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Note: Artificial intelligence was not utilized as a tool in this study.

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Sažetak

HÜRTHLE-CELL KARCINOM ŠTITASTE ŽLEZDE: KLINIČKO-PATOLOŠKE KARAKTERISTIKE I HIRURŠKI ISHODI U JEDNOJ USTANOVI

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Uvod: Hürthle-cell karcinom (HCC) predstavlja redak maligni tumor štitaste žlezde sa promenljivim biološkim ponašanjem. Ova studija procenjuje kliničko-patološke karakteristike, obrasce lečenja i dugoročne ishode kod pacijenata lečenih u jednoj tercijarnoj ustanovi.

Metode: Retrospektivno su pregledani medicinski kartoni pacijenata sa histološki potvrđenim Hürthle-cell karcinomom (HCC) u periodu od januara 2005. dodecembra 2020. godine. Analizirani su demografski podaci, karakteristike tumora, hirurško lečenje, adjuvantna terapija radioaktivnim jodom (RAI), recidivi i preživljavanje. Ishodi su upoređeni sa podacima iz prethodnih retrospektivnih serija i diskutovani u kontekstu važećih smernica Američkog udruženja za štitastu žlezdu (ATA).

Rezultati: Identifikovano je 48 pacijenata (prosečna starost 58,7 ± 11,4 godina; odnos žena i muškaraca 2,2:1). Prosečna veličina tumora bila je 38,5 ± 14,2 mm. Minimalno invazivna bolest registrovana je kod 29 pacijenata (60,4%), dok je široko invazivna bolest bila prisutna kod 19 pacijenata (39,6%). Totalna tireoidektomija izvršena je kod 36 pacijenata (75%), a lobektomija kod 12 pacijenata (25%). RAI terapija primenjena je kod 30 pacijenata (62,5%), uglavnom u slučajevima ši-

roko invazivnog tumora. Medijana praćenja bila je 104 meseca (opseg 24–192 meseca). Recidiv se javio kod 8 pacijenata (16,7%), sa medijanom vremena do relapsa od 78 meseci. Petogodišnje i desetogodišnje ukupno preživljavanje (OS) iznosilo je 91,3% i 81,5%, respektivno. Preživljavanje specifično za bolest (DSS) bilo je 95,6% na 5 godina i 90,2% na 10 godina. Desetogodišnje preživljavanje bez bolesti (DFS) iznosilo je 82,1%.

Zaključak: Naši rezultati potvrđuju postojeće dokaze da minimalno invazivni Hürthle-cell karcinom (HCC) ima odličnu prognozu, dok široko invazivni tumori nose veći rizik od recidiva. Dugoročno praćenje je od suštinskog značaja zbog potencijala za kasni recidiv. Ovi nalazi su u skladu sa važećim smernicama Američkog udruženja za štitastu žlezdu (ATA), koje preporučuju lečenje i nadzor prilagođen riziku.

Ključne reči: Hürthle-cell karcinom, karcinom štitaste žlezde, minimalno invazivno, široko invazivno, recidiv, preživljavanje, ATA smernice.

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PATIENT PERCEPTIONS AND EXPERIENCES OF ENDODONTIC TREATMENT IMPLICATIONS FOR ORAL HEALTH CARE

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Abstract: **Background:** Endodontic treatment is an essential procedure for preserving natural teeth and preventing further oral health complications. However, patients' perceptions, knowledge, and anxiety related to root canal treatment may influence their willingness to undergo the procedure and their overall satisfaction with dental care.

Aim: The aim of this study was to examine the association between demographic characteristics—such as gender, age, and educational level—and patients' perceptions, attitudes, and expectations regarding endodontic treatment.

Materials and Methods: A cross-sectional study was conducted using an anonymous online questionnaire among patients residing in Sarajevo Canton. A total of 171 participants who had previously undergone endodontic treatment completed the questionnaire. The questionnaire collected demographic data and information about patients' knowledge of endodontic treatment, previous treatment experience, satisfaction with the information provided by the dentist, perceived pain or discomfort, communication with the dentist, and overall treatment experience. Data were analyzed using IBM SPSS Statistics version 22. Descriptive statistics were used to summarize the data, while the independent samples Student's t-test and one-way analysis of variance (ANOVA) were applied to assess differences between groups. Statistical significance was set at $p < 0.05$.

Results: The majority of participants were female (80.1%), and most had a university degree (60.8%). Male participants reported significantly higher satisfaction with the information provided, the dentist's professionalism, and comfort during treatment compared to female participants ($p < 0.05$). Participants aged 41 years and older reported significantly higher satisfaction with communication, information provided, and overall treatment experience than younger age groups. Participants with a lower level of education reported significantly higher levels of pain or discomfort during or after treatment ($p < 0.004$).

Conclusion: Patients generally showed a positive perception of endodontic treatment. Effective communication, adequate patient education, and the dentist's professionalism play an important role in reducing anxiety and improving patient satisfaction and treatment experience.

Keywords: endodontic treatment, patient perception, patient satisfaction, oral health.

INTRODUCTION

Endodontic treatment, commonly referred to as root canal treatment (RCT), involves the removal of infected or inflamed pulp tissue in order to prevent pulpal and periradicular pathology, eliminate infection, and protect the disinfected tooth from reinfection. When endodontic therapy is indicated, neither a simple restoration nor antibiotic therapy can resolve the underlying infection. If treatment is postponed, progressive carious destruction may severely compromise the tooth and reduce the possibility of preservation (1). Toothache remains the most frequent reason patients seek dental care and often results in either endodontic treatment or extraction. However, extraction may initiate a cascade of functional and aesthetic consequences, including tooth migration, impaired mastication, and compromised appearance. Preservation of natural dentition, therefore, represents a fundamental objective of contemporary dentistry.

Although endodontic therapy is a predictable and effective method for maintaining teeth, studies evaluating patient awareness and understanding of this procedure remain limited. Doumani et al. reported significant variations in knowledge and awareness of endodontic therapy among different populations (2). Similarly, Janczarek et al. observed an increase in awareness among Polish patients, largely influenced by mass media (3). These findings suggest that knowledge and perception are shaped by cultural, educational, and sociodemographic factors.

Oral health is defined as a state free from disease that enables proper function, aesthetics, and overall well-being. It is widely recognized as an integral component of general health, reflecting systemic conditions and contributing to quality of life. Evaluation of healthcare services, including patient satisfaction and perceived quality of care, represents an important public health tool for improving clinical practice and healthcare planning (4).

Despite advances in modern endodontics and the emphasis on painless and efficient treatment, fear and anxiety remain common among patients (1, 5). Anticipation of pain, insufficient knowledge about the procedure, and misconceptions regarding its complexity frequently discourage patients from seeking timely care. Sociodemographic status, personal attitudes, and previous experiences may further influence decision-making, sometimes leading patients to delay treatment or opt for extraction instead (6, 7). Reports indicate considerable variability in treatment preferences across different populations (3).

Contemporary endodontic practice offers multiple strategies to ensure patient comfort, including effective local and regional anesthesia, sedation techniques such as nitrous oxide, and, when necessary, general anesthesia (8). Nevertheless, persistent beliefs about pain and procedural difficulty continue to affect patient expectations and behavior.

Patient education regarding endodontic procedures can significantly improve attitudes toward treatment and reduce anxiety. By providing clear, accurate, and comprehensible information, dental professionals can help patients understand the importance of tooth preservation and the benefits of endodontic therapy. Variations in patients' levels of knowledge and awareness may substantially influence their expectations, emotional responses, and overall treatment experience (9). Informing patients about the technical aspects of the procedure, anticipated outcomes, duration of treatment, and available pain-control strategies—including management of post-operative discomfort—may enhance cooperation, increase trust in the clinician, and promote more positive perceptions of care.

A patient-centered approach that integrates clinical excellence with effective communication is therefore essential in contemporary endodontics. Strengthening educational efforts and improving dialogue between clinicians and patients may contribute to greater acceptance of recommended treatment, reduced treatment avoidance, and ultimately better preservation of natural dentition (10).

The aim of this study is to examine the association between demographic characteristics—such as gender, age, and educational level—and patients' perceptions, attitudes, and expectations regarding endodontic treatment.

MATERIALS AND METHODS

This cross-sectional study was conducted through an anonymous online questionnaire among patients residing in the Sarajevo Canton. A total of 171 adult participants (aged 18 years and older) who had previously undergone endodontic treatment completed the questionnaire. The study was approved by the Ethics Committee of the Faculty of Dentistry, University of Sarajevo (UNSA), approval number 02-3-4-19-1-11/2024.

Demographic data collected included gender, age, and educational level. The survey explored patients' perceptions of endodontic treatment, encompassing their knowledge of endodontic procedures, the number of treatments previously received, satisfaction with the information provided and the professionalism of the treating dentist, pain experienced during or after treatment, and perceived effectiveness of treatment in maintaining oral and overall health.

Statistical analyses were performed using IBM SPSS Statistics, version 22. Descriptive statistics were used to summarize continuous variables as means and standard deviations, and categorical variables as absolute and relative frequencies. Parametric tests were applied to examine differences in quantitative variables, including the independent samples Student's t-test and one-way analysis of variance (ANOVA). All statistical tests were conducted at a significance level of 0.05. Results are presented in both tabular and graphical formats to facilitate interpretation

RESULTS

Descriptive Statistics

A total of 171 participants who had all previously undergone endodontic treatment were included in the study, comprising 34 males and 137 females. The mean age of male participants was approximately 31 years (SD ±12), while the mean age of female participants was around 27 years (SD ± 10) (Table 1).

Table 1. *Mean age of participants by gender*

	Gender					
	Male			Female		
	n	Mean	SD	n	Mean	SD
Age	34	31.09	12.07	137	27.31	9.68

Table 2. *Educational level of participants*

Educational level of participants	Frequency	%
SE	55	32.2
UE	104	60.8
PG	12	7.0
Total	171	100

SE – Secondary Education; UE – University Education; PG – Postgraduate (Master's/Doctorate)

Table 3. *Number of endodontic treatments received*

Number of Previous Endodontic Treatments	Frequency	%
Once	62	36.3
Twice	59	34.5
Three times	19	11.1
More than three times	31	18.1
Total	171	100

Regarding educational level, the majority of participants held a university degree (104; 60.8%), followed by secondary education (55; 32.2%), and a smaller proportion had a master's or doctoral degree (12; 7%) (Table 2).

Concerning previous endodontic experience, 36.3% of respondents reported undergoing endodontic treatment for the first time. A substantial proportion (34.5%) had undergone treatment twice, 11.1% three times, and 18.1% had received endodontic treatment more than three times (Table 3).

Independent samples Student's t-test and one-way analysis of variance (ANOVA) were used to compare mean values of quantitative variables across gender and age groups. Male participants reported significantly higher satisfaction with the information provided about the procedure compared to female participants ($t = 2.94$, $p < 0.005$), although the male sample size was considerably smaller.

Additionally, men rated the courtesy and professionalism of their dentist during endodontic treatment significantly higher than women ($t = 2.47$, $p < 0.015$) and reported feeling more comfortable during the procedure ($t = 2.34$, $p < 0.020$). No statistically significant gender differences were observed for other variables. Results are presented in Table 4.

Table 4. *Comparison of mean values of variables between participants by gender*

	Gender							
	Male			Female				
	n	Mean	SD	n	Mean	SD	t	p
How informed are you about endodontic (root canal) treatment?	34	3.65	1.22	137	3.28	1.49	1.31	0.192
How satisfied are you with the information provided about the procedure?	34	4.24	1.08	137	3.59	1.39	2.94	**0.005**
How would you rate your dentist's courtesy and professionalism during the endodontic treatment?	34	4.65	0.69	137	4.26	1.18	2.47	0.015
Did your dentist inform you about possible complications or side effects of the endodontic treatment before the procedure?	34	3.94	1.35	137	3.54	1.54	1.51	0.137
How would you rate the level of pain or discomfort during or after the endodontic treatment?	34	3.76	1.05	137	3.47	1.27	1.27	0.207
How would you rate the communication with your dentist during the treatment?	34	4.41	0.93	137	4.07	1.14	1.63	0.104
How comfortable did you feel during your dental visit for the endodontic treatment?	34	4.18	1.09	137	3.60	1.33	2.34	**0.020**

n – sample size, Mean – arithmetic mean, SD – standard deviation, t – Student's t-test value, p – probability of rejecting the null hypothesis at a 5% significance level

Table 5. *Comparison of mean values of variables between age groups*

Age		n	Mean	SD	F	p
How informed are you about endodontic (root canal) treatment?	18-30 yrs	125	3.30	1.48		
	31-40 yrs	25	3.36	1.47	0.75	0.474
	41+ yrs	21	3.71	1.23		
How satisfied are you with the information provided about the procedure?	18-30 yrs	125	3.64	1.35		
	31-40 yrs	25	3.20	1.41	9.75	**0.000**
	41+ yrs	21	4.81	0.51		
How would you rate your dentist's courtesy and professionalism during the endodontic treatment?	18-30 yrs	125	4.30	1.12		
	31-40 yrs	25	4.00	1.29	4.65	**0.011**
	41+ yrs	21	4.95	0.22		
Did your dentist inform you about possible complications or side effects of the endodontic treatment before the procedure?	18-30 yrs	125	3.50	1.53		
	31-40 yrs	25	3.32	1.60	6.26	**0.002**
	41+ yrs	21	4.67	0.73		
How would you rate the level of pain or discomfort during or after the endodontic treatment?	18-30 yrs	125	3.46	1.19		
	31-40 yrs	25	3.48	1.39	1.80	0.168
	41+ yrs	21	4.00	1.22		
How would you rate the communication with your dentist during t he treatment?	18-30 yrs	125	4.07	1.08		
	31-40 yrs	25	3.80	1.38	6.81	**0.001**
	41+ yrs	21	4.90	0.44		
How comfortable did you feel during your dental visit for the endodontic treatment?	18-30 yrs	125	3.72	1.26		
	31-40 yrs	25	2.92	1.44	10.82	**0.000**
	41+ yrs	21	4.62	0.67		

n – sample size, Mean – arithmetic mean, SD – standard deviation, F – F-test value from one-way analysis of variance (ANOVA), p – probability of rejecting the null hypothesis at a 5% significance level

Table 6. *Comparison of mean values of variables between education levels*

		n	Mean	SD	F	p
How informed are you about endodontic (root canal) treatment?	SE	55	3.15	1.50		
	UE	104	3.46	1.43	0.870	0.421
	PG	12	3.42	1.38		
How satisfied are you with the information provided about the procedure?	SE	55	3.87	1.38		
	UE	104	3.66	1.34	0.594	0.553
	PG	12	3.50	1.45		
How would you rate your dentist's courtesy and professionalism during the endodontic treatment?	SE	55	4.35	1.13		
	UE	104	4.33	1.14	0.036	0.964
	PG	12	4.42	0.79		
Did your dentist inform you about possible complications or side effects of the endodontic treatment before the procedure?	SE	55	3.93	1.36		
	UE	104	3.46	1.56	1.727	0.181
	PG	12	3.58	1.62		
How would you rate the level of pain or discomfort during or after the endodontic treatment?	SE	55	3.93	1.17		
	UE	104	3.39	1.19	5.742	0.004
	PG	12	2.83	1.40		
How would you rate the communication with your dentist during t he treatment?	SE	55	4.29	1.05		
	UE	104	4.07	1.13	0.821	0.442
	PG	12	4.00	1.28		
How comfortable did you feel during your dental visit for the endodontic treatment?	SE	55	3.89	1.29		
	UE	104	3.73	1.27	3.926	0.022
	PG	12	2.75	1.36		

SE – Secondary Education; UE – University Education; PG – Postgraduate (Master's/Doctorate)
n – sample size; Mean – arithmetic mean; SD – standard deviation; F – F-test value from one-way analysis of variance (ANOVA); p – probability of rejecting the null hypothesis at a 5% significance level

Participants aged 41 and above reported significantly higher satisfaction with the information provided about the procedure compared to other age groups ($F = 9.75$, $p < 0.001$), while those aged 31–40 were the least satisfied. This age group (41+) also rated the dentist's courtesy and professionalism during endodontic treatment significantly higher than other age groups ($t = 4.65$, $p < 0.011$).

Furthermore, participants aged 41+ expressed a significantly more positive perception regarding the information received about potential complications or side effects prior to treatment ($F = 6.26$, $p < 0.002$) and rated communication quality with the dentist higher than younger age groups ($F = 6.81$, $p < 0.001$). They also reported feeling significantly more comfortable during the endodontic procedure compared to other age groups ($t = 10.82$, $p < 0.001$). Results are summarized in Table 5.

Participants with a lower education level reported significantly higher levels of pain or discomfort during or after endodontic treatment compared to those with a university or postgraduate degree ($F = 5.742$, $p < 0.004$). Additionally, they reported feeling significantly more comfortable during the dental visit for endodontic treatment compared to participants with higher educational levels ($F = 3.926$, $p < 0.022$). Results are presented in Table 6.

DISCUSSION

In recent years, endodontics has become one of the fastest-growing fields in dentistry. The use of modern instruments, rubber dams, and microscopes has significantly improved the quality and longevity of treatment outcomes. Patients increasingly perceive endodontic procedures as less unpleasant than previously assumed. While pain during treatment can still occur, it is generally moderate rather than severe. Various pain management strategies—including local anesthesia, nitrous oxide sedation, preoperative intravenous sedatives, and, in rare cases, general anesthesia—enhance patient comfort (8).

Variability in patient knowledge and awareness can influence treatment acceptance and overall satisfaction (11). Awareness has increased in recent years not only through formal education but also via mass media, including television, internet, and newspapers (12). Improved knowledge can enhance patient experience and reduce treatment-related stress.

Patients are also aware of the benefits offered by modern clinics, such as effective pain control, high-quality procedural care, postoperative follow-up, and radiological monitoring to ensure long-term treatment success and timely intervention if necessary. Anxiety can amplify perceived pain during dental procedures, including endodontic treatment (13), while perceptions of dental aesthetics may influence overall satisfaction (14).

This study aimed to examine patients' perceptions of endodontic treatment, focusing on factors such as gender, age, and educational level. The findings provide insights into patient experiences, which can inform improvements in clinical practice and enhance patient satisfaction.

The study included a total of 171 participants, of whom 80.1% were female and 19.9% male. The mean age of male participants was 31.09 ± 12.07 years, while females had a slightly lower mean age of 27.31 ± 9.68 years, suggesting that the sample was relatively young, which may influence their expectations and experiences regarding dental treatments.

Regarding educational level, most participants held a university degree (60.8%), followed by secondary education (32.2%), and a small proportion had a master's or doctoral degree (7%). These findings may reflect varying levels of health literacy and the ability to understand the complexity of endodontic procedures. The majority of participants (36.3%) reported undergoing endodontic treatment for the first time, while a substantial number (34.5%) had experience with two procedures. Smaller proportions had undergone three (11.1%) or more than three treatments (18.1%), indicating that most patients lacked extensive experience with endodontic therapy, which may affect their perception and expectations.

Concerning the number of visits required to complete the treatment, the largest group of participants (33.3%) reported that three visits were necessary. Two visits were reported by 24.6%, while 14.6% required more than four visits. These data suggest that treatment duration and the number of appointments may influence patient satisfaction, particularly if the treatment takes longer than expected. Participants typically sought dental care within 24 hours (35.1%) or 2–3 days (35.7%) of experiencing pain, while smaller proportions waited 1–2 weeks (16.4%) or over a month (12.9%). This indicates that most patients seek professional help relatively promptly, which may positively impact treatment outcomes and reflect awareness of oral health importance.

Most participants (63.2%) felt that the duration of endodontic treatment met their expectations, whereas 10.5% were dissatisfied and 26.3% were uncertain. Regarding treatment success, 74.6% believed the procedure effectively resolved their dental problem, 8.8% considered it unsuccessful, and 16.6% were unsure. Furthermore, 77.5% reported that endodontic treatment improved their oral and general health.

These findings indicate a generally positive attitude among patients toward endodontic treatment. High levels of satisfaction may be linked to the dentist's professionalism, treatment efficiency, and quality of communication. Statistical analysis showed that male participants reported significantly higher satisfaction with the information provided about the procedure ($t = 2.94$, $p < 0.005$), the dentist's courtesy and professionalism ($t = 2.47$, $p < 0.015$), and overall comfort during the visit ($t = 2.34$, $p < 0.020$) compared to female participants. These differences may reflect variations in expectations, prior experiences, or gender-based perceptions of healthcare services, with men possibly having lower expectations or being less critical of the care received.

Participants aged 41 and older reported significantly higher satisfaction with the information provided ($F = 9.75$, $p < 0.001$), the dentist's courtesy and professionalism ($F = 4.65$, $p < 0.011$), and communication during treatment ($F = 6.81$, $p < 0.001$), as well as greater comfort during visits ($F = 10.82$, $p < 0.001$). These results suggest that older patients perceive endodontic treatment more positively, potentially due to greater experience with medical procedures or differing expectations compared to younger patients.

Bansal et al. (1) similarly explored patient perceptions of endodontic treatment using a questionnaire. Their findings highlight key factors influencing patient experience and satisfaction, notably the importance of thorough explanations from the dentist before treatment begins. Patients feel more secure when well-informed about the procedure, potential risks, and expected outcomes. Effective communication, including addressing questions and providing emotional support, significantly reduces anxiety and enhances satisfaction. The study also notes that while most patients perceive minimal impact of endodontic treatment on daily life, some express concern about postoperative pain and discomfort.

Ahmed et al. (9) highlighted several key findings regarding patient perceptions of endodontic treatment. The authors report that patients generally exhibit low levels of knowledge and awareness about root canal procedures, leading to unrealistic expectations and frequent misunderstandings about the purpose and outcomes of treatment. The study suggests that patients often associate endodontic therapy with negative experiences, such as pain and prolonged procedures, largely due to lack of information and fear. Patients who received adequate information from their dentist reported higher satisfaction and lower anxiety levels. The authors recommend enhanced patient education on root canal treatments to reduce fear and improve satisfaction, emphasizing the importance of effective dentist–patient communication to build trust and optimize treatment outcomes.

Similarly, Gautama et al. (7) found that in Nepal, patients had limited knowledge and awareness of endodontic procedures. Most participants had a restricted understanding of the treatment process, its purpose, and expected results, which contributed to misconceptions, fear, and preoperative anxiety. The study also showed that patients with higher levels of information were less prone to negative emotions such as fear and anxiety. The researchers stressed the critical role of dentists in patient education, noting that better communication and accurate information can significantly improve patient experience and satisfaction with treatment outcomes.

Purra et al. (12) reported similar findings in Kashmir, where patients had limited awareness and knowledge of root canal therapy. Most participants were not sufficiently informed about the purpose, process, or benefits of treatment, resulting in fear, uncertainty, and doubts about the success of the procedure.

Perković et al. (15) highlighted that patients often experienced high levels of anxiety prior to endodontic treatment, which directly influenced their perception of pain during the procedure. The study found a significant correlation between anxiety levels and perceived pain, with patients experiencing greater fear reporting more intense pain. Patient satisfaction with dental care, including endodontic treatment, can serve as a key indicator of the quality of services provided (16).

Dugas et al. (17) demonstrated that endodontic treatment positively impacts patients' quality of life, particularly by reducing pain and improving oral health. Comparative studies suggest that endodontic therapy can be as effective as dental implants in enhancing quality of life (18). Post-treatment, patients reported high satisfaction levels, which were associated with successful outcomes and reduced discomfort. Perceived service quality plays a critical role in patients' choices regarding dental treatments and can influence their decision-making (19). Variations in patient satisfaction depending on their endodontic experiences underscore the need for better patient education (20).

In our study, participants with a medium level of education reported significantly higher pain or discomfort during or after treatment ($F = 5.742$, $p < 0.004$) compared to those with higher education or academic degrees. These findings suggest that educational level may influence the perception of pain and discomfort, possibly due to differences in understanding the procedure or expectations of the treatment. The results highlight the importance of an individualized approach, taking patients' demographic characteristics

into account. Dentists should pay particular attention to communication with patients, especially women and younger individuals, to increase satisfaction and reduce anxiety. Providing detailed information about the procedure, possible complications, and expected outcomes can enhance patients' perceptions of the treatment.

Patient education is important not only for anxiety reduction but also for treatment success. Awareness of treatment benefits, prompt access to care, and realistic expectations can improve patient compliance and overall outcomes (21).

Several limitations of this study should be considered when interpreting the findings. First, the sample was predominantly composed of female participants, which may have influenced the results and limits the ability to generalize findings across genders. Second, the overall sample was relatively young, which may affect the perception of endodontic treatment and does not fully represent older populations.

Additionally, the use of a self-reported online questionnaire introduces the possibility of response bias, as participants may have provided subjective or socially desirable answers. The cross-sectional design of the study further limits the ability to establish causal relationships between demographic factors and patient perceptions.

These factors may reduce the generalizability of the results to broader populations. Future studies should include more balanced and diverse samples, as well as longitudinal designs, to provide a more comprehensive understanding of patient perceptions and experiences related to endodontic treatment.

CONCLUSION

The findings of this study indicate that patients generally demonstrate a positive attitude toward endodontic treatment, with satisfaction largely influenced by the dentist's professionalism, courtesy, and effective communication throughout the procedure. Older patients and male participants reported higher levels of satisfaction compared with younger patients and female participants, suggesting that expectations and perceptions of treatment may vary across demographic groups.

Patients with a moderate level of education reported higher levels of discomfort and pain, emphasizing the importance of a personalized approach that takes into account individual patient characteristics. The results also highlight the significant role of comprehensive patient education. Providing clear explanations about the procedure, potential risks, and expected outcomes can help reduce anxiety and improve the overall treatment experience.

Improving communication, offering clear and detailed information, and tailoring the approach to different age, gender, and educational groups may contribute to reducing discomfort, increasing patient satisfaction, and ultimately optimizing the outcomes of endodontic treatment.

From a clinical perspective, the findings of this study highlight the need for a more individualized, patient-centered approach in endodontic practice. Providing comprehensive, understandable, and tailored information about the procedure, potential complications, and expected outcomes may help reduce anxiety and improve the overall patient experience.

Furthermore, targeted educational strategies should be developed for patients with lower levels of education, focusing on improving understanding of endodontic procedures and pain management, as this group reported higher levels of discomfort. The implementation of standardized communication protocols and patient education tools may contribute to increased treatment acceptance, enhanced satisfaction, and better clinical outcomes.

Abbreviations

RCT - root canal treatment

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Sažetak

STAVOVI I ISKUSTVA PACIJENATA O ENDODONTSKOM TRETMANU: IMPLIKACIJE NA ORALNO ZDRAVLJE

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Uvod: Endodontski tretman je ključna procedura za očuvanje prirodnih zuba i sprečavanje daljih oralnih komplikacija. Međutim, percepcija pacijenata, njihovo znanje i anksioznost u vezi sa lečenjem kanala korena mogu uticati na njihovu spremnost da pristupe tretmanu i na ukupno zadovoljstvo stomatološkom uslugom.

Cilj: Cilj ovog istraživanja bio je ispitati povezanost demografskih karakteristika—poput pola, starosti i nivoa obrazovanja—sa percepcijom, stavovima i očekivanjima pacijenata u vezi sa endodontskim tretmanom.

Materijali i metode: Sprovedena je studija preseka korišćenjem anonimnog onlajn upitnika među pacijentima koji žive u Kantonu Sarajevo. Ukupno 171 učesnik koji je ranije imao endodontski tretman popunio je upitnik. Upitnik je prikupljao demografske podatke, informacije o znanju pacijenata o endodontskom tretmanu, prethodnom iskustvu, zadovoljstvu pruženim informacijama od strane stomatologa, doživljenoj boli ili nelagodnosti, komunikaciji sa stomatologom i ukupnom iskustvu tretmana. Podaci su analizirani pomoću IBM SPSS Statistics verzija 22. Deskriptivna statistika korišćena je za sumiranje podataka, dok su Studentov t-test za nezavisne uzorke i jednosmerna analiza varijanse (ANOVA) primenjeni za procenu razlika između grupa. Statistička značajnost je postavljena na $p < 0,05$.

Rezultati: Većina učesnika su bile žene (80,1%), a najveći deo je imao univerzitetsku diplomu (60,8%). Muški učesnici su prijavili značajno veće zadovoljstvo informacijama koje su dobili, profesionalnošću stomatologa i udobnošću tokom tretmana u poređenju sa ženskim učesnicima ($p < 0,05$). Učesnici stariji od 41 godine prijavili su značajno veće zadovoljstvo komunikacijom, informacijama i ukupnim iskustvom tretmana u odnosu na mlađe starosne grupe. Učesnici sa nižim nivoom obrazovanja prijavili su značajno veći nivo bola ili nelagodnosti tokom ili nakon tretmana ($p < 0,004$).

Zaključak: Pacijenti su generalno pokazali pozitivnu percepciju endodontskog tretmana. Efikasna komunikacija, adekvatna edukacija pacijenata i profesionalnost stomatologa igraju važnu ulogu u smanjenju anksioznosti i poboljšanju zadovoljstva pacijenata i iskustva tretmana.

Ključne reči: endodontski tretman, percepcija pacijenta, zadovoljstvo pacijenta, oralno zdravlje.

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CONTEMPORARY BIOMARKERS OF BLOOD-BRAIN BARRIER INJURY AND NEUROINFLAMMATION IN PRETERM INFANTS WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY

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Abstract: **Background:** Hypoxic–ischemic encephalopathy (HIE) is a major cause of neonatal morbidity and long-term neurodevelopmental impairment, particularly in preterm infants. Early diagnosis remains challenging, and there is growing interest in biomarkers that reflect underlying mechanisms such as neuroinflammation and blood–brain barrier disruption.

Objective: To evaluate the diagnostic and prognostic value of selected circulating biomarkers in preterm infants with HIE, with emphasis on a multimarker approach.

Methods: This prospective cohort study included 120 preterm infants (gestational age 28–36 weeks), divided into HIE (n = 90) and control (n = 30) groups. Serum levels of NR2 antibodies, endothelin-1, glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL) were measured at 24–48 hours, day 5–7, and day 14. Statistical analysis included t-test, ANOVA, correlation analysis, logistic regression, and ROC curve analysis.

Results: Biomarker levels were significantly higher in the HIE group ($p < 0.001$). GFAP and NfL showed the highest diagnostic performance (AUC 0.86 and 0.88). The combined model achieved the best accuracy (AUC = 0.89). Biomarker levels correlated with disease severity.

Conclusion: A multimarker approach improves diagnostic accuracy and may support early risk stratification and individualized management in preterm infants with HIE.

Keywords: hypoxic–ischemic encephalopathy, preterm infants, biomarkers, GFAP, neurofilament light chain, endothelin-1, NR2 antibodies, neuroinflammation.

INTRODUCTION

Hypoxic–ischemic encephalopathy (HIE) remains a major cause of neonatal mortality and long-term neurodevelopmental impairment, particularly in preterm infants (1, 2). Despite advances in neonatal intensive care, early diagnosis and precise assessment of brain injury severity continue to represent significant clinical challenges.

The pathophysiology of HIE involves a complex cascade of events, including primary energy failure followed by secondary injury mechanisms such as excitotoxicity, oxidative stress, inflammation, and apoptosis (3, 4). Excessive glutamate release and NMDA receptor activation play a central role in neuronal injury, while disruption of the blood–brain barrier further contributes to disease progression (5, 6). In addition, endothelial dysfunction and impaired cerebral autoregulation, partly mediated by endothelin-1, exacerbate ischemic damage and worsen neurological outcomes (7, 8).

Conventional diagnostic approaches, including clinical assessment, neuroimaging, and electrophysiological monitoring, have important limitations, especially in the early phase of injury (5, 9). Therefore, increasing attention has been directed toward circulating biomarkers that may provide objective and early information about brain injury.

Recent studies have identified glial fibrillary acidic protein (GFAP) as a marker of astroglial injury and

blood–brain barrier disruption, while neurofilament light chain (NfL) reflects axonal damage (6, 10). Additional biomarkers, including NR2 antibodies, endothelin-1, and S100B, may further contribute to the evaluation of neuronal, glial, and vascular injury (11-14).

The aim of this study was to evaluate the diagnostic and prognostic value of selected biomarkers in preterm infants with HIE, with particular emphasis on the potential advantages of a multimarker approach.

MATERIALS AND METHODS

Subjects and Study Design

A prospective cohort study was conducted at the University Clinical Center Sarajevo, Clinic for Neonatology, over a 12-month period (January–December 2025). The study included a total of 120 preterm infants with a gestational age between 28 and 36 weeks.

The sample size was calculated based on an expected medium-to-large effect size (Cohen's d = 0.7), with a statistical power of 80% and a significance level of 0.05. The minimum required sample size was estimated at 102 participants; therefore, 120 infants were included to improve the robustness of the analysis and account for potential dropouts.

Participants were divided into two groups: preterm infants diagnosed with hypoxic–ischemic encephalopathy (HIE) (n = 90) and a control group of clinically stable preterm infants without evidence of perinatal asphyxia (n = 30).

The diagnosis of HIE was established based on a combination of clinical and laboratory criteria, including an Apgar score ≤ 5 at 5 minutes, the need for resuscitation at birth, evidence of metabolic acidosis (pH < 7.0 or base deficit ≥ 12 mmol/L), and neurological signs consistent with encephalopathy (1, 2).

The severity of HIE was classified according to the Sarnat and Sarnat staging system into three categories (1, 2):

• Stage I (mild): irritability, hyperreflexia, absence of seizures

• Stage II (moderate**):** lethargy, hypotonia, seizures, impaired reflexes

• Stage III (severe): coma, areflexia, severe central nervous system depression

Infants with major congenital anomalies, confirmed or suspected infections, or genetic syndromes were excluded from the study.

Methods

Blood samples were collected at predefined time points: within the first 24–48 hours of life, between days 5 and 7, and on day 14. Samples were obtained via venipuncture, centrifuged to separate serum, and stored at −80 °C until analysis.

The analyzed biomarkers included NR2 antibodies, endothelin-1, glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL). Quantitative measurements were performed using enzyme-linked immunosorbent assay (ELISA) kits (Elabscience Biotechnology Inc., Houston, TX, USA), in accordance with the manufacturer's instructions.

Based on receiver operating characteristic (ROC) curve analysis, optimal cut-off values for differentiating HIE from controls were determined as follows:

• GFAP: > 2.5 ng/mL
• NfL: > 3.0 ng/mL
• Endothelin-1: > 2.0 pg/mL
• NR2 antibodies: > 2.0 AU

All infants underwent serial cranial ultrasound examinations as part of routine clinical care. Magnetic resonance imaging (MRI) of the brain was performed in selected cases to further characterize the extent of brain injury. Continuous monitoring of cerebral activity was performed using amplitude-integrated electroencephalography (aEEG), which has proven value in early neurological assessment (5).

Clinical and demographic data, including gestational age, birth weight, Apgar scores, need for respiratory support, and the occurrence of complications (e.g., intraventricular hemorrhage), were collected prospectively from medical records.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages.

Normality of data distribution was assessed using the Kolmogorov–Smirnov test. Differences between groups were analyzed using Student's t-test or one-way analysis of variance (ANOVA), as appropriate. The chi-square test was used for categorical variables.

Pearson correlation analysis was applied to evaluate relationships between biomarker levels and clinical parameters. Multivariate logistic regression analysis was performed to identify independent predictors of HIE.

Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic performance of individual biomarkers and their combinations. The area under the curve (AUC), sensitivity, specificity, and 95% confidence intervals were calculated.

A post hoc power analysis confirmed that the study achieved a statistical power of 0.83 for detecting differences in primary biomarker outcomes.

A p-value < 0.05 was considered statistically significant.

Ethical approval

The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the institutional Ethics Committee. Written informed consent was obtained from the parents or legal guardians of all participants prior to inclusion in the study.

RESULTS

A total of 120 preterm infants were included in the study, of whom 90 (75%) were diagnosed with hypoxic–ischemic encephalopathy (HIE), while 30 (25%) served as controls. There were no statistically significant differences in gestational age between the groups (31.5 ± 2.1 vs 32.1 ± 1.8 weeks, p = 0.08) or birth weight (1650 ± 320 vs 1720 ± 290 g, p = 0.12). However, Apgar scores at 1 minute were significantly lower in the HIE group (4 ± 1 vs 8 ± 1, p < 0.001), indicating more severe perinatal distress (Table 1).

At 24–48 hours of life, all analyzed biomarkers were significantly elevated in the HIE group compared to controls. Mean GFAP levels were 4.2 ± 1.1 ng/mL in the HIE group versus 1.3 ± 0.5 ng/mL in controls (p < 0.001), while NfL levels were 5.1 ± 1.4 ng/mL versus 1.7 ± 0.6 ng/mL (p < 0.001). Endothelin-1 levels were also significantly higher (3.8 ± 1.0 vs 1.5 ± 0.4 pg/mL, p < 0.001), as well as NR2 antibodies (2.9 ± 0.9 vs 1.2 ± 0.3 AU, p < 0.001).

A decreasing trend in biomarker levels was observed over time; however, values remained significantly higher in the HIE group at all time points. By day 5–7, GFAP decreased to 3.6 ± 1.0 ng/mL, and further to 2.8 ± 0.9 ng/mL by day 14 (p < 0.001 for trend). Similarly, NfL levels decreased from 5.1 ± 1.4 ng/mL at baseline to 4.3 ± 1.2 ng/mL (day 5–7) and 3.5 ± 1.0 ng/mL (day 14), remaining significantly elevated compared to controls (p < 0.001) (Table 2).

Table 1. *Demographic and clinical characteristics*

Variable	HIE (n = 90)	Control (n = 30)	p
Gestational age (weeks)	31.5 ± 2.1	32.1 ± 1.8	0.08
Birth weight (g)	1650 ± 320	1720 ± 290	0.12
Apgar score (1 min)	4 ± 1	8 ± 1	< 0.001

Table 2. *Biomarker levels over time*

Biomarker	24–48 h	Day 5–7	Day 14	p
GFAP (ng/mL)	4.2 ± 1.1	3.6 ± 1.0	2.8 ± 0.9	< 0.001
NfL (ng/mL)	5.1 ± 1.4	4.3 ± 1.2	3.5 ± 1.0	< 0.001

Table 3. *Multivariate logistic regression analysis*

Variable	OR	95% CI	p
GFAP	2.8	1.9–4.1	< 0.001
NfL	3.2	2.1–4.8	< 0.001
Endothelin-1	2.1	1.4–3.2	0.002

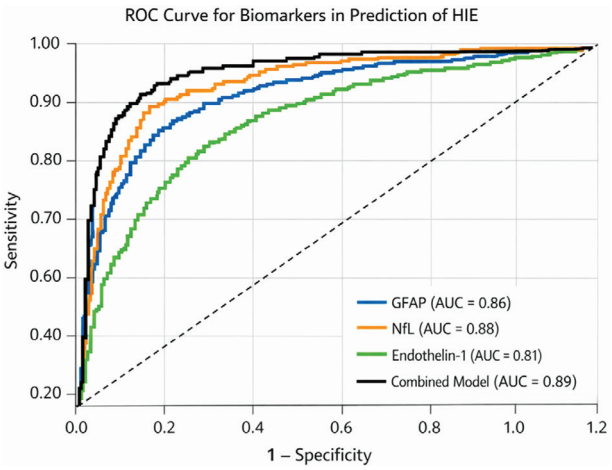

Figure 1. *Receiver operating characteristic (ROC) curves for GFAP, NfL, endothelin-1, and the combined biomarker model in predicting hypoxic–ischemic encephalopathy. The combined model demonstrated the highest diagnostic accuracy (AUC = 0.89)*

Subgroup analysis showed that infants with moderate-to-severe HIE (n = 52) had significantly higher biomarker levels than those with mild HIE (n = 38). Mean GFAP levels were 5.0 ± 1.2 ng/mL in the moderate-to-severe group compared to 3.2 ± 0.8 ng/mL in mild cases (p < 0.001), while NfL levels were 6.0 ± 1.5 ng/mL versus 4.0 ± 1.0 ng/mL (p < 0.001).

Correlation analysis demonstrated a significant negative correlation between Apgar score at 1 minute and biomarker levels: GFAP (r = –0.62, p < 0.001) and NfL (r = –0.68, p < 0.001).

Multivariate logistic regression analysis identified GFAP and NfL as independent predictors of HIE. GFAP showed an odds ratio (OR) of 2.8 (95% CI 1.9–4.1, p < 0.001), while NfL had an OR of 3.2 (95% CI 2.1–4.8, p < 0.001). Endothelin-1 was also a significant predictor (OR 2.1, 95% CI 1.4–3.2, p = 0.002) (Table 3).

Receiver operating characteristic (ROC) curve analysis demonstrated good diagnostic performance for individual biomarkers. GFAP achieved an area under the curve (AUC) of 0.86 (95% CI 0.79–0.92), while NfL showed slightly higher accuracy with an AUC of 0.88 (95% CI 0.82–0.94). Endothelin-1 demonstrated moderate diagnostic value (AUC 0.81, 95% CI 0.73–0.89).

The combined biomarker model (GFAP + NfL + endothelin-1) showed the highest diagnostic performance, with an AUC of 0.89 (95% CI 0.83–0.95), sensitivity of 87%, and specificity of 82% (Figure 1).

In terms of clinical outcomes, 34% of infants with HIE required mechanical ventilation, 48% required non-invasive respiratory support, and 29% developed intraventricular hemorrhage (grade II–IV). Higher biomarker levels were significantly associated with adverse outcomes, particularly in infants with severe HIE ($p < 0.001$).

DISCUSSION

The findings of this study highlight the clinical relevance of contemporary biomarkers in assessing brain injury in preterm infants with HIE. Biomarkers reflecting different pathophysiological pathways—neuronal, astroglial, inflammatory, and vascular—demonstrated significant diagnostic and prognostic value (15, 16, 17).

Consistent with previous studies, GFAP and NfL showed the strongest association with HIE severity. GFAP reflects astrocytic injury and blood–brain barrier disruption, while NfL serves as a sensitive indicator of axonal damage (17, 18). Their elevation in our cohort is in line with recent evidence demonstrating their role in early detection and severity assessment of neonatal brain injury (19, 20, 21).

In addition, NR2 antibodies demonstrated a significant increase in infants with HIE, supporting their role as markers of excitotoxic neuronal injury. NR2 subunits of the NMDA receptor are released following hypoxic–ischemic insult and reflect early glutamate-mediated neuronal damage (9, 18). Although their diagnostic performance was lower compared to GFAP and NfL, NR2 antibodies contributed additional pathophysiological insight, particularly in the early phase of injury, complementing the multimarker approach.

The observed decrease in biomarker levels over time likely reflects the dynamic nature of injury and repair processes. However, persistently elevated levels in the HIE group suggest ongoing secondary injury mechanisms, including neuroinflammation and delayed neuronal damage (18, 22).

Endothelin-1 also demonstrated significant diagnostic value, supporting the role of vascular dysfunction and impaired cerebral perfusion in HIE pathophysiology (18, 23). These findings reinforce the concept that neonatal hypoxic–ischemic injury involves not only neuronal damage but also vascular and endothelial components.

Importantly, the combined biomarker model showed the highest diagnostic accuracy. The multivariate model included GFAP, NfL, endothelin-1, and NR2 antibodies as independent variables, together with key clinical parameters such as Apgar score and gestational age. This integrative approach allowed simultaneous assessment of neuronal, glial, and vascular injury pathways, resulting in improved predictive performance compared to single biomarkers. These findings are consistent with studies suggesting that multimarker strategies provide superior clinical utility (3, 9, 18).

The strong correlation between low Apgar scores and elevated biomarker levels confirms their clinical relevance in reflecting the severity of perinatal hypoxia (1, 10). Furthermore, their association with adverse outcomes supports their potential use in prognostic stratification and individualized patient management (20).

From a clinical perspective, early identification of high-risk infants is essential, as timely interventions such as therapeutic hypothermia significantly improve outcomes (16, 17). Integration of biomarker profiling into clinical practice may enhance early decision-making and optimize treatment strategies.

Although our study provides valuable insights, further multicenter studies with long-term follow-up are needed to validate these findings and establish standardized biomarker thresholds for routine clinical use. Regional studies, including those reported in the *Sanamed* journal, also emphasize the importance of perinatal asphyxia as a significant contributor to neonatal morbidity (18, 21, 22).

Strengths and limitations

The strengths of this study include its prospective design and serial biomarker measurements. However, several limitations should be acknowledged. The study was conducted in a single center, which may limit generalizability. Additionally, long-term neurodevelopmental outcomes were not assessed, and future studies should explore the predictive value of these biomarkers for long-term prognosis.

CONCLUSION

Contemporary biomarkers, particularly when used in combination, represent a valuable tool for the early diagnosis and prognostic assessment of hypoxic–ischemic encephalopathy (HIE) in preterm infants. By reflecting multiple dimensions of brain injury, including astroglial damage, axonal disruption, and endothelial dysfunction, these biomarkers provide a more comprehensive understanding of the underlying pathophysiological processes.

The application of a multimarker model demonstrated high diagnostic accuracy and a strong associ-

ation with disease severity and clinical outcomes. Importantly, these findings suggest that biomarker profiling could enable earlier identification of infants at high risk for severe brain injury, even before overt clinical deterioration occurs.

In clinical practice, this approach has the potential to significantly modify current diagnostic and therapeutic strategies. Early biomarker-based risk stratification could support more timely initiation of neuroprotective interventions, including therapeutic hypothermia, as well as closer neurological monitoring and individualized supportive care. Furthermore, it may reduce reliance on delayed or less sensitive diagnostic modalities and improve decision-making in the critical early postnatal period.

Integration of biomarker assessment into routine neonatal protocols could also facilitate more precise prognostication, guide parental counseling, and optimize allocation of intensive care resources.

Although these results are promising, further multicenter studies with larger cohorts and long-term neurodevelopmental follow-up are necessary to validate these findings and to establish standardized cut-off values for routine clinical implementation.

Abbreviations

aEEG – Amplitude-Integrated Electroencephalography

GFAP – Glial Fibrillary Acidic Protein

HIE – Hypoxic–Ischemic Encephalopathy

MRI – Magnetic Resonance Imaging

NfL – Neurofilament Light Chain

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Note: Artificial intelligence was not utilized as a tool in this study.

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Sažetak

SAVREMENI BIOMARKERI OŠTEĆENJA HEMATOENCEFALNE BARIJERE I NEUROINFLAMACIJE KOD NEDONOŠČADI SA HIPOKSIČNO-ISHEMIJSKIM OŠTEČENJEM MOZGA

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Uvod: Hipoksično-ishemijska encefalopatija (HIE) predstavlja značajan uzrok neonatalnog morbiditeta i dugoročnih neuroloških oštećenja, posebno kod nedonoščadi. Rana dijagnoza je otežana, a sve veći značaj pridaje se biomarkerima koji odražavaju patofiziološke procese poput neuroinflamacije i oštećenja hematoencefalne barijere.

Cilj: Proceniti dijagnostičku i prognostičku vrednost odabranih cirkulišućih biomarkera kod nedonoščadi sa HIE, s posebnim osvrtom na multimarker pristup.

Metode: Prospektivna kohortna studija obuhvatila je 120 nedonoščadi (gestacijska dob 28–36 sedmica), podeljenih u HIE (n = 90) i kontrolnu grupu (n = 30). Određivani su serumski nivoi NR2 antitela, endotelina-1, glijalnog fibrilarnog kiselog proteina (GFAP) i neurofilamentnog lakog lanca (NfL) u periodu 24–48 sati, 5–7 dana i 14. dana života. Statistička analiza uključivala je t-test, ANOVA, korelacijsku analizu, logističku regresiju i ROC analizu.

Rezultati: Vrednosti biomarkera bile su značajno više u HIE grupi ($p < 0,001$). GFAP i NfL pokazali su

najbolju dijagnostičku vrednost (AUC 0,86 i 0,88). Kombinovani model imao je najveću tačnost (AUC = 0,89). Vrednosti biomarkera korelirale su sa težinom bolesti.

Zaključak: Multimarker pristup poboljšava dijagnostičku tačnost i može doprineti ranoj proceni rizika i individualizaciji lečenja kod nedonoščadi sa HIE.

Ključne reči: hipoksično-ishemijska encefalopatija, nedonoščad, biomarkeri, GFAP, neurofilamentni laki lanac, endotelin-1, NR2 antitela, neuroinflamacija.

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ASSOCIATION OF THE TP53 PIN3 16-BP DUPLICATION POLYMORPHISM WITH ORAL SQUAMOUS CELL CARCINOMA RISK AND PROGNOSIS

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Abstract: **Background/Aim:** Oral squamous cell carcinoma (OSCC) is associated with multiple risk factors, including genetic variations such as the TP53 PIN3 16-bp duplication polymorphism. This study aimed to assess the association between this polymorphism and susceptibility to OSCC in the Montenegrin population and to evaluate its influence on OSCC prognosis and progression.

Materials and Methods: Genomic DNA extracted from 60 patients with OSCC and 71 cancer-free controls was analyzed using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) technique to identify TP53 PIN3 genotypes and allele frequencies. Clinical and pathological data, along with three-year follow-up outcomes, were also analyzed.

Results: During the follow-up period, 12 patients (20%) experienced local recurrence of disease and 6 patients (10%) developed regional metastases, with no distant metastases detected. No significant associations were observed between the PIN3 16-bp duplication polymorphism and patient age, tumor site, grade, disease recurrence, or metastasis ($p > 0.05$). A significant association between TP53 genotypes and advanced stage of disease was found ($p = 0.006$). There were no significant differences in disease-free survival among genotypes: A1A1 (28.26 ± 1.70 months), A1A2 (35.00 ± 0.94 months), and A2A2 (30.00 ± 5.20 months) ($p = 0.38$). Additionally, no significant differences in allele or genotype frequencies between patients and controls were observed ($p > 0.05$).

Conclusion. The TP53 PIN3 16-bp duplication polymorphism cannot be considered a risk factor for OSCC development in the Montenegrin population. Furthermore, this polymorphism does not modulate susceptibility to OSCC progression.

Keywords: TP53, PIN3 16-bp polymorphism, oral cancer.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is ranked as the 11th most common type of cancer worldwide (1). Carcinogenesis is a complex, multifactorial process influenced by environmental factors and genetic alterations in oncogenes and tumor suppressor genes (2).

The tumor suppressor gene TP53 is the most frequently altered gene across human cancers. It encodes the TP53 protein, a central transcriptional regulator that maintains genomic stability by controlling genes involved in cell cycle arrest, DNA damage response, apoptosis, and cellular senescence (3, 4). Therefore, disruption of TP53 function through either somatic mutations or inherited polymorphic variants can promote malignant transformation and tumor progression, including in OSCC (2).

To date, more than 200 polymorphisms (SNPs) have been identified in both exonic and intronic regions of TP53 (5). Among them, the 16-bp duplication polymorphism (rs17878362) within intron 3 has been widely investigated for cancer susceptibility due to its potential influence on TP53 transcriptional regulation and post-transcriptional processing (3). Accordingly, the insertion allele of this polymorphism has been associated with decreased TP53 expression, possibly through altered splicing efficiency, leading to an increased risk of cancer development (6).

Over the last two decades, a number of studies have shown that the TP53 PIN3 16-bp duplication polymorphism is associated with an increased risk of various malignant tumors, most often breast (5), colon (6), and lung cancer (7). However, data regarding its role

in oral carcinogenesis remain limited and inconsistent. Additionally, the relationship between the TP53 PIN3 16-bp duplication polymorphism and the risk of oral squamous cell carcinoma has not been evaluated in our population.

Therefore, we conducted the present study to investigate the association between the TP53 PIN3 16-bp duplication polymorphism and the risk of OSCC in the Montenegrin population and to evaluate the impact of this polymorphism on OSCC prognosis and progression.

MATERIAL AND METHODS

The study population comprised 60 patients with histopathologically confirmed oral squamous cell carcinoma involving the lower lip, tongue, or floor of the mouth, who underwent surgical treatment at the Clinic for Maxillofacial Surgery, Clinical Center of Montenegro, between 2005 and 2009. The research adhered to the standards of the Declaration of Helsinki (2002 version) and was conducted with the consent of the institutional Ethical Committee.

Patients were followed for three years after surgical treatment, and survival time was measured from the end of primary treatment to the first detection of local recurrence or regional recurrence (nodal metastasis), defined as the disease-free interval (DFI).

The KAPA Express Extract Kit (Kapa Biosystems, Inc., Wilmington, MA, USA) was used for DNA isolation from 60 formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. DNA isolated from peripheral blood samples of 71 healthy individuals, age- and gender-matched to OSCC patients, was used for the association study. The concentration of DNA isolated from blood samples and OSCC tissue was determined spectrophotometrically.

TP53 PIN3 Ins16bp genotyping was performed using the polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) method. The reaction mixture (25 µl) for detection of the PIN3 Ins16bp polymorphism consisted of the following components: 2.5 µl of 10× PCR buffer (MBI Fermentas, Lithuania), 1.5 µl of $MgCl_2$, 0.2 mM dNTPs, 0.375 µM of each primer, 200 ng of DNA isolated from OSCC samples or peripheral blood of healthy individuals, and 1 unit of Taq DNA polymerase.

The PIN3 Ins16bp duplication was amplified using the following primers: 5′-CTGGTAAGGACAAGGGTTGG-3′ and 5′-TCATCTGGACCTGGGTCTTC-3′. PCR products were 185 bp or 201 bp in length and were resolved on an 8% polyacrylamide gel.

Restriction digestion was performed using the MspI enzyme (MBI Fermentas, Lithuania). The A1A1 genotype was identified by a single fragment of 185 bp, the A1A2 genotype by two fragments of 185 bp and 201 bp, and the A2A2 genotype by a single fragment of 201 bp.

Statistical analyses were conducted using SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA). The chi-square test was applied to evaluate correlations between the PIN3 Ins16bp duplication polymorphism and clinicopathological parameters. The relationship between the TP53 PIN3 Ins16bp duplication polymorphism and the risk of OSCC development was evaluated by calculating odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was set at $p < 0.05$. Survival analysis was performed using Kaplan–Meier curves and the log-rank test. A p value < 0.05 was considered statistically significant.

RESULTS

The study included 60 patients with OSCC, comprising 13 females (21.7%) and 47 males (78.3%), aged 37–86 years (mean age: 62 years) (Table 1). Among the 60 patients, the majority of cases (two-thirds) were in the early stages (I and II) of the disease. The A1A1 and A1A2 genotypes were approximately equally distributed among the age groups 40–60 years and over 60 years.

During the three-year follow-up period, 12 patients (20%) experienced local recurrence of disease and 6 patients (10%) developed regional (nodal) metastases, with no distant metastases detected. Accordingly, 18 patients (12 + 6; 30.0%) developed disease progression, whereas 42 patients (70.0%) remained recurrence- and metastasis-free.

No significant associations were observed between the TP53 PIN3 Ins16bp duplication polymorphism and clinicopathological features, including patient age, gender, tumor site, grade, disease recurrence, or metastasis ($p > 0.05$). However, a significant association between TP53 genotypes and disease stage was found ($p = 0.006$), with the A2A2 genotype being significantly more frequent in advanced stages of disease (III and IV).

Kaplan–Meier analysis showed no significant differences in disease-free survival among genotypes: A1A1 (28.26 ± 1.70 months), A1A2 (35.00 ± 0.94 months), and A2A2 (30.00 ± 5.20 months) ($\chi^2 = 1.95$; $p = 0.38$; Figure 1). Cox regression analysis confirmed that PIN3 Ins16bp genotypes were not predictive of disease recurrence or metastasis (−2 log likelihood = 132.65; $\chi^2 = 1.64$; $p = 0.44$).

To determine whether the TP53 PIN3 16-bp polymorphism modulates the risk of oral cancer development in the studied population, genotype distributions

Table 1. *Correlation of PIN3 Ins16bp duplication polymorphism of TP53 with clinicopathological parameters in OSCCs*

Category	Variable	Patients n (%)	PIN3 Ins16bp genotype n (%)			P-value
			A1A1	A1A2	A2A2	
		60	47 (78.3)	9 (15.0)	4 (6.7)	
Age	≤ 40	2 (3.0)	2 (100.0)	0.0	0.0	
	> 40 < 60	27 (45.0)	22 (81.5)	5 (18.5)	0.0	0.752
	≥ 60	31 (52.0)	23 (74.0)	4 (13.0)	4 (3.0)	
Gender	Female	13 (22.0)	10 (77.0)	2 (15.0)	1 (8.0)	0.867
	Male	47 (78.0)	37 (79.0)	7 (15.0)	3 (6.0)	
Stage	I + II	36 (60.0)	26 (72.0)	9 (25.0)	1 (3.0)	0.006*
	III + IV	24 (40.0)	21 (87.5)	0.0	3 (12.5)	
Tumor differentiation	Well	35 (58.0)	26 (74.3)	5 (14.3)	4 (11.4)	
	Moderately	23 (38.0)	20 (87.0)	3 (13.0)	0.0	0.520
	Poorly	2 (4.0)	1 (50.0)	1 (50.0)	0.0	
Localisation (site)	Lip	28 (47.0)	22 (79.0)	4 (14.0)	2 (7.0)	
	Tongue	18 (30.0)	14 (78.0)	3 (17.0)	1 (5.0)	0.977
	Floor of mouth and tongue	14 (23.0)	11 (79.0)	2 (14.0)	1 (7.0)	
Disease recurrence	+	12 (20.0)	11 (92.0)	1 (8.0)	0.0	0.209
	–	48 (80.0)	36 (75.0)	8 (17.0)	4 (8.0)	
Metastasis (node)	+	6 (10.0)	5 (83.0)	0.0	1 (17.0)	0.916
	–	54 (90.0)	42 (78.0)	9 (17.0)	3 (5.0)	

Table 2. *Genotype and allele frequencies of the PIN3 16-bp polymorphism among OSCC cases and control subjects and their associations with the risk of OSCC*

Genotype/ allele	OSCCs n = 60 (%)	Controls n = 71 (%)	OR	95% CI	p
A1A1	47 (78.0)	56 (79.0)	1.00	Reference	
A1A2	9 (15.0)	13 (18.0)	0.83	0.32-2.10	0.322
A2A2	4 (7.0)	2 (3.0)	2.38	0.42-13.6	0.800
A1A2+A2A2	13	15	1.03	0.45-2.38	0.342
A1A1+A1A2	56	69	2.46	0.43-13.97	0.452
A1	103 (86.0)	125 (88.0)	1.00	Reference	
A2	17 (14.0)	17 (12.0)	1.21	0.59-2.49	0.598

OR – odds ratio; CI – confidence interval; p – probability; n – number of individuals

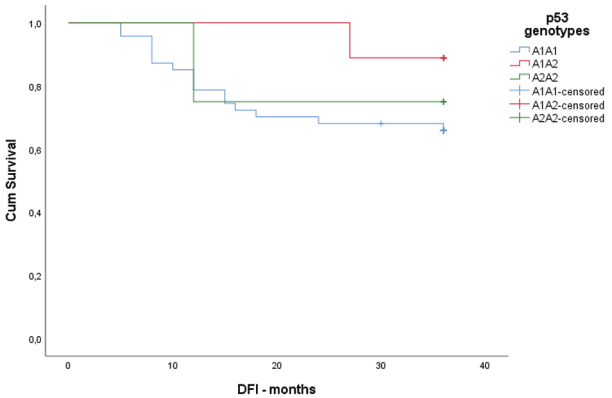

Figure 1. *Kaplan-Meier survival plot regarding TP53 genotypes in oral carcinoma*

among OSCC patients and healthy controls were analyzed (Table 2).

Genotype and allele frequencies of the PIN3 16-bp polymorphism showed no significant differences between the two groups. Carriers of the A2A2 genotype (homozygous for insertion of the 16-bp sequence in intron 3) were more frequent in the OSCC group; however, this difference was not statistically significant (p = 0.800).

Additionally, carriers of the A2A2 genotype showed a non-significant trend toward an increased risk of OSCC development (OR = 2.38–2.46). However, more definitive conclusions would require a larger study population.

DISCUSSION

Our results indicate that the TP53 PIN3 16-bp duplication polymorphism does not appear to influence disease risk or progression. No statistically significant associations between TP53 genotypes and clinicopathologic parameters were observed, suggesting that, within this cohort, this polymorphism does not affect clinical outcomes. Previous reports on the prognostic and predictive significance of this polymorphism in head and neck cancers, including OSCC, have reported limited results.

Some studies of breast cancer (5) have noted that patients with the A2A2 genotype were more likely to present with invasive ductal carcinoma histology, larger tumor size (T3), lymph node involvement, and absence of distant metastases compared to carriers of the A1A1/A1A2 genotypes. These authors observed a correlation between the TP53 genotype and histological type of breast cancer but found no correlations with other clinicopathological parameters.

Another study (8) in breast cancer confirmed that variation in the PIN3 16-bp polymorphism was not significantly associated with survival; however, within a subgroup of patients treated with chemotherapy without anthracycline, carriers of the A2A2 genotype exhibited significantly poorer overall survival compared with carriers of other genotypes. Similarly, survival assessment showed no significant association between TP53 polymorphism and overall survival in head and neck cancer patients (9).

The literature on the TP53 PIN3 16-bp polymorphism in cancer progression is inconsistent. In our study, carriers of the A2A2 genotype (homozygous for the 16-bp insertion in intron 3) were more frequent among OSCC patients, but these differences were not statistically significant. Furthermore, no correlation was found between this polymorphism and recurrence or metastasis within the 36-month follow-up period. Investigation of clinicopathological features, including age, tumor location, and histological grade, revealed no significant associations with PIN3 16-bp polymorphism genotypes. Additionally, the PIN3 16-bp polymorphism was not identified as a risk factor for the development of OSCC.

An interesting finding in our study is the association of TP53 PIN3 genotypes with disease stage: carriers of the A2A2 genotype were more frequently in the advanced stages (III and IV). This finding correlates with research on 106 gastric cancer samples (10), which also reported a statistically significant association between the A2A2 genotype and advanced disease stage. Overall, the presence of the A2A2 genotype may indicate a more aggressive biological behavior of malignancy.

Literature data regarding the contribution of TP53 polymorphism (rs17878362) to cancer susceptibility are also inconsistent. A meta-analysis including 25 published studies revealed that individuals homozygous for the duplicated allele (A2A2) exhibited a significantly elevated risk of cancer development compared with A1A1 individuals (11). Furthermore, by cancer site, increased susceptibility among A2A2 individuals was observed for breast and colorectal cancer, but no such association was observed for lung cancer. Some other reports have suggested that carriers of the PIN3 Ins16-bp allele (A2) and the A2A2 genotype are correlated with elevated risk for esophageal and gastric cancer (12).

In contrast, the TP53 PIN3 polymorphism has not been identified as a risk factor for breast cancer in the Azeri population (13), Chinese Han women (14), or the Moroccan population (15). Additionally, no significant correlations have been reported between this polymorphism and prostate cancer (16) or triple-negative breast cancer (17). Some studies have indicated that the A1A1 and A1A2 genotypes of this polymorphism, when combined with the Arg/Pro genotype at codon 72 (exon 4) of TP53, may have a protective role in oral cancer development (18).

These discrepancies among studies may be attributable to several factors, including sample size, inclusion of tumors from different anatomical sites (e.g., oral cavity and oropharynx), and variability in therapeutic approaches (8). Additional contributing factors include regional environmental influences, ethnic differences, and genetic background (5).

Finally, to further validate the prognostic significance of the TP53 PIN3 16-bp polymorphism in OSCC, larger multicenter studies with increased sample sizes and detailed clinical follow-up data are necessary.

CONCLUSION

The TP53 PIN3 16-bp duplication polymorphism does not modulate susceptibility to oral squamous cell carcinoma in the Montenegrin population. This polymorphism does not appear to influence OSCC risk or progression in the studied cohort.

Abbreviations

OSCC - oral squamous cell carcinoma
DFI - disease-free interval

Note: This study is part of the PhD thesis of Marija Antunović (19).

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Note: Artificial intelligence was not utilized as a tool in this study.

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Sažetak

ZNAČAJ PIN3 16-BP POLIMORFIZMA P53 GENA ZA RIZIK I PROGNOZU ORALNOG KARCINOMA

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Uvod: Oralni skvamocelularni karcinom (OSCC) je povezan sa više faktora rizika, uključujući i genetske faktore kao što je PIN3 16-bp polimorfizam p53 gena. Cilj ovog rada je bio da ispita ulogu PIN3 16-bp polimorfizma u nastanku OSCC u populaciji Crne Gore kao i njegov uticaj na prognozu/progresiju OSCC.

Materijal i metode: Istraživanje je obuhvatilo 60 pacijenata sa OSCC i 71 zdravog pojedinca kod kojih je metodom PCR-RFLP ispitivana frekvencija alela i genotipova PIN3 16-bp polimorfizma p53 gena. Analizirane su i kliničko-patološke varijable, a svi pacijenti su praćeni 3 godine.

Rezultati: U trogodišnjem periodu praćenja, 12 pacijenata (20%) je imalo recidiv bolesti, a 6 pacijenata (10%) je razvilo regionalne metastaze, bez udaljenih metastaza. Nije utvrđena povezanost između PIN3 16-bp polimorfizma i starosti pacijenata, lokalizacije tumora, gradusa, recidiva bolesti i metastaza ($p > 0.05$). Utvrđena je statistički značajna povezanost PIN3 16-bp polimorfizma i stadijuma bolesti ($p = 0.006$). Nije utvrđena statistički značajna razlika u dužini vremenskog intervala bez ponovne pojave bolesti kod nosilaca različitih genotipova PIN3 16-bp polimorfizma: A1A1 (28.26 ± 1.70 mjeseci), A1A2 (35.00 ± 0.94 mjeseci) i A2A2 (30.00 ± 5.20 mjeseci) ($p = 0.38$). Takođe, nije bilo statistički značajnih razlika u frekvenciji alela i genotipova PIN3 16-bp polimorfizma između OSCC pacijenata i kontrolne grupe.

Zaključak: PIN3 16-bp polimorfizam p53 gena se ne može smatrati faktorom rizika za nastanak OSCC u populaciji Crne Gore. Takođe, polimorfizam PIN3 16-bp ne utiče na progresiju OSCC u ispitivanoj populaciji.

Ključne reči: TP53, PIN3 16-bp polimorfizam, oralni karcinom.

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ERGONOMIC RISK AND MUSCULOSKELETAL PAIN IN DENTAL PRACTICE

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Abstract: **Objective:** Ergonomics in dental practice plays a crucial role in maintaining professional health, as prolonged static postures and repetitive movements significantly increase the risk of work-related musculoskeletal disorders among dental professionals. Understanding ergonomic risk factors and their impact on musculoskeletal health is essential for identifying vulnerable groups and developing effective preventive strategies in dental practice.

Aim: The aim of this study was to assess the occurrence of musculoskeletal pain as a manifestation of work-related musculoskeletal disorders among dentists and to analyze its association with demographic characteristics, work habits, and dental specialization.

Materials and Methods: This cross-sectional study included 130 dentists from various dental specialties. Data were collected using a structured questionnaire addressing demographic variables, work habits, ergonomic conditions, and the presence of musculoskeletal pain. Descriptive statistical methods were applied, and chi-square tests were used to analyze associations between categorical variables, with statistical significance set at $p < 0.05$.

Results: The results indicated that the majority of participants experienced work-related musculoskeletal disorders, with prevalence increasing with age and length of professional experience. Occupational factors such as prolonged sitting or standing, improper working posture, lack of ergonomic chairs, and insufficient physical activity were significantly associated with the occurrence of work-related musculoskeletal disorders ($p < 0.05$). A statistically significant association was also observed between dental specialty and the presence of work-related musculoskeletal disorders ($\chi^2(9) = 25.83$; $p < 0.01$). The highest prevalence was reported among specialists in prosthodontics, pediatric dentistry, orthodontics, and endodontics, while lower prevalence was observed among oral surgeons, general dental practitioners, and periodontists.

Conclusion: These findings emphasize the importance of implementing ergonomic interventions, regular physical activity, and preventive strategies in dental practice to reduce the occupational risk of work-related musculoskeletal disorders.

Keywords: ergonomics, dentistry, WMSDs, musculoskeletal pain, occupational risk, specialization.

INTRODUCTION

Ergonomics is a multidisciplinary scientific discipline that examines the interaction between humans and their working environment, including tools, equipment, tasks, and organizational systems, with the aim of optimizing performance while reducing physical strain, fatigue, and the risk of injury (1, 2). The term ergonomics originates from the Greek words *ergon* (work) and *nomos* (law or system) and refers to an applied science focused on adapting workplaces, instruments, and working procedures to human physical and cognitive capacities in order to promote comfort, efficiency, safety, and long-term well-being. Proper implementation of ergonomic principles not only enhances productivity but also plays a crucial role in the prevention of occupational injuries and chronic health conditions.

The dental profession is particularly vulnerable to occupational hazards due to prolonged static working postures, repetitive movements, sustained fine motor

activity, and high visual and cognitive demands. These factors significantly increase the risk of developing work-related musculoskeletal disorders (WMSDs), which represent one of the most common occupational health problems among dental professionals. WMSDs are often underreported or underestimated in their early stages, despite their tendency to progress into chronic conditions that negatively affect professional performance, work ability, and quality of life. The most frequently reported WMSDs among dentists include neck and lower back pain, shoulder and trapezius muscle strain, tendinitis, carpal tunnel syndrome, neuralgia, and early degenerative joint changes. In addition to musculoskeletal complaints, dentists may also experience visual strain and hearing-related problems as a result of prolonged exposure to dental equipment and specific environmental conditions (3).

Preventive strategies aimed at reducing the risk of WMSDs include maintaining appropriate working posture, using ergonomically designed dental instruments and equipment, optimizing workplace layout, and incorporating regular physical activity, stretching exercises, and short breaks during the working day (4–7). However, despite growing awareness of ergonomic risks, inadequate implementation of ergonomic principles remains common in daily dental practice.

Ergonomics is traditionally divided into three interrelated domains: physical, cognitive, and organizational ergonomics. Physical ergonomics focuses on anatomical, physiological, and biomechanical characteristics and their relationship to physical work demands. Cognitive ergonomics addresses mental processes such as perception, memory, decision-making, and motor control that influence human–system interaction. Organizational ergonomics aims to optimize sociotechnical systems, including workflow organization, work schedules, communication, and team dynamics, in order to improve efficiency and reduce occupational stress (8).

Dental practice requires sustained physical precision and mental concentration, and prolonged working hours combined with insufficient ergonomic awareness often result in awkward postures, repetitive strain, and cumulative biomechanical loading. The development of WMSDs in dentistry is therefore multifactorial, arising from the interaction of biomechanical, biological, physical, chemical, and psychosocial factors. This complexity highlights the need for a comprehensive and multidisciplinary preventive approach (9, 10, 11). Understanding and systematically applying ergonomic principles in dental practice is essential not only for the prevention of WMSDs but also for preserving long-term occupational health, professional longevity, and the quality of patient care.

Study Objectives

The main objective of this study was to assess the prevalence of work-related musculoskeletal disorders (WMSDs) among dentists and to investigate the factors contributing to their occurrence. Specifically, the study aimed to:

1. Examine the relationship between demographic characteristics (age, gender, professional -experience) and the presence of musculoskeletal pain.

2. Evaluate the association between work habits, including posture, use of ergonomic equipment, and frequency of physical activity, with the prevalence of WMSDs.

3. Analyze the distribution of musculoskeletal pain across different dental specialties and identify those at higher occupational risk.

4. Highlight the importance of ergonomic practices in reducing WMSDs and promoting occupational health in dental practice.

MATERIAL AND METHODS

This cross-sectional study was conducted among practicing dentists to assess the prevalence of work-related musculoskeletal disorders (WMSDs) and their association with demographic characteristics, work habits, and dental specialties. A structured, self-administered questionnaire was used as the primary data collection tool. The survey included sections on demographic information (age, gender, years of professional experience), work-related factors (posture, type of practice, use of ergonomic equipment), physical activity habits, and the occurrence and frequency of musculoskeletal pain. Additionally, participants were asked about their dental specialization to evaluate differences in occupational risk. The questionnaire was pilot-tested prior to the main study by approximately fifteen doctors of dental medicine in order to assess its clarity, relevance, and comprehensibility.

A total of 130 dentists participated in the study. Participation was voluntary, and informed consent was obtained from all respondents prior to completion of the questionnaire. The study was conducted in accordance with ethical guidelines for research involving human participants.

Data were analyzed using descriptive and inferential statistical methods. Continuous variables measured on interval or ratio scales were summarized using means and standard deviations, while categorical variables were presented as frequencies and percentages. **Chi-square (χ^2) tests** were performed to assess associations between categorical variables, including musculoskeletal pain, demographic characteristics, work habits, and specialization. **One-way analysis of var-**

iance (ANOVA) was applied to examine differences in continuous outcomes, such as the average number of musculoskeletal pain episodes, across dental specialties. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS version 26.

RESULTS

Table 2 presents the descriptive indicators of variables measured on an interval/ratio scale. The symbol M denotes the mean value, while SD represents the standard deviation. The results show that, on average, respondents experienced work-related musculoskeletal pain 9.16 times during the past six months. The first occurrence of such pain was reported relatively early, after an average of 1.28 years of work in dental practice.

The level of perceived stress varied depending on the source of stress. The highest level of stress was attributed to work-related factors (M = 6.10), followed by financial factors (M = 4.17), while personal prob-

Table 1. *Descriptive indicators of variables measured on a nominal scale*

Question	Alternative frequency				
	25-35 yrs	**35-45 yrs**	**46-56 yrs**	**56+ yrs**	
1. Age (in years)	81	40	7	2	
	Male	**Female**			
2. Sex	59	71			
	Public	**Private**	**Both**		
3. Type of practice	31	76	23		
	Left	**Right**			
4. Dominant hand	8	122			
	5-10 yrs	**11-20 yrs**	**21-30 yrs**	**31-40 yrs**	
5. How many years have you been in practice?	81	35	12	2	
	Always sitting	**Mostly sitting, sometimes standing**	**Mostly standing, sometimes sitting**	**Always standing**	
6. How do you work in the dental office?	21	60	49	0	
	Yes	**No**			
7. Use of ergonomic chairs	33	97			
	Very good	**Good**	**Average**	**Poor**	
8. How would you rate your posture while performing clinical procedures?	26	48	56		
	Yes	**No**			
9. Do you perform muscle stretches (light exercises) during your workday?	73	57			
	Yes	**No**			
10. Have you attended any continuing education courses or training closely related to ergonomics in the dental profession?	7	123			
	Every day	**5–6 days**	**3-4 days**	**1-2 days**	**Never**
11. How many days per week do you exercise (gym, fitness, aerobics, yoga, Pilates, running, etc.)?	0	6	34	34	56
	Yes	**No**	**Partially**	**I don't exercise**	
12. Do you believe that exercising helps you maintain your work-related physical fitness in dentistry?	73	1	19	37	
	Yes	**No**			
13. Do you experience any work-related musculoskeletal pain?	38	92			
		Work environment	**Existing condition/injury**		
14. What do you consider to be the main cause of your musculoskeletal pain?		128	2		

	Yes	**No**			
15. Have you had to take medication to relieve musculoskeletal pain?	36	94			
	Yes	**No**			
16. Have you ever consulted a physician for work-related musculoskeletal pain?	16	114			
	Yes	**No**			
17. Do you undergo physical therapy related to musculoskeletal pain?	33	97			
	Yes	**No**			
18. Have you tried any alternative methods to manage musculoskeletal pain (e.g., acupuncture, massage)?	56	74			
	Yes	**No**			
19. Do you have any workplace protocols aimed at reducing musculoskeletal disorders?	130	0			
	Yes	**No**	**First dose only**		
20. Have you completed hepatitis B vaccination, including booster doses?	39	43	49		
	Yes	**No**			
21. Do you wear protective glasses/visors while working?	95	35			
	Yes	**No**	**First dose only**		
22. Have you been vaccinated against COVID-19?	83	5	42		
	Yes	**No**			
23. Is adequate protective equipment provided by your employer?	7	123			
	Yes	**No**			
24. Do you have any allergies to substances you are exposed to at work (latex, chemicals, etc.)?	10	120			
	Yes	**No**			
25. Do you have vision problems?	73	57			
	Yes	**No**	**Sometimes**		
26. Do you use dental magnifying loupes while working?	12	96	22		
	Yes	**No**			
27. Are you exposed to X-ray radiation at your workplace (RVG, OPG, 3D CBCT)?	18	112			
	Yes	**No**			
28. If you use X-ray devices, do you monitor the level of radiation your body absorbs (e.g., do you wear dosimeters in the clinic)?		18			
	Yes	**No**	**Partially**		
29. Do you experience any negative effects from working with a polymerization light?	6	62	62		
	Yes	**No**	**Partially**		
30. Does stress from your work environment affect your personal life?	59	9	62		
	Yes	**No**			
31. Have you ever visited a psychologist or psychiatrist due to work-related reasons?	3	127			

Table 2. *Descriptive indicators of variables measured on an interval/ratio scale*

Question	M	SD
1. In the last 6 months, how often have you experienced work-related musculoskeletal pain in dentistry?	9.16	6.16
2. How old were you when you first felt work-related musculoskeletal pain?	1.28	0.45
3. Rate your stress exposure on a scale from 1 to 10: **personal issues**	2.71	1.40
4. Rate your stress exposure on a scale from 1 to 10: **work**	6.10	1.46
5. Rate your stress exposure on a scale from 1 to 10: **finances**	4.17	2.23
6. Do you consider the job of a dentist stressful on a scale 1–10?	6.41	1.12

Table 3. *Correlation of musculoskeletal pain with demographic and occupational characteristics (chi-square tests)*

Question		Do you experience any work-related musculoskeletal pain?		p
		Yes	No	
1. Age (in years)	**25-35 yrs**	4	77	< 0.01
	36-45 yrs	25	15	
	46-56 yrs	7	0	
	56+ yrs	2	0	
5. How many years have you been in practice?	**5-10 yrs**	4	77	< 0.01
	11-20 yrs	20	15	
	21-30 yrs	12	0	
	31-40 yrs	2	0	
6. How do you work in the dental office?	**Always sitting**	2	19	< 0.05
	Mostly sitting, sometimes standing	16	44	
	Mostly standing, sometimes sitting	20	29	
	Always standing	0	0	
7. Use of ergonomic chairs	**Yes**	15	18	< 0.05
	No	23	74	
8. How would you rate your posture while performing clinical procedures?	**Very good**	2	24	< 0.05
	Good	15	33	
	Average	21	35	
	Poor	0	0	
9. Do you perform muscle stretches (light exercises) during your workday?	**Yes**	11	62	< 0.01
	No	27	30	
10. Have you attended any continuing education courses or training closely related to ergonomics in the dental profession?	**Yes**	0	7	> 0.05
	No	38	85	
11. How many days per week do you exercise (gym, fitness, aerobics, yoga, Pilates, running, etc.)?	**Every day**	0	6	< 0.01
	5-6 days	5	29	
	3-4 days	3	31	
	1-2 days	30	26	
	Never	0	0	

lems were rated as the least stressful (M = 2.71). In addition, on a scale from 1 to 10, respondents assessed the dental profession overall as highly stressful, with a mean score of 6.41.

In Table 3, participants' age showed a highly statistically significant association with the presence of musculoskeletal pain ($p < 0.01$). While the majority of respondents in the 25–35 age group reported no such pain, a significantly higher number of participants in older age groups reported musculoskeletal complaints. A particularly pronounced increase in pain prevalence was observed in the 36–45, 46–56, and 56+ age groups, in which almost all respondents reported the presence of pain.

Similarly, length of work experience demonstrated a statistically significant association with the occurrence of musculoskeletal pain ($p < 0.01$). Respondents with shorter work experience (5–10 years) rarely reported pain, whereas the frequency of musculoskeletal complaints increased significantly with a longer duration of professional practice, particularly among those with more than 20 years of work experience.

Working posture in the dental office was also significantly associated with the presence of pain ($p < 0.05$). Respondents who worked predominantly in a standing position with occasional sitting reported musculoskeletal pain more frequently than those who worked mainly in a seated position. None of the respondents worked exclusively in a standing position.

The use of ergonomic chairs showed a statistically significant association with the occurrence of pain ($p < 0.05$). Respondents who did not use ergonomic chairs reported musculoskeletal complaints significantly more often than those who did, suggesting a protective role of ergonomic equipment.

Self-assessment of posture during clinical procedures was also significantly associated with the presence of musculoskeletal pain ($p < 0.05$). Respondents who rated their posture as average or good more frequently reported pain compared to those who rated their posture as very good, among whom the lowest prevalence of pain was observed.

The practice of muscle stretching during the working day demonstrated a highly statistically significant association with the occurrence of musculoskeletal pain ($p < 0.01$). Respondents who did not perform stretching exercises reported pain significantly more often, whereas a lower frequency of pain was observed among those who regularly performed light exercises during work.

In contrast, participation in continuous education or courses in the field of ergonomics did not show a statistically significant association with the occurrence of musculoskeletal pain ($p > 0.05$), which may be attributed to the very small number of respondents who had attended such educational programs.

Table 4. *Frequencies and percentage distribution of different dental specialties in the sample*

Specialty	f	%
General dentistry	40	30.8
Prosthodontics	36	27.7
Endodontics / Restorative dentistry	19	14.6
Pediatric dentistry	11	8,4
Oral surgery	9	6.9
Orthodontics	9	6.9
Periodontics	6	4.6

Table 5. *Differences between dental specialties in the mean frequency of musculoskeletal pain over the past six months (ANOVA)*

Specialty	Average number of musculoskeletal pain episodes in the past 6 months
General dentistry	7.07
Prosthodontics	11.74
Pediatric dentistry	11.33
Endodontics / Restorative dentistry	9.22
Oral surgery	8.00
Orthodontics	11.66
Periodontics	5

Weekly physical activity showed a highly statistically significant association with the occurrence of musculoskeletal pain ($p < 0.01$). Respondents who exercised 1–2 days per week most frequently reported pain, while a substantially lower prevalence of musculoskeletal complaints was observed among those who exercised more frequently or on a daily basis.

Table 5 presents the results of the ANOVA analysis, which indicated a statistically significant difference in the mean frequency of musculoskeletal pain among the observed dental specialties ($p < 0.05$), suggesting that the type of dental practice has a significant impact on the occurrence of musculoskeletal complaints. The highest mean frequency of musculoskeletal pain was observed among respondents working in prosthodontics (M = 11.74), orthodontics (M = 11.66), and pediatric dentistry (M = 11.33). Slightly lower, yet still elevated, values were recorded for endodontics (M = 9.22) and oral surgery (M = 8.00). Conversely, lower mean frequencies of musculoskeletal pain were reported among general dental practitioners (M = 7.07) and periodontists (M = 5.00).

DISCUSSION

This study included 130 dentists employed in private and public dental institutions, with the aim of assessing the prevalence of work-related musculoskeletal disorders, their potential causes, and their association with ergonomic, occupational, and demographic factors. The sample structure showed a predominance of younger working-age individuals, with the majority of participants belonging to the 25–35-year age group, while significantly fewer were represented in older age groups.

Descriptive statistics indicate that musculoskeletal pain appears relatively early in dentists' professional careers, as participants reported experiencing pain for the first time on average after slightly more than one year of practice. At the same time, the average number of musculoskeletal pain sites in the past six months was high, confirming that these complaints are both common and clinically significant among dentists (Table 1). These findings are consistent with previous studies, which suggest that musculoskeletal disorders do not occur exclusively after many years of work experience but can also arise in the early stages of professional development, particularly due to improper posture, repetitive movements, and static load (12–15).

The results of the nominal analysis indicated that the majority of participants work in private practice and predominantly adopt a seated position with occasional standing during work. However, a concerning finding is that most participants do not use ergonomic chairs, despite a large number of them rating their posture during work as average or good (Table 1). This discrepancy between subjective assessment of posture and objective ergonomic conditions is frequently reported in the literature and may indicate insufficient awareness of proper ergonomic principles or adaptation to suboptimal working conditions (16).

Analysis of stress levels revealed that participants perceive the dental profession as highly stressful, with an average stress rating above the midpoint of the scale. Although participants differentiated between sources of stress (personal, professional, and financial), the overall perception of dentistry as a stressful profession further underscores its complexity, where physical strain is often combined with psychological demands, responsibility toward patients, and high expectations regarding precision and quality of work (Table 2) (17–22).

Regarding daily physical activity, a significant portion of participants either do not exercise or exercise very infrequently (e.g., gym training), although the majority recognize the positive impact of physical activity on work-related fitness. A smaller number of participants use pharmacological therapy, consult a physician, or opt for alternative treatment methods, which may indicate a normalization of pain as an "integral part" of the profession. Notably, none of the participants reported the existence of a formal workplace protocol for the prevention of musculoskeletal disorders, despite the recognized need for its implementation (Table 1).

Analysis of the association between musculoskeletal pain and demographic and occupational characteristics showed that both age and length of professional experience were highly statistically significantly associated with the occurrence of pain. In older age groups and among participants with longer professional tenure, the frequency of musculoskeletal complaints was substantially higher, consistent with the cumulative effect of prolonged biomechanical load (Table 3).

In addition to biomechanical factors, dentists are exposed to numerous biological, chemical, physical, and psychogenic risks, including infections, allergies, radiation, noise, artificial lighting, polymerization light, and chronic stress. Although most participants reported adequate vaccination against hepatitis B and COVID-19, as well as the use of basic protective equipment, few had access to complete and adequate protective equipment provided by their institution, further highlighting the need for systemic improvement of working conditions (23).

In this study, more than 75% of participants reported not using magnifying loupes during work. A study conducted in Beijing investigated the impact of using magnifying loupes and microscopes among prosthodontic specialists during tooth preparation for prosthetic procedures, with the aim of analyzing posture and body positioning in the context of ergonomics. The results showed that both tools significantly improved working posture and facilitated the procedure, with the microscope yielding slightly better outcomes compared to the loupe. Although both aids had a positive effect, their contribution from an ergonomic perspective was considered highly significant, emphasizing the potential of such technologies in preventing musculoskeletal disorders among dentists (24, 25).

A one-way analysis of variance revealed statistically significant differences in the frequency of musculoskeletal pain between different dental specialties. The highest frequency was observed among specialists in prosthodontics, pediatric dentistry, orthodontics, and endodontics, whereas lower values were noted among oral surgeons, general dental practitioners, and periodontists. These findings confirm that specialties requiring prolonged static postures, high precision, and repetitive movements are at greater risk of developing musculoskeletal disorders (Tables 4, 5) (26–29).

Data from Croatia provide additional insight into the health status of practicing dentists. The results of a survey conducted among 506 dentists revealed concerning figures: 78.18% of respondents reported pain in the upper back, while 76.97% experienced lower back pain. Skin problems were reported by 29.29% of participants, vision issues by 46.87%, and hearing problems by 19.03%. Neurological disorders were reported by 15.76% of dentists. This study represents the first detailed investigation in Croatia of dentists' health status, with the high prevalence of problems largely associated with limited workplace ergonomics, numerous potential occupational risk factors, and inadequate professional equipment. The findings highlight an urgent need to improve ergonomic standards and provide education on proper posture in dental practice (30, 31, 32).

Although more than half of our participants reported performing muscle stretching exercises during the workday, a very small number had attended continuous training or courses in ergonomics. This finding is particularly significant, as it indicates a systemic lack of formal education despite the high prevalence of musculoskeletal complaints. Similar results have been observed in other studies, demonstrating that informal knowledge and personal experience cannot fully replace structured ergonomics training (31).

In our study, continuous education in ergonomics did not show a statistically significant association with the occurrence of musculoskeletal pain. This finding can be partly explained by the very small number of participants who had the opportunity to attend such training, indicating a systemic lack of formal education in this area. In contrast, physical activity proved to be a significant protective factor: participants who exercised regularly reported a substantially lower frequency of musculoskeletal complaints, supporting previous evidence on the preventive role of movement and targeted exercises in reducing the risk of work-related musculoskeletal disorders (WMSDs).

Particularly interesting data come from the population of dental students. In one survey, knowledge of ergonomics was assessed before and after training. Before the lecture, students demonstrated very limited understanding of basic ergonomic principles, whereas after the training they correctly answered 88% of the questions. These results clearly emphasize the importance of formally integrating ergonomic principles into educational curricula, as proper knowledge of ergonomic standards at an early stage of training can reduce the long-term risk of developing WMSDs (32).

A similar issue was investigated by Muthuraj and colleagues, who conducted an experimental study analyzing the posture of students during supragingival calculus removal using the standard photometric assessment method (SPAM). The study included 90 students, and their posture during the procedure was photographed and subsequently analyzed. The results showed that the majority of students practiced inadequate posture, significantly increasing the risk of developing work-related musculoskeletal disorders. These findings further underscore the importance of practical ergonomics in everyday dental education, as well as the need for continuous monitoring and correction of working habits in the early stages of a professional career (33).

CONCLUSIONS

1. Musculoskeletal pain occurs relatively early in dentists' careers, already after slightly more than one year of professional practice, and is common within the professional population. These findings indicate that such disorders are not solely the result of long-term work experience, but are associated with working posture, repetitive movements, and static load.

2. The majority of participants work primarily in a seated position with occasional standing, yet do not use ergonomic chairs. There is a discrepancy between subjective assessment of posture and actual ergonomic conditions, suggesting insufficient awareness of ergonomic principles and adaptation to suboptimal working conditions.

3. The dental profession is perceived as highly stressful. Physical strain, combined with psychological demands and responsibility toward patients further increases the risk of occupational health issues.

4. Specialties requiring prolonged static postures and precise repetitive movements (prosthodontics, orthodontics, pediatric dentistry, endodontics) exhibit a significantly higher frequency of musculoskeletal pain.

5. Most dentists lack adequate protective equipment and formal WMSD prevention protocols, highlighting the need for institutional improvements and the implementation of standardized preventive measures.

6. Formal education on ergonomics and the use of technologies such as magnifying loupes and microscopes improve posture and reduce the risk of musculoskeletal disorders, emphasizing the importance of integrating ergonomic principles into both educational curricula and clinical practice.

Abbreviations

WMSDs - Work-related musculoskeletal disorders

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Sažetak

ERGONOMSKI RIZIK I MIŠIĆNO-SKELETNI BOL U STOMATOLOŠKOJ PRAKSI

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Uvod: Ergonomija u stomatološkoj praksi ima ključnu ulogu u očuvanju profesionalnog zdravlja, jer produženi statički položaji i ponavljajući pokreti značajno povećavaju rizik od profesionalnih mišićno-skeletnih oboljenja kod stomatoloških radnika. Razumevanje ergonomskih faktora rizika i njihovog uticaja na mišićno-skeletno zdravlje od suštinskog je značaja za identifikaciju rizičnih grupa i razvoj efikasnih preventivnih strategija u stomatološkoj praksi.

Cilj: Cilj ove studije bio je proceniti učestalost mišićno-skeletnog bola kao manifestacije profesionalnih mišićno-skeletnih oboljenja kod stomatologa te analizirati njegovu povezanost sa demografskim karakteristikama, radnim navikama i stomatološkom specijalizacijom.

Materijal i metode: Ova studija preseka obuhvatila je 130 stomatologa različitih specijalnosti. Podaci su prikupljeni putem strukturiranog upitnika koji je obuhvatio demografske varijable, radne navike, ergonomijske uslove i prisustvo mišićno-skeletnog bola. Primenjene su deskriptivne statističke metode, a hi-kvadrat test korišten je za analizu povezanosti između kategorijskih varijabli, uz nivo statističke značajnosti $p < 0,05$.

Rezultati: Rezultati su pokazali da je većina ispitanika imala profesionalna mišićno-skeletna oboljenja, pri čemu je prevalencija rasla sa starošću i dužinom radnog staža. Profesionalni faktori poput produženog sedenja ili stajanja, nepravilnog radnog položaja, nedostatka ergonomskih stolica i nedovoljne fizičke aktivnosti bili su značajno povezani s pojavom profesionalnih mišićno-skeletnih oboljenja ($p < 0,05$). Takođe je uočena statistički značajna povezanost između stomatološke specijalizacije i prisustva profesionalnih mišićno-skeletnih oboljenja ($\chi^2(9) = 25,83$; $p < 0,01$). Najveća prevalence zabeležena je kod specijalista protetike, dečije stomatologije, ortodoncije i endodoncije, dok je niža prevalence uočena kod oralnih hirurga, doktora opšte stomatologije i parodontologa.

Zaključak: Ovi nalazi naglašavaju značaj implementacije ergonomskih intervencija, redovne fizičke aktivnosti i preventivnih strategija u stomatološkoj praksi radi smanjenja profesionalnog rizika od mišićno-skeletnih oboljenja.

Ključne reči: ergonomija, stomatologija, WMSDs, mišićno-skeletni bol, profesionalni rizik, specijalizacija.

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Case report

SURGICAL TREATMENT OF PEDIATRIC SUBPERIOSTEAL ABSCESS SECONDARY TO ACUTE BACTERIAL RHINOSINUSITIS - A CASE REPORT

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Abstract: **Introduction:** Rhinosinusitis, an inflammation of the mucosal lining of the nasal cavity and paranasal sinuses, can be classified by the European Rhinologic Society as acute or chronic, based on the duration of symptoms and signs. Acute bacterial rhinosinusitis (ABRS), caused by bacterial invasion of the nasal and paranasal sinus mucosa, may lead to severe complications if untreated. Among these, orbital complications are the most common, including pre-septal cellulitis, orbital cellulitis, subperiosteal abscess (SPA), orbital abscess, and cavernous sinus thrombophlebitis. They can be associated with visual impairment and intracranial extension. SPA is a rare but serious complication in children. It arises from infection spreading to the subperiosteal space, often following ABRS involving the ethmoid sinuses, due to developmental, anatomical, and immunological factors. Early diagnosis and intervention are critical to prevent long-term sequelae.

Case presentation: A 14-year-old boy presented with complications of ABRS, including progressive right eyelid swelling and impaired ocular mobility. Imaging revealed complete opacification of the right ethmoid and maxillary sinuses with bony erosion of the ethmoidal bony septa and lamina papyracea, but without signs of intracranial extension. Laboratory findings showed elevated white blood cell count, elevated C-reactive protein (CRP), and prior exposure to cytomegalovirus and Epstein-Barr virus, with immunoglobulin G (IgG) levels > 500.00 IU/mL. Despite initial antibiotic therapy with amoxicillin-clavulanic acid and metronidazole, clinical deterioration required a change in antimicrobial therapy and surgical intervention. Endoscopic sinus surgery (ESS) was performed, successfully evacuating the purulent collection within the SPA, as well as from the ethmoid and maxillary sinuses. Postoperatively, a combination of broad-spectrum intravenous antibiotics, including vancomycin, meropenem, and clindamycin, guided by bacteriological analysis of the pus sample, was administered to target potentially resistant microorganisms, resulting in near-complete resolution of symptoms.

Conclusion: SPA, especially in the pediatric population, requires prompt and aggressive treatment to prevent life-threatening complications. Initial therapy includes intravenous antibiotics, but surgical drainage becomes essential if there is no improvement within 48 hours or if there is impending visual loss. ESS is a safe, minimally invasive technique for managing SPA unresponsive to conservative treatment. Early surgical intervention should be further explored to optimize outcomes and minimize morbidity in pediatric cases.

Keywords: Abscess, Anti-Bacterial Agents, Child, Ethmoid Sinus, Nasal Surgical Procedures, Rhinosinusitis.

INTRODUCTION

According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020, rhinosinusitis—an inflammation of the mucosal lining of the nasal cavity and paranasal sinuses—is classified by symptom duration into acute (<12 weeks) and chronic (>12 weeks). Acute rhinosinusitis is most of-

Table 1. *Chandler's classification of orbital complications of ABRS*

Chandler's classification system	
Group I **Pre-septal orbital cellulitis**	Inflammation and edema anterior to the orbital septum
Group II **Post-septal orbital cellulitis**	Extension of the inflammation and edema beyond the orbital septum
Group III **Subperiosteal abscess**	Abscess between the peri-orbit and the bony wall of the orbit
Group IV **Intra-orbital abscess**	Purulent collection occurs within the orbit
Group V **Cavernous sinus thrombophlebitis**	Cavernous sinus thrombosis posterior extension through the superior ophthalmic veins

ten viral but may progress to acute bacterial rhinosinusitis (ABRS), with secondary bacterial infection of the nasal and paranasal sinus mucosa. While antibiotics have reduced complications, untreated ABRS can lead to severe osseous, orbital, intracranial, or systemic complications. Orbital complications are the most common, including pre-septal or periorbital cellulitis, orbital cellulitis, subperiosteal abscess (SPA), orbital abscess, and cavernous sinus thrombophlebitis, potentially resulting in visual impairment, optic neuritis, and Brown syndrome (1, 2).

During the 1970s, Chandler et al. (3) introduced a classification scheme for orbital complications that remains widely used today. As presented in Table 1 and Figure 1, Group 3 refers to a subperiosteal abscess (SPA), characterized by the accumulation of pus between the periosteum of the orbital wall and the bony wall separating the ethmoid sinus from the orbit.

A subperiosteal abscess (SPA) is a rare but potentially serious complication of pediatric rhinosinusitis, characterized by the accumulation of purulent material between the periorbita and the underlying ethmoid bone, often resulting from the spread of infection from adjacent structures such as the paranasal sinuses, most commonly through the lamina papyracea. While subperiosteal abscesses can occur in any age group, they are most commonly seen in children and adolescents due to anatomical and immunological factors that increase susceptibility to sinus infections and their complications. In the pediatric population, the ethmoid sinuses, which are the first to pneumatize, are particularly vulnerable to infections that may spread to the orbit. The proximity of the orbit to the paranasal sinuses and the thinner bony structures in children contribute to this increased risk of developing subperiosteal abscesses (3, 4). The immune system is often highly reactive during rapid pubertal development, and the emissary veins connecting the mucosa of the paranasal sinuses, bony compartments, and orbit lack valves,

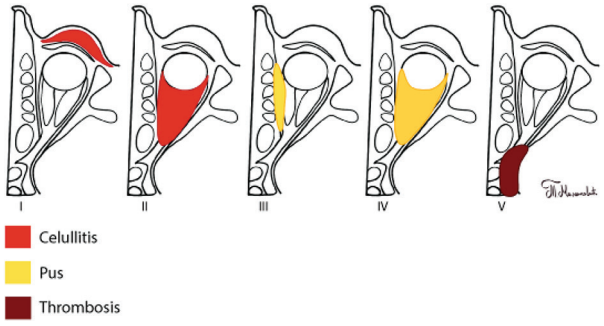

Figure 1. *Chandler's classification for orbital complications of ABRS includes pre-septal orbital cellulitis (I), post-septal orbital cellulitis (II), subperiosteal abscess (III), intraorbital abscess (IV), and cavernous sinus thrombophlebitis (V). Tijana Milenković created this illustration. (The image is from author's archive.)*

allowing retrograde thrombophlebitis and facilitating the spread of infection between these regions (3, 4).

The clinical presentation of subperiosteal abscess in children typically includes fever, rapid-onset unilateral periorbital edema, severe erythema, chemosis (conjunctival swelling), proptosis (bulging of the eye), and restricted ocular movement. Patients often appear toxic, with high fever, severe pain on eye movement, and potentially decreased vision (5). However, symptoms may vary in severity depending on the extent and progression of infection. Early diagnosis and prompt treatment are crucial to prevent complications that may lead to permanent vision loss and intracranial extension (5).

By understanding the complexities and nuances of subperiosteal abscesses in children, healthcare providers can optimize patient outcomes and reduce the risk of long-term complications. Through a thorough review of the available literature and recent advancements in the field, this paper aims to contribute to the ongoing discussion on best practices for diagnosing

and managing this potentially life-threatening condition in pediatric patients.

CASE PRESENTATION

A 14-year-old male with no significant medical history was transferred on April 15, 2024, to a tertiary care center from a secondary care facility due to clinical deterioration during hospitalization for rhinosinusitis. Several days before initial admission, the patient developed nasal congestion, impaired nasal breathing, and high fever, with temperatures reaching 39 °C. Treatment with azithromycin (0.5 g for three days), along with a topical decongestant (xylometazoline 0.05%), was prescribed in primary care. As symptoms did not resolve and the condition worsened, the patient bypassed secondary care and was referred directly to tertiary pediatric care.

Following admission to the pediatric hospital, he developed progressive swelling of the right upper and lower eyelids, accompanied by restricted ocular mobility. The patient received intravenous antibiotic therapy with metronidazole (0.5 g, three times daily) and amoxicillin-clavulanic acid (1.2 g, three times daily). However, the response to therapy was insufficient, and the patient was transferred to our institution.

Investigations and imaging

Upon evaluation in our emergency department on April 22, a routine otorhinolaryngological examination revealed warm edema and hyperemia of the right upper eyelid. Anterior rhinoscopy and rigid endoscopic examination (Karl Storz endoscope, 0°) detected thick purulent discharge in the right nasal cavity, particularly in the middle nasal meatus, also observed draining into the oropharynx.

Urgent contrast-enhanced multi-slice computed tomography (MSCT) of the paranasal sinuses revealed a localized, encapsulated lesion involving the right middle nasal meatus, right ethmoid cells (anterior and posterior), the entire right maxillary sinus, and the medial orbit, located between the periorbita, lamina papyracea, and the remaining bony wall of the ethmoid sinus (Figures 2, 3, 4). The right frontal recess and sinus showed soft-tissue opacification. The lesion demonstrated erosion of the bony structures of the medial orbital wall. No abnormalities of the skull base were observed, and there was no evidence of intracranial extension (Figures 2, 3, 4).

Ophthalmological examination showed no impairment of visual acuity or color vision; however, diplopia was present, along with reduced and painful ocular mobility. Neck ultrasound identified enlarged reactive lymph nodes bilaterally, predominantly on the right side along the major vascular axis.

Given the clinical presentation and radiological findings, the patient was admitted to our Department of Otorhinolaryngology on April 23, 2024, for further management. Although the illness initially presented as an upper respiratory tract infection, it rapidly progressed, prompting further laboratory evaluation. Results showed leukocytosis (14.21×10^9/L) and elevated C-reactive protein (CRP) levels (95 mg/L).

In consultation with an infectious disease specialist, serological testing for cytomegalovirus and Epstein-Barr virus was performed, both showing positive IgG antibodies (> 500.00 IU/mL; reference positivity > 1 IU/mL), consistent with past exposure.

Given the patient's age and lack of response to initial therapy, empirical parenteral antibiotic treatment was initiated preoperatively as recommended by the infectious disease specialist: vancomycin (1 g/12 h),

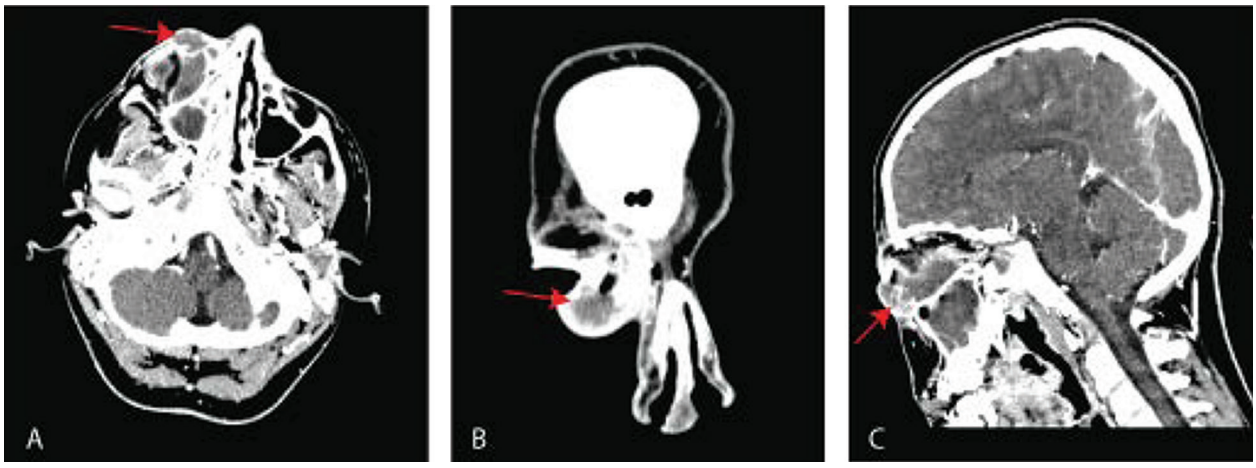

Figure 2. *MSCT of the paranasal sinuses with contrast injection in axial (A), coronal (B), and sagittal (C) planes shows an opacification of anterior and posterior ethmoid cells, right maxillary sinus, medial orbital wall, and right frontal recess (red arrow). (The image is from author's archive.)*

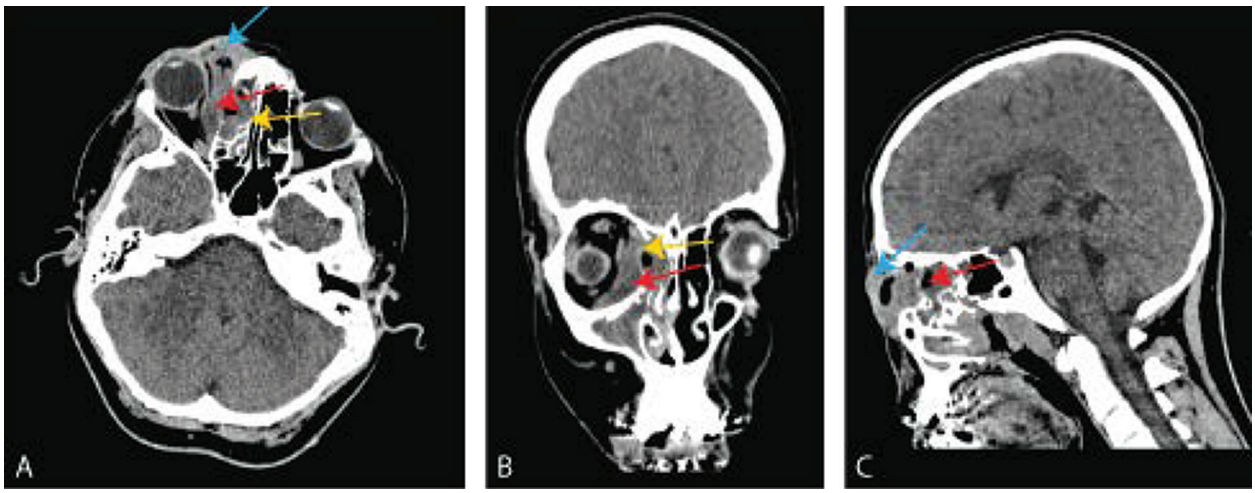

Figure 3. *Axial (A) and sagittal (C) planes reveal eyelid edema and cellulitis (blue arrow). Axial (A) also shows soft tissue opacification in the ethmoid sinuses, suggesting inflammation or infection (yellow arrow). Coronal (B) highlights partial dehiscence of the medial orbital wall with pus accumulation in the medial part of the right orbit (yellow arrow). (The image is from author's archive.)*

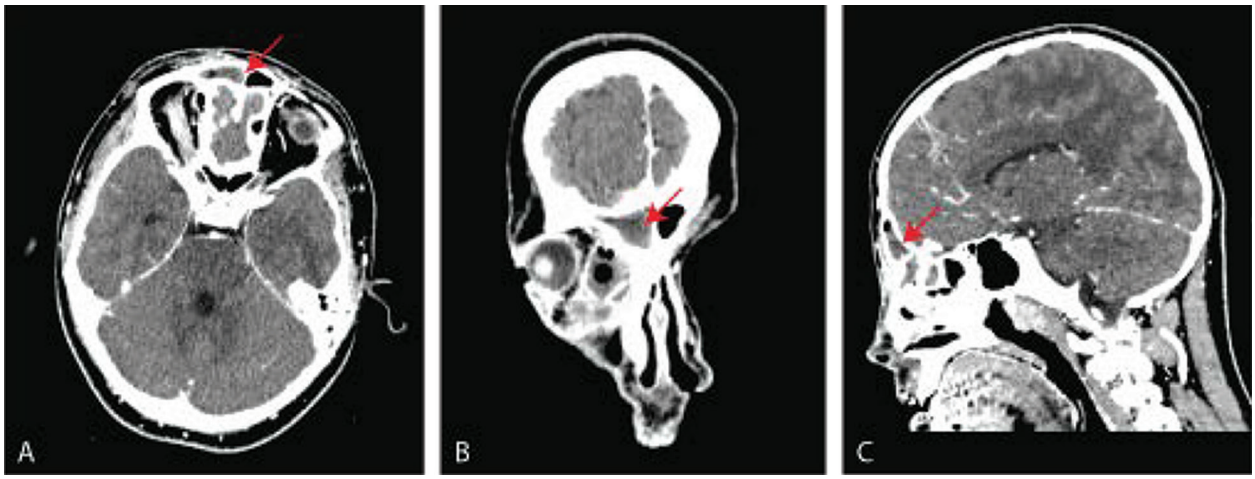

Figure 4. *MSCT of the paranasal sinuses, evaluated in axial (A), coronal (B), and sagittal (C) planes, demonstrates opacification of the right frontal sinus shown by the arrow. (The image is from author's archive.)*

meropenem (1 g/8 h), and clindamycin (600 mg/8 h). Adjunct therapy included xylometazoline nasal drops (0.1%, three times daily in both nostrils) and mometasone furoate nasal spray (50 µg, two puffs in both nostrils, twice daily).

Blood cultures were obtained due to concern for systemic involvement and clinical deterioration, and all results were negative. Procalcitonin levels were elevated (35 ng/mL), while D-dimer was also elevated (5 ng/mL). B-scan ultrasonography of the right eye revealed an abscess measuring 22.98 mm in diameter.

Given diplopia, restricted ocular movement, and imaging-confirmed abscess formation, the patient was urgently scheduled for endoscopic surgical treatment.

Surgical treatment

On April 24, under general anesthesia, following adequate visualization and mucosal decongestion, a septoplasty was performed to optimize the surgical corridor for endoscopic access. Under endoscopic guidance, an uncinectomy was initially performed, resulting in the release of thick, yellow, trapped secretions from the right maxillary sinus. Similar purulent material was observed upon opening the anterior and posterior ethmoid cells and accessing the frontal recess. Exploration of the medial orbital wall revealed a complete absence of the lamina papyracea. A fluctuating abscess was identified, and an incision of the periorbita was made, yielding purulent content consistent with that obtained during the uncinectomy. Swabs for aerobic and anaerobic bacteria cultures were collected.

Postoperative care

Bacterial culture showed growth of *Haemophilus influenzae*, *Staphylococcus aureus*, and anaerobic *Fusobacterium necrophorum*. Following surgical

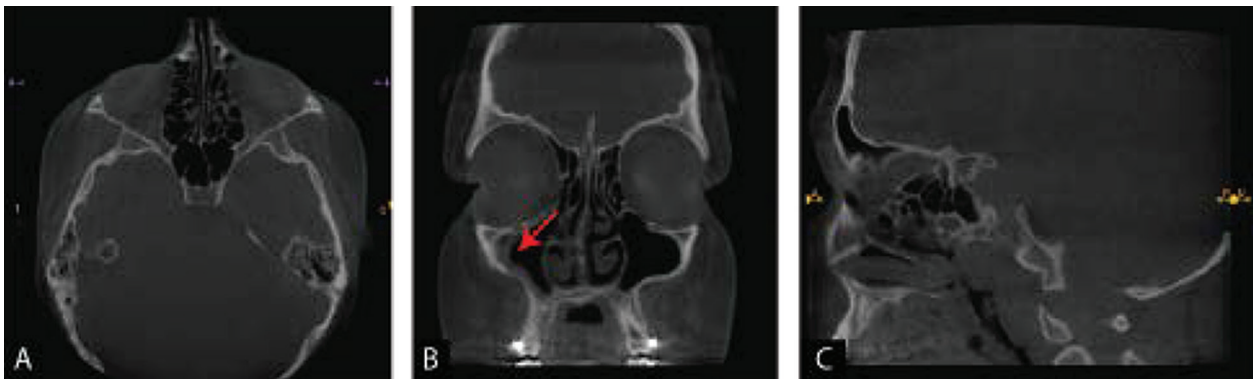

Figure 5. *Postoperative CBCT of the paranasal sinuses, evaluated in axial (A), coronal (B), and sagittal (C) planes, demonstrates relatively normal postoperative anatomy (A, C). Note a focal soft tissue thickening within the right maxillary sinus, as indicated by the arrow (B). (The image is from author's archive.)*

drainage, the patient was treated with the previously noted parenteral antibiotic therapy (vancomycin, meropenem, clindamycin) for 7 days in consultation with the specialist of infectious diseases, and supportive management (intranasal decongestant drops, mometasone-furoate nasal spray). The patient demonstrated consistent daily improvement, both clinically and in laboratory parameters. Postoperatively, a follow-up B-scan ultrasonography of the eye was performed, which showed an intact ocular bulb with no signs of abscess formation. At the time of discharge, laboratory results were within normal reference ranges, and the patient was afebrile. The patient was discharged from the clinic in good general condition, with the recommendation to take cefuroxime tablets 500 mg, two times daily, and metronidazole tablets 400 mg, three times daily, for another 5 days.

Outpatient follow-up

Upon discharge, the patient experienced an uneventful recovery, reporting no complaints during regular monthly follow-ups. Clinical examinations consistently revealed normal findings. A cone beam computed tomography (CBCT) scan performed six months postoperatively confirmed the expected postoperative status, with mild mucosal thickening in the right maxillary sinus but no evidence of the prior condition (Figure 5).

DISCUSSION

Although rare, SPA is a serious condition due to its potential for severe ophthalmologic and neurologic complications. Despite its rarity, SPA is clinically significant, as it is both preventable and treatable when promptly addressed.

A notable feature in our patient was the lack of clinical improvement despite early antibiotic therapy. An increased titer of IgG antibodies to cytomegalovirus and Epstein–Barr virus indicates that the immune status of the patient was probably previously impaired by these viruses, which may have contributed to a weak response to the initial antibiotic therapy. To that, it should be added that the level of resistance of bacterial strains to azithromycin, especially in the post-COVID era, is very high. The diagnosis of ABRS and subsequent SPA was established based on a combination of clinical findings and confirmed through CT imaging. We agree with Deutsch et al. (6) that diagnosing SPA solely based on clinical presentation is challenging, especially in pediatric patients, where signs of deterioration may not become evident until considerable damage has already occurred. CT scans, with approximately 80% accuracy in detecting SPA, remain the gold standard for visualizing bony structures (7, 8). Magnetic resonance imaging (MRI) serves as a valuable adjunct by offering superior soft tissue detail and early detection of intracranial complications, although CT remains the preferred initial modality due to its widespread availability.

We anticipated certain bacterial pathogens from the intraoperative swab, as described in a narrative review of the literature by Werner et al. (9), which identified *Streptococcus anginosus*, *Staphylococcus aureus*, and group A Streptococcus as the most commonly isolated microorganisms, with methicillin-resistant *Staphylococcus aureus* (MRSA) reported in 9% of cases by Burek et al. (10). These studies emphasize the importance of anaerobic microorganisms in the pathogenesis of orbital complications. Despite their relatively frequent occurrence, anaerobes are often not detected due to inadequate sampling of purulent content; they die upon exposure to oxygen and therefore cannot be demonstrated. Consequently, we continued broad-spectrum antibiotic therapy without modification, given the patient's progressive clinical and laboratory improvement, especially after a prior clinical decline observed during treatment with intra-

venous metronidazole and amoxicillin-clavulanic acid in the initial phase of hospitalization. The pathogenesis of SPA involves bacterial spread through valveless venous plexuses, direct extension via neurovascular foramina, or dehiscent orbital walls (11, 12). In our case, *Fusobacterium necrophorum* was also isolated among the bacteria, which is now considered one of the important pathogens in orbital complications of ABRS (13). Previously, anaerobic microorganisms were rarely reported as causes of these complications. This is less the case today, due to improved sampling of purulent material from the paranasal sinuses and orbital abscesses. It is essential to immediately place the swab in transport medium to avoid exposure to oxygen, which can lead to loss of anaerobic viability (13).

As McDermott et al. (14) note, the management of orbital complications of ABRS is heterogeneous, with no definitive surgical indications for early-stage disease, except in rare cases where vision is at risk, while SPA, orbital abscess, and intracranial extension are well-established indications for surgery. We argue that early surgical drainage not only allows for abscess culture but also aids in identifying the causative microorganism, facilitating targeted antimicrobial therapy. In addition, ensuring ventilation of the pneumatic spaces enables the eradication of anaerobes by exposure to oxygen. This strategy supports judicious and effective antibiotic use, optimizing treatment outcomes by tailoring therapy to the specific infection. While external surgical approaches have traditionally been favored, endoscopic sinus surgery (ESS) has emerged as a less invasive and highly effective alternative (13, 14, 15). Authors from Graz University Hospital (15, 16) demonstrated the success of ESS in managing ABRS with orbital complications, particularly for abscesses located medially or inferomedially. In our case, since the abscess was located inferomedially, ESS was performed to remove edematous and inflamed mucosa, open the sinus drainage pathways, and facilitate effective evacuation of purulent content. ESS provides substantial benefits, including avoidance of facial scarring, effective abscess drainage, and restoration of sinus ventilation, thereby reducing the risk of recurrence (15, 16). Our case underscores the importance of early recognition, appropriate imaging, and a combined medical–surgical approach in managing SPA, ensuring optimal outcomes while minimizing complications.

The study by Santos et al. (17) shows that most patients with SPA can improve with careful monitoring and conservative treatment. Neurological symptoms, the patient's overall clinical condition, the degree of proptosis, pain or limitation of eye movements, and worsening laboratory findings are key factors in assessing the need for surgical intervention. Similarly, Tzelnick et al. (18) point out that children who do not respond to conservative treatment or who present with established abscess formation often require surgery. In recurrent cases where the cause is not clear, elective surgery or prophylactic antibiotics should be considered. These studies highlight the need for tailored treatment plans and close monitoring to achieve the best outcomes. We agree with the literature, including Cantone et al. (19), that worsening symptoms within 48 hours despite appropriate antibiotics is a clear indication for surgical intervention in children with orbital complications.

CONCLUSION

Prompt and effective treatment is critical to prevent complications. While intravenous antibiotics are typically the first line of management, surgical drainage of the orbit and affected sinuses becomes essential if there is no significant improvement in the patient's overall condition. For medial or medial-inferior abscesses, timely surgical intervention often yields favorable outcomes. ESS offers a safe and effective, minimally invasive approach for managing SPA. We should bear in mind that anaerobes are an important factor in the development of these complications. Therefore, it is important to collect pus samples appropriately. Further research is needed to evaluate the potential benefits of earlier surgical intervention using ESS to improve outcomes in this complex condition.

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Consent for Publication: The patient gave written consent for the publication of his case and images.

Note: Artificial intelligence was not used in this study.

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Sažetak

HIRURŠKO LEČENJE DEČJEG SUBPERIOSTALNOG APSCESA KAO KOMPLIKACIJE AKUTNOG BAKTERIJSKOG RINOSINUZITISA – PRIKAZ SLUČAJA

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Uvod: Rinosinuzitis, zapaljenje sluznice nosa i paranazalnih sinusa, klasifikuje se, prema smernicama Evropskog rinološkog udruženja, na akutni i hronični, prema dužini trajanja simptoma i znakova. Akutni bakterijski rinosinuzitis (ABRS), izazvan bakterijskom infekcijom sluznice nosa i paranazalnih sinusa može dovesti do ozbiljnih komplikacija ukoliko se ne leči adekvatno. Među njima, orbitalne komplikacije, poput preseptalnog i orbitalnog celulitisa, subperiostalnog apscesa (SPA), orbitalnog apscesa i tromboflebitisa kavernoznog sinusa, predstavljaju najčešće izazove, često povezane sa gubitkom vida ili intrakranijalnom propagacijom. SPA, iako retka, ozbiljna je komplikacija kod dece, koja se javlja usled širenja infekcije u subperiostalni prostor, obično zahvatajući etmoidalne sinuse, usled specifičnih anatomskih i imunoloških razloga. Pravovremena dijagnoza i intervencija ključni su za sprečavanje dugoročnih posledica.

Prikaz slučaja: Prikazujemo slučaj četrnaestogodišnjeg dečaka sa komplikacijama ABRS, uključujući progresivno oticanje desnog kapka i ograničenu pokretljivost oka. Radiološka dijagnostika je pokazala prisustvo SPA, neposredno u regiji desnog etmoidalnog sinusa, uz kompletnu zasenčenost desnog etmoidalnog i maksilarnog sinusa, razaranje koštanih gredica ćelija etmoidalnog labirinta i lamine papiracee, ali bez endokranijalne propagacije procesa. Laboratorijski nalazi su ukazali na povećan broj leukocita, povišen C-reaktivni protein (CRP), kao i prethodnu izloženost citomegalovirusu i Epstein-Barr virusu sa izmerenim vrednostima imunoglobulina G višim od 500,00 IU/mL. Pogoršanje opšteg stanja pacijenta, uprkos inicijalnoj antibiotskoj terapiji, koja se sastojala od amoksicilina sa klavulonskom kiselinom i metronidazola, sugerisalo je promenu antibiotske terapije i hiruršku intervenciju. Endoskopska hirurgija sinusa (EHS) uspešno je uklonila gnojni sadržaj iz SPA, kao i iz etmoidnog i maksilarnog sinusa. Postoperativno je primenjena kombinacija intravenskih antibiotika širokog spektra, uključujući vankomicin, meropenem i klindamicin, kako bi se delovalo na potencijalno rezistentne mikroorganizme. To je rezultiralo gotovo potpunom rezolucijom simptoma.

Zaključak: SPA, naročito u pedijatrijskoj populaciji, zahteva hitnu i opsežnu terapiju kako bi se izbegle komplikacije opasne po život. Inicijalna terapija uključuje intravenske antibiotike, dok hirurška drenaža postaje neophodna u slučaju odsustva poboljšanja u roku od 48 sati ili ukoliko postoji rizik od gubitka vida. EHS predstavlja bezbednu i minimalno invazivnu metodu za lečenje SPA. Dalja istraživanja su potrebna za procenu prednosti rane hirurške intervencije, s ciljem optimizacije ishoda i smanjenja morbiditeta u pedijatrijskoj populaciji.

Ključne reči: Apsces, Antibakterijski agensi, Dete, Etmoidni sinus, Hirurške procedure u nosu, Rinosinuzitis.

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Review article

POST-LAPAROSCOPIC SHOULDER PAIN: A NARRATIVE REVIEW OF A FREQUENT POSTOPERATIVE SEQUELA

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Abstract: While the adoption of laparoscopic surgery has enhanced patient safety, comfort and satisfaction, a considerable number of patients experience post-laparoscopic shoulder pain (PLSP), which can slow down recovery. The literature in English language was reviewed after searching major academic databases and engines, including PubMed, Google Scholar, ResearchGate, and Web of Science to summarize the current understanding of the etiopathogenesis, associated risk factors, and management strategies for post-laparoscopic shoulder pain. The precise etiology remains undefined, and several theories have been proposed to account for PLSP. The most accepted theory suggests that PLSP is a form of referred pain caused by irritation of the diaphragm due to stretching from the pneumoperitoneum or the presence of residual gases and fluids. Currently, there are no universally accepted protocols for either the prevention or treatment of PLSP; consequently, a wide range of modalities are applied based on the surgeon's expertise and preference. There is a clear need to improve awareness of this condition to enable the standardization of management options, thus optimizing patient benefits.

Keywords*:* laparoscopic surgery, shoulder pain, referred pain, pneumoperitoneum, carbon dioxide, diaphragm, Phrenic nerve.

INTRODUCTION

The widespread integration of the minimally invasive laparoscopic techniques has transformed surgical practice in recent decades. This approach offers distinct advantages such as reduced blood loss, quicker recovery, shorter hospital stays, fewer complications, reduced risk of intestinal adhesions, and faster return to daily activities. Nevertheless, this approach has introduced a unique spectrum of complications (1).

Post-laparoscopic shoulder pain (PLSP) represents a frequent, yet often underappreciated, adverse outcome of laparoscopic abdominal operations (2). This is shoulder pain that typically manifests within hours of a laparoscopic procedure. It is classically defined as a referred pain phenomenon, wherein the perceived pain location differs from the actual site of the noxious stimulus. Although PLSP is typically self-limiting, it can significantly impair a patient's immediate postoperative quality of life (3, 4).

This narrative review critically examines the etiopathogenesis, identifies the established risk factors, and outlines the management strategies for PLSP, intending to offer a thorough overview for both clinicians and researchers.

MATERIAL AND METHODS

A comprehensive review of the available literature was conducted via electronic searches of PubMed, Google Scholar, ResearchGate, and Web of Science. The search employed Medical Subject Headings (MeSH) and keywords, including "Laparoscopic Surgery," "Shoulder Pain," "Referred Pain," and "Pneumoperitoneum". No restrictions were placed on the date of publication.

Inclusion criteria were restricted to articles published in peer-reviewed English-language journals, with publications in other languages being excluded. The search was performed in September 2025, and the methodology involved scrutinizing the titles, abstracts, and full texts of the identified articles. A total of 62 articles were selected and utilized as references for developing this narrative review.

Since this review relies exclusively on previously published data and involves no new experimentation on human or animal subjects, institutional ethical committee approval was not required.

Etiopathogenesis of PLSP

While various theories have been proposed (Table 1), the precise etiology of PLSP remains unclear. The key mechanisms that have been suggested include:

i. Referred pain

The phrenic nerve originates in the neck from the anterior branches of cervical spinal nerves C3-C5 (primarily C4) and descends to innervate the diaphragm. The supraclavicular nerve, a cutaneous branch of the cervical plexus, also arises from C3-C4 and provides sensation to the skin over the upper chest, neck, and shoulder.

During laparoscopic surgical operations, the abdomen is inflated with carbon dioxide (CO_2) gas to create an operative pneumoperitoneum. This gas gets converted to carbonic acid on the moist surfaces of the peritoneum and diaphragm, due to the action of carbonic anhydrase, resulting in reduction of peritoneal pH value. This acidic environment leads to diaphragmatic irritation. Due to the shared nerve pathways (C3-C4), the brain misinterprets the signal from diaphragm as pain perceived in the shoulder area, a phenomenon termed "referred pain" (5, 6).

ii. Residual gas and fluids

At the conclusion of the laparoscopic operation, CO□ gas is vented out before the port site closure, but some residual gas often persists. Similarly, blood clots or excess fluids may become sequestered under the diaphragm. These residual pockets of gas and fluids are believed to induce diaphragmatic irritation andthereby initiate PLSP.

Jackson et al. (7) conducted a prospective study on 20 patients undergoing laparoscopic gynaecological operations. Postoperative erect chest X-rays were performed at discharge to estimate the volume of trapped CO_2 bubbles beneath each hemidiaphragm. Telephonic interviews revealed a statistically significant correlation between the volume of residual gas bubbles on the right side and the reported pain score. Consistent with this study, Song et al. (8) evaluated 203 patients undergoing laparoscopy for benign gynaecological conditions and concluded that the volume of residual pneumoperitoneum, visible on 24-hour postoperative chest X-ray, was positively correlated with the intensity of PLSP.

iii. Tissue trauma

The passive stretch imposed by the pneumoperitoneum may cause traction on visceral ligaments, microvascular rupture in the peritoneum, nerve traction/neuropraxia, and the local release of inflammatory mediators that heighten pain sensitization (9). Specifically, Dixon et al. (10) attributed PLSP to mechanical trauma to the diaphragmatic crura during bariatric surgical procedures.

iv. Surgical Position

The positioning of the patient during surgery may contribute to PLSP by inducing strain on the shoulder muscles. Fujimoto et al. (11) investigated the correlation between the operative side and PLSP and concluded that left-sided surgery, performed in the lateral recumbent position for urologic laparoscopy, was associated with a higher incidence of PLSP. Additionally, Kojima et al. (12) suggested that arm abduction during gynaecological laparoscopy could be a contributing factor to PLSP.

v. Drains

The presence of a subdiaphragmatic drain may potentially irritate the phrenic nerve, triggering shoulder pain. Suzuki et al. (13) observed that symptoms improving in a sitting or standing position, which allows the drain to fall away from the diaphragm due to gravity, suggest a subphrenic drain as the cause of PLSP.

Pain Characteristics

The characteristics of PLSP (Table 1), as mentioned below, are influenced by factors such as the amount and pressure of CO_2 used, the nature and du-

Table 1. *Etiopathogenesis, clinical characteristics, and risk factors of post-laparoscopy shoulder pain*

Etiopathogenesis	Clinical characteristics	Risk factors
Referred pain due to phrenic nerve irritation	Sharp, dull, or throbbing shoulder-tip discomfort	Female sex
Residual intraperitoneal gas and fluids	Unilateral or bilateral shoulder involvement	Low body mass index
Tissue trauma	Mild to moderate intensity	Trendelenburg positioning
Surgical positioning	Onset within 24 h; peak at 12–24 h	Higher insufflation pressure
Use of intra-abdominal drains	Resolves within 2–3 days	
	Often less responsive to conventional analgesics	

Abbreviations: h-hours.

ration of the surgery, and the significant subjective patient variability (14).

Character: The pain is commonly described as a sharp, dull, or throbbing discomfort (14, 15).

i. Location: Patients typically localize the discomfort to the "shoulder-tip," meaning the superior aspect of the shoulder. PLSP may manifest unilaterally (right or left) or bilaterally, but right-sided pain is frequently reported, especially following gynaecological surgery. In a series of 97 patients undergoing various laparoscopic procedures for benign disorders, 58.7% felt PLSP on the right side (9), whereas Dixon et al. (10) found that PLSP following laparoscopic adjustable gastric band (LAGB) placement predominantly affected the left side.

ii. Intensity: PLSP is generally mild to moderate in intensity. A study by Panditrao et al. (16) utilized a 0–10 Numerical Visual Analog Scale (VAS) and reported an average PLSP score of 6.5.

iii. Timing: PLSP usually occurs within a few hours after laparoscopic surgery. It generally begins within a few hours following the laparoscopic operation and typically peaks between 12- and 24-hours post-surgery before gradually subsiding over the subsequent few days (17). However, some studies have noted a delayed onset. Li et al. (18) investigated 442 cases of gynaecological laparoscopic surgery and found that over 90% of patients first experienced PLSP on the first postoperative day rather than the day of surgery.

iv. Duration: For most patients, PLSP is transient, resolving within 2–3 days. Nevertheless, in some cases, it can persist for up to 5 weeks or longer, negatively affecting quality of life. In the series by Dixon et al. (10), 66% and 21% of patients reported pain at 1 and 5 weeks, respectively. At 5 weeks, however, only 7% remained concerned about the pain, and 5% still required analgesics.

v. Response to treatment: A characteristic feature of PLSP is its often-reduced responsiveness to conventional analgesics compared to incisional or visceral abdominal pain (8, 10).

Incidence of PLSP

PLSP is a very prevalent complication, with reported incidence rates varying widely, from 30% to over 90%, depending on the specific type of laparoscopic procedure (19). Kaloo et al. (20) identified PLSP in 80% of females following gynecological laparoscopic procedures. A different series by Li et al. (18) reported PLSP in 77.3% of cases undergoing laparoscopic operations for benign gynecological disorders. Conversely, Panditrao et al. (16) questioned whether the incidence is overestimated, as their series reported a lower incidence of 16.8%.

Potential risk factors

Several factors have been identified as potentially increasing the risk of developing PLSP (4):

i. Gender: Although the underlying reason is unclear, studies suggest a higher incidence of PLSP in females.

ii. Surgical position: Positions that facilitate the pooling of carbon dioxide gas beneath the diaphragm (e.g., head-up position) tend to increase the risk of PLSP.

iii. Body Mass Index (BMI): Patients with a lower BMI may be more vulnerable to developing PLSP (21, 22).

iv. Insufflation pressure: A positive correlation exists between higher insufflation pressures and both the incidence and intensity of discomfort (23).

Awareness about PLSP

The laparoscopic approach has enabled early discharge and shorter in-hospital stays. This success, however, has inadvertently contributed to a lack of familiarity with PLSP among both patients and clinicians, often resulting in missed diagnoses, inadequate evaluation, suboptimal management, and delayed recovery (19-25).

Management of PLSP

The management of PLSP constitutes a comprehensive, integrated strategy focusing on prevention through meticulous surgical technique, followed by the management of any residual pain using a multimodal approach of non-pharmacological and non-opioid pharmacological methods (Table 2).

Table 2. *Multimodal strategies for the prevention and management of post-laparoscopic shoulder pain*

Approach	Specific options and interventions
Surgical / Technical	Low-pressure pneumoperitoneum; active intraperitoneal gas aspiration; pulmonary recruitment manoeuvres; intraperitoneal saline or Ringer's lactate instillation
Pharmacological	Non-steroidal anti-inflammatory drugs (NSAIDs); Gabapentinoids; intraperitoneal local anaesthetics; opioid analgesics when required
Physical / Positioning	Early mobilization; Trendelenburg positioning during gas evacuation; local heat application to the shoulder region

Prevention of PLSP

i. Active gas aspiration: Multiple studies have confirmed a positive association between the volume of residual gas post-laparoscopy and PLSP severity (7, 8). Consequently, in addition to passive deflation at the end of the operation, surgeons are increasingly employing suction to actively evacuate as much residual gas as possible. A meta-analysis by Haneef et al. (26), including five Randomized Clinical Trials (RCTs) with 367 participants, found that active gas aspiration resulted in significantly lower residual gas volume, reduced PLSP scores at 24 hours postoperatively, and decreased overall analgesic requirements compared to passive aspiration, without a significant increase in operative time or cost.

ii. Pulmonary recruitment manoeuvre (PRM): The PRM is performed during positive pressure ventilation and involves the brief application of significantly supra-physiological positive pressure to the airways and alveoli. This maneuver increases transpulmonary pressure, leading to the re-expansion of collapsed alveoli and facilitating the expulsion of CO_2 from the peritoneal cavity. Several studies have validated its role in reducing PLSP when used alone or combined with other preventive strategies (6). Samarah et al. (27) demonstrated in a randomized controlled trial (RCT) that using a PRM (five manual inflations lasting five seconds at a maximum pressure of 25 mm Hg at the conclusion of laparoscopic cholecystectomy (LC) significantly reduced PLSP. Similar findings were reported by Kihlstedt Pasquier et al. (28) and Noh et al. (29). A meta-analysis by Deng et al. (30), including 1,504 patients, concluded that PRM is effective in alleviating PLSP. Kietpeerakool et al. (31) found that PRM using 40 pressure shows promise for reducing PLSP within 48 hours following gynecologic laparoscopic surgery.

Although most studies have not reported significant adverse effects, high airway pressure carries a theoretical risk of pulmonary barotrauma or cardiovascular complications. Ryu K et al. (32) assessed PRM efficacy and safety at maximum inspiratory pressures of 40 and 60mm Hg and concluded that both levels were equally effective in removing residual gas, supporting the safe use of PRM at 40mm Hg for PLSP reduction.

While the studies have not reported any significant negative effects due to PRM, high airway pressure can result in pulmonary barotrauma or other cardiovascular complications. Ryu K et al. (32) evaluated the efficacy and safety of a PRM for reducing PLSP, applying maximum inspiratory pressures of 40 and 60 cm H_2O. They concluded that PRM with a maximum inspiratory pressure of 40 cm H_2O can be used safely for the reduction of PLSP since they established that both pressure levels are equally effective in removing residual gas from the peritoneal cavity.

iii. Low-Pressure Pneumoperitoneum (LPP): During laparoscopic surgeries, the standard pneumoperitoneum pressure (SPP) is usually set between 12 and 16 mmHg. Given the link between PLSP and excessive diaphragm stretching, the impact of using LPP has been investigated. Barczynski et al. (33) compared LPP (7 mmHg) and SPP (12 mmHg) pneumoperitoneum during LC and reported a 2.1-fold reduced incidence of PLSP with LPP. Yasir et al. (23) found that LPP (8 mm Hg) during LC decreased the intensity of PLSP, leading to reduced analgesic requirements at 4, 8, and 24 hours. In gynecological operations, Bogani et al. (34) compared the use of LPP (8 mm Hg) vs SPP (12 mm Hg) during mini-laparoscopic hysterectomy (MLH) and concluded that LPP is safe in experienced hands and offers the benefit of less shoulder-tip pain. A combination of LPP (8 mm Hg) and deep neuromuscular blockade (NMB) was also found to significantly reduce PLSP following laparoscopic hysterectomy (35). Sarli et al. (36) reported a significant reduction in the frequency and severity of PLSP with LPP (9 mm Hg) during LC, with no observed increase in operative duration. However, a related study by Gurusamy et al. (37) found a two-minute increase in operating time. Therefore, further research is warranted to determine if the routine use of LPP is universally advisable for all laparoscopic surgeries.

iv. Phrenic Nerve Block (PNB): As PLSP is thought to be caused by irritation of the phrenic nerve, hence phrenic nerve block (PNB), which prevents phrenic neural impulses from entering the central nervous system (CNS), has been investigated as a potential treatment (6). As the irritation of the phrenic nerve is considered a major cause of PLSP, PNB has been studied as a potential intervention to prevent neural impulses from reaching the central nervous system (CNS). Yi et al. (38) conducted an RCT using ultrasound-guided PNB on patients undergoing LC and reported a substantial decrease in PLSP without any respiratory complications, despite a dramatic decrease in right-sided diaphragmatic excursion one-hour post-surgery.

v. Intraperitoneal instillation of local anesthetics: Several studies (39, 40) have demonstrated that the incidence and severity of PLSP may be decreased by administering local anesthetics (LA) into the abdomen cavity, either before the insufflation of CO_2 or at the end of the procedure. This analgesic effect is believed to result from the LAs' capacity to interrupt pain signal transmission from injured intra-abdominal tissues (40).

The most frequently used LAs for this purpose are bupivacaine, followed by lidocaine and ropivacaine. Cha et al. (41) assessed the effect of ropivacaine, administered peritrocally, intraperitoneally, or as a combination, following LC and found that intraperitoneal instillation significantly reduced visceral pain and PLSP.

Nebulization of intraperitoneal ropivacaine was also shown to significantly reduce PLSP and improve the duration of independent walking, though a higher rate of postoperative vomiting following LC was noted (42). Ingelmo et al. (43) compared preoperative and postoperative nebulization of ropivacaine (1%) to a placebo (normal saline, NS) during LC and concluded that ropivacaine nebulization, whether applied before or after surgery, reduced PLSP and morphine requirements, facilitating earlier mobility

Daghmouri et al. (44) concluded that intraperitoneal ropivacaine instillation is a valuable component of multimodal pain management, as it considerably lowers opioid consumption and enhances postoperative recovery markers. Despite these promising results, they advised that more studies are required to validate the safety and effectiveness of this management option.

vi. Intraperitoneal Dexamethasone: Given the known anti-inflammatory properties of steroids and the hypothesized inflammatory component of diaphragmatic/peritoneal irritation following laparoscopy, dexamethasone has been investigated as a therapy option. Asgari et al. (45) conducted a study wherein they administered 16 mg of intraperitoneal dexamethasone to a study group versus a placebo to a control group, and observed that dexamethasone significantly reduced the intensity of PLSP and the need for opioid analgesia.

vii. Sub-diaphragmatic irrigation with sodium bicarbonate: One theory of PLSP etiology involves diaphragmatic irritation from the acidic carbonic acid created by the pneumoperitoneum. Consequently, neutralizing the subphrenic acidic environment has been explored as a management strategy. Liu et al. (46) compared sub-diaphragmatic irrigation with a sodium bicarbonate-containing solution to standard saline irrigation during total laparoscopic hysterectomy (TLH) for benign indications and found that sodium bicarbonate safely and effectively reduced PLSP. Similarly, Saadati et al. (47) reported that peritoneal irrigation with sodium bicarbonate reduced PLSP intensity and improved early postoperative Quality of Life (QOL).

viii. Intraperitoneal saline instillation: Some evidence suggests that a subdiaphragmatic wash with intraperitoneal normal saline (NS) can significantly reduce PLSP and lower analgesic requirements in the postoperative period, thereby promoting early mobilization and discharge (48). Tsimoyiannis et al. (49) found that the benefit was greater when the saline was suctioned after pneumoperitoneum deflation. The effect was further enhanced when a subhepatic closed drain was left in place to continue suctioning fluid during the initial postoperative hours. Esmat et al. (50) found that combining low-pressure pneumoperitoneum with intraperitoneal NS infusion reduced the intensity of PLSP, though not its frequency. Ryu KH et al. (51) concluded that the prevention of PLSP and removal of residual CO_2 achieved by saline infusion alone is as effective as when combined with PRM.

ix. Warm and humidified CO_2 insufflation: Cold, dry CO_2 gas can lead to peritoneal tissue desiccation, which may result in inflammation and cellular damage. In contrast, warm, humidified prevents desiccation and could potentially reduce postoperative pain. Herrmann and De Wilde (52) conducted an RCT comparing warm, humidified to cold, dry in patients undergoing surgery for benign uterine diseases and demonstrated that the warm, humidified gas significantly reduced both PLSP and morphine demand. Kordestani et al. (53) compared warm gas insufflation to local heat application in LC and found that both interventions were effective in reducing PLSP.

x. Preoperative clonidine / Gabapentinoid: Clonidine is an antihypertensive agent acting on alpha-adrenergic and imidazoline receptors. Mirhosseini et al. (54) administered 0.2 of oral clonidine 90 minutes before anesthesia induction for LC patients. They found that while it did not decrease the incidence of PLSP, it significantly reduced its intensity. Gabapentinoids, including gabapentin and pregabalin, act as analogs of gamma-aminobutyric acid (GABA). Pre-emptive administration of these drugs can reduce PLSP and improve sleep quality on the first postoperative night (55). Valadan et al. (56) assessed the prophylactic effect of oral gabapentin (600 mg) given 30 minutes before induction in patients undergoing laparoscopic ovarian cystectomy, concluding it was a safe and effective strategy for reducing both the incidence and severity of PLSP.

Treatment of PLSP

i. Postoperative position: The Trendelenburg position facilitates the movement of residual CO_2 in the abdominal cavity away from the diaphragm and towards the pelvis, where the abundant vascularity accelerates the absorption of CO_2. This position also reduces the stretching of visceral ligaments. Zeeni et al. (24), in a study involving 108 patients, evaluated the effect of nursing the patients postoperatively in the Trendelenburg position and found that the severity of PLSP at 12 hours decreased by 76%. Nursing in an

exaggerated lithotomy position has also been found to be effective in relieving PLSP after laparoscopic cholecystectomy (25).

ii. Non-steroidal anti-inflammatory drugs: Lee et al. (9) found that Naproxen 250mg orally every 12 h post-operatively was effective in PLSP. NSAIDs can be given orally or via injection, but studies have indicated that they are significantly less effective in alleviating PLSP compared to pain at the abdominal surgical site. Lee et al. (9) reported that Naproxen 250 orally every 12 hours postoperatively was effective for PLSP management.

iii. Transcutaneous Electrical Nerve Stimulation (TENS): TENS delivers mild electrical currents to the skin, stimulating neurons to reduce pain via two mechanisms: the release of natural painkillers (endorphins) and the gate-control theory, which inhibits pain impulses in the spinal cord. The electrical pulses activate large, touch-sensing nerve fibers, blocking the transmission of pain-sensing nerve messages to the brain. Asgari Z et al. (57) compared the effect of TENS to 50 mg of fentanyl and found that TENS was not superior to fentanyl in any way. They suggested that future evaluations should focus on defining specific TENS parameters optimized for PLSP alleviation.

iv. Local anesthesia of shoulder tip: It has been demonstrated that local anesthetic (LA) administration directly to the area of referred pain, rather than the inflamed area, can successfully reduce referred pain. This analgesic effect is thought to be due to the interruption of pain signals in peripheral nociceptors. A study by Kim HY et al. (58) found that a 5% lidocaine patch applied directly to the shoulder reduced PLSP intensity at 24- and 48-hours following LC. The local patch provides the benefits of minimal systemic absorption and negligible side effects. Kim JE et al. (59) also demonstrated the analgesic effect of trigger point injection and eutectic mixture of local anaesthetics (EMLA) for PLSP after total laparoscopic hysterectomy.

v. Alternative medicine: Kreindler et al. (60) studied the impact of acupuncture in 25 patients with moderate-to-severe PLSP resistant to conventional analgesia. They observed no notable adverse effects and a significant decrease in PLSP. The study concluded that customized acupuncture, when integrated with traditional therapies, may be beneficial for PLSP. Zerkle et al. (61) explored a 25-minute single-session massage focusing on passive touch to the shoulder and diaphragm area in a 17-year-old patient with PLSP after laparoscopic abdominal surgery, which resulted in complete pain relief. Mottahedi et al. (62) compared conventional pharmacological treatment to massage plus conventional pharmacological treatment and TENS plus conventional pharmacological treatment.

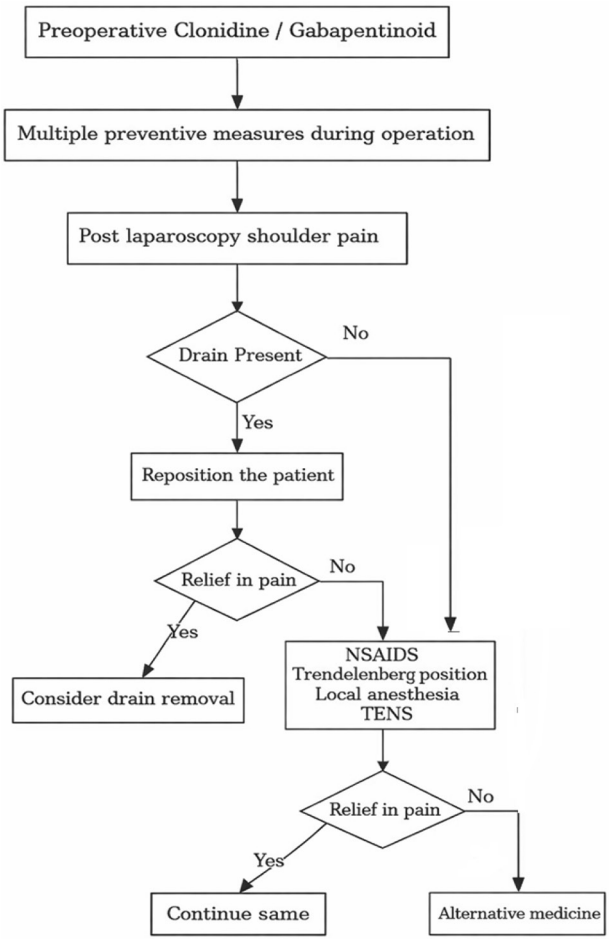

Figure 1. *Algorithm for management of post laparoscopy shoulder pain. (Image credits: Saleh AlSuwaydani - Author)*

Massage and TENS were administered three consecutive times after the patient regained consciousness in the inpatient wards, and both were found to decrease the PLSP intensity.

Based on the preceding review of the current literature, a suggested management algorithm is depicted in Figure 1. This approach emphasizes that PLSP management must be multimodal, spanning the preoperative, operative, and postoperative phases.

Limitations

This review is subject to several limitations. Firstly, the literature search was restricted to open-access databases and specific academic search engines (PubMed, Google Scholar, ResearchGate, and Web of Science), which may have led to the exclusion of other relevant publications. Secondly, bias in article selection may be present due to the varying experience and expertise of the researchers. Finally, limiting the inclusion criteria to English-language publications may have inadvertently overlooked potentially significant articles written in other languages.

CONCLUSION

Post-laparoscopic shoulder pain is a frequent complication of the laparoscopic surgical approach. It is often overlooked because it commonly manifests after the patient has been discharged from the medical facility. The etiopathogenesis remains unclear, yet a variety of management strategies have been proposed in recent years. To ensure that patients receive the benefits of the various available management options, increasing awareness of PLSP is essential.

Abbreviations

PLSP - Post-laparoscopic shoulder pain
QOL - Quality of life
NS - Normal saline
TLH - Total laparoscopic hysterectomy
SPP - Standard pneumoperitoneum pressure
LPP - Low pneumoperitoneum pressure
TENS - Transcutaneous electrical nerve stimulation
LA - Local anesthetic
PNB - Phrenic nerve block
CNS - Central nervous system
PRM - Pulmonary recruitment manoeuvre
CO_2 - Carbon dioxide

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Note: Artificial intelligence was not utilized as a tool in this study.

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Sažetak

BOL U RAMENU NAKON LAPAROSKOPSKE OPERACIJE: PRIKAZ OVE ČESTE POSTOPERATIVNE SEKVELE

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Iako je primena laparoskopske hirurgije unapredila bezbednost, udobnost i zadovoljstvo pacijenata, kod značajnog broja pacijenata je prisutan bol u ramenu nakon laparoskopske operacije (PLSP), što može usporiti postoperativni oporavak. Pregledana je literatura na engleskom jeziku putem pretrage glavnih akademskih baza i pretraživača, uključujući PubMed, Google Scholar, ResearchGate i Web of Science, kako bi se sumiralo trenutno razumevanje etiopatogeneze, povezanih faktora rizika i strategija lečenja PLSP. Precizna etiologija još uvek nije definisana, a predložene su različite teorije koje objašnjavaju PLSP. Najšire prihvaćena teorija sugeriše da je PLSP oblik reflektovanog bola izazvan iritacijom dijafragme usled istezanja prouzrokovanog pneumoperitoneumom ili prisustvom preostalih gasova i tečnosti. Trenutno ne postoje univerzalno prihvaćeni protokoli za prevenciju ili lečenje PLSP; stoga se primenjuje širok spektar modaliteta u zavisnosti od iskustva i preferencija hirurga. Jasna je potreba za povećanjem svesti o ovom stanju kako bi se omogućila standardizacija opcija lečenja i optimizovali ishodi za pacijente.

Ključne reči: laparoskopska hirurgija, bol u ramenu, reflektovani bol, pneumoperitoneum, ugljen-dioksid, dijafragma, n.phrenicus.

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Review article

PSYCHOTIC MANIFESTATIONS IN PRIMARY SJÖGREN'S SYNDROME: CLINICAL CHARACTERISTICS AND PATHOPHYSIOLOGICAL INSIGHTS

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Abstract: Psychotic manifestations in primary Sjögren's syndrome (SS) represent a rare but clinically meaningful complication of the disease. The aim of this paper was to analyze the clinical characteristics, potential pathophysiological mechanisms, therapeutic approaches, and outcomes of psychotic symptoms in patients with SS.

A narrative review of the available literature was conducted, with particular focus on case reports and small case series describing psychosis in the context of SS.

Psychotic manifestations in SS may arise from central nervous system involvement, immune-inflammatory mechanisms, cytokine dysregulation, and neurotransmitter alterations, as well as from corticosteroid therapy. Pro-inflammatory cytokines, particularly interleukin-6, have been linked to dopaminergic dysfunction and the emergence of positive psychotic symptoms. Corticosteroids may induce psychotic episodes depending on dose and duration of treatment. Chronic somatic symptoms, including ocular and oral dryness, pain, and fatigue, may be vulnerable to delusional misinterpretation. In several reported cases, psychotic symptoms improved following immunosuppressive therapy, supporting a potential immune-mediated subtype of psychosis in this population.

Psychosis in primary Sjögren's syndrome likely has a multifactorial etiology. Early recognition of a possible autoimmune basis is essential, as treatment strategies may require immunomodulatory therapy in addition to standard psychiatric management.

Keywords: Sjögren's syndrome, psychosis, neuroinflammation, cytokines, corticosteroids, autoimmune diseases.

INTRODUCTION

Primary Sjögren's syndrome (SS) is a chronic systemic autoimmune disease primarily characterized by sicca symptoms, including xerostomia and xerophthalmia. In addition to glandular involvement, up to half of patients develop extraglandular manifestations, with neuropsychiatric symptoms being relatively common. While mood disorders and cognitive impairment predominate, psychotic symptoms—such as hallucinations, delusions, and disorganized thinking—are rare but clinically significant. These manifestations may result from central nervous system involvement, immune-mediated mechanisms, chronic pain, or corticosteroid therapy. Despite their clinical relevance, psychotic symptoms in SS remain poorly investigated, with existing evidence largely limited to case reports and small case series.

The aim of this narrative review is to analyze psychotic symptoms in patients with Sjögren's syndrome, with a focus on clinical characteristics, potential triggers, therapeutic approaches, and outcomes, while proposing a conceptual framework linking the pathophysiology of SS to psychotic manifestations.

PSYCHOTIC SYMPTOMS IN SJÖGREN'S SYNDROME

Sjögren's syndrome, also referred to as "autoimmune epithelitis", is a chronic, slowly progressive autoimmune disease characterized by immune-mediated dysfunction and destruction of the salivary and lacrimal glands, accompanied by a broad range of systemic manifestations (1, 2). It represents the second most common autoimmune rheumatic disease after rheumatoid arthritis and predominantly affects women (1, 3). Owing to its potential involvement of the peripheral, central, and autonomic nervous systems, Sjögren's syndrome may be associated with various neuropsychiatric manifestations (1, 4). Among these, depressive and anxiety disorders are most frequently reported, whereas psychotic disorders are less common but

remain clinically relevant (4). Although considered rare, psychotic symptoms have been consistently documented in the available literature. According to the literature, the prevalence can range from 2.5 to 60% due to the non-specific presentation of symptoms and different diagnostic criteria (5, 6). On the other hand psychosis is a clinical syndrome characterized by impaired perception of reality, leading to disturbances in cognition, behavior, and daily functioning. Core manifestations include delusions and hallucinations (7, 8).

This paper addresses the question of where psychotic symptoms in Sjögren's syndrome originate. The discussion focuses on the possible mechanisms involved, including central nervous system involvement, immune processes, and treatment-related factors, particularly corticosteroid therapy. We also examine how Sjögren's syndrome may affect patients with pre-existing psychotic disorders by triggering symptom relapse or reducing treatment response. In addition, the paper considers the role of genetic and environmental vulnerability, as well as the occurrence of psychotic symptoms in patients without an identifiable predisposition. The overall aim of this work is to improve understanding of the relationship between Sjögren's syndrome and psychotic manifestations and to highlight their clinical relevance.

CNS MECHANISMS

Sjögren's syndrome can affect many parts of the central nervous system, including the brain, brainstem, spinal cord, optic nerves, and cerebellum (8).Neuropsychiatric manifestations are increasingly recognized as part of systemic autoimmune diseases, reflecting the complex interaction between immune dysregulation and central nervous system function (9). Patients may experience a range of neurological problems such as headaches, seizures, cognitive difficulties, movement disorders, and sensory deficits. Cognitive impairments often involve attention, memory, and executive functions, while psychiatric symptoms can include depression, psychosis, and catatonia. These manifestations are thought to result from immune-related dysfunction in the brain, which may disrupt normal thinking, perception, and emotional regulation. CNS involvement can therefore contribute directly to the emergence of psychotic symptoms, highlighting the need for early recognition and management (10, 11).

One potential pathway through which Sjögren's syndrome may influence psychotic symptoms is impairment in emotional processing and regulation. Several studies have investigated emotional interpretation and expression in patients with Sjögren's syndrome, a domain that is also critically impaired in psychotic disorders, often in the context of alexithymia (12, 13). It is important to remember that this chronic disease is frequently accompanied by reactive emotional symptoms, such as emotional lability, masked depression, and withdrawal, which can obscure the presence of true alexithymia. Patients often appear detached, sometimes anhedonic, and emotionally blunted. Beyond these general reactions, there is evidence of a specific difficulty in understanding and decoding both one's own and others' emotions. This impairment may reflect an organic substrate and can interact with cognitive dysfunction (6). All of this creates conditions that resemble those seen in psychosis, where patients similarly struggle with emotion recognition and regulation. Such deficits may therefore contribute to the development or worsening of psychotic symptoms in susceptible individuals (14, 15).

IMMUNE-INFLAMMATORY PATHWAYS

Sjögren's syndrome is increasingly recognized as a condition capable of inducing immune-mediated neuroinflammation that extends beyond the classic sicca manifestations and involves the central nervous system. Pro-inflammatory cytokines, including interferon-γ (IFN-γ), interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), have been implicated in Sjögren-related CNS involvement. These mediators can activate metabolic pathways such as indoleamine-2,3-dioxygenase, leading to alterations in kynurenine metabolism and subsequent disruption of serotonergic and glutamatergic neurotransmission in the hippocampus and other brain regions (16, 17).

Importantly, similar inflammatory mechanisms have been described in psychotic disorders. Elevated levels of pro-inflammatory cytokines have been reported in patients with first-episode psychosis and schizophrenia and have been associated with cognitive deficits and impaired social functioning (18). In particular, IL-6 has beenshown to increase dopaminergic activity in striatal regions, which is closely associated with positive psychotic symptoms. Conversely, dopamine signaling can influence inflammatory pathways, indicating a reciprocal relationship between immune activation and dopaminergic neurotransmission (19).

STEROID-INDUCED PSYCHOSIS

Corticosteroids are widely prescribed due to their potent anti-inflammatory and immunosuppressive effects and are commonly used in the management of various conditions, including Sjögren's syndrome. However, their use is associated with a range of psychiatric adverse effects collectively known as corticos-

teroid-induced psychiatric disorders (CIPDs) (20, 21). These manifestations may include mood disturbances, sleep disorders, irritability, agitation, manic symptoms, and psychosis. Psychotic features can present as hallucinations, delusional thinking, disorganized thought processes, and affective instability (22, 23). Such symptoms may emerge soon after the initiation of therapy, at any stage during treatment, or even following the discontinuation of corticosteroids (24). Evidence suggests a clear dose-response relationship, with higher doses conferring greater risk. Data from the Boston Collaborative Drug Surveillance Program demonstrated psychiatric adverse effects in 18.6% of patients receiving more than 80 mg/day of prednisone or methylprednisolone, compared with 4.6% in those receiving 41–80 mg/day and only 1.3% in patients treated with doses below 40 mg/day (25). In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), these conditions are categorized under substance- or medication-induced psychotic disorders, occurring in approximately 5–18% of patients receiving corticosteroid therapy (26, 27).

Prolonged use of corticosteroids affects the hypothalamic–pituitary–adrenal (HPA) axis, leading to changes in the body's response to stress and in normal feedback regulation. These disturbances, together with imbalances in neurotransmitter systems, can result in various psychiatric symptoms. Corticosteroids influence dopamine pathways, which may increase the risk of developing psychotic symptoms. In addition, long-term corticosteroid exposure has been linked to structural changes in the brain, such as hippocampal atrophy associated with memory problems and depression, as well as increased activity of the amygdala, which contributes to anxiety and emotional instability. These mechanisms help explain the wide range of psychiatric effects seen with corticosteroid use (28).

SOMATIC SYMPTOM MISINTERPRETATION

The next important question we wanted to address is the relationship between Sjögren's syndrome and psychosis. More specifically, we aimed to explore how the key symptoms of Sjögren's syndrome may affect patients with psychotic disorders, and in what ways these symptoms can worsen existing psychosis or lead to the development of new psychotic symptoms. We were particularly interested in identifying which symptoms are more likely to exacerbate psychosis and how they might be experienced or interpreted by patients who are already psychotic.

Primary Sjögren's syndrome is defined by chronic ocular and oral dryness resulting from autoimmune damage to lacrimal and salivary glands, with sicca symptoms present in the majority of patients. These persistent somatic symptoms have been associated with a range of psychiatric manifestations, including psychosis, and case reports describe patients with psychotic features occurring alongside or following prominent dryness symptoms (29). These symptoms provide persistent, ambiguous bodily sensations that are vulnerable to delusional misinterpretation in patients with impaired reality testing. Severe dry eye disease is associated with burning, foreign-body sensation, blurred or fluctuating vision, and visual discomfort (30, 31). In psychotic individuals, this may be experienced as externally caused or threatening, thereby becoming incorporated into persecutory or somatic delusions. Similarly, xerostomia and the oral discomfort seen in Sjögren's syndrome often lead to a range of oral symptoms, including speech difficulties, trouble swallowing (dysphagia), changes in taste perception, and a burning sensation in the mouth (32). Psychotic patients often report disturbances in the way they perceive and interpret bodily sensations, including unusual bodily experiences and alterations in body representation (33). Case reports and clinical observations indicate that these individuals may misinterpret physical discomfort or other bodily sensations, and these misinterpretations can sometimes intensify psychotic symptoms when patients are unable to accurately contextualize or articulate their experiences (34). These sensations may be distorted and incorporated into somatic delusions, depersonalization, and cenesthetic or ksenopathic phenomena, where patients experience abnormal bodily perceptions or feel as if external forces are acting upon their bodies. Several case reports of primary Sjögren's syndrome have documented severe psychiatric features, including persecutory and referential delusions, paranoia, anxiety, auditory hallucinations, and even suicidal ideation (35, 36, 37). Catatonic phenomena such as mutism, negativism, immobility, and Gegenhalten have also been reported in association with neuropsychiatric involvement in Sjögren's syndrome (36, 37). In some of these cases, the psychotic symptoms appeared to be closely intertwined with the underlying autoimmune process and bodily distress, and improved with immunosuppressive therapy rather than with antipsychotics alone. Besides the typical dry eyes and mouth, many patients with Sjögren's syndrome experience persistent fatigue and widespread pain. These ongoing physical symptoms can make individuals more sensitive to perceived threats and may shape the way they interpret their bodily discomfort, which can in turn affect their psychological well-being (37).

THERAPEUTIC IMPLICATIONS

Antipsychotics remain the cornerstone of treatment for psychotic symptoms in primary psychiatric disorders (38, 39). Despite their well-recognized adverse effect profile, they occupy a central position in the therapeutic hierarchy for psychosis and are among the most frequently prescribed classes of psychotropic medications overall (40, 41).

In contrast, the management of psychotic symptoms occurring secondary to Sjögren's syndrome appears to differ substantially. Based on case reports published over the past decade, treatment strategies in this context often extend beyond conventional antipsychotic therapy (35, 36, 37). Given that Sjögren's syndrome is primarily an immune-mediated systemic disease, immunosuppressive and immunomodulatory treatments are frequently employed and, in many cases, lead to significant improvement of psychiatric symptoms. This therapeutic response mirrors observations in other immune-mediated neurological conditions, where similar treatment strategies have proven effective (42). The aforementioned supports the hypothesis that psychosis associated with Sjögren's syndrome may be driven by underlying immune and inflammatory mechanisms rather than by primary psychiatric pathology.

CONCLUSION

Psychotic symptoms in primary Sjögren's syndrome constitute a rare but clinically meaningful manifestation of the disease. Evidence from published case reports and small case series suggests that psychosis in this context may arise from multiple, potentially interacting mechanisms, including immune-mediated neuroinflammation, cytokine dysregulation, central nervous system involvement, corticosteroid exposure, and the psychological and perceptual impact of chronic somatic symptoms.

The observation that psychotic symptoms in several reported cases improved with immunosuppressive or immunomodulatory therapy—sometimes more robustly than with antipsychotic treatment alone—strengthens the hypothesis of an immune-driven subtype of psychosis in this population.

Clinicians should maintain a high index of suspicion for autoimmune etiologies when encountering atypical, treatment-resistant, or late-onset psychosis, particularly in patients presenting with sicca symptoms, systemic autoimmune features, or neurological signs. Early identification is critical, as treatment strategies may differ substantially from those used in primary psychiatric disorders and may require targeted immunotherapy.

Future prospective studies are needed to determine the true prevalence of psychotic manifestations in Sjögren's syndrome, to better characterize their pathophysiology, and to establish evidence-based treatment algorithms. Improved recognition of this association may enhance both psychiatric and rheumatologic outcomes and contribute to a more integrated understanding of immune–brain interactions in psychosis.

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Sažetak

PSIHOTIČNE MANIFESTACIJE U PRIMARNOM SJOGRENOVOM SINDROMU: KLINIČKE KARAKTERISTIKE I PATOFIZIOLOŠKI MEHANIZMI

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Psihotične manifestacije u primarnom Sjögrenovom sindromu (SS) predstavljaju retku, ali klinički značajnu komplikaciju bolesti. Cilj rada je analiza kliničkih karakteristika, mogućih patofizioloških mehanizama, terapijskih pristupa i ishoda psihotičnih simptoma kod bolesnika sa SS.

Sproveden je narativni pregled dostupne literature sa posebnim osvrtom na prikaze slučajeva i manje serije bolesnika koje opisuju pojavu psihoze u kontekstu SS.

Psihotične manifestacije u SS mogu se javiti kao posledica zahvatanja centralnog nervnog sistema, imuno-inflamatornih mehanizama, disfunkcije citokina i poremećaja neurotransmisije, kao i usled terapije kortikosteroidima. Proinflamatorni citokini, naročito interleukin-6, povezani su sa dopaminergičkom disfunkcijom i pojavom pozitivnih psihotičnih simptoma. Kortikosteroidi mogu indukovati psihotične epizode u zavisnosti od doze i trajanja primene. Hronični somatski simptomi, poput suvoće očiju i usta, bola i umora, mogu biti podložni pogrešnoj interpretaciji i inkorporaciji u sumanute ideje. U pojedinim slučajevima zabeleženo je poboljšanje psihotičnih simptoma nakon imunosupresivne terapije, što ukazuje na moguću imunološku osnovu poremećaja.

Psihoza u primarnom Sjögrenovom sindromu najverovatnije ima multifaktorsku etiologiju. Pravovremeno prepoznavanje autoimmune osnove psihotičnih simptoma od ključnog je značaja, jer terapijski pristup može zahtevati primenu imunomodulatorne terapije pored standardnog psihijatrijskog lečenja.

Ključne reči: Sjögrenov sindrom, psihoza, neuroinflamacija, citokini, kortikosteroidi, autoimmune bolesti.

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Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

Treba navesti statističke metode koje su korišćene u obradi rezultata.

Rezultati. Rezultati treba da budu jasni i sažeti, sa minimalnim brojem tabela i slika neophodnih za dobru prezentaciju.

Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

Reference se citiraju prema tzv. Vankuverskim pravilima, koja su zasnovana na formatima koja koriste *National Library of Medicine* i *Index Medicus*.

Primeri:

1. **Članak:** (svi autori se navode ako ih je šest i manje, ako ih je više navode se samo prvih šest i dodaje se *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad.

Slike. Sve ilustracije (fotografije, grafici, crteži) se smatraju slikama i označavaju se arapskim brojevima u tekstu i na legendama, prema redosledu pojavljivanja. Treba koristiti minimalni broj slika koje su zaista neophodne za razumevanje rada. Slova, brojevi i simboli moraju biti jasni, proporcionalni, i dovoljno veliki da se mogu reprodukovati. Pri izboru veličine grafika treba voditi računa da prilikom njihovog smanjivanja na širinu jednog stupca teksta neće doći do gubitka čitljivosti. Legende za slike se moraju dati na posebnim listovima, nikako na samoj slici.

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A short title of less than 50 spaces, for use as a running head, is included.

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Review of the literature include: an introduction, subheadings, conclusion, references.

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References are cited by the so-called Vancouver rules, which are based on formats that use the National Library of Medicine and Index Medicus. The following are examples:

1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first six are listed followed by *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg. 2003; 29(2): 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

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