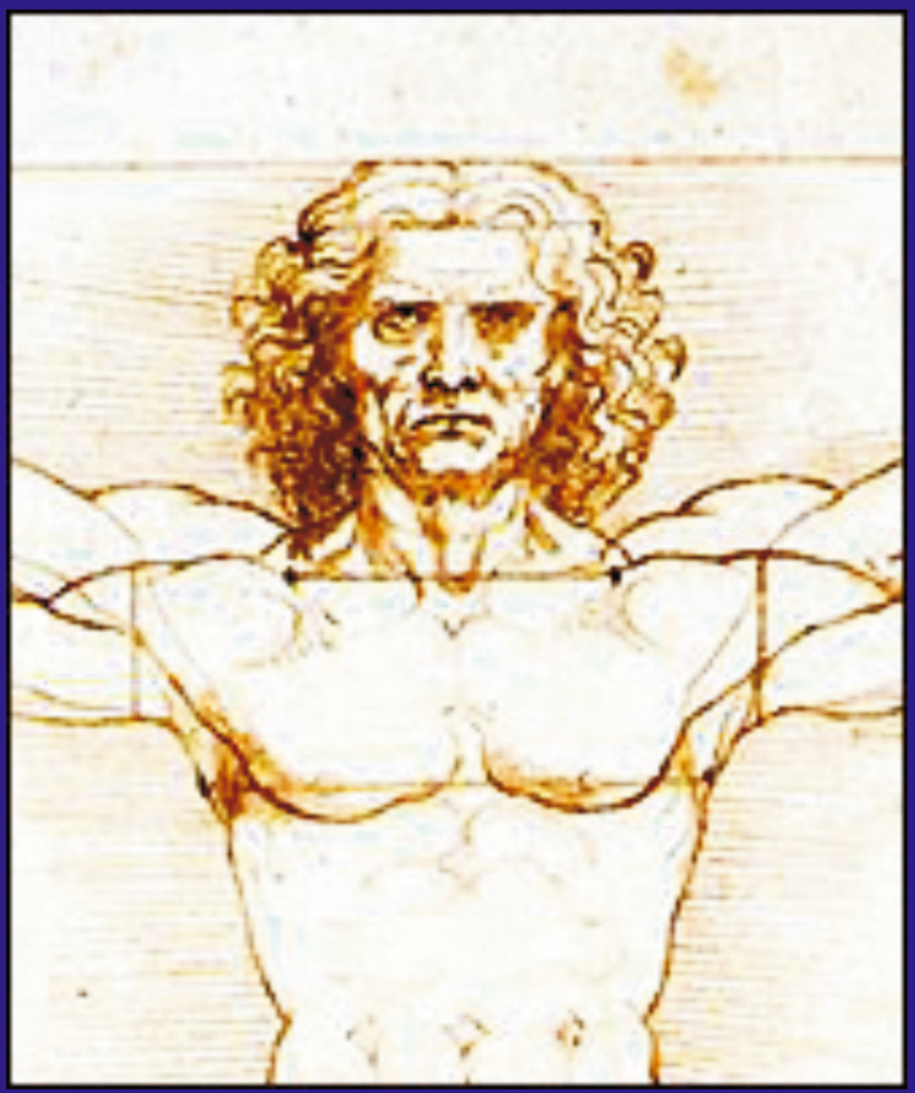
SANAMED

ISSN-1452-662X



Vol 19 (3) 2024.

MEDICAL JOURNAL

ISSN-1452-662X

IZDAVAČ
Udruženje lekara Sanamed, Novi Pazar

ČASOPIS IZLAZI TRI PUTA GODIŠNJE

ADRESA UREDNIŠTVA
„SANAMED“,
Ul. Palih boraca 52, 36300 Novi Pazar, Srbija,
email: sanamednp2006@gmail.com, www.sanamed.rs

ŠTAMPA
„OFSET“, Kraljevo

TIRAŽ
500

PRETPLATA
Godišnja pretplata: 4500 din. za domaće ustanove; 1500 din. za pojedince; za inostranstvo 75 eura (u dinarskoj protivrednosti po kursu na dan uplate). Pretplatu vršiti na račun 205-185654-03, Komercijalna banka. Za sve dodatne informacije kontaktirati Uredništvo.

ISSN-1452-662X

PUBLISHER
Association ofmedical doctors “Sanamed”, Novi Pazar

ISSUED THREE TIMES A YEAR

EDITORIAL ADDRESS
“SANAMED”,
St. Palih boraca 52, 36300 Novi Pazar, Serbia,
email: sanamednp@gmail.com, www.sanamed.rs

PRINT
“OFSET”, Kraljevo

CIRCULATION
500

SUBSCRIPTION
Annual subscriptions: 4500 RSD for domestic institutions and 1500 RSD for individuals. For readers abroad, annual subscription is 75 Euro (in Dinar equivalent at the exchange rate on the day of payment). For further instructions and informations, contact Editorial Board.

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ISSN-1452-662X

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Piši da preneseš

Uradi da te pamte

* * *

Read to understand

Write to impart

Work to be remembered

Avdo Ćeranić

SANAMED
2024; 19(3): 263–265
ISSN-1452-662X

DOI: 10.5937/sanamed0-52781
UDK: 616.12-085
ID: 160164873
Letter to editor

CARVEDILOL: A BETA BLOCKER OF CHOICE FOR THE TREATMENT OF PATIENTS WITH REYNAUD'S PHENOMENON AND CARDIOVASCULAR DISEASES

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Primljen/Received: 15. 08. 2024. Prihvaćen/Accepted: 29. 09. 2024. Published online first: 09. 10. 2024.

Reynaud's phenomenon (RP) is characterized by vasospasm of the digital arteries, leading to episodic color changes. It is named after Maurice Raynaud, who first described this phenomenon in 1862 in a female patient presenting with transient digital ischemia (1). The discoloration of the affected area is typically triphasic: the skin first becomes white due to vasospasm (ischemic phase), then purple (cyanotic phase), and finally red (hyperemic phase). RP is often precipitated by cold exposure or emotional stress and can be accompanied by pain and paresthesia. Its prevalence in the general population is around 5% (2), and it can be classified as primary ("idiopathic") or secondary (SRP). Primary RP is an isolated vasospastic disorder driven by vascular functional abnormalities that typically do not cause permanent damage to the skin.

In contrast, SRP is prevalent in many rheumatic diseases (RD), particularly in connective tissue diseases like systemic sclerosis (SSc) and systemic lupus erythematosus (SLE). The pathogenesis of SRP is complex, involving various vascular structural and functional abnormalities (1). If untreated, SRP can progress to ulceration, gangrene, and scarring, especially in patients with SSc.

Cardiovascular diseases (CVD) are common in patients with RD. Rheumatoid arthritis (RA) patients have a 48% increased risk of cardiovascular events (3), while 20-30% of deaths in SSc patients are attributed to cardiovascular causes (4). Furthermore, the relationship between SLE and atherosclerosis is well established, with these patients at higher risk for coronary artery disease (CAD), cerebrovascular, and peripheral vascular diseases (5). Traditional risk factors like arterial hypertension (HTN) and dyslipidemia cannot solely account for the increased risk of CVD in patients with RD. It is likely that inadequate immune and inflammatory responses in RD contribute to endothelial dysfunction, leading to atherosclerosis and CVD (6).

The most prevalent CVDs in patients with RD include HTN, CAD, and heart failure (HF). Treatment for these CVDs usually involves beta blockers (BBs) (7, 8, 9). Their effectiveness in preventing cardiovascular morbidity and mortality in HF, CAD, and HTN patients is well documented in large randomized studies. However, beta blockers can exacerbate RP (10), with prevalence rates of RP in patients receiving beta-blocker therapy reaching up to 15% (11). It is assumed that by blocking β-adrenoceptors, BBs mimic the norepinephrine-induced vasoconstriction of digital arteries via α1-adrenoceptors. Nevertheless, the exact mechanism by which BBs worsen RP remains unclear.

Consequently, when faced with a patient who has RP and, for example, HF, clinicians may hesitate to prescribe BBs, fearing they might worsen RP, despite knowing that these medications prevent premature mortality in such patients (7). The resolution to this common clinical dilemma lies in recognizing the heterogeneity within the beta blocker class. Indeed, indications and contraindications differ among beta blockers, as they exhibit several distinct pharmacological activities (12, 13). In this context, initiating treatment with a drug that blocks both α-receptors and β-receptors appears logical. However, to date, only one medication with these specific properties has been investigated—labetalol (14).

Labetalol is a non-selective BB that acts as a competitive antagonist of β-receptors and postsynaptic α-receptors (15). Its β-adrenoceptor-blocking activity leads to a reduction in heart rate (HR), while α-adrenoceptor blockade reduces systemic vascular resistance (SVR), resulting in vasodilation and lower blood pressure (BP). Due to this dual blocking activity, labetalol is widely used for treating HTN, especially during hypertensive crises (9). In the previously mentioned study, labetalol demonstrated clinical improvement in patients with RP (14). However, its role in treating CVD is limited to HTN management (9).

Carvedilol, similar to labetalol, is a non-selective beta blocker with β-adrenoceptor antagonist and α_1-adrenoceptor antagonist activity, but it also possesses antioxidative and antiproliferative effects (16). While it primarily lowers BP by reducing SVR through its alpha-1-blocking activity (17), its effect on HR is less pronounced than that of other (selective) BBs (17). The beneficial effects of carvedilol are well established, not just in HTN but also in HF and CAD (7,8,9, 17). The COPERNICUS trial demonstrated that carvedilol administration significantly reduces the risk of death and hospitalizations due to HF in patients with HF and reduced ejection fraction (18). Furthermore, the CAPRICORN study found that administering carvedilol after myocardial infarction significantly reduces all-cause mortality in these patients (19). Therefore, carvedilol exhibits similar effects to labetalol but offers additional benefits (antioxidative and antiproliferative properties), a broader range of indications, and proven beneficial effects on CVDs, as demonstrated in numerous randomized clinical trials.

RP is common in RD, often accompanied by CVD, necessitating the use of BBs in therapy. Carvedilol emerges as a reasonable choice due to its documented benefits in patients with CVD and its dual adrenoreceptor antagonist activity, suggesting it may reduce RP episodes. However, no research has been published on this topic to date. Perhaps a well-designed randomized clinical trial will determine whether carvedilol is the appropriate choice for patients with RP and CVD, and we advocate for this research.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: No.

Author contribution: All authors have contributed equally

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

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***How to cite this article**:* Stojanović M, Nedović J, Ilić S. Carvedilol: a beta blocker of choice for the treatment of patients with Reynaud's phenomenon and cardiovascular diseases. Sanamed. 2024; 19(3): 263-265. doi: 10.5937/sanamed0-52781.

SANAMED
2024; 19(3): 267–274
ISSN-1452-662X

DOI: 10.5937/sanamed0-54887
UDK: 616.9:615.33.015.8
ID: 160132361
Original article

PERINATAL PREDICTORS OF NEURODEVELOPMENTAL OUTCOMES IN HIGH-RISK NEONATES

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Primljen/Received: 05. 11. 2024. Prihvaćen/Accepted: 04. 12. 2024. Published online first: 12. 12. 2024.

Abstract: **Background:** Thanks to advancements in neonatal medicine, perinatal morbidity has been significantly reduced, but the number of high-risk neonates continues to rise. Efforts to predict neurodevelopmental outcomes at an early age remain limited. The aim of this study was to analyze perinatal predictors of neurodevelopmental outcomes in high-risk neonates.

Methods: A prospective, longitudinal two-year study was conducted at the Pediatric Clinic of the University Clinical Center in Tuzla. The study included 151 neonates, with 99 in the test group (with known perinatal risk factors) and 52 in the control group (without risk factors). Early neurodevelopment was assessed using the Alberta Infant Motor Scale (AIMS). Standard statistical methods were applied for data processing. The study was approved by the Institutional Ethics Committee.

Results: Of the 151 neonates observed, 108 (71.5%) had normal neurodevelopment at 18 months, 29 (19.2%) had mild disorders, and 14 (9.3%) had developmental delays. In the group with suboptimal neurodevelopment, significantly more twin pregnancies, health problems during pregnancy, unnatural births, artificial fertilization, and pregnancy complications were recorded. In neonates, there were significantly more premature births, hypoxic-ischemic encephalopathy, and intracranial hemorrhages. Significant correlations were found between the mother's age and parity and delayed neurodevelopment. Additionally, correlations were found between birth weight, gestational age, Apgar score, length of hospitalization, and NICU stay with neurodevelopmental delay. Gestational age and the Apgar score at 1 minute showed significant negative predictive value for neurodevelopmental delay.

Conclusion: Prematurity and perinatal asphyxia remain the greatest risks for adverse neurodevelopmental outcomes in neonates. These factors should be the focus of continued medical research and clinical practice. Neonates at the highest risk of developmental delay and their families should be prioritized for early identification, long-term follow-up, and timely interventions.

Keywords: perinatal risk factors, high-risk neonates, neurodevelopmental outcomes, predictors.

INTRODUCTION

Thanks to advancements in neonatal medicine, perinatal morbidity has been significantly reduced, but the number of high-risk neonates continues to rise (1). However, efforts to predict neurodevelopmental outcomes at the earliest stages remain limited. During pregnancy, childbirth, and early infancy, various factors can affect the developing nervous system, potentially leading to permanent consequences. The term "baby at risk" was first introduced in the United Kingdom around 1960 (2). In 1978, the World Health Organization defined a high-risk child as one who presents certain risk factors prenatally, perinatally, and postnatally. In developed countries, the incidence of such children is approximately 10% (3).

High-risk neonates need to be identified immediately after birth, using anamnestic data, clinical risk factors, and early neonatal neuroimaging of the brain. These neonates are highly dependent on their environment and are vulnerable, but they also have great potential for positive adaptation and overcoming difficulties if provided with a favorable environment (4, 5). Neurodevelopmental deviations can be expected in approximately 50% of high-risk children. Today, it is estimated that 70-80% of children with developmental disabilities belong to the group of high-risk children (6).

The registry and long-term follow-up of high-risk children, along with the strategy of early detection of neurodevelopmental deviations, were introduced by Victoria Sheridan in the United Kingdom in 1964 and

have been applied for the longest time (7). New research may enhance our ability to identify infants at high risk of developmental delays as early as possible, in line with evidence that early intervention can improve outcomes for these infants (8, 9, 10). Therefore, the timely identification of associated perinatal factors and focused work on their prevention can improve outcomes for high-risk neonates later in life (11).

The aim of this study was to analyze perinatal predictors of neurodevelopmental outcomes in high-risk neonates up to 18 months of age.

PATIENTS AND METHODS

The research was conducted prospectively and longitudinally over a two-year period (from August 1, 2017, to August 1, 2019) at the Pediatric Clinic of the University Clinical Center in Tuzla. Following the inclusion and exclusion criteria, 151 neonates were selected consecutively to participate in the study. The test group consisted of 99 neonates with known risk factors associated with pregnancy, childbirth, and the early neonatal period. This group included 49 term neonates with a gestational age (GA) of ≥ 37 weeks (GW) and 50 preterm neonates with a GA of < 37 GW. The control group included 52 neonates aged 37-42 weeks, without known risk factors.

Data collected from the mothers in the first phase of the study included their age, body weight, number of prenatal visits, any diseases during pregnancy, medication use, lifestyle and habits, and socioeconomic status. This information was obtained from medical records and an additional questionnaire.

Perinatal and postnatal data were collected for the neonates, which included gestational age, birth weight, birth length, head circumference, Apgar score, resuscitation procedures, morbidity, therapeutic treatments during the perinatal and postnatal periods, diet, examination records, health monitoring, growth and development observations, developmental deviations, and any diagnostic or therapeutic procedures performed, including physical treatment. These data were obtained from medical records and an additional questionnaire.

All neonates were monitored with brain ultrasound during the first 6 months of life, and for some, further examinations were conducted up to a year, or up to 18 months, when necessary. Magnetic resonance imaging (MRI) of the brain was performed on selected cases where indicated.

Early neurodevelopment was assessed using the Alberta Infant Motor Scale (AIMS) protocol (12, 13, 14) at 4, 8, 12, and 18 months of age.

Standard descriptive statistics were used for data processing. Categorical variables were analyzed using the $\chi 2$ test and Fisher's exact test. Spearman's non-parametric correlation was employed to assess significant relationships between variables. A difference between samples was considered significant if $p < 0.05$. All statistical tests were conducted with a 95% confidence level ($p < 0.05$).

All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committees, following the 1964 Helsinki declaration and its later amendments or comparable ethical standards (15). The study was approved by the Institutional Ethics Committee.

RESULTS

During the study follow-up, it was found that, out of 151 observed infants, 108 (71.5%) exhibited normal neurodevelopment at 18 months of age. A mild disorder was recorded in 29 infants (19.2%), while 14 infants (9.3%) experienced a delay in neurodevelopment. Additionally, 15 infants (9.9%) were diagnosed with a muscle tone disorder, and 6 infants (4.0%) had a significant movement disorder.

Infants in the high-risk group had statistically significantly lower scores on the Alberta Infant Motor Scale compared to the control group at all age assessments ($p < 0.001$).

The prevalence of perinatal risk factors was analyzed in relation to early neurodevelopmental outcomes, with the results presented in the following tables. Table 1 shows the prevalence of maternal-related perinatal risk factors in the two groups of infants, categorized by their neurodevelopmental outcomes.

In the group with neurodevelopmental delay, there were significantly more cases of twin pregnancies, health problems during pregnancy, infections, treated infertility, drug use during pregnancy, and more frequent use of antibiotics. Additionally, there was a significantly higher prevalence of smoking, alcohol use, and psychological trauma. A statistically significant correlation between these factors and delayed neurodevelopment was observed (Table 1). Table 2 shows the prevalence of obstetric risk factors in the two groups of subjects with different neurodevelopmental outcomes.

In the group with neurodevelopmental delay, there were significantly more unnatural births, artificial fertilization, and pregnancy complications. A statistically significant correlation was found between these factors and delayed neurodevelopment (Table 2).

Table 3 shows the prevalence of child-related perinatal risk factors in the two groups of subjects with different neurodevelopmental outcomes.

Table 1. *Prevalence of maternal-related risk factors in neurodevelopmental outcome groups*

Mother-related specifications	Neurodevelopment				χ^2	p	φ	p
	Normal		Delayed					
	n	%	n	%				
Pregnancy					7.748	**0.006**	0.235	**0.003**
Single	95	88.0	29	67.4				
Twins	13	12.0	14	32.6				
Health problems in pregnancy	28	25.9	20	46.5	5.099	**0.024**	0.196	**0.014**
Infections	14	13.0	13	30.2	5.126	**0.024**	0.199	**0.012**
Treated Sterility	2	1.9	5	11.9	4.728	**0.019***	0.209	**0.009**
Medicines in pregnancy	28	25.9	19	44.2	3.970	**0.046**	0.175	**0.029**
Antibiotics	14	13.0	13	30.2	5.126	**0.024**	0.199	**0.012**
Smoking	20	18.5	16	37.2	4.933	**0.026**	0.194	**0.015**
Alcohol	0	0.0	3	11.5	5.767	**0.013***	0.287	**0.002**
Mental trauma	13	12.0	19	44.2	17.157	**< 0.001**	0.335	**< 0.001**

* Fisher's exact test; χ^2 - chi-squared test; φ - phi coefficient (mean square contingency coefficient; p - probability value

Table 2. *Prevalence of obstetric risk factors in neurodevelopmental outcome groups*

Obstetric specifications	Neurodevelopment				χ^2	p	CC	p
	Normal		Delayed					
	n	%	n	%				
Type of delivery					9.57	**0.009***	0.257	**0.013**
Natural	80	74.1	22	51.2				
Induced	3	2.8	2	4.7				
Section	25	23.1	17	39.5				
Vacuum extraction	0	0.0	2	4.7				
Fertilization method					6.259	**0.020***	0.210	**0.030**
Natural	105	97.2	38	88.4				
Assisted	1	0.9	0	0.0				
Artificial	2	1.9	5	11.6				
Pregnancy complications					13.251	**0.002***	0.305	**0.001**
No complications	101	93.5	34	79.1				
Bleeding	5	4.6	1	2.3				
Cervical cerclage	2	1.9	4	9.3				
Premature uterine contractions	0	0.0	4	9.3				

* Fisher's exact test; χ^2 - chi-squared test; CC - correlation coefficient; p - probability value

Table 3. *Prevalence of the child-related perinatal risk factors in neurodevelopmental outcome groups*

Child-related specifications	Neurodevelopment				χ^2	p	φ	p
	Normal		Delayed					
	n	%	n	%				
Gestational age					15.459	< 0.001	-0.336	**< 0.001**
Preterm	25	23.1	25	58.1				
Term neonates	83	76.9	18	41.9				
Twins	18	19.4	14	41.2	5.186	0.023	0.223	**0.012**
Oxygen therapy	28	25.9	29	67.4	20.826	< 0.001	0.387	**< 0.001**
HIE	19	17.6	25	58.1	22.563	< 0.001	0.403	**< 0.001**
Sepsis	7	6,5	17	39.5	22.724	< 0.001	0.408	**< 0.001**
Ordered MRI of the brain	0	0.0	5	11.6	9.610	0.002	0.293	**< 0.001**

* Fisher's exact test; χ^2 - chi-squared test; φ - phi coefficient (mean square contingency coefficient; p - probability value; HIE: Hypoxic ischemic encephalopathy; MRI: magnetic resonance imaging

Table 4. *Prevalence of postnatal risk factors in neurodevelopmental outcome groups*

Postnatal specifications	Neurodevelopment				χ^2	p	CC	p
	Normal		Delayed					
	n	%	n	%				
Intracranial hemorrhage					15.628	0.001*	0.321	0.002
No	74	68.5	19	44.2				
first degree	22	20.4	8	18.6				
second degree	12	11.1	13	30.2				
Third/fourth degree	0	0.0	3	7.0				
Ultrasound follow-up					38.223	< 0.001	0.449	< 0.001
Up to 12 months	41	38.0	26	60.5				
Up to 18 months	6	5.6	14	32.6				
Speech development					115.021	< 0.001	0.650	< 0.001
Normal	76	70.4	1	2.3				
Mild speech delay	31	28.7	8	18.6				
Significant delay	1	0.9	21	48.8				

* Fisher's exact test; χ^2 - chi-squared test; CC - correlation coefficient; p - probability value

Table 5. *Correlation of perinatal risk factors with neurodevelopmental delay*

Perinatal risk factors	Neurodevelopmental delay	
	r	p
Mother's age	0.226	**0.005**
Parity	0.356	**< 0.001**
History of abortion	0.172	**0.034**
Birth weight	-0,228	**0,005**
Gestational age	-0,372	**< 0,001**
Apgar score in the 1st minute	-0,468	**< 0,001**
Apgar score in the 5th minute	-0,480	**< 0,001**
Length of hospitalization	0,490	**< 0,001**
NICU stay (days)	0,490	**< 0,001**
Antibiotic therapy	0,426	**< 0,001**
Duration of antibiotic therapy	0,507	**< 0,001**
AIMS score, percentiles	-0,640	**< 0,001**
AIMS score for age 8 months, percentiles	-0,791	**< 0,001**
AIMS score for age 12 months, percentiles	-0,775	**< 0,001**
AIMS score for age 18 months, percentiles	-0,704	**< 0,001**

r - Pearson correlation coefficient; p - probability value; NICU – neonatal intensive care unit; AIMS – Alberta Infant Motor Scale;

Table 6. *Predictive value of perinatal risk factors for neurodevelopmental delay*

Perinatal risk factors	B	S.E.	Wald	p	OR	95% C.I.	
						Lower	Upper
Mother's age	0.048	0.046	1.120	0.290	1.049	0.960	1.148
Parity	0.554	0.246	5.090	**0.024**	1.741	1.075	2.818
Abortion	0.542	0.373	2.114	0.146	1.720	0.828	3.573
Health problems in pregnancy	0.487	0.639	0.582	0.445	0.614	0.176	2.148
Birth weight	0.000	0.000	0.025	0.873	1.000	0.999	1.001
Gestational age	-0.447	0.179	6.259	**0.012**	0.640	0.451	0.908
Apgar score in th e 1st min.	-0.614	0.297	4.287	**0.038**	0.541	0.302	0.968
Apgar score in the 5th min.	0.105	0.477	0.049	0.826	1.111	0.436	2.827
Length of hospitalization	0.062	0.176	0.125	0.724	1.064	0.753	1.504
Days of NICU stay	0.114	0.083	1.848	0.1 74	1.120	0.951	1.319
Antibiotic therapy	-0.079	0.226	0.121	0.728	0.924	0.594	1.440

B – unstandardized regression weight; S.E. - possibilities of varying the unstandardized regression weight; Wald - test statistic for the individual predictor variable; p - probability value; OR – odds ratio; C.I. - confidence interval; Statistical model: $R^2 = 0,386$ (Cox & Snell), $R^2 = 0,555$ (Nagelkerke); $\chi^2 = 71,115$; d f= 9; $p < 0,001$; overal = 82,2

In the group with neurodevelopmental delay, there were significantly more premature births, more twins, more instances of oxygen therapy, hypoxic-ischemic encephalopathy, sepsis, and a higher number of ordered brain magnetic resonance imaging (MRI) exams. A statistically significant correlation was found between these factors and delayed neurodevelopment (Table 3).

Table 4 shows the prevalence of postnatal risk factors in the two groups of subjects with different neurodevelopmental outcomes.

In the group with delayed neurodevelopment, there were significantly more intracranial hemorrhages ($p = 0.002$), more brain ultrasound follow-ups, and more cases of delayed speech development ($p < 0.001$) (Table 4).

The correlation between perinatal risk factors and early neurodevelopmental outcomes, as well as the sequence of neurodevelopmental delay, was analyzed. The results are presented in the following table (Table 5).

A statistically significant positive correlation was found between the mother's age, parity, number of abortions, and delayed neurodevelopment. Additionally, a statistically significant negative correlation was observed between birth weight ($p = 0.005$), gestational age, Apgar score, AIMS score, and delayed neurodevelopment. Furthermore, a statistically significant positive correlation was found between the length of hospitalization, number of days in the NICU, antibiotic therapy, and the duration of therapy with delayed neurodevelopment ($p < 0.001$) (Table 5).

These indicators were tested as predictors of neurodevelopmental delay using a logistic regression statistical model, as presented in Table 6.

Parity showed a significant positive predictive value for neurodevelopmental delay. The model was statistically significant, explaining between 20.5% and 29.5% of the variance, and correctly classified 75.2% of the cases. The other maternal-related risk factors did not show a significant predictive value. Among child-related risk factors, gestational age and the Apgar score at the 1st minute showed a significant negative predictive value for neurodevelopmental delay. The model was statistically significant, explaining between 38.6% and 55.5% of the variance, and correctly classified 82.2% of the cases. The other indicators did not show a significant predictive value (Table 6).

DISCUSSION

High-risk neonates are attracting attention due to numerous still unresolved dilemmas related to their assessment, monitoring, and treatment. The age for their selection is getting lower and lower, in the perinatal period, and earlier, because their neurodevelopmental outcome is dubious, and largely depends on both biomedical and environmental factors. The analysis of perinatal risk factors is important, in an attempt to select the most significant, those that can have the greatest impact on the long-term outcome of the affected children. The aim of this study was to analyze perinatal predictors of neurodevelopmental outcomes for high-risk neonates up to 18 months of age.

In our research, AIMS was used to monitor the early neurodevelopment of the examined neonates. During the 18-month follow-up of early neurodevelopment, children from the high-risk group showed statistically significantly lower scores on the Alberta Infant Motor Scale at all age assessments, with $p < 0.001$. AIMS can be used as a screening tool to detect and monitor early developmental delay. In our study, AIMS correlated well with early neurodevelopmental outcomes. The latest recommendations for dealing with high-risk children dictate that imaging tests such as brain ultrasound or brain magnetic resonance imaging (MRI) should be performed in children with an abnormal examination (1). The common clinical practice is to perform brain MRI before discharge (16), which was the case in our study as well. In our study, 108 infants (71.5%) had normal neurodevelopment at the age of 18 months. A mild disorder was recorded in 29 subjects (19.2%), while 14 (9.3%) had neurodevelopment delay. Additionally, 15 subjects (9.9%) had a confirmed diagnosis of muscle tone disorder, while 6 (4.0%) had a significant movement disorder. These results are generally in agreement with studies by others (3, 4, 6).

Functional outcomes should be assessed with a follow-up of at least 2 years (1, 10). Some studies observed that cognitive performance at 6 months in neuro-risk neonates was not a reliable predictor of cognitive status at 24 months and found that early intervention could improve their functional outcomes (17). On the other hand, the longitudinal study of high-risk infants (18), observed that cognitive performance at the age of 12 months, serves only as a general predictor for cognition at the age of 12 months and preschool age. Therefore, supervision of early development and early interventions should be implemented until at least 2 years of age.

In our study, significantly more mother-related, obstetrical, and child-related risk factors were found in the group with suboptimal neurodevelopment compared to healthy subjects which is consistent with previous reports. Many studies have analyzed perinatal and postnatal risk factors, their significance, and correlation with early neurodevelopment (19, 20). A study by Tskimanauri et al. (11) on the correlation between perinatal risk factors and neurodevelopmental outcomes in children at 24 months of age reports that gestational age and neonatal sepsis were strongly correlated with

adverse neurological disorders, and a less significant correlation was with hypoxic-ischemic encephalopathy and intracranial hemorrhage. Risk factors for neonatal sepsis partly overlap with risk factors for neurodevelopmental delay (21). The most significant single risk factor for abnormal neurodevelopmental outcomes in this study was gestational age, maternal age, and pregnancy pathology. Also, an Indian study (22) reports a higher prevalence of neurodevelopmental delay in neonates from the low birth weight, preterm, and twin groups. Neonatal sepsis, convulsions, and perinatal asphyxia also showed significant association with adverse neurodevelopmental outcomes. Critically ill neonates who require treatment in the NICU deserve special attention. In our study, in the group with delayed neurodevelopment, there were significantly more premature births, oxygen therapy, hypoxic-ischemic encephalopathy, sepsis, and intracranial hemorrhages. Most previous studies conclude that higher gestational age at birth and higher birth weight are associated with a lower risk of developmental delay. Cohort studies focused on motor development showed that the degree of impairment decreased over time (23). A significant number of studies analyze perinatal brain injuries and their neurodevelopmental outcome. Research on the outcome of neonatal encephalopathy suggests that a mild form of encephalopathy does not affect later development, while a severe form of encephalopathy results in marked delay. Great variability occurs in children who have moderate encephalopathy (19). Severe intraventricular hemorrhage is also associated with severe cognitive impairment and paraventricular leukomalacia. The development of motor, cognitive, and speech functions is directly related to the degree of intracranial hemorrhage (20).

Gestational age and Apgar score in the 1st minute showed a significant negative predictive value for neurodevelopmental delay. Many perinatal risk factors are intertwined with prematurity, however, the incidence of neurodevelopmental disorders among these infants remained high and was inversely related to gestational age (23).

Prematurity and perinatal asphyxia remain the greatest risks for neurodevelopmental adverse outcomes in neonates and should be the focus of medical science and practice. This study has its limitations, given that it is a single-center study with a small sample. A multicenter study on a larger sample is needed, based on which we can obtain more reliable guidelines for further action in this area.

CONCLUSION

In our study, a mild neurodevelopmental disorder was observed in one-fifth of the participants, while 9.3% had delayed neurodevelopment. The Alberta Infant Motor Scale demonstrated a strong correlation with early neurodevelopmental outcomes. A significantly higher number of perinatal risk factors were found in the group with suboptimal neurodevelopment compared to the healthy group. A significant correlation was identified between the mother's age, parity, number of abortions, and delayed neurodevelopment. Additionally, a correlation was found between birth weight, gestational age, Apgar score, AIMS score, length of hospitalization, days of NICU stay, and antibiotic therapy with delayed neurodevelopment. Gestational age and the 1st-minute Apgar score showed significant negative predictive values for neurodevelopmental delay. Children at the highest risk of developmental disabilities, along with their families, should be prioritized for timely identification, monitoring, and early intervention. Early supervision, development monitoring, and rehabilitation of high-risk neonates should continue until at least 2 years of age."

List of abbreviations

AIMS - Alberta Infant Motor Scale
GA - Gestational age
GW- Gestational week
MRI - Magnetic resonance imaging
HIE - Hypoxic ischemic encephalopathy
NICU – Neonatal intensive care unit
χ^2 - chi-squared test
φ - phi coefficient (mean square contingency coefficient)
CC - correlation coefficient
r - Pearson correlation coefficient
B – unstandardized regression weight;
S.E. - possibilities of varying the unstandardized regression weight;
Wald-test statistic for the individual predictor variable;
OR – odds ratio;
C.I. - confidence interval

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: No

Author contributions: Conception and design: DH, ZH, FS; Acquisition, analysis, and interpretation of data: DH and FS; Drafting the article: ZH and DH; Revising the article critically for intellectual content: DH and FS; Approved the final version of the manuscript: ZH, DH, FS.

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

Sažetak

PERINATALNI PREDIKTORI NEURORAZVOJNIH ISHODA KOD VISOKORIZIČNIH NOVOROĐENČADI

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Uvod: Zahvaljujući napretku neonatalne medicine, perinatalni morbiditet je značajno smanjen, ali se povećava broj visokorizične novorođenčadi. Međutim, napori da se predvidi neurorazvojni ishod u najranijoj dobi su ograničeni. **Cilj** ovog istraživanja bio je analizirati perinatalne prediktore neurorazvojnog ishoda kod visokorizičnih novorođenčadi. **Metode:** Prospektivno, longitudinalno dvogodišnje istraživanje sprovedeno na Klinici za dečije bolesti, Univerzitetskog kliničkog centra u Tuzli, obuhvatilo je 151 novorođenče, 99 u grupi sa poznatim perinatalnim faktorima rizika i 52 u kontrolnoj grupi bez rizika. Rani neurorazvoj je procenjen AIMS (Alberta Infant Motor Scale) skalom. U statističkoj obradi korištene su standardne metode. Studiju je odobrio Etički komitet ustanove. **Rezultati:** Od 151 posmatrane novorođenčadi, u dobi od 18 meseci, njih 108 (71,5%) imalo je normalan neurorazvoj, blagi poremećaj je zabeležen kod 29 ispitanika (19,2%), dok je 14 (9,3%) imalo zastoj u neurorazvoju. U grupi sa suboptimalnim neurorazvojem bilo je značajno više blizanačkih trudnoća, zdravstvenih problema tokom trudnoće, više artificijalnih porođaja, veštačkih oplodnji i komplikacija u trudnoći. Kod novorođenčadi je bilo značajno više prevremenih porođaja, hipoksične ishemijske encefalopatije, intrakranijalnih krvarenja. Pronađena je značajna korelacija između starosti majke i pariteta sa zaostajanjem u neurorazvoju. Utvrđena je korelacija između porođajne težine novorođenčeta, gestacijske dobi, Apgar skora, dužine hospitalizacije, dana boravka u neonatalnoj intenzivnoj nezi, sa odgođenim neurorazvojom. Gestacijska dob i Apgar skor u 1. minuti pokazali su značajnu negativnu prediktivnu vrednost za predviđanje zaostajanja u neurorazvoju. **Zaključak:** Prevremeno rođenje i perinatalna asfiksija ostaju najveći rizici za neurorazvojne neželjene ishode kod novorođenčadi i trebali bi biti u fokusu medicinske nauke i prakse. Novorođenčad koja su u najvećem riziku od kašnjenja u razvoju i njihove porodice treba da imaju prioritet za pravovremenu identifikaciju, dugoročno praćenje i ranu intervenciju.

Ključne reči: perinatalni faktori rizika, visokorizična novorođenčad, neurorazvojni ishod, prediktori.

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***How to cite this article**:* Hajric Z, Hadzic D, Skokic F. Perinatal Predictors of Neurodevelopmental Outcomes in High-Risk Neonates. Sanamed. 2024; 19(3): 267-274. doi: 10.5937/sanamed0-54887.

SANAMED
2024; 19(3): 275–279
ISSN-1452-662X

DOI: 10.5937/sanamed0-50158
UDK: 577.213.3.083.3
ID: 159929097
Original article

RIBONUCLEIC ACID ISOLATION FROM HUMAN MONONUCLEAR CELL CULTURE WITH MAGNETIC BEADS PRE-ENRICHMENT FOR MOLECULAR ANALYSIS

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Primljen/Received 31. 03. 2024. Prihvaćen/Accepted 15. 05. 2024. Published online first: 24. 05. 2024.

Abstract: **Introduction**: In order to develop immunotherapies and therapeutic humoral molecules, ribonucleic acid (RNA) from cultured mononuclear cells (MNCs) is needed. However, it is not possible to isolate RNA using the standard mini column method from older MNC cultures. Therefore, the aim of this study was to develop a method to isolate RNA from MNC cultures, particularly older ones.

Materials and Methods: MNC cultures were grown from human buffy coats. The media from the cell culture was centrifuged to generate a pellet, to which CD45-specific magnetic beads were added. RNA was then isolated using the mini column method. The housekeeping gene beta-actin was used to confirm the success of RNA isolation through both real-time and conventional PCR tests.

Results: RNA was successfully isolated from MNC cultures, especially those that were a few months old, after pre-enrichment with magnetic beads. Without the magnetic bead pre-enrichment step, RNA isolation was not achieved. The results of the housekeeping gene tests indicated successful RNA isolation in all cases through both real-time and conventional PCR. Additionally, spectrophotometric values of the isolated RNA confirmed successful isolation.

Conclusion: This study is the first to demonstrate that it is possible to isolate RNA from human MNC cultures, particularly older ones, using specific magnetic beads. This method opens new opportunities for conducting genetic analyses, biomarker confirmation, and the development of antibodies.

Keywords: Mononuclear cells, RNA isolation, Mini column method, Polymerase chain reaction.

INTRODUCTION

Human mononuclear cell (MNC) cultures are generated for various purposes, such as gene therapies, immunotherapies, and antibody production. The applications of these cell cultures are increasing as the isolation of MNCs becomes feasible in many laboratories worldwide. There is a need to isolate nucleic acids from these cell cultures for different molecular analyses. These cultures can be successfully stored in various freezing media for later use (1-7).

Nucleic acid isolation is crucial for conducting various analyses, including the detection of pathogens, genetic mutations, and specific biomarkers. Different methods exist for nucleic acid isolation, such as the mini column and magnetic beads methods (8-12).

The difficulty arises when attempting to isolate nucleic acids, especially ribonucleic acid (RNA), from MNC cultures that are several months old. In our laboratory, we attempted to isolate nucleic acids from such MNC cultures using both the mini column and magnetic beads methods for over two years without success. It appears that mononuclear cells become resistant to nucleic acid isolation after being cultured for extended periods. Other research groups have also reported facing similar challenges (oral communications from different research groups and discussed elsewhere). The literature lacks protocols for isolating RNA in these cases.

Therefore, we decided to develop a method to isolate nucleic acids from MNC cultures older than four months. This method is based on magnetic beads pre-enrichment.

MATERIAL AND METHODS

Human buffy coats were provided by the Red Cross, Germany. They were supplied with numbers instead of names, ensuring donor anonymity and eliminating the need for ethics committee approval.

Isolation of MNCs: Isolation was performed using an MNC isolator. 500 µl of buffy coat was mixed with 4500 ml PBS (Biochrome, Germany). This mix-

ture was kept at room temperature for 10 minutes, then centrifuged and washed twice. The number of cells was counted using a Neubauer chamber under a microscope (13).

Culturing of MNCs: The MNCs were cultured in DMEM (Dulbecco's Modified Eagle Medium) and RPMI (Roswell Park Memorial Institute) solutions with 1% antibiotics (streptomycin, penicillin), 1% glutamine, and 2-3% FCS. Cultures were maintained in a CO_2 incubator at 37°C. All media components were sourced from Biochrome, Germany, or Lonza, USA (11). The cells were fed once a week, and the media was collected for various assays. Cell health was regularly monitored under a microscope, and cultures were maintained for over six months.

Isolation of Ribonucleic Acid: For RNA isolation, 5 ml of media containing MNCs was centrifuged to generate a pellet. Pellets were also generated from cultures using trypsin. This pellet was diluted in 100 µl of PBS and used to isolate RNA with a mini column kit (Genekam, Germany). This method, referred to as Method 1, failed consistently over two years (12).

Development of a New Method Using Magnetic Beads: In the new method, 10 to 20 µl of CD45 magnetic beads (Genekam) were added to the diluted pellet and incubated at room temperature for 15 minutes in a 2 ml microtube. Then, 1.5 ml PBS was added, and the microtube was placed in a magnetic rack (Genekam). Cells attached to the magnetic beads were attracted to the magnets, forming a pellet. The supernatant was discarded, and the pellet was washed twice with PBS in the magnetic rack. The collected pellet with magnetic beads was resuspended in 50 µl of PBS or used directly for nucleic acid isolation. Alternatively, magnetic beads were added directly to 3 ml of media containing cells and incubated at room temperature for 15 minutes. The microtubes containing bead-bound cells were placed in a magnetic rack to generate a pellet (1.5 ml media was pipetted into two microtubes for use in the magnetic rack) and washed as described above (Figure 1).

Nucleic Acid Isolation: RNA isolation was performed using a mini column isolation kit (Genekam, Germany). Briefly, 20 µl of the suspended pellet was added to lysis buffer 1 (Tube A) with proteinase K and incubated at 56°C for 15 minutes. Lysis buffer 2 and molecular ethanol were then added. This solution was passed through a mini column and washed twice. Finally, RNA was eluted in 50 to 100 µl of elution buffer and stored at -20°C for further use. The complete isolation protocol is available from the manufacturer (12).

Confirmation of Successful RNA Isolation: The success of RNA isolation was confirmed using a spectrometric instrument, Nanodrop (ThermoFisher, USA), and spectrophotometric values were measured.

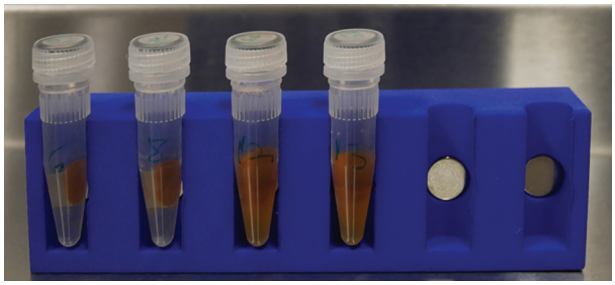

Figure 1. *Magnetic rack with microtubes containing magnetic beads with MNC*

The machine was calibrated with elution buffer, and 2 µl of isolated RNA per isolation was used to measure the yield. The yield per µl was recorded.

PCR Assays: Confirmation of successful RNA isolation was performed using conventional and real-time PCR assays for the human internal control beta-actin. For conventional PCR, 2 µl of RNA in a total volume of 20 µl was used with a PCR kit (Genekam) in a thermocycler (Biometra, Germany), and the results were visualized as bands in 2% agarose gel. For real-time PCR, 2 µl of RNA in a total volume of 20 µl was used in a real-time PCR assay on a thermocycler (ABI 7500, ThermoFisher, USA), and results were observed as smooth curves and Ct values. Positive and negative controls were used. Full protocols for these assays are available from the manufacturers.

Further assays were performed after converting RNA into cDNA, but these will be detailed in future publications.

RESULTS

There was no RNA isolation without using magnetic beads for two years with Method 1. After introducing CD45-specific magnetic beads, successful RNA isolations were achieved in all samples, as shown in Table 1. The results of 15 isolations are presented as examples. In total, over 100 such isolations were performed successfully over three years, confirmed through spectrometric values. Further confirmation was obtained through conventional PCR and real-time PCR for the human housekeeping gene beta-actin (Figure 2), with Ct values ranging between 17 and 22.

The isolated volume was 100 µl per sample, sufficient for multiple molecular analyses. Using 20 µl of magnetic beads was adequate to isolate RNA from MNC cultures, even those older than six months. The method was also successful with fresh MNC cultures (a few days old).

Magnetic bead isolation using CD45-specific magnetic beads was quick, taking less than 30 minutes. The quality of the magnetic rack was crucial; the rack used in this work was designed to fit microtubes

Table 1. *Results of RNA isolation from MNC cultures with and without magnetic beads with different parameters*

Experiment	RNA isolations without magnetic beads	RNA isolations with magnetic beads	Real time PCR (beta actin)	cDNA synthesis	Spectrometric measurement
1	failure	–	–	–	–
2	failure	–	–	–	–
3	failure	–	–	–	–
4		successful	+	+	+
5		successful	+	+	+
6		successful	+	+	+
7		successful	+	+	+
8		successful	+	+	+
9		successful	+	+	+
10		successful	+	+	+
11		successful	+	+	+
12		successful	+	+	+
13		successful	+	+	+
14		successful	+	+	+
15		successful	+	+	+

tightly, allowing for easy disposal of the supernatant by tilting the rack into a waste container. This method worked with both pellets and culture media, where magnetic beads were added directly into MNC media without generating a pellet.

These isolations were successfully converted into cDNA and used for further applications, which will be detailed in future publications.

DISCUSSION

In this research, we developed a method to isolate RNA from MNC cultures. Many laboratories working with MNC cultures face the challenge of isolating RNA from these cells. We encountered significant difficulties isolating nucleic acids from our cell cultures, and our sales representatives frequently received the same questions during visits to various universities in Germany. This motivated us to solve the problem.

The method presented here uses magnetic beads to isolate MNCs, which are then used to isolate nucleic acids with the mini column method. This method yields a sufficient quantity of nucleic acid (100 µl per sample) for various molecular analyses. In comparison, direct isolation without magnetic beads was unsuccessful, as PCR tests of such isolations failed to produce any signals.

The magnetic bead isolation method works well with both pellets and cell culture media containing MNCs. This step is completed within 30 minutes, and

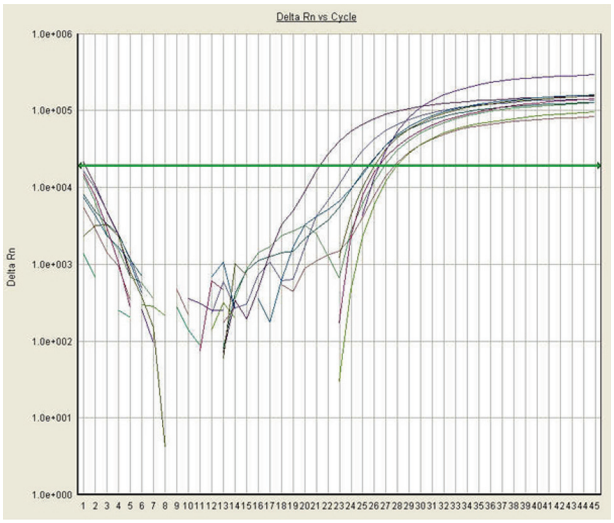

Figure 2*. The result for successful presence of isolated RNA from MNC cultures with real time PCR*

RNA isolation with the mini column takes an additional 35 minutes, resulting in a total isolation time of about an hour. The results were comparable to those obtained from isolations of different human tissue samples in our other research (14).

In this study, we used 2-3% FCS, consistent with existing literature, thus reaffirming that 2-3% FCS can be effectively used in cell culture, saving costs and improving animal rights (11).

Other groups adopting this method should consider the quality of magnetic racks, as some available on

the market have drawbacks, such as microtubes shaking during the process, leading to the need for many pipette tips. In our case, the microtubes fit well in the magnetic rack, allowing for quick disposal of the supernatant by tilting the rack, which makes the process faster (Figure 1).

Developing this method took us two years and involved numerous experiments, though we have presented only a few in our results.

CONCLUSION

This work may be the first to report the development of a robust method for isolating RNA from human MNC cultures, particularly those a few months old, using a magnetic beads pre-enrichment step followed by mini column isolation. The nucleic acid isolated can be used for various molecular applications, including the analysis of genetic targets, isolation of protein-specific genes, and creating the basis for generating new types of antibodies for therapeutic and diagnostic use.

Abbreviations

Ct - Threshold Cycle
DMEM - Dulbecco's Modified Eagle Medium
FCS - Fetal Calf Serum
MNC - Mononuclear Cells
PCR - Polymerase Chain Reaction
RNA - Ribonucleic Acid
RPMI - Roswell Park Memorial Institute

Funding: There was no external funding.

Conflicts of Interest: There are no conflicts of interest.

Note: No artificial intelligence tools were used in these studies.

Acknowledgements: Ms. Kornelia Niklis assisted in the laboratory work. Mr. Suppers assisted in designing the graphics.

Sažetak

IZOLACIJA RIBONUKLEINSKE KISELINE (RNA) IZ LJUDSKIH MONONUKLEARNIH ĆELIJA SA PRETHODNIM OBOGAĆIVANJEM MAGNETNIM PERLAMA ZA MOLEKULARNU ANALIZU

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Uvod: Za razvoj imunoterapija i terapijskih antitela, neophodna je ribonukleinska kiselina (RNA) iz kultivisanih mononuklearnih ćelija (MNC). Međutim, nije moguće izolovati RNA standardnom metodom mini kolona iz starijih MNC kultura. Stoga je cilj ovog istraživanja bio razviti metod za izolaciju RNA iz MNC kultura, posebno starijih.

Materijali i metode: MNC kulture su bile uzgajane iz humanih „buffy coats". Medijum iz ćelijske kulture je centrifugiran kako bi se generisao pelet, a kome su dodate CD45-specifične magnetne perle. RNA je zatim izolovana koristeći metodu mini kolona. Housekeeping gen beta-aktin korišćen je kako bi se potvrdio uspeh izolacije RNA putem realno-vremenskih i konvencionalnih PCR testova.

Rezultati: Izolacija ribonukleinske kiseline (RNA) iz MNC kultura je postignuta uspešno, posebno kod onih koje su bile nekoliko meseci stare, nakon predobogaćivanja magnetnim perlama. Bez koraka predobogaćivanja magnetnim perlama, izolacija RNA nije bila ostvariva. Rezultati testova housekeeping gena su pokazali uspešnu izolaciju RNA u svim slučajevima putem realno-vremenskih i konvencionalnih PCR metoda. Dodatno, spektrofotometrijske vrednosti izolovane RNA su potvrdile uspešnu izolaciju.

Zaključak: Ova studija prva pokazuje da je moguće izolovati RNA iz ljudskih MNC kultura, posebno starijih, korišćenjem specifičnih magnetnih perli. Ovaj metod otvara nove mogućnosti za sprovođenje genetičkih analiza, potvrdu biomarkera i razvoj antitela.

***Ključne reči**:* Mononuklearne ćelije, Izolacija RNA, Metoda mini kolona, Lančana reakcija polimeraze.

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How to cite this article*:* Bhatia S. Ribonucleic Acid Isolation from Human Mononuclear Cell Culture with Magnetic Beads Pre-enrichment for Molecular Analysis. Sanamed. 2024; 19(3): 275-279. doi: 10.5937/sanamed0-50158.

SANAMED
2024; 19(3): 281–288
ISSN-1452-662X

DOI: 10.5937/sanamed0-51804
UDK: 616.62-008.22-055.2
ID: 160164361
Original article

PREVALENCE, PATTERN, AND RISK FACTORS FOR URINARY INCONTINENCE AMONG WOMEN IN A LOW-RESOURCE SETTING

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Primljen/Received: 25. 06. 2024. Prihvaćen/Accepted: 18. 08. 2024. Published online first: 14. 10. 2024.

Abstract: **Introduction**: Urinary incontinence (UI) is a common but under-reported condition among women in low-resource settings. The prevalence and pattern of UI, as well as associated risk factors must be examined to inform appropriate health interventions. This study investigated the prevalence, pattern, and risk factors for UI among women in a low-resource setting.

Methods: This community-based cross-sectional study was conducted among 400 women ≥ 15 years old in Ilorin South Local Government Area, Kwara State, Nigeria. An interviewer-administered questionnaire was used to collect socio-demographic and health-related data on UI The prevalence of UI was determined using the International Consultation on Incontinence Modular Questionnaire-Urgency Frequency Scale (ICIQ-UFS). Analysis was done using SPSS version 20.

Results: The mean age of the respondents was 47.9 (± 4.5), and 200 (50.0%) were grand-multipara. The prevalence of UI among women in our study setting was 52.7%. The most common pattern of UI was stress incontinence at 140 (67%), followed by mixed incontinence at 45(21%) and urge incontinence at 26 (12%). Age ($p < 0.001$), parity ($p = 0.006$), and BMI ($p < 0.001$) were significantly associated with UI.

Conclusion: The findings of this study suggest that UI is highly prevalent among our study population and that age, parity, and BMI are associated with the occurrence of UI. There is a need for interventions that focus on preventing and managing UI among women in low-resource settings.

Keywords: prevalence, pattern, risk factors, urinary incontinence, women.

INTRODUCTION

Urinary incontinence, which is the involuntary loss of bladder control, affects women of all ages and races and may have severe psychological effects. The International Continence Society defines urinary incontinence as *"the complaint of any involuntary leakage of urine"* (1, 2). Several disorders of lower urinary tract function and other conditions may lead to urine incontinence, which manifests in various ways. Stress urinary incontinence is *"the involuntary loss of urine in response to physical exertion, such as sneezing or coughing"*. Urge urinary incontinence is the involuntary loss of urine that occurs during or shortly before an episode of urgency (a strong, sudden need to urinate that can't be put off for long). The involuntary loss of urine due to urgency and physical activity (sneezing, coughing, etc.) is known as "mixed urinary incontinence". The symptoms of an overactive bladder include urgency, frequency, and nighttime urination, with or without urine incontinence (1, 2, 3).

Embarrassment, a lack of awareness about treatment choices, and a fear of surgery may all make patients hesitant to begin conversations regarding incontinence and urinary symptoms (3). Previous surveys reported that between 26% and 61% of women who live in the community have urinary incontinence, but only 18% seek treatment for it (4, 5). Urge and stress incontinence are often mentioned in Western nations (6, 7). These latter ailments certainly occur, but in Nigerian culture, they are not often seen as severe enough to need a trip to the hospital (8, 9).

Women still see urinary incontinence as a taboo because of how it presents (10). Worldwide, urinary

incontinence is primarily unrecognized, unreported, and untreated (10, 11).

Usually, women's continence is aided by the pelvic floor muscles, which assist in holding urine in the urinary bladder and, when necessary, release it. The bladder expands progressively in relation to the volume of urine stored in it (12). Urine is forced into the urethra when the bladder muscles contract in response to certain stimuli with a concomitant relaxation of the muscles of the sphincter encircling the urethra to allow urination. However, incontinence develops when the expulsive force in the bladder is greater than the closure force in the urethra, leading to involuntary urine leakage. A dysfunctional urethra sphincter may also cause urinary incontinence (13).

Although it's sometimes thought that only older women have urinary incontinence, there are women of all ages who deal with this condition (14). According to Seshan et al. (12), women of reproductive age who had specific risk factors were more likely to have urinary incontinence. Urinary incontinence has a detrimental influence on women's quality of life, especially as they age (15, 16). Rogers argues that age is a significant risk factor, particularly for women who have given birth vaginally. These women are more likely to experience stress incontinence due to the destruction of their pelvic muscles (8).

The detrusor muscles are further weakened by obesity, a significant risk factor (15). Turkish research found that obesity, urinary tract infections, and constipation are all risk factors for urinary incontinence in women over the age of 65 (15).

Age brings about hormonal changes in women, particularly after childbirth. This increases the possibility of urinary tract infections and, therefore, incontinence. Hygiene plays a role in why there are more illiterate women experiencing urinary incontinence (16). Urinary incontinence was a common problem among women with body mass indexes of 26 or above (14). Women are more likely to get urinary incontinence when their parity increases (14). This is because there is an increase in urethral mobility during pregnancy, and this worsens by injury to the pelvic floor muscles with the widening of the hiatus during vaginal birth (15, 16, 17). Urinary incontinence has a negative impact on quality of life and may lead to a loss of self-esteem; thus, it is essential to identify the prevalence and risk factors of this condition among our population so that we can take appropriate preventative actions. The prevalence, pattern, and risk factors for urinary incontinence among Nigerian women were examined in this research. This study will add to the body of knowledge on urinary incontinence among Nigerian women.

MATERIAL AND METHODOLOGY

Study design

This was a community-based cross-sectional study conducted in Ilorin South Local Government Areas (LGAs) in Kwara State, Nigeria, between January and July 2022. This LGA has a projected population of 248,759 (2018 census) (14). The study population comprised women aged ≥ 15 years living permanently within Ilorin South LGA, which constitutes 22% of the total population in this LGA.

Included in the study were non-pregnant women, irrespective of their parity experience, those who were not on medication for urinary symptoms, and women who resided in Ilorin South LGA. Pregnant women, women in the puerperium, and those who were too ill to participate in the study were excluded. We also excluded those who refused to participate in the study. The STROBE Checklist was used to review this manuscript.

Sample size determination

The projected population of Ilorin South LGA is 248,759 (2006 census), of which women aged 15 years and above are 54,727 (18). Fisher's formula was used to determine the minimum sample size, where the population is greater than 10,000, as shown below:

$$n = \frac{z^2 pq}{d^2}$$

Where:

n = The desired sample size (when the population is greater than 10,000)

z = The standard normal deviation, usually set at 1.96, corresponds to the 95% confidence level.

p = the proportion of women with urinary incontinence using an estimated prevalence rate of 30.6% (11).

$q = 1.0 - p$

d = degree of accuracy, set at 0.05 for this study

Therefore:

$n = (1.96)^2 (0.306) (0.694) / (0.05)$

$= 326.33$

The minimum sample size for this study was 362 (assuming a 10% attrition rate).

Sampling techniques

A multistage sampling technique was employed in the selection of the respondents. Proportional allocation was used to distribute the sample size across the selected wards and communities.

Stage 1: Selection of Wards: Five out of the eleven wards in Ilorin South LGA were selected by simple random sampling using balloting without re-

placement. The wards set were Akanbi IV, Akanbi III, Akanbi V, Balogun Fulani I, and II.

Stage 2: Communities: Simple random sampling using the balloting method was used to select two communities each from the five wards earlier chosen to make ten communities. The communities selected were Ago-Aiyekale, Tanke-Akata, Agbabiaka, Oke-Ogun, Ogidi, Kulende, Erubu Asunara, Makana, Idiagbon, and Gbodofu.

Stage 3: Selection of Houses: A systematic sampling technique was used to select the required houses in each community. Every fourth house in each district was selected (or balloted when more than one) until the sampling frame was exhausted.

Stage 4: Selection of subjects: One eligible woman in each house was interviewed. When the respondent refused, the next eligible woman was interviewed. An eligible woman was selected by simple random sampling by balloting in households with more than one.

Data collection

A pre-test of the questionnaire was conducted in Ilorin East Local Government using 10% of the study sample. Necessary amendments were made before administering the questionnaire to the study participants. Data were collected by trained research assistants using the International Consultation on Incontinence Modular Questionnaire-Urgency Incontinence Short Form (ICIQ-UI Short Form) (2). It is a validated, interviewer-administered semi-structured questionnaire that assesses the presence or absence of any form of involuntary loss of urine within the last four weeks prior to the study. The questionnaire gathered information on the socio-demographics and obstetric characteristics of the respondents, along with more specific questions related to the prevalence, pattern, and risk factors for urinary incontinence. The severity of urinary incontinence was measured using the Sandvik Severity Index (15). This severity index was created by multiplying the reported frequency (four levels) by the amount of leakage (two levels) (Appendix 1). The resulting index value (1-8) was further categorized into slight (1-2), moderate (3-4), and severe (6-8). Typically, slight incontinence denotes leakage of drops a few times a month, moderate incontinence daily leakage of drops, and severe incontinence, larger amounts at least once a week.

Appendix I. *Questions used to assess the degree of urinary incontinence in women*

(1)	How often do you experience urinary leakage? 1 Less than once a month 2 One or several times a month 3 One or several times a week 4 Every day or night
(2)	How much urine do you lose each time? 1 Drop or little 2 More

The severity index is created by multiplying the results of questions (1) and (2): 1 2 = slight three 4 = moderate 6-8 = severe

Data analysis

The data were sorted manually, edited (cleaned), and responses were checked for errors and completeness before they were coded. Data were analyzed statistically using the SPSS 20.0 statistical package. Descriptive analysis was used to determine the socio-demographic characteristics of the respondents and the prevalence and pattern of urinary incontinence among the study population. Descriptive analysis, as well as Pearson's Chi-squared test, was used with a p-value of 0.05. Multivariable logistic regression was used to identify factors that increased the odds of urinary incontinence.

Ethical considerations

Ethical approval was obtained from the ethical review committee of the Kwara State Ministry of Health. All participants were fully informed about the study and reserved the right to voluntarily withdraw for whatever reason at any stage of the study without penalty. Written informed consent was obtained from eligible participants. Written assent was obtained from eligible participants below the age of 18 years, while written consent was obtained from either their guardians or parents. Information collected was kept confidential, and respondents' names were not requested in the questionnaires.

RESULTS

Four hundred eligible participants were recruited for the study. Most respondents were between the ages of 31 and 60 (63.8%). The mean age of the respondents was 47.9 ± 4.5 years. The majority of the respondents were married (72%). Among the respondents, 116 (29%) were traders and full-time housewives, while 105 (26.3%) were in other occupations. The respondents were mainly Muslims (60.5%). About one-third of the respondents, 136 (34%), had tertiary education, while 29.7% were secondary school leavers, as shown in Table 1.

The study population's mean body mass index (BMI) was 30.4 ± 2.7. The prevalence rate of urinary incontinence was 52.7%. Over three-quarters of the participants, 318 (79.5%), had experienced at least

Table 1. *Socio-demographic characteristics of respondents*

Characteristics	Frequency (n= 400)	Percentage (%)
Age Groups		
15-30	84	(21.0)
31-45	135	(33.8)
46-60	120	(30.0)
> 60	61	(15.2)
Mean ± SD	47.9 (± 4.5)	
Marital Status		
Single	52	(13.0)
Married	288	(72.0)
Divorced	31	(7.7)
Widowed	29	(7.3)
Occupation		
Housewife	105	(26.3)
Trader	116	(29.0)
Artisan	13	(3.2)
Students	63	(15.8)
Civil servant	81	(20.2)
Professional	22	(5.5)
Religion		
Islam	242	(60.5)
Christianity	157	(39.3)
Traditional	1	(0.2)
Level of Education		
No formal Education	55	(13.8)
Primary	55	(13.8)
Secondary	119	(29.7)
Tertiary	136	(34.0)
Islamic	35	(8.7)

three parous experiences, while 189 (47.2%) had episiotomies or perineal lacerations during their previous vaginal deliveries, as shown in Table 2.

Among the 211 respondents with urinary incontinence, about 140 (67.0%) leaked urine when coughing, sneezing, laughing, or during physical activities or when feeling pressure on the bladder (stress urinary incontinence). In comparison, 26 (12.0%) respondents experienced leakage or loss of urine with the urge to urinate (urge urinary incontinence). The mixed type of urinary incontinence accounted for 45 (21.0%) respondents, as shown in Figure 1.

Table 3 shows that more than half of the respondents, 111 (52.6%), had lived with urinary incontinence for at least six years. The majority of the women with

Table 2. *Obstetric and medical-related characteristics of respondents*

Variables	Frequency (n = 400)	Percentage (%)
Parity		
0–2	82	(20.5)
3–4	118	(29.5)
≥ 5	200	(50.0)
Mean (± SD)	4.3 (± 1.2)	
Place of birth		
PHC	35	(8.8)
SHC	81	(20.2)
THC	87	(21.8)
Private Hospitals	151	(37.8)
TBAs Centers	24	(6.0)
Home	22	(5.4)
Patient's BMI (Kg/M²)		
< 19.5	41	(12.2)
19.5-24.9	80	(20.0)
25.0-29.9	55	(13.8)
≥ 30.0	224	(56.0)
Mean (± SD)	30.4 (± 2.7)	
Episiotomy		
Yes	189	(47.3)
No	211	(52.7)
Presence of U.I.		
Yes	211	(52.7)
No	189	(47.3)

*PHC = Primary Health Care, SHC = Secondary Health Care, THC = Tertiary Health Care, TBAs = Traditional Birth Attendants

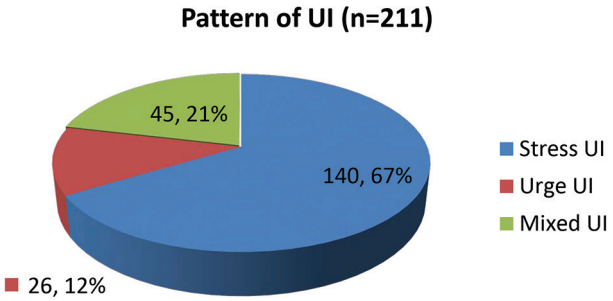

Figure 1. *Pattern of urinary incontinence among the study population*

urinary incontinence, 156 (73.9%), only leaked a few drops of urine, while only 16 (7.4%) experienced leakage both day and night. Using the Sandvik severity index scoring, 22.1% of the respondents reported severe symptoms. Even though 122 (57.8%) had some concern about the impact of urinary incontinence, on-

ly 85 (40.3%) consulted medical personnel about the condition.

Table 4 demonstrates a significant relationship between high parity and the occurrence of urinary incontinence (X^2 = 10.291, p = 0.006, AOR = 3.0, CI 1.9-3.3). There is also a significant association between obesity and the occurrence of urinary incontinence (X^2 = 21.602, p < 0.001, AOR = 5.0, CI = 2.4-5.1). Women with four or more parous experiences are three times more likely to develop urinary incontinence than those with lower parity (X^2 = 10.291, p = 0.006, AOR = 3.0, CI = 1.9 – 3.3).

DISCUSSION

In our sample, 52.7% of participants had urinary incontinence. This figure is within the range of findings seen in other research, which vary from 16.2% to 81.9% (8, 19-22). Our study reveals a higher prevalence than that reported by Hunskaar et al. (17), who conducted a comprehensive analysis of urinary incontinence rates among European women. In Spain, the prevalence was 23%; in Germany, 41%; in the United Kingdom, 42%; and in France, it was 44% (20). Compared to a comprehensive evaluation of research conducted on women in Sub-Saharan Africa, which

Table 3. *Quantity, severity, and Impac10 of incontinence among the respondents*

Variables	Frequency (n = 211)	Percentage (%)
Quantity		
Drops or little	156	73.9
More	55	26.1
Frequency		
Less than once a month	88	41.9
Once or more per month	76	36.0
Once or more per week	31	14.7
Every day and night	16	7.4
Severity Index		
Slight	95	45.2
Moderate	69	32.7
Severe	47	22.1
Duration of U.I. (in years)		
0-5	100	47.4
6-10	95	45.2
> 10	16	7.4
Impact of UI		
No problem	89	42.4
A minor nuisance	40	18.9
Some bother	35	16.6
Much bothered	31	14.7
A significant problem	16	7.4
I consulted a doctor on U.I.		
Yes	85	40.3
No	126	59.7

Table 4. *Association between urinary incontinence and selected characteristics of the respondents*

Variables	Urinary Incontinence		Statistical Indices		OR	95% CI
	Yes (n = 211)%	No (n = 189)%	X^2	P values		
Patient Age						
15-30	12 (25)	62 (75)	89.15	P < 0.001	4.1	3.90 - 5.40
31-45	60 (44.4)	75 (55.6)				
46-60	86 (71.7)	34 (28.3)				
> 60	53 (86.9)	08 (13.1)				
Occupation						
Unemployed	50 (47.6)	55 (52.4)	8.645	P = 0.124	1.45	0.7 -3.6
Trader	66 (56.9)	50 (43.1)				
Artisan	05 (38.5)	08 (61.5)				
Students	33 (52.4)	30 (47.6)				
Civil servants	40 (47.1)	45 (52.9)				
Professionals	17 (77.3)	05 (22.7)				
Level of Education						
No formal education	27 (49.1)	28 (50.9)	1.801	1.717	1.0	0.95 – 1.34
Primary	28 (50.9)	27 (49.1)				
Secondary	57 (48.3)	62 (51.7)				
Tertiary	76 (55.9)	60 (44.1)				
Islamic education	23 (51.1)	22 (48.9)				
Parity						
0-2	30 (37.0)	51 (63.0)	10.291	P = 0.006	3.0	1.9 – 3.3
3-4	70 (64.8)	38 (35.2)				
≥ 5	111 (52.6)	100 (47.4)				
BMI (KG/M²)						
< 19.5	10 (24.4)	31 (75.6)	21.602	P < 0.001	5.0	2.4 – 5.1
19.5 – 24.9	35 (43.8)	45 (56.2)				
25.0 – 29.9	30 (54.5)	25 (45.5)				
≤ 30.0	136 (60.7)	88 (39.3)				

*OR = Adjusted Odd Ratio

indicated a frequency between 0.6% and 42.1%, our study's prevalence is significantly greater (22). In contrast, Aly et al. reported an even higher prevalence—80%—among the Egyptians they studied (23). Our study reveals one of the highest prevalence rates ever recorded in Nigeria (12, 24, 25, 26). The reasons for this discrepancy are not known; however, the differences in age groups, diagnostic criteria for urinary incontinence, survey formats, and data collection strategies might all contribute to the variability in prevalence rates (26).

Two-thirds of the women in our study who experienced urinary incontinence were diagnosed with stress urinary incontinence. This finding is consistent with the results of previous surveys (24, 25, 26). However, this finding contradicts research conducted by Akinlusi et al. among women in Lagos State, Nigeria, who found urge incontinence to be the most prevalent type (11). This discrepancy may be attributed to a higher rate of urinary tract infections in their Lagos sample group.

Our research showed that obesity and having more than four previous pregnancies were significant risk factors for urinary incontinence, regardless of the method of delivery. In our logistic regression analysis, these factors also served as predictors of urinary incontinence incidence. These findings corroborate previous research that established a link between obesity, advanced age, high parity, and urinary incontinence (2, 41, 24). Ojengbede et al. discovered that various factors, including age, number of children, location, birth style, and a history of diabetes, were significantly associated with urge incontinence; however, only location remained significant in the logistic model (23). Similar results have been found in research conducted in other parts of the world (25, 26, 27). Epidemiological research indicates that overweight and obesity are major risk factors for urinary incontinence (14, 25, 26, 27). Surgical and less invasive weight loss methods can be effective treatments for urinary incontinence and should be considered a first-line therapy for overweight or obese women suffering from this condition (25, 26, 27). Song and his associates (26) emphasized that damage to the pelvic floor muscles and structures during childbirth may result in stress urinary incontinence.

Age above 45 years is another strong predictor of urinary incontinence in our study. This finding aligns with previous studies where aging, especially menopausal age, was established as a significant risk factor for urinary incontinence (21-25). Muscle atrophy, weaker contractions, and altered hormonal stimulation are all consequences of aging and being overweight. Injury to the muscles, connective tissue, and nerves of the pelvic floor is common during pregnancy and childbirth.

Despite over half of our study population exhibiting varying patterns of urinary incontinence, only 40.3% sought medical attention for this condition. In the study by Liang et al., only 24% of patients visited a physician for urinary incontinence, 38% in the survey by Rashidi et al., 27% in the study by Li et al., and 27.7% according to Akinlusi et al. (11, 26, 27, 28). The exact reasons for this behavior among our study participants are not known. However, literature suggests several factors, including hope for symptom recovery, shyness, hesitance to discuss the problem with a physician, fear of surgery, the assumption that it is a natural consequence of childbirth and aging, and a lack of knowledge about available treatments (11, 30).

Study Limitations

The findings from this study should be interpreted in light of the following limitations. First, being a cross-sectional study, a causal relationship cannot be established between the occurrence of urinary incontinence and various risk factors. Additionally, the small sample size may limit the generalizability of the study's findings. A more robust multi-center survey on this subject will be needed.

CONCLUSON

The findings of this study suggest that urinary incontinence is highly prevalent among our study population, and that age, parity, and obesity are associated with its occurrence. The prevalence of urinary incontinence can potentially be decreased by addressing modifiable risk factors and enhancing treatment-seeking behavior. Given the high prevalence of urinary incontinence among women in this study, health officials need to prioritize treatment and rehabilitation efforts and consider diagnostic procedures for affected individuals.

Abbreviations

UI – Urinary Incontinence

ICIQ-UFS – International Consultation on Incontinence Modular Questionnaire-Urgency Frequency Scale

BMI – Body Mass Index

LGA – Local Government Area

ICIQ-UI - International Consultation on Incontinence Modular Questionnaire-Urinary Incontinence Short Form

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: No.

Authors' Contributions: BSO and HOR contributed to the design; BSO, AOF, and HOR conducted the statistical analysis and participated in most of the study steps. BSO, AOF, OEA, and FZA prepared the manuscript. SBO, HOR, FZA, ADA, and EOA assisted in designing the study and helped interpret it. All authors have read and approved the content of the manuscript.

Availability of Data and Materials

Datasets are available through the corresponding author upon reasonable request.

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

Sažetak

PREVALENCIJA, OBRASCI I FAKTORI RIZIKA ZA URINARNU INKONTINENCIJU KOD ŽENA U SREDINI SA OGRANIČENIM RESURSIMA

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Uvod: Urinarna inkontinencija (UI) je česta, ali nedovoljno prijavljena pojava među ženama u sredinama sa ograničenim resursima. Potrebno je istražiti prevalenciju i obrasce UI, kao i povezane faktore rizika, kako bi se informisale o odgovarajućim zdravstvenim intervencijama. Ova studija je istražila prevalenciju, obrasce i factore rizika za UI među ženama u sredini sa ograničenim resursima.

Metode: Ova studija preseka sprovedena je među 400 žena starijih od 15 godina u opštini Južni Ilorin, država Kwara, Nigerija. Upitnik koji je vodio intervjuer korišćen je za prikupljanje podataka o socio-demografskim i zdravstvenim aspektima UI. Prevalencija UI utvrđena je korišćenjem Međunarodnog upitnika o inkontinenciji (ICIQ-UFS). Analiza je rađena pomoću SPSS verzije 20.

Rezultati: Prosečna starost ispitanica bila je 47,9 (± 4,5), a 200 (50,0%) su bile višerotke. Prevalencija UI među ženama u našem istraživačkom uzorku iznosila je 52,7%. Najčešći oblik UI bile su stresna inkontinencija, 140 (67%), zatim mešovita inkontinencija sa 45 (21%) i urgentna inkontinencija sa 26 (12%). Starost ($p < 0,001$), paritet ($p = 0,006$) i BMI ($p < 0,001$) bili su značajno povezani sa UI.

Zaključak: Rezultati ove studije sugerišu da je UI visoko prisutna među našom istraživačkom populacijom i da su starost, paritet i BMI povezani sa pojavom UI. Postoji potreba za intervencijama koje se fokusiraju na prevenciju i upravljanje UI među ženama u sredinama sa ograničenim resursima.

Ključne reči: Prevalencija, obrazac, faktori rizika, urinarna inkontinencija, žene.

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***How to cite this article**:* Okesina SB, Fehintola OA, Raji OH, Abdur-Rahim ZF, Ajiboye DA, Ayegbusi EO. Prevalence, pattern, and risk factors for urinary incontinence among women in a low-resource setting. Sanamed. 2024; 19(3): 281-288. doi: 10.5937/sanamed0-51804.

SANAMED
2024; 19(3): 289–292
ISSN-1452-662X

DOI: 10.5937/sanamed0-53867
UDK: 616.717.7-001.5-089
ID: 160160265
Original article

HEADLESS COMPRESSION SCREW FOR SURGICAL TREATMENT OF SCAPHOID FRACTURES

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Primljen/Received: 02. 10. 2024. Prihvaćen/Accepted: 01. 12. 2024. Published online first: 12. 12. 2024.

Abstract: **Introduction:** Scaphoid bone fractures are common and present unique challenges due to the bone's specific fracture patterns and vascular supply. Prompt diagnosis and treatment of acute scaphoid fractures are crucial to prevent nonunion and subsequent wrist arthritis. While non-displaced fractures can often be managed conservatively, advancements in diagnostics, surgical techniques, and implant materials have driven an increasing preference for early surgical fixation.

Patients and Methods: Over a 12-month period, 10 male patients with scaphoid fractures underwent surgical treatment at the University Clinic of Traumatology in Skopje, from January 2022 to March 2024. The patients' mean age was 27.3 years. Diagnosis was confirmed using CT scans and X-rays, with four fractures affecting the left hand and six the right. All patients underwent open reduction and internal fixation using a headless compression screw. A volar approach was used in nine cases, and a dorsal approach in one.

Six patients were treated surgically within 4–14 days post-injury, while four were treated for nonunion after previous conservative management. Among these four, two presented at three months and two at seven months post-injury. The latter group required spongyoplasty and osteosynthesis due to scaphoid deformity, resorption, and bone loss.

Results: Patients were followed up at 1, 3, 6, and 12 months post-surgery. Physical therapy commenced four weeks after surgery, and radiographic monitoring continued until fracture healing was confirmed. No cases of wrist osteoarthritis were observed during the follow-up period.

Conclusion: Although this study represents a small series, it highlights the importance of individualized clinical decision-making for scaphoid fractures. Early surgical intervention can enhance comfort, facilitate quicker return to daily activities, and reduce immobilization duration.

Keywords: Scaphoid fracture, surgical treatment, headless compression screw, nonunion.

INTRODUCTION

Scaphoid fractures represent up to 70% of carpal bone fractures and 2–7% of all fractures (1). Secure fixation procedures with shorter immobilization durations allow patients to return to normal activities more quickly.

Operative screw fixation is a widely accepted method for managing displaced scaphoid fractures, reducing the risk of malunion or nonunion. There is a growing trend toward surgical treatment for non-displaced scaphoid fractures as well.

Current evidence does not support the long-term benefits of surgery over conservative treatment for undisplaced scaphoid fractures. The SWIFFT study, published by Dias et al. in 2020, compared nonsurgical and conservative treatments for minimally displaced scaphoid fractures (2). The results showed no significant differences in union rates, wrist movement, or strength at the 1-year follow-up.

All implants aim to provide solid fragment congruence and strong interfragmentary compression, which aids in the early recovery of wrist mobility. The screw size and threading vary, as do the cannulated and non-cannulated insertion methods. Jason et al. (3) found that headless compression screws were the preferred surgical fixation method among nearly all surgeons in their study.

Our study aimed to assess the effectiveness of headless compression screws in treating acute scaphoid

fractures and, in two cases, nonunions following prior conservative treatment.

PATIENTS AND METHODS

Over a 12-month period, 10 patients with scaphoid fractures received surgical treatment at the University Clinic of Traumatology in Skopje from January 2022 to March 2024. The mean age of the patients was 27.3 years, and all were male. Diagnosis was confirmed using CT(*Computed tomography*) scans and X-rays. Four fractures occurred on the left hand, and six on the right. A tourniquet was applied in all cases for better visualization during surgery.

All patients underwent open reduction and internal fixation with a headless compression screw. A volar approach was used in 9 cases, and a dorsal approach in 1. Six patients were treated surgically within 4–14 days after injury, while four underwent surgery due to nonunion after previous conservative management—two at 3 months and two at 7 months post-injury.

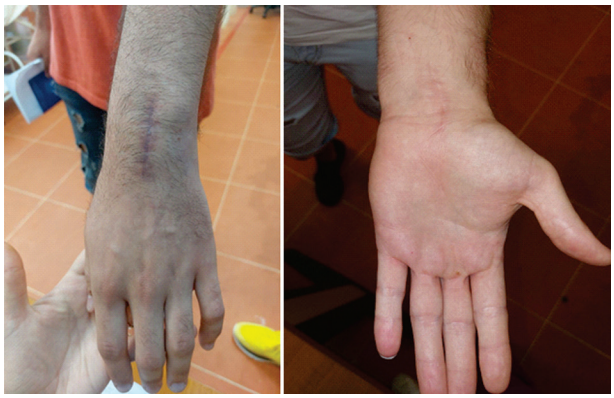

Figure 1. *Volar and dorsal approaches. Post-operative pictures of our patients*

For both approaches (Figure 1), a lengthwise incision of approximately 3 cm was made, and reduction was controlled using an image intensifier. After careful dissection at the level of the scaphoid, a guide wire

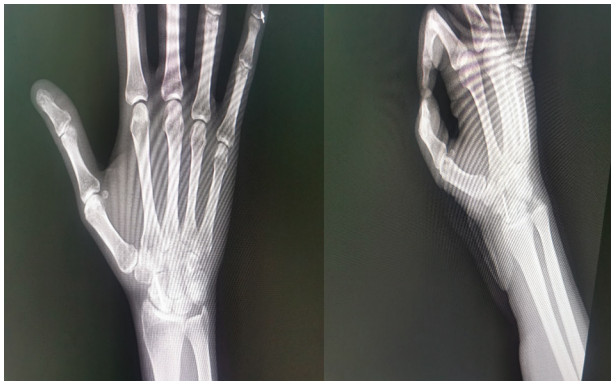

Figure 2. *Anteroposterior and lateral X-rays following the insertion of the headless compression screw*

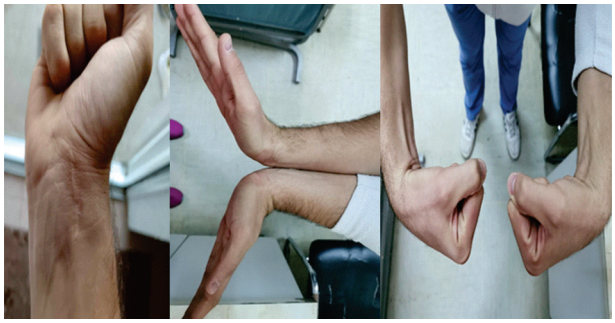

Figure 3. *Comparative photos of wrist range of motion and grip strength between the operated and healthy hand, one year after surgery*

was placed under fluoroscopic guidance. The screw length was measured, and a cannulated reamer was inserted over the wire. Drilling was stopped before passing through the cortex of the proximal scaphoid pole.

A 2.5 mm headless screw of the appropriate length was placed after removing the reamer. Screw placement was confirmed by intraoperative fluoroscopy (Figure 2).

After surgery, a short-arm orthosis was applied, allowing unrestricted thumb interphalangeal movement while maintaining slight wrist extension. Stitches were removed 14 days post-surgery.

Physical therapy and active motion exercises were recommended after four weeks, and full weight-bearing was permitted after three months.

RESULTS

The patients were followed up at 1, 3, 6, and 12 months after surgery. Four weeks post-surgery, the patients were referred for physical therapy. No postoperative complications were observed, including wound infections, hardware failure or loosening, malunions, or avascular necrosis. Screw insertion was also without issues. Radiographic images were obtained until the fractures healed. A comparative follow-up evaluation of wrist range of motion and grip strength after surgery is shown in Figure 3. No development of wrist osteoarthritis was observed during the follow-up period.

DISCUSSION

Surgical treatment of acute unstable and/or displaced scaphoid fractures, as well as two cases of nonunions following previous conservative treatment, resulted in good functional and radiological outcomes. The nonunion cases, associated with scaphoid deformity, resorption, and bone loss, were treated with spongyoplasty and osteosynthesis using the headless compression screw.

In a study by Sebastian V. Gehrmann et al. (4), 21 patients with scaphoid fractures treated with head-

less compression screws achieved positive functional and radiographic outcomes. The compression screw provided stable fixation, promoting bone healing. At the final follow-up, a low DASH score was recorded, alongside promising wrist motion and grip strength (88% compared to 86% of the uninjured side). The union of the fractures was challenging to assess, as it is difficult to measure the fracture gap after compression, which is the primary purpose of the screw. Therefore, patient satisfaction with postoperative results is a more appropriate conclusion.

Patterson et al. (5) identified three risk factors predicting scaphoid nonunion: age at the time of surgery, dominant hand injury, and previous surgery on the affected scaphoid. These factors can guide collaborative decision-making between the patient, surgeon, and healthcare team. In our study, two of these risk factors were addressed—mean age was 27.3 years, and no previous surgeries on the injured hand were reported. The third risk factor, dominant hand injury, was not assessed.

Our study has limitations, including a small sample size. Surgeons should consider individual circumstances, physical activity, and the type of work when making clinical decisions about the treatment of scaphoid fractures.

CONCLUSION

Although this study represents a small series, it highlights the importance of individualized clinical decision-making in the treatment of scaphoid fractures. Early surgical healing can provide greater comfort, a quicker return to daily activities, and earlier removal of immobilization.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: No

Authors' Contributions: All authors have contributed equally

Availability of Data and Materials: Datasets are available through the corresponding author upon reasonable request.

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

Sažetak

KOMPRESIVNI ZAVRTANJ ZA OPERATIVNO LEČENJE PRELOMA SKAFOIDNE KOSTI

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Uvod: Prelomi skafoidne kosti su česti i predstavljaju specifičan izazov zbog karakterističnih obrazaca preloma i vaskularizacije. Pravovremena dijagnoza i lečenje akutnih preloma skafoida od suštinskog su značaja kako bi se sprečilo nesrastanje i kasniji razvoj osteoartritisa zgloba. Iako se neprilagođeni prelomi često mogu lečiti konzervativno, napredak u dijagnostici, hirurškim tehnikama i materijalima za implantate doveo je do sve veće sklonosti ka ranom hirurškom fiksiranju.

Pacijenti i metode: Tokom perioda od 12 meseci, 10 muških pacijenata sa prelomima skafoidne kosti podvrgnuto je hirurškom lečenju na Univerzitetskoj klinici za traumatologiju u Skoplju, od januara 2022. do marta 2024. godine. Prosečna starost pacijenata bila je 27,3 godine. Dijagnoza je potvrđena pomoću CT-a i rendgenskih snimaka, pri čemu su četiri preloma bila na levoj ruci, a šest na desnoj. Svi pacijenti su prošli kroz otvorenu redukciju i unutrašnju fiksaciju korišćenjem bezglavog kompresivnog zavrtnja. Volarni pristup je primenjen u devet slučajeva, a dorzalni pristup u jednom. Šest pacijenata je hirurški tretirano u periodu od 4 do 14 dana nakon povrede, dok su četiri pacijenta tretirana zbog nesrastanja nakon prethodnog konzervativnog lečenja. Među ovim pacijentima, dva su se javila tri meseca nakon povrede, a dva sedam meseci nakon povrede. Grupa koja se kasnije javila zahtevala je spongioplastiku i osteosintezu zbog deformiteta skafoida, resorpcije i gubitka kosti.

Rezultati: Pacijenti su praćeni tokom 1, 3, 6 i 12 meseci nakon operacije. Fizikalna terapija je započeta četiri nedelje nakon operacije, a radiografsko praćenje je nastavljeno dok nije potvrđeno izlečenje preloma. Nisu zabeleženi slučajevi osteoartritisa zgloba šake tokom perioda praćenja.

Zaključak: Iako ovaj rad predstavlja mali broj slučajeva, on naglašava važnost individualnog donošenja kliničkih odluka u lečenju preloma skafoidne kosti. Rana hirurška intervencija može poboljšati komfor, omogućiti brži povratak svakodnevnim aktivnostima i smanjiti trajanje imobilizacije.

Ključne reči: Prelom skafoidne kosti, hirurško lečenje, bezglavi kompresivni zavrtanj, nesrastanje.

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***How to cite this article**:* Kostov H, Gavrilovski A, Merdzanoski I, Spasov M, Gjorikj Petrushevka M, Mihajlova Ilie RM. Headless Compression Screw for Surgical Treatment of Scaphoid Fractures. Sanamed. 2024; 19(3): 289-292. doi: 10.5937/sanamed0-53867.

SANAMED
2024; 19(3): 293–300
ISSN-1452-662X

DOI: 10.5937/sanamed0-51776
UDK: 612.4.05:577.112.85(669)
ID: 160102921
Original article

ABH SECRETOR STATUS AMONG THE UNIVERSITY OF CALABAR UNDERGRADUATES, NIGERIA

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Primljen/Received: 22. 06. 2024. Prihvaćen/Accepted:16. 10. 2024. Published Online First: 21. 10. 2024.

Abstract: Introduction: Secretor status is a critical component of human biology that depends on specific glycoproteins in body fluids and secretions. Its importance lies in its significant impact on health and disease, making it a compelling subject for medical research. This study aimed to determine the prevalence and understanding of secretor status among undergraduates at the University of Calabar, Nigeria. The findings could revolutionize our understanding of secretor status and open new research opportunities.

Materials and Methods: The study used a cross-sectional approach, analyzing blood samples from 100 undergraduate students using the adsorption-inhibition method. Most participants were single (94.0%), and the majority were 100-level students (51.0%). 48 students were in the 21 to 28-year range, while 6.0% were 30 or older.

Results: The findings of this study are significant, revealing that a substantial proportion of the participants were secretors, 82 (82.0%), while 18 (18.0%) were non-secretors.Interestingly, most participants (83.0%) were unaware of their secretor status, indicating a potential knowledge gap. Blood group O had the highest number of secretors, 58 (96.7%), followed by blood group A 11 (55.0%), blood group B 7 (63.6%), and the minor blood group AB 6 (66.7%). The most prevalent ethnic group was found among the Efiks (18.1%) followed by Yakurr (16.6%) and the least the Ijaws (3.8%).

Conclusion: This study underscores the importance of public education and awareness regarding secretor status and its impact on health and disease.

Keywords: Secretor status, glycoproteins, blood groups, undergraduates.

INTRODUCTION

The blood group system is controlled by genes closely linked to the same chromosome.Blood group antigens are inherited stable characteristics that have proven helpful in transfusion medicine, the prevention and management of haemolytic transfusion reactions, and resolving cases of doubtful parentage. ABO blood group antigens are present not only in red blood cells but also in bodily fluids such as saliva, tears, sperm, breast milk, and gastrointestinal fluids. Secretors secrete ABH blood group antigens in their body fluids according to their blood type, while non-secretors do not release these antigens into their bodily fluids. The secretor gene, FUT2 (fucosyl transferase 2), located on chromosome 19, plays a crucial role in determining an individual's secretor status by influencing the expression of blood group antigens in body fluids and secretions (1).

The inheritance pattern of the secretor gene (FUT2) follows an autosomal recessive pattern. This means an individual's secretor status is determined by the combination of alleles inherited from both parents: a) Homozygous dominant (SeSe): Secretor (expresses blood group antigens in body fluids); b) Heterozygous (Sese): Secretor carrier (expresses blood group antigens but can pass on the non-secretor allele); c) Homozygous recessive (sese):Non-secretor (does not express blood group antigens in body fluids) (2).

The expression of ABO blood group antigens depends on the interaction of three genes: FUT1 (H gene), responsible for the H antigen (a precursor to ABO antigens); the ABO gene, which controls A and B antigen expression on red blood cells; and the secretor gene (FUT2 or Se), governing A and B antigen expression in

bodily fluids. These genes encode enzymes (glycosyltransferases) that modify precursor substances to form new antigens (3).

The FUT2 gene controls individuals' capacity to secrete ABH antigens in bodily fluids. Meanwhile, the H (FUT1) gene encodes the H antigen found in red blood cells, while Se (FUT2) governs H antigen expression in secretions. The homozygosity of an inactive H (FUT1) and Se leads to the Bombay phenotype; individuals of the Bombay group do not have the H antigen on their red blood cells or in secretions but produce a strong anti-H antibody. Conversely, individuals who lack the H antigen in their secretions (those deficient in the Se (FUT2) gene) but possess the H antigen in their red blood cells (those who possess only the H (FUT1) gene) are referred to as non-secretors; in contrast, those with both the H antigen in their red blood cells and bodily fluids (active FUT1 and FUT2 genes) are referred to as secretors (4).

The H antigen plays a crucial role in forming ABO blood group antigens, while the Se gene controls the production of H antigens in bodily secretions by encoding the enzyme 2-L- fucosyltransferase. This enzyme converts precursor substances in body fluids into the H antigen in individuals with the secretor genotype.Subsequently, glycosyltransferases encoded by the ABO blood type modify this antigen. Non-secretors cannot express soluble ABO antigens due to their inability to generate the H antigen in bodily fluids (5).

According to Rydell et al. (6), approximately 80% of Caucasian individuals (with genotypes SeSe or Sese) are secretors, while 20% are non-secretors (genotype sese). Non-secretors are more exposed to endogenous and exogenous infections than secretors due to the lack of ABO blood group antigens in their bodily fluids. IgA levels in serum and saliva have been reported to be low in non-secretors; as a result, non-secretor individuals may have a diminished immune response at mucosal surfaces compared to secretors. Additionally, their IgG levels are reduced, which may explain why non-secretor individuals are more susceptible to autoimmune disorders (7).

MATERIALS AND METHODS

StudyArea

The study was conducted at the University of Calabar, Nigeria, a federal university located in Cross River State, South-South Nigeria. Established in 1975, it comprises one postgraduate school, one medical college, twenty faculties, three academic centers, three institutes, and one hundred and sixteen departments.

Study Population

Undergraduates from various departments at the University of Calabar participated in the study. Ten faculty members were selected via balloting using a multistage sampling technique. Two departments were chosen from each faculty through a simple random balloting method. The selected departments covered various disciplines, including English, Biochemistry, Haematology, Sociology, and more. The final sample size consisted of 100 students, with 15 from each department.

Study Design

A cross-sectional survey was adopted for this research.

Eligibility Criteria

Inclusion Criteria: Students of either gender who are undergraduates of the University of Calabar and provide informed consent were recruited as inclusion criteria. **Exclusion Criteria:** Non-consenting undergraduates of the University of Calabar were excluded.

Ethical Considerations

We obtained ethical clearance from the Research and Ethical Committee of the Ministry of Health, Cross River State. Participants received a comprehensive explanation of the study's purpose, objectives, risks, benefits, and confidentiality. Verbal consent was obtained, and participants were assured of their right to refuse or withdraw from the study at any time.

Collection of Samples

A sterile syringe and needle were used to obtain 2 ml of blood from each subject, ensuring that all aseptic techniques were observed. The samples were dispensed into clean sample bottles labeled with laboratory numbers. Samples were stored in a flask containing ice blocks and later transported to a refrigerator. Additionally, 5 ml of whole unstimulated saliva was collected into a clean, wide-mouthed, labeled container from each subject by having them bend their heads for two minutes and directly collecting the saliva into the container. Blood grouping was performed for the collected blood using the ABO standard tube method, and the estimation of salivary blood group antigens was conducted using the standard absorption inhibition method.

Determination of ABH Secretor Status by Absorption Inhibition Method Procedures

Saliva-filled test tubes were cooled in a boiling water bath for 10 minutes. Subsequently, the cooled tubes underwent centrifugation at 3000 rpm for 10

minutes. After discarding the supernatant, clear saliva was collected using a pipette. One drop of saline was added to each control test tube.

Four test tubes were prepared, two labeled as TEST and two as CONTROL. The controltubes serve as a crucial reference point in the procedure, ensuring that the antisera is not excessively diluted for agglutination. The stock agglutinating reagent was meticulously adjusted to a 1:8 titer, and one drop of diluted antisera was added to each tube. Clear saliva was also added to each test tube, while the control tube received one drop of saline. After mixing, both tubes were incubated at room temperature for a minimum of 10 minutes. Next, one drop of the appropriate indicator erythrocytes was added to each tube, followed by another 10-minute incubation. For the saline reaction in the control, the tubes underwent centrifugation for 10 minutes. Agglutination reactions were recorded, and negative results were re-evaluated using the same procedure.

Interpreting test results is crucial. In the control samples, clumping occurred, signifying no antigen presence. In the test group, a lack of agglutination indicated an antigen-antibody reaction between saliva and antisera, suggesting the presence of the blood group. The same principle applied to negative test samples, where the absence of agglutination indicated antigen presence.

ABO Blood Grouping Procedures

In forward grouping, blood cells were mixed with saline in two test tubes. Next, one drop of anti-A and one drop of anti-B were separately added to these samples. After centrifugation, the resulting mixture was gently shaken to observe agglutination.

Statistical Analysis

The data collected during the study were recorded, checked, and entered into Microsoft Excel, then exported to the Statistical Package for the Social Sciences (SPSS) (version 22.0) software for statistical analysis. A chi-square analysis was conducted and expresse data 95% confidence interval. P-values were considered significant at $p < 0.05$, and the results were presented using tables and figures.

RESULTS

This study investigated the prevalence of secretor and non-secretor status among undergraduate students at the University of Calabar in Cross River State. The parameter analyzed included ABO blood group and secretor status. The research involved 100 undergraduates, comprising 52 females and 48 males.

Table 1. *Sociodemographic characteristics of respondents*

VARIABLE	NUMBER ENROLLED (N = 100)	PERCENT AGE ENROLLED (%)
Gender		
Male	48	48.0
Female	52	52.0
Age group (Years)		
15-20	25	25.0
21-25	48	48.0
26-30	21	21.0
> 30	6	6.0
Marital status		
Married	6	6.0
Single	94	94.0
Divorced	0	0
Widowed	0	0
Level		
100	51	15.0
200	25	25.0
300	30	30.0
400	20	20.0
500	6	6.0
600	4	4.0

Table 1 presents the demographic characteristics of the undergraduates. The most common age group was 21-25 years, with a frequency of 48.0%. The majority of participants were single (94.0%), with married individuals making up 6.0%. Most participants were first-year students (100-level class), representing 51.0% of the sample, followed by 300-level students (30.0%), 200-level students (25.0%), 400-level students (20.0%), 500-level students (6.0%), and 600-level students (4.0%).

Table 2 summarizes respondents' knowledge of secretor status. Participants displayed limited awareness of their secretor status; none of the 100% of respondents tested knew their secretor status.

Table 3 presents the respondents' knowledge levels. The total knowledge score was 8, with scores categorized as poor (0-2), fair (3-5), and good (6-8). The mean knowledge score was 1.89 ± 1.23, indicating that participants generally had poor knowledge. Among the 100 respondents, 83.0% had inadequate knowledge, 14.0% had fair knowledge, and 3.0% had good knowledge.

Table 4 shows the influence of various demographics on respondents' levels of knowledge of secre-

Table 2. *Respondents' knowledge about secretor and non-secretor status*

VARIABLES	Yes	No	Idon't know
Have you heard of secretor and non-secretor status?	5 (5.0%)	58 (58.0%)	37 (37.0%)
Do you know your secretor status?	0 (0.0%)	89 (89%)	11 (11.0%)
Are secretors individuals whose blood group can also be detected in bodily fluids other than blood?	17 (17.0%)	21 (21.0%)	62 (62.0%)
Are non-secretors individuals whose blood group can only be detected in their blood, not body fluids?	14 (14.0%)	10 (10.0%)	76 (76.0%)
Are non-secretor individuals prone to reoccurring episodes of infections?	19 (19.0%)	35 (35.0%)	46 (46.0%)
ABH blood group antigen present in an individual's blood tells the individual's blood type.	41 (41.0%)	25 (25.0%)	34 (34.0%)
An individual might possess the ABH antigens in their blood but lack the antigens in their secretion.	23 (23.0%)	28 (28.0%)	49 (49.0%)
Is the secretor gene more common with males than females?	34 (34.0%)	15 (15.0%)	51 (52.0%)

Table 3. *Respondents' level of knowledge*

VARIABLE	FREQUENCY
Level of knowledge	
0-2 (Poor)	83 (83.0%)
3-5 (Fair)	14 (14.0%)
6-8 (Good)	3 (3.0%)
Mean knowledge score	1.89 ± 1.23

Table 4. *Relationship between secretor status knowledge & some demographic characteristics*

VARIABLE	FREQUENCY n = (100%)	PROPORTION (%)	LEVEL OF KNOWLEDGE			P-VALUE
			POOR	FAIR	GOOD	
Age group (Years)						
15-20	25	25.0	21 (84.0%)	3 (12.0%)	1 (4.0%)	0.061
21-25	48	48.0	41 (85.4%)	6 (12.5%)	1 (2.1%)	
26-30	21	21.0	16 (76.2%)	5 (23.8%)	0 (0.0%)	
> 30	6	6.0	5 (83.3%)	0 (0.0%)	1 (16.7%)	
Gender						
Male	48	48.0	41 (85.4)	5 (10.4)	2 (4.2)	0.567
Female	52	52.0	42 (80.8)	9 (7.3%)	1 (1.9)	
Marital status						
Married	6	5 (83.3)	0 (0.0)	1 (16.7)	0 (0.09)	0.209
Single	94	78 (83.0)	14 (14.9)	2 (2.1)	2 (2.2)	
Divorced	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Widowed	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Level						
100	51	15.0	15 (100.0)	0 (0.0)	0 (0.0)	0.388
200	25	25.0	20 (80.0)	5 (20.0)	0 (0.0)	
300	30	30.0	23 (76.7)	4 (13.3)	3 (10.0)	
400	20	20.0	16 (80.0)	4 (20.0)	0 (0.0)	
500	6	6.0	6 (100.0)	0 (0.0)	0 (0.0)	
600	4	4.0	3 (75.0)	1 (25.0)	0 (0.0)	

Table 5. *Distrinution of secretor status*

STATUS	FREQUENCY	PERCENTAGE (%)
Secretors	82	82.0
Non-secretors	18	18.0
Total (n = 100)	100	100.0

Table 6. *Relationship between ABO blood group and secretor status*

BLOOD GROUP	FREQUENCY	SECRETOR STATUS		PVALUE
		Se POSITIVE	Se NEGATIVE	
A	20	11 (55.0%)	9 (45.0%)	0.001
B	11	7 (63.6)	4 (36.4)	
AB	9	6 (66.7%)	3 (33.3)	
O	60	58 (96.7)	2 (3.3)	
Total	100	82	18	

Table 7. *Comparison of secretor status in the studied population with published data from previous studies*

SECRETOR STATUS	PRESENT STUDY (2022)	Emeribe *et al.* (8)	Jaff (9)	Tejasiv *et al.* (10)	p-value	χ^2value
Se positive	82.0%	86.9%	76.1%	86.6%	0.157	2.000
Se negative	18.0%	13.1%	23.9%	13.4%		

tor status, grouped into poor, fair, and good knowledge categories. Among those aged 15-21, knowledge levels were 84.0%, 12.0%, and 4.0%, respectively. For those aged 21-25, the distribution was 85.4%, 12.5%, and 2.1%. Those aged 26-30 showed frequencies of 76.2%, 23.8%, and 0.0%, while individuals above 30 years had levels of 16.7%, 0.0%, and 83.3%, respectively. Regarding gender, males exhibited poor, fair, and good knowledge of secretor status at rates of 85.4%, 10.4%, and 4.0%, respectively, while females had 80.8%, 7.3%, and 1.9%. Concerning marital status, singles recorded knowledge levels of 0.0%, 16.7%, and 0.9%, while married individuals had 14.9%, 2.1%, and 2.2%. In terms of education level, knowledge scores were as follows:100-level students (100.0%, 0.0%, 0.0%), 200-level students (80.0%, 20.0%, 0.0%), 300-level students (76.7%, 13.3%, 0.0%), 400-level students (80.0%, 20.0%, 0.0%), 500-level students (100.0%, 0.0%, 0.0%), and 600-level students (75.0%, 25.0%, 0.0%) for poor, fair, and good knowledge, respectively. No statistical differences existed between the knowledge levels of the groups examined ($p > 0.05$).

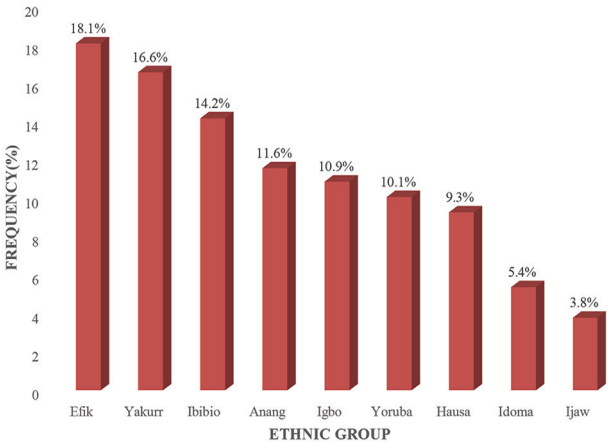

Figure 1. *Bar-chart representation of ethnicity of respondents*

Table 5 shows the prevalence of secretor status among undergraduates at the University of Calabar. Of the 100 participants in this study, 82.0% were secretor-positive (Se), while 18.0% were secretor-negative (se).

Table 6 presents the influence of blood group on the secretor status of undergraduates. Blood group

O had the highest prevalence at 60.0%, followed by group A (20.0%), group B (11.0%), and group AB (9.0%). For secretor status, blood group O had 58 (98.7%) secretors and 2 (3.3%) non-secretors; blood group A had 18 (55.7%) secretors and 9 (45.0%) non-secretors; blood group B had 7 (66.6%) secretors and 4 (36.4%) non-secretors; and blood group AB had 6 (66.7%) secretors and 3 (33.3%) non-secretors.

Table 7 compares secretor status in the studied population with published data from earlier studies. Previous studies reported secretor and non-secretor status of 86.9% and 13.1% (8), 76.1% and 23.9% (9, 10), and 86.6% and 13.4%, respectively.

Figure 1 is a bar chart representing participants based on their ethnicity. The most prevalent ethnic group was found among the Efiks, with a frequency of 18.1%, followed by Yakurr (16.6%), Ibibio (14.2%), Anang (11.6%), Igbo (10.9%), Yoruba (10.1%), Hausa (9.4%), Idoma (5.4%), and the least represented group was Ijaw (3.8%).

DISCUSSION

This study aimed to provide insights into the prevalence of secretor status among undergraduate students at the University of Calabar. Most participants fell within the age range of 21-25 years (48.0%), while only 6.0% were above 30 years. Among the students, those in the 100-level constituted the highest proportion (51.0%), followed by the 300-level (30.0%), with the 600-level showing the least representation (4.0%).

The relationship between ABO blood groups and secretor status in this study indicated that the majority of secretor-positive individuals were of blood group O, with a prevalence of 58.0%. In contrast, blood group O had only 2.0% secretor-negative participants. Blood group A showed a prevalence of 11.0% for secretor-positive and 9.0% for secretor-negative, while blood group B had 7.0% secretor-positive and 4.0% secretor-negative. Blood group AB recorded 6.0% secretor-positive and 3.0% secretor-negative individuals. This indicates that individuals with blood group O have a significantly higher frequency of secretor status compared to other groups, a finding consistent with Emeribe et al (8) and Jaff (9) who also reported that most secretor-positive individuals belonged to blood group O. This higher prevalence of secretor status in blood group O individuals may help explain the lower incidence of certain diseases in this group compared to others. Regarding ethnicity, the majority of participants were Efiks (18.1%), followed byYakurr (16.6%), with the least represented being the Ijaw (3.0%).

Out of the 100 enrolled students, 82 (82.0%) tested secretor-positive (Se), and 18 (18.0%) tested secretor-negative (se). This prevalence aligns with findings from Tejasiv et al. (10) and Akhter et al. (11), which reported secretor-positive rates of 76.1%, 60.0%, and 86.6%, respectively. The research included 100 undergraduates, comprising 52 females and 48 males. consistent with findings by Sherwani et al. (12), who reported a higher female representation.

The secretor status, determined by the FUT2 gene, influences the expression of ABH antigens in body fluids beyond blood cells. However, its direct impact on haemoglobin levels remains less understood. While secretor status is associated with protection against certain infections (such as *Helicobacter pylori*, noro virus, and cholera), its specific effect on hemoglobin levels warrants further investigation (13, 14, 15).

The participants' knowledge about secretor and non-secretor status was notably low, with none being aware of their secretor status before testing. This finding highlights the need for increased public education and awareness regarding secretor status, as no published evidence supports this level of ignorance.

CONCLUSION

In conclusion, this study found that 82.0% of undergraduate students at the University of Calabar were secretors, with blood group O individuals exhibiting the highest secretor frequency (96.7%) and blood group AB the lowest (66.7%). Notably, the ability to secrete ABH substances appears to be independent of ABO blood group antigens.

Acknowledgments

We extend our gratitude to all the participants who contributed to this study, as well as to the head of the department and the staff of the Haematology Department at the University of Calabar Teaching Hospital for allowing us to use their laboratory facilities.

Abbreviations

FUT1 - Fucosyltransferase1
FUT2 - Fucosyltransferase2

Conflict of Interest: All authors declare that they have no conflicts of interest.

Source of Funding: The authors received no external funding for this study.

Note: AI was not used as a tool in this study.

Sažetak

ABH STATUS SEKRETORA MEĐU STUDENTIMA UNIVERZITETA U KALABARU, NIGERIJA

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Uvod: Sekretorski status je ključna komponenta ljudske biologije koja zavisi od specifičnih glikoproteina u telesnim tečnostima i sekretima. Njegov značaj leži u značajnom uticaju na zdravlje i bolest, čineći ga privlačnom temom za medicinska istraživanja. Ova studija imala je za cilj da odredi učestalost i razumevanje sekretorskog statusa među studentimana Univerzitetu u Kalabaru, Nigerija. Nalazi bi mogli transformisati naše razumevanje sekretorskog statusa i otvoriti nove mogućnosti za istraživanje.

Materijali i metode: U ovoj studiji preseka, analizirani su uzorci krvi 100 studenata koristeći metodu adsorpcije-inhibicije. Najveći broj učesnika su bili samci (94,0%), a većinu su činili student prve godine (51,0%). 48 studenata bilo je u uzrastu od 21 do 28 godina, dok je 6,0% imalo 30 ili više godina.

Rezultati: Rezultati ove studije su značajni, pokazujući da je značajan deo učesnika bio sekretor, 82 (82,0%), dok je 18 (18,0%) njih označeno kao nesekretori. Zanimljivo je da je većina učesnika (83,0%) bila nesvesna svog sekretorskog statusa, što ukazuje na potencijalnu prazninu u znanju. Krvna grupa O imala je najveći broj sekretora, 58 (96,7%), dok je u krvnoj grupi A taj broj 11 (55,0%), u krvnoj grupi B 7 (63,6%), a u krvnoj grupi AB 6 (66,7%).

Najrasprostranjenija etnička grupa među ispitanicima je bila Efik (18,1%), zatim Yakurri (16,6%), a najmanji broj je među Ijawima (3,8%).

Zaključak: Ova studija naglašava važnost javnog obrazovanja i svesti o sekretorskom statusu i njegovom uticajuna zdravlje i bolest.

Ključne reči: Sekretorski status, glikoproteini, krvne grupe, studenti.

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***How to cite this article**:* **Etura J,** Abam J, Akpan U, Jeremiah Z. ABH secretor status among the university of Calabar undergraduates, Nigeria. Sanamed. 2024; 19(3): 293-300. doi: 10.5937/sanamed0-51776.

SANAMED
2024; 19(3): 301–305
ISSN-1452-662X

DOI: 10.5937/sanamed0-52725
UDK: 616.36-002.9-089; 616.98:578.834
ID: 160096009
Case report

SURGICAL TREATMENT OF COMPLICATED DUCTUS CHOLEDOCHUS HYDATIDOSIS DURING THE COVID-19 PANDEMIC: EFFECTIVENESS AND LIMITATIONS OF RADIOLOGICAL SERVICES AND SURGERY IN EXTRAORDINARY CONDITIONS

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Primljen/Received:13. 08. 2024. Prihvaćen/Accepted: 05. 10. 2024. Published online first: 14. 10. 2024.

Abstract: **Introduction:** While uncomplicated echinococcal cysts can grow in the liver for years without symptoms, complicated hydatid cysts (CHC) present distinct clinical characteristics that necessitate urgent treatment.

Case Report: We present a case of acute biliary obstruction, cholangitis, and sepsis due to massive choledocho-hydatididosis in an 84-year-old COVID-positive patient during the COVID-19 pandemic. Imaging revealed a multicystic lesion in liver segments V and VIII that compressed surrounding liver tissue, leading to intrahepatic duct dilation. A daughter cyst in the ductus choledochus was confirmed during surgery. An attempt at endoscopic retrograde cholangiopancreatography (ERCP) was unsuccessful. We performed an open pericystectomy with total cystectomy and choledochotomy, carefully evacuating all hydatid cysts. The postoperative course was uneventful, and the patient was discharged without surgical complications.

Conclusion: Complicated hydatid cysts (CHC) leading to acute biliary obstruction require prompt diagnosis and indicate the need for rapid evacuation of the cyst and correction of complications.

Keywords: Choledocho-Hydatididosis (CH), Complicated Hydatid Cysts (CHC), Intraoperative Ultrasound (IOUS), Hydatid Disease (HD), Liver Surgery.

INTRODUCTION

Liver hydatid cysts, when complicated by rupture into the bile ducts, can lead to cholangitis and bile obstruction (1, 2, 3). Uncomplicated hydatid cysts in the liver are asymptomatic for years, with an average growth rate of 1-5 mm per year (1, 2). Multiple cysts in the liver are detected in 20-40% of cases (2).

Hydatid disease (HD) originates from the larval stage of *Echinococcus granulosus*, a parasitic zoonosis historically referred to as a "liver full of water" since ancient times (1-4). It is most prevalent in regions where livestock is raised in close proximity to humans and dogs, such as the Mediterranean, the Middle East, Africa, South America, and New Zealand (1, 2, 5). Serbia is an endemic area for this parasitic infection (5).

Acute biliary obstruction caused by parasitic cysts in the bile ducts presents specific radiological signs. Ultrasonography (US) is the first step in the diagnostic algorithm and can establish a diagnosis with high sensitivity while also allowing classification of HD (6-11). Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) provide more detailed visualization of the lesions and complications of HD (8, 12). Serological tests may yield either strongly positive or negative results depending on the stage of the parasitic cyst (13).

Management options range from minimally invasive procedures to open surgery, all aimed at rapid cyst evacuation and the treatment of complications. Treatment strategies for complicated hydatid cysts (CHC) of the liver include surgery, interventional procedures such as PAIR (Puncture, Aspiration, Injection, and

Respiration), and specific antiparasitic medications (14-17).

We present the surgical case of a massive choledocho-hydatididosis with a daughter cyst in the ductus choledochus in an 84-year-old patient, treated with a multidisciplinary approach during the COVID-19 pandemic.

CASE PRESENTATION

An 84-year-old man was admitted to Emergency Surgery during the COVID-19 pandemic. The patient presented with acute biliary obstruction, pain, jaundice, cholangitis, and septicemia. The patient's medical history included cholecystectomy, appendectomy, and inguinal hernia repair. He also had atrial fibrillation. The patient lived in a rural sheep-farming area and reported owning dogs. Physical examination revealed abdominal tenderness, predominantly in the right upper quadrant, without signs of peritoneal irritation. His body temperature was 38°C. He showed signs of respiratory deterioration, and COVID-19 pneumonia was confirmed.

Laboratory tests revealed WBC count of 13.5 × 10^9/L, RBC count of 4.09 × 10^{12}/L, hemoglobin of 125 g/L, hematocrit of 0.376 L/L, and CRP of 160.6 mg/L. The International Normalized Ratio (INR) was 0.85. Liver function tests (LFTs) showed total bilirubin at 96 µmol/L, ALT at 150 U/L, AST at 141 U/L, GGT at 410 U/L, and ALP at 487 U/L.

Abdominal ultrasonography detected a 5 × 5 cm multilocular cystic lesion in the right hepatic segments, with posterior acoustic enhancement and no liver tissue infiltration. Multiple smaller (daughter) cysts completely filled the largest one, a feature often described as a "spoked wheel pattern." During patient movement, a "snowstorm pattern" was observed, caused by the dispersal of hydatid sand inside the cyst, seen as small hyperechoic foci. The cyst communicated on its medio-caudal side with the right posterior sectoral duct (RPSD), adjacent to its confluence with the right anterior sectoral duct (RASD). Our ultrasound findings corresponded to stage 3 by the Gharib ultrasound classification and to CE3b by the WHO-IWGE classification. The biliary tree was dilated, and hydatid material was detected in the right hepatic duct, common hepatic duct, and common bile duct (CBD), which measured 12 mm in diameter. No gallbladder was observed, consistent with the patient's history of cholecystectomy. No free fluid was seen in the abdomen. Other organs appeared normal on ultrasound.

An abdominopelvic multidetector computed tomography (MDCT) scan was performed after the administration of 100 ml of contrast agent. Both arterial and portal venous phases were acquired using the "bolus tracking" technique, followed by multiplanar

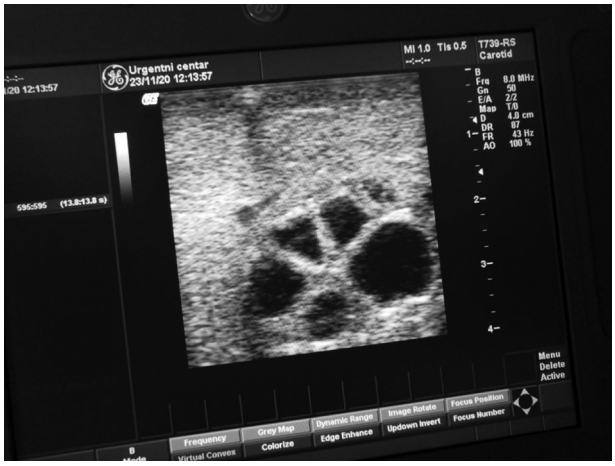

Figure 1. *Intraoperative ultrasound confirmed intrahepatic anatomical relationships of hydatid cyst*

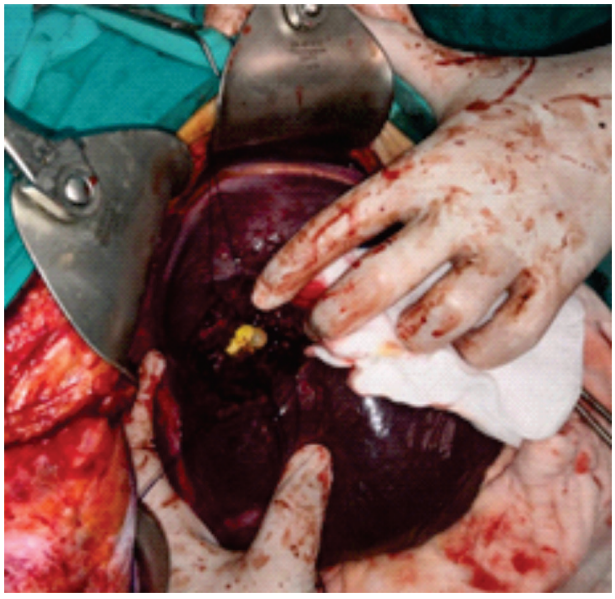

Figure 2. *The hepatic hydatid cyst was unroofed, the germinative membrane and daughter cysts are evacuated and cysto-biliary communication was sutured*

reformation and reconstruction (MPR). The liver exhibited normal CT density. A multicystic lesion measuring 55 × 45 × 57 mm was detected in liver segments V and VIII. The cyst abutted the bile duct branches for the right lobe and compressed surrounding liver tissue, causing intrahepatic ductal dilation, an indirect sign of communication with the cystic lumen. The cystic duct measured 8 mm, and the CBD was 12 mm in diameter, both almost entirely filled with inhomogeneous, low-attenuation structures.

Endoscopic procedures were unavailable, so the patient underwent open surgical treatment. A liver hydatid cyst was confirmed intraoperatively by intraoperative ultrasound (IOUS) (Figure 1), which revealed the cyst's anatomical relationship with surrounding structures. The hydatid cyst and the operating field were cov-

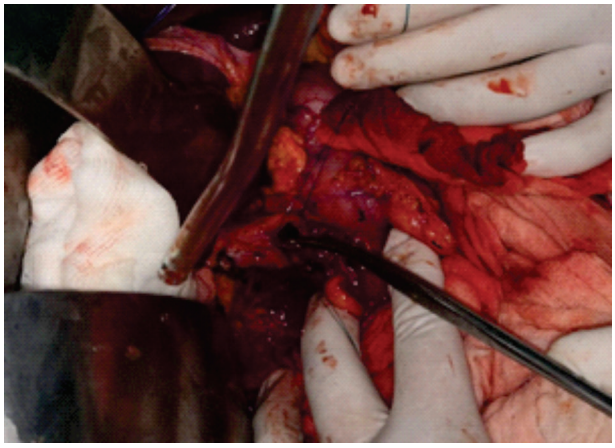

Figure 3. *After choledochotomy hydatid cysts were found inside ductus choledochus*

ered with pads soaked in hypertonic saline to prevent the spillage of parasites into the abdomen. The cyst was first punctured and aspirated, then unroofed, and the germinative membrane and daughter cysts were evacuated. The cyst cavity was explored, and a cysto-biliary communication was identified and sutured. An open pericystectomy with total cystectomy was performed, followed by a choledochotomy (Figure 2). Hydatid cysts were found in the ductus choledochus and were carefully evacuated (Figure 3). The ductus choledochus was washed, and a catheter was passed through the papilla into the duodenum. Intraoperative cholangiography was normal, and a T-tube drain was placed.

The postoperative course was uneventful, and the patient was started on early enteral nutrition. Postoperatively, he received antiparasitic drugs and antibiotic therapy. Control postoperative cholangiography was normal, showing a properly arborized biliary tree with no bile fistula. The patient was discharged on the third postoperative day without surgical complications and was transferred to the respiratory care unit for further COVID-19 treatment. After two years of follow-up, he remained free of complications.

DISCUSSION

Hydatid liver disease is most commonly detected in the right liver segments during ultrasonographic examinations (12, 14). Computed Tomography (CT) and Nuclear Magnetic Resonance (NMR) provide a more detailed view of the lesion's anatomy, including its morphological characteristics, its relationship with vascular structures, and the presence of complicated cysts or communication with the bile ducts (3, 8, 12). We presented the case of a patient treated at the emergency surgery clinic during the COVID-19 pandemic. Due to pandemic-related restrictions, we had limited access to imaging records, as no MSCT recordings were preserved. The treatment was constrained by the availability of open surgery and the exclusion of most minimally invasive and endoscopic procedures during the pandemic.

There are specific ultrasonographic signs indicative of hydatid cysts in the liver (8, 12). Ultrasonography is highly specific for diagnosing echinococcal liver disease both at initial presentation and for post-treatment follow-up (8, 12). The disease classification was first proposed by Hassan Gharbi from Tunisia in 1982 and later refined by the World Health Organization - Informal Working Group on Echinococcosis (WHO-IWGE) in 2003, with an update in 2006 (7, 10). For liver hydatid cysts in stages 3 and 4 of the Gharbi classification, there is a high likelihood of cystobiliary communication (11). In this case, the patient experienced biliary obstruction caused by daughter cysts in the ductus choledochus, which migrated through the biliary communication from a larger cyst in the right liver. Communication may also occur at the level of the common hepatic duct (2, 3, 6).

Several authors have found a positive correlation between the size of the cyst and the likelihood of biliary communication, particularly in cysts larger than 10 cm (3, 11). Hydatid cysts can compress surrounding structures, causing necrosis of the bile duct wall and the formation of biliary fistulas, allowing hydatid membranes and daughter cysts to enter the biliary tree (1, 3). This can lead to bile flow obstruction and infection. In our case, even though the cyst was smaller than 10 cm, biliary communication was confirmed.

Accurate diagnosis of the hydatid cyst stage is critical for determining treatment outcomes and avoiding postoperative complications (3, 15-20). Obstructive bile duct disease, as seen in our patient, requires precise radiological confirmation. However, preoperative detection of biliary communication is not always possible, and it is often necessary to explore the liver cavity during surgery (1, 6). Intraoperative ultrasound (IOUS) is essential for confirming the location, size, and relationships of the cyst during surgery (18). In our case, we located and punctured the cyst under IOUS control after laparotomy, ensuring both accuracy and patient safety.

Preoperative abdominal CT scans can confirm the presence of hydatid cysts in the biliary tree, as well as detect infected cysts or liver abscesses (3, 15). Secondary signs of biliary communication with a hydatid cyst include irregular cyst walls, distorted cyst shape, and air-fluid levels (8, 15). In our case, the cystic lesion compressed the surrounding liver tissue, resulting in intrahepatic duct dilation—an indirect sign of biliary communication.

Magnetic Resonance Cholangiopancreatography (MRCP) is the superior method for detecting hydatid material in the biliary tree (8). According to the American College of Gastroenterology Guidelines,

laparoscopic or open surgery is indicated for complicated echinococcal liver cysts, especially when multiple daughter cysts, fistulas, ruptures, bleeding, or secondary infections are present (16). Laparoscopic surgery is now considered safe for even large and complicated lesions (17). Radical surgical procedures, such as liver resection, offer low recurrence rates but carry higher intraoperative risks and morbidity (17). More conservative procedures, including cyst sterilization, evacuation, and partial cyst removal, are safer and simpler but may have higher recurrence rates (17, 19). Non-surgical treatments, such as percutaneous drainage, should also be considered for well-selected patients (20). Endoscopic retrograde cholangiopancreatography (ERCP) can be employed as a therapeutic option in certain cases (3).

In our case, considering the patient's general condition, we opted for an emergency open surgical approach to rapidly evacuate the cysts and relieve the biliary obstruction. The surgery proceeded without complications, and the patient recovered postoperatively without any surgical issues.

CONCLUSION

Communication between a hydatid cyst and the biliary tree is a complication of hydatid disease (HD) that necessitates timely diagnosis and appropriate therapy to reduce morbidity, mortality, and recurrence rates. Simple abdominal ultrasound and radiological imaging can confirm complications of HD, even in asymptomatic patients. Despite the extraordinary limitations on procedures during the pandemic, surgery remains the primary treatment option for patients with complicated HD.

Abbreviations

CH - Choledocho-Hydatididosis
CHC - Complicated Hydatid Cysts
IOUS - Intraoperative Ultrasound
HD - Hydatid Disease
CT - Computed Tomography
MRI - Magnetic Resonance Imaging
ERCP - Endoscopic retrograde cholangiopancreatography

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: Project No 200110 funded by Ministry of education, science and technological development Republic of Serbia.

Acknowledgement: The results of this work were reported for a poster presentation for the First SSES congress 2024.

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

Sažetak

HIRURŠKO LEČENJE KOMPLIKOVANE HIDATIDOZE DUCTUS CHOLEDOCHUS-a TOKOM PANDEMIJE COVID-19: EFIKASNOST I OGRANIČENJA RADIOLOŠKE SLUŽBE I HIRURGIJE U VANREDNIM USLOVIMA

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Uvod: Dok nekomplikovane ciste ehinokoka mogu godinama da rastu u jetri potpuno asimptomatski, komplikovane hidatidne ciste (KHC) imaju svoje kliničke karakteristike i zahtevaju hitno lečenje.

Prikaz slučaja: Prikazali smo hirurški slučaj akutne bilijarne opstrukcije i holangitisa zbog masivne holedoho-hidatididoze kod 84-godišnjeg COVID pozitivnog pacijenta. Multicistične lezije otkrivene radiološki u segmentima jetre V i VIII komprimovale su okolno tkivo jetre sa dilatacijom intrahepatičnih puteva i tokom operacije potvrđeno je postojanje ćerki cista u duktus holedohusu. Pokušaj ERCP nije uspeo. Urađena je otvorena pericistektomija sa totalnom cistektomijom i holedohotomijom. Sve hidatidne ciste su pažljivo evakuisane. Postoperativni tok je protekao uredno. Pacijent je otpušten sa hirurgije bez hirurških komplikacija.

Zaključak: Komplikovane hidatidne ciste (KHC) sa akutnom bilijarnom opstrukcijom zahtevaju brzo postavljanje dijagnose i brzu evakuaciju parazitske ciste i saniranje njenih komplikacija.

Ključne reči: Choledocho-Hidatidoza (CH), komplikovane hidatidne ciste (KHC), Intraoperativni ultrazvuk (IOUS), hidatidna bolest (HB), hirurgija jetre.

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How to cite this article: **Doklestić Vasiljev K**, Vasin D, Mićić D, Grubor N, Resanović V, Lešević I, Duka O, Bajić V,Vuković G, Mijović K, Pavlović A, Mitrović J, Lončar Z. Surgical Treatment of Complicated Ductus Choledochus Hydatidosis During the COVID-19 Pandemic: Effectiveness and Limitations of Radiological Services and Surgery in Extraordinary Conditions. Sanamed. 2024; 19(3): 301-305. doi: 10.5937/sanamed0-52725.

SANAMED
2024; 19(3): 307–312
ISSN-1452-662X

DOI: 10.5937/sanamed0-52602
UDK: 616.24-006-06; 616.11-008.64
ID: 159948553
Case report

MANAGING PNEUMOPERICARDIUM IN ADVANCED LUNG CANCER: A CASE REPORT AND LITERATURE REVIEW

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Primljen/Received: 07. 08. 2024. Prihvaćen/Accepted: 29. 09. 2024. Published online first: 05. 10. 2024.

Abstract: **Introduction:** Pneumopericardium, tho- ugh rare, can lead to severe complications such as cardiac tamponade, particularly in patients with malignancies. This case-based review examines the incidence, management, and outcomes of pneumopericardium in a patient with advanced lung cancer.

Case Report: We present a comprehensive literature review and a detailed analysis of a 57-year-old male with metastatic squamous cell carcinoma of the lung, who developed pneumopericardium. The patient's clinical presentation, diagnostic challenges, and management strategies were documented and compared with similar cases. He presented with cough and dyspnea, and imaging revealed pneumopericardium, likely due to tumor invasion into the pericardial space. Management involved conservative measures, including antibiotics and close monitoring. A literature review revealed that management strategies for pneumopericardium vary based on hemodynamic stability, ranging from conservative treatments to invasive procedures. Recurrence is common, and survival times post-diagnosis are highly variable.

Conclusion: Pneumopericardium in cancer patients requires a tailored management approach, with a multidisciplinary team essential for optimizing patient outcomes. This case underscores the need for heightened awareness and prompt, individualized treatment plans for managing such complex conditions.

Keywords: pneumopericardium, lung cancer, pericardiocentesis.

INTRODUCTION

Pneumopericardium, the accumulation of air or gas within the pericardial sac, represents a rare yet clinically significant finding. The etiology of pneumopericardium is multifaceted, encompassing direct or indirect trauma, fistula formation between the pericardium and thoracic air-containing structures, barotrauma, infectious processes, and iatrogenic complications following medical interventions (1). Studies have documented its occurrence across various clinical scenarios, emphasizing the importance of understanding its complex origins and potential implications for patient management (2, 3). Although pneumopericardium itself is rare, its association with malignancies is even less common and is seldom discussed in the literature (2). This association is crucial as malignancy-related pneumopericardium may arise due to tumor invasion directly into the pericardial space, leading to air accumulation, or indirectly through infection and necrosis within tumor tissues (4). For instance, lung cancer, particularly squamous cell carcinoma, has been noted in case reports to precipitate pneumopericardium through these mechanisms (3, 4). This underscores the need for heightened awareness and prompt management to mitigate potential complications such as cardiac tamponade, which can be life-threatening (5).

This case report elucidates a rare instance of pneumopericardium in a patient with metastatic squamous cell carcinoma of the lung, underscoring the diagnostic challenges and complex management required. The review of similar cases in the literature not only broadens the understanding of pneumopericardium's clinical trajectory in the context of cancer but also reinforces the need for an integrated, multidisciplinary approach to care in such intricate cases (3, 4, 6). By detailing this case and comparing it with existing reports, we aim to contribute valuable insights into the nuanced interplay between cancer and pericardial air accumula-

tion, enhancing strategies for diagnosis, management, and overall patient outcomes.

CASE REPORT

A 57-year-old male with a history of hypertension and left mandibular squamous cell carcinoma, treated with mandibulectomy and metallic brace replacement two years prior, presented with a relapse. Over the last 18 months, positron emission tomography (PET) scans detected metastases in his lungs, liver, kidneys, and bones. He reported a two-day history of cough and dyspnea, without fever, palpitations, or chest pain, and had a blood pressure of 122/70 mmHg. Laboratory investigations revealed leukocytosis, neutrophilia, anemia, and hypercalcemia due to bone metastasis. Physical examination noted reduced air entry and wheezing in the right lower lobe, consistent with aspiration pneumonia, along with difficulty in oral intake but without nausea or vomiting.

Prior computed tomography (CT) scans of the neck (Figure 1A-1B) and chest (Figure 1C-1D) revealed a heterogeneously enhancing lesion with central necrosis in the left submental space, involving the floor of the mouth and left digastric muscle. There was thickening in the left submandibular gland extending to the pre-epiglottic space, and a peripherally enhancing subcutaneous lesion in the right submental region. The lungs displayed four stellate lesions, the largest located near the bronchus of the right middle lobe. The heart size was normal, with no effusions or lymphadenopathy, and multiple hypodense lesions were observed in the liver.

Upon admission, a chest x-ray indicated a right lower lobe effusion suggestive of pneumonia, leading to treatment with ceftriaxone and levofloxacin, which was later switched to clindamycin due to the possibility of anaerobic infection. Subsequent CT scans showed an increased mass in the right middle lobe with multiple cavitations and bronchial com-

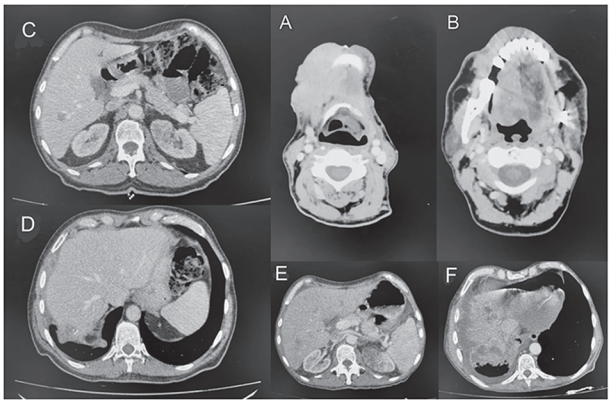

Figure 1. *Computed tomography (CT) scans of the neck and chest*

A-B: A computed tomography scan of the neck taken one year before admission. Status post (S/P) left mandibulectomy with surgical clips is seen in the subcutaneous region along with a metallic mandibular brace. There is a 4.8 × 3.3 cm heterogeneously enhancing deep soft tissue lesion showing central necrosis in the left submental space, involving the floor of the mouth and left digastric muscle, and extending to the left submandibular gland, with thickening/edema or invasion into the left pre-epiglottic space. (B) A 1.7 × 1.4 cm peripherally enhancing subcutaneous cystic soft tissue lesion/lymph node is observed in the right submental region. The thyroid gland is unremarkable, the vocal cords are symmetrical, and the infraglottic airways are normal in caliber. No abnormalities were noted in the nasopharynx.

C-D: A computed tomography scan of the chest taken five months before admission. Four irregular lesions appear in the lung, displaying a stellate appearance, the largest measuring 4.1 × 2.9 cm in the right middle lobe, abutting the anterior aspect of its bronchus. The heart is normal in size, with no pericardial or pleural effusions evident. No mediastinal or hilar lymphadenopathy is observed, and the chest wall is intact. The visualized portions of the upper abdomen show multiple hypodense liver lesions.

E-F: A computed tomography scan of the chest performed on admission. The lungs show an increase in the size of the previous heterogeneous mass in the right middle lobe, now occupying the entire right lower lobe with multiple cavitations. This mass compresses the adjacent bronchus, with surrounding post-obstructive ground-glass consolidations and atelectatic changes. The observed lesion invades the adjacent mediastinal surface, showing pneumopericardium. Multiple scattered pleural nodules are evident, the largest of which measures 4.7 × 2.6 cm in the right costodiaphragmatic recess, revealing a hypodense appearance indenting the liver, with adjacent bone erosions/lesions involving the 6th and 7th ribs. Bilateral minimal pleural effusion with nodular wall thickening is noted, along with bi-apical atelectatic/fibrotic bands. Scattered ground-glass opacities are observed in the right upper lobe. These features are suggestive of pleural, lung, and bone metastasis. The upper abdomen shows multiple small hypodense liver lesions suggestive of metastasis and a 1 × 1.2 cm benign-looking calcified lesion abutting the left side of the intrahepatic portion of the inferior vena cava. A 4.6 × 4.6 × 3.8 cm mass involving the left upper renal pole is also observed, suggesting secondary metastasis.

Table 1. *A summary of reported cases of cancer-related pneumopericardium in the literature*

Author [YOP]	Age (year)	Gender	Cancer	Interval from cancer diagnosis to presentation	Presentation	Fistula	Chest CT	Management	Outcome	Recurrence	Survival (in days)
Hirani et al., 2020 (3)	65	Male	Locally-advanced EGJ adenocarcinoma	NA	NA	Gastropericardial	Pneumopericardium in the posterior aspect with foci of gas above the esophageal stent communicating with the pericardium	Conservative approach (not described)	Improved	No	NA
Baydur et al., 1976 (2)	64	Male	SCC lung	3 months	Right-sided chest pain, progressive dyspnea, and productive cough	Bronchopericardial	Mass in the right lower lobe with a small pneumothorax plus pneumopericardium	Not clearly described	Temporary improvement, but pneumopericardium persisted until pleural effusion accumulated	No	51
Kim et al., 2000 (4)	53	Male	Double 1ry SCC lung	10 months	Progressive dyspnea on exertion and severe chest pain	Bronchopericardial	Pneumopericardium and left hydropneumothorax	Diagnostic pericardiocentesis and fluid analysis revealed exudative fluid	Fully improved	No	NA
Nakamura et al., 2021 (6)	70	Female	Stage IIIB SCC lung	6 months	Chest pain, exacerbation of cough, and severe palpitations	Bronchopericardial	Lung cancer on the left hilum abutting the pericardium (causing pneumopericardium) and invading the mediastinum (causing pneumomediastinum)	Fluoroscopy-guided urgent pericardiocentesis through the superior margin of the left 5th rib	JVD, dyspnea, and chest pain improved	No	180
Lages et al., 2018 (7)	66	Male	SCC lung	9 months	Dyspnea and chest pain	Bronchopericardial	Pneumopericardium of 28mm in maximum thickness	None	Minimal improvement in presenting symptoms	No	21
Al-Taweel et al., 2016 (8)	56	Male	SCC lung	NA	Hemoptysis and cough	Direct invasion into the left atrium	A small amount of air measuring 3-4 mm within the pericardium	Video-assisted thoracic surgery with pericardial window	Fully improved	Yes	>180
Sener et al., 2013 (9)	51	Male	NKTL	NA	Fever and cough	Gastropericardial	NA	Drainage with tube placement	Failure	No	1 (due to septic shock)
Kubisa et al., 2016 (10)	42	Male	NSCLC	6 months	Progressive weakness, fever, dry cough, and weight loss	Bronchopericardial	Severe inflammatory infiltrations in the right pulmonary hilum, with the presence of fluid and gas in the pericardium. Also, a subcarinal tumor of 80mm in the left cavity was observed with an extensive air cavity communicating with the left main bronchus and the pericardial cavity.	Mini-thoracotomy was performed above the 6th left rib and the pericardium was decompressed of air and fluid	Failed drainage and the patient underwent US-guided drainage	Yes	21
Mandal et al., 2019 (11)	81	Male	SCC esophagus	NA	Dyspnea and cough	Esophagopericardial	Pneumopericardium	Conservative approach (not described)	No improvement	NA	10

Fournel et al., 2018 (12)	84	Male	Esophagus	NA	Cardiogenic shock	Esophagopericardial	Massive pneumopericardium	Pericardiocentesis with closed drainage. A stent was applied to close the fistula.	No improvement	NA	4
Liao et al., 2017 (13)	53	Male	SCC lung	NA	Dyspnea, fever, thoracic pain	Esophagopericardial	Pneumopericardium with an anterior extent associated with a small amount of pericardial fluid	Pericardiocentesis with endoscopy-guided stent	NA	No	NA
Wang et al., 2016 (14)	53	Male	Lung	7 months	Dyspnea and chest pain	Esophagopericardial	Large pneumopericardium	Pericardiocentesis with endoscopy-guided stent	NA	No	NA
Rao et al., 2013 (15)	6	Female	Acute lymphoblastic leukemia	NA	Dyspnea and fever	Not reported	NA	Pericardiocentesis	NA	No	NA
Kasama et al., 2011 (16)	64	Male	SCC esophagus	NA	Dysphagia	Esophagopericardial	Pneumopericardium	Pericardiectomy	NA	NA	NA
Imai et al., 2008 (17)	77	Male	SCC lung	11 months	Dyspnea	Pleural space and pericardium	Pneumopericardium without mediastinal emphysema	Pericardiocentesis with drainage	NA	No	NA
Durães Campos et al., 2020 (18)	67	Male	Lung	1 month	Dyspnea, productive cough, and hemoptysis	Pleuro-pericardial	A left pulmonary mass containing areas of necrosis and gas, associated with the anterior pneumopericardium	Close monitoring and conservative management	Deterioration	No	30

pression, accompanied by post-obstructive changes and mediastinal invasion causing pneumopericardium. Additional metastatic lesions were identified as pleural nodules in the liver, kidneys, sternum, and ribs (Figure 1E-1F). Despite a negative purified protein derivative (PPD) test excluding tuberculosis, and the non-feasibility of bronchoscopy due to his oral condition, transthoracic echocardiography confirmed pneumopericardium.

The patient was discharged three days later, hemodynamically stable, but with continued elevated white blood cell counts (WBC = $17.09x10^9$/L), lower hemoglobin levels (7.9 gm/dL), and elevated neutrophils (90.6%). At discharge, he exhibited no edema, jugular vein distension, dyspnea, chest pain, or wheezing, and maintained good bilateral air entry.

DISCUSSION

Pneumopericardium is an uncommon yet significant clinical entity frequently associated with various complications (1). While often linked to trauma, infections, and iatrogenic causes, cases in cancer patients, as highlighted in our literature review (Table 1), typically arise due to tumor invasion or the development of pathological fistulas between the pericardium and air-containing structures. Our patient, a 57-year-old male with metastatic squamous cell carcinoma, developed pneumopericardium likely due to tumor invasion into the pericardial space—a finding supported by radiological evidence of a large mass invading the mediastinal surface (3).

The literature reveals a range of presentations from chest pain and dyspnea to more subtle symptoms like cough and fever, often precipitated by the cancer's progression to involve pericardial structures.

The interval from cancer diagnosis to the presentation of pneumopericardium varies widely, reflecting the aggressive nature of the underlying malignancy or the delayed manifestation of its complications. For instance, patients reported by Baydur (2) and Kim (4) developed symptoms within 3 to 10 months post-cancer diagnosis, presenting with chest pain and dyspnea. This rapid onset suggests a direct and aggressive tumor interaction with the pericardial space.

The diversity in presentation patterns, from acute chest pain and dyspnea to more insidious symptoms like cough and fever, underscores the need for clinicians to maintain a high index of suspicion in patients with known malignancies. Management approaches in reported cases range from conservative measures, such as oxygen therapy and antibiotics, to more inva-

sive procedures like pericardiocentesis and surgical intervention. The choice of management is heavily influenced by the patient's hemodynamic stability and the presence of life-threatening complications such as cardiac tamponade (5). Invasive interventions are reserved for more severe cases or those demonstrating rapid clinical deterioration, as seen in the cases reported by Nakamura (6) and Lages (7), where urgent pericardiocentesis was required to manage symptoms and prevent cardiac arrest.

Recurrence of pneumopericardium was noted in some cases, such as that reported by Al-Taweel et al. (8), indicating the persistent and recurrent nature of the underlying pathological process, often necessitating repeated interventions. Survival times post-pneumopericardium diagnosis vary significantly, ranging from as little as 1 day in severe cases like that of Sener et al. (9) to over 180 days in others (8). This highlights the variable prognosis in these patients, reflective of both the aggressive nature of the underlying cancer and the effectiveness of the intervention strategies employed (Table 1).

In **conclusion**, the review of literature alongside our patient case illustrates the complexity of pneumopericardium in cancer patients. The condition not only presents variably but also requires a tailored, often aggressive management strategy. The involvement of a multidisciplinary team is crucial to optimizing outcomes, emphasizing the role of personalized medicine in managing complex oncological complications. This synthesis of data aids in better understanding the clinical trajectory of pneumopericardium in cancer patients and reinforces the necessity for vigilant monitoring and proactive intervention to improve patient survival and quality of life.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: The authors did not receive financial or non-financial support for this work from any institutional or non-institutional organizations.

Author contribution: All authors have contributed equally

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

Sažetak

LEČENJE PNEUMOPERIKARDIJUMA KOD UZNAPREDOVALOG KARCINOMA PLUĆA: PRIKAZ SLUČAJA I PREGLED LITERATURE

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Uvod: Pneumoperikardijum, iako redak, može dovesti do ozbiljnih komplikacija kao što je srčana tamponada, posebno kod pacijenata sa malignitetima. Ova prikaz slučaja, zasnovan na pregledu literature, istražuje incidencu, lečenje i ishode pneumoperikardijuma kod pacijenata sa uznapredovalim karcinomom pluća.

Prikaz slučaja: Prikazujemo sveobuhvatan pregled literature i detaljnu analizu slučaja pacijenta starog 57 godina sa metastatskim skvamocelularnim karcinomom pluća koji je razvio pneumoperikardijum. Klinička prezentacija pacijenta, dijagnostički izazovi i strategije lečenja su dokumentovani i upoređeni sa sličnim slučajevima iz literature. Kod našeg pacijenta su prisutni kašalj i dispneja, a kasniji snimci su otkrili pneumoperikardijum, verovatno usled invazije tumora u perikardijalni prostor. Lečenje je uključivalo konzervativne mere sa antibioticima i praćenjem. Pregled literature je pokazao da se strategije lečenja pneumoperikardijuma razlikuju u zavisnosti od hemodinamske stabilnosti pacijenta, varirajući od konzervativnog lečenja do invazivnih procedura. Recidiv je čest, a preživljavanje nakon dijagnoze je veoma varijabilno.

Zaključak: Pneumoperikardijum kod pacijenata sa rakom zahteva prilagođen pristup lečenju, a multidisciplinarni tim je ključan za optimizaciju ishoda pacijenata. Ovaj slučaj naglašava potrebu za povećanom svesti i brzim, personalizovanim planovima lečenja za efikasno upravljanje ovakvim složenim stanjima.

Ključne reči: pneumoperikardijum, karcinom pluća, perikardiocenteza.

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***How to cite this article**:* Chaaban B**,** Arabi ZS, Bitar H, Abou Hamdan D. Managing Pneumopericardium in Advanced Lung Cancer: A Case Report and Literature Review. Sanamed. 2024; 19(3): 307-312. doi: 10.5937/sanamed0-52602.

SANAMED
2024; 19(3): 313–317
ISSN-1452-662X

DOI: 10.5937/sanamed0-52736
UDK: 616.717.1-006
ID: 160167689
Case report

SCHWANNOMA OF SCAPULA: CASE REPORT AND LITERATURE REVIEW

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Primljen/Received:13. 08. 2024. Prihvaćen/Accepted: 23. 09. 2024. Published online first: 09. 10. 2024.

Abstract: **Introduction:** Schwannomas are benign peripheral nerve tumors, more often localized in soft tissues than bones. Out of about 200 recorded cases of schwannoma of bone, only three cases of schwannoma of scapula have been described to date.

Case report: We present the case of a 73-year-old female patient with an asymptomatic schwannoma of the scapula. Physical examination revealed a solid, fixed, well-defined walnut-size tumefaction in the right scapula area. CT of the chest confirmed a 2.33 x 0.96 cm diameter tumor at the junction of the upper-third and middle-third of the medial border of the right scapula. After reviewing the entire medical documentation, it was decided to proceed with surgical removal of the tumor. The surgery involved partial resection of the tumor-affected part of the scapula. Histopathological examination confirmed it was a schwannoma of bone. No clinical or radiological signs of disease recurrence were observed during the one-year follow-up.

Conclusion: Schwannomas of bone are rare, slow-growing tumors. A definitive diagnosis is made based on histopathological and immunohistochemical findings. The main treatment modalities include curettage or "en bloc" resection. Recurrence is rare.

Keywords*:* neurilemmoma, tumor, surgical treatment, histopathology, radiology.

INTRODUCTION

Schwannomas (also known as neurilemmomas) are benign neurogenic tumors (1). They originate from Schwann cells forming the myelin sheath of the peripheral nervous system and account for approximately 5% of all soft tissue, benign tumors (2). They may develop in any period of life (most often in the fourth decade), with approximately equal incidence in males and females (2). Predilection sites for schwannomas include the head, neck, extremities and mediastinum (3, 4). They are generally slow-growing tumors with low malignant potential (5, 6).

Unlike schwannomas of soft tissue, which are rather common, schwannomas of bone are very rare tumors, with an incidence of less than 0.2% (7, 8). Considering that skeletal nerve fibers are mostly unmyelinated, such a low incidence of these tumors comes as no surprise (9). By 2021, about 200 cases of schwannomas of bone have been reported, with the most common localization in the maxillofacial region and the sacrum (10-13).

Our patient presents with an intraosseous schwannoma of the right scapula. According to the literature available in English, only three cases of schwannoma of scapula have been reported to date, the last being from 2021 (10). Before that, schwannoma of scapula was reported two more times, in 2014 and in 1967 (1, 7).

Given the rarity of this tumor and its even rarer occurrence in the scapula, we have chosen to present this case in detail.

CASE REPORT

A 73-year-old female patient was identified with a tumefaction in the right scapular region. The patient had no subjective complaints, and she discovered the change by accident, approximately one year before the surgery. She denied injuries in the region and previous surgeries. Her family history was negative.

She was referred to a preoperative examination by a general practitioner, with a posteroanterior and lateral chest X-ray. The surgical examination included

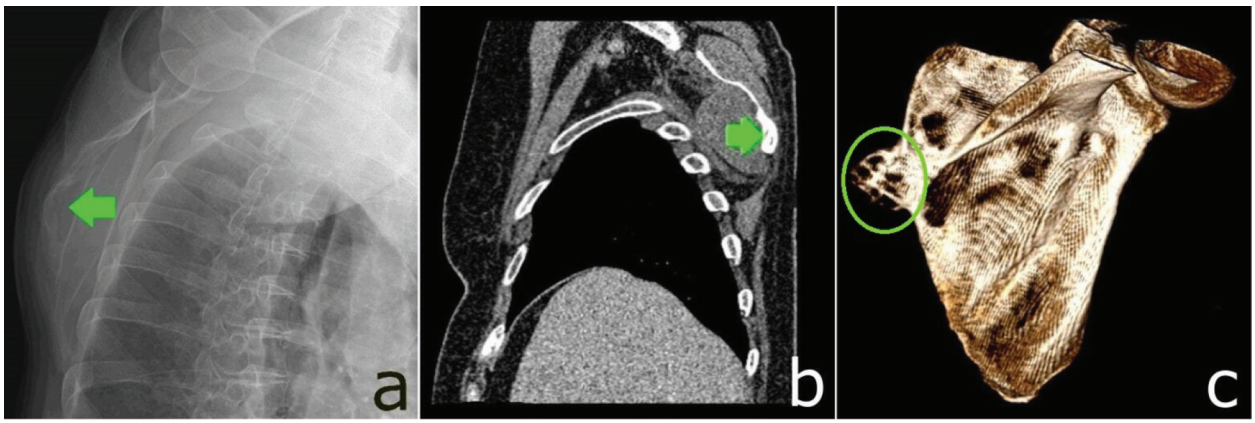

Figure 1. *Radiological features of the resected schwannoma*

Lateral chest X-ray (**1a**) shows a well-defined osteolytic tumor with a thin capsule and trabeculae. On sagittal chest tomogram (**1b**), green arrow shows a tumor on the medial border of the right scapula. Also, we can see a 3D reconstructed right scapula (**1c**) with an osteolytic lesion at the junction of the upper-third and middle-third of its medial border (by RadiAnt DICOM Viewer *v.2023.1*).

inspection and palpation of the right scapular region. Palpation revealed a walnut-size tumefaction in the medial border of the right scapula. The tumor was firm, well-defined, and fixed to the scapula, with no local swelling or skin changes. Mild tenderness to palpation was present. Lateral chest X-ray revealed a well-defined osteolytic lesion in the area of the medial border of the scapula, with a thin sclerotic capsule and trabeculae (Figure 1a). Computed tomography (CT) scan of the chest with contrast agent application was indicated and performed to achieve the most accurate diagnosis. The findings confirmed an osteolytic, well-defined tumor formation, 2.33 x 0.96 cm in diameter, located at the junction of the upper-third and middle-third of the medial border of the right scapula, without signs of pathological vascularization and infiltration of the surrounding soft tissues (Figures 1b and 1c).

After reviewing the entire medical documentation and obtaining the patient's consent, a decision was made to surgically remove the above-described change and refer it for a histopathological examination. After adequate preoperative preparation, the surgery was performed under general anesthesia. We approached the tumor through an incision in the skin and subcutaneous tissue of the right scapular region, with the patient being in the left lateral decubitus position. By preparing the surrounding soft tissues, we reached the tumor and performed a partial resection of the affected part of the scapula (Figure 2).We completely removed the change. Following tumor extirpation, we performed a revision of the area, established hemostasis, and drained the area using a four-channel drain. The postoperative course was normal and the patient was discharged home to self-care on the fifth postoperative day.

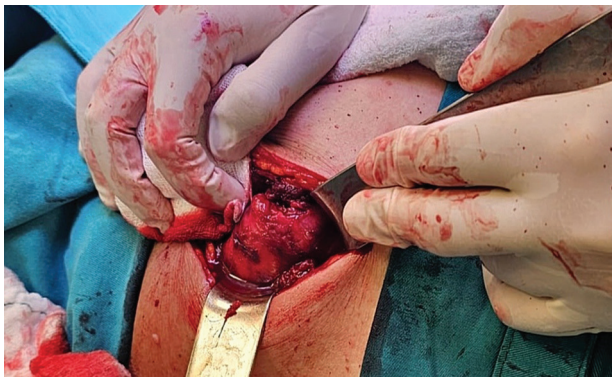

Figure 2. *Perioperative view of the tumor-affected part of the scapula (following preparation of the surrounding soft tissues)*

The specimen sent for histopathological examination contained the resected part of the scapula with tumefaction and surrounding soft tissues. Upon section, it had a colorful appearance and tough-elastic consistency, and it was partially encapsulated, measuring 8.3 x 6.5 x 4.5 cm (Figure 3a). The histopathological finding of the excised change was morphologically and immunohistochemically consistent with the schwannoma of bone. Examination of the material revealed a proliferation of spindle cells (with bent nuclei and intranuclear inclusions) arranged in the *Antoni A* (Figures 3b and 3c) and *Antoni B* (Figures 3d and 3e) patterns. The tumor parenchyma was vascularized by thickened, hyalinized blood vessels and occasionally permeated with degeneration and bleeding zones. There were no atypical cells or other signs of malignancy. *Ki67* proliferative index was < 2% (Figure 3f). Most tumor cells showed positive immunohistochemical staining with *S-100* protein (Figures 4a and 4b), *CD56* (Figures 4c and 4d), *bcl2* and *TLE1*.

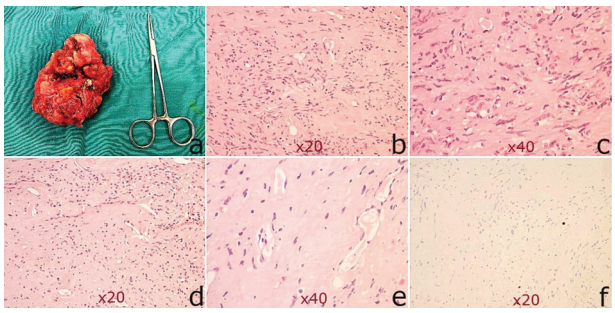

Figure 3. *Patohistological features of the resected schwannoma*

The figure shows the surgical specimen (**3a**), with a colorful appearance, tough-elastic consistency, composed of spindle cells arranged in *Antoni A* (**3b et 3c**) and *Antoni B* (**3d et 3e**) patterns (*H&E staining*). *Ki67* proliferative index was < 2% (**3f**).

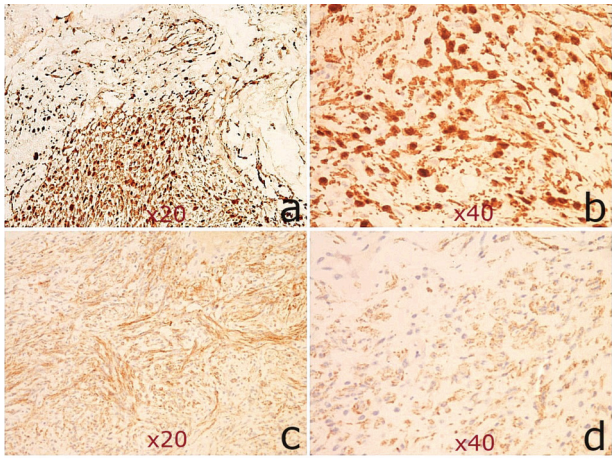

Figure 4. *Immunohistochemical features of the resected schwannoma*

Most tumor cells showed strong immunohistochemical staining positivity with *S-100* (**4a et 4b**) and *CD56* (**4c et 4d**).

The patient did not receive additional therapy. The surgical wound was healing *per primam*. After a one-year follow-up, there were no clinical or radiological signs of disease recurrence.

DISCUSSION

Neurilemmoma, now commonly known as schwannoma, was first described by Verocay in 1908 and elaborated upon by Stout in 1935 (13, 14). The disease etiology has not been fully elucidated, but the formation of this tumor seems to be caused by a mutation of *NF2* gene (15, 16). *NF2* is a tumor-suppressor gene (chromosome 22), which encodes the structure and synthesis of the *schwannomin* protein. Schwannomin is synthesized in the nervous system, predominantly in Schwann cells, and plays a significant role in the transduction of signals responsible for their structure, growth, division and adhesion. The loss of *NF2* gene function leads to disruption of these functions and the formation of tumors (16).

As mentioned in the introduction, schwannomas account for less than 0.2% of all bone tumors (7, 8). Generally, these tumors occur more in sensory than motor nerves. This is probably the reason why the tumor process most often affects the mandible and sacrum (8, 13). Unlike these bones, scapula is a rather rare site for schwannoma and has been reported only three times to date. Fawcett *et al*. were the first to describe schwannoma of the left scapula in a 24-year-old female patient, a little over 50 years ago (7). Tian et al. reported the same tumor in a 42-year-old woman in 2014 (1). The last case of schwannoma of scapula was reported by Reyniers et al. in 2021 (10). In all three cases, there were female patients with schwannoma localized on the left and affecting the glenoid cavity of the scapula, and the only symptom they had was pain. Following *in toto* tumor removal, there was no disease recurrence. In our case, the tumor was localized on the right, did not involve the glenoid cavity, and was asymptomatic. Following tumor resection and one-year follow-up, there were no signs of recurrence. So far, the recurrence of schwannoma of bone has been reported twice, probably due to incomplete resection (8, 17).

Schwannomas can involve bone in three ways: 1) by arising in the medullary cavity of the bone; 2) by arising in the nutrient canal of the bone or 3) by arising in the immediate vicinity of the bone, causing its secondary erosion (18).

The disease can be asymptomatic (25% of cases) or manifested by symptoms such as pain, swelling, and redness at the tumor site (1). Pain is reported in nearly half of the patients and typically worsens with tumor palpation. Fewer patients may experience loss of function of the affected nerve, due to its prolonged compression by the tumor (1, 19).

The diagnostic algorithm includes detailed history taking, physical examination, and additional radiological tests (ultrasound, radiography, CT, MRI). A definitive diagnosis is made solely based on the histopathological findings of the examined material. The classical radiological presentation of schwannoma of bone implies a well-defined osteolytic lesion with a thin sclerotic capsule and trabeculae (20). This radiological description largely corresponds to our case. The main histological feature of schwannoma is the presence of spindle cells arranged in the *Antoni A* and *Antoni B* patterns. Tumor cells typically show *S-100* protein positivity (*ddx.* neurofibroma) (1, 21, 22). Al-

though there are several different histological types of schwannoma (classical, epithelioid, cellular, microcystic, neuroblastoma-like, etc.), this classification has no major clinical significance in itself (23).

Schwannomas are benign tumors. Malignant alteration is rare and thus far only recorded in soft tissue, not in skeletal forms (8). Curettage or "en bloc" resection are the methods of choice for treating schwannoma of bone (8, 24). Major bone defects can be compensated with grafting (25). In our case, the patient was treated with the "en bloc" resection method without additional therapy.

CONCLUSION

Schwannomas of bone are rare tumors. They are usually slow-growing and have mild symptoms, most commonly pain. One-quarter of patients have no complaints at all. A definitive diagnosis is made based on histopathological and immunohistochemical findings. The main treatment modalities include curettage or "en bloc" resection. Recurrence is rare.

Abbreviations

Bcl2 – B-cell leukemia/lymphoma 2 protein
CD56 – Neural cell adhesion molecule
NF2 – Neurofibromatosis type 2 gene
TLE1 – Transducin-like enhancer protein 1

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: No.

Author contribution: All authors have contributed equally

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

Sažetak

ŠVANOM LOPATICE: PRIKAZ SLUČAJA I PREGLED LITERATURE

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Uvod: Švanomi su benigni tumori perifernih nerava, sa češćom lokalizacijom u mekim tkivima nego u kostima. Od oko 200 zabeleženih slučajeva koštanog švanoma, švanom lopatice je do danas svega tri puta opisan.

Prikaz slučaja: U našem slučaju je prikazana 73-godišnja pacijentkinja sa asimptomatskim švanomom lopatice. Fizikalnim pregledom je evidentiran čvrst, fiksiran, jasno ograničen tumefakt, veličine oraha, u predelu desne lopatice. CT-om grudnog koša je potvrđeno da na spoju gornje i srednje trećine unutrašnje ivice desne lopatice postoji tumorska promena dijametra 2,33 x 0,96 cm. Nakon uvida u kompletnu medicinsku dokumentaciju, doneta je odluka da se navedena promena hirurški ukloni. Operacija je obuhvatila parcijalnu resekciju tumorom zahvaćenog dela lopatice. Patohistološkim pregledom je utvrđeno da se radi o koštanom švanomu. Tokom jednogodišnjeg praćenja nisu zabeleženi klinički i radiološki znaci recidiva bolesti.

Zaključak: Koštani švanomi su retki, spororastući tumori. Definitivna dijagnoza se zasniva na rezultatima patohistoloških i imunohistohemijskih pretraga. Glavni modaliteti lečenja uključuju kiretažu ili "en bloc" resekciju. Recidivi su retki.

Ključne reči: neurilemom, tumor, hirurško lečenje, patohistologija, radiologija.

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***How to cite this article**:* Stevanović S, Petrović J, Milićević A, Petrović J, Đorđević N, Nikolić A. Schwannoma of scapula: case report and literature review. Sanamed. 2024; 19(3): 313-317. doi: 10.5937/sanamed0-52736.

SANAMED
2024; 19(3): 319–324
ISSN-1452-662X

DOI: 10.5937/sanamed19-54756
UDK: 616.89-008.454-085-055.26
ID: 160171017
Case report

TREATMENT OF DEPRESSIVE AND ANXIETY DISORDERS DURING PREGNANCY AND LACTATION: A CASE STUDY

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Primljen/Received: 13. 11. 2024. Prihvaćen/Accepted: 22. 12. 2024.

Abstract: **Introduction:** Depressive and anxiety disorders are among the most common psychiatric conditions, as stated by the WHO in 2015. These disorders often manifest during adolescence or young adulthood, making it unsurprising for women in pregnancy or lactation periods to experience either a first manifestation or a recurrence of symptoms. When these disorders occur during pregnancy or lactation, antidepressant treatment may be required per established protocols. However, concerns often arise among patients, such as: "Is this medication safe for me and my baby? Could it negatively affect my baby's development?" These hesitations can sometimes extend to healthcare providers if they lack adequate education on the topic. Therapeutic guidelines worldwide recommend psychotherapy for mild symptoms, whereas pharmacotherapy, often combined with psychotherapy, is carefully considered for moderate symptoms.

Case Report: This paper presents three case studies of pregnant women with depressive and anxiety disorders. The first case involves a patient with prenatal depression who achieved complete remission after starting antidepressant therapy. The second case highlights the recurrence of symptoms following the discontinuation of psychopharmaceuticals. The third case emphasizes the importance of individualized treatment plans and illustrates the recurrence of symptoms in a patient previously in remission.

Conclusion: Pregnant women with mental health challenges often have significant concerns about using psychopharmaceuticals during pregnancy. This paper aims to underscore that the appropriate selection and dosage of antidepressant medications can lead to remission of disorders without adverse effects on either the mother or child.

Keywords: Depression, anxiety, pregnancy, lactation, pharmacotherapy.

INTRODUCTION

Symptoms of depressive and anxiety disorders are increasingly prevalent worldwide, reaching near-epidemic proportions. This is particularly evident in the current global context, marked by pandemics, natural disasters, and conflicts. These disorders typically manifest during adolescence and young adulthood, with women being twice as likely to experience depression and anxiety as men, according to WHO epidemiological data (1, 2, 3). Unsurprisingly, pregnancy—a period of significant hormonal and life changes—often brings about either the first manifestation or a recurrence of depressive and anxiety disorders (2, 3, 4). Even in planned pregnancies, factors such as financial insecurity, inadequate living conditions, and lack of support from partners or family can exacerbate vulnerabilities and transform manageable challenges into seemingly insurmountable problems.

Treating depression and anxiety during pregnancy and lactation is a complex task for both psychiatrists and patients. Evidence suggests that depressive and anxiety disorders are more likely to recur during this critical period, particularly in individuals with a prior history of these conditions. For mild symptoms, psychotherapy is typically the first-line treatment. However, pharmacotherapy is warranted when symptoms are more severe or debilitating.

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants during pregnancy (5). While SSRIs and other medications carry potential adverse effects—such as a slightly elevated risk of preterm birth—untreated depressive and anxiety disorders pose even greater risks (6). These include an increased likelihood of pregnancy-related complications such as fetal growth restriction, higher fetal heart rate, preterm birth (before 37 weeks), and

low birth weight (under 2500 g). Additionally, untreated maternal depression is associated with neurodevelopmental challenges in children, including cognitive delays, emotional and behavioral problems, intellectual disabilities, and language impairments. Long-term consequences may include antisocial or violent behaviors during adolescence (7).

Women with a history of depression or anxiety are at heightened risk of exacerbations during the peripartum period.

This study presents three case reports to address concerns surrounding the use of pharmacotherapy during pregnancy and lactation in patients with depressive or anxiety disorders. These cases highlight the efficacy and safety of psychopharmaceuticals in managing such conditions during this critical period in patients' lives.

CASE 1

Patient, age 33, employed, married, pregnant, no children. Positive heredity, grandmother committed suicide. The patient lives with her husband and his mother in a small village. Before pregnancy, she did not have any symptoms of mental disorders. When she got pregnant, the patient was thrilled, but in the next few weeks she started to feel exhausted, she could not sleep or eat, smoked a lot, and felt anxious and unhappy. Her husband and mother-in-law thought that she felt nervous because of the pregnancy. The patient did not want to visit a psychiatrist, as she had heard that medicaments could be dangerous for the baby. In the last six weeks before her due date, the patient developed hypertension, and preeclampsia was diagnosed. She was admitted to the hospital, and a Cesarean section was performed in the 36th week of her pregnancy. She gave birth to a baby boy, but because of low-grade pulmonary hypertension, the baby was treated in the hospital for the next five weeks. After the delivery, the patient felt deeply depressed, she cried constantly, struggled to feel love for the baby, and experienced overwhelming guilt due to this emotional disconnect. She was at high risk for suicide, having developed a detailed plan, and believing that children should not be a part of this world. The patient also did not eat or sleep. When the psychiatrist visited her in the hospital, a diagnosis of serious depression was made. Sertraline and mirtazapine were prescribed, while the patient was admitted to the psychiatric clinic. During the first week, the patient became less tense, she could sleep much better, lactation was stopped, and afterward, suicidal ideas were gone. In the next four weeks, symptoms of depression became mild and the patient was dismissed from the hospital. Recovery continued and in the following weeks the patient attained full remission.

During the year following her hospitalization, regular psychiatric check-ups were conducted, and remission persisted, with both mother and child remaining in good condition.

CASE 2

Patient, age 39, married, employed, first pregnancy. She visited a psychiatrist for several years and was treated for depression and anxiety**.** The patient finished her studies and found a job. She continued with regular psychiatric check-ups and had no symptoms of mental disorders. Over time, her psychopharmaceutical dosages were gradually reduced. For the six months preceding her pregnancy, she was prescribed sertraline (100 mg/die) and clonazepam (0.5 mg/die) and had remained asymptomatic. The pregnancy was unplanned. Three weeks after discovering she was pregnant, the patient consulted her general practitioner (GP) regarding the safety of continuing her medications. The GP discontinued both sertraline and clonazepam, citing concerns about potential malformations in the fetus. Within days, the patient became tense, anxious, and unable to sleep or eat. Obsessive thoughts emerged about harming her husband, as well as unknown individuals on the street, along with irrational fears that her baby would have various physical deformities. She did not go out, had no activities planned, and cried a lot. She was examined at the psychiatric outpatient clinic where sertraline, as well as clonazepam, were prescribed, but the symptoms got worse. The patient was consumed with suicidal plans, so she was admitted to the hospital. In the next period, the patient felt depressed, would cry excessively, could not eat or sleep, and was at an extremely high risk of suicide. The doses of psychopharmaceuticals were reviewed, and antipsychotic chlorpromazine in doses of 100 mg/die was added to antidepressant sertraline (200 mg/die) and diazepam (2,5 mg/die). The next week, she got better, could eat and sleep well, her obsessions about the baby being deformed disappeared, and her mood and functioning improved. She was hospitalized for three weeks during which the fetus was carefully monitored, all parameters were well. After three weeks the patient felt good enough to be dismissed from the hospital and was willing to continue with the regular psychiatric check-ups. At demission, the patient was euthymic, relaxed, and in good condition. Till delivery sertraline was reduced to 100 mg/die, chlorpromazine was excluded and diazepam was prescribed in doses of 2,5 mg when needed in the evening. Two weeks before delivery sertraline was prescribed at 50 mg/die,

trying to avoid the syndrome of rapid discontinuation in newborns. As the patient became hypertensive a few weeks before the delivery, sectio cesarea was indicated, and a healthy baby boy was born, while the mother's health remained good. After birth, there were no symptoms of mental disorders in this patient, but in the prevention of recurrent depression, doses of sertraline were 100 mg/die**.** Lactation was not initiated. During the next two years the mother maintained in full remission, and the baby showed normal progress in physical and mental development.

CASE 3

The patient is 37 years old, married, and employed. In her 20s, she underwent psychiatric treatment for two years due to generalized anxiety disorder (GAD) with panic attacks. Treatment included both psychotherapy and pharmacotherapy, resulting in complete symptom resolution. During her first pregnancy, she remained in remission, and her first child, now five years old, was born without complications. Since then, she experienced a miscarriage and is now four months pregnant.From the beginning, the patient felt uncomfortable and restless. She was frightened about what would happen with her pregnancy and cried often. She found it difficult to leave the house and could only do it if her husband was by her side. She complained to her GP about experiencing anxiety, daily panic attacks, trembling, lack of sleep, and inability to eat. The patient was willing to take antidepressants since they already helped her with these kinds of symptoms in the past, but her GP prescribed her with just benzodiazepines. The patient decided to come to a psychiatrist in an urgent ambulance since she recognized that she needed professional help. As symptoms of anxiety were intense, sertraline (100 mg/die) was prescribed, and due to good effect during the previous episode, mirtazapine was also added to the combination (15 mg/die). Benzodiazepines were slowly excluded. In the next 6 weeks, her symptoms became milder and less frequent. The patient felt much better, she could sleep the whole night and function normally for the rest of her pregnancy. After three months of such therapy in combination with CBT weekly full remission was acquired.

At the beginning of the 36th week of pregnancy doses of sertraline were gradually reduced to 25 mg/die, and mirtazapine was excluded. The baby was delivered on time, and both the mother and baby boy were in good condition. After childbirth, the patient was taking 50 mg of sertraline and 3 mg of bromazepam. She decided to avoid breastfeeding, although it was permitted. Over the following six months, the patient remained in good mental health, and the baby exhibited normal physical and developmental progress.

DISCUSSION

The period of pregnancy and lactation is unique for women. While often filled with happiness, it also presents a significant risk for the recurrence of depressive or anxiety symptoms, particularly in women who experienced a primomanifestation of these disorders before pregnancy. Additionally, the likelihood of experiencing a first episode of depression or anxiety is heightened during this time.

In today's world, where an overwhelming amount of information is readily available, pregnant women—especially those facing mental health challenges—often find themselves confused and uncertain about the best course of action. Psychiatrists and patients alike face complex decisions regarding the use of psychopharmaceuticals during pregnancy and lactation. These decisions involve weighing the risks of prenatal exposure to psychotropics, potential negative effects such as teratogenicity, neonatal toxicity, and long-term behavioral changes, against the risks of untreated psychiatric disorders. The primary goal is to minimize fetal exposure while addressing the dangers posed by untreated maternal mental illness (1).

Depression during pregnancy, known as prenatal or antenatal depression, is closely linked to the term "with peripartum onset" and is often underestimated as a critical health concern. According to the American College of Obstetricians and Gynecologists, all pregnant women should undergo screening for depression at least once during pregnancy. However, depression is frequently undiagnosed, and even when identified, treatment is often refused due to concerns about the baby's health. Evidence suggests that untreated depressive disorders during pregnancy are associated with adverse outcomes, including fetal growth restriction, preterm birth, low birth weight, maternal anemia, diabetes, hypertensive disorders (such as preeclampsia), cesarean delivery, and postpartum depression. Infants born to mothers with untreated prenatal depression may display irritability, reduced activity, and developmental challenges (8).

Although some studies offer conflicting views on the role of obstetric complications in maternal depression, the consensus remains that untreated mental illness significantly increases the risk of suicidal ideation and behavior, contributing to higher maternal morbidity and mortality. It is estimated that untreated depression during pregnancy carries a 50–62% likelihood of progressing to postpartum depression and may exacerbate pre-existing psychiatric conditions. Psychi-

atric grounds for pregnancy termination are also not uncommon (9).

Case 1 exemplifies antenatal depression that culminated in a cesarean delivery and neonatal health complications. Throughout the pregnancy and postpartum period, the mother exhibited severe depressive symptoms, with intermittent psychotic manifestations that posed significant risks to both her and her newborn.

Discontinuation of antidepressants during pregnancy frequently leads to withdrawal effects, which may appear within days or weeks. These effects include mood disturbances, general somatic symptoms, insomnia, gastrointestinal discomfort, and, often, a gradual recurrence of psychiatric symptoms (3). This phenomenon is clearly demonstrated in Case 2, where medication cessation led to the rapid onset of severe psychiatric symptoms, including suicidal ideation. Following reintroduction and adjustment of psychopharmacological treatment, the patient showed significant improvement, with a marked reduction in symptoms.

Beyond depression, pregnant women are vulnerable to anxiety, post-traumatic stress disorder (PTSD), postpartum psychosis, eating disorders, and obsessive-compulsive disorder. Effective treatment of peripartum psychiatric disorders aims to alleviate symptoms while supporting family dynamics. It is essential to provide comprehensive information about treatment options, including their risks and benefits (9, 10).

Selective serotonin reuptake inhibitors (SSRIs) are among the most commonly prescribed medications during pregnancy. These medications can cross the placenta and are also transferred to the newborn through breastfeeding (11). Concerns have been raised about potential associations between SSRIs and congenital heart defects. However, numerous studies indicate that SSRI exposure during pregnancy, including the first trimester, does not carry significantly higher risks compared to pregnancies where SSRIs were discontinued (12, 13, 14). According to the FDA, SSRIs approved for use during pregnancy include fluoxetine, sertraline, paroxetine, citalopram, and escitalopram (15). Among these, paroxetine has been implicated in a higher risk of major malformations, particularly cardiac defects such as septal anomalies and right ventricular outflow tract obstruction (16).

For anxiety during pregnancy, treatment typically involves antidepressants, benzodiazepines (BZDs), Z-hypnotics, and beta-blockers. SSRIs remain the first-line treatment, but benzodiazepines are still frequently used either alone or in combination with other therapies (15, 17). Early pregnancy exposure to benzodiazepines or Z-hypnotics has not been associated with an increased risk of stillbirth or preterm birth, but it has been linked to lower birth weight and a slightly elevated risk of congenital malformations and cardiac anomalies, especially at higher doses. Late-pregnancy use of benzodiazepines may result in floppy infant syndrome or neonatal withdrawal symptoms, ranging from hypotonia and mild sedation to apneic complications and metabolic instability (18).

Despite these potential risks, benzodiazepines can be considered when clinically indicated. To mitigate risks, non-pharmacological interventions should be prioritized for anxiety and insomnia during pregnancy. When benzodiazepines are necessary, they should be prescribed at the lowest effective dose, particularly during the early stages of pregnancy (19).

CONCLUSION

For treating these common mental disorders during pregnancy and breastfeeding, psychotherapy is the first choice, due to various therapeutical protocols (ICE, CANADIAN, South Africa, Australian, etc). However, when symptoms are moderate to severe, psychopharmaceuticals are often necessary in addition to psychotherapy.

The decision to initiate pharmacotherapy requires a careful evaluation of the risks and benefits. Emerging evidence suggests that the prevalence of fetal malformations is comparable between treated and untreated depressive patients. According to the NICE guidelines, psychotherapy is recommended for mild symptoms, while moderate to severe cases warrant a thorough discussion of pharmacological options.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: No

Author contribution: All authors have contributed equally

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

Sažetak

LEČENJE DEPRESIVNIH I ANKSIOZNIH POREMEĆAJA TOKOM TRUDNOĆE I PERIODA LAKTACIJE: STUDIJA SLUČAJA

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Uvod: Depresivni i anksiozni poremećaji su najučestaliji od svih mentalnih poremećaja prema podacima SZO iz 2015. Primomanifestacija ovih poremećaja najčešće se ispoljava u adolescenciji i ranom odraslom dobu. Neretko, simptomi se ispoljavaju tokom trudnoće ili perioda laktacije, koji predstavljaju specijalan ali i veoma vulnerabilan period u životu žene. Zabrinute zbog transplacentarnog prelaza lekova u krvotok ploda, pacijentkinje postavljaju pitanja o bezbednosti preporučenog antidepresiva. Ukoliko medicinsko osoblje nije dobro edukovano, takođe se ispoljava nedoumica o bezbednosti psihofarmaka u trudnoći. Širom sveta protokoli u lečenju preporučuju primenu psihoterapijskih intervencija ukoliko su simptomi anksioznosti ili depresivni simptomi blagi, a ukoliko su intenzivniji, terapija izbora je pažljiva kombinacija psihofarmaka i psihoterapije.

Prikaz slučaja: U ovom radu su data tri prikaza slučaja pacijentkinja koje su se tokom trudnoće suočile sa depresivnim i anksioznim poremećajima. Kod prve pacijentkinje je došlo do razvoja prenatalne depresije zbog čega su propisani antidepresivi koji su doveli do potpune remisije. Drugi prikaz slučaja objašnjava vezu između diskontinuacije psihofarmaka i ponovnog proboja simptoma mentalnog poremećaja, dok treći naglašava značaj individualizovanog tretmana pacijenata i ponovne pojave simptoma mentalnih poremećaja tokom trudnoće kod pacijentkinja koje su prethodno bile u remisiji.

Zaključak: Studija od tri slučaja je prikazana u svrhu edukacije lekara o efikasnosti i bezbednosti primene antidepresiva kod pacijentkinja u trudnoći i periodu laktacije.

Ključne reči: depresija, anksioznost, trudnoća, laktacija, psihofarmakoterapija.

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***How to cite this article**:* **Ini**ć **T**, Cvjetković Bošnjak M, Kuljančić D. Treatment of Depressive and Anxiety Disorders During Pregnancy and Lactation: A Case Study. Sanamed. 2024; 19(3): 319-324. doi: 10.5937/sanamed19-54756.

SANAMED
2024; 19(3): 325–332
ISSN-1452-662X

DOI: 10.5937/sanamed0-51327
UDK: 637.413.064:616-097
ID: 159909129
Review article

OVOMUCOID (THE MOST IMPORTANT EGG WHITE ALLERGEN) AS A CAUSE OF SEVERE EGG ALLERGY: A REVIEW

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Primljen/Received 31. 05. 2024. Prihvaćen/Accepted 13. 08. 2024. Published online first: 05. 10. 2024.

Abstract: Hypersensitivity, or an allergy to highly valuable chicken egg proteins, is a prevalent symptomatic condition. It occurs when the immune system of a hypersensitive or allergic individual overreacts upon contact with egg allergens (egg proteins), triggering a complex immune response. Among these allergens, ovomucoid is the most allergenic, making up 11% of egg white. Ovomucoid is both thermostable and resistant to digestion, distinguishing it from other egg white proteins. While ovalbumin is the most abundant protein in egg white, ovomucoid is responsible for the majority of its allergic properties. Humans generally lack tolerance to both raw and cooked eggs due to the presence of this allergenic protein.

Given the significance of ovomucoid in egg allergy, it has a direct impact on the quality of life of affected individuals. A better understanding of the role of various drug classes is essential for managing and treating egg allergy. Additionally, insights into embryogenesis may be critical in understanding the efficacy of these treatments in alleviating egg allergies. This knowledge could not only benefit individuals with egg allergies but also the egg production industry and society as a whole. Maintaining good health is one of the most crucial factors in serving our community, and addressing egg allergy is an important part of that.

Keywords: Egg allergy, ovomucoid, IgE-mediated food allergies, epidemic, embryogenesis, management, florfenicol, immunotherapies.

INTRODUCTION

The term “allergy” refers to an abnormal or hypersensitive reaction of the human body’s immune system to environmental stimuli or substances. One of the major challenges in today’s society is food allergies, which are increasingly prevalent (1). Among these, egg allergy is one of the most common allergic conditions affecting infants and children worldwide (2). Chicken egg allergy is a global health issue, impacting 1–2% of children globally. Four major allergens are found in egg white: ovotransferrin, ovalbumin, ovomucoid, and lysozyme. These proteins are the primary culprits behind egg allergy (hypersensitivity), while egg yolk allergens, including chicken serum albumin and YGP42, also play a role (1).

These egg allergens—ovotransferrin, ovalbumin, ovomucoid, and lysozyme—can cause serious medical conditions such as rhinitis, conjunctivitis, laryngeal edema, anaphylaxis, and chronic urticaria (3). Egg white consists of the following protein composition: ovomucin (4%), ovalbumin or conalbumin (Gal d 2, 55%), ovotransferrin (Gal d 3, 12%), lysozyme (Gal d 4, 3%), and ovomucoid (Gal d 1, 11%) (4).

Previous studies have shown that ovomucoid’s allergenicity is not affected by enzymatic proteinase activity (5, 6). The linear IgE binding epitopes on ovomucoid’s structure align with conformational epitopes across all domains, making cooking ineffective at reducing the allergic properties of ovomucoid. Targeted immunotherapies, such as producing hypoallergenic variants of ovomucoid, are under investigation as potential treatment options. Ovalbumin is the second most significant allergen in egg white. However, treatments like urea, carboxymethylation, or heating at 95°C have little effect on its allergenic potential, as reported by Mine and Zhang et al (7). Still, ovalbumin’s IgE-binding capacity can be altered by digestive enzymes in the gut. Its exact biological function remains unclear, though it is believed to resist protease activity. The third allergen, ovotransferrin, has also been extensively studied for its allergenicity and conformational changes during cooking. Tong et al. reported a critical link between these structural changes and increased al-

lergenicity (8). Finally, lysozyme, which provides antimicrobial protection to the egg, has multiple sequential conformational epitopes. Though it causes fewer allergies compared to ovomucoid and ovalbumin, it still poses some allergenic risk (3).

Egg allergy in infants is closely associated with atopic dermatitis and significantly increases the risk of sensitization to aeroallergens and respiratory conditions like asthma. Influenza vaccination can also pose risks for individuals with severe egg allergies. Anaphylaxis further complicates immunization in children with egg allergies, making this a major health concern (9). Egg-associated allergies primarily trigger immune responses via food proteins, manifested by the presence of immunoglobulin E (IgE), a key biomarker for antibody-mediated allergies. Other conditions, such as eosinophilic esophagitis (EOE) and atopic dermatitis, are also linked to egg allergies (10).

Ovomucoid is resistant to acid and heat, and individuals allergic to ovomucoid tend to have low tolerance for both raw and cooked eggs. While the allergenicity of ovalbumin may be reduced by high temperatures, allowing some allergic individuals to tolerate cooked eggs, this is not the case for ovomucoid (11). A key question remains: which egg protein is the most allergenic? Ovomucoid, despite being resistant to heat and not coagulable by it, is the most persistent allergen, while other egg proteins are disrupted by heat. A landmark study conducted in Japan by Urisu et al. (12) used a double-blind, placebo-controlled food challenge to establish ovomucoid as the primary allergen responsible for egg white-induced allergic conditions in humans. The study also highlighted the allergenic properties of ovalbumin and ovotransferrin, with lysozyme having the weakest allergenicity. These conclusions were based on the comparative levels of IgE antibodies for ovomucoid, ovalbumin, ovotransferrin, and lysozyme (12).

There are many commercially available drugs that increase chicken egg production (embryogenesis), which in turn has significant implications for human allergies, their diagnosis, and management (Table 1). While increased egg production can serve as a valuable revenue-generating tool globally, understanding how to minimize human allergies in relation to these drugs is equally important. This could be a game-changer for middle-class families involved in the egg production industry, as it can lead to greater prosperity and economic development in today's challenging financial climate.

On the other hand, there are also drugs that decrease chicken egg production (inhibit embryogenesis), and this, too, has serious implications for human allergies, their diagnosis, and management (Table 2). If the effects of these drugs on human populations are not well understood, the global egg production industry may suffer severe consequences. Communities involved in the egg industry must be informed about which drugs can negatively impact their income, both annually and periodically.

Moreover, this review establishes a link between the severity, consequences, management, and treatment of egg allergies in humans and the various drug classes used in egg production (Table 3). If further studies focus on the relationship between these drugs and the pattern of egg allergies, particularly in children, it may lead to the development of novel strategies to counteract egg allergies. This could answer more complex and multifaceted questions related to human allergic conditions.

The primary objective of this review is to explore the relationship between ovomucoid (egg allergy) and different classes of drugs, particularly those that either increase or decrease egg production. Understanding this association is essential for developing improved management and treatment strategies for human allergic conditions, especially those caused by eggs during infancy or early childhood. Therefore, it is crucial to develop a comprehensive understanding of egg allergens, their impact on allergic reactions, and their prevalence. This approach is key to improving the diagnosis and treatment of egg allergies, which will shape future healthcare strategies.

For this review, data from reputable and reliable sources such as Google Scholar, Cochrane Library, PubMed, and ScienceDirect have been utilized, covering research from the past 30 years. Keywords like "egg allergy," "ovomucoid allergy," and "human allergies" were extensively used to search for relevant studies. The focus of this review is on ovomucoid, the primary cause of egg allergy, which is heat-stable, acid-resistant, and not degraded by cooking. Other egg white allergens are generally excluded from the scope of this review.

Significance of Ovomucoid in egg allergy

Ovomucoid is the most significant egg white allergen, comprising about 11% of egg white. It is a trypsin-inhibitory glycoprotein with a molecular weight of 28 kDa, consisting of 186 amino acids arranged in three tandem domains. Each domain contains about 60 amino acids, five carbohydrate side chains, and nine intra-domain disulfide bonds.

Trypsin inhibition occurs through the second domain, which contains the reactive site for inhibitory activity. Ovomucoid's domain alignment is similar to that of pancreatic trypsin inhibitor activity. Its key characteristic is the ability to resist degradation by heat

and proteinase activity. This is due to the linear trajectory of its IgE-binding epitopes, some of which have conformational features. Cooking does not reduce the allergenicity of ovomucoid, making it a prime candidate for exploration in targeted therapies and treatment strategies (3).

Eggonomics: impact and hazards of egg production

Egg production often fluctuates based on global demand and supply, leading to increased production in some cases and halting it in others. Certain drugs that boost egg production can also have serious side effects, spreading diseases and causing significant medical conditions in humans (Table 1). On the other hand, essential drugs like amphenicols, sulfonamides, and coccidiostats, which reduce egg production, can cause severe health issues such as mutagenicity, cancer, diabetes, neuropathy, and bone marrow toxicity (Table 2). The egg industry must adopt scientific approaches to mitigate these adverse health outcomes while improving the livelihood of poultry workers and others connected to the industry.

Role of drugs in managing human allergies

Many diverse classes of drugs, including nitrofurans, tetracyclines, imidazoles, beta-lactams, aminoglycosides, macrolides, amphenicols, ionophores, sulfonamides, and coccidiostats, can trigger severe allergic reactions (as outlined in Table 1 and Table 2). These drugs can also cause various conditions such as cancer, eye and skin allergies, nephropathy, hepatotoxicity, gastrointestinal disorders, and cardiac complications. To manage and alleviate human allergies, a thorough understanding of these drugs' side effects is necessary. The use of these drugs must be closely monitored to ensure a healthy poultry industry and improve human quality of life.

Biomarkers in clinico-commercial diagnostics

Biomarkers, or biological parameters, play a critical role in diagnosing and investigating allergic conditions. Many drug-induced disorders, linked to increased egg production, require biomarker testing for accurate clinical diagnosis and effective treatment initiation (Table 1). Similarly, drugs that significantly reduce egg production and cause severe side effects (Table 2) require proper diagnosis through validated biomarker identification**.** Failing to do so may lead to lethal consequences.

Future strategies for managing human allergies

Looking ahead, researchers have developed crucial strategies and therapies to improve allergy management and provide effective alleviation. These efforts include the following treatments (Table 3).

1. Oral Immunotherapy (OIT)
2. Monoclonal Anti-IgE Antibody Therapy
3. Allergen-Specific Immunotherapy
4. Chinese Herbal Formulations
5. Diets Containing Extensively Heated Eggs
6. Omalizumab
7. DNA Vaccines
8. Epicutaneous Immunotherapy (EPIT)
9. Subcutaneous Immunotherapy (SCIT)
10. Biologics have shown promising results in treating severe allergies, such as psoriasis, by providing a balance between safety and efficacy (13)
11. Additionally, breastfeeding has been found to help in reducing food allergies (14).

CONCLUSION

Egg allergy remains a significant challenge, both in the past and present. With advancing research, we now recognize that several proteins, most notably ovomucoid, play a pivotal role in this phenomenon. Ovomucoid offers valuable insights into the management, treatment, and future strategies for addressing egg allergies. Furthermore, understanding the impact of drugs on egg production is essential for shaping future strategies aimed at combating allergic conditions and improving public health.

Social welfare and well-being should be at the forefront, with particular attention given to the poultry industry and those involved. The concept of "eggonomics" emphasizes balancing commercial egg production with prioritizing human health and therapeutic needs. The use of specialized biomarkers can aid in the development of diagnostic and treatment strategies, addressing allergic conditions and disorders related to drugs influencing egg production.

Looking ahead, therapies should be designed to provide more effective treatments for human allergies. The egg and poultry industries must also acknowledge their responsibility to society, establishing robust research and development programs to better manage and prevent allergic conditions through innovative anti-allergy regimens and therapies.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: No.

Table 1. *Drugs that increase egg production and their effects on humans*

CLASS	DRUGS	EFFECT ON EGG PRO-DUCTIONON	EFFECT ON HUMANS	TREATMENT / MANAGEMENT	BIO-MARKS
Nitrofurans (15)	Furazolidone	Increase	• Autoimmunity • Carcinogenicity • bone marrow toxicity • nephropathy • reproductive disorders • hepatic disorders • vaginal adenocarcinoma • neoplasia (15)	• Boiling (heat treatment) (15)	• C-reactive protein (CRP) • glomerular filtration rate • albumin, creatinine • blood urea nitrogen
Tetracyclines (15)	Oxytetracycline	Increase	• poor development of fetus • staining of teeth in children • immuno-pathological effects • gastrointestinal disorders • proinflammatory • cytotoxicity • allergic reactions (15)	• Thin layer chromatograph • Microbial inhibition tests • Boiling (15,16)	• placental growth factor (plgf) • (CRP) c-reactive protein • Insulin-like growth factor who are bindingprotein-1 & -3 • total IgE • specific IgE (sIgE) • IgG4
Imidazole	Methimazole	Increase	• Hives and itching • Hepatotoxicity • Teratogenicity • Hypothyroidism	• Heat treatment (microwaving) (15)	• alanine aminotransferase (ALT) • lipid profile test • thyroid profile test • cytokine test
Supplements	Vitamin A	Increase	• prevent any symptoms for the deficiency • hair loss • Problems of skin • an increased risk of infections and dry eyes	—	—
	Vitamin E	Increase	• promoting the avoidance of certain cancers • age related eye disorders gets very low • it also shows cognitive decline related with aging	—	—
	Vitamin C	Increase	• protective effect of higher intake from cardiovascular disease and certain cancers • protect from eye diseases like cataracts and macular degeneration	—	—
	Carotenoids	Increase	• macula is protected from deterioration by blue light • Decreases the risk of cataractsand age-related macular degeneration • Heart associated cardiovascular diseases • possibly different cancersand Alzheimer's • improve visual acuity (17)	—	—

Beta-lactams (15)	Penicillin	Increase	• Dermatitis • cutaneous eruptions • anaphylaxis • hemolytic anemia • vasculitis • acute interstitial nephritis (15)	• Refrigeration • microbiological inhibition assay (screening method) (15, 16)	• Tryptase • (ESR) Erythrocyte sedimentation rate • (CRP) C-reactive protein • blood urea nitrogen • serum creatinine
Amino-glycosides (15)	Streptomycin	Increase	• Allergic reactions (15)	• microbiological inhibition assay (screening method) • boiling • steaming • frying • microwaving (15, 16)	• total IgE • specific IgE(sIgE) • IgG4
Macrolides (15)	Erythromycin	Increase	• Carcinogenicity • Liver injury as an answerto macrolide metabolite-modified hepatic cells (15)	• microbiological inhibition assay (screening method) • boiling • steaming • frying • microwaving (15, 16)	• transaminases alanine aminotransferase (ALT) • aspartate aminotransferase (AST, or SGOT) • Cytokeratin 10 (CK18)

Table 2. *Drugs that decrease egg production and their effects on humans*

CLASS	DRUGS	EFFECT ON EGG PRO-DUCTIONON	EFFECT ON HUMANS	TREATMENT / MANAGEMENT	BIOMARKERS
Amphenicol (15)	Florfenicol	Decrease	• Hepatotoxicity • Mutagenicity • bone marrow toxicity (15)	• Heat treatment • Microbiological • Inhibition method • Boiling • Steaming • Frying • microwaving (15)	• (ALT) alanine aminotransferase • (AST) aspartate aminotrans-ferase • alkaline phosphatase (ALP) • (GGT) glutamyl transpeptidase • (TBIL) total bilirubin.
	Azasterol (18)	Decrease	• Heart diseases • Diabetes • Certain cancers		• Myoglobin • Cardiac Troponin • creatine kinase • increased blood pressure • decreased HDL cholesterol • increased triglycerides
Coccidiostat (Anticoccidial) (15)	Nicarbazin (19)	Decrease	• Toxic effects (if high dose)	• solid-phase extraction & purification (20)	
	Amprolium (21)	Decrease	—	—	
Ionophore (Anticoccidial) (15)	Monensin (19, 22)	Decrease	• Irritation • Allergic reactions (15)	• solid-phase extraction & purification (20)	• skin prick testing (SPT) • total IgE • specific IgE • IgG4
Sulfonamides (15)	Sulfanilamide (23)	Decrease	• Skin Allergic reactions • bone marrow toxicity • neuropathy • carcinogenicity (15)	• Thermal treatment • Vaccine • Application of probiotics • Agricultural management (15)	• skin prick testing (SPT) • total IgE • specific IgE (sIgE) • IgG4 • Rateof glomerular filtration • creatinine and albumin • blood urea nitrogen
	Sulfamerazine (24)	Decrease			
Coccidiostat (15)	Buquinolate	Decrease	• Toxic effects	• solid-phase extraction & purification (20)	

Table 3. *Management, treatment, and future therapy prospects for egg allergy (focusing on Ovomucoid)*

SEVERITY OF OVOMUCOID ALLERGY	CONSEQUENCES OF UNTREATED EGG ALLERGY	TRADITIONAL MANAGEMENT OF EGG ALLERGIES	FUTURE PERSPECTIVE AND NOVEL THERAPIES FOR EGG ALLERGY
• Anaphylaxis • Severe eczema • Rhinitis • Skin rashes or hives • Mild to severe cutaneous reactions • severe vomiting or diarrhea • Respiratory symptoms (cough, wheeze or swelling of throat, choking, affect breathing) • cramps • nasal congestion • Asthma (25, 26)	• Scarring and thickening of the skin. • Irreversible lung damage. • Diarrhea • Abdominal pain • anaphylactic shock • Low blood pressure • Swelling (25, 26)	• Saline nasal irrigation • Acupuncture • Completely avoid food containing egg • Probiotics • Stinging nettle • Antihistamines • Epinephrine auto-injector • MSM Supplements (Methylsulfonylmethane) • Peppermint and eucalyptus essential oils • Food rich in Vitamin C • Ginger & Garlic (25-29)	• Oral immunotherapy (OIT) • Monoclonal anti-IgE antibody therapy • Allergen-specific immunotherapy • Chinese herbal formulation • Diets containing extensively heated eggs • Omalizumab • DNA vaccines • Epicutaneous immunotherapy (EPIT) • Subcutaneous immunotherapy (SCIT) (30-33)

Acknowledgment: I would like to extend my gratitude to my teacher, Prof. Dr. Farzana Sadaf, for her guidance.

Author contribution: All authors have contributed equally

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

Sažetak

OVOMUKOID (NAJVAŽNIJI ALERGEN BELANCA) KAO UZROK TEŠKE ALERGIJE NA JAJA

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Hipersenzitivnost, ili alergija na proteine iz kokošijih jaja, je rasprostranjeno simptomatsko stanje. Do nje dolazi kada imunološki sistem hipersenzitivne ili alergične osobe reaguje na kontakt sa alergenima iz jaja (proteini iz jaja), izazivajući složen imunološki odgovor. Među ovim alergenima, ovomukoid je najpotentniji, čineći 11% belanca. Ovomukoid je i termostabilan i otporan na varenje, što ga razlikuje od drugih proteina u belancetu. Dok je ovalbumin najzastupljeniji protein u belancetu, ovomukoid je odgovoran za većinu njegovih alergijskih svojstava. Ljudi generalno nemaju toleranciju ni na sirova ni na kuvana jaja zbog prisustva ovog alergenskog proteina.

S obzirom na značaj ovomukoida u alergiji na jaja, on direktno utiče na kvalitet života pogođenih pojedinaca. Bolje razumevanje uloge različitih klasa lekova je od suštinskog značaja za kontrolu i lečenje alergije na jaja. Pored toga, uvid u embriogenezu može biti ključan za razumevanje efikasnosti ovih tretmana u ublažavanju alergija na jaja. Ovo znanje može koristiti ne samo pojedincima sa alergijom na jaja, već i industriji proizvodnje jaja i društvu u celini. Održavanje dobrog zdravlja je jedan od najvažnijih faktora za služenje našoj zajednici, a rešavanje alergije na jaja je važan deo toga.

***Ključne reči**:* Alergija na jaja, ovomukoid, IgE--posredovane alergije na hranu, epidemija, embriogeneza, kontrola, florfenikol, imunoterapije.

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***How to cite this article**:* Ahmed T, Ayaz H, Nisar D, Moin A. Ovomucoid (the most important egg white allergen) as a cause of severe egg allergy: a review. Sanamed. 2024; 19(3): 325-332. doi: 10.5937/sanamed0-51327.

SANAMED
2024; 19(3): 333–341
ISSN-1452-662X

DOI: 10.5937/sanamed0-52803
UDK: 616.348/.35-006.6:575.113
ID: 160155145
Review article

ANALYSIS OF TP53, APC, KRAS, AND MMR GENETIC MUTATIONS IN COLORECTAL CANCER: A REVIEW ARTICLE

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Primljen/Received: 15. 08. 2024. Prihvaćen/Accepted: 05. 10. 2024. Published Online First: 21. 10. 2024.

Abstract: **Introduction:** Colorectal cancer (CRC) is one of the most common malignancies with significant global health and economic implications. Genetic mutations in genes such as TP53, APC, KRAS, and MMR play a crucial role in the development and progression of this cancer. This review paper analyzes current knowledge about the impact of these mutations on colorectal carcinogenesis, using available literature.

Objective: To provide a comprehensive review of the role of genetic mutations in TP53, APC, KRAS, and MMR genes in the development of colorectal cancer and to consider their impact on diagnosis and treatment.

Materials and Methods: This review examines peer-reviewed research articles and reports sourced from databases such as PubMed, Google Scholar, and other academic sources. The focus was on studies investigating genetic mutations, their prevalence, and their role in the pathogenesis of CRC.

Results: Mutations in the TP53 gene, present in more than 50% of CRC cases, are critical for malignant cell transformations. KRAS mutations, found in about 50% of cases, lead to abnormal signaling contributing to unchecked proliferation. APC mutations are associated with hereditary predisposition to CRC, while MMR genes, such as MLH1 and MSH2, play a key role in DNA repair and are linked to hereditary nonpolyposis colorectal cancer.

Conclusion: Genetic mutations in TP53, APC, KRAS, and MMR genes play a significant role in the development of colorectal cancer. A deeper understanding of these mutations may significantly enhance diagnostic and therapeutic strategies, guiding future research in this rapidly evolving field.

Keywords: Colorectal Neoplasms, Carcinogenesis, Mutation, Genes, Tumor Suppressor.

INTRODUCTION

Colorectal carcinoma (CRC) is a malignant tumor that originates in the epithelium of the colon and rectum. According to recent statistical data, the incidence of CRC in this region shows a decline, but the mortality rate remains high, indicating the need for improved prevention, diagnosis, and treatment strategies (1).

The carcinogenesis of CRC is a complex process that typically develops from benign adenomas. Adenomas, which are precursors to carcinoma, undergo stages of dysplasia and hyperplasia before becoming malignant. During this process, a series of genetic and epigenetic changes occur, leading to malignant transformation (2). The mechanisms underlying these changes include mutations in specific oncogenes and tumor suppressor genes. The most important genes involved in the development of CRC are TP53, KRAS, APC, and those that are part of the DNA mismatch repair system (MMR genes such as MLH1, MSH2, MSH6, and PMS2) (3, 4).

TP53 encodes the tumor suppressor protein p53, whose functions include the regulation of the cell cycle and the induction of apoptosis in cells with damaged DNA. Mutations in the TP53 gene are associated with many types of tumors, including CRC (5). KRAS is an oncogene that plays a key role in cell signaling; its mutations can lead to abnormal cell proliferation and tumorigenic signaling (6). The APC gene is associated with familial adenomatous polyposis (FAP) and plays a role in regulating cell proliferation and apoptosis (7). MMR genes are responsible for recognizing and correcting errors in DNA during replication; their dysfunction leads to microsatellite instability (MSI) and increases the risk of CRC (8).

Although specific genetic mutations associated with CRC are well documented, significant gaps still

exist in understanding their roles and interactions (9). This review paper aims to identify unexplored areas, such as the impact of combinations of mutations and environmental factors, as well as unknown genetic variants that could play a role in the development of CRC.

AIM

To provide comprehensive insights into the genetic and molecular mechanisms involved in the development of colorectal carcinoma. This paper focuses on analyzing various genetic mutations and their roles in carcinogenesis, including genes associated with both hereditary and sporadic forms of CRC. Special emphasis is placed on exploring advanced mutation detection methods that enable precise diagnosis and personalized treatment for CRC patients. Understanding these mechanisms can contribute to improving strategies for early detection, prevention, and therapy of CRC, thereby significantly enhancing patient outcomes and reducing the associated mortality rate.

MATERIALS AND METHODS

This review paper relies on the analysis of available literature and previous research in the field of CRC. The material for analysis includes articles published in relevant medical and genetic journals, as well as data from clinical studies and meta-analyses.

Literature Review

Relevant bibliographic databases, including PubMed, Google Scholar, Scopus, and Web of Science, were used to identify key studies and peer-reviewed articles. The search was conducted using Boolean operators (AND, OR, NOT) to include relevant publications investigating the genetic aspects of CRC. The keywords used in the search included "colorectal carcinoma," "genetic mutations," "TP53," "KRAS," "APC," "MMR," "hereditary cancer," and "sporadic cancer." Additionally, relevant research in the field of meta-analysis addressing the prevalence and pathogenesis of CRC was explored.

Data Analysis and Synthesis

After identifying relevant studies, the data were analyzed to uncover key mechanisms and trends related to genetic mutations and their roles in CRC development. Qualitative analysis and synthesis methods were employed to review current knowledge and gaps in this area. Special attention was given to analyses that thoroughly examined the roles of genes such as TP53, KRAS, APC, and MMR in carcinogenesis. The analysis also included studies investigating advanced mutation detection methods, aiming to identify opportunities for precise diagnosis and personalized treatment for CRC patients.

RESULTS

Genetic Mutations and Their Frequency

The analysis of available literature and existing studies identified key genetic mutations that play a significant role in the development of CRC. These mutations affect various genetic pathways that contribute to carcinogenesis.

TP53

The cell cycle consists of several phases, with a key regulatory checkpoint at the transition from the G1 to the S phase. The tumor suppressor gene TP53, located on the short arm of chromosome 17 (position 13.1) (Figure 1), encodes the p53 protein, known as the "guardian of the genome" (5, 10). This protein plays a crucial role in regulating the cell cycle by activating genes responsible for DNA repair or apoptosis. Increased concentrations of p53 due to DNA damage cause cell cycle arrest, allowing for DNA repair or, if the damage is too severe, the initiation of apoptosis (10).

If mutations occur in the TP53 gene, the function of the p53 protein may be compromised, allowing the replication of damaged DNA during the S phase. Even a small change in a single amino acid can severely impair p53 function, leading to the accumulation of mutations and potentially the development of tumor cells. These mutations are present in more than 50% of all tumors, including a significant number of CRC cases (11).

KRAS

The KRAS gene encodes the K-RAS protein, which plays a key role in intracellular signaling. This protein is activated by binding to GTP and inactivated by hydrolyzing GTP to GDP. KRAS, located on chromosome 17p12.1, is one of the most frequently activated oncogenes (Figure 2). Mutations in this gene are detected in 17-25% of all tumors and are particularly prevalent in approximately 50% of CRC cases (12).

Under normal conditions, external signals stimulate the accumulation of GTP, which binds to K-RAS, activating it. K-RAS is then inactivated when GTP is converted to GDP, halting the signal (12). However, mutations in the KRAS gene, particularly in exons 12, 13, and 61, lead to reduced GTPase activity of the protein. These changes cause constant activation of K-RAS, disrupting cell cycle control and contributing

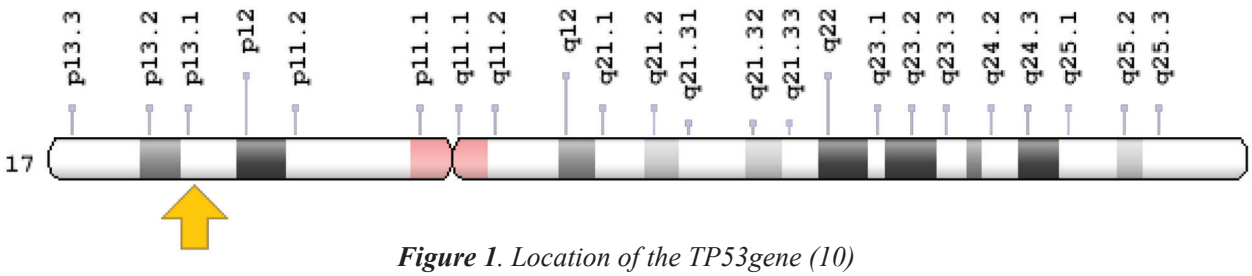

***Figure 1**. Location of the TP53gene (10)*

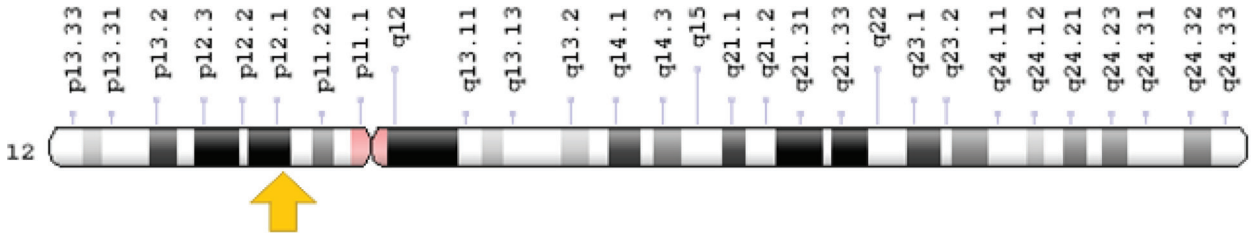

***Figure 2.** Location of the KRAS gene (12)*

to the abnormal karyotype known as chromosomal instability (CIN). K-RAS is also associated with disruptions in cytoskeleton organization during cell division, further contributing to CIN (13). Additionally, recent studies show that cells from patients with specific KRAS mutations are resistant to apoptosis that should be induced by chemotherapy. This finding indicates low chances of curing patients with KRAS mutations but also opens up opportunities for developing new therapeutic strategies (14).

APC

The APC gene, located on the long arm of chromosome 5 (5q22.2), encodes a protein that plays a key role in regulating the cell cycle, cell adhesion and migration, as well as chromosome segregation (Figure 2) (15). Mutations in this gene, including deletions, frameshift mutations, and point mutations, have been recorded in over 700 cases of individuals with familial adenomatous polyposis (FAP) (16).

Under normal conditions, the APC protein associates with the cytoskeleton, specifically microtubules, and is involved in spindle formation during cell division. When the APC gene functions properly, the APC protein, as part of a complex that includes other proteins, binds to β-catenin and phosphorylates it, signaling its degradation. However, in the presence of WNT signaling or in cases of a dysfunctional APC protein, β-catenin is not phosphorylated and translocates to the nucleus, where it activates the transcription of genes responsible for cell proliferation (Figure 3) (17).

This improper activation of β-catenin causes the constitutive expression of proliferation-related genes, contributing to the development of tumor cells. Mutations in the APC gene, therefore, play a significant role in the WNT/β-catenin signaling pathway, which regulates cell proliferation. In addition to APC mutations,

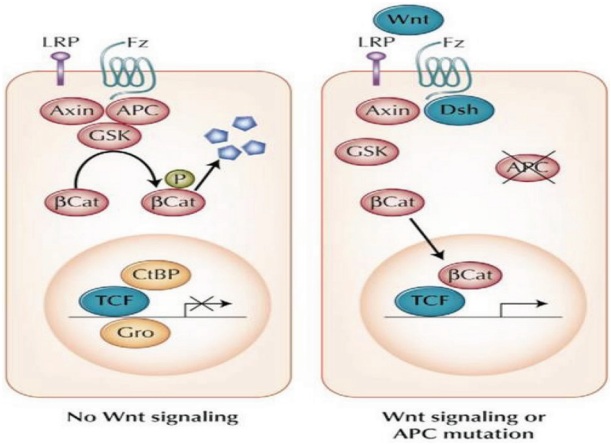

***Figure 3.** WNT/β-catenin Signaling pathway (17)*

a small number of CRC cases have also identified mutations in the CTNNB1, AXIN1, and AXIN2 genes, which encode proteins of this signaling pathway (18).

Chromosomal abnormalities associated with APC mutations contribute to the phenotype known as chromosomal instability, which is characteristic of many CRC cases. According to available data, the location of the mutation in the APC gene determines the number of polyps and the age at which they appear, providing key insights into the disease's progression(19).

MMR Genes

Mismatch Repair (MMR) genes, including MSH2, MLH1, PMS1, PMS2, MSH6, and MSH3, play a crucial role in recognizing and repairing mismatched bases during DNA replication (8). Mutations in these genes are the main cause of hereditary nonpolyposis colorectal cancer (HNPCC) syndrome and are also present in sporadic cases of CRC. The most common mutations occur in the MSH2 and MLH1 genes, while other genes are less frequently affected (20).

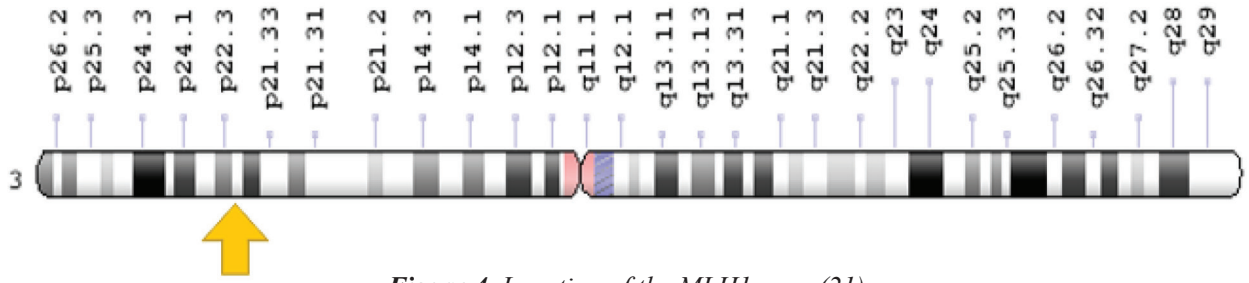

Figure 4. *Location of the MLH1 gene (21)*

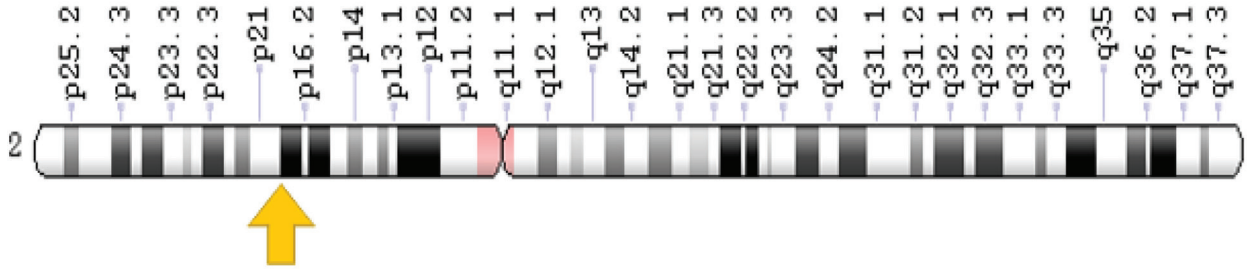

Figure 5. *Location of the MSH2 gene on the short arm of chromosome 2 at position 21(22)*

MLH1

The MLH1 gene, located on chromosome 3p21.3, encodes a protein that forms a complex with PMS2, which is essential for recognizing and repairing mismatched nucleotides (Figure 4). Mutations in MLH1 can cause HNPCC syndrome and variants such as Turcot syndrome and Muir-Torre syndrome. This gene plays a vital role in maintaining the accuracy of DNA replication (21).

MSH2

The MSH2 gene is located on chromosome 2 and encodes a protein that forms a complex with MSH6 or MSH3, enabling the identification of DNA errors (Figure 5). Mutations in MSH2 account for approximately 40% of HNPCC cases and are associated with various skin cancers (22).

EPCAM

The EPCAM gene encodes the epithelial cell adhesion molecule (EpCAM), a membrane protein that facilitates cell adhesion and can shed the intracellular domain (EplCD). Deletion of the 3' end of EPCAM leads to a truncated mRNA transcript and hypermethylation of the MSH2 promoter, resulting in reduced functional MSH2 protein. This mutation occurs in approximately 6% of HNPCC cases (23).

MUTYH

The MUTYH gene, located at position 34.1 on chromosome 1, encodes the MYH glycosylase enzyme, which is crucial for repairing oxidative damage to bases. Autosomal recessive mutations in this gene cause MUTYH-associated polyposis (MAP), which can lead to CRC. The most common mutations are tyrosine-cysteine (Tyr179Cys) and glycine-aspartic acid (Gly396Asp), present in 2% of the population but varying among ethnic groups (24).

SMAD4

The SMAD4 gene, located on chromosome 18, encodes a protein involved in the TGF-β signaling pathway, inhibiting cell growth and functioning as a tumor suppressor. Mutations in this gene lead to Peutz-Jeghers syndrome (PJS) and affect extracellular matrix protein synthesis, potentially contributing to metastasis and the development of sporadic CRC (25).

STK11

The STK11 gene, located on chromosome 19, encodes the tumor-suppressor enzyme serine/threonine kinase 11 (STK11), which regulates cell polarization, energy balance, and apoptosis. Hereditary mutations in STK11 cause Peutz-Jeghers syndrome, which is associated with an increased risk of CRC. Mutations in this gene can be deletions, insertions, or changes in the sequence, leading to functional protein disorders (26).

Advanced Detection Methods

With advancements in technology, various sophisticated methods have been developed for detecting genetic mutations associated with CRC. These methods enable precise identification of mutations and enhance diagnosis and personalized treatment.

Fluorescent In Situ Hybridization (FISH)

The FISH technique uses fluorescent probes that specifically recognize and bind to certain DNA sequences. This method allows visualization of chromosomal abnormalities and mutations at the cellular level. FISH is useful for identifying amplifications and deletions in genes such as HER2 in breast cancer and MYC in various tumor types, including CRC (27).

Comparative Genomic Hybridization (CGH)

The CGH technique allows for the detection of genetic changes such as amplifications, deletions, and other chromosomal aberrations. This method uses DNA hybridization of the sample with a reference genome on microarrays, enabling quantification and identification of genetic changes present in tumors, including CRC (28).

Allele-Specific PCR (AS-PCR)

AS-PCR is a method that allows for the detection of specific genetic mutations based on different alleles in DNA. This technique is highly precise and is used to identify specific mutations in genes such as KRAS and TP53, enabling personalized therapy and better management of CRC patients (29).

DNA Sequencing

DNA sequencing, including next-generation sequencing, allows for a detailed exploration of the genome and identification of all present mutations. This method provides a comprehensive overview of all variations in the genetic material, including rare and unknown mutations that may play a significant role in CRC development (30).

Shield Test

The Shield test is a blood test that utilizes a multimodal approach for early detection of CRC in individuals at average risk over the age of 45. This test integrates genomics, epigenomics, and proteomics to detect circulating tumor DNA (ctDNA) in the bloodstream, with a sensitivity of 91% for detecting CRC and 20% for advanced adenomas, and a specificity of 92%. Although it is not a replacement for standard methods, it could significantly increase the number of individuals participating in screening and thereby reduce CRC mortality. The clinical validation of the test was conducted through a large study called ECLIPSE (31).

DISCUSSION

This review aimed to provide a comprehensive overview of the genetic and molecular mechanisms contributing to the development of colorectal cancer (CRC), with a specific focus on analyzing genetic mutations and the application of advanced detection methods. The methodological approach employed facilitated a relevant review of current knowledge in this field.

The results of the analysis clearly indicate that mutations in the **TP53**, **KRAS**, **APC**, and **MMR** genes are central to understanding CRC carcinogenesis (32). These mutations not only contribute to the development of CRC but also provide valuable information for the diagnosis and treatment of the disease (33, 34, 35).

Mutations in the **TP53** gene, present in over 50% of CRC cases, have a profound impact on malignant cell transformation. The p53 protein plays a crucial role in regulating the cell cycle and responding to DNA damage. Loss of function of this protein allows cells to survive and proliferate despite genetic damage. Our analysis confirms previous findings regarding the role of TP53 in a broad spectrum of cancers, including CRC (11, 36, 37). However, further research is needed to elucidate the specific mechanisms through which TP53 mutations contribute to CRC development.

Mutations in the **KRAS** gene, particularly in exons 12, 13, and 61, are found in about 50% of CRC cases. KRAS is a key regulator of signaling pathways that affect cell growth and differentiation. Our analysis supports previous studies showing that abnormal signaling due to KRAS mutations contributes to uncontrolled cell proliferation. It is important to note that different KRAS mutations may have varying effects on tumors, which could influence therapeutic approaches (33, 38-41).

Mutations in the **APC** gene are associated with the development of familial adenomatous polyposis (FAP) and contribute to chromosomal instability that can lead to malignant transformations. Our analysis confirms the role of APC mutations in CRC, consistent with previous work (42, 43). However, since APC mutations are often detected in later stages of the disease, there is a pressing need to explore early biomarkers that could enable timely recognition and intervention (31).

Mutations in the **MMR** genes, including **MLH1** and **MSH2**, are critical for hereditary nonpolyposis colorectal cancer (HNPCC). These mutations impair DNA mismatch repair and contribute to the accumulation of mutations that lead to tumor formation (44, 45). Although we confirmed the significance of MMR mutations, further research is necessary to better un-

derstand their role in different stages of CRC carcinogenesis (39).

One of the main limitations in current research is the lack of data on interactions between different genetic mutations and environmental factors. While some of these factors have been studied, many remain unexplored (46). Additionally, methodological variations across studies can affect results and complicate data comparisons.

To improve CRC diagnosis and treatment, future research should focus on several key areas. First, it is essential to identify new genetic variations that may play a role in CRC development. These novel variations could reveal previously unrecognized biomarkers, paving the way for the development of innovative and more effective therapeutic approaches (47).

Second, it is crucial to investigate the interactions between genetic predispositions and environmental factors. Understanding how these factors collectively influence CRC development can provide new insights essential for disease prevention and treatment (45).

Third, continuous advancements in detection technology, particularly in sequencing, can significantly enhance CRC diagnosis. The introduction of advanced technologies, such as next-generation sequencing (NGS), allows for more precise identification of genetic mutations and earlier disease detection. These technologies offer the potential to better understand tumor genetic profiles and tailor therapeutic approaches according to each patient's specific characteristics (48).

In addition to insights gained regarding genetic mutations in CRC, it is essential to consider the implications of these mutations on the choice of biological and immunotherapy. As our understanding of the molecular mechanisms underlying CRC evolves, targeted therapies are increasingly being developed to address specific genetic alterations (49).

For instance, the presence of KRAS mutations can influence the effectiveness of certain treatments. Patients with KRAS wild-type tumors may benefit from anti-EGFR therapies, while those with mutated KRAS do not typically respond to these agents (50). This highlights the necessity of genetic testing to guide treatment decisions, ensuring that patients receive the most appropriate therapy based on their tumor's genetic profile (49, 50).

Similarly, the role of MMR mutations in determining treatment strategies is becoming more evident. Patients with MMR-deficient tumors often exhibit higher levels of microsatellite instability (MSI), making them more responsive to immune checkpoint inhibitors such as pembrolizumab and nivolumab (51). Understanding the presence of MMR mutations thus not only aids in diagnosis but also provides critical information for selecting immunotherapeutic options that may lead to better patient outcomes (51).

Furthermore, ongoing research into the impact of TP53 and APC mutations on treatment responses is essential for developing more effective therapeutic strategies (52). TP53 mutations, often associated with poorer prognosis, can lead to resistance against standard chemotherapeutic agents. Understanding the specific pathways affected by these mutations may help identify alternative drugs or combination therapies that could improve patient outcomes (53).

Similarly, APC mutations, which contribute to tumorigenesis, may influence how tumors respond to targeted therapies. By investigating the molecular mechanisms behind these mutations, researchers can uncover potential biomarkers that predict treatment efficacy. This knowledge could guide oncologists in selecting the most appropriate therapies tailored to each patient's genetic profile, ultimately refining treatment protocols and enhancing the precision of CRC management (53, 54).

This review provides a comprehensive overview of the genetic mutations **TP53**, **APC**, **KRAS**, and **MMR** in the context of CRC, highlighting their pivotal roles in disease development and the potential implications for diagnosis and treatment. Understanding these mutations not only contributes to a better recognition of pathogenic mechanisms but also facilitates the development of personalized therapeutic approaches.

In addition to genetic factors, investigating the impact of these mutations on responses to biological and immunotherapy opens new therapeutic avenues. As specific interactions between genetic variants and treatment responses are elucidated, there is potential to enhance treatment protocols and optimize patient care.

Future research should prioritize the integration of genetic studies with clinical data and biostatistics. This multidisciplinary approach will enable deeper insights into the mechanisms of CRC and contribute to the development of innovative treatment strategies. Ultimately, the goal is to improve patient outcomes and reduce the global burden of this serious disease.

CONCLUSION

Understanding the genetic and molecular mechanisms contributing to colorectal cancer (CRC) development is fundamental for improving the diagnosis and treatment of this disease. Identifying specific mutations in genes such as **TP53**, **KRAS**, **APC**, and **MMR** enhances the management and treatment of CRC. Studying known genes and identifying new genetic factors responsible for carcinogenesis allows for

faster, more precise, and effective treatments for tumors, including colorectal cancer.

Abbreviations

CRC - Colorectal carcinoma
FAP - Familial adenomatous polyposis
MMR - Mismatch repair
HNPCC - Hereditary nonpolyposis colorectal cancer
TP53 - Tumor protein p53
KRAS - Kirsten rat sarcoma viral oncogene homolog
APC - Adenomatous polyposis coli
MLH1 - MutL homolog 1
MSH2 - MutS homolog 2
MSH6 - MutS homolog 6
PMS2 - Postmeiotic segregation increased 2
CTNNB1 - Catenin beta 1
AXIN1 - Axin 1
AXIN2 - Axin 2
EpCAM - Epithelial cell adhesion molecule
MAP - MUTYH-associated polyposis
PJS - Peutz-Jeghers syndrome
TGF-β - Transforming growth factor beta
NGS - Next-generation sequencing
FISH - Fluorescent in situ hybridization
CGH - Comparative genomic hybridization
AS-PCR - Allele-specific PCR
ctDNA - Circulating tumor DNA

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: No.

Author contribution: All authors have contributed equally.

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

Sažetak

ANALIZA GENETSKIH MUTACIJA TP53, APC, KRAS I MMR KOD KOLOREKTALNOG KARCINOMA: PREGLED LITERATURE

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Uvod: Kolorektalni karcinom (KRK) predstavlja jedan od najčešćih malignih tumora sa značajnim zdravstvenim posledicama širom sveta. Genetske mutacije u genima, kao što su TP53, APC, KRAS i MMR geni, igraju značajnu ulogu u razvoju i progresiji ovog karcinoma. U ovom preglednom radu, analizirane su dosadašnje spoznaje o uticaju ovih mutacija na karcinogenezu kolorektalnog karcinoma-a, koristeći dostupnu literaturu.

Cilj: Pružiti uvid u ulogu genetskih mutacija u TP53, APC, KRAS i MMR genima u razvoju kolorektalnog karcinoma i razmotriti njihov uticaj na dijagnostiku i lečenje bolesti.

Materijal i metode: U ovom pregledu analizirani su relevantni istraživački članci i izveštaji iz baze podataka PubMed, Google Scholar i drugih akademskih izvora. Fokus je bio stavljen na studije koje istražuju genetske mutacije, njihovu prevalenciju i ulogu u patogenezi KRK-a.

Rezultati: Mutacije u TP53 genu, koje su prisutne u više od 50% slučajeva KRK-a, ključne su za maligne transformacije ćelija. KRAS mutacije, prisutne u oko 50% slučajeva, dovode do abnormalne signalizacije koja doprinosi nekontroliranom rastu ćelija. APC mutacije povezane su sa naslednom predispozicijom za KRK, dok MMR geni, kao što su MLH1 i MSH2, igraju ključnu ulogu u popravku DNK i povezani su sa sindromom nasledne nepolipozne kolorektalne karcinomatoze.

Zaključak: Genetske mutacije u TP53, APC, KRAS i MMR genima igraju značajnu ulogu u razvoju kolorektalnog karcinoma. Razumevanje ovih mutacija može unaprediti strategije za dijagnozu i lečenje bolesti, kao i pružiti smernice za buduća istraživanja u ovom području.

***Ključne re*čи**: Kolorektalni tumori, Karcinogeneza, Mutacija, Geni, Tumorski supresorski geni,

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How to cite this article: **Gavrić I,** Hodžić E, Sarajlić L, Salibašić M, Bajramagić S, Dizdarević A, Kulović E. Analysis of TP53, APC, KRAS, and MMR genetic mutations in colorectal cancer: a review article. Sanamed. 2024; 19(3): 333-341. doi: 10.5937/sanamed0-52803

SANAMED
2024; 19(3): 343–356
ISSN-1452-662X

DOI: 10.5937/sanamed0-53358
UDK: 615.371.06
ID: 160166665
Review article

CARDIOVASCULAR EFFECTS OF DUAL VACCINATION WITH PNEUMOCOCCAL PV23 AND INFLUENZA: A SYSTEMATIC REVIEW

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Primljen/Received:10. 09. 2024. Prihvaćen/Accepted: 21. 10. 2024. Published online first: 23. 11. 2024.

Abstract: The pneumococcal vaccine may reduce cardiovascular events. This systematic review examines the impact of PV23 and seasonal influenza vaccination on major cardiovascular outcomes compared to unvaccinated populations. We systematically reviewed clinical trials, cohort studies, and case-control studies published between 2000 and 2019 evaluating cardiovascular outcomes in adults vaccinated with PV23 and seasonal flu vaccines versus unvaccinated adults. Nineteen articles encompassing 617,411 patients were included. PV23 vaccination alone was not significantly associated with reduced acute myocardial infarction risk (RR 1.21 [95% CI: 1.18–1.23]). Dual vaccination showed a protective effect against stroke (RR 0.52 [95% CI: 0.45–0.61]) and significantly improved heart failure outcomes (RR 0.26 [95% CI: 0.22–0.31]). PV23 and dual vaccination also decreased episodes of acute heart failure decompensation and stroke development.

Keywords: Influenza vaccination, pneumococcal vaccine, myocardial infarction, heart failure, stroke.

INTRODUCTION

Cardiovascular events represent one of the most serious complications of community-acquired pneumonia, increasing 30-day mortality more than fivefold (1, 2). Violi et al. conducted a prospective study of 1,182 patients hospitalized for pneumonia, finding that 32.2% experienced in-hospital cardiovascular morbidity, and 2.4% died from cardiovascular events within 30 days (3).

Patients with pneumonia have a higher cardiovascular risk both in the short and long term, with events most frequent in the first year of follow-up (2, 4, 5). Previous studies have evaluated the association between respiratory tract infections and the first occurrence of myocardial infarction and stroke (6, 7, 8). *Streptococcus pneumoniae* remains the most frequently identified pathogen in community-acquired pneumonia (9). The 23-valent pneumococcal polysaccharide vaccine (PV23) effectively prevents invasive pneumococcal disease and pneumonia in adults over 50 (10, 11), similar to the 13-valent pneumococcal conjugate vaccine (12). PV23 is currently recommended for individuals aged 65 and older, as well as those at risk (13).

Most pneumococci are encapsulated pathogens with surfaces covered by polysaccharides, a major determinant of pathogenicity (14). Acquired immunity to pneumococcal capsular polysaccharides is robust in early adulthood but declines with age, especially in individuals over 70 or 80 years old (15). In young adults, immunity is stimulated by occasional episodes of asymptomatic colonization (16, 17), while in older adults, lower colonization rates result in a higher risk of pneumococcal disease (15). Pneumonia prevalence is highest at the extremes of age, and older adults—who tend to have an elevated risk of cardiovascular disease along with more comorbidities—may benefit from pneumococcal vaccination. This study aims to assess whether pneumococcal vaccination impacts cardiovascular event reduction, as current evidence shows mixed results and a need for consensus.

Evidence-Based Medicine emphasizes a critical gap: there are insufficient randomized controlled trials (RCTs) evaluating the impact of pneumococcal vaccination on cardiovascular disease (18). Mixed results from existing studies underscore the need for large, targeted RCTs that include a wide range of cardiovascular disease presentations, such as different etiologies, arrhythmias, and ejection fraction variations, with a focus on younger populations (under 65) who are less studied (19). Additionally, understanding regional differences, especially in areas with distinct pneumonia seasons, may provide insights into vaccine effectiveness based on serotype distribution, vaccine uptake, and monitoring practices.

METHODS

We conducted an evaluation of existing evidence on cardiovascular effects that may be associated with the use of PV23, employing the following steps:

1. A search strategy was developed to investigate potential adverse cardiovascular effects related to the vaccine. The relevant databases for this strategy were identified.

2. Eligibility criteria for the articles were defined to allow comparison between patients vaccinated only with PV23 and those who additionally received the influenza vaccine.

3. Statistical analysis was performed using data published in the selected articles.

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Strategy

The initial part of this systematic review was conducted by two researchers (AS and CR) through independent searches in electronic databases, including MEDLINE, Scopus, and LILACS, covering the first two decades of the 21st century. Articles from 2020 onward were excluded to avoid potential biases related to the COVID-19 pandemic, ensuring that observed vaccine effects were not influenced by the disease or related vaccination efforts. No language restrictions were applied.

The research question was framed using the PICO strategy (Population, Intervention, Comparison, Outcome). The search terms included: "Cardiovascular Diseases," "Pneumococcal Vaccines," "Myocardial Infarction," "Mortality," "Arteriosclerosis," "Cardiovascular Diseases/mortality," "Coronary Disease," "Myocardial Ischemia," "Angioplasty, Balloon, Coronary," "Coronary Artery Bypass," "Heart Failure," "Heart Failure/complications," "Heart Failure/mortality," "Heart Failure, Systolic," "Heart Failure, Diastolic," "Heart Failure, Diastolic/complications," "Heart Failure, Diastolic/mortality," "Cardiac Edema," "Patient Admission," "Hospital Mortality," "Stroke," "Stroke/mortality," "Brain Infarction," "Posterior Cerebral Artery Infarction," "Cerebral Artery," "Lacunar Stroke," "Angina," "Unstable Angina," "Intracranial Hemorrhages," "ST-Elevation Myocardial Infarction," and "Non-ST Elevation Myocardial Infarction." Terms that could restrict or reduce the results, as well as those potentially introducing biases toward unrelated cardiovascular effects in older populations, were excluded.

Eligibility Criteria

Case-control studies, cohort studies, and clinical trials conducted in adult humans that reported relative risk and 95% confidence intervals were included. These studies evaluated cardiovascular outcomes in the study population, comparing individuals vaccinated with the pneumococcal polysaccharide vaccine PV23 alone and those dually vaccinated with PV23 and influenza (Table 1).

Data Extraction

Two independent researchers collected information from the articles and recorded it in standardized formats to apply the methodologies described above. The collected data included authors, publication year, study design, country, study population, number of participants, duration of follow-up, person-years of follow-up, reported outcomes, effect measures (RR; adjusted HR or OR), and funding sources. Discrepancies were resolved through discussion between the researchers.

Table 1. *PICOS criteria for eligibility of studies*

Population	Persons 65 years and over, healthy or with age-typical underlying diseases living in any countries and not belonging to indigenous minority populations
Intervention	Vaccination with PPV23
Comparator	Dually vaccinated for PV23 and influenza.
Outcomes	Cardiovascular Diseases
Study Design	RCTs and Observational studies, if adjusted at least for age and comorbidities

Statistical Analysis

A systematic review and meta-analysis of studies evaluating pneumococcal vaccination alone and those evaluating dual influenza plus pneumococcal vaccination were performed. The Mantel-Haenszel method was used to obtain relative risks (RRs) and 95% confidence intervals (95% CI) for the evaluated outcomes. The RR was calculated for vaccinated, unvaccinated, and dual vaccination groups, the latter if the primary study reported it.

Heterogeneity between studies was assessed using Cochran's Q statistic. The degree of heterogeneity was tested with I^2 statistics using Review Manager software; values < 25% indicated low heterogeneity, while values between 25% - 60% and > 60% indicated moderate and high heterogeneity, respectively. Meta-analysis was conducted using Review Manager 5.0.24 (COCHRANE Library software).

Funding

This systematic review was financed by the authors' respective institutional budgets without extramural funding.

RESULTS

The initial database search yielded 1,902 articles. Figure 1 illustrates the search process and reasons for initial exclusion, with 1,881 articles discarded due to duplicate titles, title content, abstracts, and non-primary studies. Ultimately, 21 studies were selected, of which 2 were excluded: one was a case series, and the other evaluated mortality from pneumonia as the primary outcome, which did not align with the objective of this systematic review. This left 19 studies for complete review, encompassing a total of 617,411 patients. Table 1 displays the selected studies and their characteristics.

The quality of the cohort and case-control studies was assessed using the Newcastle-Ottawa scale, resulting in 14 studies classified as good quality, 4 studies of acceptable quality, and one randomized clinical trial with a Jadad score of 1 point (indicating low quality).

Regarding demographic aspects, all included studies provided information about the age and gender of patients, with an average age of 69 years. The population was predominantly male, with 337,567 men (54.6%) represented (Table 2).

PV23 and Acute Myocardial Infarction

Nine studies were included in this analysis. The unvaccinated group comprised 165,062 participants, while 65,880 were vaccinated against pneumococcus. No decrease in the incidence of acute myocardial infarction was found among immunized patients, with a relative risk (RR) of 1.21 (95% CI: 1.18-1.23), indicating an increased risk of heart attack. However, the heterogeneity rate was very high (I^2 = 98%), precluding definitive conclusions. Studies showing a protective effect of PV23 vaccination for myocardial infarction contributed little weight in terms of the number of cases and follow-up time; the study with the greatest weight was that of Siriwardena (25), which indicated a neutral effect on infarction outcomes (Figure 2).

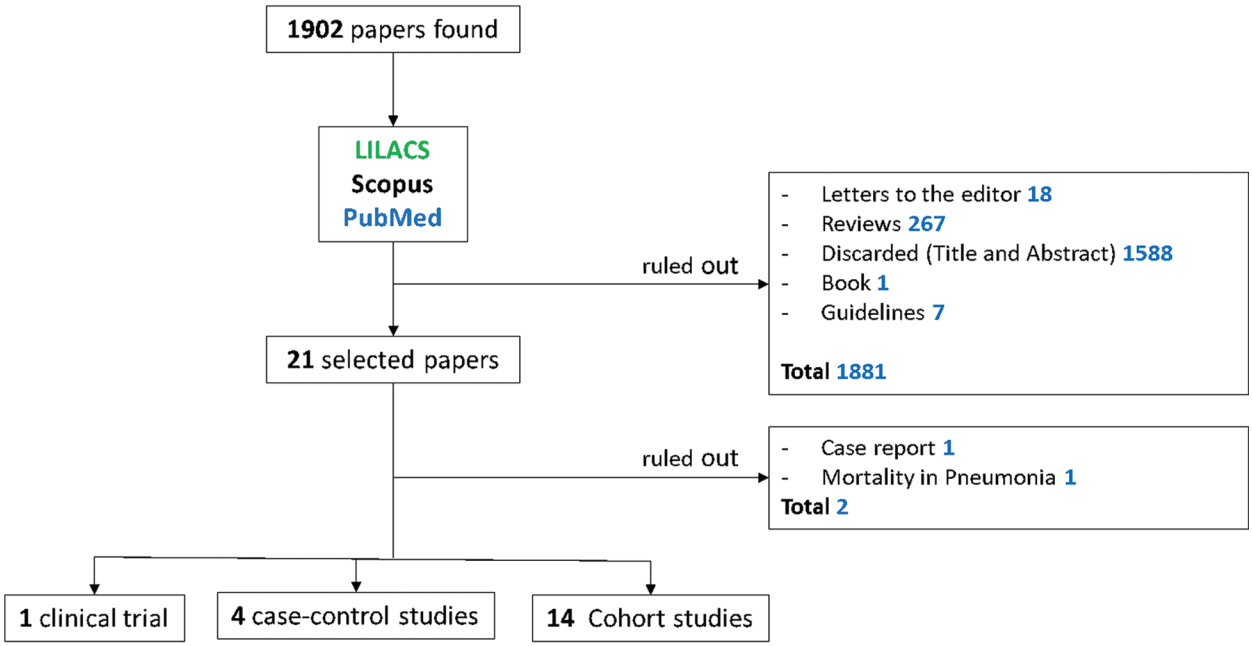

Figure 1. *Search results, selection and, inclusion of studies*

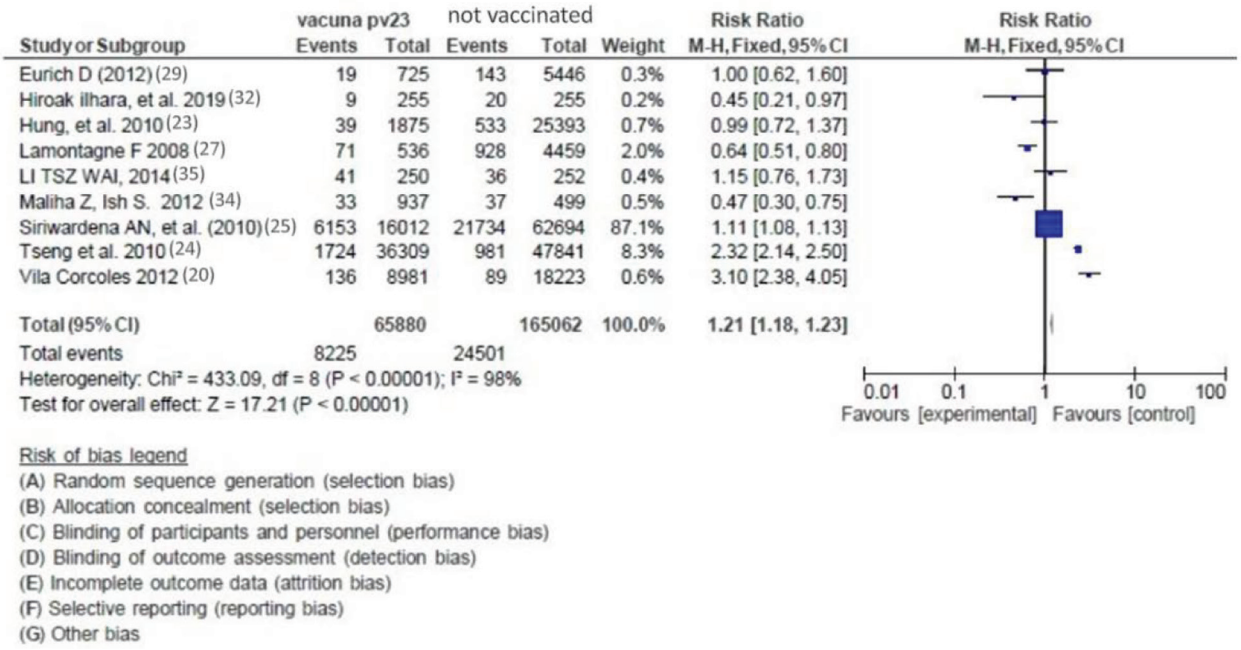

Figure 2. *PV23 and Acute Myocardial Infarction*

Table 2. *Studies characteristics*

	First author, year	Sample size	Mean age	Follow	Male	Primary	outcome influenza	Vaccine Pneumo-coccal vaccine	CVD	Adjusted for variables	**Mortality in vaccinated pV23**	**Reported results**	**Type of study**	**Newcastle-Ottawa Quality Scale**
1	Vila-Corcoles et to the. 2012, Spain (20)	27204	71.7 (SD: 8.6)	1 year.	8074 (44.3)	Hospitalized for AMI and/ or ischemic stroke	14368 (52%)	8981 (34%)	1733	Yes	Not reported	stroke: HR: 0.65 (CI: 0.42-0.99) P: 0.046 AMI HR: 0.83 (CI: 0.56-1.22) P: 0.347	Cohorts	**Selection:** 3/4 **Comparability:** 2/2 **Outcomes:** (cohort)/ exposure (case–control) 3/3
2	Ochoa-Gondar O et al. 2014, Spain (21)	27204	> 80 years old (20.2%) 70-79 years old (34.12%) 60-69 years old (45.5%)	3 years	12082 (44.4%)	Hospitalized for AMI, mortality due to AMI at 30 days and death from all causes	14,368 (52%)	8,981 (34%)	1,733	yes	Not associ-ated with a reduction in death from AMI or from all causes	AMI HR: 0.95 (CI: 0.76-1, 18) P: 0.63	cohorts	**Selection:** 3/4 **Comparability:** 2/2 **Outcomes:** (cohort)/ exposure (case–control) 3/3
3	Vila-Corcoles A, et al. 2014, Spain (22)	27204	> 80 years (20.2%) 70-79 years (34.12%) 60-69 years (45.5%)	3 years	12082 (44.4%)	Hospital-ization for ischemic stroke and death from any cause.	14368 (52%)	8981 (34%)	1733	if	PPV23 was not associated with reduced risk of death from stroke or death from any cause.	PV23 did not alter stroke risk: HR: 1.04 95% CI (0.83 - 1.3) P: 0.752.	Prospective cohort	**Selection:** 3/4 **Comparability:** 2/2 **Outcomes:** (cohort)/ exposure (case–control) 3/3

4	Hung IF, et al. 2010 (23)	36636	75	15 months.	16611 (45%)	Rates of death, hospitalization, pneumonia, ischemic stroke, AMI, admission to ICU or coronary care unit	2076	7292: PV23 and influenza, 1875 (5.1%) received PPV only	2118 (8)	Yes	PV23-Influenza risk of death [HR], 0.65; 95% CI, 0.55–0.77; P<0.001).	Pneumonia HR: 0.57 (95% CI: 0.51-0.64) p < 0.001. Coronary ICU admission: HR 0.59 (95% CI 0.44-0.79) p < 0.001. ICU admission: HR: 0.45 (95% CI 0.22-0.94) p < 0.03. CVA (HR, 0.67; 95% CI, 0.54-0.83; p < 0.001). AMI (HR, 0.52; 95% CI, 0.38-0.71; p < 0.001)	Prospective cohort	***Selection*** 3/4 ***Comparability*** 0/2 ***Results*** (cohort)/ exposure (case–control) 3/3
5	Tseng et al. 2010, United States(24).	84170	58.4 +/- 7.1	56.4 months	84170 (100%)	Incidence of acute myocardial infarction and stroke.	NR	47861 (56.8%)	AMI before the study 6020 (7.2%) Stroke before the study 2849 (3.4%)	Yes	NR	No association between pneumococcal vaccination and reduced risk of AMI (HR 1.09; CI95: 0.98- 1.21) or stroke (adjusted HR 1.14 CI95% 1.00-1.31)	Prospective cohort. California, USA	***Selection 3/4 Comparability 2/2 results (cohort)/ exposure (case–control) 2/3***
6	Siriwardena AN, et al. 2010, United Kingdom (25)	Cases: 16012. Controls: 62694	40 - 64 years: 33.4%. >equalto 65 years: 66.6%	67 months	cases: 6168 (38.5%) controls: 24171 (38.5%)	Association of influenza vaccination and PV23 with AMI	vaccine in the previous year cases (52.9%) and Controls: (51.2%)	Only pneumococcus: (3.6%). Dual vaccination: (31.7%)	chronic heart disease: 12%. ACV or TIA 6.25%. PAD: 4.194%	Yes	NR	Pneumococcal vaccination not associated with AMI reduction (OR 0.96, 95% CI 0.91–1.02)	Case–control	***Selection 2/4 Comparability 2/2 results (cohort)/ exposure (case–control) 3/ 3***
7	Siriwardena AN, et al. 2014, United Kingdom (26)	Cases: 47011 Controls: 47011	< 65 years 23.2%. ≥ 65: 76.8%	7.9 years	Cases 22,584 (48.0%) Controls 22,584 (48.0%)	Stroke or TIA associated with pneumococcal vaccination	Influenza vaccine the previous year: 7021 (7.4%)	For pneumococcus 12,153 (12.9%) Dual vaccination: 48,673 (51.7%)	FCC: 17519 (8.8%) PAD: 2467 (1.35%)	Yes	Notreported	Pneumococcal vaccination was not associated with a reduction in the risk of stroke or TIA	Case-control Study	***Selection 3/4 Comparability 2/ 2 Outcome (cohort)/ exposure (cases–controls) 3/3***

8	Lamontagne F, et al. 2008 (27)	4995 (Cases n = 999), (Controls n = 3996)	Cases 59.2 Controls 58.8	6 years	Cases 684 (68.5%); Control 2736 (68.5%)	Association of pneumococcal vaccination and AMI rate.	NR	Cases 71 (7.1%); Controls 465 (11.6%)	NR	Yes	NR	Vaccination 1 year before AMI OR: 0.85; (95% CI: 0.54 to 1.33). Vaccination > 2 years before AMI: OR: 0.33 (95% CI: 0.20-0.46) to 0.46).	Case-control study	***Selection 2/4 Comparability 1/2 Results (cohort)/ exposure (case-control) 3/3***
9	Meyers D, et al. 2003, United States(28)	Cases = 335 Controls = 199	66 +/- 11	5 months	Cases 63% control 34%	Association between pneumococcal vaccine and myocardial infarction	Cases: 177 Controls: 126	Cases 107 Controls: 78	172 (32.2%)	Yes	NR	Neither influenza nor pneumococcus vaccination reduced AMI	Study cases and controls	***Selection 3/4 Comparability 1/2 Results (cohorts)/exposure (cases–controls) 2/3***
10	Eurich DT, et al. 2012, Canada (29)	6171	59	2000 - 2002	3261 (53%)	Association between acute coronary syndrome and pneumococcal vaccination status	NR	725 (12%)	1105	Yes	Composite of death or hospitalization for ACS: HR 0.42 (0.27 - 0.66, p < 0.001) Onlydeath: HR: 0.92 (0.33-2.6)	Hospitalization for ACS: HR: 0.35 (0.21-0.57)	Cohort study	***Selection 2/4 Comparability 2/2 Results (cohort)/exposure (cases–controls) 3/3***
11	Ahmed MB, et al. 2016, United States (30)	5290	83	13 years	2539 (48%)	-Primary: incidence of heart failure and mortality from any -Secondary: cardiovascular and non-cardiovascular cause of death, hospitalization for all causes	NR	1,424 (26.92%)	Coronary heart disease: 17.22%; AMI: 7.88%; stroke 3.8%; Heart failure 19.9%. Total: CVD: 2587 (48.9%)	If	Octogenarians: I- all causes: HR: 1.23 (1.09–1.49); II-Cardiovascular HR: 1.45 (1.06–1.98) III-Non-cardiovascular HR: 1.10 (0.87–1.40)	Heart failure (Octogenarians) HR: 1.37 (1.01–1.85); P = 0.044 Heart failure in 65-79 years) HR: 0.88 (0.74-1.04); P = 0.126	Prospective epidemiologicalstudy (cohort)	***Selection: 3/4 Comparability: 1/2 Outcome; 3/3***
12	Wen-Chih Wu, et al. 2014, United States (31)	107045	72	7 years	105,118 (98.2%)	Mortality at 30 days and at 1 year.	2087	7108	AMI: 3636 (33.8%)	Yes	Mortality at 30 days: OR: 0.66 (0.42-1.05), Mortality at 1 year: OR: 0.76 (0.61-0.95)	NR othersofinterest	Retrospective cohort	Selection: 3/4 Comparison: 1/2 Outcome: 3/3

13	HiroakiIhara, et al. 2019, Japan (32, 5, 10)	PPSV 23	64	5 years	67.85%	on the risk of hospitalization and death from pneumonia and acute cardiac events	391 (76.6%)	255 (50%)	Total:495 (97.05%) . Coronary heart disease: 27.64%, FCC: 25.29%. stroke: 21.96%. PSE: 2.15%.	yes	Mortality from all causes: HR: 0.62, [CI] 95%; 0.46–0.83, P = 0.002). Cardiac death: HR: 0.36; CI 95%; 0.18 to 0.71; p = 0.003)	Hospitalization for cardiac events: HR 0.44, 95% CI; 0.20-0.96, P = 0.040).	Retrospective cohort	Selection: 3/4 Comparison: 1/2 Outcome: 3/3
14	Mahamat Aba, et al. 2013, France (33)	68,897	75.2	1 year	39.8%	Demonstrate whether vaccination against pneumococcus and influenza reduces all causes of mortality and consumption of antibiotics	18,651 (27.1%)	pneumococcus alone: 3,769 (5.5%) dual vaccination: 21,303 (30.9%).	NR	Yes	Decrease in mortality in dual vaccination of 27 (95% CI 20-34) HR: 0.73 (0.66 0.80). In vaccination only for PV23 the mortality reduction-. 9 (95% CI: -8-23) HR: 0.91 (0.77-1.08)	Pneumococcal vaccine did not reduce antibiotic consumption	Prospective cohort	Selection: 3/4 Comparison: 1/2 Outcome: 3/3
15	Maliha Z, et al. 2012, United States (34)	1436	69 years (InterquartileRange 58 - 77)	6 months	1403	Associations between pneumococcal vaccine and mortality or AMI at 6 months of follow-up in hospitalized patients with suspected ACS	503 (35.0%) vaccinated 12 months prior	937 received pneumococcal vaccine; 667: dual vaccine	**-Coronary Disease:** 53.2% ***-History of AMI*** 22.9% **-FCC:** 18.45% -CVA: 11.9%	Yes	Mortality PV23 vs no vaccination: HR: 0.12 (95% CI 0.06 – 0.21) in dual vaccination: HR : 0.60 (0.42-0.85)	AMI in PV23 vs no vaccination: HR: 0.60 (95% CI: 0.32 - 1.10). In dual vaccination: HR: 0.22 (0.22-0.89) Prospective Cohort	Study	Selection: 3/4 Comparison: 1/2 Outcome: 3/3
16	LI TSZ WAI. 2014, China (35)	1006	48	2 years	85.90%	Dual vaccination, only pneumococcus, only influenza and no vaccination on effects on general hospitalization, hospitalization for CVD, respiratory, neurological and mortality	254 (25.24%)	Only pneumococcus: 250 (24.8%). dual vaccination: 250 (24.8%).	534 (53.08%).	No	No differences in mortality between groups	Dual vaccination was the only independent factor associated with a reduction in the relative risk of hospitalization p<0.001. RR 0.288 CI95% 0.101 - 0.154.	Open-label randomized clinical study.	Jadad 1 point: lowquality

17	Shu Ren, et al. 2018, Australia (36)	863	72 years	7 – 11 years	45%	Hospitalization or mortality in vaccinated vs unvaccinated patient	Influenza: 190. Dual vaccinated: 451	26	0	Yes	No association found between PPV or influenza vaccine and time to event of CVD or all-cause mortality	Pv23 showed a 35% reduction in days hospitalized for CVD	Cohort-Study	Selection: 2/4 Comparison: 1/2 Outcome: 3/3
18	Joon Young Song, et al. 2018, South Korea. (37)	2119	76	During three influenza seasons from October 1 – April 30, 2014–2015, 2015–2016 and 2016–2017	1091 (51.5%)	Effectiveness of influenza and pneumococcal vaccination against pneumonia and acute exacerbation of cardio-pulmonary diseases	1302 (61.4%)	Vaccination PPV23:871 (41.1%) PCV13 vaccination: 74 (3.5%)	I) Stroke: 296 (14.0%) II) Chronic heart disease: 444 (21.0%)	If	PPV23 did not reduce mortality at 30 days.	PV23 did not significantly reduce pneumonia, exacerbation of cardio-pulmonary disease, or hospitalizations	Prospective Multi-centerCohort	Selection: 3/4 Comparison: 1/2 Outcome: 3/3
19	Chang, et al. 2012, China (38)	43399	80 years	4 months	11147 (45.6%)	1: all-cause mortality 2: Incidence and hospitalization costs for CAP and influenza, enf. respiratory, COPD, FCC in seasonal influenza.	8142	8142 (33.32%)	10910.28 (44.66%)	Yes	All causes of mortality: Dual vaccination vs. unvaccinated group RR: 0.50 CI95 (0.39-0.63),	Hospitalization expenses for all diseases: Dual vaccination vs. unvaccinated group RR: 0.89 CI95 (0.83-0.96)	Retrospective cohort	Selection: 3/4 Comparison: 1/2 Outcome: 3/3

PV23 and Heart Failure

A total of 34,677 patients from three studies were analyzed. Heart failure occurred in 209 vaccinated patients compared to 2,155 cases in unvaccinated patients, yielding an RR of 0.86 (95% CI: 0.75-1), suggesting a potential reduction in heart failure decompensation. However, the wide confidence interval, which includes 1, and the moderate heterogeneity (I^2 = 60%) indicate that further studies are needed to clarify the protective effect of PV23 vaccination (Figure 3).

PV23 and Stroke

The likelihood of experiencing a stroke was found to be 1.98 times higher (95% CI: 1.80-2.18) in individuals who received pneumococcal vaccination compared to those who were unvaccinated. These results are inconclusive due to the high rate of heterogeneity among the studies (I^2 = 97%) (Figure 4).

Mortality and PV23

To evaluate mortality outcomes, 128,479 patients were included, representing 20% of those identified in the meta-analysis. Across the 9 studies, 933 deaths were reported, revealing a statistically significant reduction in mortality risk associated with vaccination, with an RR of 0.83 (95% CI: 0.76-0.91) (Figure 5).

Acute Myocardial Infarction and Dual Vaccination

Dual vaccination did not demonstrate significant differences in the reduction of acute myocardial infarction (Figure 6).

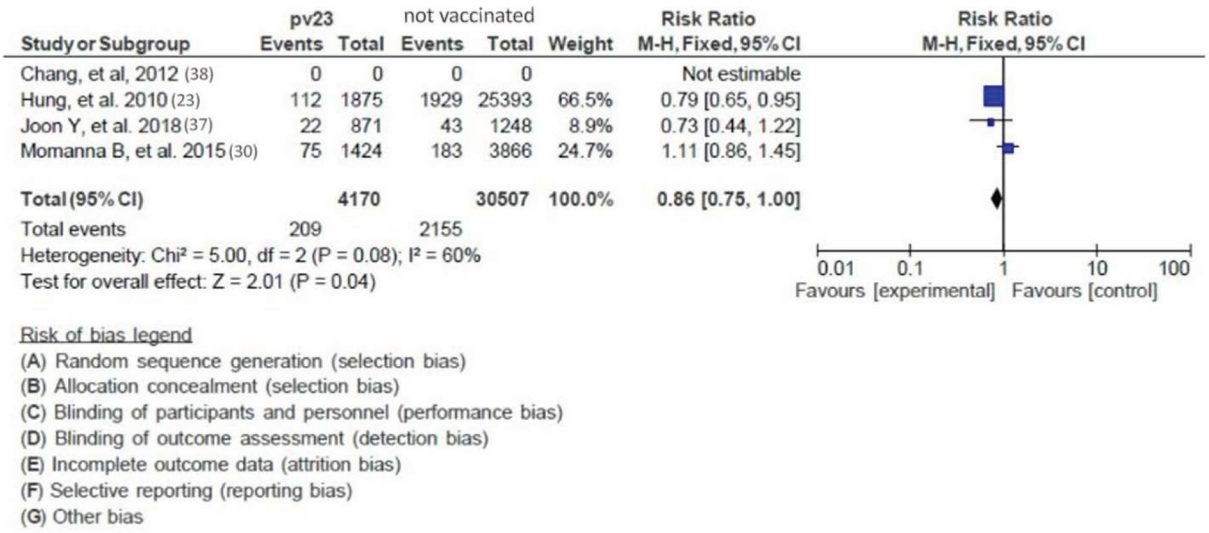

Figure 3. *PV23 and heart failure*

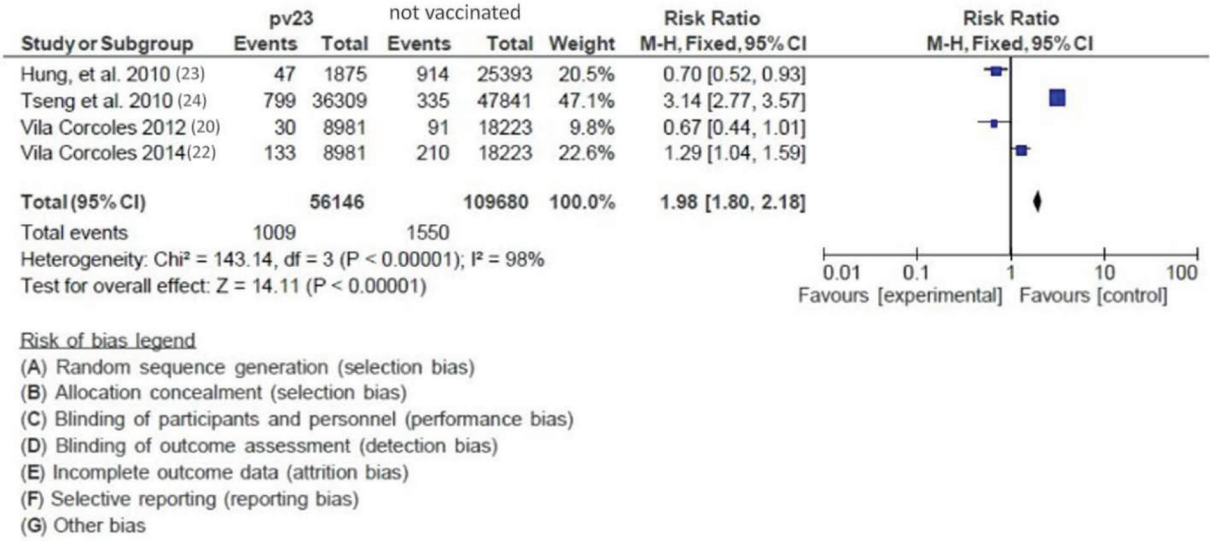

Figure 4. *PV23 and Stroke*

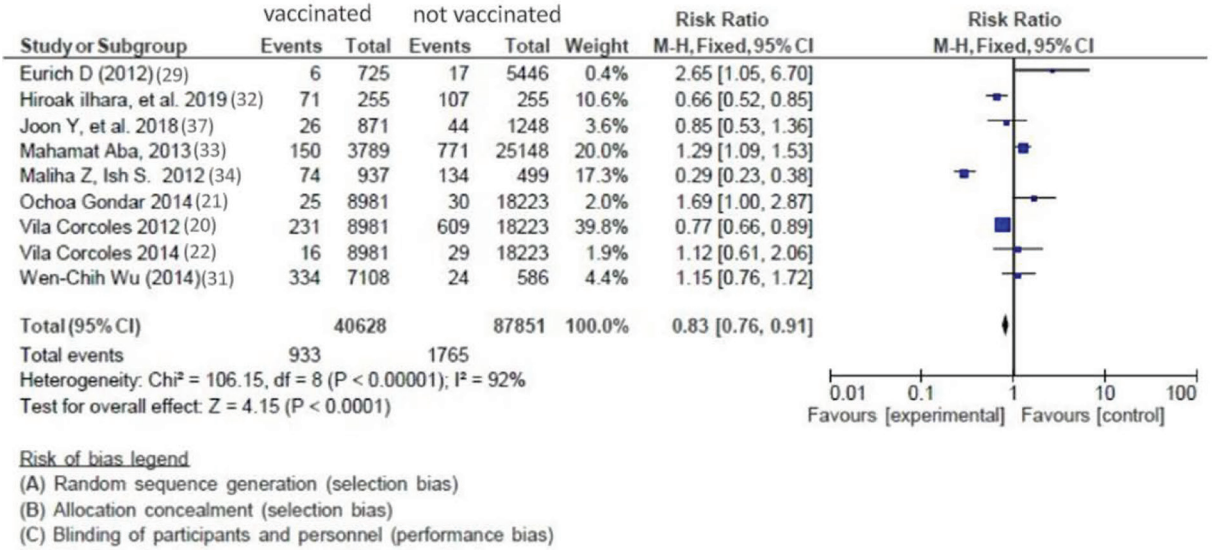

Figure 5. *Mortality and PV23*

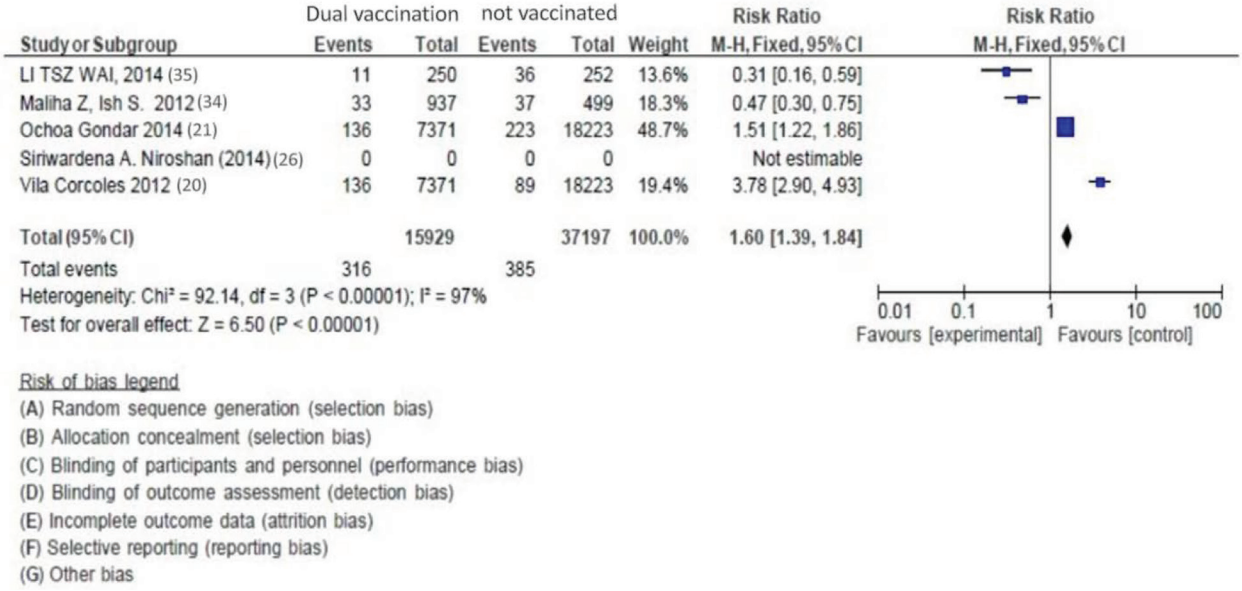

Figure 6. *Acute Myocardial Infarction and Dual Vaccination*

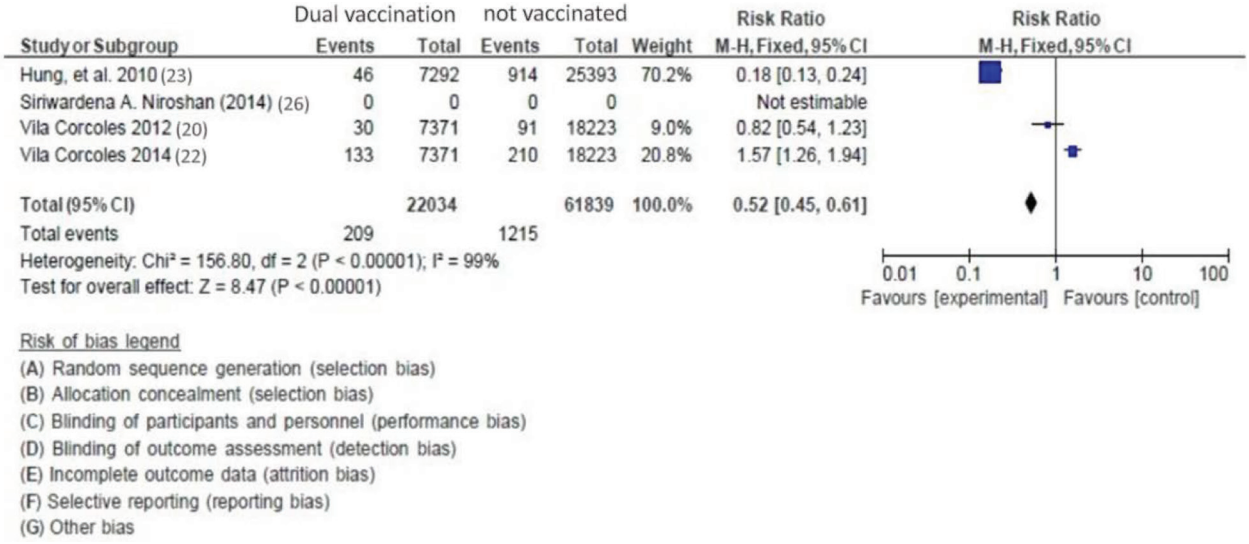

Figure 7. *ACV and dual vaccination*

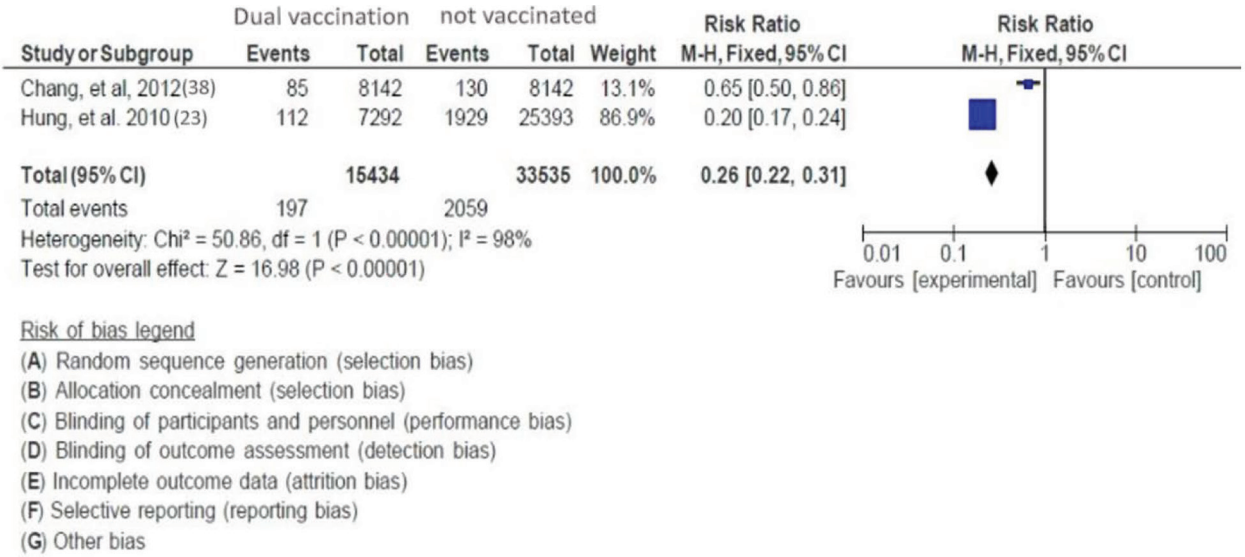

Figure 8. *Heart failure and dual vaccination*

Stroke and Dual Vaccination

Among a total of 83,873 individuals, 26% received dual vaccination. The Forest Plot analysis indicated a reduction in cerebrovascular events in more than half of the patients evaluated, suggesting a protective factor, with a narrow confidence interval and high statistical significance (RR 0.52 [95% CI: 0.45-0.61], P < 0.00001) (Figure 7).

Heart Failure and Dual Vaccination

Dual vaccination significantly reduced heart failure decompensation compared to single pneumococcal vaccination; however, the interpretation of these results is limited by the small number of studies evaluating this finding.

DISCUSSION

This systematic meta-analysis reviews the evidence regarding the effects of PV23 vaccination and dual vaccination (PV23 + seasonal influenza) on cardiovascular outcomes, given the current contradictions in the literature. Nineteen studies were evaluated, encompassing a significantly larger population than previous analyses.

As a conclusive result of this meta-analysis, evidence suggests a decrease in cerebrovascular events and episodes of decompensated heart failure among individuals who received dual vaccination. Post-viral bacterial pneumonia (39) is proposed as a serious complication of any lower respiratory tract influenza infection (26); thus, there is biological plausibility that dual vaccination (seasonal influenza and PV23) may offer better protection than single vaccination. However, no net protective effect for stroke or heart failure was found with PV23 alone.

The reduced mortality risk associated with the influenza vaccine, PPV, and the combined pneumococcal and influenza vaccinations has been documented. Evidence suggests that administering pneumonia and influenza vaccines during hospitalization is safe and reinforces the cardiovascular benefits of combined vaccination in hospital settings (40). However, the protective effect of dual vaccination on heart failure decompensation requires further investigation, given the small number of studies reporting this outcome. This consideration is particularly relevant for patients with a history of chronic heart failure.

All results were evaluated comparing individuals vaccinated with PV23 to those receiving dual vaccination. Acute myocardial infarction as a primary outcome showed no reduction in risk for either the PV23 group or the dual vaccination group (PV23 + seasonal influenza). This finding, indicating no benefit of vaccination in reducing acute myocardial infarction, cannot be conclusively accepted due to high heterogeneity among the studies, which limits the reliability of the results. The case-control study by Lamontagne et al. indicated a reduction in the risk of myocardial infarction when vaccination was administered between the second and fifth year post-vaccination, suggesting the need for stratifying results based on the time since vaccination (27). Conversely, the epidemiology of pneumonia has evolved significantly, especially after the introduction of pneumococcal vaccination, leading to an increase in other causes such as various viruses and pathogens like *S. aureus* and *Pseudomonas aeruginosa* (41).

In the studies included in this analysis, individuals were considered vaccinated against influenza if they had received the vaccine within the 12 months prior to inclusion. Notably, early seasonal influenza vaccination (September to mid-November) has been associated with a greater reduction in stroke risk compared to later vaccination (from mid-November onward) (26).

The vaccinated population ranged from 45 years to octogenarians, but the results were not stratified by age range. Momanna et al. 2016. evaluated mortality and heart failure decompensation in octogenarians and non-octogenarians (ages 65-79), finding better outcomes in non-octogenarians (30). These results are significant and may relate to the senescence of the immune system and its response to vaccination. Given the greater burden of comorbidities in octogenarians, further studies focusing on this population would be valuable.

Mortality for all causes was reported since not all registries specified mortality due to cardiovascular causes, as evidenced by the high rate of heterogeneity. The outcome of death favored vaccination with PV23 in decreasing mortality. Among the advantages of this meta-analysis, a mean follow-up of 48.1 months stands out, corresponding to double the follow-up duration of previous meta-analyses (42, 43). Furthermore, a greater number of studies were included. Rates of encephalitis/encephalomyelitis, Guillain-Barré Syndrome (GBS), or transverse myelitis were not elevated following the 2022-2023 seasonal influenza vaccinations among U.S. adults aged 65 and older (44). However, there was an increased rate of anaphylaxis post-influenza vaccination, which may have been influenced by concomitant vaccination. In a self-controlled risk interval study, no significant increase in risk was observed for most cardiovascular, neurological, or immunological adverse events following PPSV23. The updated safety profile of PPSV23 provides supportive evidence for establishing immunization strategies for older adults (45).

CONCLUSION

Future studies should conduct comprehensive risk-benefit assessments to ascertain the overall impact on cardiovascular health, weighing the benefits of vaccination against respiratory infections against potential risks. Public health policies may need to evolve based on emerging evidence, ensuring that dual vaccination is recommended as our understanding of cardiovascular effects improves. As with any vaccination program, addressing vaccine hesitancy and ensuring public confidence in the safety and efficacy of dual vaccination will be crucial.

Abbreviations

PV23 - pneumococcal 23-valent polysaccharide vaccine

RR - relative risks

HR or OR - Hazard ratios or Odds Ratios

Acknowledgments: We extend special thanks to our colleagues and mentors for insightful discussions. We appreciate the valuable feedback from peer reviewers that enhanced the quality of this article, particularly Jose Celey for epidemiological advice and Sergio Vallejo for translation into English.

Conflict of interest: We declare that there is no conflict of interest associated with this work. We have no financial, personal, or professional relationships that could influence the objectivity or integrity of this undertaking. This statement encompasses any affiliations, financial holdings, or connections with organizations that might have a direct or indirect interest in the subject matter discussed.

Author Contributions:AS, CR, and I.R. contributed to the conception, design, or planning of the study. AS and CR contributed to the acquisition of the data. AS, CR, and AM contributed to the interpretation of the results. All authors contributed to drafting and critically reviewing the manuscript for important intellectual content and approved the final version.

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

Sažetak

KARDIOVASKULARNI EFEKTI KOD DVOSTRUKE VAKCINACIJE PNEUMOKOKNOM PV23 I VAKCINOM PROTIV GRIPA: SISTEMATSKI PREGLED

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Pneumokokalna vakcina može smanjiti kardiovaskularne komplikacije. Ova sistematska analiza ispituje uticaj vakcinacije PV23 i sezonske vakcine protiv gripa na glavne kardiovaskularne ishodne parametre u poređenju sa nevakcinisanim populacijama. Sistematski smo pregledali klinička ispitivanja, kohortne studije i case-control studije objavljene između 2000. i 2019. godine koje su procenjivale kardiovaskularne ishode kod odraslih vakcinisanih sa PV23 i sezonskim vakcinama protiv gripa u odnosu na nevakcinisane odrasle. Uključeno je devetnaest članaka koji obuhvataju 617.411 pacijenata. Vakcinacija PV23 sama po sebi nije bila značajno povezana sa smanjenim rizikom od akutnog infarkta miokarda (RR 1.21 [95% CI: 1.18–1.23]). Dvostruka vakcinacija pokazala je zaštitni efekat protiv moždanog udara (RR 0.52 [95% CI: 0.45–0.61]) i značajno poboljšala ishode kod srčane insuficijencije (RR 0.26 [95% CI: 0.22–0.31]). Vakcinacija PV23 i dvostruka vakcinacija takođe su smanjile epizode akutne dekompenzacije srčane insuficijencije i razvoj moždanog udara.

Ključne reči: Vakcinacija protiv gripa, pneumokokna vakcina, infarkt miokarda, srčana insuficijencija, moždani udar.

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***How to cite this article**:* Sotelo-Velasquez YA, Rincón AC, Rojas Ruiz TI, Novoa-Alvarez AR, Ramos Espinosa G, Méndez Toro A. Cardiovascular Effects of Dual Vaccination with Pneumococcal PV23 and Influenza: A Systematic Review. Sanamed. 2024; 19(3): 343-356. doi: 10.5937/sanamed0-53358

SANAMED
2024; 19(3): 357–365
ISSN-1452-662X

DOI: 10.5937/sanamed0-52856
UDK: 613.21:616-036.1-053.6
ID: 160137993
Review article

CHRONIC NON-COMMUNICABLE DISEASES CAUSED BY ADOLESCENT EATING DISORDERS

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Primljen/Received: 19. 08. 2024. Prihvaćen/Accepted: 15. 10. 2024. Published Online First: 21. 10. 2024

Abstract: Decreased satisfaction with physical appearance during adolescence is significantly linked to reduced self-esteem and an increased prevalence of obesity and other chronic non-communicable diseases (NCDs). A major issue in today's world is the influence of media, which serves as the primary channel through which ideals of physical appearance and attractiveness are transmitted. According to a 2015 study, adolescents spend an average of 17 hours per week watching television. Scientific evidence indicates that an active lifestyle provides health benefits and prevents the occurrence of numerous chronic non-communicable diseases, while improper diet and physical inactivity among adolescents contribute to the development of these diseases. Improper nutrition during adolescence can be a significant risk factor for the development of NCDs. These diseases, including cardiovascular diseases, diabetes, and certain forms of cancer, often have complex causes, but dietary habits can be identified as a common risk factor. Excessive intake of saturated and trans fats, cholesterol, and a high consumption of processed foods are associated with an increased risk of cardiovascular diseases. Improper dietary habits can also contribute to the development of type 2 diabetes and increase cancer risk. Adopting a balanced and nutritionally rich diet, along with regular physical activity, can help prevent and manage these conditions. This review paper is based on a search of the scientific literature published in the last ten years, with a special focus on original research articles published in the last five years from the scientific databases: PubMed, SCOPUS, MEDLINE, and SCI index.

Keywords: public health, prevention, nutrition, risk factors.

INTRODUCTION

The prevalence of chronic non-communicable diseases caused by eating disorders is evident, with data showing that one in five deaths worldwide is a consequence of dietary issues (1). Despite this, the marketing of unhealthy foods and beverages on television, in newspapers, and online continues unabated. It is well-known that our food purchasing and consumption decisions are not solely based on evidence-based information but are significantly influenced by our environment, shaped by the culture of the surroundings, including advertising and media, which are readily available to everyone today (2). This leads to diminished control or moderation in the intake of healthy foods among both adults and children, resulting in either overweight or malnutrition, which consequently leads to the development of numerous non-communicable chronic diseases (2). Obesity, defined as excessive body weight, poses a significant public health challenge due to its wide range of metabolic complications, particularly type 2 diabetes mellitus and other components of metabolic syndrome. This issue affects both adult and pediatric populations, leading to an increased risk of associated endocrine, metabolic, cardiovascular, and other health disorders among adolescents. Globally, the prevalence of obesity among adolescents is estimated at 2-3%, while the prevalence of excessive weight, including obesity, is approximately 10%. This growing trend underscores the need for effective public health interventions aimed at promoting healthy lifestyles and reducing obesity rates in young people (3). It's important to note that the prevalence of these nutritional disorders among youth is not evenly distributed globally. In some countries in Africa and Asia, the prevalence of overweight and

obesity is below 10%. In contrast, in certain European and American countries, this figure exceeds 20%. This disparity highlights the need for tailored public health strategies that address the specific needs and circumstances of different regions (4, 5, 6). Diabetes mellitus is a chronic metabolic disorder characterized by impaired glucose metabolism, significantly affecting the quality of life for those affected. In recent decades, the prevalence of this condition has dramatically increased, largely due to poor dietary habits and physical inactivity, especially among younger populations. According to the International Diabetes Federation, approximately 463 million people worldwide aged 20 to 79 have diabetes, representing 9.3% of the population. Estimates suggest that as many as 50% of those affected are unaware of their condition. The World Health Organization predicts that by 2030, the number of people with diabetes could rise to 578 million, and by 2045, it may reach 700.2 million, marking a 51.2% increase from 2019. In Europe, as of 2019, around 59 million people (8.9% of the population) live with diabetes, with projections indicating that this number may grow to 66 million (9.8%) by 2030 and 68 million by 2045 (7, 8). Particularly concerning is the rise of type 2 diabetes among children and adolescents, often linked to factors such as obesity, reduced physical activity, and aging. In this context, prevention and education are crucial for combating this pandemic (9, 10).

When researching eating disorders in adolescents, we face numerous challenges and limitations. Challenges related to eating disorders encompass various forms, such as anorexia, bulimia, and binge eating, and improper and unbalanced nutrition can lead to numerous complications and chronic diseases like type 2 diabetes. Each of these disorders has specific characteristics that make uniform research difficult. Many adolescents with eating disorders do not acknowledge their problem or are unaware of it, which can hinder the collection of accurate data. Stigmatization is often a factor that may prevent adolescents from seeking help or participating in research.

Methodological limitations

Qualitative methods, such as interviews and focus groups, are prone to biases, while quantitative methods (e.g., surveys) may face issues with self-assessment. The ability to include diverse samples (e.g., age, gender, socio-economic status) may be limited. Small sample sizes or insufficient representativeness can reduce the generalizability of results. Many respondents rely on self-assessment of their habits, which can be unreliable due to body image awareness or shame.

Due to these challenges and limitations, conclusions about eating disorders in adolescents should be interpreted with caution. While the results may provide useful insights, it is important to consider the context and potential sources of bias. Approaches and methodologies should be comprehensive and tailored to minimize the possibility of errors and ensure greater accuracy in understanding this complex issue.

METHODOLOGY

This review paper is based on a search of the scientific literature published in the last ten years, with a special focus on original research articles published in the last five years from the scientific databases PubMed, SCOPUS, MEDLINE, and SCI Index. The literature we used dates back to at least ten years ago, and the keywords utilized to search the databases included: adolescence, nutritional deficiencies, obesity, diabetes mellitus type 2, and others.

PROPER NUTRITION

The preference for different types of food changes throughout life, from childhood to old age, influenced by numerous factors that significantly impact food choices and diet quality (11). One of the factors affecting food preferences is genetic predisposition, but this factor is not exclusive. This means that genetic predisposition to accept or reject food can be corrected if environmental factors positively influence an individual in shaping **healthy** attitudes toward nutrition (12). For instance, research has shown that regular physical activity positively impacts reducing the prevalence of obesity, insulin resistance, and metabolic syndrome in children and adolescents (13).

The factors that can significantly affect food choices have been divided into four groups:

1. Genetic predisposition (genetic inclination toward a particular type of food).
2. Personal factors (attitudes, demographic, and biological factors).
3. Social environment (interaction with family and peers).
4. Physical environment (availability of food in the surroundings where individuals eat or purchase food).
5. External factors (food advertisements, societal norms in which an individual lives, and agricultural policy) (13).

Principles of Proper Nutrition

The most commonly used guidelines for proper nutrition worldwide are those issued by the American Diabetic Association (ADA) in 2006. ADA defined several principles of proper nutrition (14). The main principles of proper nutrition are:

1. Understanding the primary nutrients in the food being consumed.

2. Using the healthy eating pyramid.

3. Knowing the glycemic index of foods.

4. Knowing how to create a daily meal plan.

5. Understanding the nutrient content of the menu and the representation of meals.

6. Knowing the recommended frequency of food consumption.

7. Learning how to calculate daily energy needs (14, 15).

According to most literature, the three key principles of proper nutrition are:

1. Balance, which implies that energy intake should match energy expenditure.

2. Moderation, which means limiting the intake of foods that can have negative health effects.

3. Variety, which means consuming a diverse range of foods from different food groups (16).

Healthy Eating Pyramid

The development of a new graphic representation to illustrate dietary patterns led to the creation of the healthy eating pyramid. The healthy eating pyramid was first published in 1992 in the United States, originally designed to help Americans choose foods that meet nutritional standards while limiting energy intake and those food components often consumed in large quantities. The pyramid's appearance has changed significantly from the original. The most significant changes were introduced in 2005 when "My Pyramid" was created (Figure 1). My Pyramid has six equal sections, indicating the variety and proportions of all food groups that should be represented in the daily diet. The importance of moderation in the diet is reflected in the pyramid's design, where the lines narrow from the base to the top. The pyramid's broader base represents foods with lower amounts of refined sugar and saturated fats, which should be most prevalent in the diet. Proportionality is shown by the different widths of the pyramid's colorful sections, indicating how much of each food group should be consumed daily, while the usefulness of regular physical activity is represented by a figure climbing toward the top of the pyramid. In My Pyramid, all foods are divided into six groups:

1. The first group consists of grains, represented in orange.

2. The second group consists of fruits, represented in red.

3. The third group consists of vegetables (green).

4. The fourth group consists of dairy and dairy products, represented in blue.

5. The fifth group consists of meat, eggs, fish, nuts, and legumes, represented in purple.

Figure 1. *Depiction of the Food Pyramid (Retrieved from: https://studylib.net/doc/8370805/my-pyramid.gov.)*

6. The sixth group consists of fats and dietary supplements, represented in yellow (Figure 1) (17).

Smith et al. (18) explained that the main mechanisms by which whole grains reduce the risk of type 2 diabetes and cardiovascular mortality include reducing obesity, significantly improving lipid profiles, and facilitating glucose metabolism (18). The importance of regular whole grain intake is demonstrated by the findings of Barton et al. (19), showing that children and adolescents aged 9 to 19 who eat breakfast cereals eight or more times during two weeks have a significantly lower Body Mass Index (BMI) compared to those who consume breakfast cereals three or fewer times during two weeks (19). Fruits and vegetables contain high concentrations of vitamins (especially vitamins A and C), minerals (especially electrolytes), and antioxidants. The Dietary Guidelines for Americans recommend that people consume at least nine servings of fruits and vegetables daily, i.e., four servings of fruits and five servings of vegetables, based on a 2,000 kcal diet (20). Dairy and dairy products are considered an essential part of the diet, being a source of protein, calcium, amino acids, essential fatty acids, and water-soluble vitamins. Calcium and vitamin D from dairy products positively influence bone mineralization in children and adolescents (21). Meat is a primary source of protein and fats, ensuring the intake of essential fatty acids. Consuming meat improves the absorption of many vitamins and minerals, such as vitamin A, vitamin B, iron, and zinc, which are highly bioavailable to the human body (22). The American Dietary Guidelines note that fish has numerous positive effects on heart and vascular health, and adults should consume about 227 grams of fish and seafood per week if their diet is based on 2,000 kcal per day (23). Eggs are also an important source of energy, protein, essential amino acids and fatty acids, vitamins, minerals, and especially iron (24).

Adolescent Nutrition

Adolescence is a period of human development and growth, representing a transition from childhood to adulthood, usually lasting from 10 to 19 years, during which rapid physiological, social, and cognitive changes occur, making proper nutrition crucial for optimal growth and development (25, 26). The World Health Organization (WHO) defines adolescence as the period from 10 to 19 years, youth as the period from 15 to 24 years, and the term "young people" encompasses individuals aged 10 to 24 years (27). A recent Lancet Commission on adolescent health further divided this time into three five-year categories:

1. Early adolescence (10 to 14 years)
2. Late adolescence (15 to 19 years)
3. Youth (20 to 24 years) (27, 28).

Adolescents represent an age group that poses a challenge as they require a complex approach due to the impact of their habits, attitudes, and behaviors on future health (25,26). Proper nutrition during adolescence involves meeting the body's needs for sufficient energy and nutrients necessary to maintain physiological functions, especially during this period of life when demands are higher due to rapid physical growth (29). Proper nutrition during adolescence is crucial to ensure adequate physical, cognitive, and psychosocial growth and development (30). Many behavioral patterns, such as developing lifestyle habits, health behaviors, and eating habits, are formed during adolescence (25). However, adolescents are at a higher risk of replacing regular meals at home with irregular meals outside due to long school hours, numerous obligations outside the home, and busy parents. The importance of developing dietary habits during childhood and adolescence is well known. It is also known that health problems related to diet acquired at a younger age can be corrected during adolescence (29). Adolescents develop responsibility for their body's health during this period, making it an ideal time for educating young people about healthy lifestyle habits to prevent future complications (14). Poor eating habits in adolescents can lead to health problems such as delayed sexual maturation, osteoporosis, reduced final body height, hyperlipidemia, anemia, obesity, anorexia, bulimia, and dental caries. A balanced diet can prevent long-term health problems such as cancer, stroke, osteoporosis, and hypertension (14, 31). Such a diet leads to increased intake of saturated and total fats, trans fats, cholesterol, salt, and rapidly absorbed sugars. About 25% of adolescents base their daily energy intake on these nutrients by consuming fast food, which contains many calories, fats, salt, and additives but very few vitamins, minerals, and fibers (14). Adolescents frequently exhibit specific deficiencies in iron, calcium, riboflavin, zinc, vitamins A and C, as well as thiamine, which result from an unbalanced diet. The role of nutrients is to ensure an adequate energy supply, regulate metabolism, and facilitate the proper development of tissues and organs (32). One of the most significant public health issues that arise during adolescence due to poor nutrition is overweight and obesity, which pose a considerable risk for the development of cardiovascular diseases. The prevalence of childhood obesity worldwide is steadily increasing; from 1999 to 2010, the prevalence of overweight and obesity rose from 4.2% to 6.7%, marking a 60% increase. It was estimated that this prevalence would reach 9.1% by 2020, with the number of children affected by these health problems reaching 60 million globally (17, 33). However, studies have shown that this number is significantly higher. According to research by the Noncommunicable Diseases (NCDs) Center from 2016, it was estimated that 124 million children and adolescents aged 5 to 19 years were obese, while 213 million were overweight. Furthermore, this study indicated that 190 million children in this age group were undernourished, particularly in developing countries (34). According to the Regulations on Nutrition Standards for Students in the Republic of Serbia, the ratio of animal-based to plant-based foods should be approximately 75% plant-based and 25% animal-based. Daily meals should be planned so that proteins account for 15% of total energy intake; lipids 25%; and carbohydrates 60%. The menu is planned so that the energy contribution of meals throughout the day is as follows: breakfast 25-30% of daily needs; lunch 35-45%; and dinner 30-35% of daily needs (35).

Overweight and Obesity

Excessive accumulation of fat in the body occurs when energy intake from food exceeds energy expenditure, and this condition is known as obesity. Obesity is considered one of the most significant public health issues and represents the second most common cause of preventable death. In 2011, 43 million children (7%) under the age of five were overweight, representing a 54% increase from 1990 when there were 28 million overweight children under five years old (28). An analysis of the burden of chronic noncommunicable diseases in 2017 concluded that the prevalence of obesity had doubled in more than 70 countries worldwide and continued to rise in all other countries (36). Statistical projections suggest that by 2030, over 85% of people living in America will be obese (37). Somer and colleagues (38) demonstrated in their study that adolescents with a BMI at the upper limit have a significantly

higher risk of developing cardiovascular diseases compared to adolescents with normal BMI values (38). The importance of overweight and obesity as risk factors for cardiovascular diseases is evident from data showing that around 30% of coronary heart diseases and strokes, as well as 60% of diseases related to arterial hypertension, result from elevated BMI values (38). Overweight or obesity increases the risk of developing metabolic syndrome, type 2 diabetes, cardiovascular diseases, certain types of cancer, reproductive disorders, depression, and other health disorders during adolescence (39). To reduce childhood obesity, it is necessary to instill habits of proper, balanced, and varied nutrition in children early on, along with daily moderate physical activity. For children who have reduced their weight to normal levels through food intake restriction and/or increased physical activity under the supervision of a nutritionist or doctor, it is essential to make permanent lifestyle changes to maintain normal body weight (39). It has been proven that weight loss achieved through restrictive diets is short-lived and does not have a positive effect on health, as the lost weight is quickly regained, and frequent sudden weight changes pose an additional risk for the development of certain diseases. Today, the most commonly used method for assessing nutritional status is BMI, which involves the ratio of body weight in kilograms to the square of height in meters. However, when calculating BMI, no distinction is made between muscle and fat tissue, so if the overall picture, previous habits, and the individual's diet are not taken into account, errors in assessing nutritional status can occur (39).

Malnutrition – Anorexia and Bulimia

During adolescence, body size is one of the best parameters for assessing nutritional status. Overnutrition manifests as overweight or obesity, while undernutrition manifests as stunted growth and/or development, weight loss, or nutrient deficiencies that do not necessarily result in changes in body size (26). Research has shown that protein malnutrition is one of the ten leading causes of death among children and adolescents, with a study reporting **an estimated** 225,906 adolescent deaths in 2013 due to malnutrition (40). Globally, approximately 34 deaths per 100,000 children and adolescents are caused by malnutrition, with this number varying significantly between developing countries (38.5 per 100,000) and developed countries (0.2 per 100,000) (40). Bulimia nervosa involves episodes of uncontrolled, compulsive, and rapid consumption of large amounts of food within a short period, leading to physical discomfort like nausea, stomach pain, and the urge to vomit, often followed by actual vomiting. This is then followed by feelings of guilt, depression, and disgust with one's own body. Bulimia usually begins in late adolescence or early adulthood (41).

Diabetes, Cardiovascular Diseases, and Cancer

Diabetes mellitus is a condition of chronic hyperglycemia where the metabolism of carbohydrates, proteins, and lipids is disrupted due to complete or partial pancreatic insufficiency in insulin secretion and/or insulin resistance at the cellular level. There are two main types of diabetes: Type 1 diabetes mellitus (T1DM), which is insulin-dependent, and Type 2 diabetes mellitus (T2DM), which is not insulin-dependent (41). T1DM is thought to result from the destruction of the insulin-producing beta cells of the endocrine pancreas, a process that is believed to be immunologically mediated. It typically occurs between the ages of 10 and 12 in girls or 12 and 14 in boys. Although previously considered a disorder of children and adolescents, T1DM can also occur in adults, so age is not a limiting factor. The main symptoms in children and adolescents with T1DM include polyuria, polydipsia, polyphagia, and weight loss. About 30% of children and adolescents experience an acute complication called diabetic ketoacidosis (42). T2DM is caused by a combination of factors, including genetic predisposition and poor lifestyle choices such as an unhealthy diet, physical inactivity, and obesity—the most significant risk factor for T2DM (43). Research has shown that preventive measures, like increasing physical activity and consequent weight loss, are more effective at reducing the risk of T2DM than any medication currently available for this purpose. Furthermore, T2DM can often be managed through proper diet and regular physical activity, without the need for medications like oral antidiabetics. For children and adolescents with diabetes, it is crucial to maintain a healthy and balanced diet, increase physical activity, and ensure that both the adolescent and their parents receive adequate education about diabetes. To maintain normal blood glucose levels, regular meals, careful planning of meal composition, and daily caloric intake are necessary (43). Cardiovascular diseases encompass a group of disorders affecting the heart and blood vessels, with atherosclerosis being the most common underlying cause. Atherosclerosis can be triggered by various etiological factors such as obesity, physical inactivity, smoking, hypertension, T2DM, and dyslipidemia. The World Health Organization (WHO) reports that approximately 70% of all cardiovascular disease deaths could be prevented through appropriate preventive measures (44). The foundation of cardiovascular dis-

ease prevention is smoking cessation, while a central element is a healthy diet that includes sufficient intake of saturated fatty acids (less than 10% of total daily caloric intake), less than 5 grams of salt per day, at least 45 grams of fiber per day, a minimum of 200 grams of fruits and vegetables daily, and fish consumption at least twice a week. Regular moderate physical activity has also been shown to be associated with a reduced risk of developing cardiovascular diseases such as myocardial infarction, stroke, or hypertension (45). Recent guidelines recommend 2 to 5 hours per week of moderate-intensity physical activity or aerobic exercise, or 1 to 2 hours per week of high-intensity physical activity, to minimize future cardiovascular disease risk. Reducing body weight in obese individuals is also an important aspect of cardiovascular prevention, as it lowers the risk of developing high blood pressure, dyslipidemia, or insulin resistance (45). A tumor is a mass of abnormal cells that grow uncontrollably and progressively. Tumors can be either malignant or benign. The difference between them lies in the aggressiveness of their growth; malignant tumors metastasize and spread to surrounding tissues, infiltrating healthy tissue, whereas benign tumors do not metastasize to other organs and do not infiltrate healthy tissue, instead growing expansively and displacing surrounding tissue. Benign tumors are typically treated with surgical removal (46). Diet and physical activity have been identified as important factors in the development of various types of cancer. The World Cancer Research Fund has shown that aflatoxins are linked to the development of hepatocellular carcinoma, red meat and/or processed meat consumption is linked to colorectal cancer, and frequent alcohol consumption is strongly associated with gastrointestinal cancers (47). In 2016, the World Cancer Research Fund (48) issued guidelines and recommendations for a lifestyle that can prevent and reduce the likelihood of developing cancer. These recommendations include achieving and maintaining a healthy weight throughout life, adopting a physically active lifestyle, maintaining healthy and moderate eating habits with an emphasis on plant-based foods, and limiting alcohol consumption (48). Studies show that about 35% of all cancers are linked to poor diet and dietary habits, making these dietary recommendations crucial for cancer prevention. Thousands of epidemiological and meta-analytic studies have shown that individuals with overweight and obesity have a significantly higher risk of developing various types of cancer. The mechanisms explaining the causal link between obesity and cancer are tissue-specific and involve complex interactions between multiple molecular signaling pathways (49). However, the primary cause is systemic inflammation induced by obesity, known to promote the development of several different types of cancer. The International Agency for Research on Cancer has concluded that maintaining a normal weight, i.e., avoiding overweight and obesity, significantly reduces the risk of developing colorectal cancer, esophageal cancer, breast cancer, uterine cancer, liver cancer, and several other types of cancer (50).

CONCLUSION

Improper nutrition during adolescence can be a significant risk factor for the development of chronic non-communicable diseases (NCDs). These diseases, including cardiovascular diseases, diabetes, and certain forms of cancer, often have complex causes, but dietary habits can be identified as a common factor. Excessive intake of saturated and trans fats, as well as cholesterol, are major risk factors for cardiovascular diseases. A diet high in processed foods and low in fruits, vegetables, and whole grains can lead to atherosclerosis, a condition characterized by the buildup of plaque in the arteries. Research shows that reducing intake of harmful fats and increasing consumption of heart-healthy foods can significantly lower the risk of cardiovascular diseases. Type 2 diabetes is closely related to improper dietary habits, particularly the consumption of sugary and high-calorie foods. These eating patterns contribute to obesity, which is a primary risk factor for insulin resistance and the subsequent development of type 2 diabetes. Reducing sugar and high-calorie food intake, along with adopting a balanced diet and regular physical activity, can help prevent and manage diabetes. Certain dietary habits are also associated with an increased risk of various types of cancer. For instance, high intake of red meat and processed foods is linked to a higher risk of colorectal cancer. It is recommended to increase the consumption of fruits, vegetables, whole grains, and healthy fats to reduce cancer risk. To lower the risk of chronic non-communicable diseases, it is important to adopt a balanced and nutritionally rich diet and engage in regular physical activity. This includes reducing the intake of harmful fats and sugars, increasing the intake of nutrient-dense foods, and leading an active lifestyle.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: No.

Author contribution: All authors have contributed equally.

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

Sažetak

HRONIČNE NEZARAZNE BOLESTI UZROKOVANE POREMEĆAJIMA ISHRANE KOD ADOLESCENATA

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Smanjeno zadovoljstvo fizičkim izgledom tokom adolescencije značajno je povezano sa smanjenjem samopouzdanja i povećanom prevalencijom gojaznosti i drugih hroničnih nezaraznih bolesti (HNZB).Veliki problem u današnjem vremenu predstavlja uticaj medija, koji je glavni kanal kroz koji se prenose ideali fizičkog izgleda i privlačnosti. Prema istraživanju iz 2015. godine, adolescenti provode u proseku 17 sati nedeljno gledajući televiziju. Postoje naučni dokazi da fizički aktivan način života donosi zdravstvene koristi i sprečava pojavu brojnih hroničnih nezaraznih bolesti, dok nepravilna ishrana i fizička neaktivnost kod adolescenata doprinose razvoju tih bolesti. Nepravilna ishrana tokom adolescencije može predstavljati značajan faktor rizika za razvoj HNZB. Ove bolesti, uključujući kardiovaskularne bolesti, dijabetes i određene oblike raka, često imaju složene uzroke, ali se prehrambene navike mogu identifikovati kao čest faktor rizika. Prekomerni unos zasićenih i trans masti, holesterola i visok unos procesuirane hrane povezani su sa većim rizikom od kardiovaskularnih bolesti. Nepravilne prehrambene navike takođe mogu doprineti razvoju dijabetesa tipa 2 i povećati rizik od raka. Usvajanje uravnotežene i nutritivno bogate ishrane, zajedno sa redovnim fizičkim aktivnostima, može pomoći u prevenciji i upravljanju ovim stanjima. Ovaj pregledni rad se temelji na pretraživanju naučne literature objavljene u poslednjih deset godina, sa posebnim fokusom na originalne naučne članke objavljene u poslednjih pet godina u naučnim bazama podataka: PubMed, SCOPUS, MEDLINE i SCI index.

Ključne reči: Javno zdravlje, prevencija, ishrana, faktori rizika.

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***How to cite this article**:* Konatar R, Pelicic D, Maras B, Music K. Chronic non-communicable diseases caused by adolescent eating disorders. Sanamed. 2024; 19(3): 357-365. doi: 10.5937/sanamed0-52856.

SANAMED
2024; 19(3): 367–372
ISSN-1452-662X

DOI: 10.5937/sanamed0-52708
UDK: 616.711-007.5-089
ID: 159951113
Review article

MINIMALLY INVASIVE BIPOLAR FIXATION FOR THE TREATMENT OF NEUROMUSCULAR SCOLIOSIS-MILADI's TECHNIQUE

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Primljen/Received:12. 08. 2024. Prihvaćen/Accepted: 4. 12. 2024. Published online first: 16. 12. 2024.

Abstract: This paper presents the minimally invasive bipolar technique, also known as Miladi's technique, for the treatment of neuromuscular scoliosis. This approach involves bipolar spinal fixation extending from T1 to the pelvis. Proximal fixation is achieved using laminar and pedicular hooks configured as claws, while distal fixation employs iliosacral connectors and screws. The proximal and distal anchors are connected by a bilateral double-rod sliding construct, allowing for correction of spinal curvature and pelvic obliquity. This technique demonstrates reduced morbidity and complication rates compared to traditional methods.

Keywords: neuromuscular scoliosis, minimally invasive technique, iliosacral screws.

INTRODUCTION

Neuromuscular scoliosis is caused by diseases of the nervous system (brain, spinal cord, motor neurons) or muscular system of varying etiologies. The most common causes include cerebral palsy, Duchenne muscular dystrophy, myelomeningocele, spinal muscular atrophy, Friedreich's ataxia, and spinal cord injury (1). Vertebral deformity is progressive in most patients, particularly in those with severe neurological and systemic diseases (1).

While vertebral deformities appear similar across different etiologies, the specific clinical characteristics of each condition must be considered. The deformity often manifests at an early age, frequently resulting in trunk imbalance. The progression of spinal deformity is influenced by the patient's age, severity of motor injury, and curve magnitude. In patients with spastic quadriplegia aged 12 years, it has been observed that curves of ≤ 40 degrees progress more slowly (2, 3, 4). Associated problems such as intellectual disability, digestive disorders, and cardiac issues may also aggravate the clinical condition (5).

The outcomes of neuromuscular scoliosis progression are consistent across different etiologies. The deformity can impair positioning for daily care, sitting, standing, and ambulation in those capable of walking. Over time, it may lead to pain, skin lesions, and respiratory and cardiovascular complications (6, 7).

Conservative treatment options have limited effectiveness in managing neuromuscular scoliosis but are initially employed to provide external support for trunk balance in sitting positions for patients with flexible curves (8). Long-term success with bracing is rare. However, improvements in sitting balance, Cobb angle, and care facilitation have been reported with the use of three-point and molded braces (9).

Surgical treatment is indicated for progressive deformities accompanied by trunk imbalance or pelvic obliquity, which affect sitting or standing balance. In spinal muscular atrophy, early surgical intervention may be warranted to address increasing deformity and respiratory restriction caused by bracing (10).

In the past, combined anterior and posterior approaches were commonly used, but the posterior approach is now preferred. For patients with pelvic obliquity, spinal fixation typically extends from T1-T2 to the pelvis. In patients without pelvic obliquity and with flaccid or nonspastic paralysis, fixation may end at L5 (11, 12, 13). However, surgical correction of neuromuscular scoliosis carries significant risks. Among 8975 patients undergoing surgical correction for spinal deformity, neuromuscular scoliosis was the only group with recorded deaths within the first postoperative month (14).

The drawbacks of limiting trunk growth and its impact on lung development have driven the evolution of growth-sparing techniques. Although such tech-

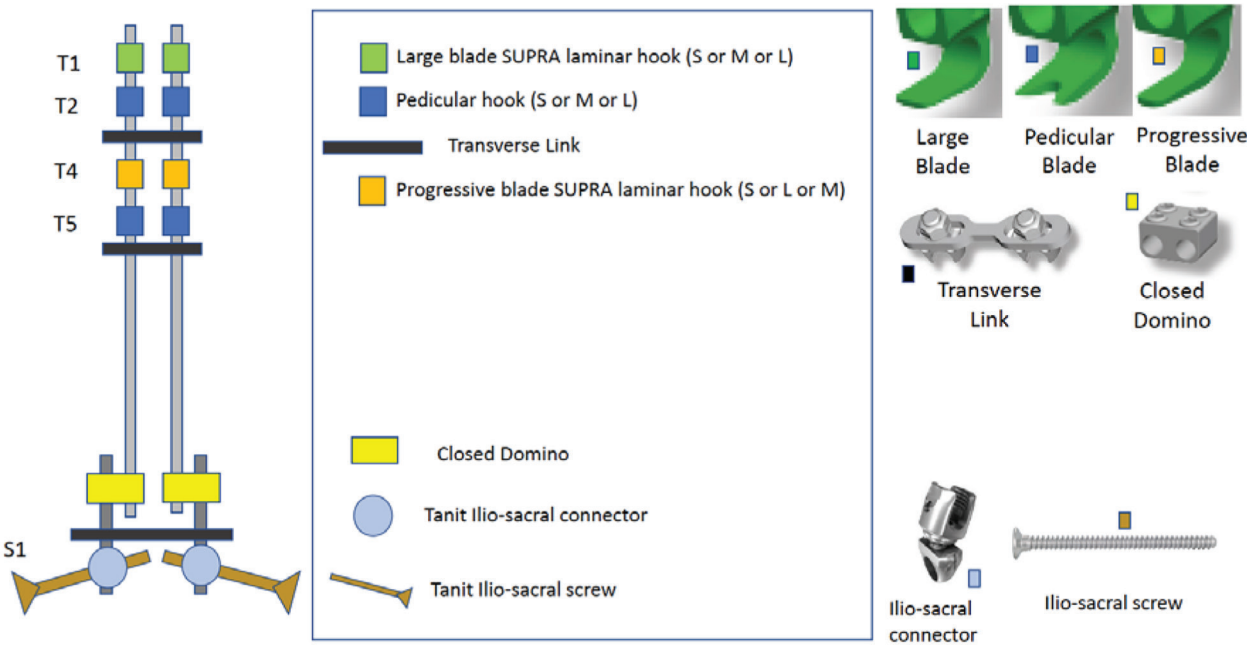

Figure 1. *Illustration of the assembly of the bipolar system and its components (Source: EUROS)*

niques allow for spinal growth, they are associated with high complication rates, including screw malposition, rod breakage, hook migration, screw pullout, infection, and skin issues, requiring reintervention in 40% to 60% of cases (15, 16).

The bipolar technique (Figure 1), a minimally invasive, fusionless method for neuromuscular scoliosis, was first described by Miladi in 2018 (16). This technique offers an alternative approach with reduced surgical morbidity and lower risks of mechanical and infectious complications (16, 17). It has since been expanded to address other deformities, including kyphosis and early-onset scoliosis. In young children, the technique enables effective correction of spinal deformities while preserving spinal growth through a device coupled to the rods (16, 17).

Bipolar operative technique

The patient is operated on under traction, with proximal traction applied using a skull clamp and distal traction applied to the legs. In patients with pelvic obliquity, the traction is asymmetric. The distal traction applies 10% to 15% of the patient's body weight.

The construct extends proximally from T1 to the sacrum. Proximal fixation is achieved using hook-claws on each side (laminar and pedicular hooks) (Figure 2). In some cases, pedicular screws may also be used, depending on the surgeon's preference. The proximal construct includes fixation of the first thoracic vertebra.

Distal fixation is performed using an iliosacral connector and iliosacral screw (Figure 3). The iliosacral connector is inserted into the sacrum laterally to the L5-S1 joint and proximal to the first posterior sacral foramina. A transmuscular paramedian (Wiltse) approach is employed following a short midline lumbopelvic incision to expose the posterior sacral cortex and the site for connector insertion on both sides. After placing the connector into the sacrum, the iliosacral screw is inserted percutaneously from the posterior part of the iliac bone in an oblique posterior-to-ante-

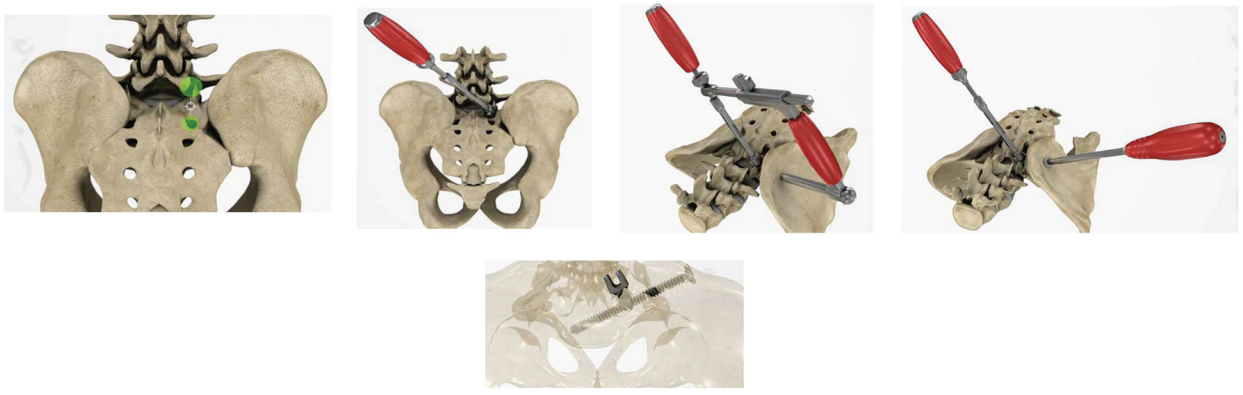

Figure 2. *Drawing illustrating the placement of the iliosacral connector and screw (Source: EUROS)*

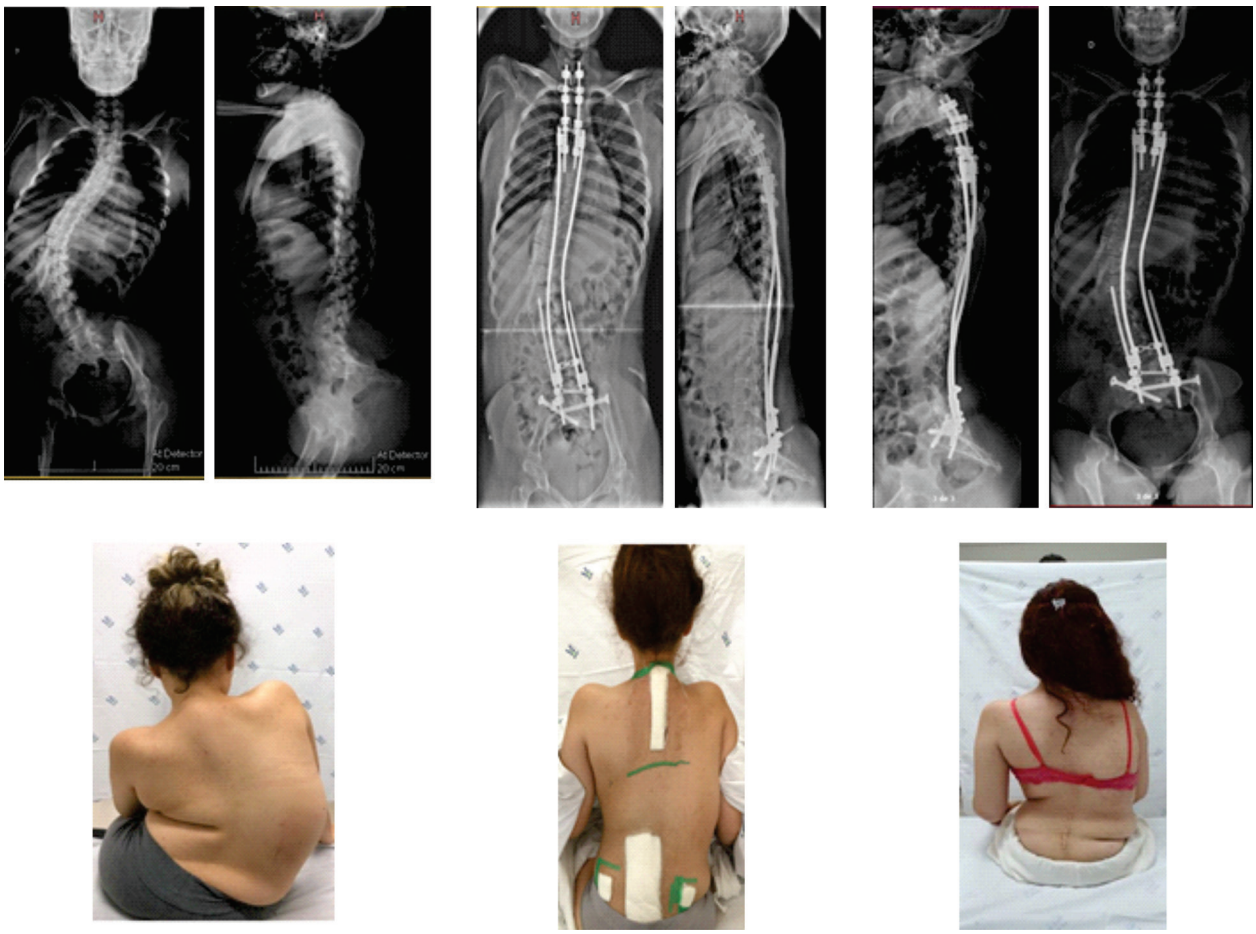

Figure 3. *Radiographs and photos of a 15-year-old female patient with progressive spinal amyotrophy. From left to right: preoperative, immediate postoperative, and 1-year follow-up (Source: author's own archive)*

rior direction using a guide. A 7 mm screw extending from the external iliac to the vertebral body of S1 is placed inside the deep ring of the connector. The iliosacral screw provides strong and stable fixation, and the connector's low profile allows its use in very young and thin patients.

The proximal and distal constructs are connected using two rods. The proximal rod is positioned medially, while the distal short rod is placed laterally. These rods are connected by a side-to-side domino (Figure 1). The rod on the concave side is inserted first, and deformity correction is achieved through progressive rod distraction at the domino, which connects the proximal and distal short rods. Before insertion, the rod should be contoured to accommodate the sagittal and coronal planes.

The rod on the convex side is inserted after the concave rod. Pelvic obliquity can be corrected by applying distraction on the concave side rod or compression on the convex side rod.

The rods on the concave and convex sides are further stabilized using three cross-link devices. Two cross-links are placed on the proximal rod, and one is placed on the distal rod near the iliosacral connectors. This configuration provides strong and stable fixation while allowing for future rod lengthening (Figure 3).

Problems related to neuromuscular spinal deformities

Treating neuromuscular spinal deformities is challenging and often associated with high complication rates. Spinal deformities typically manifest early and progress in most patients despite conservative treatments. Factors such as frailty, underlying clinical conditions, and osteoporosis contribute to the high incidence of complications. Treatment is particularly difficult in children under 10 years of age, as preserving spinal growth is crucial for lung development. Techniques like growing rods were developed for this age group but are associated with numerous complications (18-21).

To reduce complications and morbidity in the surgical treatment of neuromuscular scoliosis, Miladi developed the bipolar technique (16, 17). This technique offers greater stability compared to traditional methods, with lower morbidity and complication rates, and allows for growth without the need for additional

surgeries (22). The NEMOST device enables spinal development without requiring further surgeries (23).

Miladi et al. reported the outcomes and complications of 100 consecutive patients with neuromuscular scoliosis who underwent minimally invasive fusionless surgery between 2011 and 2015 (16). The Cobb angle was corrected by 63%, and pelvic obliquity improved by 83%. Complications included wound infections, implant dislodgement, superior mesenteric artery syndrome, and pneumonia (2, 12, 16). The results demonstrated significant correction of spinal deformities and pelvic obliquity with a lower complication rate, avoiding the need for final arthrodesis (16). A high rate of spontaneous fusion was observed on CT (computed tomography) scans at the end of the lengthening period in patients undergoing bipolar minimally invasive fusionless surgery (5).

Long-term follow-up in patients with spinal muscular atrophy who underwent minimally invasive fusionless surgery showed preserved spinal and thoracic growth without compromising respiratory function. Definitive fusion was not required at the end of growth, and significant deformity correction was achieved (5, 15).

Pelvic obliquity, the fixed angulation of the pelvis relative to the horizontal axis in the frontal plane, is a common issue in patients with spinal deformities. It can interfere with sitting posture (24). Pelvic fixation is often necessary in non-ambulatory patients, especially when pelvic obliquity exceeds 15 degrees or when lumbar curvatures are present, to achieve coronal and sagittal balance (25). Several techniques for pelvic fixation have been developed, all of which carry mechanical complications (26). The pelvic extension of minimally invasive fusionless surgery originated from the ileo-sacral screw of the Cotrel-Dubousset system (22). Fixation is further enhanced by using the Wiltse approach, introducing the connector into the sacrum, and fixing it with a percutaneous screw inserted through the iliac and sacrum (S1) without violating the sacroiliac joint (Fig. 3). This fixation method, encompassing S1 and two cortices of the ilium, results in a high rate of pelvic obliquity correction (61%) and significantly reduces the rates of lumbosacral pseudarthrosis (0-0.65%) (17, 22).

Pelvic obliquity correction is more effective in patients undergoing minimally invasive fusionless surgery compared to traditional open procedures due to the repeated surgeries for lengthening (16, 17). The sacral alar iliac screw provides better correction of pelvic obliquity compared to traditional techniques, although it does not significantly affect lumbar curve correction (17, 22). Screw malposition was reported in 3.4% of cases, leading to root irritation and necessitating revision (17, 22). The deep placement of the ilio-sacral screw, along with its low profile, reduces the risk of implant prominence, reported in 11% of iliac screw fixation cases (Modi), as well as skin ulceration and postoperative pain when sitting (17, 22). The rod connection in the center of the screw, aligned perpendicularly to the iliac crest, crossing both cortices and ending in the S1 body, may explain the absence of screw pullout. This method offers lower mechanical complication rates compared to other pelvic fixation techniques (15).

When comparing fusionless surgery to standard fusion surgery in neuromuscular scoliosis, both methods achieved similar curve corrections, but fusionless surgery resulted in significantly fewer complications and reduced intraoperative blood loss (27).

One common complication of growth-sparing techniques is rod breakage, which occurs in 15%-42% of cases (5, 12, 15). Rod breakage can lead to pain, loss of correction, and skin rupture, necessitating reintervention. The bipolar technique, however, has a lower rate of rod breakage (6.9%) in neuromuscular deformities, with a mean follow-up of 5.2 years. The rate of rod failure is higher in ambulatory, dystonic, and hyperactive patients, and a four-rod construct is recommended to reduce rod breakage (5, 12, 15, 24).

CONCLUSION

The bipolar technique for the surgical treatment of neuromuscular scoliosis enables the achievement of a balanced, stable spine, prevents deformity progression, and allows for growth. This minimally invasive approach offers fewer complications and better deformity correction than traditional techniques.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: No

Authors' Contributions: All authors have contributed equally

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

Sažetak

MINIMALNO INVAZIVNA BIPOLARNA FIKSACIJA ZA LEČENJE NEUROMIŠIĆNE SKOLIOZE-MILADI TEHNIKA

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Ovaj rad predstavlja minimalno invazivnu bipolarnu fiksaciju, poznatu i kao Miladi tehnika, za lečenje neuromišićne skolioze. Ovaj pristup uključuje bipolarno fiksiranje kičme od T1 do karlice. Proksimalna fiksacija se postiže korišćenjem laminarnih i pedikularnih kukica koje su oblikovane kao kandže, dok distalne fiksacije koriste ilio-sakralne konektore i šrafove. Proksimalna i distalna sidra su povezana bilateralnim dvostrukim kliznim konstrukcijama, što omogućava korekciju krivljenja kičme i pelvične nagnutosti. Ova tehnika pokazuje smanjeni morbiditet i stopu komplikacija u poređenju sa tradicionalnim metodama.

***Ključne reči**:* neuromišićna skolioza, minimalno invazivna tehnika, ilio-sakralni šrafovi.

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***How to cite this article**:* Defino LA H, Defino P M, Dorigão T. Minimally Invasive Bipolar Fixation for the Treatment of Neuromuscular Scoliosis – Miladi's Technique. Sanamed. 2024; 19(3): 367-372. doi: 10.5937/sanamed0-52708.

SANAMED
2024; 19(3): 373–380
ISSN-1452-662X

DOI: 10.5937/sanamed19-53857
UDK: 616.9:615.33.015.8
ID: 160114697
Review article

INFECTIOUS DISEASES AND ANTIMICROBIAL RESISTANCE: CURRENT CLINICAL DEVELOPMENTS AND UPDATE

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Primljen/Received: 01. 10. 2024. Prihvaćen/Accepted: 28. 11. 2024.

Abstract: Four years into the most virulent disease outbreaks of our generation—where COVID-19 became the most widely discussed infection, claiming millions of lives and leaving countless others suffering from long-term symptoms—host-pathogen interactions has never been more significant. This interplay between hosts and pathogens, alongside evolving risks of emerging infectious diseases, has been exacerbated by the exponential growth of human activities. This review focuses on host-pathogen interactions, the fight against antimicrobial resistance, the current status of antimicrobial usage, and alternative strategies to address this global health crisis.

Keywords: Infectious diseases, host-pathogens interactions, microbial drug resistance, drug design, vaccine development.

INTRODUCTION

The causative agents of infectious diseases are bacteria, viruses, fungi, and parasites that threaten humans, animals, and plants (1). Once inside the host, pathogens employ various mechanisms to cause disease and trigger immune response. Due to their high replication and tissue invasion rates, microbes and fungi cause symptoms within the host. The ever-changing dynamics of genomes in interphase between plants and the corresponding pathogen agents are the backbone of their interactions (2).

The initial step in the host-pathogen interaction starts at the point of entry into the host organism and ends at the final stage of transmission (3). Biochemical interactions occur at every step, enabling the pathogen to exploit energy and resources that facilitate replication. The cell-specific tropism of pathogens is controlled by molecular mechanisms that allow them to modify host cells and their environment (4). Over time, an evolutionary biological arms race has resulted in pathogens adopting evasion strategies to survive (1). A deeper understanding of the molecular basis of host-pathogen interactions is essential for identifying future diagnostic and therapeutic targets to combat harmful agents (5).

In 2019, 13.7 million people worldwide died from syndromes caused by infectious diseases, with 5.2 million cases coinciding with non-communicable diseases. Of these, 3 million deaths occured among children under five years old. Globally, respiratory and bloodstream bacterial infections were the leading causes of death (6).

The rise in antimicrobial resistance (AMR) continues to pose serious challenges to the effective treatment of many infections (7). While some vaccines exist, their effectiveness against all strains remain partial. Since the 1940s, antibiotics have been instrumental in combating microbial infections, but their use has also had unintended detrimental effects on human and animal health (8). The indiscriminate use of antibiotics has led to global problems, with resistance arising from genetic adaptations in microbes exposed to residual concentrations of antibiotics (9).

According to a 2014 World Health Organization report (10), deaths attributed to antimicrobial resistance could increase from 700,000 annually to 10 million by 2050. Key factors contributing to this resistance include a lack of public awareness about antimicrobial-resistant bacteria, poor health conditions, environmental influences, dietary practices involving genetically modified products, increasing cases of infectious disorders, and a decline in the discovery of new antimicrobials by pharmaceutical companies (11). In fact, research and development in the pharmaceutical industry have dwindled over the years as companies cut corners in their efforts to develop novel products, resulting in reduced efficacy.

Host-pathogen interactions

The term “host-pathogen interactions” primarily describes disease-causing microbes, though not all microbes are pathogenic to all hosts. These interactions

encompass how a pathogen thrives within its host across molecular, cellular, organismal, or population levels. Historically, the concept dates back to Filippo Pacini's work in the 1600s, with its roots traced more formally to 1884 (12).

The interaction between a pathogen and its host is determined by the type of relationship involved. The three main categories of symbiotic relationships are commensalism, mutualism, and parasitism (13). The RNA sequencing data from an infected host has helped to uncover the rewiring of the interactome and the relative fitness of the pathogen during infection.

The total cost of developing a novel antibiotic in ten years on a marketing pipeline is estimated to be $1.7 billion (14). As the monetary reward is very low, there is little impetus for pharmaceutical companies to develop new medicines. To bring novel agents into the market requires push incentives, such as grants and pull ones that are awarded upon successful regulatory approval, independent of actual usage (15). There are calls for multiple pull incentives on a global scale with the United Kingdom responding with a pilot subscription business model, while the United States has implemented the PASTEUR Act (16).

Non-antibiotic approaches to mitigate antimicrobial-resistant pathogens

With the increasing rate of antimicrobial resistance, the onus of responsibility lies on looking for alternatives to avert this global dilemma for pharmaceuticals as it is getting to a crisis point (17) (Table 1). The prospective application of unconventional techniques (18) is the use of bacteriophages (19), antimicrobial peptides (AMPs) (20) or ribosomal synthesized peptides (21), antibiotic adjuvants (22), poop transplants and probiotics (23).

As there is a pressing need to find novel antibiotics, scientists and policy makers are looking at other angles to tackle the resistance problem (24). Plasma-activated

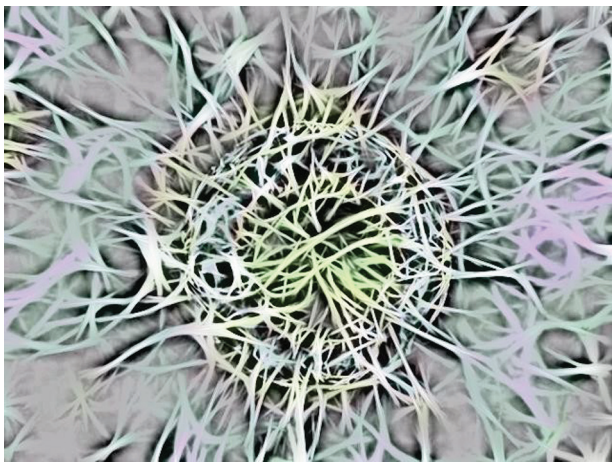

Figure 1. *Structure of an infectious pathogen with varying dendritec cells (personal communication)*

water (aka as a washing process), when enriched with oxygen and nitrogen derivatives that are chemically unstable, otherwise called free radicals and reactive forms is being considered as a potential new disinfectant (25). If bacteria are exposed to these radicals, they are effectively killed. A biochemical researcher, Katharina Richter, and her colleagues from the University of Adelaide in Australia are studying how fast plasma-activated water can heal infected wounds with methicillin-resistant *Staphylococcus aureus* (MRSA) versus untreated wounds (26). They are also investigating its potential as a supplement to intravenous antibiotics. Their findings suggest that plasma-activated water enhances wound infection elimination more quickly, with promising results for MRSA treatment (25).

Though bacteria are unicellular in nature, they can form communities and help each other to evade drugs and antiseptics (27). One mechanism by which they do this is by biofilm formation (28). These biofilms protect individual cells with approximately 80% of chronic infections in humans being attributed to biofilm-producing bacteria (29). Gallium, a metallic element, disrupts bacterial iron uptake, essentially starving mi-

Table 1. *Alternative non-antibiotic strategies to prevent antimicrobial resistance and classes of nanoparticles for antimicrobial chemotherapy (modified from (17))*

Alternative non-antibiotic strategies	**Classes of nanoparticles**
Vaccines	Inorganic and metallic nanoparticles
Stem cell AMPs	Polymeric nanoparticles (PNPs)
Immuno therapy/Antibody-antibiotic conjugates	Liposomes
CRISPR/Cas9 edits	Nanoemulsions
Nanobiotics/Enzybiotics	Nanostructured lipid carriers (NLCs)
Fecal microbiota transplantation (FMT)	Solid lipid nanoparticles (SLNs)
Phage therapy	Mesoporous silica nanoparticles (MSNPs)
Probiotics/Microbial therapies	Biomimetic nanoparticles (BNPs)

crobes of nutrients. Scientists are investigating gallium-laced drugs to combat biofilms, as demonstrated in research at the University of Manchester, UK, where gallium-based compounds reduced bacterial growth by up to 87% (30). Similar studies at Shanghai JiaoTong University, China, showed that gallium could dissolve MRSA biofilms, making it possible to kill the bacteria with just one-tenth of the typical antibiotic dose (31).

An ideal antibiotic should possess three key features: solubility, the ability to bind readily to bacteria, and the ability to penetrate cell membranes (32, 33). Designing antibiotics that meet these criteria remains a challenge. To address this, researchers are now using large digital libraries to predict these properties, screening existing compounds for the necessary characteristics (34). However, further research is required to develop a model that integrate these properties and improves cell permeability.

Application of nanobiotics in infectious diseases

Nanotechnology provides a brilliant alternative in the treatment of drug-resistant infections (35). Antimicrobials can be delivered using nanomaterials, or the nanomaterials themselves can contain drugs (36). Nanoparticles with enhanced antibacterial, antiviral, and anticancer efficacy, due to reduced toxicity, are emerging as potential drug candidates for future applications (37). These days, clinical infectious disease specialists use an increasing array of tools in their practice to harness unique features that are related to nanotechnology. Such procedures involve rapid and point-of-care diagnostic assays, antibiotics and their delivery vectors, vaccines, and materials for the purification of food and water (38).

The key benefits of nano-based drug delivery systems include reduced irritant reactions, improved bioavailability, and enhanced penetration within the body owing to their small particle size, which allows for intravenous and other routes of administration.

Nanoformulations based on lipids, namely nanoemulsions, liposomal compositions, and solid lipid nanoparticles (SLNs), are commonly used to transport antibacterial drugs (39). The targeted delivery of antibiotics directly to bacteria could be done through lipid nanoparticles fused with cell membranes (40). The liposomes, which are delivery vectors for drugs, can extend the duration of circulation and facilitate cellular absorption, thereby overcoming the resistance to antibiotics (41). The low cytotoxicity of solid lipid nanoparticles (SLNs) (42), nanostructured lipid carriers (NLCs) (43) and nanoemulsions (44) make them suitable as drug-delivery systems. These systems differ primarily in their core composition. SLNs consist of a solid support in a crystalline state, while NLCs have a lipid matrix that combines solid liquid lipids, making them a more advanced generation of lipid-based drug delivery systems (45).

The merits of nanotechnology include a stable release in a controlled manner, lipophilic molecules infiltrated into different layers, solubility, bioavailability enhancement, drug encapsulation with low-cost biocompatible and biodegradable polymers, and improvement in the effectiveness of various treatments. However, there are disadvantages involving toxicity characteristics when using different additives/polymers, side reactions and lack of standardized regulatory protocols (46).

Averting resistance to drugs through innovations

Drug resistance is a noted phenomenon in several pathogens that cause infectious diseases, namely tuberculosis, nosocomial infections, malaria, and acquired immunodeficiency syndrome (AIDS). New strains of the human immunodeficiency virus (HIV) that are resistant to antiretroviral drugs have also been reported (47). These strains therefore require the development of novel therapeutic drugs (48) (Table 2).

Table 2. *List of infectious diseases and corresponding replicates per condition (48)*

Disease	Replicates
Campylobacteriosis	1
Dengue	1
Hepatitis A	1
Pertussis	2
Salmonellosis	1
Influenza	3
Measles	7
Brucellosis	2
COVID-19	7
Scarlet fever	2
Western equine encephalitis	2
Diphtheria	5
Saint Louis encephalitis	4
Poliomyelitis	5
Typhoid	8
SARS	4
Japanese encephalitis	3
MERS	1
Typhus	1
Smallpox	6
Yellow fever	2
Cholera	14
Lassa fever	4
AIDS	1
Tuberculosis	2
Meningococcal meningitis	3
Ebola	2
Plague	10

Machine intelligence (MI) and structure-guided approaches have been applied in designing immunogens for the development of vaccines against SARS-CoV-2 and other disease-causing agents (49). The approach uses bioinformatics to identify genes associated with specific pathogens, allowing for the determination of key features that provide specificity for antigen binding, making them potential targets for vaccines (50). New candidates are being synthesized and tested in vivo through reverse vaccinology (51). Additionally, clinical research and trials can be streamlined and monitored by leveraging MI or artificial intelligence (AI) (52).

Interestingly, new strategic approaches to treat viral, bacterial and parasitic infections are being explored these days. While weakened versions of whole pathogens have been applied, vaccines now also include mRNA (53) or plasmid DNA (54) which has been applied to target parasitic infections, such as malaria. In 2017, the European Economic Area (EEA) approved the use of bezlotoxumab to combat *Clostridium difficile* and recurrent cases (55).

The World Health Organization (WHO) is leading a global effort to tackle antimicrobial resistance. Although most physicians recognize the severity of the problem, many still underestimate it in their own hospitals, continuing to prescribe antibiotics inappropriately. Strategic efforts to combat this global challenge include educating the public, raising awareness about inappropriate prescribing among general practitioners through continuous professional development (CPD), engaging pharmaceutical companies in research and development of new antimicrobials, and adopting innovative treatment strategies enabled by technological advancements. The five strategic objectives include: a) enhancing knowledge and understanding of antimicrobial resistance; b) strengthening science through monitoring and research; c) reducing infection rates; d) maximizing the use of antimicrobial agents; and e) advocating for long-term investments to meet the needs of all countries, including investment in new drugs, diagnostic tools, vaccines, and further actions (inspired from: https://infectionsinsurgery.org/5-strategies-to-combat-antibiotic-resistance-in-healthcare/).

Though still in its early stages, a new mechanism for killing bacteria is being explored through the use of antibody-antibiotic conjugates (AACs) (56). This technique involves AAC binding to bacteria, which are then internalized by host cells. Once inside, the unconjugated AAC kills the bacteria. This novel combination immunotherapy strategy, when used alongside conventional therapy, could yield promising results for combating more resilient pathogens.

What is the current development that has happened with antimicrobial resistance?

The alarming rate of antimicrobial resistance (AMR), as reported by the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) in 2022, highlights the prevalence of resistant bacterial pathogens (57). The median rates reported in 76 countries were 42% for *Escherichia coli* resistant to third-generation cephalosporins and 35% for *Staphylococcus aureus* resistant to methicillin. In urinary tract infections caused by *E. coli*, one in five cases showed reduced treatment effectiveness with antibiotics like ampicillin, co-trimoxazole, and fluoroquinolones, making it more difficult to treat common infections. Since 1990, there have been at least 1 million deaths annually associated with antimicrobial resistance, and by 2050, more than 39 million lives are expected be lost, according to the Global Research on Antimicrobial Resistance (GRAM).

There were high levels of resistance against critically important antibiotics by a common intestinal bacterium, *Klebsiella pneumoniae*. Based on the Organization for Economic Cooperation and Development (OECD) projections, there will be a two-fold increase in resistance by 2035, stressing the urgent necessity for robust antimicrobial management practices and strengthened supervision worldwide (inspired from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance).

Drug resistance among fungi

Drug-resistant fungal infections are also on the rise as WHO monitors their magnitude and impact on public health. These infections can be difficult to treat, particularly in patients with other diseases such as AIDS (inspired from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance).

Drug resistance among HIV, *Mycobacterium tuberculosis* bacteria, and *Plasmodium malariae* parasites

Resistance to HIV drugs occurs due to modifications in its genome, which impair the ability of antiretrovirals (ARV) to block the virus replication. The transmission of this resistance could occur when people are first infected or it is acquired as a result of compliance problems with treatment or drug interactions. WHO is recommending that nations should conduct investigations on the resistance to HIV drugs for careful selection of an optimized regimen for ARV prevention and therapy (inspired from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance).

Tuberculosis is an important contributing factor to the resistance to antibiotics. Multidrug-resistant tuberculosis disease (MDR-TB) is a type caused by germs not reactive to a combination of two antibiotics, isoniazid and rifampicin, these are the first-line treatments most effective for TB. Resistance to second-line therapies further limits treatment options, posing a public health emergency (inspired from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance).

Drug-resistant parasites pose a significant threat to malaria treatment and control. For uncomplicated *Plasmodium falciparum* cases, artemisinin combination therapies are the first-line treatments used in many countries with endemic malaria. In the Greater Mekong Subregion, resistance to this antibiotic or its partner drug has been observed since 2001. In the eastern Mediterranean region, resistance to Fansidar (sulfadoxine and pyrimethamine), a partner drug, has led to treatment failures in some countries, prompting a shift to alternative combination therapies. On the African continent, mutations associated with artemisinin partial resistance have been noticed in a number of countries (inspired from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance).

Since November 2023, 178 nations have developed national action plans on antimicrobial resistance (AMR) in alliance with a Global Action Plan (GAP). Worldwide, the tracking progress of an AMR action plan could be captured through cross-sectoral actions like the annual Tracking AMR Country Self-Assessment Survey (TrACSS) that was initiated in 2016 with previously published work on https://www.amrcountryprogress.org/.

Excess usage of antibiotics

One of the major issues with antibiotics is their overuse or misuse in treating infections in humans, animals, and plants (58). Bacteria can mutate, altering their cell walls to resist antibiotics or breaking them down, while some strains can share their antimicrobial resistance genes. Misuse or poor compliance with prescribed antibiotics provides a pathway for resistance to spread, allowing microbes to multiply and evolve.

How governments handle outbreaks?

The major objective in managing an outbreak is to safeguard public health by identifying the source, causes of infection, and transmission dynamics, then implementing control measures to contain further spread or recurrence. A secondary goal is to refine outbreak management, using evidence from infection sources, transmission and actions, taken, and improving training for better future responses. For example, the UK Health Security Agency (UKHSA) is responsible for reporting international health treats to the WHO under the International Health Regulations of 2005. Incidents meeting the definition of a serious cross-border health threat are also be reported to the EU Commission.

Every responsible government must take the outbreak of any infection seriously, given its potential impact on domestic and global health. It should not be dismissed due to the leader's ego, religious beliefs, national reputation, or desire to protect their image internationally. In such cases, collaboration with the World Health Organization (WHO) is crucial to effectively reduce the spread, transmission and containment of the infection. Unfortunately, some global leaders, including autocrats and dictators, prioritize their personal or political agendas over the well-being of their people and the international community, which undermines global peace, security, and health.

The confusion surrounding the COVID-19 outbreak remains unresolved, with full clarity in the chain of events leading to the pandemic still uncertain. Given the mishandling of the situation and the resulting loss of lives, it is essential for any government—regardless of its cultural, religious, geographical, or political background—to be transparent and cooperate fully with the World Health Organization (WHO) in managing outbreaks. This cooperation is vital for identifying the origin, modes of transmission, and effective containment strategies. Collaborating with WHO will mobilize global expertise to reduce transmission and limit the spread of infections worldwide.

CONCLUSION

Antimicrobial resistance will continue to pose a serious challenge to the healthcare system worldwide as long as both emerging and re-emerging infectious diseases persist. The problem could be controlled through the development of novel antimicrobials, strategic use of existing antibiotics, application of innovative technologies, and minimizing artificial host-pathogen interactions that drive cross-border transmissions.

Health is paramount and a fundamental human right. With the global population increasing and compounded by environmental catastrophes, authoritarian regimes, human cruelty, wars, populist extremism, and fascism, these factors are driving forces behind future infectious disease outbreaks. The ability to effectively address these challenges may be hindered by these forces. The role of irresponsible dictators and autocratic leaders—who disregard humanity and dismiss scientific expertise—cannot be underestimated.

COVID-19 has significantly reshaped global working conditions, with many companies, organizations, institutions, and government bodies transitioning to remote or hybrid work models for their employees, establishing these as the new standard.

As health authorities, clinicians and pharmaceutical companies tackle the crisis of antimicrobial resistance, vaccines may offer potential solutions, provided that side effects in certain groups of individuals are carefully monitored.

Novel recombinant vaccine technologies have been crucial in minimizing the use of antimicrobial combinations. One of the most significant ways to prevent them is being. achieved by vaccines. There are a few at the mid-stage of their clinical development by pharma companies against pathogenic bacteria that are deadly, namely *Clostridium difficile* (phase III), *Mycobacterium tuberculosis* (phase II), Group B *Streptococcus* (phase II) and *Staphylococcus aureus* (phase II) (inspired from: https://iris.who.int/bitstream/handle/10665/359172/9789240052451-eng.pdf?sequence=1).

The unnecessary prescription and overuse of antibiotics can be avoided by healthcare professionals. Instead, patients should be educated on proper hygiene practices to reduce the spread of diseases and minimize infections to the greatest extend possible.

Applications of genomics screening, as a fundamental tool in infectious disease studies and drug development, have played a prominent role in understanding host-pathogen interactions, including those of viruses such as Zika, Dengue and SARS-CoV-2 viruses.

In tropical regions affected by malaria, governments could make significant progress by utilizing all available resources to address sanitation, approve appropriate hygiene methods, and ensure effective drainage systems, especially during rainy periods, to minimize breeding opportunities for *Plasmodium falciparum*. This strategic combination, along with medical treatments, would help reduce the mortality rate in both children and adults in these regions. Ultimately, it comes down to accountability and the willingness to improve the health and quality of life for the affected populations.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: No

Author contribution: All authors have contributed equally

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

Sažetak

INFEKTIVNE BOLESTI I ANTIMIKROBNA REZISTENCIJA: TRENUTNI KLINIČKI RAZVOJ I NAJNOVIJA DOSTIGNUĆA

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Četiri godine nakon jedne od najvirulentnijih epidemijskih bolesti naše generacije—u situaciji u kojoj je COVID-19 postao infekcija o kojoj se najviše diskutuje, koja je odnela milione života i ostavila bezbroj drugih ljudi sa dugoročnim simptomima—interakcije domaćin- patogen nikada nisu bile značajnije. Odnos između domaćina i patogena, zajedno sa rastućim rizicima od novih zaraznih bolesti, dodatno je pogoršan eksponencijalnim rastom ljudskih aktivnosti. Ovaj rad se fokusira na interakcije domaćin-patogen, borbu protiv rezistencije na antibiotike, trenutni status upotrebe antibiotika, kao i alternativne strategije za rešavanje ove globalne zdravstvene krize.

Ključne reči: Infektivne bolesti, interakcije domaćin-patogen, rezistencija na antibiotike, dizajn lekova, razvoj vakcina.

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How to cite this article: **Herbert E**, Fournier D. Infectious disease and antimicrobial resistance:current clinical developments and update. Sanamed. 2024; 19(3): 373-380. doi: 10.5937/sanamed19-53857.

SANAMED
2024; 19(3): 381–387
ISSN-1452-662X

DOI: 10.5937/sanamed19-55036
UDK: 616.311.2-007-089
ID: 160169737
Review article

COMPARATIVE REVIEW OF THE EFFECTIVENESS OF DIFFERENT SURGICAL TECHNIQUES IN THE MANAGEMENT OF GINGIVAL RECESSION

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Primljen/Received: 27. 11. 2024. Prihvaćen/Accepted: 21. 12. 2024.

Abstract: Mucogingival anomalies arise from anatomical and morphological irregularities within the mucogingival complex of periodontal tissues, representing deviations from the normal dimensions and morphology of the gingiva-alveolar mucosa relationship. According to the American Academy of Periodontology glossary, gingival recessions are defined as the exposure of the tooth root surface caused by the apical displacement of the gingiva relative to the cemento-enamel junction.

In addition to aesthetic concerns, gingival recessions lead to increased sensitivity and ineffective plaque control, which can ultimately result in tooth loss. To address these issues, procedures are performed to cover exposed roots and restore the normal function and appearance of the mucogingival complex. The treatment for gingival recessions is primarily surgical, aiming for complete root coverage with long-term stability. Various methods are available, but the gold standard involves using a connective tissue graft in combination with a coronally advanced flap.

This paper compares three treatment methods: the coronally advanced flap (CAF), CAF combined with a connective tissue graft, and CAF with porcine collagen matrix application. The primary objective is to identify which surgical method yields the best clinical outcomes.

Nine studies involving 303 patients demonstrated that the highest root coverage is achieved with CAF combined with a connective tissue graft, showing a reduction in recession depth of 2.64 mm, an increase in the keratinized gingival zone of 1.05 mm, and a reduction in pocket depth of 0.36 mm. CAF combined with porcine collagen matrix provided slightly lower results, while CAF alone yielded the lowest outcomes.

Keywords: mucogingival complex, mucogingival anomalies, gingival recessions, connective tissue graft, coronally advanced flap.

INTRODUCTION

Gingival recession is a mucogingival anomaly defined as the apical displacement of the gingival margin relative to the cemento-enamel border (1). Mucogingival anomalies are the result of anatomical and morphological irregularities in the mucogingival complex of periodontal tissues. This complex consists of the keratinized gingiva (free and attached), alveolar mucosa, and the mucogingival border line (2).

It has been established that there is a mutual relationship between the occurrence of gingival recessions and aging (3, 4). Research shows that 88% of people over 65 years of age and 50% of participants between the ages of 18 and 64 have had at least one gingival recession in their mouths (4). Considering the frequency of gingival recessions, particularly in younger patients, solving this problem is a big challenge.

Advancements in measurement techniques have improved the assessment of recession depth. Digital methods, such as scanners, provide greater accuracy and reliability compared to traditional periodontal probes. Instruments like ultrasound biometers further enhance the precision of these measurements, reducing variability and increasing validity.

Restoring the structure of the mucogingival complex is considered the fundamental and ideal method for treating gingival recession. The goal of gingival recession therapy is to cover the tooth root while satisfying aesthetic parameters and achieving a stable result for a longer period of time.

Indications for treating gingival recessions

The surgical treatment procedure using grafts aims to correct disturbances within the mucogingival complex. The main goal of gingival recession therapy is to cover the exposed tooth root with healthy tissue and bone, achieving appropriate aesthetic results (5). Miyamoto et al. (6) showed that gingiva could remain healthy even in areas where attached gingiva is minimal or absent, as long as proper oral hygiene is maintained and plaque accumulation is prevented. On the other hand, Lang et al (7) suggest that a minimum width of 2 mm is necessary for gingival health. According to their report, areas with 1 mm or less of attached gingiva often show clinical signs of inflammation.

Aesthetic concerns, root hypersensitivity, prevention of root caries, non-carious cervical lesions, and patient discomfort during oral hygiene are primary indications for root coverage procedures (8). The clinical goal of gingival recession surgery is to achieve complete root coverage without visible inflammation (9). However, an adequately positioned gingival margin may not guarantee favorable aesthetic results, as poor aesthetics can arise from uneven contours, poor color match, or scar tissue (10).

At the site of recession, dentin hypersensitivity can develop due to cementum damage and dentin exposure. As a consequence, the patient may experience discomfort, and maintaining good oral hygiene may become challenging (11). Cortellini et al. (12) conducted a multicenter study with 85 participants to demonstrate the benefits of root coverage procedures in reducing tooth sensitivity. Approximately 40% of participants cited root sensitivity as the reason for seeking treatment. Six months after undergoing a coronally advanced flap procedure, with or without connective tissue grafting, the prevalence of root sensitivity decreased to approximately 10%.

In treating gingival recessions, the primary challenge lies in repairing and regenerating the periodontal tissues in the affected area. Soft tissue autografts have become a common procedure because, in addition to covering the exposed tooth root, they can also increase the width of keratinized gingiva. Autogenous grafting methods include free gingival grafts and connective tissue grafts, where soft tissues are transplanted from a distant region to cover the defect. For good therapeutic results, the recipient region must meet the following criteria: it must support rapid revascularization of the free graft, allow the formation of a new vascular network, and enable effective nutrient diffusion.

Free gingival graft

The free gingival graft was first described by Nabers in 1966 and systematized by Sullivan et al (13). A free gingival graft is an epithelialized, keratinized soft tissue, most commonly taken from the palatal mucosa in the area of canines and premolars to avoid injury to the palatine artery. A horizontal incision, approximately 1 mm thick, is made parallel to the dental arch. The shape and size of the graft are chosen based on the availability of tissue and the size of the defect that needs to be covered. The graft is harvested from the palate once the specific shape and size are achieved. It is important that the graft is 1 mm thick, containing a subepithelial connective tissue layer, which is then transplanted into the region of the gingival recession (14). This procedure can address the problem of a narrow zone of keratinized gingiva in a single surgical act and eliminate isolated gingival recession (14).

Connective tissue graft

The most significant progress in autogenous grafting procedures occurred in 1985 with the introduction of the connective tissue graft, which not only provides excellent aesthetic results but also promotes the formation of new connective tissue (15). The histological compatibility of the hard palate mucosa and gingiva led to the idea of using a subepithelial connective tissue graft from the palate for treating recessions. The connective tissue graft has become the gold standard for covering recessions (14). The main advantages of this graft are its dual blood supply from both the periosteum and the graft itself, as well as its perfect integration and optimal aesthetic outcome (16). Since the success of the therapy is determined by the survival of the graft, it is recommended that the flap covering the graft should cover most of the graft to ensure adequate blood supply (9). After four weeks, the tissue closely resembles the surrounding tissue, which is a key aspect of rapid graft survival and biointegration, significantly influencing the effectiveness of the treatment (17).

The connective tissue graft is most commonly harvested from the palate. To prevent the development of palatal recessions, tissue approximately 2 mm from the gingival margin should remain intact. A horizontal incision is made around 3 mm apical to the gingival margin in the premolar region. A second vertical incision determines the width of the graft. A raspatorium is used to release the graft after the vertical incision, both mesially and distally.

Non-autogenous gingival graft

Despite the potential advantages of autogenous tissue grafting, there are also significant drawbacks

and limitations, such as morbidity, pain associated with the secondary surgical site, and the limited dimensions of donor tissue (18). The development of connective tissue substitutes of xenogenic, allogenic, or synthetic origin has gained increasing importance to overcome the inadequacies of autogenous connective tissue. These biomaterials can reduce the duration of the surgical procedure, patient morbidity, and recovery time, but they must also have good biocompatibility, allowing for remodeling and stability of the graft volume over time (18, 19).

Acellular dermal matrix of allogenic (human) origin is frequently used in the United States. Alloderm® (LifeCell, Bridgewater, USA) is an artificial acellular dermal matrix from which the epidermis and cells that could potentially lead to failure in periodontal surgery have been removed. In a meta-analysis conducted by Gapski et al (20), no statistically significant differences were found in the degree of recession coverage between acellular dermal matrix and free connective tissue grafts. On the other hand, the coronally advanced flap with acellular dermal matrix had better aesthetic outcomes, as reported by both clinicians and patients, compared to the coronally advanced flap with a free connective tissue graft, even though it showed a lower degree of root coverage (21). In support of free connective tissue grafts, which remained stable even after four years, Harris (22) showed that recession coverage with human-derived acellular dermal matrix decreased from 93% to 66% after four years (22).

Xenogenic (animal-derived) materials are now also used as alternatives to free connective tissue grafts and human acellular dermal matrices (20). For the European market, the main representative of xenogenic material from pig tissue is Mucograft® (Geistlich Biomaterials, Switzerland). It consists of a compact layer that contributes to stability and a thick, porous layer that serves as a base into which the host's connective tissue grows. Its advantages (according to the manufacturer) include unlimited material availability, shortened procedure time, faster healing, reduced postoperative pain, and better patient acceptance. In comparison to the coronally advanced flap alone, histological studies have shown that the porcine matrix was able to stimulate the formation of new cementum in experimental recessions in an animal model (23). Mucograft® is indicated for covering implants in the immediate or late stages of implantation, localized gingival augmentation to increase keratinized tissue around teeth and implants, alveolar ridge reconstruction for prosthetic treatment, and surgical treatment of gingival recessions. Contraindications include the presence of symptomatic infections, collagen allergies, and it should be used with caution in patients with autoimmune diseases, uncontrolled diabetes, thyroid disorders, and in cases of prolonged corticosteroid therapy or head and neck radiotherapy.

OBJECTIVES

The primary objective of this study is to evaluate the effectiveness of three different surgical methods: coronally advanced flap, coronally advanced flap with connective tissue graft, and coronally advanced flap with porcine collagen matrix. The parameters for recession depth, width of keratinized gingiva, and pocket depth will serve as measures of the effectiveness and success of the therapeutic procedure. All these values were recorded in millimeters before the treatment and six months after the surgery.

Nine studies with a total of 303 patients were analyzed in this research. All studies used as research material are from the period between 2009 and 2022. A detailed literature search was performed in the PubMed database, which included all available studies related to the surgical treatment of gingival recessions. The search criteria included the keywords: gingival recessions, gingival graft, coronally advanced flap, and collagen matrix. For the purposes of the preliminary literature review, the titles and abstracts of all published studies found as a result of the search were reviewed to identify studies that met the inclusion criteria. Publications were included in the research only if they contained data on the performed intervention, the result of the therapy, and a comparison of the outcomes.

CORONALLY ADVANCED FLAP

This therapeutic procedure involves the use of the coronally advanced flap alone, without the use of any type of graft. A total of 86 patients were included in this group across five studies. The study by Mathias-Santamaria et al. (24), which included the largest number of patients (31), was compared to smaller studies such as those by Kanmaz et al. (25) and Rotundo et al. (26), which involved only 12 patients.

Kanmaz et al. (25) reported an average reduction in recession depth of 2.68 mm, whereas Rasperini et al. (27) reported a reduction of 1.7 mm. An increase in the width of the keratinized gingiva was observed in four out of five studies, with the highest result achieved in the study by Rasperini et al. (27). On the other hand, Rotundo et al. (26) found a reduction of 0.9 mm. The probing depth was reduced by an average of 0.14 mm in all five studies. Jepsen et al. (28) reported the largest reduction in probing depth, with a decrease of 0.31 mm, while Kanmaz et al. (25) and Mathias-Santama-

***Table 1**. Comparison of results for Coronary Advanced Flap*

Study	Number of patients	Depth of recession	Width of keratinized gingiva	Probing depth
Rasperini et al., (27)	13	1.7	0.7	0.1
Jepsen et al., (28)	18	2.54	0.61	0.31
Kanmaz et al., (25)	12	2.68	0.46	0
Mathias-Santamaria et al., (24)	31	2	0.4	0
Rotundo et al., (26)	12	2.1	-0.9	0.3
	86	**2.20**	**0.25**	**0.14**

***Table 2.** Comparison of results for Coronary Advanced Flap with Connective Tissue Graft*

Study	Number of patients	Depth of recession	Width of keratinized gingival	Probing depth
Rasperini et al., (27)	12	1.6	0.4	0.2
Nahas et al., (29)	15	2.5	1.2	0.4
Barakat, Dayoub and Alarkan (30)	10	3.19	1.42	0.17
McGuire et al., (31)	30	3.35	1.3	0.6
Maluta et al., (32)	15	2.54	0.91	0.41
	82	**2.64**	**1.05**	**0.36**

ria et al. (24) did not record a significant reduction in probing depth (Table 1).

CORONALLY ADVANCED FLAP WITH CONNECTIVE TISSUE GRAFT

In this group, five studies used the coronally advanced flap with a connective tissue graft (27, 29, 30-32). The average number of patients in these studies was 16.4, with the study by McGuire et al. (31) including the highest number of patients, 30. In contrast, the lowest number of patients was reported in the 2009 study by Barakat et al (30).

Based on the data extracted, McGuire et al. (31) reported the largest average reduction in recession depth, followed by Barakat et al (30) and Maluta et al. (32) with reductions of 3.35, 3.19, and 2.54 mm, respectively. On the other hand, the studies by Rasperini et al. (27) and Nahas et al. (29) had the lowest recession depth reductions, both reporting a reduction of 2.5 mm. The overall average reduction in recession depth for all five studies was 2.64 mm.

The increase in the width of keratinized gingiva was measured in each of the five studies. In one of the two studies (Rasperini et al. (27) and Maluta et al. (32)), the width of the keratinized gingiva was found to be smaller, while three other studies (Nahas et al. (29), McGuire et al. (31), and Barakat et al (30)) reported a greater width, with an average increase of 1.05 mm across all five studies.

All five studies reported a reduction in probing depth, with an average reduction of 0.36 mm. Several factors may influence these results, including gingival phenotype, lack of adequate bone support for the gingival graft, and excessive tooth brushing. During the studies, it was difficult to control all external variables that may impact the outcomes (Table 2).

CORONALLY ADVANCED FLAP WITH THE USE OF XENOGENEIC GRAFT

This group includes data from a total of seven studies that used a coronally advanced flap in combination with a xenogeneic graft. The sum of all seven studies includes a total of 135 patients, with an average of 19.28 patients per study. The largest number of patients was included in two studies, one published in 2022 by Mathias-Santamaria et al. (24) and the oth-

Table 3. *Comparison of results obtained with Coronary Advanced Flap and Xenogeneic Graft*

Study	Number of patients	Depth of recession	Width of keratinized gingival	Probing depth
Jepsen et al., (28)	22	2.86	1.42	0.22
Mathias-Santamaria et al., (24)	31	2	0.6	-0.1
Nahas et al., (29)	15	2	0.4	0.1
Barakat, et al (30)	10	3.06	1.58	0.14
McGuire et al., (31)	30	2.55	0.7	0.6
Maluta et al., (32)	15	2.43	0.74	0.34
Rotundo et al., (26)	12	2	-0.5	0
	135	**2.41**	**0.71**	**0.19**

er in 2021 by McGuire et al. (31), with a total of 31 and 30 participants, respectively. On the other hand, Barakat et al (30) conducted a study with the smallest number of participants, which included 10 patients. All studies achieved results that were greater than or equal to 2, with the study by Barakat et al (30) showing a reduction in recession depth of up to 3.06 mm. The average reduction in recession depth across these seven studies was 2.41 mm, and all studies achieved results greater than or equal to 2. Additionally, the largest increase in the width of the keratinized gingiva was observed in the study by Barakat et al (30), with a result of 1.56 mm, while four out of the seven studies reported an increase of less than 1 mm. Conversely, Rotundo et al. (26) reported a loss of 0.5 mm. When all data were considered, the average gain in keratinized gingiva width was 0.71 mm. Five studies showed a reduction in probing depth, with an average reduction of 0.19 mm across all seven studies. On the other hand, Mathias-Santamaria et al. (24) observed an increase in probing depth by 0.1 mm. Furthermore, Rotundo et al. (26) did not observe any significant change in probing depth, but Maluta et al. (32) in 2021 reported the largest percentage decrease in probing depth, which amounted to 0.34 mm (Table 3).

CONCLUSION

These clinical results were chosen because they are objective, measurable criteria that can be compared. In the treatment of gingival recessions, the coronally advanced flap is most commonly used. Of the 303 patients, 86 were treated with the coronally advanced flap alone. The average recession depth was 2.20 mm, the gain in the width of the keratinized gingiva was 0.25 mm, and the probing depth was 0.14 mm. A study examining long-term stability concluded that this method alone does not appear to be completely stable in the long term. However, the 2018 study had the highest average width of keratinized gingiva, which was 0.7 mm. On the other hand, of all the studies, only the study by Rotundo et al. showed a negative result for the width of the keratinized gingiva, with a decrease of 0.9 mm. This was attributed to reduced blood flow to the flap during the initial healing phase. In mucogingival surgery, the use of free connective tissue grafts is considered the gold standard for covering gingival recession.

We conclude that significant coverage of defects can be achieved using the coronally advanced flap, either alone or with the use of grafts: connective tissue and porcine collagen. The coronally advanced flap combined with a connective tissue graft is the most effective procedure and the gold standard method for root coverage. The effectiveness of the porcine collagen matrix is lower than that of the connective tissue graft, but porcine collagen can be considered an alternative to the connective tissue graft. The use of porcine collagen and connective tissue grafts, in combination with the coronally advanced flap, gives superior results when compared to the use of the coronally advanced flap alone.

Conflict of Interests: The authors declare no conflicts of interest related to this article.

Funding: No

Author contribution: All authors have contributed equally

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

Sažetak

UPOREDNI PREGLED EFIKASNOSTI RAZLIČITIH HIRURŠKIH TEHNIKA U MENADŽMENTU RECESIJA GINGIVE

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Mukogingivalne anomalije se ispoljavaju kao posledica anatomomorfoloških nepravilnosti u mukogingivalnom kompleksu parodontalnih tkiva i predstavljaju odstupanje od normalne dimenzije i morfologije u međusobnom odnosu gingive i alveolarne mukoze. Prema rečniku pojmova koji je objavila Američka akademija za parodontologiju, recesije se definišu kao izlaganje površine korena zuba koje je prozrokovano apikalnim pomeranjem gingive u odnosu na cementno-gleđnu granicu.

Pored estetskih problema, recesije gingive su takođe i uzrok preosteljivosti zuba i neefikasne kontrole plaka što na kraju može dovestii do gubitka zuba. Iz tog razloga sprovode se procedure koje za cilj imaju pokrivanje korena zuba i vraćanje normalne funkcije i izgleda mukogingivalnog kompleksa. Terapija gingivalnih recesija je hirurška sa ciljem komplentnog prekrivanja površine korena zuba koje bi bilo stabilno u značajnom vremenskom periodu. Mogu se tretirati na više različitih načina, a primena transplantata vezivnog tkiva u kombinciji sa koronarno pomerenim režnjem predstavlja zlatni standard.

Koronarno pomereni režanj, koronarno pomereni režanj sa primenom grafta vezivnog tkiva i koronarno pomereni režanj u kombinaciji sa matriksom svinjskog kolagena su tri metode lečenja koje će biti prikazane i upoređene. Primarni cilj ovog istraživanja je da se otkrije koja od tri hirurške metode lečenja recesija gingive daje najbolje kliničke rezultate.

Devet studija sa ukupno 303 pacijenta pokazalo je da najveću pokrivenost korena daje koronarno pomereni režanj uz primenu transplantata vezivnog tkiva sa smanjenjem dubine recesije od 2,64 mm i dobijenom zonom keretinizovane gingive od 1,05 mm i smanjenjem dubine džepa od 0,36 mm. Nešto niže rezultate dao je koronarno pomereni režanj uz primenu svinjskog kolagena dok je samo koronarno pomereni režanj dao najniže rezultate.

***Ključne re**či:* mukogingivalni komleks, mukogingivalne anomalije, gingivalne recesije, transplantat vezivnog tkiva, koronarno pomeren režanj.

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***How to cite this article**:* Mijatović J, Jovičić B, Urošević Z, Okičić N, Milovanović B,Tričković V, Smiljanić M, Tesla Z. Comparative review of the effectiveness of different surgical techniques in the management of gingival recession. Sanamed. 2024; 19(3): 381-387. doi: 10.5937/sanamed19-55036.

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Originalni rad treba da ima sledeće podnaslove: uvod, cilj rada, metod rada, rezultati, diskusija, zaključak, literatura.

Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura.

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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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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Tri puta godišnje. — Tekst na engl. jeziku. — Drugo izdanje na drugom medijumu: Sanamed (Online) = ISSN 2217-8171

ISSN 1452-662X = Sanamed

COBISS.SR-ID 135154444

ISSN 1452-662X