KLINIČKI CENTAR UNIVERZITETA U SARAJEVU

ISSN (print) 1512-5866
ISSN (online) 2232-853X
April/June 2026 · Vol. 32, No. 2

MJ Medical Journal

of the Discipline for Research and Development - Clinical Center University of Sarajevo

Volume 32

Disciplina za nauku i nastavu

PUBLISHER:
Discipline for Research and Development
Clinical Center University of Sarajevo
71000 Sarajevo, Bolnička 25
Bosnia and Herzegovina

For publisher:
Alen Pilav, MD, PhD
General Manager
CCUS

Publishing editor:
Refet Gojak, MD, PhD

AIMS AND SCOPE

The Medical Journal is the official quarterly journal of the Discipline for Research and Development of the Clinical Center University of Sarajevo and has been published regularly since 1994. It is published in the languages of the people of Bosnia and Herzegovina i.e. Bosnian, Croatian and Serbian as well as in English.

The Medical Journal aims to publish the highest quality materials, both clinical and scientific, on all aspects of medicine. It offers the reader a collection of contemporary, original, peer-reviewed papers, professional articles, review articles, editorials, along with special articles and case reports.

EDITORIAL OFFICE

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SUBSCRIPTION

Annual subscription rates: Bosnia and Herzegovina € 50;
Europe € 80; and other € 100.

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ONLINE PUBLISHING

Discipline for Research and Development, CCUS
Online - Open Access

Medical Journal is Indexed in

EBSCO publishing USA
www.ebscohost.com

Member of National Journals Networks of the European Society of Cardiology

This project is supported by the Federal Ministry of Education and Science

EDITORIAL | A New Era for the CCUS: The Largest Post-War Investment in the Institution's History Completed

The Clinical Center University of Sarajevo is set to open the newly constructed and fully equipped facilities of the Central Medical Block (CMB), marking the completion of the largest and most complex post-war investment in the history of this health institution.

As part of the project, approximately 8,000 m² of new hospital space have been built, with a total investment value of BAM 42.3 million. The two newly constructed floors will accommodate four clinics, that have until now operated in buildings more than 130 years old: – Abdominal Surgery Clinic, Gastroenterohepatology Clinic, Urology Clinic with Kidney Transplantation, and Thoracic Surgery Clinic.

The new facilities are designed in accordance with the highest international standards and equipped with modern medical and non-medical equipment. Patients will have access to single, double and triple rooms with private bathrooms, enhanced care units, isolation rooms and minor intervention rooms. Special attention has also been paid to ensuring accessibility for people with mobility impairments.

The project was implemented in extremely complex conditions, while maintaining uninterrupted hospital operations and performing the most complex surgical procedures in the Central Operating Block located directly beneath the newly constructed floors.

In addition to modern inpatient capacities, the project includes a multimedia conference hall, technical support areas, and prayer rooms for all confessions in Bosnia and Herzegovina.

With the opening of new facilities, the CCUS will provide an environment that meets the standards of modern medicine, offering patients and healthcare professionals a safer, more functional, and higher-quality setting for treatment and work. This project represents a major step forward in the development of Bosnia and Herzegovina's healthcare system and marks the beginning of a new chapter in the functioning of the largest healthcare institution in the country.

Editor-in-Chief

Morbidities and Mortality of Late Preterm Infants

Morbiditeti i mortalitet kasnih prematurusa

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ABSTRACT

Introduction: Late preterm infants (LPI) are infants born between 34+0/7 and 36+6/7 weeks of gestation. Due to their size and weight they are often treated as developmentally mature with a low morbidity rate. As a result, they are unjustifiably underestimated and their morbidity and mortality risks are often overlooked. Aim: to present the epidemiological and clinical characteristics LPI, analyze their most common morbidities and mortality, and identify risk factors for the hospitalization in an immediate postnatal period. Materials and methods: A retrospective, descriptive analysis of medical records of patients born as LPI at the Clinic of Gynecology and Obstetrics and hospitalized at Pediatric Clinic of the Clinical Center University of Sarajevo (CCUS) in the period from 1st January 2022 to 31st December 2022. The study included 198 patients. Results: The frequency of LPI in the NICU during the study period was 18.83%. LPI born at 34 weeks of gestation were the most commonly hospitalized (51.35%), and the most common morbidity observed was RDS (21.21%). Association was found between gestational week, birth weight, mother's risk factors, and Apgar score at 1st and 5th minute with the hospitalization at NICU. We found association between the duration of hospitalization, the use of inotropes, and the occurrence of NEC with treatment outcomes. The mortality rate for LPI was 5.41%. Conclusion: Although they account for 5.56% of the total number of births, LPI make up almost one fifth of NICU patients. High-risk pregnancy is a significant predictive factor for their hospitalization in the immediate postnatal period. LPI most often suffer from RDS, and their mortality rate is 5.41%. LPI, regardless of the almost complete maturity, should be viewed in the context of prematurity and the complications it carries.

Keywords: late preterm infant, morbidity, mortality

SAŽETAK

Uvod: Kasni prematurusi (KP) su djeca rođena između 34+0/7 i 36+6/7 sedmica gestacije. Zbog svoje veličine i težine često su tretirani kao razvojni zreli s niskom stopom morbiditeta. Kao rezultat toga, neopravdano su podcijenjeni, a njihovi rizici morbiditeta i mortaliteta često se zanemaruju. Cilj: predstaviti epidemiološke i kliničke karakteristike KP, analizirati njihove najčešće morbiditete i mortalitet te identificirati faktore rizika za hospitalizaciju u neposrednom postnatalnom periodu. Materijali i metode: Retrospektivna, deskriptivna analiza medicinskih kartona pacijenata rođenih kao KP na Klinici za ginekologiju i akušerstvo i hospitaliziranih na Pedijatrijskoj klinici Kliničkog centra Univerziteta u Sarajevu u periodu od 1. januara 2022. do 31. decembra 2022. godine. Studija je obuhvatila 198 pacijenata. Rezultati: učestalost KP u Jedinici neonatalne intenzivne njege tokom perioda istraživanja bila je 18,83%. KP rođeni u 34. sedmici gestacije bili su najčešće hospitalizirani (51,35%), a najčešći uočeni morbiditet bio je RDS (21,21%). Utvrđena je značajna povezanost između gestacijske sedmice, porođajne težine, faktora rizika majke i Apgar skora u 1. i 5. minuti sa hospitalizacijom u Jedinici neonatalne intenzivne njege. Pronašli smo povezanost između trajanja hospitalizacije, upotrebe inotropa i pojave NEC sa ishodima liječenja. Stopa smrtnosti KP bila je 5,41%. Zaključak: Iako čine 5,56% ukupnog broja porođaja, KP čine gotovo petinu pacijenata na odjeljenju neonatalne intenzivne njege. Visokorizična trudnoća je značajan prediktivni faktor za njihovu hospitalizaciju u neposrednom postnatalnom periodu. KP najčešće obolijevaju od RDS-a, a njihova stopa smrtnosti je 5,41%. KP, bez obzira na gotovo potpunu zrelost, treba posmatrati u kontekstu prijevremenog rođenja i komplikacija koje ono nosi.

Ključne riječi: kasni prematurus, morbiditet, mortalitet

INTRODUCTION

The categorization of preterm infants into clearly defined groups is of great importance for risk assessment, monitoring, development of new health guidelines, research, patient care and counseling (1). Neonates born between 34+0/7 and 36+6/7 weeks of gestation (GW), or "late preterm infants" (LPI), account for more than 70% of all preterm infants (2,3), often have the same size and weight as term infants. Because of this fact, LPI are mistakenly treated by parents, caregivers and medical professionals as developmentally mature infants with low morbidity rates (2). However, a large number of studies have shown that this group of infants has a higher rate of morbidity and mortality (1,3). Due to physiological and metabolic immaturity, LPI are at much higher risk than term infants for the development of numerous morbidities, as well as mortality. They have a higher incidence of hospital rehospitalization during their neonatal period compared to term infants (2).

Causes of preterm birth include spontaneous preterm labor, preterm premature rupture of membranes (PPROMs), as well as maternal, placental/uterine, or fetal pathology, increased rates of induction, cesarean section, and changes in maternal demographics (3,4). Assisted reproduction is also known to increase the risk of preterm birth (3). After 34 GW, no effort is generally made to maintain the pregnancy (3,5), as the survival rate of infants born at 34 GW varies by 1% compared to term infants, and that prolonging a pregnancy beyond 34 weeks may expose the mother and fetus to unnecessary risk (3,6-8). Maternal pathology leading to preterm birth includes: hypertensive conditions, preeclampsia, diabetes mellitus, intrahepatic cholestasis and meny others (3,9). The most common placental pathologies are: placenta previa, accreta, percreta or increta; previous uterine rupture; vasa previa; previous cesarean section; and previous myomectomy requiring cesarean section (3,9). Fetal pathological conditions responsible for preterm birth include: oligohydramnios, polyhydramnios, intrauterine growth restriction, multiple pregnancy and alloimmunization, genetic malformations, congenital anomalies (3,9).

Studies show that during the initial postpartum hospitalization, LPI have a 4-fold higher risk of being diagnosed with one medical condition and a 3.5-fold higher risk of being diagnosed with two or more conditions. The most common are: temperature instability, hypoglycemia, respiratory distress, apnea, infection, jaundice, and feeding problems (2,3). The likelihood of readmission for LPI is more than twice that of term infants. The rate of neonatal morbidity doubles for each week of gestation before 38 weeks, and it can be as high as 51% for infants born at 34 weeks (10). For these reasons, institutions around the world have developed specific criteria for discharge of late preterm infants from the maternity ward (2,11). In general, the death rate for LPI is much lower than for extremely preterm infants, but higher than for their full-term peers. Increased mortality includes a higher risk of death during the first weeks of life, the first year after birth, and in later years. However, only a few studies reported specific causes of mortality (12). Among the long-term consequences of interrupted intrauterine maturation are delays in cognitive development and speech and cerebral palsy (12,13), attention deficit hyperactivity disorder (ADHD), autism, difficulties in school, behavioral problems (11,12). Santos et al. concluded that late preterm infants are at a greater risk of being short and underweight at the age of 1 and 2 compared to their peers (14). Also, other medical diagnoses, including diabetes treated with oral antidiabetics or insulin, and hypertension, occur more often in LPI in later stages of life (11).

AIM

The aim of this paper was to present the epidemiological and clinical characteristics of late preterm infants born at the Clinic of Gynecology and Obstetrics, Clinical Center University of Sarajevo (CCUS), in the period from 1 January to 31 December 2022, as well as LPI admitted to the Neonatal Intensive Care Unit of the Pediatric Clinic, NICU-CCUS, in the same period, to determine the frequency of late preterm infants among neonates hospitalized in the NICU-CCUS, to analyze the most common morbidities and mortality of late preterm infants, and to determine risk factors for hospitalization of late preterm infants in the NICU immediately after birth.

MATERIALS AND METHODS

The research includes a retrospective, descriptive analysis of medical records of LPI hospitalized and treated in the NICU-CCUS, as well as medical records of patients hospitalized at the Clinic of Gynecology and Obstetrics of the CCUS over a period of 1 year (1 January to 31 December 2022). During the aforementioned period, a total of 393 patients were hospitalized at the NICU, and the total number of births was 2751. All patients defined as late preterm infants were included in our study, a total of 198 patient. A high-risk pregnancy was defined as a pregnancy in which there was the presence of a pathological entity on the part of the mother, fetus or placenta.

For continuous quantitative variables, the following were determined: arithmetic mean ($\bar{X}$), median (Me), standard deviation (SD). The normality of the distribution was determined by the Shapiro-Wilk test, and statistical significance was tested by an independent t-test (for two groups). For variables that were not normally distributed, statistical significance was tested by the non-parametric Mann-Whitney U (for two groups). Binary logistic regression was performed to identify independent predictors of the outcome. For qualitative variables, the following were determined: frequencies (f), relative frequencies (rf), and statistical significance was tested by the Chi square test. Statistical significance was tested at a significance level of α=0.05.

RESULTS

During the one-year period, a total of 393 admissions to the Neonatal Intensive Care Unit (NICU) were recorded, of which 74 were LPI (18.83%). During the same period, 2751 deliveries were recorded, of which 153 (5.56%) were LPI. Of the 153 LPI, 29 were hospitalized in the NICU. The remaining 45 hospitalized patients in the NICU were preterm infants who were transferred postnatally from other hospitalis. The study also included 124 LPI who did not require transfer to the NICU after delivery. Out of the total number of patients hospitalized in the NICU, 51.35% were born in the 34th week of gestation, 35.14% were born in the 35th week of gestation, and 13.51% were born in the 36th week of gestation. Of the total number of subjects, 103 were male (52.02%), and the predominant mode of delivery was cesarean delivery in 85.86%. Table 1 shows the descriptive statistics of the examined population of late preterm infants.

Table I **Descriptive statistics of the examined population**.

Variable		
Sex, n (%)	Male	103 (52.02)
	Female	95 (47.98)
Delivery mode, n (%)	CS	170 (85.86)
	Vaginal	28 (14.14)
Mode of conception, n (%)	Natural	21 (10.61)
	IVF	177 (89.39)
Antenatal steroids, n (%)	Yes	28 (14.14)
	No	170 (85.86)
PPROM, n (%)	Yes	34 (17.17)
	No	164 (82.83)
Mother's risk factors, n (%)	Yes	66 (33.33)
	No	132 (66.67)
Fetal risk factors, n (%)	Yes	99 (50.00)
	No	99 (50.00)
Placental risk factors, n (%)	Yes	13 (6.57)
	No	185 (93.43)
High-risk pregnancy, n (%)	Yes	146 (73.74)
	No	52 (26.26)
Maternal age, mean ± standard deviation (years)		31.70 ± 5.44
Gestational age, median (IQR) (week)		35.00 (34.00; 36.00)
Birth weight, mean ± standard deviation (grams)		2564.69 ± 561.41
Apgar 1, median (IQR)		9.00 (8.00; 9.00)
Apgar 5, median (IQR)		9.00 (9.00; 10.00)
IUGR, n (%)	Yes	15 (7.58)
	N0	183 (92.42)
Twins, n (%)	Yes	73 (36.87)
	No	125 (63.13)
RDS, n (%)	Yes	42 (21.21)
	No	156 (78.79)
Mechanical ventiltion, n (%)	Yes	7 (3.54)
	No	191 (96.46)
CPAP, n (%)	Yes	42 (21.21)
	No	156 (78.79)
Congenital anomalies, n (%)	Yes	8 (4.04)
	No	190 (95.96)

CS – Cesarean section); IVF – in-vitro fertilisation; IQR – interquartile range; PROM – Premature rupture of membranes; IUGR – intrauterine growth restriction; NICU – neonatal intensive care unit; RDS – respiratory distress syndrome; CPAP – continuos positive airway pressure

The median duration of hospitalization was 9 days. Out of 74 NICU patients 19 (25.68%), brain ultrasound was pathological, and the most common diagnosis was TSV – thalamostriatal vasculopathy. Milder form of IVH (grade 1 and 2) was found in 2 cases. Table 2 shows the morbidities of LPI in NICU.

Table 2 **Morbidities of LPI in NICU.**

Variable		
RDS, n (%)	Yes	42 (56.76)
	No	32 (43.24)
TTN, n (%)	Yes	9 (12.16)
	No	65 (87.84)
PPHN, n (%)	Yes	0 (0)
	No	74 (100)
NEC, n (%)	Yes	2 (2.7)
	No	72 (97.3)
Inotropes, n (%)	Yes	2 (2.7)
	No	72 (97.3)
Outcome, n (%)	Survived	70 (94.59)
	Died	4 (5.41)
Start of feeding, median (IQR) (days)		2.0 (2.0; 3.0)
Full enteral feeding age, median (IQR) (days)		6.0 (5.0; 7.0)
Hospital stay median (IQR) (days)		9.0 (8.5; 16.0)
Brain US, n (%)	Normal	55 (74.32)
	Pathological	19 (25.68)

RDS- Respiratpry distress syndrome, TTN – transient tachypnea of the newborn); PPHN –persistent pulmonary hypertension of the newborn); NEC –necrotizing enterocolitis, US - ultrasound

In the analysis of risk factors for NICU hospitalization, we found a significant influence of gestational age, birth weight, Apgar score at 1 and 5 minutes, use of antenatal steroids (AS), occurrence of risk factors on the part of the mother and fetus, and risky pregnancy. Among the pathological diagnoses of the mother, hypertension stood out as the most common 39.06% p=0.003. Table 3 shows risk factors for hospitalization in NICU.

Table 3 **Risk factors for hospitalization in NICU.**

Variable	Total (N=198)	Maternity ward (n=124)	NICU (n=74)	P-value
Mother's age mean ± sd (years)	31.70 ± 5.44	32.11 ± 5.05	31.30 ± 6.20	0.319
Gestational age median (IQR) (weeks)	35.00 (34.00; 36.00)	35.00 (35.00; 36.00)	34.00 (34.00; 35.00)	<0.001
Birth weight, mean ± sd (grams)	2564.69 ± 561.41	2688.7097 ± 537.7463	2348.6486 ± 566.1582	**<0.001**
Apgar 1, median (IQR)	9.00 (8.00; 9.00)	9.00 (9.00; 10.00)	8.00 (6.00; 9.00)	**<0.001**
Apgar 5, median (IQR)	9.00 (9.00; 10.00)	10.00 (9.00; 10.00)	9.00 (8.00; 9.50)	**<0.001**
Sex				0.658 (0.196)
Male	103	63	40	
Female	95	61	34	
Delivery mode				
CS	170	109	61	0.285 (1.142)
Vaginal	28	15	13	
Antenatal Steroids				
Yes	25	0	25	<0.001 (51.237)
No	167	123	44	
PPROM				0.859 (0.032)
Yes	32	21	11	
No	161	103	58	
Mother's risk factors				
Yes	64	31	33	**0.002 (9.924)**
No	130	93	37	
Fetal risk factors				
Yes	99	54	45	**0.019 (5.524)**
No	99	70	29	
Placental risk factors				
Yes	13	9	4	0.611 (0.259)
No	185	115	70	
Risk pregnancy				
Yes	145	84	61	**0.024 (5.102)**
No	51	38	13	
Birth weight/gestational age				
SGA	19	8	11	0.064 (5.512)
AGA	147	92	55	
LGA	32	24	8	

CS –cesarean section; IVF – in-vitro fertilisation, PROM – premature rupture of membranes; SGA – small for gestational age, AGA –appropriate for gestational age, LAG – large for gestational age

Binary logistic regression analysis found that gestational age has a statistically significant predictive value with a negative coefficient, also the chances of admission to the NICU are 3.599 times higher for newborns from mothers with risk factors. During hospitalization, out of 74 subjects hospitalized in the NICU, in 4 subjects the outcome was fatal (5.41%).

DISCUSSION

In 2022, out of the total number of births at the Clinic of Gynecology and Obstetrics of the CCUS the incidence of late preterm births was 5.56%, which was slightly lower than the incidence reported in the literature 8% (15,16). This discrepancy could be explained by the small sample and short frame of one year in our study. In contrast to the small share of LPI in the total number of live births (5.56%), they account for almost one fifth of all NICU hospitalizations (18.83%). This percentage decreases with increasing gestational age from 51.35% at 34 weeks to 13.51% at 36 weeks of gestation, which is in line with the results of several different studies (17-20). The mortality rate among late preterm infants hospitalized in the NICU in our study was 5.41%, which is much higher than that reported by McIntire DD, et al. (21). The median length of hospitalization, which is 9 days, differs significantly in relation to gestational age, as found in other studies (20,22), and is highest in LPI born at 34 weeks. The predominant mode of delivery was cesarean section in 85.86%, as reported by Tsai ML, et al. and Ma X, et al. (23,24), while others reported vaginal delivery as the dominant mode (25,26). In vitro fertilization as an assisted conception method was recorded in 10.61% of cases.

The mean birth weight of LPI in our study was 2564.69 ± 561.41 grams, similar to the studies (26,27). We demonstrated a significant association between birth weight and NICU hospitalization, which is in line with most similar studies (28,29). The mean Apgar scores at 1 and 5 minutes were 9 in the total population. However, if we only look at those hospitalized in the NICU, the mean Apgar score at 1 minute is 8 and at 5 minutes is 9, which is the same result reported in the study by Wang ML, et al. (26). Twin pregnancy, which itself carries a risk of preterm birth, was present in 36.87% of cases, and a similar result was found by Jefferies et al (29). Contrary to other studies where it is less than 50% (28), the proportion of RDS diagnoses among NICU hospitalizations exceedes 50% (56.76%) most probably due to still insufficient antenatal steroid coverage. As expected, the incidence of RDS increased with decreasing gestational age (45.16% at 34 weeks, 14.71% at 35 weeks, and 5.88% at 36 weeks). Very similar results were found by Madar J, et al. (30), and Ghartey K, et al. (31). The incidence of RDS requiring mechanical ventilation was directly proportional to the degree of maturity: 6.45% at 34 weeks of gestation and 4.41% at 35 weeks of gestation, and no infants born at 36 weeks were on mechanical ventilation. Similar results have been reported in other studies (20). The most significant risk factor from the side of the fetus for hospitalization in the NICU, was lower gestational age. The same results were found in almost all studies that deal with morbidity and hospitalization of LPI (20,21,27). Using binary logistic regression as an independent predictor of admission to the NICU, we found statistical significance in the presence of risk factors on the part of the mother (especially hypertension) that is, newborns of mothers who have any of the risk factors have a 3.599 times greater risk of admission to the NICU, similar to others (20,21).

There are several limitations to this study, including the retrospective nature of data collection, relatively small sample size compared to some other studies, short follow-up period for preterm infants, and focus on a single health center. Multicenter, prospective studies would certainly give much greater strenght to the conclusions.

CONCLUSION

Although they account for only 5.56% of the total number of live births, the prevalence of LPI among NICU hospitalizations was 18.83%, with RDS as the most common morbidity. Risk factors for admission to the NICU are gestational age, birth weight, Apgar score at 1 and 5 minutes, and high-risk pregnancy (the chances of admission to the NICU are 3.599 times higher for late preterm infants whose mothers have any of the risk factors), especially in the presence of maternal hypertension. The mortality rate of late preterm infants hospitalized in the NICU was 5.41%. LPI, regardless of the almost complete maturity, should be viewed in the context of prematurity and the complications it carries.

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Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

The Significance of Video-Assisted Thoracoscopic Surgery in the Surgical Treatment of the Thymus and Thymic Tumors

Značaj videoasistirane torakoskopske hirurgije u hirurškom tretmanu timusa i tumora timusa

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ABSTRACT

Introduction: video-assisted thoracoscopic surgery (VATS) offers distinct advantages over open surgical approaches in the management of thymic diseases, with particular emphasis in treatment of myasthenia gravis (MG). Given the existing controversies, the aim was to provide a clearer understanding of the potential benefits of the VATS approach. Aim: the primary aim was to compare the length of hospital stay and the incidence of postoperative complications between patients undergoing VATS and those treated with conventional open approaches. Moreover, we wanted to assess the impact of the surgical method on symptom regression in patients with MG. Materials and methods: this retrospective, analytical, comparative, and quantitative study included a review of medical records of 32 patients who underwent thoracic surgery between 2015 and 2025. Patients were divided into two groups according to the surgical approach. Results: a higher rate of symptom regression in myasthenia gravis was observed in the VATS group. Among patients with thymic tumors, VATS significantly reduced the length of hospital stay compared to open surgical methods. While no statistically significant difference was found in the incidence of postoperative complications between the groups, hospital stay was significantly shorter in the VATS group. Conclusion: VATS demonstrates significant advantages, particularly in reducing the length of hospital stay in all patients, especially those with thymic tumors. No statistically significant difference was observed in the incidence of postoperative complications between patients treated with VATS and those undergoing conventional surgical approaches. VATS is a safe surgical technique associated with substantially reduced operative trauma, shorter hospital stay, faster postoperative recovery, and earlier return to everyday activities.

Keywords: VATS, thymus, thoracotomy, length of hospital stay, postoperative complications

SAŽETAK

Uvod: video-asistirana torakoskopska hirurgija (VATS) ima određene prednosti u odnosu na otvorene metode u liječenju bolesti timusa, s posebnim fokusom na mijasteniju gravis (MG). Zbog postojećih kontroverzi, cilj je bio pružiti jasniji uvid u potencijalne koristi VATS pristupa. Cilj: primarni cilj je bio uporediti dužinu hospitalizacije i učestalost postoperativnih komplikacija između pacijenata operisanih VATS-om i onih sa konvencionalnim pristupom kao i uticaj hirurške metode na regresiju simptoma kod pacijenata s mijastenijom gravis. Materijali i metode: studija je retrospektivna, analitičko-komparativna i kvantitativna. Obuhvatila je analizu dokumentacije 32 pacijenta operisanih u periodu od 2015. do 2025. godine podijeljenih u dvije grupe. Rezultat: zabilježena je procentualno veća regresija simptoma MG kod VATS pristupa. Kod pacijenata sa tumorima timusa, VATS je značajno skratio dužinu hospitalizacije u odnosu na otvorene hirurške metode. Postoperativne komplikacije nisu bile statistički značajno različite između grupa, ali je hospitalizacija bila statistički značajno kraća kod VATS metode. Zaključak: VATS pokazuje značajne prednosti, posebno u skraćenju hospitalizacije kod svih pacijenata, a posebno pacijenata sa tumorima timusa. Nema statistički značajne razlike učestalosti postoperativnih komplikacija pacijenata koji su operisani VATS i konvencionalnim metodama. VATS je sigurna hirurška metoda koja nudi znatno manju operativnu traumu, skraćuje vrijeme hospitalizacije, dovodi do bržeg postoperativnog oporavka pacijenta i povratka pacijenata u svakodnevne aktivnosti.

Ključne riječi: VATS, timus, torakotomija, dužina hospitalizacije, postoperativne komplikacije

INTRODUCTION

Mediastinal tumors comprise a heterogeneous group of lesions arising within the anterior, middle, or posterior mediastinal compartments, with the anterior mediastinum representing the most frequent anatomical site of occurrence (1). Recent literature indicates that lesions of the anterior mediastinum are associated with a substantial risk of malignancy, particularly thymic epithelial tumors, lymphomas, and germ cell tumors, emphasizing the importance of accurate diagnostic and surgical evaluation (2). Thymic epithelial tumors are considered the most frequent primary neoplasms of the anterior mediastinum and represent a distinct group of rare thoracic malignancies with important diagnostic and therapeutic implications (3).

These tumors vary widely in size, ranging from 1 mm to as large as 30 cm, and in consistency from soft to firm. They are typically encapsulated by a fibrous capsule with internal septations that divide the tumor into lobules, giving rise to a nodular external appearance. Macroscopically, they are usually whitish-yellow in color; on the cut surface, cysts of varying size and characteristics may be observed, often containing fluid, along with areas of necrosis. Such necrotic areas are more commonly associated with malignant tumors, particularly carcinomas, which also tend to exhibit more invasive behavior (4).

Surgical treatment remains a cornerstone in the management of thymic diseases, although it presents a significant clinical challenge. Traditionally, open surgical approaches, particularly median sternotomy, have been regarded as the gold standard in thymic surgery. With technological advancements, minimally invasive techniques such as video-assisted thoracoscopic surgery (VATS) have become increasingly adopted. However, despite these developments, the literature continues to highlight ongoing debate regarding the relative advantages of VATS compared to conventional open approaches in the treatment of thymic diseases.

AIM

The aim of the study was to evaluate the length of hospital stay, postoperative complications, disease status, and potential advantages of two surgical approaches - VATS and conventional open techniques - in patients undergoing surgery for thymic diseases. By analyzing parameters such as the presence and type of myasthenia gravis (MG), acetylcholine receptor antibody levels, clinical symptomatology, and postoperative disease status, this study aimed to assess the extent to which the choice of surgical approach influences symptom regression, disease remission, and the quality of postoperative recovery.

MATERIALS AND METHODS

Study design

This retrospective, observational, analytical-comparative, quantitative study was conducted at the Clinic of Thoracic Surgery, Clinical Center University of Sarajevo, over a ten-year period, from 2015 to 2025. Based on the analysis of medical records of patients who underwent thoracic surgery for thymic disease using either VATS or thoracotomy, the study aimed to evaluate whether there is a statistically significant difference in overall effectiveness and disease outcomes between VATS and conventional surgical approaches.

Continuous variables were expressed as mean ± standard deviation (SD) for data demonstrating normal distribution, whereas variables with non-normal distribution were presented as median values with interquartile range (IQR). Categorical variables were summarized using absolute frequencies and corresponding percentages. Prior to inferential statistical analysis, the distribution of continuous variables was assessed using appropriate tests of normality and graphical evaluation methods.

For comparisons between two independent groups, Student's t-test was applied for normally distributed continuous variables with homogeneity of variance, while the non-parametric Mann-Whitney U test was used for variables that did not meet assumptions of normality. Associations between categorical variables were analysed using the chi-square test, whereas Fisher's exact test was additionally considered in cases of small expected cell frequencies.

A two-tailed p-value <0.01 was considered statistically significant. Compared with the conventionally accepted threshold of $p<0.05$, the adoption of a more stringent significance level was intended to reduce the likelihood of type I error resulting from multiple comparisons and the relatively limited study sample. This approach was selected in order to improve the robustness, internal validity, and overall reliability of the statistical findings, particularly in the context of exploratory subgroup analyses and retrospective data interpretation.

Study population

A total of 32 patients with previously diagnosed thymic disease were included in this study.

Inclusion criteria were: patients with histopathologically confirmed thymic or anterior mediastinal disease; patients with complete medical documentation; patients who underwent surgery using either VATS or conventional open methods; and patients who were followed for a minimum of one month after the surgical procedure.

Group allocation

A total of 32 patients with thymic disease who underwent thoracic surgery were included in this study, divided into the following groups:

- **Group I**: Patients who underwent VATS, either multiportal or uniportal approach;
- **Group II**: Patients who underwent conventional open surgical procedures, including thoracotomy, median sternotomy, and resternotomy.

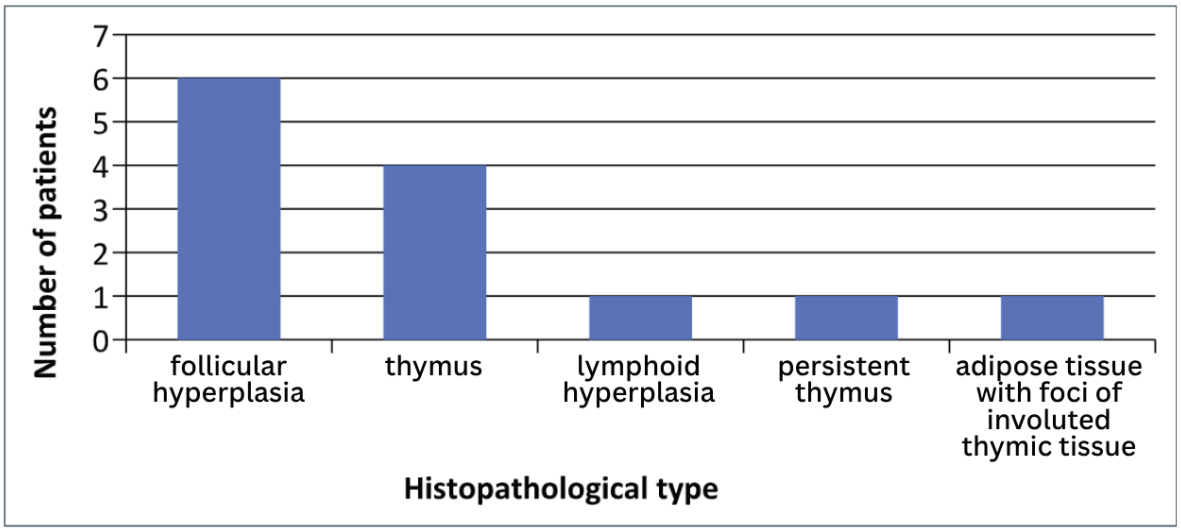
RESULTS

In the period from January 2015 to January 2025, a total of 32 surgical procedures for thymic pathology were performed at the Clinical Center University of Sarajevo. Out of that number, 17 procedures were carried out using a minimally invasive approach, specifically VATS, including eight multiportal and nine uniportal procedures, while 15 procedures were performed using an open approach, comprising nine thoracotomies, five median sternotomies, and one resternotomy. Out of a total of 32 patients, 17 were male and 15 were female, with the highest proportion observed in the age groups 36-46 years (25%) and 47-57 years (25%).

Among 32 patients, the histopathological distribution included 16 thymomas, 10 thymic hyperplasia, two cases of persistent thymus, two thymic carcinomas, one thymic cyst, and one case of adipose tissue with foci of involuted thymic tissue. MG was diagnosed in 13 patients, most commonly in association with follicular hyperplasia (six cases), followed by thymoma (four cases), lymphoid hyperplasia (one case), persistent thymus (one case), and adipose tissue with foci of involuted thymic tissue (one case). Overall, a slightly higher number of procedures were performed using VATS (17) compared to open surgical approaches (15).

Overall, 13 patients were diagnosed with MG. The condition was most frequently associated with follicular hyperplasia (six cases; 46%), followed by thymoma (four cases; 31%), lymphoid hyperplasia (one case; 7%), persistent thymus (one case; 8%), and adipose tissue with foci of involuted thymic tissue (one case; 8%), as demonstrated in Figure 1.

Figure 1 **Distribution of myasthenia gravis across different thymic pathologies.**



To evaluate the effectiveness and potential advantages of any type of surgical approach in the treatment of MG, an analysis was performed using key outcome variables such as length of hospital stay and postoperative complications. These parameters were used as indicators of comparative clinical performance.

Out of 13 patients diagnosed with MG, 10 underwent VATS, while only three were treated using open surgical techniques. The mean length of hospital stay for patients with myasthenia gravis who underwent open surgery was 9.33 days, which was on average approximately two days longer than in the VATS group, with a standard deviation (SD) of 3.21, indicating greater variability in hospitalization duration among these patients. In contrast, patients treated with VATS had a mean hospital stay of 7.30 days, with an SD of 2.03, suggesting a more consistent length of hospitalization across this group (Table 1).

Out of a total of 13 patients with MG, 10 underwent VATS and three were treated with open surgical approaches. Among 10 patients in the VATS group, postoperative complications occurred in three cases, including two minor complications - minimal right-sided apical pneumothorax that did not require active thoracic surgical intervention, and a right pectoral abscess - as well as one severe complication, cardiorespiratory arrest on the third postoperative day followed by coma. The remaining seven patients experienced no postoperative complications.

In the group of patients treated with open surgical methods, only one case was associated with a complication, specifically deep sternal wound infection (DSWI), while the remaining two patients had no postoperative complications. A p-value of 1.00 ($p > 0.01$) indicated that there was no statistically significant difference in the incidence of postoperative complications between the surgical approaches (Table 2).

Table 1 **Mean postoperative hospital stay in patients with myasthenia gravis according to surgical approach.**

Surgical approach	Total number of patients (n)	Mean lenght of hospital stay	Standard deviation (days)	Standard error (days)	95% Confidence interval (days)
VATS	10	7.30	2.03	0.64	5.85 to 8.75
Open approach	3	9.33	3.21	1.85	1.37 to 17.29
Total	13	7.77	2.29	0.64	6.36 to 9.18

$p = 0.39$. There was no statistically significant difference in the length of hospital stay between patients with MG treated with VATS and those treated with open surgical approaches ($p > 0.01$).

Table 2 **Postoperative complications in patients with myasthenia gravis according to surgical approach.**

Surgical approach	No complications	With complications	Total	% of complications
Open approach	2	1	3	33.3%
VATS	7	3	10	30.0%

Another important indication when comparing two surgical approaches refers to the postoperative symptom resolution, i.e., disease status following surgery. A key limitation of this study was small sample size, which was reflected in the absolute numbers: in the open surgery group, one patient showed no improvement and two demonstrated partial regression, with no cases of complete remission or cure. This finding should be interpreted with caution, as it likely reflects the limited sample rather than an inherent inferiority of open techniques.

In contrast, among the 10 patients treated with VATS, five achieved complete remission, whereas four had partial regression, and only two showed no regression. Moreover, in two remaining cases the postoperative status was unknown due to various reasons. A p-value of 0.208 indicates that there was no statistically significant difference between the surgical approaches with respect to postoperative disease status, as demonstrated in Table 3.

Table 3 **Postoperative regression of myasthenia gravis symptoms according to surgical approach.**

Surgical approach	No regression	Partial regression	Unknown status	Complete regression	Total
Open approach	1	2	0	0	3
VATS	1	2	2	5	10
Total	2	4	2	5	13

With regard to patients with thymic tumors, a total of 18 neoplasms were confirmed, including 16 thymomas and two carcinomas. Among thymomas, the most frequent subtype was stage IIa according to the Masaoka–Koga classification, observed in seven patients, followed by stage IIb in six patients. Additionally, 13 of the 18 neoplastic cases occurred in male patients, while only five were female.

Out of 18 patients with thymic tumors, 13 underwent open surgical procedures, whereas five were treated using VATS. The mean length of hospital stay for the five patients treated with VATS was 7.6 days, representing nearly half the duration compared to open surgery, with a standard deviation (SD) of 0.55, indicating low variability and a more uniform length of stay. In contrast, patients treated with open surgical approaches had an average hospital stay of nearly 14 days, with an SD of 4.8, reflecting greater variability in hospitalization duration. A p-value of 0.00072 ($p < 0.01$) indicates a statistically significant difference in the length of hospital stay between patients with thymic tumors treated with VATS and those undergoing open surgical methods (Table 4).

Table 4 **Comparison of postoperative hospital stay in patients with thymic tumors according to surgical approach.**

Surgical approach	Total number of patients (n)	Mean lenght of hospital stay	Standard deviation (days)	Standard error (days)	95% Confidence interval (days)	Upper limit of the 95% Confidence interval
VATS	5	7.6	0.55	0.24	6.92	8.28
Open approach	13	13.58	4.8	1.33	10.67	16.48

$p = 0.00072$. Using analysis of variance (ANOVA), a statistically significant difference was found in the mean length of hospital stay between patients with thymic tumors treated with VATS and those treated with open surgical approaches ($p < 0.01$).

The mean length of hospital stay from admission to surgery, due to preoperative preparation - which included neurological evaluation and pulmonary assessment, and in some cases more extensive radiological diagnostics - ranged from one to three days and was consistent for all patients, regardless of the surgical approach. One the other hand, a statistically significant difference was observed when comparing total hospital stay between patients undergoing VATS and those treated with open surgical techniques. The mean length of hospital stay was shorter in the VATS group, with an average of 7.18 days, compared to 12.53 days in patients treated with open surgery. These findings indicate that the postoperative hospital stay was nearly twice as short in patients undergoing VATS.

In addition, the standard deviation (SD) in the VATS group was 2.038, indicating lower variability and a more uniform length of hospital stay, while the standard error (SE) was also lower, suggesting a more reliable estimate of the mean. In contrast, patients treated with open surgical approaches showed greater variability in hospital stay, as reflected by a higher SD and a higher SE, indicating less precision in the estimation of the mean.

A p-value of < 0.01 confirms that there is a statistically significant difference in the length of hospital stay between patients treated with VATS and those treated with open surgical approaches, as demonstrated in Table 5.

Table 5 **Comparison of postoperative hospital stay between patients undergoing VATS and open surgical**

Surgical approach	Total number of patients (n)	Mean lenght of hospital stay	Standard deviation (days)	Standard error (days)	Lower limit of the 95% Confidence interval	Upper limit of the 95% Confidence interval	Minimum	Maximum
VATS	17	7.18	2.038	0.494	6.13	8.22	4	10
Open approach	15	12.53	5.436	1.404	9.52	15.54	6	28
Total	32	9.69	4.782	0.845	7.96	11.41	4	28

$F=14.28$; $p<0.01$

Using analysis of variance (ANOVA), a statistically significant difference ($p < 0.01$) was found in the length of hospital stay between patients undergoing video-assisted thoracoscopic surgery (VATS) and those treated with open surgical approaches.

DISCUSSION

This study included patients of all age groups and both sexes, comprising a total of 32 patients. Out of that number, 17 were male and 15 were female, indicating a slight predominance of male patients. Similar sex distribution patterns have been reported by Truong Giang Nguyen, Jian-Feng Li, and Guo-Wen Wang (5-7).

Out of 32 patients, 13 had a confirmed diagnosis of myasthenia gravis (MG). The most common thymic pathologies associated with MG were follicular thymic hyperplasia and thymoma, consistent with findings reported by Brascia D, et al., who demonstrated that approximately 40-70% of MG patients had follicular hyperplasia, while 10-21% have thymoma (8).

MG patients were analysed separately from other thymic pathologies given that postoperative neurological recovery and symptom regression represent clinically relevant outcomes that may differ substantially from oncological endpoints observed in thymic tumors without MG. This distinction enabled a more precise assessment of the therapeutic impact of VATS in this specific subgroup.

The mean length of hospital stay in patients with MG who underwent VATS was 7.30 days, compared with 9.33 days in patients treated with open surgical techniques. Similar reductions in hospitalization following minimally invasive thymectomy was also reported in previous studies by Meyer DM, et al.

The shorter postoperative recovery associated with VATS is of particular clinical importance as it may facilitate earlier mobilization, reduce postoperative pain, decrease pulmonary complications, and potentially lower overall healthcare costs.

Postoperative disease status was additionally evaluated through the degree of symptom regression in MG patients. Previous studies demonstrated that patients with thymoma and MG may develop complications such as diaphragmatic paralysis, pneumothorax, pleural effusion, and respiratory insufficiency (9-12).

Among 10 MG patients treated with VATS in our cohort, postoperative complications occurred in three cases. One patient developed a minimal right-sided apical pneumothorax without the need for surgical intervention, while two patients experienced uncommon complications, including cardiorespiratory arrest followed by coma and a right pectoral abscess. Importantly, no procedure-related mortality was observed.

Complete remission was achieved in five of 10 patients treated with VATS, whereas only one patient demonstrated no clinical improvement. Comparable remission rates following minimally invasive thymectomy have also been described by Meyer DM, et al., and Keating CP, et al. (13,14).

Although these findings suggest a potential functional advantage of VATS, interpretation of remission outcomes should be made cautiously due to the limited sample size and the retrospective nature of the study. In addition, the possibility of selection bias must be acknowledged, as patients selected for VATS generally had more favorable anatomical and clinical characteristics, including smaller tumors and lower extent of local invasion.

In the overall cohort, 17 patients underwent VATS and 15 underwent open surgical procedures. Most patients in both groups had an uneventful postoperative course. Statistical analysis demonstrated no significant difference in the overall incidence of postoperative complications between the two surgical approaches. Similar observations were reported by Jurado J, et al. (16). However, some other studies demonstrated significantly lower complication rates following VATS.

Patients treated with VATS had a significantly shorter mean hospital stay compared with patients undergoing open surgery (7.18 vs. 12.53 days; $p < 0.01$).

This finding represents one of the most clinically relevant advantages of minimally invasive surgery, since prolonged hospitalization after thoracic procedures is associated with increased risk of nosocomial infections, delayed rehabilitation, and higher treatment costs.

tomy. Similar conversion rates have been described in previous studies, most commonly due to intraoperative bleeding, large tumor size, or extensive local invasion (17).

The observed conversion rate may additionally reflect the learning-curve effect associated with minimally invasive thymic surgery. VATS thymectomy requires advanced thoracoscopic skills, precise dissection within the anterior mediastinum, and familiarity with complex mediastinal anatomy. Consequently, outcomes such as operative duration, complication rates, and conversion frequency may improve with increasing surgical experience and institutional case volume.

The present study has several limitations, including its retrospective design, relatively small sample size, and single-center setting, which may limit the generalizability of the findings. Nevertheless, the study provides clinically relevant data supporting the feasibility and potential perioperative advantages of VATS in selected patients undergoing thymic surgery.

LIMITATIONS

This study has several limitations that should be acknowledged. Firstly, the retrospective single-center design might have introduced selection bias and limited the generalizability of the findings to other institutions and patient populations. Secondly, the relatively small sample size reduced the statistical power of the analysis, particularly in subgroup comparisons between VATS and open surgical approaches.

In addition, patient selection for VATS was influenced by tumor characteristics, extent of local invasion, and surgeon preference, which might have affected postoperative outcomes and complication rates. The potential impact of the surgical learning curve associated with minimally invasive thymic surgery should also be considered, as increasing institutional and operator experience might influence conversion rates, operative time, and perioperative results.

Finally, long-term oncological and functional outcomes could not be comprehensively assessed due to limited follow-up data. Therefore, larger prospective multicenter studies are required to further validate the observed advantages of VATS in the surgical treatment of thymic diseases.

CONCLUSION

Although patients treated with VATS demonstrated numerically better postoperative symptom regression, these findings should be interpreted cautiously due to the small sample size and limited statistical power. In patients with thymic tumors, VATS significantly reduced the length of hospital stay compared to open surgery, while no significant difference was observed in the incidence of postoperative complications between the two approaches. Overall, our findings suggest that VATS may represent a safe and effective alternative to open surgery in selected patients with thymic disease, particularly concerning postoperative recovery and hospital stay.

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Declaration of patient consent: the author certifies that they obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal.

Authors' contribution: IP, MH, OČ, AA-P and FZ gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial support and sponsorship: nil.

Conflict of interest: there are no conflicts of interest.

The Impact of Lower Gestational Age and Postnatal Weight Loss on Postnatal Bilirubin Levels in Term Newborns

Uticaj niže gestacijske dobi i postnatalnog gubitka na tjelesnoj masi na postnatalne vrijednosti bilirubina kod terminske novorođenčadi

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ABSTRACT

Introduction: Neonatal hyperbilirubinemia is one of the most common conditions requiring medical evaluation and hospitalization during the early neonatal period. Significant hyperbilirubinemia remains the leading cause of rehospitalization among term neonates after early discharge from maternity hospitals. Early identification of risk factors is essential for timely treatment and prevention of bilirubin-induced neurological complications. Aim: to evaluate the clinical characteristics and risk factors associated with intensified hyperbilirubinemia in term neonates. Materials and Methods: A retrospective-prospective observational study was conducted at the Department of Neonatology and Neonatal Intensive Care of the Clinical Center University of Sarajevo. The study included 50 term neonates hospitalized due to intensified hyperbilirubinemia in the period from 1 June 2025 to 31 January 2026. Intensified hyperbilirubinemia was defined as total serum bilirubin >255 μmol/L after discharge from the maternity hospital. Demographic, perinatal and clinical data were analyzed, including gestational age, birth weight, postnatal weight loss, mode of delivery, bilirubin levels, duration of phototherapy and hospitalization. Statistical analysis was performed using descriptive and inferential statistical methods, with $p<0.05$ considered statistically significant. Results: The mean maximal serum bilirubin level was 327 ± 51 μmol/L. Neonates with postnatal weight loss >10% had significantly higher bilirubin levels compared to neonates with weight loss ≤10% (358 ± 44 μmol/L vs. 301 ± 36 μmol/L; $p<0.001$). They also demonstrated earlier onset of jaundice, longer duration of phototherapy and prolonged hospitalization. Neonates with gestational age 37–38 weeks had higher maximal bilirubin values compared to neonates aged 39-40 weeks (341 ± 46 μmol/L vs. 296 ± 38 μmol/L). Logistic regression analysis identified postnatal weight loss >10% (OR 4.8; 95% CI 1.6–14.2; $p=0.004$) and gestational age 37–38 weeks (OR 3.2; 95% CI 1.1–9.5; $p=0.031$) as significant risk factors for severe hyperbilirubinemia (>340 μmol/L). Conclusion: Postnatal weight loss greater than 10% and lower gestational age within the term range were significantly associated with severe neonatal hyperbilirubinemia. Careful monitoring of body weight, breastfeeding adequacy and bilirubin levels in early-term neonates may contribute to earlier recognition and timely treatment of hyperbilirubinemia, thereby reducing the risk of severe complications.

Keywords: neonatal hyperbilirubinemia, term neonates, postnatal weight loss, risk factors

SAŽETAK

Uvod: Neonatalna hiperbilirubinemija predstavlja jedno od najčešćih stanja koje zahtijeva medicinski nadzor i hospitalizaciju tokom ranog neonatalnog perioda. Značajna hiperbilirubinemija i dalje je najčešći razlog rehospitalizacije terminske novorođenčadi nakon ranog otpusta iz porodilišta. Pravovremeno prepoznavanje faktora rizika od velikog je značaja za rano liječenje i prevenciju bilirubin-indukovanih neuroloških komplikacija. Cilj: ispitati klinička obilježja i faktore rizika povezane sa intenziviranom hiperbilirubinemijom kod terminske novorođenčadi. Materijali i metode: Provedeno je retrospektivno-prospektivno opservaciono istraživanje na Odjelu neonatologije i neonatalne intenzivne njege Pedijatrijske klinike Kliničkog centra Univerziteta u Sarajevu. U istraživanje je uključeno 50 terminskih novorođenčadi hospitaliziranih zbog intenzivirane hiperbilirubinemije u periodu od 1. juna 2025. do 31. januara 2026. godine. Intenzivirana hiperbilirubinemija definisana je kao koncentracija ukupnog serumskog bilirubina >255 μmol/L nakon otpusta iz porodilišta. Analizirani su demografski, perinatalni i klinički podaci, uključujući gestacijsku dob, porođajnu masu, postnatalni gubitak tjelesne mase, način poroda, vrijednosti bilirubina, trajanje fototerapije i hospitalizacije. Statistička analiza provedena je primjenom deskriptivnih i inferencijalnih statističkih metoda, uz nivo statističke značajnosti $p<0,05$. Rezultati: Prosječna maksimalna vrijednost serumskog bilirubina iznosila je 327 ± 51 μmol/L. Novorođenčad sa postnatalnim gubitkom tjelesne mase >10% imala su značajno više vrijednosti bilirubina u odnosu na novorođenčad sa gubitkom tjelesne mase ≤10% (358 ± 44 μmol/L prema 301 ± 36 μmol/L; $p<0,001$). Također su imali raniju pojavu žutice, duže trajanje fototerapije i produženu hospitalizaciju. Novorođenčad gestacijske dobi 37–38 sedmica imala su više maksimalne vrijednosti bilirubina u poređenju sa novorođenčadi gestacijske dobi 39-40 sedmica (341 ± 46 μmol/L prema 296 ± 38 μmol/L). Logistička regresiona analiza pokazala je da su postnatalni gubitak tjelesne mase >10% (OR 4,8; 95% CI 1,6–14,2; $p=0,004$) i gestacijska dob 37–38 sedmica (OR 3,2; 95% CI 1,1–9,5; $p=0,031$) značajni faktori rizika za razvoj teške hiperbilirubinemije (>340 μmol/L). Zaključak: Postnatalni gubitak tjelesne mase veći od 10% i niža gestacijska dob unutar terminskog raspona značajno su povezani sa razvojem težih oblika neonatalne hiperbilirubinemije. Pažljivo praćenje tjelesne mase, uspješnosti dojenja i vrijednosti bilirubina kod rizične novorođenčadi može omogućiti ranije prepoznavanje hiperbilirubinemije i pravovremeno liječenje, čime se smanjuje rizik od ozbiljnih komplikacija.

Ključne riječi: neonatalna hiperbilirubinemija, terminska novorođenčad, postnatalni gubitak tjelesne mase, faktori rizika

INTRODUCTION

Neonatal jaundice is the most common condition requiring medical supervision and monitoring during the early neonatal period (1,2,3). Neonatal hyperbilirubinemia is an extremely common occurrence, as nearly every newborn develops elevated levels of unconjugated serum bilirubin during the first week of life, while clinically visible jaundice occurs in approximately 60% of term and up to 80% of preterm newborns (2,4).

Although in most cases it is a physiological and transient condition, a certain number of newborns develop significant hyperbilirubinemia requiring hospitalization and phototherapy (1,5). In recent decades, early discharge of healthy term newborns from maternity hospitals has become common practice for medical, economic, and social reasons. However, hyperbilirubinemia remains the most frequent cause of rehospitalization during the early neonatal period (3,6).

Rehospitalization due to hyperbilirubinemia not only represents an additional financial burden for the healthcare system and the family, but may also negatively affect the establishment of breastfeeding, increase parental stress, and expose the newborn to the hospital environment (4,7). Therefore, in recent years, special attention has been focused on the early identification of newborns at increased risk of developing severe hyperbilirubinemia and bilirubin-induced neurological dysfunction (1,8).

Current guidelines recommend routine bilirubin monitoring during the first 24–48 hours of life, as well as assessment of perinatal and neonatal risk factors prior to discharge from the maternity hospital (1,5,9,10). Among the most important risk factors are lower gestational age within the term range, significant postnatal weight loss, difficulties in establishing breastfeeding, hemolytic disease, and increased enterohepatic circulation of bilirubin (2,11).

Particular importance is attributed to postnatal weight loss, which is often associated with insufficient milk intake and dehydration during the first days of life. Inadequate enteral intake may increase enterohepatic recirculation of bilirubin and contribute to the development of more pronounced unconjugated hyperbilirubinemia (6,12). Furthermore, newborns of lower gestational age within the term period show a greater tendency to develop hyperbilirubinemia due to the relative immaturity of hepatic enzymes responsible for bilirubin conjugation (2,11).

Timely identification of at-risk newborns enables early initiation of therapeutic measures, reduction in the need for rehospitalization, and prevention of serious complications, including acute bilirubin encephalopathy and kernicterus (1,5). Therefore, investigating the clinical characteristics and risk factors associated with intensified hyperbilirubinemia in term newborns is of great importance for improving neonatal healthcare and reducing hyperbilirubinemia-related morbidity.

MATERIALS AND METHODS

Study Design

A retrospective-prospective observational clinical study was conducted at the Department of Neonatology and Neonatal Intensive Care, Pediatric Clinic, Clinical Center University of Sarajevo.

Participants and Study Period

A total of 50 term newborns hospitalized due to intensified hyperbilirubinemia were included in the study during the period from June 1, 2025, to January 31, 2026.

Data were collected through analysis of medical records and patient histories of newborns treated at the Department of Neonatology and Neonatal Intensive Care of the Pediatric Clinic, CCUS.

Significant neonatal hyperbilirubinemia was defined as bilirubin levels requiring hospitalization and phototherapy according to the infant's postnatal age, gestational age, and current clinical guidelines. In most cases included in this study, total serum bilirubin values exceeded 255 μmol/L after discharge from the maternity hospital.

Inclusion Criteria

The study included:

- term newborns with gestational age ≥37 weeks,
- newborns hospitalized due to intensified hyperbilirubinemia.

Exclusion Criteria

The following were excluded from the study:

- preterm newborns (<37 gestational weeks),
- term newborns with congenital anomalies,
- newborns with systemic infections and sepsis.

Data Collection

The following data were collected from medical records:

- newborn sex,
- age at admission expressed in days of life,
- primary diagnosis of intensified or prolonged hyperbilirubinemia,
- associated diagnoses at hospitalization,
- total serum bilirubin values,
- need for phototherapy and duration of phototherapy,
- birth weight,
- body weight at hospital admission,
- percentage of postnatal weight loss,
- mode of delivery,
- gestational age,
- length of hospitalization,

Statistical Analysis

Data were analyzed using descriptive and inferential statistical methods. Categorical variables were presented as frequencies and percentages, while continuous variables were presented as mean ± standard deviation or median with interquartile range, depending on data distribution. Student's t-test or Mann–Whitney U test was used for comparison of continuous variables, while the χ^2 test was used for categorical variables. Statistical significance was defined as $p < 0.05$.

Ethical Considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The confidentiality of all participants' data was fully protected throughout the study.

RESULTS

Characteristics of the Participants

A total of 50 term newborns hospitalized due to intensified hyperbilirubinemia were included in the study. Demographic, perinatal, and clinical characteristics of the participants were analyzed, including gestational age, mode of delivery, birth weight, postnatal weight loss, and total serum bilirubin values.

Bilirubin Levels and Weight Loss

Newborns with postnatal weight loss greater than 10% had significantly higher total serum bilirubin levels compared to newborns whose weight loss was less than 10%. In addition, hyperbilirubinemia occurred earlier in this group and more frequently required prolonged phototherapy.

Gestational Age and Hyperbilirubinemia

Lower gestational age within the term range was associated with higher bilirubin values and a greater incidence of intensified hyperbilirubinemia. Newborns born during the early-term period showed a greater need for hospitalization and longer treatment duration.

Mode of Delivery and Clinical Course

Analysis of the mode of delivery demonstrated differences in the incidence and severity of hyperbilirubinemia between newborns delivered vaginally and those delivered by cesarean section, with a more frequent occurrence of significant weight loss among exclusively breastfed newborns.

Treatment Outcomes

Most newborns were successfully treated with phototherapy without the development of severe neurological complications. Length of hospitalization was longer in newborns with higher bilirubin levels and greater postnatal weight loss.

Final Findings

The study results indicate that greater postnatal weight loss and lower gestational age are significant factors associated with more severe forms of neonatal hyperbilirubinemia in term newborns.

Table 1 **Demographic and perinatal characteristics of term newborns included in the study.**

Variable	Total (n=50)
Male sex, n (%)	28 (56.0)
Female sex, n (%)	22 (44.0)
Gestational age (weeks), mean ± SD	38.4 ± 1.1
Birth weight (g), mean ± SD	3320 ± 420
Age at admission (days), median (IQR)	4 (3–6)
Vaginal delivery, n (%)	31 (62.0)
Cesarean section, n (%)	19 (38.0)

Table 2 **Clinical characteristics and treatment outcomes of neonatal hyperbilirubinemia**

Variable	Value
Total bilirubin at admission (µmol/L), mean ± SD	298 ± 42
Maximum bilirubin (µmol/L), mean ± SD	327 ± 51
Prolonged hyperbilirubinemia, n (%)	11 (22.0)
Need for phototherapy, n (%)	50 (100)
Duration of phototherapy (days), mean ± SD	2.8 ± 1.1
Length of hospitalization (days), mean ± SD	4.1 ± 1.6

Table 3 **Comparison of bilirubin levels and clinical outcomes according to postnatal weight loss.**

Variable	Weight loss ≤10% (n=32)	Weight loss >10% (n=18)	p
Maximum bilirubin (µmol/L), mean ± SD	301 ± 36	358 ± 44	<0.001
Age at onset of jaundice (days), mean ± SD	4.6 ± 1.2	3.2 ± 0.9	0.002
Duration of phototherapy (days), mean ± SD	2.3 ± 0.8	3.7 ± 1.0	<0.001
Length of hospitalization (days), mean ± SD	3.5 ± 1.1	5.2 ± 1.4	<0.001

Table 4 **Maximum bilirubin levels by gestational age group.**

Gestational age	n	Maximum bilirubin (µmol/L), mean ± SD	p value
37–38 weeks	24	341 ± 46	
39–40 weeks	26	296 ± 38	<0.001

Table 5 **Comparison of hyperbilirubinemia characteristics according to mode of delivery.**

Variable	Vaginal delivery (n=31)	Cesarean section (n=19)	p
Maximum bilirubin (µmol/L)	334 ± 49	315 ± 43	0.118
Weight loss >10%, n (%)	15 (48.4)	3 (15.8)	0.021
Duration of phototherapy (days)	3.1 ± 1.2	2.4 ± 0.9	0.041

Table 6 **Factors associated with severe hyperbilirubinemia (>340 µmol/L).**

Risk factor	OR	95% CI	p
Weight loss >10%	4.8	1.6–14.2	0.004
Gestational age 37–38 weeks	3.2	1.1–9.5	0.031
Vaginal delivery	1.9	0.7–5.6	0.182
Male sex	1.3	0.4–4.1	0.644

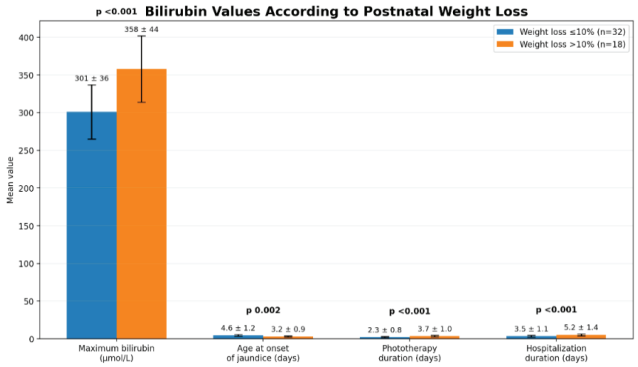

Figure 1 **Comparison of bilirubin levels and clinical outcomes according to postnatal weight loss in term neonates.**

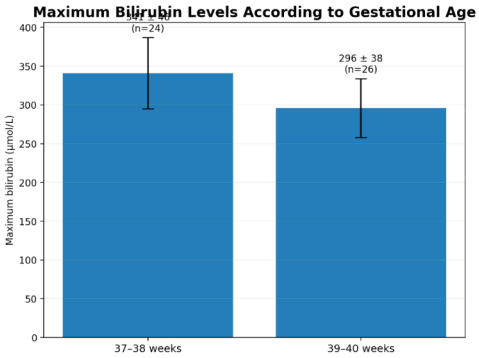

Figure 2 **Comparison of maximum bilirubin levels gestational age in term neonates.**

DISCUSSION

The results of this study showed that postnatal weight loss greater than 10% and lower gestational age within the term range were significantly associated with higher serum bilirubin levels and more severe forms of neonatal hyperbilirubinemia. The obtained findings confirm the importance of early identification of at-risk newborns in order to initiate timely treatment and prevent possible bilirubin neurotoxic complications (1,4,10).

The demographic and perinatal characteristics of the participants are presented in Table 1. In our study, the majority of participants were male newborns (56%), while the mean gestational age was 38.4 ± 1.1 weeks. A greater number of newborns were delivered vaginally (62%), which is consistent with epidemiological data from similar neonatal studies (4,12).

The clinical characteristics of hyperbilirubinemia are presented in Table 2. The mean maximum bilirubin value was 327 ± 51 μmol/L, indicating that most newborns developed clinically significant hyperbilirubinemia requiring hospitalization and phototherapy. The need for phototherapy was present in all participants, while the mean duration of treatment was 2.8 ± 1.1 days. These results are consistent with contemporary studies reporting that hyperbilirubinemia remains one of the most common causes of rehospitalization of term newborns after early discharge from maternity hospitals (1,3,5,7).

A particularly important finding of our study is the association between greater postnatal weight loss and the severity of hyperbilirubinemia. As shown in Table 3 and Figure 3, newborns with weight loss greater than 10% had significantly higher maximum bilirubin levels (358 ± 44 μmol/L vs. 301 ± 36 μmol/L; p<0.001), earlier onset of jaundice, longer duration of phototherapy, and prolonged hospitalization. These findings support previously published results indicating that dehydration and insufficient enteral intake increase enterohepatic circulation of bilirubin and contribute to the development of more pronounced unconjugated hyperbilirubinemia (6,12). Clinically, significant weight loss is often associated with difficulties in establishing breastfeeding and inadequate milk intake during the first days of life (4,10).

Bilirubin values according to gestational age are presented in Table 4 and Figure 4. Newborns with gestational age of 37–38 weeks had higher maximum bilirubin values compared to newborns with gestational age of 39–40 weeks. This finding may be explained by the relative functional immaturity of hepatic enzymes responsible for bilirubin conjugation in early-term newborns, as well as increased enterohepatic circulation of bilirubin in this population (1,12).

The analysis of mode of delivery is presented in Table 5. The results showed a higher incidence of postnatal weight loss >10% among newborns delivered vaginally compared to those delivered by cesarean section. Although the difference in maximum bilirubin values between these two groups did not reach statistical significance, newborns delivered vaginally required a longer duration of phototherapy. A possible explanation for these findings is the earlier establishment of exclusive breastfeeding after vaginal delivery, which in some cases may be associated with insufficient fluid intake during the first days of life (4,10).

Factors associated with severe hyperbilirubinemia (>340 μmol/L) are presented in Table 6. Logistic regression analysis showed that weight loss >10% was the strongest predictive factor for the development of severe hyperbilirubinemia, with an odds ratio of 4.8. Additionally, gestational age of 37–38 weeks was significantly associated with an increased risk of developing more severe forms of hyperbilirubinemia. These results have important practical value, as they enable identification of newborns requiring more intensive monitoring after discharge from the maternity hospital (1,5,10).

In our study, there were no severe neurological complications or need for exchange transfusion, which likely reflects timely recognition and adequate treatment of hyperbilirubinemia. Nevertheless, the fact that hyperbilirubinemia was the most common reason for rehospitalization confirms the need for organized postnatal follow-up, especially in newborns discharged early from maternity hospitals (3,4,5).

The limitations of this study include the relatively small sample size and the retrospective study design, which may affect the generalizability of the results. In addition, not all potential etiological factors of hyperbilirubinemia were analyzed, such as maternal and neonatal blood groups, Coombs test results, or feeding method after discharge. Despite these limitations, the study results clearly indicate the importance of postnatal weight loss and lower gestational age as significant risk factors for the development of intensified hyperbilirubinemia in term newborns (1,12).

Based on the obtained results, it can be concluded that careful monitoring of body weight, assessment of breastfeeding success, and early bilirubin screening in newborns with lower gestational age may contribute to earlier recognition of hyperbilirubinemia and reduction of the risk of severe complications (1,4,10).

CONCLUSION

Postnatal weight loss greater than 10% and lower gestational age within the term range were significantly associated with more severe neonatal hyperbilirubinemia in term newborns. Early-term newborns and neonates with excessive weight loss may require closer postnatal monitoring, including assessment of body weight and bilirubin levels. Early recognition and timely treatment of hyperbilirubinemia may reduce rehospitalization and prevent bilirubin-induced neurological complications.

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Declaration of patient consent: the author certifies that they obtained all appropriate patient consent forms. In the form, the patients have given their consent for the images and other clinical information to be reported in the journal.

Authors' contributions: AH, ĐŠ, SB and EH gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial support and sponsorship: nil.

Conflict of interest: there are no conflicts of interest.

Relationship Between Subjective Symptoms and Objective Neurophysiological Findings in Diabetic Polyneuropathy: A Cross-Sectional Study at the Clinical Center University of Sarajevo

Odnos subjektivnih simptoma i objektivnih neurofizioloških nalaza dijabetičkoj polineuropatiji: presječna studija u Kliničkom centru Univerziteta u Sarajevu

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ABSTRACT

Introduction: diabetic polyneuropathy (DPN) is a common complication of diabetes mellitus and a major cause of morbidity. A frequent challenge is the mismatch between subjective symptoms and objective neurophysiological findings: some patients show electrophysiological abnormalities before symptoms, while others report symptoms despite normal nerve conduction studies. Aim: to evaluate the correlation between subjective neuropathic symptoms and objective neurophysiological findings in diabetic polyneuropathy, and to compare these parameters between type 1 and type 2 diabetes groups. Materials and methods: we analyzed 150 subjects: 90 diabetic patients (60 with type 2 diabetes 30 with ≤5 years and 30 with 5-10 years of disease and 30 with type 1 diabetes) and 60 non-diabetic controls. All participants underwent structured symptom assessment and comprehensive electromyoneurography (EMNG). Results: diabetic patients showed significant neurophysiological impairment compared to controls (all p<0.001), including prolonged latencies, reduced conduction velocities, and decreased amplitudes. Abnormalities were more frequent and pronounced in type 2 diabetes, particularly with longer disease duration, while type 1 patients had relatively preserved EMNG findings. Symptoms did not always match EMNG results: many diabetics had abnormal EMNG with minimal symptoms, and some symptomatic patients especially in early disease had normal or only mildly altered EMNG. Tingling sensations were significantly more common in type 2 than in type 1 diabetes (p=0.004), paralleling higher rates of abnormal nerve conduction. Conclusion: There is a frequent dissociation between clinical symptoms and objective neuropathy in diabetes. Type 2 patients develop earlier and more severe abnormalities than type 1. These findings support early neurophysiological screening, even in asymptomatic patients, to detect subclinical neuropathy and enable timely intervention.

Keywords: diabetic polyneuropathy; diabetic neuropathy; nerve conduction study (NCS); electromyography (EMG); subjective symptoms; type 1 vs type 2 diabetes; subclinical neuropathy

SAŽETAK

Uvod: dijabetička polineuropatija (DPN) jedna je od najčešćih komplikacija šećerne bolesti i značajan uzrok morbiditeta. Čest je nesklad između subjektivnih simptoma i objektivnih neurofizioloških nalaza: kod nekih pacijenata se elektrofiziološke promjene javljaju prije simptoma, dok drugi imaju tegobe uz uredne nalaze provodljivosti živaca. Cilj: procijeniti korelaciju između subjektivnih neuropatskih simptoma i objektivnih neurofizioloških nalaza kod dijabetičke polineuropatije te uporediti te parametre između grupa s dijabetesom tipa 1 i tipa 2. Materijali i metode: Analizirano je 150 ispitanika: 90 dijabetičara (60 s dijabetesom tipa 2 – 30 s trajanjem ≤5 godina i 30 s trajanjem 5-10 godina, te 30 s dijabetesom tipa 1) i 60 kontrola bez dijabetesa. Svi su prošli strukturiranu procjenu simptoma i sveobuhvatnu elektromioneurografiju (EMNG). Rezultati: dijabetičari su imali značajno lošije neurofiziološke parametre u odnosu na kontrole (svi p<0,001), uključujući produžene latencije, smanjene brzine provođenja i niže amplitude. Promjene su bile češće i izraženije kod dijabetesa tipa 2, naročito s dužim trajanjem bolesti, dok su kod tipa 1 nalazi bili relativno očuvani. Simptomi nisu uvijek odgovarali EMNG nalazima: mnogi dijabetičari imali su patološki EMNG uz minimalne tegobe, dok su neki simptomatski pacijenti - posebno u ranoj fazi bolesti – imali uredan ili blago promijenjen EMNG. Trnjenje je bilo značajno češće kod tipa 2 nego kod tipa 1 (p=0,004), paralelno s većom učestalošću poremećaja provodljivosti. Zaključak: Postoji čest nesklad između kliničkih simptoma i objektivnih dokaza neuropatije kod dijabetesa. Pacijenti s dijabetesom tipa 2 razvijaju ranije i teže promjene nego oni s tipom 1. Ovi nalazi naglašavaju važnost ranog neurofiziološkog skrininga, čak i kod asimptomatskih bolesnika, radi otkrivanja subkliničke neuropatije i pravovremene intervencije.

Ključne riječi: dijabetička polineuropatija, dijabetička neuropatija, ispitivanje provodljivosti živaca (NCS), elektromiografija (EMG), subjektivni simptomi, dijabetes tipa 1 naspram tipa 2, subklinička neuropatija

INTRODUCTION

Diabetic polyneuropathy (DPN) is a distal, symmetric sensorimotor polyneuropathy and one of the most common chronic complications of diabetes mellitus. It is considered a mixed axonal and demyelinating neuropathy resulting from hyperglycemia-induced metabolic and microvascular changes in peripheral nerves. Clinically, DPN usually develops gradually and presents with distal numbness, tingling ("pins-and-needles"), burning pain, or weakness in a length-dependent distribution. Loss of ankle reflexes and vibration sense are common objective findings. If left unrecognized, DPN may lead to serious complications, including foot ulceration and amputation; therefore, early detection remains an important component of diabetes care (1).

A major challenge in clinical practice is the frequent discrepancy between subjective symptoms and objective neurophysiological findings. DPN may be present even in asymptomatic individuals, while nerve conduction abnormalities can be detected before clinical symptoms become evident. Conversely, some patients report neuropathic complaints despite normal nerve conduction studies (NCS), particularly in early small-fiber neuropathy. Reliance on symptoms alone may therefore result in underdiagnosis or misjudgment of neuropathy severity. Dyck et al. reported that neuropathic symptoms and signs accounted for only 5–25% of the variance in nerve conduction measures, highlighting the often-weak correlation between clinical and electrophysiological assessments. These observations support a combined clinical and neurophysiological approach to DPN diagnosis(2-3).

Another important consideration is the difference in neuropathy manifestation between type 1 and type 2 diabetes. Patients with type 2 diabetes may experience prolonged periods of undetected hyperglycemia, and electrophysiological evidence of neuropathy can be present even at the time of diagnosis. In contrast, neuropathy in type 1 diabetes typically develops after years of chronic hyperglycemia and is more closely associated with disease duration and glycemic control. Epidemiological studies have shown that DPN prevalence increases with age and diabetes duration in both types but tends to be higher in type 2 diabetes. These differences warrant direct comparison of subjective symptoms and objective neurophysiological findings between patients with type 1 and type 2 diabetes (4).

This study aimed to explore the relationship between subjective neuropathic symptoms and objective neurophysiological findings in diabetic polyneuropathy, with particular emphasis on differences between type 1 and type 2 diabetes. Understanding the discordance between symptomatology and nerve conduction results may contribute to improved diagnostic accuracy and patient management.

AIM

The aim of this study was to evaluate the correlation between subjective neuropathic symptoms and objective neurophysiological findings in diabetic polyneuropathy, and to compare these parameters between type 1 and type 2 diabetes groups. We seek to determine to what extent patients' reported symptoms such as tingling and numbness align with electromyoneurographic (EMNG) measures of nerve function (latencies, conduction velocities, amplitudes), and to highlight any delay or absence of clinical symptoms despite clear pathological findings on EMNG and vice versa. This investigation also examines differences in neuropathy prevalence and severity between type 1 and type 2 diabetics, given their distinct disease characteristics.

MATERIALS AND METHODS

This research was designed as a prospective, observational case series with a comparative analysis. A total of 150 subjects were enrolled. The diabetic cohort consisted of 90 patients with diabetes mellitus, subdivided into three groups of 30 based on diabetes type and duration: Group 1 included 30 patients with type 2 diabetes of short duration (≤5 years since diagnosis); Group 2 included 30 patients with type 2 diabetes of moderate duration (5–10 years); Group 3 included 30 patients with type 1 diabetes of varying disease duration. Additionally, 60 age-appropriate individuals without diabetes or neuropathy constituted the control group. Controls were selected from patients referred for EMNG evaluation of conditions not involving peripheral polyneuropathy (e.g. radiculopathies or musculoskeletal complaints) and had no history or signs of diabetes or generalized neuropathy. All participants provided informed consent, and the study was approved by the local institutional review board, in compliance with the Declaration of Helsinki.

Diabetic patients of both sexes, aged over 18, who were referred for routine EMNG analysis by their treating physicians, were eligible for inclusion. Each diabetic subject had a confirmed diagnosis of type 1 or type 2 diabetes. Subjects were required to be able to provide reliable answers to symptom questionnaires and cooperate with the examination procedures. Exclusion criteria included the presence of other causes of polyneuropathy (e.g. alcoholism, vitamin deficiencies, renal failure, thyroid dysfunction), acute illnesses or metabolic derangements that could affect nerve function, severe psychiatric conditions interfering with evaluation, or incomplete data. Any patient with an acute diabetic decompensation or other severe comorbidity at the time of testing was deferred until stabilization.

All enrolled subjects underwent a thorough clinical assessment by a neurologist. A structured questionnaire and interview were used to document subjective neuropathic symptoms, specifically focusing on distal extremity sensory disturbances. Patients were asked about the presence of tingling, numbness, burning pain, "pins-and-needles" sensations, nocturnal cramps, and any weakness in the legs or feet. Symptom onset, duration, and severity were noted. A standardized neurological examination was performed, emphasizing lower limb findings. Deep tendon reflexes especially ankle jerks were tested and graded, and sensory testing for vibration and pinprick was conducted in the feet. This clinical evaluation allowed classification of patients as having symptomatic vs. asymptomatic neuropathy, and provided an objective neuropathy score based on signs (though formal scoring scales were not explicitly used, reflex status and sensory loss were qualitatively noted).

Subsequently, all subjects underwent electromyoneurography, comprising nerve conduction studies (NCS) and electromyography as needed. Standardized NCS were performed using surface stimulation and recording electrodes at skin temperature of approximately 32–33°C. Motor conduction studies were carried out on the median and ulnar nerves (upper limbs), and the peroneal (fibular) and tibial nerves (lower limbs). For each motor nerve, distal latency (ms), compound muscle action potential (CMAP) amplitude (mV), and motor conduction velocity (m/s) were measured using conventional techniques (e.g. stimulating at the wrist/ankle and knee/elbow for proximal segments). Sensory conduction studies were performed for the median and ulnar nerves (antidromic or orthodromic recording in the hand) and for the sural nerve (calf to ankle). Sensory distal latency (ms), sensory nerve action potential (SNAP) amplitude (μV), and sensory conduction velocity (m/s) were recorded. Late responses were also assessed: F-wave latencies were obtained for the tibial and peroneal nerves (and median/ulnar nerves in some cases) by recording minimal F latency (ms) from a series of supramaximal stimulations. Additionally, the H-reflex (reflecting the S1 reflex arc via the tibial nerve) was elicited from

the soleus muscle to evaluate tibial nerve proximal conduction and reflex pathway integrity.

All EMNG tests were conducted using standard electromyography equipment in the EMG laboratories of the Neurology Clinic, Clinical Center University of Sarajevo, by experienced clinical neurophysiologists. The examiners were blinded to the patients symptom status to reduce bias in interpretation. Definition of Neuropathy: For analysis, an EMNG finding was considered "pathological" or indicative of neuropathy if any measured parameter lay outside the normal reference range for our lab (adjusted for age and limb temperature). In particular, prolonged distal latency, slowed conduction velocity, reduced CMAP or SNAP amplitude, absent response, or prolonged F-wave latency were considered abnormal signs of neuropathy. A diagnosis of polyneuropathy was made if multiple nerve tests were abnormal in a length-dependent pattern (e.g. abnormalities in both lower limbs, or both sensory and motor deficits distal>proximal).

Data from symptom questionnaires, clinical exams, and EMNG results were recorded and grouped by cohort (control vs. diabetes; and by diabetes type/duration group). We performed descriptive statistics for key variables. Group comparisons (e.g. each diabetic group vs. controls, and between the three diabetic subgroups) were done using appropriate statistical tests. Continuous EMNG measures (latencies, velocities, amplitudes) were compared using Student's t-test or ANOVA with post-hoc tests for multiple group comparisons, assuming approximate normal distribution. Categorical data (e.g. presence of symptoms, proportion of abnormal findings) were compared using Chi-square tests. A p value <0.05 was considered statistically significant. We also explored correlation between subjective symptom presence (or symptom severity reported) and objective measures (like sural SNAP amplitude or peroneal conduction velocity) using Pearson's correlation for continuous measures and point-biserial correlation for dichotomous symptom variables. The strength of associations was interpreted with caution due to the semi-quantitative nature of symptom data. All analyses were performed using SPSS v25.0 (IBM Corp).

RESULTS

The 90 diabetic patients had a mean age of 55.1 ± 12.3 years, while the control group had a mean age of 50.3 ± 11.0 years. Fifty-four percent of the diabetic cohort were male. Among the diabetic subgroups, patients in Group 1 (type 2, ≤5 years) and Group 2 (type 2, 5–10 years) tended to be older (mean ages ~58 and 62 years, respectively) than those in Group 3 (type 1, mean age ~45 years, reflecting earlier onset of type 1 diabetes). Mean disease duration in Group 3 was 11 ± 7 years (range 2–25 years). Glycated hemoglobin (HbA1c) levels (available for most patients) indicated generally suboptimal glycemic control in the type 2 groups (mean ~8.2% in Group 1 and 8.7% in Group 2) and somewhat better control in the type 1 group (mean ~7.5%). These differences and the older age of type 2 patients are noted as they could influence neuropathy findings. The control group had no history of diabetes; their mean age was 50.3 ± 11.0 years, and 52% were male. By design, controls did not have any known peripheral neuropathy; most were referred for evaluations such as suspected radiculopathy or carpal tunnel syndrome, and any with evidence of neuropathy on EMNG were excluded from the control dataset.

Among the 90 diabetic patients, 57 (63%) reported at least one symptom indicative of peripheral neuropathy (tingling, numbness, burning, or distal limb pain). The most common complaint was numbness in the feet (often described as "feet falling asleep" or loss of sensation), followed by paresthesias such as tingling and prickling sensations in the toes. Burning pain in the feet (especially at night) was reported by 15% of patients, and about 10% noted frequent muscle cramps in the calves at night. Patients with symptoms often had multiple concurrent complaints. In contrast, 33 diabetic patients (37%) denied any neuropathic symptoms; many of these asymptomatic patients were in the type 1 group or had shorter disease duration. Notably, a significant difference was observed between the type 2 and type 1 diabetic groups in terms of symptom frequency. Patients in Group 1 and Group 2 (type 2 diabetes) reported tingling and "pins-and-needles" sensations far more often than those in Group 3 (type 1 diabetes). In fact, distal sensory symptoms were significantly more frequent in the type 2 groups than in the type 1 group ($p = 0.004$). For example, about 70% of type 2 diabetics (combining Groups 1 and 2) experienced intermittent numbness or tingling in their feet, compared to roughly 30% of the type 1 diabetics. Correspondingly, on neurological exam, ankle reflexes were absent or reduced in a higher proportion of type 2 patients, whereas reflexes were largely preserved in the majority of type 1 patients ($p = 0.001$). These findings suggest that clinically overt neuropathy was more common in the type 2 diabetes cohort.

It is worth highlighting individual subgroup differences: in Group 2 (type 2 diabetes for 5–10 years), over 80% of patients acknowledged some neuropathic symptoms, making it the most symptomatic group. Group 1 (type 2 ≤5 years) had about half of patients symptomatic. Group 3 (type 1 diabetes) had the lowest frequency of symptoms – only about one-third had clear neuropathic complaints, and many of those had longstanding type 1 diabetes (>10 years). Thus, type 1 diabetics in early or mid stages of disease often appeared asymptomatic from a neuropathy standpoint despite having diabetes for several years.

All nerve conduction parameters in the diabetic groups were compared against control values. Overall, the diabetic patients showed clear evidence of peripheral neuropathy on EMNG, with the most pronounced changes in the lower limbs. Key findings are summarized below:

The distal motor latencies of the peroneal (fibular) and tibial nerves were prolonged in diabetic patients relative to controls. Group 1 and Group 2 (type 2 diabetics) had significantly longer distal latencies on average than controls (e.g. mean peroneal distal latency ~6.5 ms in Group 2 vs ~5.0 ms in controls, $p<0.001$). In contrast, Group 3 (type 1 diabetics) did not show prolonged distal latencies; in fact, the average distal latency in type 1 patients was similar to, or slightly shorter than, the control mean. When comparing within diabetic groups, type 2 patients (especially Group 2) had significantly longer distal latencies than type 1 patients ($p<0.05$). Motor conduction velocities (MCV) in the legs (peroneal and tibial nerves) were markedly reduced in all diabetic groups compared to controls. The average peroneal MCV in diabetic patients ranged from ~38–40 m/s (Group 1 and 2) to ~45 m/s (Group 3), all lower than controls (~50 m/s; $p<0.001$ for each group vs control). Group 3 (type 1) had significantly faster mean MCV than Groups 1 and 2, again indicating milder conduction slowing in type 1 diabetics. Compound muscle action potential (CMAP) amplitudes of the distal muscles (e.g. extensor digitorum brevis for peroneal nerve, abductor hallucis for tibial nerve) demonstrated an axonal loss pattern in type 2 diabetics. Mean CMAP amplitudes in Group 1 and Group 2 were significantly lower than in controls (e.g. peroneal CMAP ~2–3 mV vs 5 mV in controls, $p<0.01$). By contrast, Group 3 (type 1) patients had relatively preserved amplitudes; their mean CMAP was not significantly different from controls and was in fact higher on average than those of Group 1 and 2. For instance, the mean tibial CMAP in type 1 patients was ~5 mV versus ~3 mV in long-duration type 2 patients ($p<0.001$). No significant differences were observed between Group 1 and Group 2 in velocity or amplitude, suggesting that even within ≤5 years of type 2 diabetes, neuropathic changes were already well-established and not dramatically worse by 5–10 years (although Group 2 tended to have slightly more pronounced slowing).

The sural nerve, a purely sensory nerve in the lower limb, was tested as it is often the first to show diabetic neuropathy changes. All three diabetic groups had prolonged sural nerve distal latencies compared to controls (mean sural latency ~3.7 ms in diabetics vs ~3.0 ms in controls, $p<0.001$). Sural sensory conduction velocity was consequently reduced. There were no significant differences among the three diabetic groups in sural latency or velocity – even the type 1 group showed a similar degree of slowing as the type 2 groups. Despite slowed conduction, the sural SNAP amplitudes remained within normal ranges for most patients. Mean sural amplitude did not differ significantly between diabetic groups and controls, except that Group 3 (type 1) had a slightly higher average amplitude than Group 2 (type 2, 5–10 y). Importantly, when looking at frequency of abnormal sural results, there were differences: In Group 1 (short-duration type 2), 40% of patients had an abnormally slow sural conduction velocity (below normal threshold), and in Group 2 (longer-duration type 2) this proportion was 50%. Group 3 (type 1) had 30% of patients with abnormal sural velocity. None of the controls had sural abnormalities. Thus, about half of type 2 diabetics had large-fiber sensory neuropathy detectable by sural NCS, even when asymptomatic, whereas in type 1 diabetics this was present in about one-third of patients.

For the upper limb sensory nerves (median and ulnar), the changes were less pronounced, reflecting the length-dependent nature of DPN. Still, sensory nerve conduction velocities (SCV) in the median and ulnar nerves were modestly but significantly reduced in diabetic patients versus controls (e.g. median nerve SCV in diabetics ~48–50 m/s vs 55 m/s in controls, $p<0.001$). All three diabetic groups showed slower median and ulnar SCVs than controls. Interestingly, the type 1 group (Group 3) exhibited slightly greater slowing of median nerve SCV compared to the type 2 groups. In the ulnar nerve, there were no significant differences between the diabetic subgroups. Median and ulnar sensory amplitudes (SNAP amplitudes) were generally normal or only mildly reduced in diabetics, with no consistent pattern of significant differences; any mild amplitude reductions did not reach statistical significance compared to controls. Overall, upper limb sensory conduction remained relatively preserved in many diabetic patients, aligning with the distal gradient of DPN that affects the feet earlier and more than the hands.

Late response tests provided additional insight into proximal nerve segment and overall polyneuropathy involvement. F-wave latencies were prolonged in a notable subset of diabetic patients. For the tibial nerve F-wave, an abnormal prolongation was observed in 23.3% of Group 1 and 30.0% of Group 2 patients, but only in 3.3% of Group 3 (type 1) patients. The control group had only 1.7% with any prolonged F-wave (essentially normal variation). Similar proportions were seen with peroneal F-waves (in fact, peroneal F-wave abnormalities were slightly more frequent in Group 1 at 33.3% vs 26.6% in Group 2, and 13.3% in Group 3). The H-reflex, which specifically tests the S1 reflex arc (often obtained via tibial nerve stimulation), was obtainable in most subjects except those with severe neuropathy. The average H-reflex latency in controls was within normal limits (~30–32 ms). In Group 2 (type 2, 5–10 y), the H-reflex latency was significantly prolonged compared to controls (by about 2–3 ms on average, $p<0.05$), consistent with neuropathic delay in the reflex pathway. In Group 1 (type 2 ≤5 y) and Group 3 (type 1), mean H-reflex latencies did not differ significantly from controls. Notably, all mean H-reflex values remained within the broad physiological range, and prolongation was only evident when comparing group means statistically. The proportion of absent H-reflexes was small and mainly in patients with clinically evident neuropathy in the type 2 groups.

We examined the relationship between patients' subjective symptoms and their objective EMNG findings. As anticipated, there was not a one-to-one correspondence. Many patients with significant EMNG abnormalities reported only mild or no symptoms (particularly in the type 2 short-duration group), illustrating subclinical neuropathy. For example, of the 12 patients in Group 1 who had abnormal sural conduction, only half of them reported tingling or numbness in the feet; the others were asymptomatic despite clear large-fiber sensory loss on NCS. Similarly, several patients in Group 2 with markedly reduced CMAP amplitudes and slowed MCV (indicating axonal neuropathy) described no neuropathic pain or numbness – some were only diagnosed because of screening. On the other hand, a minority of reported classic neuropathic symptoms (burning pain, numbness) yet had relatively normal nerve conduction studies. In our cohort, 8 diabetic patients (9%) fell into this category of "clinically symptomatic but EMNG-negative." These cases might represent small-fiber predominant neuropathy or early neuropathy not detectable by standard conduction studies. Their complaints were still taken as evidence of neuropathy, even though large-fiber tests were normal.

We found that the presence of tingling and numbness had a sensitivity of about 70% for detecting any neuropathic EMNG abnormality in type 2 diabetics, but the specificity was only ~50% (since many asymptomatic type 2 patients had abnormalities). In type 1 diabetics, symptoms were less sensitive (~50%) but more specific (~80%) for EMNG-confirmed neuropathy - meaning most type 1 patients without symptoms truly had normal EMNG, and those with symptoms often did show some EMNG changes. We also noted that loss of ankle reflexes on exam correlated more strongly with EMNG abnormalities than patient-reported symptoms did. Almost all diabetics with absent ankle jerks had at least one abnormal nerve conduction parameter. Reflex status had an overall concordance of ~75% with the presence of neuropathy on EMNG, making it a useful clinical sign.

Summarizing the inter-group differences, our results demonstrated that type 2 diabetic patients (Groups 1 & 2) had more frequent and more severe neurophysiological deficits compared to type 1 diabetic patients (Group 3). They also reported symptoms more commonly. Even within a few years of disease onset, type 2 diabetics exhibited significant slowing of nerve conduction and axonal loss, whereas type 1 diabetics often maintained near-normal conduction in early years. By ~5–10 years of disease, type 2 patients showed a high prevalence of neuropathy (as evidenced by ~50% with abnormal sural velocities, ~25-30% with prolonged F-waves, etc.), while type 1 patients with similar or longer durations had lower prevalence and milder changes. These differences held despite the type 1 group having longer mean disease duration than Group 1. When comparing type 1 patients vs. age-matched type 2 patients (a subset analysis controlling for age ≈45–50 in both), the type 2 patients still had more frequent abnormalities, suggesting that factors inherent to type 2 diabetes (possibly chronic metabolic syndrome or a longer period of occult hyperglycemia before diagnosis) contribute to earlier neuropathy.

Below is a grouped bar chart showing the comparison of motor conduction velocity (MCV) and compound muscle action potential (CMAP) of the peroneal nerve across the study groups. Values are approximate and derived from the reported ranges in the thesis: type 2 diabetics (≤5 years duration, Group 1), type 2 diabetics (5–10 years duration, Group 2), type 1 diabetics (Group 3), and a healthy control group. The chart illustrates the progression of nerve damage and the differences between type 2 and type 1 diabetes, consistent with literature indicating that motor and sensory neuropathy are more prevalent and severe in type 2 diabetes.

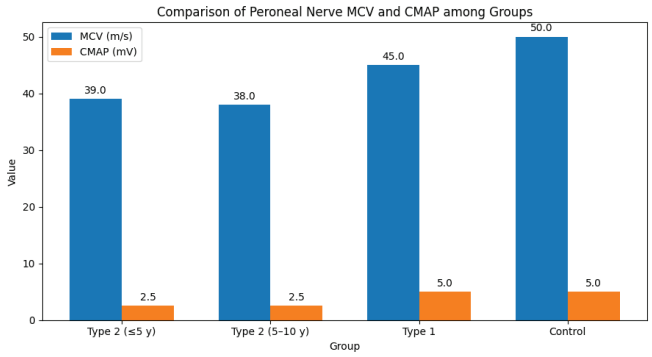

Figure 1 **Motor conduction velocity (MCV) and compound muscle action potential (CMAP) of the peroneal nerve across study groups. Each bar represents the approximate mean MCV (blue) and CMAP amplitude (orange) for four groups: type 2 diabetes mellitus (DM) with ≤5 years of disease, type 2 DM with 5–10 years of disease, type 1 DM,and non-diabetic controls.**

The chart illustrates that type 2 diabetics regardless of disease duration exhibit lower conduction velocities and amplitudes than type 1 patients and controls, consistent with reports that motor and sensory neuropathies are more pronounced in type 2 diabetes

Both type 2 groups show markedly reduced conduction velocity and amplitude compared with the control group, indicating greater axonal damage and demyelination.

These findings underscore why early and comprehensive neurophysiological testing is important in diabetes: many patients especially those with type 2 diabetes may have significant nerve damage before symptoms appear

DISCUSSION

This observational cross-sectional study provides further evidence of the frequent discordance between subjective symptoms and objective electrophysiological findings in diabetic polyneuropathy (DPN). In our cohort, a substantial proportion of patients demonstrated abnormal electromyoneurographic (EMNG) findings despite minimal or absent neuropathic symptoms, while a smaller group reported neuropathic complaints despite normal routine nerve conduction studies.

Our findings are consistent with those of Dyck PJ, et al. (2010), who demonstrated that clinical symptoms and signs explain only a limited proportion of the variability in nerve conduction measures, emphasizing that reliance on symptoms alone may result in both underdiagnosis and overdiagnosis of diabetic neuropathy (5). This observation highlights the importance of integrating clinical assessment with objective neurophysiological testing when evaluating patients with suspected DPN.

The higher prevalence and greater severity of neuropathy observed in our type 2 diabetes cohort are also in agreement with the systematic review by Sempere-Bigorra M, et al. (2021), which reported that peripheral neuropathy occurs more frequently in type 2 than in type 1 diabetes and increases with advancing age and longer disease duration (6). Similar risk factors were evident in our study population, where patients with type 2 diabetes demonstrated more frequent symptoms and more pronounced electrophysiological abnormalities than patients with type 1 diabetes.

Our observation that many asymptomatic patients already exhibited abnormal EMNG findings supports previous evidence that neurophysiological abnormalities may precede clinical manifestations of neuropathy. Gao L, et al. (2024) reported that neurologically asymptomatic patients with type 2 diabetes had significantly slower nerve conduction velocities and prolonged F-wave latencies compared with healthy controls, suggesting that peripheral nerve dysfunction may be present before symptoms become clinically apparent (7). Together with our findings, these data support the value of early neurophysiological screening, particularly in patients with type 2 diabetes.

Conversely, several patients in our cohort reported neuropathic symptoms despite normal conventional EMNG findings. Such cases may reflect early or predominantly small-fiber neuropathy, which is not adequately assessed by routine nerve conduction studies. Pan H, et al. demonstrated that the cutaneous silent period may serve as an early marker of small-fiber dysfunction in diabetic patients (8). This mechanism may explain the discrepancy observed between subjective symptoms and normal large-fiber neurophysiological parameters in a subset of our patients.

Additional diagnostic value may be obtained through late-response studies. Oda H, et al. (2019) reported that incorporation of the H-reflex into routine neurophysiological evaluation increased the sensitivity of polyneuropathy detection and provided greater diagnostic specificity than clinical reflex examination alone (9). Consistent with these findings, prolonged H-reflex latencies were more frequently observed in our patients with type 2 diabetes and more advanced neuropathic involvement.

Taken together, our results reinforce the concept that diabetic neuropathy cannot be reliably assessed through symptoms alone. Comprehensive evaluation should include clinical assessment, neurological examination, and objective neurophysiological testing. Early recognition of subclinical neuropathy may facilitate timely interventions, including optimization of glycaemic control, lifestyle modification, and preventive foot-care measures, while symptomatic patients with normal routine EMNG should be considered for additional investigations targeting small-fiber dysfunction.

Several limitations of this study should be acknowledged. The assessment of subjective symptoms was based on patient self-report and a structured questionnaire rather than validated neuropathy symptom scales, which may have introduced reporting variability. The sample size of individual diabetic subgroups was relatively modest, potentially limiting the power of certain subgroup comparisons. In addition, conventional EMNG primarily evaluates large-fiber dysfunction and may not adequately detect small-fiber neuropathy, which could explain the presence of neuropathic symptoms in some patients with normal nerve conduction studies. Future studies incorporating larger cohorts and additional diagnostic modalities, such as quantitative sensory testing or skin biopsy, may provide a more comprehensive understanding of the relationship between subjective symptoms and objective neurophysiological abnormalities in diabetic neuropathy.

CONCLUSION

This study demonstrated a frequent dissociation between subjective neuropathic symptoms and objective neurophysiological findings in diabetic polyneuropathy. A considerable proportion of diabetic patients exhibited abnormal EMNG findings despite the absence of symptoms, while a smaller subset reported neuropathic complaints despite normal routine nerve conduction studies. Patients with type 2 diabetes showed earlier and more pronounced neurophysiological abnormalities and a higher frequency of neuropathic symptoms compared with patients with type 1 diabetes. These findings suggest that diabetic neuropathy may develop subclinically, particularly in type 2 diabetes. Comprehensive evaluation of diabetic neuropathy should therefore include both clinical assessment and objective neurophysiological testing. Early detection of subclinical neuropathy may facilitate timely intervention and contribute to improved patient management and prevention of long-term complications.

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Declaration of patient consent: the author certifies that they obtained all appropriate patient consent forms. In the form, the patients have given ther consent for the images and other clinical information to be reported in the journal.

Authors' contributions: SD, HJ, EĆ-V, AM, FZ and EM-S gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial support and sponsorship: nil.

Conflict of interest: there are no conflicts of interest.

Perioperative Metabolic Response in Breast Cancer Surgery: Impact of the PECS Block on Tissue Injury Enzymes – A Retrospective Study

Perioperativni metabolički odgovor kod operacije karcinoma dojke: uticaj PECS bloka na enzime oštećenja tkiva – retrospektivna studija

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ABSTRACT

Introduction: Surgical treatment of breast cancer induces a pronounced perioperative metabolic and tissue-trauma response, which can be reflected by postoperative increases in enzymes such as creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT). Regional techniques, including the PECS block, may attenuate the stress response and reduce the extent of tissue trauma. Aim: to evaluate whether the PECS block influences perioperative changes in CK, LDH, AST, ALT, and GGT in patients undergoing surgery for breast cancer. Materials and methods: This retrospective study included 40 patients divided into a PECS group (n=20) and a control group (n=20). Parameters were measured preoperatively, and at 24 h and 72 h postoperatively. The primary outcomes were perioperative changes in each biomarker over time. The secondary outcome was to compare baseline demographic and surgical characteristics (age, ASA status, type of surgery, sentinel lymph node biopsy (SLNB) / axillary lymph node dissection (ALND), and operative time) to confirm group homogeneity. Results: An increase in CK, LDH, AST, ALT, and GGT was observed postoperatively in both groups. The PECS group demonstrated numerically smaller increases in CK and LDH compared with the control group. Similar trends were observed for AST, ALT, and GGT. However, none of these differences reached statistical significance (all $p > 0.05$).The differences were not statistically significant ($p > 0.05$), but a more favorable metabolic response pattern was observed in the PECS group. Conclusion: The present study demonstrated numerically lower postoperative levels of several tissue injury enzymes in patients receiving a PECS block; however, these differences were not statistically significant. Although the findings suggest a possible beneficial effect of PECS block on the perioperative metabolic response, larger prospective studies are required before definitive conclusions can be drawn.

Keywords: PECS block; breast cancer; metabolic response; tissue-trauma enzymes

SAŽETAK

Uvod: Hirurško lečenje karcinoma dojke izaziva izražen perioperativni metabolički i tkivni odgovor na traumu, što se može odraziti povećanjem enzima nakon operacije, kao što su kreatin kinaza (CK), laktat dehidrogenaza (LDH), aspartat aminotransferaza (AST), alanin aminotransferaza (ALT) i gama-glutamil transferaza (GGT). Regionalne tehnike, uključujući PECS blok, mogu ublažiti stresni odgovor i smanjiti obim tkivne traume. Cilj: procijeniti da li PECS blok utiče na perioperativne promjene CK, LDH, AST, ALT i GGT kod pacijenata koji se podvrgavaju operaciji karcinoma dojke. Materijali i metode: Ovo retrospektivno istraživanje uključilo je 40 pacijenata podijeljenih u PECS grupu (n=20) i kontrolnu grupu (n=20). Parametri su mjerili preoperativno, te 24 h i 72 h postoperativno. Primarni ishodi bili su perioperativne promjene svakog biomarkera tokom vremena. Sekundarni ishod bio je poređenje osnovnih demografskih i hirurških karakteristika ((starost, ASA status, vrsta operacije, biopsija sentinel limfnih čvorova (SLNB) / disekcija aksilarnih limfnih čvorova (ALND), i vrijeme operacije) kako bi se potvrdila homogenost grupa. Rezultati: Povećanje CK, LDH, AST, ALT i GGT je uočeno postoperativno u obje grupe. Grupa sa PECS blokom pokazala je numerički manja povećanja CK i LDH u poređenju sa kontrolnom grupom. Slični trendovi su uočeni i za AST, ALT i GGT. Međutim, nijedna od ovih razlika nije dosegnula statističku značajnost (svi $p > 0.05$). Razlike nisu bile statistički značajne ($p > 0.05$), ali je u grupi sa PECS blokom uočen povoljniji obrazac metaboličkog odgovora. Zaključak: Ova studija je numerički pokazala niži postoperativni nivo nekoliko enzima oštećenja tkiva kod pacijenata kojima je primijenjen PECS blok; međutim, ove razlike nisu bile statistički značajne. Iako nalazi sugeriraju mogući povoljan učinak PECS bloka na perioperativni metabolički odgovor, potrebne su veće prospektivne studije prije nego što se mogu donijeti konačni zaključci.

Ključne riječi: PECS blokada; karcinom dojke; metabolički odgovor; enzimi traume tkiva

INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy in women and remains a major cause of morbidity and mortality worldwide (1,2). Surgical management represents the cornerstone of treatment and may involve either mastectomy or breast-conserving procedures, accompanied by evaluation and treatment of regional lymph nodes (sentinel lymph mode biopsy - SLNB or axillary lymph node dissection - ALND) (3). Surgical trauma induces a complex metabolic and inflammatory response, including the release of enzymes related to muscle and tissue injury (4). Biomarkers such as creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) are commonly used as surrogate markers of tissue injury and hepatocellular stress during breast cancer surgery (5,6).

Regional analgesia has gained an increasingly important role in oncologic surgery. The pectoral nerve block (PECS I/II) is a minimally invasive, ultrasound-guided regional technique that provides effective analgesia of the anterior chest wall and axillary region (7). Previous studies suggest that regional analgesia may attenuate neuroendocrine stress, reduce inflammatory response and opioid consumption, and contribute to a more stable perioperative course. This may result in a smaller increase in tissue-trauma biomarkers and a more favorable postoperative metabolic profile (7,8). Despite the widespread use of the PECS block for analgesia in breast surgery, data on its influence on perioperative metabolic and tissue injury markers remain limited. Most existing studies focus primarily on pain scores and opioid consumption rather than biochemical indicators of surgical stress.

Given the limited available data on the influence of the PECS block on metabolic response in oncologic surgery, further investigation is required to clarify whether this technique can reduce tissue trauma and perioperative stress (7,8).

AIM

The aim of the study was to analyze whether the use of the PECS block results in a more favorable metabolic response compared to standard general anesthesia without the block.

MATERIALS AND METHODS

This retrospective controlled clinical study was conducted over six-month period at the Department of Anesthesiology and Reanimation in collaboration with the Department of Glandular Surgery, Clinical Center University of Sarajevo. It included 40 patients undergoing surgery for breast cancer. Patients were divided into two groups: the PECS group (n=20) and the control group without a regional block (n=20). Adult patients with biopsy-confirmed breast cancer were included. Patients with infections, pre-existing liver disease, or muscle disorders that could affect laboratory values were excluded from the study.

PECS Block Technique

In the PECS group, an ultrasound-guided PECS I/II block was performed after induction of general anesthesia under aseptic conditions using a high-frequency linear probe. The patient was positioned supine with the ipsilateral arm on the side surgery was abducted at 90°. A 100-mm peripheral nerve block needle was used. For the PECS I component, 10 mL of 0.25% levobupivacaine was injected into the interfascial plane between the pectoralis major and pectoralis minor muscles. For the PECS II component, 20 mL of 0.25% levobupivacaine was deposited between the pectoralis minor and serratus anterior muscles. This technique providesanalgesia of the anterior chest wall and axillary region.The block was performed according to institutional protocol.

Laboratory Measurements

Clinical and laboratory data were obtained from medical records and anesthesia charts as part of routinely collected clinical data. Values were analyzed at three perioperative time points as part of routine laboratory monitoring: preoperatively, and at 24 and 72 hours postoperatively. Creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT) andgamma-glutamyl transferase (GGT) levels were recorded.

Demographic and Perioperative Data

Demographic and perioperative variables included age, ASA status, tumor laterality, axillary technique (sentinel lymph node biopsy (SLNB) / axillary lymph node dissection (ALND) and operative time in minutes.

Ethical Approval

The institutional ethics committee approved the study (Approval No 06-04-9-7601, of 3 March 2026), and the requirement for informed consent was waived due to the retrospective design.

Statistical Analysis

Statistical analysis was performed using descriptive and analytical methods. The normality of data distribution was assessed with the Shapiro-Wilk test. For comparison of independent groups (PECS vs. control), the Student's t-test was used for parametric data, while the Mann–Whitney U test was applied for non- normally distributed data. Changes across three time points were analyzed using repeated-measures ANOVA in the case of normal distribution, or the Friedman test when the distribution was non-normal. Categorical variables (type of surgery, SLNB/ALND, ASA status) were compared using the chi-square test or Fisher's exact test. A p value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (26). No imputation was performed for missing data.

RESULTS

Baseline demographic and surgical characteristics were comparable between groups, with no statistically significant differences observed (Table 1).This indicates that the groups were comparable in key clinical characteristics, allowing for an unbiased comparison of metabolic and tissue markers between the PECS and control groups

Table 1 **Baseline demographic and clinical characteristics of patients (N = 40).**

Variable	PECS group (n=20)	Control group (n=20)	p-value
Age (years), mean ± SD	59.5 ± 11.2	57.1 ± 11.1	0.52
ASA status	I: 0 II: 13 III: 7	I: 0 II: 14 III: 6	0.74
Tumor laterality	L:12 R:8	L:10 R:10	0.53
Type of surgery	Mastektomija: 15 BCS: 5	Mastektomija: 14 BCS: 6	0.72
Axillary staging	SLNB: 8 ALND: 12	SLNB: 10 ALND: 10	0.53
Operative time (min), mean ± SD	136 ± 33	143 ± 38	0.54

Abbreviations: ASA – American Society of Anesthesiologists; SD – standard deviation; L – left; R – right; BCS – breast-conserving surgery; SLNB – sentinel lymph node biopsy; ALND – axillary lymph node dissection

After confirming the homogeneity of the groups, changes in metabolic and tissue enzymes (CK, LDH, AST, ALT, GGT) at three time points were analyzed. The values and comparisons between the groups are shown in Table 2.

Table 2 **Perioperative changes in metabolic and tissue injury markers.**

Biomarker	Time	PECS group (mean ±SD)	Control group (mean ±SD)	p-value
CK (U/L)	Preop	130 ± 54	128 ± 56	0.88
CK (U/L)	24 h	177 ± 62	198 ± 66	0.29
CK (U/L)	72 h	165 ± 59	185 ± 63	0.32
LDH (U/L)	Preop	210 ± 38	215 ± 40	0.63
LDH (U/L)	24 h	254 ± 45	278 ± 50	0.12
LDH (U/L)	72 h	246 ± 48	265 ± 52	0.20
AST (U/L)	Preop	22 ± 6	23 ± 7	0.55
AST (U/L)	24 h	29 ± 8	33 ± 9	0.18
AST (U/L)	72 h	27 ± 7	30 ± 8	0.22
ALT (U/L)	Preop	21 ± 7	22 ± 6	0.66
ALT (U/L)	24 h	28 ± 9	32 ± 10	0.17
ALT (U/L)	72 h	27 ± 8	30 ± 9	0.24
GGT (U/L)	Preop	24 ± 10	25 ± 11	0.79
GGT (U/L)	24 h	31 ± 12	35 ± 14	0.28
GGT (U/L)	72 h	30 ± 11	34 ± 13	0.25

DISCUSSION

In the present study, patients receiving a PECS block showed numerically lower postoperative values of CK, LDH, AST, ALT, and GGT compared with patients receiving general anesthesia alone. Nevertheless, none of the observed between-group differences reached statistical significance. Therefore, the findings should be interpreted cautiously and viewed primarily as hypothesis-generating rather than confirmatory.

Recent studies have demonstrated that PECS block provides effective perioperative analgesia, reduces opioid consumption, and improves postoperative recovery following breast cancer surgery (16,17,18). Several authors have suggested that regional anesthesia techniques may attenuate neuroendocrine and inflammatory responses to surgical trauma, potentially contributing to a more favorable perioperative physiological profile (19,20). However, evidence regarding the influence of the PECS block on biochemical markers of metabolic stress and tissue injury remains limited. In this context, the present findings add preliminary data suggesting a possible trend toward lower enzyme elevations, although larger prospective studies are required to determine whether these observations represent true biological effects.

The results of this study suggest that the use of the PECS block may be associated with a smaller increase in metabolic and tissue injury markers compared with the control group. Although the differences were not statistically significant, a trend toward a more favorable postoperative response was observed, particularly for CK and LDH, which are considered sensitive indicators of muscle and tissue trauma (11,12). A smaller increase in AST, ALT, and GGT may indicate reduced hepatocellular and oxidative stress in the PECS group (13). These findings support the concept that regional analgesia may reduce nociceptive input and may attenuate the systemic stress response (14,15). Previous studies have also demonstrated that the PECS I/II block can reduce the stress response and opioid requirements, which may indirectly contribute to a more favorable metabolic response (9,10).

The lack of statistical significance likely reflects the limited sample size and the retrospective nature of the study. Consequently, the study may have been underpowered to detect modest differences in perioperative biochemical responses between groups.

This study has several strengths, including a clearly defined perioperative laboratory monitoring protocol and a relatively homogeneous patient population. The clinical trends observed across all analyzed biomarkers suggest a potential benefit of the PECS block and warrant further investigation in a larger patient cohort.

CONCLUSION

The present study demonstrated numerically lower postoperative levels of several tissue injury enzymes in patients receiving a PECS block; however, these differences were not statistically significant. Although the findings suggest a possible beneficial effect of PECS block on the perioperative metabolic response, larger prospective studies are required before definitive conclusions can be drawn.

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Authors' contributions: LA, AM, SŠ, SD, ST-K, MD, AJ and ZZ gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

Perioperative Changes in Lactate Dehydrogenase, Albumin and Cortisol in Children Following Caudal Block - Impact of Caudal Block on Pediatric Perioperative Stress

Perioperativne promjene laktat dehidrogenaze, albumina i kortizola kod djece nakon kaudalnog bloka

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ABSTRACT

Intraduction: Surgical stress in children triggers complex metabolic, inflammatory, and endocrine responses. Caudal epidural block is widely used to attenuate nociceptive input during infraumbilical surgery; however, its effect on early biochemical markers of acute surgical stress remains insufficiently characterized. Aim: to evaluate the influence of caudal epidural anesthesia on acute perioperative stress in pediatric patients by comparing perioperative changes in serum cortisol, lactate dehydrogenase (LDH) and albumin between children receiving caudal block and those undergoing surgery under general anesthesia alone. Materials and methods: In this retrospective controlled study, children aged 1-6 years undergoing elective infraumbilical surgery were allocated to either a caudal block group or a control group. Blood samples were obtained immediately after skin incision and at the end of surgery. Perioperative changes in biomarker levels were calculated as the difference between end-of-surgery and post-incision values. Results: The study included 40 children (20 per group). No statistically significant differences were observed between the groups in perioperative changes in cortisol, lactate dehydrogenase (LDH) or albumin. A trend toward a greater perioperative decrease in lactate dehydrogenase (LDH) was noted in the caudal block group. Surgical duration was significantly longer in the caudal block group. Conclusions: Although caudal epidural block did not result in statistically significant attenuation of early perioperative biochemical stress markers, observed trends, particularly in lactate dehydrogenase (LDH) dynamics, suggest a potential modulatory effect on tissue stress responses. Larger studies with extended postoperative follow-up are warranted.

Keywords: caudal epidural block, cortisol, lactate dehydrogenase, albumin, perioperative stress

SAŽETAK

Uvod: Hirurški stres kod djece pokreće kompleksne metaboličke, upalne i endokrine odgovore. Kaudalni blok se koristi za ublažavanje nociceptivnog prijenosa tokom infraumbilikalne hirurgije. Međutim, njen uticaj na rane biohemijske markere akutnog hirurškog stresa ostaje nedovoljno okarakteriziran. Cilj: procijeniti uticaj kaudalnog bloka na akutni perioperativni stres kod pedijatrijskih pacijenata upoređivanjem perioperativnih promjena serumskog kortizola, laktat dehidrogenaze (LDH) i albumina između djece koja su primila kaudalni blok i one koja su podvrgnuta operaciji samo pod opštom anestezijom. Materiali i metode : u ovoj retrospektivnoj kontroliranoj studiji, djeca uzrasta od 1 do 6 godina koja su podvrgnuta elektivnoj infraumbilikalnoj hirurgiji su raspoređena u grupu sa kaudalnim blokom ili u kontrolnu grupu. Uzorci krvi su uzeti odmah nakon reza kože i na kraju operacije. Perioperativne promjene u nivoima biomarkera su izračunate kao razlika između vrijednosti na kraju operacije i nakon reza. Rezultati: U stugiju je uključeno četrdesetoro djece (20 po grupi). Nisu uočene statistički značajne razlike između grupa u perioperativnim promjenama kortizola, laktat dehidrogenaze (LDH) ili albumina. Trend prema većem perioperativnom smanjenju laktat dehidrogenaze (LDH) uočen je u grupi sa kaudalnim blokom. Trajanje operacije bilo je značajno duže u grupi sa kaudalnim blokom. Zaključak: Iako kaudalni epiduralni blok nije rezultirao statistički značajnim smanjenjem ranih perioperativnih biohemijskih markera stresa, uočeni trendovi, posebno u dinamici laktat dehidrogenaze (LDH), ukazuju na potencijalni modulatorni efekat na odgovore tkiva na stres. Potrebna su veća istraživanja sa produženim postoperativnim praćenjem.

Ključne riječi: kaudalni epiduralni blok, kortizol, laktat dehidrogenaza, albumin, perioperativni stres

INTRODUCTION

Surgical procedures represent a substantial physiological and psychological stressor in pediatric patients (1). In addition to immediate neuroendocrine activation, children may develop persistent psychological sequelae following hospitalization and surgery, with a significant proportion experiencing stress-related symptoms several months postoperatively (2). The surgical stress response is primarily mediated through the activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, resulting in hemodynamic alterations and measurable changes in metabolic and immune function (3). Caudal epidural block is the most used regional anesthesia technique in pediatric practice, particularly for procedures performed below the umbilicus. Owing to its technical simplicity and favorable safety in children, it is frequently combined with general anesthesia. Clinical experience and previous studies suggest that the combination of regional and general anesthesia provides superior hemodynamic stability, improved analgesia, and reduced perioperative stress, thereby facilitating earlier recovery and rehabilitation (4,5). In infraumbilical pediatric surgery, surgical trauma typically induces a pronounced neuroendocrine response, manifested by increased serum cortisol levels during and immediately after surgery (6). Lactate dehydrogenase (LDH), a nonspecific marker of tissue injury and cellular stress, may show mild to moderate perioperative elevations, whereas serum albumin, an established negative acute-phase protein, often decreases in the early postoperative period due to inflammation, hemodilution, and increased capillary permeability (7-9). Regional anesthetic techniques, particularly caudal block, may attenuate these biochemical stress responses by reducing afferent nociceptive transmission and improving perioperative pain control (10).

AIM

The present study aimed to assess the impact of caudal epidural anesthesia on early perioperative biochemical stress markers in children undergoing infraumbilical surgery.

MATERIALS AND METHODS

Study design and participants

This retrospective controlled, non-randomized study included pediatric patients aged 1-6 years scheduled for elective infraumbilical surgery involving the lower abdomen or perineum. All participants were classified as having an American Society of Anesthesiologists (ASA) physical status I or II. Written informed consent was obtained from parents or legal guardians before the enrollment.

Anesthetic management

Participants were assigned to one of two groups: a caudal block group or a control group. In the caudal block group, caudal epidural anesthesia was performed after induction of general anesthesia. Patients in the control group received only general anesthesia. Apart from the anesthetic technique, perioperative management was standardized across both groups.

Data collection and laboratory analysis

Venous blood samples were collected at two predefined time points: immediately after skin incision (T1) and at the end of surgery (T2). Serum concentrations of cortisol, lactate dehydrogenase (LDH), and albumin were measured using standard laboratory methods. Perioperative changes in biomarker levels were calculated as T2-T1.The institutional ethics committee approved the study (Approval No. 06-04-9-7602 of 25 February 2026), and the requirement for informed consent was waived due to the retrospective design.

Outcomes and statistical analysis

The primary outcome measures were perioperative changes in serum cortisol, lactate dehydrogenase (LDH) and albumin. Baseline demographic and clinical variables were recorded for all patients. Continuous variables are presented as mean ± standard deviation, and categorical variables as counts and percentages. Between-group comparisons were performed using the independent-samples t-test for continuous variables and the chi-square test for categorical variables. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 40 pediatric patients were included in the study, with 20 patients allocated to the caudal block group and 20 to the control group. Baseline demographic and clinical characteristics are summarized in Table 1. The two groups were comparable with respect to age, body weight, and ASA physical status, with no statistically significant differences observed (all p > 0.05).

A statistically significant difference was identified in the duration of surgery, which was longer in the caudal block group compared with the control group (48.25 ± 12.28 vs. 38.95 ± 15.94 minutes, respectively; p = 0.046).

Table 1 **Baseline demographic and clinical characteristics of the study participants.**

Variable	Caudal block (n = 20)	Control (n = 20)	p-value
Age, years	3.7 ± 1.4	3.1 ± 1.0	0.147
Weight, kg	16.4 ± 5.6	15.9 ± 3.1	0.729
ASA physical status (I/II)	15 / 5	15 / 5	1.000
Duration of surgery, min	48.3 ± 12.3	39.0 ± 15.9	0.046

Abbreviations: Data are presented as mean ± standard deviation or number of patients, as appropriate. ASA - American Society of Anesthesiologists. A p-value < 0.05 was considered statistically significant.

Perioperative changes in serum biomarkers are presented in Table 2. Changes were calculated as the difference between values measured at the end of surgery (T2) and those obtained immediately after surgical incision (T1). No statistically significant differences were observed between the caudal block and control groups in perioperative changes in serum cortisol levels (52.45 ± 168.35 vs. 30.75 ± 207.74 μg/dL; p = 0.173), lactate dehydrogenase (LDH) levels (24.35 ± 26.26 vs. −11.50 ± 16.08 U/L; p = 0.071), or albumin levels (2.20 ± 3.37 vs. 1.95 ± 1.67 g/dL; p = 0.768). Although not reaching statistical significance, a trend toward a greater reduction in lactate dehydrogenase (LDH) levels was observed in the caudal block group compared with the control group, suggesting a potential attenuation of perioperative tissue injury or cellular stress in patients receiving caudal anesthesia.

Table 2 **Perioperative changes in serum biomarkers (T2 - T1).**

Biomarker	Caudal block	Control	p-value
Cortisol, µg/dL	−52.5 ± 168.4	30.8 ± 207.7	0.173
LDH, U/L	−24.4 ± 26.3	−11.5 ± 16.1	0.071
Albumin, g/dL	−2.2 ± 3.4	−2.0 ± 1.7	0.768

Abbreviations: Data are presented as mean ± standard deviation or number of patients, as appropriate. T1 - immediately after skin incision; T2 – at end of surgery; LDH - lactate dehydrogenase. A p-value < 0.05 was considered statistically significant

DISCUSSION

The study examined perioperative biochemical stress responses in pediatric patients receiving caudal epidural block versus general anesthesia alone. The primary findings showed no statistically significant attenuation of early perioperative changes in serum cortisol, lactate dehydrogenase (LDH) or albumin in the caudal block group compared with controls. Nonetheless, caudal block demonstrated a trend toward a greater reduction in lactate dehydrogenase (LDH) levels, consistent with potential dampening of tissue stress. The pediatric surgical stress response is mediated through the activation of the hypothalamic pituitary adrenal (HPA) axis, resulting in increased secretion of cortisol and catecholamines, as well as associated metabolic changes (e.g., hyperglycemia) that reflect neuroendocrine activation rather than mere pain perception alone (11,12).

Pediatric patients often exhibit more robust, yet transient, cortisol and catecholamine responses compared to adults (13,14). These hormonal surges can occur rapidly in the early perioperative period (e.g., immediately after incision) and diminish thereafter, complicating the timing of biomarker assessment (12,14).

Several clinical trials have demonstrated that caudal blocks can significantly attenuate neuroendocrine stress responses in children compared with general anesthesia alone. For instance, plasma cortisol and prolactin concentrations were significantly reduced in the caudal group compared with controls at 1 hour postoperatively, and this effect correlated with lower pain scores (16). Similarly, a randomized trial involving 60 pediatric patients undergoing herniorrhaphy reported significantly lower postoperative serum cortisol and glucose levels in the caudal block group (17). Presurgical caudal blocks have also been shown to attenuate perioperative glucose increases, a surrogate marker of stress response, and decrease postoperative narcotic use (10). Recent literature continues to support the role of regional anesthesia in modulating the perioperative stress response in pediatric patients. Contemporary studies have demonstrated that caudal epidural block contributes to improved perioperative analgesia, greater hemodynamic stability, and reduced postoperative analgesic requirements. Furthermore, recent systematic reviews have emphasized that attenuation of nociceptive input through regional techniques may influence neuroendocrine and inflammatory pathways involved in the surgical stress response. Although statistically significant differences in biochemical stress markers were not demonstrated in our cohort, the observed trends are consistent with the growing body of evidence suggesting a potential stress-modulating effect of caudal anesthesia in children (20,21).

Pediatric cortisol responses are often short-lived, peaking early post-incision and potentially returning toward baseline within hours after surgery, as summarized in broader pediatric stress literature (15,18).

Moreover, serum biomarkers such as albumin may not reflect rapid changes because acute-phase protein responses manifest more clearly in the later postoperative period (6-72h) rather than intraoperatively (7,8). Although lactate dehydrogenase (LDH) is a nonspecific biomarker, it reflects cellular injury and metabolic stress. The observed trend toward a greater lactate dehydrogenase (LDH) reduction in the caudal block group is biologically plausible, as regional anesthetic techniques reduce afferent nociceptive transmission and may attenuate neuroendocrine and metabolic stress responses to surgery (15,18). Caudal blocks also confer well-established analgesic and hemodynamic benefits including lower pain scores, decreased opioid requirements, and improved intraoperative stability (4,19). While these functional outcomes are not direct biochemical stress measures, they may indirectly reflect mitigated nociceptive pathways, which contribute to the overall surgical stress response. The significantly longer surgery duration in the caudal block group in our study may have acted as a confounding factor by increasing cumulative stress exposure. Prolonged operative times are independently associated with greater activation of endocrine and inflammatory pathways (15). Thus, the observed lactate dehydrogenase (LDH) trend despite longer surgeries may indicate that caudal block partially modulates stress responses even under increased surgical burden.

Finally, future studies should consider broader and longitudinal biomarker panels including cytokines (e.g., IL-6, TNF-α), acute phase proteins, and additional endocrine markers to comprehensively characterize stress trajectories over the early and late postoperative period. Neuroendocrine responses and immune modulation during surgery are complex and involve multiple interacting pathways that extend beyond single markers like cortisol or lactate dehydrogenase (LDH) (e.g., systemic pro- and anti-inflammatory mediators) (20).

This study has several limitations. Firstly, the relatively small sample size might have reduced the statistical power to detect subtle differences in perioperative stress markers between the groups. Secondly, the retrospective and non-randomized design introduced a potential risk of selection bias and limits the ability to establish causal relationships. Thirdly, biomarker assessment was restricted to two intraoperative time points without postoperative follow-up, which might have underestimated delayed endocrine and inflammatory responses. Finally, the significant difference in operative duration between groups might have acted as a confounding factor.

CONCLUSION

Despite the absence of statistically significant differences, the observed lactate dehydrogenase (LDH) trend suggests that caudal block may exert a modest modulatory effect on tissue stress responses in pediatric surgery. Given the well-established benefits of caudal anesthesia in pain control and perioperative stability, future studies should explore its impact on broader inflammatory and metabolic pathways, incorporating serial postoperative measurements and larger cohorts.

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Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

Epidural and Single-Shot Spinal Analgesia in Vaginal Delivery: Clinical Practice and Outcomes at the Clinic of Gynecology and Obstetrics, Clinical Center University of Sarajevo (CCUS)

Epiduralna i jednokratna spinalna analgezija u vaginalnom porođaju: Klinička praksa i ishodi na Klinici za ginekologiju i akušerstvo, Univerziteta Kliničkog centra Sarajevo (KCUS)

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ABSTRACT

Introduction: Regional analgesia is a part of modern obstetric care. Aim: to analyze the clinical use of epidural and single-shot spinal analgesia in vaginal delivery and their impact on maternal and neonatal outcomes. Materials and methods: A retrospective study included women who received epidural or single-shot spinal analgesia during vaginal delivery at the Clinic of Gynecology and Obstetrics, of the Clinical Center University of Sarajevo, in the period between 2023 and 2025. Results: A total of 647 deliveries were analyzed. A high proportion of newborns in both groups achieved an Apgar score ≥9 at 1 minute. The rate of cesarean section did not differ significantly between analgesia methods. Conclusion: Epidural and single-shot spinal analgesia are safe and effective methods for pain relief during vaginal delivery in a tertiary care setting.

Keywords: epidural analgesia, single-shot spinal analgesia, vaginal delivery, pain

SAŽETAK

Uvod: Regionalna anesteziju je dio moderne opstetričke skrbi. Cilj: analizirati kliničku upotrebu epiduralne i jednokratne spinalne analgezije u vaginalnom porodu i njihov utjecaj na majčinske i neonatalne ishode. Materijali i metode: Retrospektivna studija obuhvatila je žene koje su primile epiduralnu ili jednokratnu spinalnu analgeziju tijekom vaginalnog poroda na Klinici za ginekologiju i opstetriciju Kliničkog centra Univerziteta u Sarajevu u periodu između 2023. i 2025. godine. Rezultati: Analizirano je ukupno 647 poroda. Visok udio novorođenčadi u obje skupine postigao je Apgar rezultat ≥9 u 1 minuti. Stopa carskih rezova nije se značajno razlikovala između metoda analgezije. Zaključak: Epiduralna i jednokratna spinalna analgezija sigurne su i učinkovite metode za ublažavanje boli tijekom vaginalnog poroda u tercijarnom okruženju.

Ključne riječi: epiduralna analgezija, jednokratna spinalna analgezija, vaginalni porod, bol

INTRODUCTION

Regional analgesia has been shown to be effective in providing pain relief in labour. Regional analgesia can be an epidural, a spinal or a combination of the two. An epidural is when the pain-relieving drugs are injected into the part of the body which surrounds the spinal column (epidural space). It is most common for these drugs to be infused through a very fine tube (catheter) positioned in the epidural space. Traditionally, high concentrations of local anaesthetic drugs were used. These numbed the woman from the waist downwards giving pain relief for most women. However, it also caused leg weakness, poor mobility and difficulty for the mother giving birth. This led to increased instrumental vaginal births with subsequent increased bruising, pain and incontinence later on for the mother. More recently with epidurals, low-dose local anaesthetic drugs have been used in combination with opioid drugs. Here there is less numbing of the woman's legs but the opioid drugs cross the placenta and may make the baby sleepy (1).

Recently, one of the problems in developing countries is pregnant women who insist on cesarean section due to the fear of painful vaginal delivery. Childbirth is known as one of the most painful emotional experiences to deal with severe pain during a woman's life (2). Labour pain has several physiologic and emotional consequences for the mother and even fetus, like the leftward shift of oxyhemoglobin dissociation curve and fetus low oxygen delivery afterward (3). There are various methods to reduce labor pain, including medical and non-medical methods. Other non-medical methods are physiological delivery, delivery in water, childbirth in the presence of the family, massage, Lamaze technique, relaxation, hypnotism, aromatic therapy, shiatsu, subdermal, intradermal sterile water injection, etc. to ameliorate delivery. Unfortunately, these methods require more time and facilities (4-6). Other medical methods are Entonox, epidural or spinal analgesia, intravenous infusion, or using intramuscular drugs, like meperidine, promethazine, remifentanil, and ketamine (7-9). Another way to reduce pain in the second stage of labor that can be effective is to use transvaginal local anesthetic cream (10). In developing countries, the vast majority of pregnant women want to have labor analgesia, but less than 40% can get analgesia (11).

Several medical analgesic methods have been proposed, and neuraxial techniques are considered as the most acceptable and practical ways to reduce labor pain (12). Epidural analgesia is one of the best medical methods to reduce labor pain (13). The epidural method does not need advanced technical and clinical considerations (14).

AIM

The aim of the study was to analyze the clinical practice of using epidural and single-shot spinal analgesia in vaginal delivery at the Clinical Center University of Sarajevo and to evaluate early neonatal outcomes.

MATERIALS AND METHODS

This retrospective analysis included births conducted in the 2023-2025 period. The type of analgesia, the way the labor ended and the Apgar score in the first minute were monitored.

The criteria for inclusion in the study were: Clinical status: Term pregnant women (gestational age \(\ge \) 37 weeks) with a singleton pregnancy and a present indication for vaginal delivery. Applied method: Patients in whom analgesia during vaginal delivery was exclusively epidural analgesia (EDA) or single-shot spinal analgesia (SSA). Time frame: Delivery performed in the period from 1 January 2023 to 31 December 2025. Documentation: Complete and orderly medical documentation (maternity history and temperature chart of the newborn) containing all analyzed maternal and neonatal outcomes.

Statistical data are presented in tables and graphically. Categorical variables, including clinical categories of Apgar score (newborns with Apgar score ≥ 9 versus < 9), are presented in the form of absolute numbers and percentages (n, %).

RESULTS

In the 2023-2025 period, at the Clinic of Gynecology and Obstetrics of the Clinical Center University of Sarajevo (CCUS), two methods of regional analgesia were applied in vaginal delivery: epidural analgesia and single-shot spinal analgesia.

The total number of women in labor who received epidural analgesia was 379 (2023: 48, 2024: 147, 2025: 184). Out of that number, delivery was completed by caesarean section (SC) in 44 parturients (2023: 8, 2024: 19, 2025: 17).

Single-shot spinal analgesia was applied to a total of 268 parturients (2023: 38, 2024: 90, 2025: 140). 31 parturients ended their labor by caesarean section (2023: 9, 2024: 10, 2025: 12).

Table 1 **Use of epidural and single-shot spinal analgesia and completion of cesarean delivery (2023-2025).**

Year	Epidural (total)	Epidural → SC	Single-shot (total)	Single-shot → SC
2023	48	8	38	9
2024	147	19	90	10
2025	184	17	140	12
Total	379	44	268	31

In the observed period, a continuous increase in the use of both methods of analgesia was recorded, especially in 2025. The proportion of deliveries completed by caesarean section is present in both groups, without a significant disproportionate increase, which indicates the clinical safety and justification of the use of regional analgesia in vaginal delivery in a tertiary institution.

In the observed period (2023-2025), the Apgar score in the 1st minute was analyzed in newborns born with epidural and single-shot spinal analgesia.

Table 2 **Apgar score of newborns after epidural analgesia (2023-2025).**

Year	Apgar 10	Apgar 9	Apgar 8	Total
2023	35	10	3	48
2024	111	15	11	137*
2025	120	20	8	148*
Total	266	45	22	333

*The difference in the total number compared to all epidural births refers to births completed by caesarean section.

Table 3 **Apgar score of newborns after single-shot spinal analgesia (2023-2025).**

Year	Apgar 10	Apgar 9	Apgar 8	Apgar 7	Apgar 6	Total
2023	23	13	–	2	–	38
2024	73	9	6	–	2	90
2025	116	8	10	6	–	140
Total	212	30	16	8	2	268

Apgar scores of 9-10 were dominantly recorded with both analgesia methods, indicating good neonatal condition immediately after delivery. Epidural analgesia was associated with a higher number of neonates with Apgar scores of 10, while lower values (Apgar 6-7) were rarely recorded in the single-shot spinal analgesia group, without a clinically significant increase in adverse outcomes.

Percentage analysis of Apgar score (≥9)

Epidural analgesia

2023
- Apgar ≥9: (35 + 10) / 48 = 93.8%
- Apgar 8: 6.2%

2024
- Apgar ≥9: (111 + 15) / 137 = 92.0%
- Apgar 8: 8.0%

2025
- Apgar ≥9: (120 + 20) / 148 = 94.6%
- Apgar 8: 5.4%

Total (2023–2025)
- Apgar ≥9: 93.1%
- Apgar ≤8: 6.9%

Single-shot spinal analgesia

2023
- Apgar ≥9: (23 + 13) / 38 = 94.7%
- Apgar ≤7: 5.3%

2024
- Apgar ≥9: (73 + 9) / 90 = 91.1%
- Apgar ≤8: 8.9%

2025
- Apgar ≥9: (116 + 8) / 140 = 88.6%
- Apgar ≤8: 11.4%

Total (2023–2025)
- Apgar ≥9: 90.3%
- Apgar ≤8: 9.7%

In the analyzed period, the majority of newborns in both groups had an Apgar score ≥9 in the first minute. Epidural analgesia was associated with a consistently high percentage of favorable neonatal outcomes (92–95%) over all three years. A high proportion of Apgar ≥9 was also noted in the single-shot spinal analgesia group, with a slight increase in lower values in 2025, without clinically significant adverse outcomes.

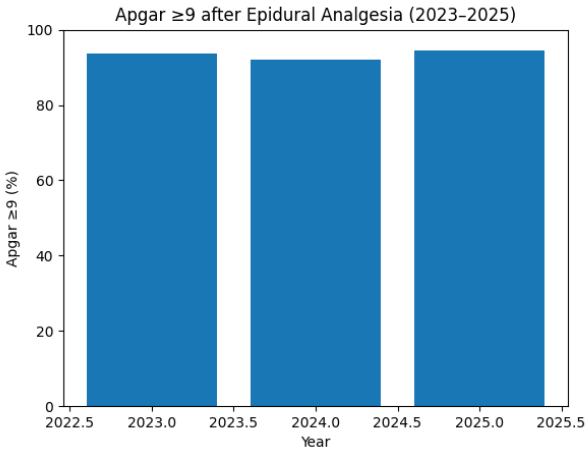

Figure 1 **Percentage of newborns with Apgar score ≥9 after epidural analgesia (2023-2025), CCUS.**

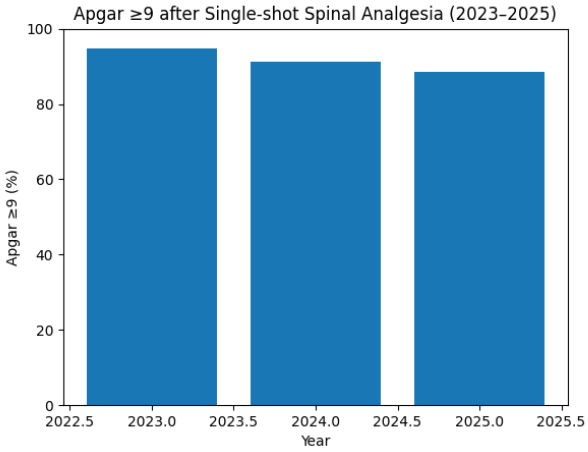

Figure 1 **Percentage of newborns with Apgar score ≥9 after single-shot spinal analgesia (2023-2025), CCUS.**

DISCUSSION

Epidural analgesia has been shown to be the most effective method of providing pain relief in labour (15) when compared with non-epidural methods (16). On a national level, an epidural technique is used for pain relief in approximately 25% of labouring women in the UK (17) and in as many as 58% in the USA (18).

The research results show that in the observed period, a continuous increase in the use of both methods of analgesia was recorded, especially in 2025. The proportion of deliveries completed by caesarean section is present in both groups, without a significant disproportionate increase, which indicates the clinical safety and justification of the use of regional analgesia in vaginal delivery in a tertiary institution.

In the observed period (2023-2025), the Apgar score in the 1st minute was analyzed in newborns born with epidural and single-shot spinal analgesia.

In the analyzed period, the majority of newborns in both groups had an Apgar score ≥9 in the first minute. Epidural analgesia was associated with a consistently high percentage of favorable neonatal outcomes (92-95%) over all three years. A high proportion of Apgar ≥9 was also noted in the single-shot spinal analgesia group, with a slight increase in lower values in 2025, without clinically significant adverse outcomes.

The obtained results are in accordance with the available literature, which confirms that regional analgesia in vaginal delivery does not negatively affect the early neonatal outcome. A high percentage of Apgar score ≥9 in both groups indicates a good perinatal adaptation of the newborns. The slightly higher variability of the Apgar score in the single-shot spinal group can be explained by the faster onset of action and hemodynamic changes in the mother, but without a clinically significant effect on the neonatal outcome.

Mardirosoff C, et al. (19) reported a link between fetal bradycardia and intrathecal opioid injection. In our research, only two cases of the spinal group had FHR variation. In these cases, it was only a variable deceleration and improved by general maneuvers, such as dextrose infusion. If patients with spinal analgesia need an immediate cesarean section, there is no contraindication to spinal or even epidural anesthesia (20).

In this study, 5 patients from the spinal group and 7 patients from the epidural group were scheduled for emergent cesarean section due to labour arrest and placental abruption, and there was no significant difference between the groups. In the spinal group, only 10 women needed repeated blocks once, and in the epidural group, 16 women received reinfusion of analgesia. No additional differences or side effects have been reported in these patients.

Abdel Barr T, et al. (21) compared the two spinal and epidural groups. In the spinal group, 3.75 mg hyperbaric bupivacaine and 25 mcg fentanyl with 0.75 mL saline, and for the epidural group, 4 ml hyperbaric bupivacaine with 4 mL saline and 1 mL (50 mcg) fentanyl were infused. Pain relief was recorded by the VAS and verbal expression, and ot her variables were recorded at the end of the study. They believed that spinal analgesia was better than epidural analgesia and it can be a good alternative for the epidural block. Spinal analgesia is easier to perform, cost-effective, and can provide effective analgesia than epidural analgesia (21), which is consistent with our research. However, in this study, they did not report any renewed doses for the prolonged spinal or epidural blocks.

Kuczkpwski KM, et al. (22) evaluated 62 pregnant women with spinal analgesia during delivery. They received 2.5 mg bupivacaine, 0.25 mg morphine, and 45 μg clonidine via a small 25-gauge needle. They assessed satisfaction with analgesia and other side effects. Also, 81% of the patients expressed higher satisfaction, and approximately 11% were satisfied with this method (22). In our research, satisfaction with spinal and epidural analgesia was 79.2% and 70.5%, respectively.

Mazur-Sunko B, et al. (23) compared spinal and epidural analgesia and suggested spinal analgesia as a suitable option for the epidural method because of the rapid onset and similar side effects, which is in line with our findings.

Minty RG, et al. (24) evaluated unique spinal and other pain-relieving techniques. Yeh et al. (25) evaluated the efficacy of morphine in combination with bupivacaine and fentanyl to cause spinal analgesia. The analgesic effects were long-lasting, and the other criteria were not different from the epidural method (25).

Due to time constraints of single-shot spinal analgesia, it is not possible to make a maternal indication to start analgesia at the beginning of labor, which seems to be the main limitation of the spinal method.

CONCLUSION

Epidural and single-shot spinal analgesia represent safe and efficient methods of painless delivery, without negative impact on the early neonatal outcome assessed by the Apgar score. The results confirm the justification of their application in the clinical practice of a tertiary healthcare institution.

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Authors' contributions: MEIA, NI-G, ES, SB, JM and DžŠ gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

Chronic Wound Management Practice and Associated Factors among Nurses in Public Healthcare Institutions in Bosnia and Herzegovina

Praksa liječenja hroničnih rana i povezani faktori među medicinskim sestrama u javnim zdravstvenim ustanovama u Bosni i Hercegovini

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ABSTRACT

Introduction: Nurses play a key role in chronic wound management. Variability in the quality of clinical practice represents a challenge to effective wound care. Aim: To assess the quality of chronic wound management practices among nurses in public healthcare institutions in Bosnia and Herzegovina and to identify sociodemographic, professional, and institutional factors associated with practice quality. Materials and methods: A quantitative, cross-sectional, observational-analytical study was conducted among 699 nurses. Data were collected using a structured questionnaire developed in accordance with the recommendations of the European Wound Management Association. Results: A total of 426 participants (60.94%) demonstrated unsatisfactory practice, 261 (37.34%) showed practice with significant deficiencies requiring improvement, and only 12 (1.72%) achieved satisfactory practice in chronic wound management. Conclusion: Chronic wound management practice among nurses was predominantly suboptimal. Strengthening institutional protocols, providing advanced practical education, and implementing structured quality improvement initiatives may enhance evidence-based chronic wound management.

Keywords: chronic wounds, wound management, nurses, nursing practice, quality of health care

SAŽETAK

Uvod: Medicinske sestre imaju ključnu ulogu u tretmanu hroničnih rana. Varijabilnost u kvalitetu kliničke prakse predstavlja izazov za efektivan tretman rana. Cilj: Procijeniti kvalitet prakse liječenja hroničnih rana među medicinskim sestrama u javnim zdravstvenim ustanovama u Bosni i Hercegovini i identificirati sociodemografske, profesionalne i institucionalne faktore povezane sa kvalitetom prakse. Materijali i metode: Kvantitativna, presječna, opservacijsko-analitička studija provedena je među 699 medicinskih sestara. Podaci su prikupljeni korištenjem strukturiranog upitnika razvijenog u skladu sa preporukama Evropskog udruženja za tretman rana. Rezultati: Ukupno 426 ispitanika (60,94%) pokazalo je nezadovoljavajuću praksu, 261 ispitanik (37,34%) imao je praksu sa značajnim nedostacima koji zahtijevaju poboljšanje, dok je samo 12 ispitanika (1,72%) postiglo zadovoljavajući nivo prakse u tretmanu hroničnih rana. Zaključak: Praksa tretmana hroničnih rana među medicinskim sestrama bila je pretežno suboptimalna. Jačanje institucionalnih protokola, napredna praktična edukacija i strukturirane inicijative za poboljšanje kvaliteta mogu unaprijediti tretman hroničnih rana zasnovan na dokazima.

Ključne riječi: hronične rane; tretman rana; medicinske sestre; sestrinska praksa; kvalitet zdravstvene zaštite.

INTRODUCTION

Chronic wounds represent a growing global health challenge driven by population ageing, the increasing prevalence of diabetes and obesity, rising healthcare expenditures, and the emergence of difficult-to-treat infections associated with biofilms and antimicrobial resistance (1). Unlike acute wounds, chronic wounds fail to progress through the normal stages of healing in a timely and orderly manner and often remain in a prolonged inflammatory state. Consequently, they require continuous monitoring and multidisciplinary management to prevent severe complications, including infection, oedema, gangrene, bleeding, and limb amputation (2). These complications may result in disability and further impair wound healing, creating a vicious cycle with substantial physical, psychological, and social consequences for affected individuals (2,3).

Chronic wounds are frequently under-recognized because they are often documented as secondary conditions rather than primary diagnoses. Nevertheless, they constitute a significant public health burden worldwide. It is estimated that approximately 1–2% of individuals in developed countries will experience a chronic wound during their lifetime, and this burden is expected to increase further as populations continue to age (2). In the United States, approximately 6.5 million individuals are affected annually, while prevalence studies conducted in Europe report rates of three to four persons with one or more wounds per 1,000 population (7,8). Furthermore, approximately 15% of chronic wounds remain unhealed after one year despite treatment, reflecting the complexity of their management (8). Diabetic foot ulcers affect between 5.3% and 10.5% of individuals with diabetes and remain one of the leading causes of non-traumatic lower-limb amputation worldwide (8). Pressure injuries also continue to represent a substantial healthcare challenge, particularly among older adults, hospitalized patients, and individuals with limited mobility, contributing significantly to morbidity, prolonged hospitalization, and healthcare costs (9).

The consequences of chronic wounds extend far beyond tissue damage. Patients frequently experience persistent pain, impaired mobility, anxiety, depression, social isolation, prolonged hospitalization, reduced quality of life, and increased mortality (3,4). In addition to their clinical impact, chronic wounds impose a considerable economic burden on healthcare systems. A retrospective analysis of Medicare beneficiaries reported that 8.2 million individuals were treated for wounds with or without infection, resulting in annual healthcare expenditures ranging from 28.1 to 96.8 billion USD (1). Surgical wounds and diabetic foot ulcers accounted for the highest treatment costs, while the increasing shift toward outpatient wound management continues to influence healthcare resource utilization. Globally, expenditures related to wound care continue to rise, emphasizing the need for effective, cost-efficient, and evidence-based management strategies (1,4).

Chronic wounds are commonly classified according to their underlying aetiology, including pressure injuries, diabetic foot ulcers, venous leg ulcers, and arterial ulcers (2). Effective management requires comprehensive assessment and treatment not only of the wound itself but also of the underlying local and systemic factors that impair healing (5). Although substantial advances have been achieved in understanding wound healing mechanisms and developing innovative diagnostic and therapeutic approaches, the implementation of evidence-based wound care remains inconsistent across healthcare settings (5,6).

Nurses play a pivotal role in the prevention, assessment, treatment, and long-term monitoring of patients with chronic wounds. Wound care has historically been a fundamental component of nursing practice, encompassing wound assessment, dressing selection and application, patient education, nutritional support, mobilization, and psychosocial care (1). As wound management has become increasingly complex, specialized educational initiatives and professional development programmes have sought to strengthen nurses' competencies and promote evidence-based practice (11,16,18,19). Research consistently demonstrates that nurses' knowledge, attitudes, and clinical competence significantly influence the quality of wound care delivered and ultimately affect patient outcomes (12-17).

Despite the availability of evidence-based guidelines and educational resources, considerable variation in wound care practice persists. Barriers to the implementation of evidence-based wound management include insufficient formal education, limited access to continuing professional development, time constraints, resource limitations, organizational challenges, and uncertainty regarding the selection of appropriate wound care interventions and products (10,11,17,19). Recent evidence further suggests that adequate nursing resources, organizational support, and access to continuing education are associated with improved wound management outcomes and higher quality of care (20).

Despite the growing body of evidence supporting evidence-based wound management, substantial variations in nursing practice continue to be reported across healthcare settings. Differences in education, clinical experience, access to training, institutional support, and resource availability may significantly influence the quality of wound care delivered. However, data regarding the quality of chronic wound management practice among nurses and the factors associated with optimal performance remain limited in many healthcare systems. Therefore, assessing current practice patterns and identifying determinants of high-quality wound care are essential for developing targeted educational and organizational interventions aimed at improving patient outcomes and promoting evidence-based wound management.

AIM

The aim of this study was to evaluate the quality of chronic wound management practices among nurses employed across different levels of healthcare in Bosnia and Herzegovina and to identify factors associated with variations in practice quality. Specifically, the study examined the implementation of evidence-based wound care practices among nurses working in primary care institutions, secondary and tertiary hospitals, intensive care units, surgical services, and other clinical departments, while exploring the influence of sociodemographic characteristics, professional qualifications, workplace characteristics, certification in wound care, and institutional support mechanisms on clinical practice performance.

MATERIALS AND METHODS

This study was designed as a quantitative, cross-sectional, observational–analytical study. The research was conducted among nurses and nursing technicians working in healthcare institutions in Bosnia and Herzegovina. Participants were recruited through registered Chambers and Associations of Nurses and Nursing Technicians in Bosnia and Herzegovina. The study included nurses from different levels of healthcare, including primary, secondary, and tertiary healthcare institutions.

The study population consisted of nurses and nursing technicians involved in clinical practice and patient care. Participants worked in various healthcare settings, including primary healthcare services, hospital departments, surgical disciplines, internal medicine departments, intensive care units, emergency medicine, paediatrics, geriatric care, and other clinical areas in which chronic wound prevention, monitoring, or treatment may be performed. According to the original doctoral research, respondents came from all administrative parts of Bosnia and Herzegovina, including

the Federation of Bosnia and Herzegovina, Republika Srpska, and Brčko District. In the final analysis of the present manuscript, 699 fully completed questionnaires were included.

Data were collected using an anonymous online questionnaire distributed via Google Forms. Data collection was conducted during the period November 2021 – March 2022. Participation was voluntary and anonymous. Before completing the questionnaire, participants were informed about the purpose and aim of the study, confidentiality of the collected data, and the exclusive use of data for scientific research purposes. Completion and submission of the online questionnaire were considered as informed consent.

The questionnaire was developed based on a review of relevant scientific and professional literature related to chronic wound management. It was adapted and modified according to the recommendations of the European Wound Management Association (EWMA) and the Croatian Wound Association (HUR). Selected items were adapted from previously published instruments and literature, including the Quality of Life with Chronic Wounds Questionnaire (Wound-QoL), the Wound Care Survey, and other scientific sources related to chronic wound care. The original instrument contained 64 items divided into four domains: sociodemographic characteristics, knowledge, attitudes, and practice. However, the present paper reports only findings related to the practice domain.

The practice domain included 24 items assessing routine clinical procedures related to chronic wound prevention, assessment, monitoring, dressing selection, wound cleansing, microbiological sampling, pain management, use of supportive therapy, and application of institutional protocols. A total practice score was calculated by summing item responses, with higher scores indicating better implementation of recommended wound care practices. The total practice score ranged from 0 to 19. In addition, a relative practice score was calculated by transforming the total score to a 0–100 scale. Based on predefined cut-off values, practice quality was categorized into four levels: unsatisfactory practice, practice with significant deficiencies requiring improvement, satisfactory practice, and excellent practice.

The internal consistency of the practice scale was assessed using Cronbach's alpha coefficient. Given the exploratory nature of the study and the heterogeneity of the practice domain, which included chronic wound prevention, assessment, monitoring, and treatment, a Cronbach's alpha value of 0.611 was considered acceptable for preliminary reliability assessment. Since deletion of individual items did not substantially improve the overall coefficient, all items were retained in the final analysis.

Statistical analysis was performed using JASP software, version 0.95. Descriptive statistics were used to summarize sociodemographic, professional, institutional, and practice-related characteristics of the participants. Continuous variables were presented as mean ± standard deviation (SD) and range, while categorical variables were presented as absolute numbers and percentages.

To identify factors associated with chronic wound management practice quality, multiple linear regression analysis was performed. The relative practice score (%) was used as the dependent variable. Independent variables included sex, level of healthcare, years of work experience, education level, workplace position, presence of institutional protocols for monitoring chronic wound healing, clinical field, and certification in chronic wound management.

Categorical variables were entered into the regression model using dummy coding, with reference categories defined before analysis. The primary healthcare level was used as the reference category for healthcare level. For dichotomous predictors, such as the presence of institutional protocols and certification in chronic wound management, the absence of the characteristic was treated as the reference category unless otherwise specified in the model. Other categorical predictors, including education level, workplace position, and clinical field, were analyzed according to their respective predefined reference categories.

Regression coefficients (B), standard errors (SE), 95% confidence intervals (CI), and p-values were reported. Model fit was evaluated using R^2, adjusted R^2, and root mean square error (RMSE). A p-value <0.05 was considered statistically significant.

RESULTS

A total of 699 nurses and nursing technicians were included in the final analysis. The largest age group consisted of participants aged 36-45 years (255; 36.5%). Regarding healthcare level, 248 (35.48%) participants worked in primary healthcare, 177 (25.32%) in secondary healthcare, and 274 (39.20%) in tertiary healthcare. The distribution of participants across different healthcare levels indicates that the sample included nurses from primary, secondary, and tertiary healthcare settings, allowing comparison of practice quality across different institutional contexts.

Analysis of individual practice items demonstrated substantial variability in the implementation of chronic wound management procedures. Preventive and assessment-related practices showed relatively better results. The use of specialized beds, mattresses, or pressure-relieving cushions for pressure ulcer prevention was reported as satisfactory by 427 participants (61.1%), while risk assessment for chronic wounds and the use of assessment tools were satisfactory in 512 participants (73.2%). Mandatory procedures applied to chronic wounds were reported as satisfactory by 516 participants (73.8%).

However, several clinically important areas demonstrated considerable deficiencies. Unsatisfactory practice was observed in wearing sterile gloves during dressing changes and chronic wound treatment in 587 participants (84.0%), and in the administration of analgesics or local anaesthetics before wound treatment in 592 participants (84.7%). The use of enzymes for the removal of necrotic tissue was unsatisfactory in 559 participants (80.0%), while the use of hydrocolloid dressings in vascular chronic wounds was unsatisfactory in 574 participants (82.1%). Monitoring and surveillance of chronic wounds were also unsatisfactory in 435 participants (62.2%).

Microbiological sampling in chronic wounds was satisfactory in 440 participants (62.9%); however, appropriate sampling in infected chronic wounds was satisfactory in only 277 participants (39.6%), indicating an important gap in infection-related wound care practice. Pressure ulcer assessment showed the most favorable results, with 421 participants (60.2%) achieving excellent practice, while only 31 participants (4.4%) were categorized as unsatisfactory.

The overall mean practice score was 9.54 ± 2.62, with a range from 0 to 19. The corresponding relative practice score was 50.18 ± 13.81%, ranging from 0 to 100%. Based on predefined practice categories, 426 participants (60.94%) demonstrated unsatisfactory practice, while 261 participants (37.34%) had practice with significant deficiencies requiring improvement. Only 12 participants (1.72%) achieved satisfactory practice, and none of the participants achieved excellent practice (Table 1).

Table 1. **Overall practice score and classification of chronic wound management performance**

Variable	Value
Practice score, mean ± SD	9.54 ± 2.62
Practice score range	0–19
Relative practice score, mean ± SD	50.18 ± 13.81%
Relative practice score range	0–100%
Unsatisfactory practice	426 (60.94%)
Practice with significant deficiencies requiring improvement	261 (37.34%)
Satisfactory practice	12 (1.72%)
Excellent practice	0 (0.00%)

These findings indicate that the overall quality of chronic wound management practice among nurses was predominantly suboptimal. Although some preventive and assessment-related procedures were implemented more consistently, major practical gaps were identified in sterile technique, pain management, enzymatic debridement, use of advanced dressings, appropriate sampling of infected wounds, and systematic wound monitoring.

Multiple linear regression analysis was performed to identify factors associated with the relative practice score. Employment at the tertiary healthcare level was significantly associated with higher practice scores (B = 7.273, 95% CI: 3.024 to 11.523, $p < 0.001$). A university degree was also positively associated with better practice performance (B = 3.428, 95% CI: 0.775 to 6.080, $p = 0.011$). Nurses working as ward nurse managers had significantly higher practice scores compared with the reference category (B = 4.635, 95% CI: 0.987 to 8.283, $p = 0.013$). In contrast, the absence of an institutional protocol for monitoring chronic wound healing was significantly associated with lower practice scores (B = −3.938, 95% CI: −6.200 to −1.676, $p < 0.001$). Working in other clinical fields was also associated with lower practice scores (B = −6.258, 95% CI: −10.960 to −1.550, $p = 0.009$), while certification in chronic wound management showed a negative association with practice score (B = −2.261, 95% CI: −4.490 to −0.032, $p = 0.047$). Other examined variables, including sex, secondary healthcare level, years of work experience, chief nursing officer position, and most specific clinical fields, were not significantly associated with the relative practice score ($p > 0.05$) (Table 2).

Table 2. **Multiple linear regression analysis of factors associated with relative practice score**

Predictor	B	95% CI	p-value
Tertiary healthcare level	7.273	3.024 to 11.523	<0.001
University degree	3.428	0.775 to 6.080	0.011
College degree	3.980	−0.267 to 8.227	0.066
Ward nurse manager	4.635	0.987 to 8.283	0.013
No institutional wound monitoring protocol	−3.938	−6.200 to −1.676	<0.001
Other clinical field	−6.258	−10.960 to −1.550	0.009
Certified nurse for chronic wound management	−2.261	−4.490 to −0.032	0.047

Overall, the regression model indicated that better chronic wound management practice was associated with employment in tertiary healthcare institutions, higher educational level, and ward-level managerial position. Conversely, the absence of institutional wound monitoring protocols, employment in less specialized or heterogeneous clinical fields, and certification in chronic wound management were associated with lower practice scores. These findings emphasize the importance of standardized protocols, structured education, institutional support, and further evaluation of the content and practical effectiveness of wound care certification programs.

DISCUSSION

The findings of this study demonstrate that chronic wound management practice among nurses in Bosnia and Herzegovina was predominantly suboptimal. The mean relative practice score was 50.18 ± 13.81%, while 426 participants (60.94%) were classified as having unsatisfactory practice and 261 (37.34%) showed significant deficiencies requiring improvement. Only 12 participants (1.72%) achieved satisfactory practice, and none reached an excellent level. These results indicate a substantial gap between recommended standards of chronic wound care and their implementation in routine nursing practice.

This finding is clinically important because chronic wound management requires consistent application of evidence-based procedures, including prevention, risk assessment, wound monitoring, dressing selection, infection control, pain management, and documentation. Inadequate implementation of these procedures may contribute to delayed healing, infection, prolonged hospitalization, higher healthcare costs, and reduced quality of life among patients with chronic wounds (1–4). Therefore, the low overall practice score should be interpreted not only as an educational issue, but also as an indicator of broader organizational and institutional weaknesses in wound care delivery.

At the item level, several important deficiencies were identified, particularly in the use of sterile gloves during dressing changes, administration of analgesics or local anaesthetics before wound treatment, enzymatic debridement, use of hydrocolloid dressings in vascular chronic wounds, and systematic wound monitoring. These findings suggest that routine wound care may still rely partly on habit-based or institution-specific routines rather than standardized evidence-based protocols. Similar concerns have been reported in previous studies, where wound care practice among nurses was influenced by insufficient structured education, limited access to guidelines, uncertainty in wound product selection, and weak translation of evidence into bedside decision-making (10,11,14,17,19).

The observed gaps in pain management are particularly relevant because chronic wounds are frequently associated with persistent pain, procedural pain, anxiety, impaired mobility, and reduced quality of life (3,4). Failure to provide adequate analgesia before wound treatment may reduce patient cooperation, increase psychological distress, and negatively affect trust in healthcare providers. This finding indicates that pain assessment and pain control should be integrated into chronic wound care protocols as essential nursing responsibilities.

Deficiencies in enzymatic debridement and the use of advanced dressings may reflect limited availability of wound care products, insufficient practical training, or uncertainty regarding indications for specific interventions. Although advanced wound care technologies and structured treatment approaches may improve healing outcomes and reduce costs in selected patient groups, their effectiveness depends on appropriate patient selection, staff competence, and consistent implementation in clinical practice (5,10,11,21-23).

Microbiological sampling also showed mixed results. Although general microbiological sampling was satisfactory in 440 participants (62.9%), appropriate sampling in infected chronic wounds was satisfactory in only 277 participants (39.6%). This discrepancy may indicate uncertainty regarding when and how wound samples should be obtained. Inappropriate sampling may lead to misleading microbiological results, unnecessary antimicrobial therapy, or delayed targeted treatment. Given the growing importance of biofilm-associated infections and antimicrobial resistance in chronic wounds, this finding has direct implications for infection control and antimicrobial stewardship (1,24).

Employment at the tertiary healthcare level was significantly associated with higher practice scores. This may be explained by greater exposure to complex chronic wounds, better access to specialist teams, more frequent interdisciplinary collaboration, and greater availability of diagnostic and therapeutic resources. However, the overall practice score remained modest even with this positive association, indicating that tertiary-level employment alone is not sufficient to ensure optimal chronic wound management.

Higher educational level was also associated with better practice performance. Nurses with a university degree had significantly higher practice scores, while college-level education showed a borderline association. This supports the importance of advanced nursing education in improving clinical reasoning, evidence-based decision-making, and the ability to apply guidelines in complex wound care situations. Similar findings have shown that higher educational preparation, stronger nursing resources, and better work environments are associated with improved quality of care and better outcomes among patients with chronic wounds (11,18,20). However, formal education should be complemented by continuous practical training, clinical mentorship, and institution-specific protocols.

Ward nurse managers demonstrated significantly higher practice scores compared with the reference category. This may reflect greater clinical experience, responsibility for supervising nursing procedures, involvement in quality control, and stronger familiarity with institutional standards. Ward-level leadership may therefore represent an important mechanism for improving wound care practice through protocol implementation, monitoring of adherence, identification of training needs, and promotion of evidence-based care.

One of the strongest organizational findings was the negative association between the absence of institutional protocols for monitoring chronic wound healing and practice score. Without written protocols, nurses may rely on individual experience, local habits, or inconsistent instructions, leading to variability in assessment, dressing selection, documentation, pain management, infection control, and follow-up. Standardized protocols could improve continuity of care between primary, secondary, and tertiary institutions and provide a shared framework for clinical decision-making (10,19,20).

Working in less specialized or heterogeneous clinical fields was associated with lower practice scores. This may be explained by lower exposure to chronic wound cases, reduced access to wound care training, or weaker integration of wound management into routine departmental protocols. Therefore, educational interventions should not be limited only to departments that frequently manage chronic wounds, because patients with chronic wounds may appear across a wide range of clinical settings.

An unexpected finding was the negative association between certification in chronic wound management and practice score. This result should be interpreted cautiously. It may reflect differences in the content, duration, quality, and standardization of certification programmes. Another possible explanation is that certified nurses may work more often with complex, non-healing, or high-risk wounds, making their practice environment more demanding. Certification alone may also be insufficient if it is not supported by institutional protocols, adequate staffing, access to wound care products, and opportunities for practical skill development. Future research should therefore examine not only whether nurses possess certificates, but also the type, recency, and practical content of certification programmes.

The findings of this study are broadly consistent with previous evidence suggesting that nurses' wound care practice is influenced by education, organizational support, resource availability, and access to evidence-based guidelines (10–14,17,19,20). The present study adds to this evidence by showing that similar challenges are present in Bosnia and Herzegovina and by identifying specific factors associated with practice quality in a large sample of nurses across different healthcare levels. Given the limited regional evidence on chronic wound management practice, these findings provide useful baseline data for planning targeted educational and organizational interventions.

From a practical perspective, the results indicate several priorities for nursing practice. Healthcare institutions should develop and implement standardized protocols for chronic wound assessment, monitoring, dressing selection, infection management, pain control, and documentation. Continuous professional education should focus on practical skill development, including sterile technique, pain management before dressing changes, appropriate use of debridement methods, advanced dressings, microbiological sampling, and systematic follow-up. Ward nurse managers and experienced nurses should be involved as clinical mentors and local champions for evidence-based wound care.

The clinical implications are substantial. Improving nurses' chronic wound management practice may contribute to earlier recognition of complications, more appropriate use of wound care products, better pain control, reduced infection risk, improved continuity of care, and potentially faster wound healing. Given the clinical, psychological, and economic burden of chronic wounds, investment in nursing education, protocols, and organizational support may benefit patients, nurses, institutions, and healthcare systems (1,4,20). Improved standardization of nursing practice may also contribute to the prevention of avoidable adverse events and better patient safety (25).

This study has several limitations. Its cross-sectional design does not allow causal conclusions regarding the relationship between associated factors and practice quality. Data were collected using a self-reported questionnaire, which may be affected by recall bias and social desirability bias. Although the sample was large and included nurses from different healthcare levels in Bosnia and Herzegovina, participation was voluntary, which may limit generalizability. The practice scale showed acceptable but modest internal consistency, which may reflect the heterogeneous nature of chronic wound management practice. In addition, the study focused on reported practice rather than direct clinical observation.

Future studies should evaluate the effectiveness of structured educational programmes, standardized protocols, and quality improvement interventions on chronic wound management practice and patient outcomes. Longitudinal and multicentre studies would be valuable for assessing whether improvements in nursing practice translate into better wound healing outcomes, reduced complications, and lower healthcare costs.

In summary, this study showed that chronic wound management practice among nurses in Bosnia and Herzegovina was predominantly suboptimal, with major gaps in several clinically important procedures. Better practice was associated with tertiary healthcare employment, higher education, and ward-level managerial roles, whereas the absence of institutional protocols and work in less specialized clinical fields were associated with poorer practice. These findings emphasize the need for standardized protocols, continuous practical education, stronger nursing leadership, and system-level support to improve evidence-based chronic wound care.

CONCLUSION

This study showed that chronic wound management practice among nurses in Bosnia and Herzegovina was predominantly suboptimal, with marked deficiencies in several essential areas of evidence-based wound care. Although some preventive and assessment-related procedures were implemented more consistently, important gaps were identified in sterile technique, pain management, debridement-related procedures, use of advanced dressings, microbiological sampling, and systematic wound monitoring. Better practice performance was associated with tertiary healthcare employment, higher educational level, and ward-level managerial roles, while the absence of institutional protocols and work in less specialized clinical settings were associated with poorer practice outcomes. These findings indicate that the quality of chronic wound management depends not only on individual nurse characteristics, but also on organizational support, availability of standardized protocols, and opportunities for continuous practical education. Improving chronic wound care in Bosnia and Herzegovina requires the development and implementation of standardized institutional protocols, structured continuing education programmes, practical competency-based training, and stronger involvement of nursing leadership in quality improvement initiatives. Future research should evaluate the effectiveness of educational and organizational interventions on nursing practice and patient-related wound care outcomes.

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Authors' Contributions: AA, EN, MG, FL, JE, AI and AO gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author had role in article drafting and in process of revision. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

Impact of Thyroid Autoantibodies on Pregnancy Outcomes in Women with Hypothyroidism

Utjecaj antitireoidnih antitijela na ishode trudnoće kod žena s hipotireozom

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ABSTRACT

Introduction: hypothyroidism in pregnancy is associated with an increased risk of adverse gestational outcomes. The role of antithyroid antibodies (anti-TPO and anti-Tg) as independent risk factors remains unclear. Aim: to examine the association between elevated titers of antithyroid antibodies and pregnancy outcomes in pregnant women with hypothyroidism. Materials and methods: this retrospective study included 94 pregnant women with hypothyroidism monitored at the Endocrinology Clinic of the Clinical Center of the University of Sarajevo during 2025. All participants were treated with levothyroxine, aiming to maintain TSH levels <2.5 uIU/mL. Two groups were formed: women with elevated (n=45) and normal (n=49) antithyroid antibody levels. Gestational outcomes were analyzed using appropriate statistical tests, including logistic regression. Results: no statistically significant association was found between elevated antibody titers and adverse pregnancy outcomes ($p > 0.05$). Non-significant trends were observed for a higher incidence of preterm birth (13.3% vs 10.2%) and cesarean section (46.7% vs 32.7%) in the antibody-positive group. TSH levels >2.5 uIU/mL were significantly associated with a higher frequency of gestational complications ($p = 0.027$). Conclusion: elevated antithyroid antibody titers are not an independent predictor of adverse pregnancy outcomes in adequately treated pregnant women with hypothyroidism. In contrast, elevated TSH levels represent a significant risk factor, highlighting the importance of optimal hormonal control during pregnancy.

Keywords: hypothyroidism, pregnancy, anti-TPO, anti-Tg, perinatal outcome

SAŽETAK

Uvod: hipotireoza u trudnoći predstavlja rizik za nepovoljne gestacijske ishode. Uloga antitireoidnih antitijela (anti-TPO i anti-Tg) kao nezavisnog faktora rizika ostaje nejasna. Cilj: Ispitati povezanost povišenog titra antitireoidnih antitijela s ishodima trudnoće kod trudnica s hipotireozom. Metode: Retrospektivna studija obuhvatila je 94 trudnice s hipotireozom praćene u Endokrinološkom savjetovalištu tokom 2025. godine u Kliničkom Centru Univerziteta u Sarajevu, koje su bile na terapiji levotiroksinom s ciljem održavanja TSH <2,5 uIU/mL. Formirane su dvije grupe: s povišenim (n=45) i normalnim (n=49) antitireoidnim antitijelima. Analizirani su gestacijski ishodi, uz primjenu odgovarajućih statističkih testova, uključujući logističku regresiju. Rezultati: Nije utvrđena statistički značajna povezanost između povišenog titra antitijela i nepovoljnih ishoda trudnoće ($p > 0,05$). Uočeni su nesignifikantni trendovi veće učestalosti prijevremenog poroda (13,3% vs 10,2%) i carskog reza (46,7% vs 32,7%). Vrijednosti TSH >2,5 uIU/mL bile su značajno povezane s većom učestalošću gestacijskih komplikacija ($p=0,027$). Zaključak: Povišen titar antitireoidnih antitijela nije nezavisan prediktor nepovoljnih ishoda trudnoće kod adekvatno liječenih trudnica s hipotireozom. Nasuprot tome, povišene vrijednosti TSH predstavljaju značajan faktor rizika, što naglašava važnost optimalne hormonske kontrole tokom trudnoće.

Ključne riječi: hipotireoza, trudnoća, anti-TPO, anti-Tg, perinatalni ishod

INTRODUCTION

Hypothyroidism in pregnancy represents an important clinical entity due to its potential impact on maternal and fetal outcomes (1,2). Particular attention is drawn to autoimmune forms of the disease, in which antithyroid antibodies (anti-TPO and anti-Tg) are present, indicating Hashimoto's thyroiditis as the most common cause of hypothyroidism in women of reproductive age (3). Although adverse pregnancy outcomes were previously thought to be primarily associated with thyroid dysfunction, more recent data suggest that the presence of antithyroid antibodies alone may also be linked to an increased risk of miscarriage, preterm birth, and other complications, even in euthyroid women (4,5). However, clinical evidence remains inconsistent. While some studies and meta-analyses indicate a significant association between thyroid autoimmunity and adverse pregnancy outcomes (4), others have not confirmed an independent effect of antibodies when thyroid function is adequately controlled with levothyroxine (6,7). Potential mechanisms are thought to include immune dysregulation, impaired placentation, and chronic low-grade inflammation in early pregnancy (3,5,8). These processes may affect implantation and placental development independently of hormonal status. Given the inconsistent findings and limited data from the local population, further investigation of this association is warranted.

AIM

The aim of the study was to examine the association between elevated titers of antithyroid antibodies and pregnancy outcomes in pregnant women with hypothyroidism, with additional analysis according to antibody type.

MATERIALS AND METHODS

This research was conducted as a retrospective study including 94 pregnant women, of whom 46 (48.9%) had a diagnosis of hypothyroidism established before pregnancy, while 48 (51.1%) were diagnosed at the beginning of pregnancy. Only 6 women presented with overt hypothyroidism at the start of pregnancy, whereas the majority had a subclinical form. All participants were followed throughout pregnancy until delivery and were treated with L-thyroxine, with the therapeutic goal of maintaining TSH levels below 2.5 uIU/mL. The participants were divided into two groups: Group 1 (n=45): elevated titers of antithyroid antibodies (anti-TPO >34 IU/mL and/or anti-Tg >115 IU/mL) Group 2 (n=49): normal titers of antithyroid antibodies. The following parameters were monitored: maternal age (20–43 years), TSH (0.27–4.2 uIU/mL), FT4 (12–22 pmol/L), FT3 (3.1–6.8 pmol/L), gestational age at delivery, neonatal birth weight, Apgar score, mode of delivery, and the presence of gestational complications. The defined outcomes included: preterm birth (≤37 weeks), pregnancy-induced hypertension (PIH), cesarean section, low birth weight (<2500 g), intrauterine death or miscarriage, and Apgar score (7). Statistical analysis: IBM SPSS Statistics version 25 was used for statistical analysis. Numerical variables were presented as mean values with standard deviation, while categorical variables were expressed as absolute numbers and percentages. Statistical analysis included the use of Student's t-test and Fisher's exact test for numerical variables, and the chi-square test for categorical variables. Statistical significance was defined as $p < 0.05$.

Ethical considerations

This retrospective study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study involved the analysis of anonymized medical records of pregnant women treated at the Clinical Center of the University of Sarajevo. All collected data were handled confidentially and used exclusively for scientific purposes. Patient identity was protected throughout the study, and no personally identifiable information was disclosed. As this was a retrospective observational study based on existing medical documentation, no additional interventions or procedures were performed on the participants.

RESULTS

Out of the total of 94 pregnant women with hypothyroidism, 45 (47.87%) had elevated, and 49 (52.13%) had normal titers of antithyroid antibodies. The baseline characteristics of the participants are presented in Table 1. There were no statistically significant differences between the groups in terms of age, TSH, FT3, and FT4 levels, gestational age at delivery, or neonatal birth weight (Table 1).

Table 1 **Baseline characteristics of pregnant women according to antithyroid antibody status.**

Variable	Elevated antibodies (n=45)	Normal antibodies (n=49)	p-value
Age (years)	32,27 ± 4,55	30,78 ± 4,94	0,42
TSH (uIU/mL)	2,59 ± 1,13	2,89 ± 1,32	0,24
FT4 (pmol/L)	12,03 ± 2,00	11,99 ± 2,47	0,21
FT3 (pmol/L)	4,17 ± 0,58	4,29 ± 0,84	0,56
Gestational age at delivery (weeks)	39,05 ± 1,39	39,09 ± 0,94	0,19
Birth weight (g)	3330,22 ± 576,60	3385,51 ± 690,80	0,27

In the analyzed pregnancy outcomes, women with elevated titers of antithyroid antibodies had a higher incidence of preterm birth, preeclampsia/pregnancy-induced hypertension (PIH), and cesarean section; however, these differences were not statistically significant compared to the group with normal antibody levels (Table 2).

Table 2 **Pregnancy outcomes according to antithyroid antibody status.**

Outcome	Elevated antibodies (n=45)	Normal antibodies (n=49)	p-value
Preterm birth	6 (13,33%)	5 (10,20%)	0,75
PIH	2 (4,44%)	0 (0%)	0,22
Cesarean section	21 (46,66%)	16 (32,65%)	0,18
Low birth weight (<2500 g)	2 (4,44%)	3 (6,12%)	1,00
Intrauterine death / miscarriage	4 (8,88%)	3 (6,12%)	0,70
Apgar score≤7	3 (6,67%)	0 (0%)	0,11

No statistically significant association was found between the presence of elevated antithyroid antibodies and preterm birth (p = 0.75). In the group of pregnant women with elevated antibodies, preterm birth occurred in 6/45 (13.3%), whereas in the group with normal antibody levels it was observed in 5/49 (10.2%) (Table 3).

Table 3 **Association between antithyroid antibodies and preterm birth.**

	Preterm birth	Term birth	Total	p-value
Elevated antibodies	6	39	45	0,75
Normal antibodies	5	44	49	

No significant association was observed between TSH levels and antithyroid antibody status (p = 0.79). The distribution of TSH values ≤2.5 and >2.5 was similar in both groups, suggesting that elevated TSH was not associated with a higher frequency of antibody presence (Table 4).

Table 4 **Association between TSH levels and antithyroid antibody status.**

TSH	Elevated antibodies (n=45)	Normal antibodies (n=49)	p-value
≤ 2,5	26 (57,8%)	30 (61,2%)	0,79
> 2,5	19 (42,2%)	19 (38,8%)	

A significant association was observed between elevated TSH levels (>2.5 uIU/L) and the occurrence of gestational complications (p = 0.027). Pregnant women with TSH >2.5 had a higher incidence of complications (17/38; 44.7%) compared to those with TSH ≤2.5 (13/56; 23.2%) (Table 5).

Table 5 **Association between TSH levels and gestational complications.**

TSH	Complications	No complications	Total	p-value
≤ 2,5	13	43	56	0,027
> 2,5	17	21	38	

No statistically significant association was found between antithyroid antibody status and gestational complications (p = 0.68). In the group with elevated antibodies, complications occurred in 13/45 (28.9%), whereas in the group with normal antibodies, they occurred in 16/49 (32.7%) (Table 6).

Table 6 **Gestational complications according to antithyroid antibody status.**

Antibody status	Complications	No complications	Total	p-value
Elevated (n=45)	13 (28,9%)	32 (71,1%)	45	0,68
Normal (n=49)	16 (32,7%)	33 (67,3%)	49	

Analysis according to the type of antithyroid antibody showed no significant association with gestational complications (p = 0.53). Although complications were observed in all subgroups (normal antibodies, elevated anti-TPO, combined anti-TPO and anti-Tg, and isolated elevated anti-Tg), the distribution did not indicate a dominant effect of any specific antibody type (Table 7).

Table 7 **Gestational complications according to the type of antithyroid antibody.**

Antibody type	Complications (n=30)	No complications (n=64)	p-value
Both normal	15	30	0,53
Elevated anti-TPO	7	13	
Elevated anti-TPO i anti-Tg	7	20	
Elevated anti-Tg	1	1	

A multivariable logistic regression model was constructed with gestational complications as the dependent variable. The independent variables included TSH level (>2.5 vs. ≤2.5 uIU/L), presence of anti-TPO antibodies, presence of anti-Tg antibodies, and maternal age. After adjustment for anti-TPO positivity, anti-Tg positivity, and maternal age, TSH >2.5 uIU/L remained a significant predictor of gestational complications (OR = 1.78, 95% CI: 1.10–2.89, p = 0.027), indicating that elevated TSH is an independent risk factor for gestational complications (Table 8).

Table 8 **Multivariable regression analysis of gestational complications.**

Predictor	OR (Odds Ratio)	95% CI	p-value
TSH >2.5 vs ≤2.5	1,78	1,10 – 2,89	0,027

DISCUSSION

In this study, no statistically significant association was found between antithyroid antibodies and adverse pregnancy outcomes in women with adequately controlled hypothyroidism. This finding aligns with parts of the literature suggesting that, with optimal hormone replacement, thyroid autoimmunity does not exert an independent clinical effect (5,6,7). Meta-analyses, however, indicate an increased risk of adverse outcomes in women with positive antibodies, even in euthyroid states, suggesting a potential role of autoimmunity as an independent risk factor (4,9). More recent prospective studies, though, suggest that this effect may be weaker or absent when TSH is adequately controlled (10). In our study, TSH >2.5 uIU/mL was the only independent predictor of gestational complications, emphasizing the importance of thyroid functional status over the mere presence of antibodies (1,5,8). Additional analysis by antibody type did not reveal a significant association with outcomes, although there was a trend toward higher prevalence of anti-TPO antibodies. Due to the limited sample size and the low incidence of adverse outcomes, there remains a possibility of error, where a true association could remain undetected because of insufficient statistical power.

CONCLUSION

Antithyroid antibodies are not an independent predictor of adverse pregnancy outcomes in pregnant women with hypothyroidism receiving levothyroxine therapy. Elevated TSH (>2.5 uIU/mL) represents a significant risk factor, highlighting the crucial role of adequate hormonal control during pregnancy. Further prospective studies with larger sample sizes are needed.

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Authors' contributions: IŠ, VK-B, ŠB, AD-B, RA, AM, MT and OS gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

Vesicoureteral Reflux as a Predictor of Renal Parenchymal Damage in Children with Urinary Tract Infections: A Prospective Study

Vezikoureteralni refluks kao prediktor oštećenja bubrežnog parenhima kod djece sa urinarnim infekcijama: prospektivna studija

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ABSTRACT

Introduction: renal parenchymal damage is a significant complication of urinary tract infections (UTIs) in children and may lead to long-term renal impairment. Vesicoureteral reflux (VUR) and recurrent infections are considered major risk factors, but their independent and combined effects require further clarification in clinical practice. Aim: to evaluate the association between VUR, recurrent UTIs, and renal parenchymal damage, and to identify independent predictors of renal injury in pediatric patients. Materials and methods: a prospective observational study included 100 children with confirmed UTI. VUR was assessed using voiding cystourethrography, and renal parenchymal damage was evaluated by dimercaptosuccinic acid (DMSA) scintigraphy. Demographic and clinical data were collected systematically. Univariate and multivariate logistic regression analyses were performed to determine predictors of renal damage. Results: renal parenchymal damage was detected in 40% of patients. VUR was present in 45% of children and was significantly associated with renal damage (OR 5.9; $p < 0.001$). Multivariate analysis identified VUR (adjusted OR 5.2; $p < 0.001$) and recurrent UTI (adjusted OR 3.1; $p = 0.01$) as independent predictors. A dose–response relationship was observed, with increasing VUR grade associated with higher risk (OR 2.1 per grade; $p < 0.001$). The highest risk was found in children with both VUR and recurrent UTIs (OR 9.5; $p < 0.001$). Conclusion: VUR, particularly higher grades, and recurrent UTIs are key predictors of renal parenchymal damage. Early identification of high-risk patients is essential for timely intervention and prevention of long-term renal complications.

Keywords: vesicoureteral reflux, urinary tract infection, renal scarring, DMSA, children

SAŽETAK

Uvod: oštećenje bubrežnog parenhima predstavlja značajnu komplikaciju urinarnih infekcija (UTI) kod djece i može dovesti do dugoročnog oštećenja bubrežne funkcije. Vezikoureteralni refluks (VUR) i rekurentne infekcije smatraju se glavnim faktorima rizika, ali njihovi nezavisni i kombinovani efekti zahtijevaju dodatno razjašnjenje u kliničkoj praksi. Cilj: procijeniti povezanost između VUR-a, rekurentnih UTI i oštećenja bubrežnog parenhima, te identifikovati nezavisne prediktore oštećenja bubrega kod pedijatrijskih pacijenata. Materijali i metode: prospektivna opservaciona studija obuhvatila je 100 djece sa potvrđenom UTI. VUR je procijenjen mikcijskom cistouretrografijom, a oštećenje bubrežnog parenhima DMSA scintigrafijom. Demografski i klinički podaci su sistematski prikupljeni. Primijenjene su univarijantna i multivarijantna logistička regresiona analiza radi utvrđivanja prediktora oštećenja bubrega. Rezultati: oštećenje bubrežnog parenhima utvrđeno je kod 40% pacijenata. VUR je bio prisutan kod 45% djece i bio je značajno povezan sa oštećenjem bubrega (OR 5,9; $p < 0,001$). Multivarijantna analiza identifikovala je VUR (prilagođeni OR 5,2; $p < 0,001$) i rekurentne UTI (prilagođeni OR 3,1; $p = 0,01$) kao nezavisne prediktore. Uočen je odnos doza-odgovor, pri čemu je viši stepen VUR-a povezan sa većim rizikom (OR 2,1 po stepenu; $p < 0,001$). Najveći rizik zabilježen je kod djece sa istovremenim VUR-om i rekurentnim UTI (OR 9,5; $p < 0,001$). Zaključak: VUR, posebno višeg stepena, i rekurentne UTI predstavljaju ključne prediktore oštećenja bubrežnog parenhima. Rana identifikacija visokorizičnih pacijenata od suštinskog je značaja za pravovremenu intervenciju i prevenciju dugoročnih bubrežnih komplikacija.

Ključne riječi: ezikoureteralni refluks, urinarna infekcija, ožiljci bubrega, DMSA, djeca

INTRODUCTION

Urinary tract infections (UTIs) are among the most common bacterial infections in childhood and represent a significant cause of morbidity, particularly in infants and young children (1,2). The clinical presentation ranges from asymptomatic bacteriuria to febrile pyelonephritis, and recurrent episodes of infection may lead to permanent renal parenchymal damage (3).

Vesicoureteral reflux (VUR) is a common anatomical and functional disorder in the pediatric population and one of the key risk factors for the development of renal damage (4). The presence of reflux enables the retrograde flow of urine from the bladder into the ureters and kidneys, facilitating the ascending spread of infection (5). The clinical significance of VUR is particularly evident in children with recurrent urinary tract infections, where it increases the risk of developing reflux nephropathy (6).

The pathophysiological mechanism of renal parenchymal damage involves the combined effect of reflux and infection. Retrograde transport of bacteria, together with the host inflammatory response, leads to injury of the tubular and interstitial tissue, resulting in scar formation (7,8). These changes may have long-term consequences, including arterial hypertension and chronic kidney disease (9).

In the diagnostic approach, voiding cystourethrography (VCUG) remains the standard method for detecting and grading VUR, while DMSA scintigraphy is considered the gold standard for identifying renal parenchymal damage (10). Ultrasonography represents an initial, non-invasive method for evaluating the urinary tract (11). However, the use of these diagnostic modalities in clinical practice remains a matter of debate, particularly regarding patient selection and the optimal timing of investigations (12).

In everyday clinical practice, the question remains which patients should undergo detailed radiological evaluation, given the need to balance early diagnosis with the avoidance of unnecessary exposure to invasive procedures and radiation. Despite numerous studies, it is still unclear which group of children with UTIs is at the highest risk for developing permanent renal parenchymal damage.

AIM

The aim of this study was to evaluate the role of vesicoureteral reflux as a predictor of renal parenchymal damage in children with urinary tract infections.

MATERIALS AND METHODS

Study design

A prospective observational study was conducted at a tertiary pediatric center from January 2024 to January 2026. The study included consecutive patient enrollment and follow-up with the aim of evaluating the association between vesicoureteral reflux (VUR) and renal parenchymal damage.

Participants

Children with clinically and laboratory-confirmed urinary tract infection (UTI) were included in the study. The total number of participants was n = 100. The diagnosis of UTI was established based on clinical presentation, positive urine culture, and laboratory findings (leukocyturia, elevated inflammatory markers).

Participants were enrolled consecutively during hospitalization or outpatient follow-up, thereby minimizing selection bias.

Inclusion criteria

- Children with first or recurrent urinary tract infection
- Positive urine culture ($\geq 10^5$ CFU/mL for midstream urine or according to standards for catheterized samples)
- Age 1 month to 10 years
- Written informed consent obtained from parents/legal guardians

Exclusion criteria

- Genetic syndromes associated with renal damage
- Previously diagnosed chronic kidney disease
- Incomplete diagnostic data or inability to complete follow-up
- Children with congenital anomalies of the urinary tract that may independently influence the development of renal parenchymal damage were excluded, including obstructive uropathies (posterior urethral valves, ureteropelvic junction obstruction, ureterovesical junction obstruction), severe structural renal anomalies (multicystic dysplastic kidney, renal dysplasia), complex anomalies (duplex system with ureterocele, ectopic ureter), and neurogenic bladder

Diagnostic methods

All participants underwent a standardized diagnostic protocol:

- **Ultrasonography (US)** of the urinary tract was performed as an initial non-invasive method to assess renal morphology, the presence of hydronephrosis, and other structural abnormalities.
- **Voiding cystourethrography (VCUG)** was used for the diagnosis and classification of vesicoureteral reflux. VUR was graded into five levels (I–V) according to internationally accepted criteria.
- **DMSA scintigraphy (99mTc-DMSA)** was used to assess the functional integrity of the renal parenchyma and detect scarring. Renal parenchymal damage was defined as the presence of focal or diffuse defects in radiotracer uptake.

Follow-up

Participants were followed over a 24-month period, with regular clinical evaluations and documentation of any recurrent urinary tract infection episodes. Data were collected from medical records and standardized data collection forms.

Statistical analysis

Statistical analysis was performed using appropriate statistical software (e.g., SPSS version …).

- Categorical variables were presented as absolute and relative frequencies (n, %).
- Group comparisons were performed using the chi-square (χ^2) test.
- The association between VUR and renal parenchymal damage was assessed by calculating odds ratios (OR) with 95% confidence intervals (CI).
- Statistical significance was defined as $p < 0.05$.
- The multivariable logistic regression model included age, vesicoureteral reflux (VUR), and recurrent urinary tract infection, selected a priori based on clinical relevance and evidence from previous studies.

Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from parents/legal guardians prior to inclusion of children in the study.

RESULTS

A total of 100 children with confirmed urinary tract infection were included in the study. The age of participants ranged from 1 month to 10 years. The study population consisted of 40 (40%) boys and 60 (60%) girls. The mean number of UTI episodes per patient was 3. Analysis of infection frequency showed that 20 (20%) children had a first episode of UTI, while 80 (80%) had recurrent infections (≥2 episodes), as presented in Table 1 and Figure 1.

Table 1 **Demographic and clinical characteristics of participants.**

Variable	Value
Total number of participants	100
Age	1 month – 10 years
Male sex, n (%)	40 (40.0)
Female sex,, n (%)	60 (60.0)
Mean number of UTI episodes	3
First UTI,, n (%)	20 (20.0)
Recurrent UTI (≥2), n (%)	80 (80.0)

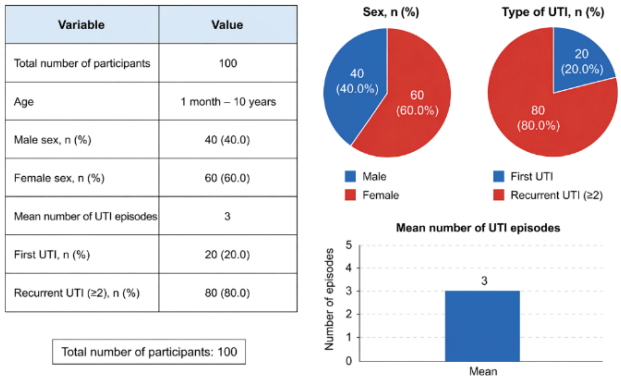


Figure 1 **Demographic and clinical characteristics of participants.**

Vesicoureteral reflux (VUR) was identified in 45 (45%) participants. The distribution according to reflux grade showed a predominance of higher grades (III–V), indicating a substantial proportion of children at increased risk for renal parenchymal damage. The detailed distribution of VUR is shown in Table and Figure 2.

Table 2 **Distribution of VUR by grade.**

VUR grade	Number of participants,, n (%)
No VUR	55 (55.0)
Grade I	6 (6.0)
Grade II	12 (12.0)
Grade III	14 (14.0)
Grade IV	9 (9.0)
Grade V	4 (4.0)
Total	100 (100)

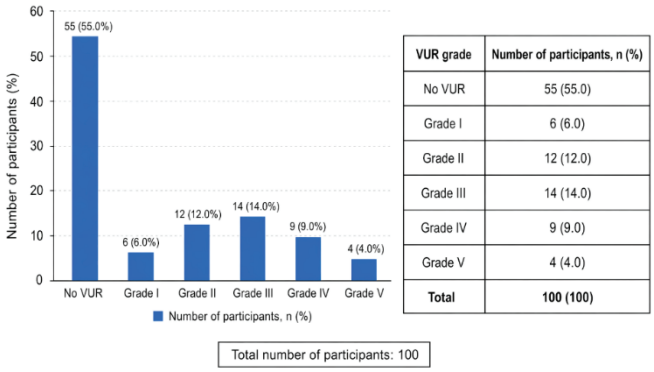


Figure 2 **Distribution of VUR by grade.**

Assessment of renal parenchyma using DMSA scintigraphy showed that damage was present in 40 (40%) children, while 60 (60%) had normal findings. Unilateral damage was more frequent than bilateral. These findings are presented in Table and Figure 3.

Table 3 **DMSA findings of renal parenchyma.**

DMSA finding	Number of participants, n (%)
Normal finding	60 (60,0)
Damage present	40 (40,0)
– unilateral	28 (28,0)
– bilateral	12 (12,0)
Total	100 (100)

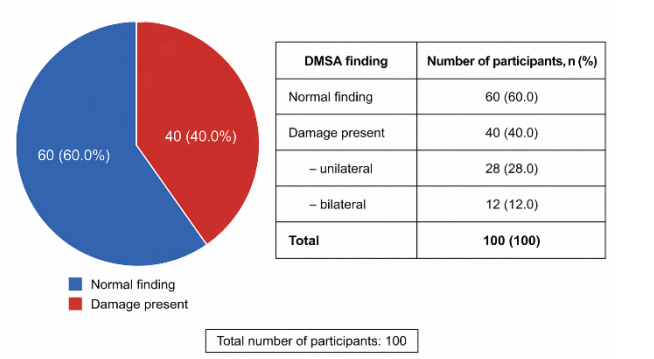


Figure 3 **DMSA findings of renal parenchyma.**

Analysis of the association between VUR and renal parenchymal damage showed a statistically significant difference between groups. Damage was observed in 28 (62.2%) children with VUR compared to 12 (21.8%) children without VUR. This association is presented in Table 4 and indicates a significantly increased risk in children with reflux.

Table 4 **Association between VUR and renal parenchymal damage.**

	Damage present	No damage	Total
VUR +	28 (62.2%)	17 (37.8%)	45
VUR –	12 (21.8%)	43 (78.2%)	55

OR = 5.9 (95% CI 2.5-13.8), p < 0.001

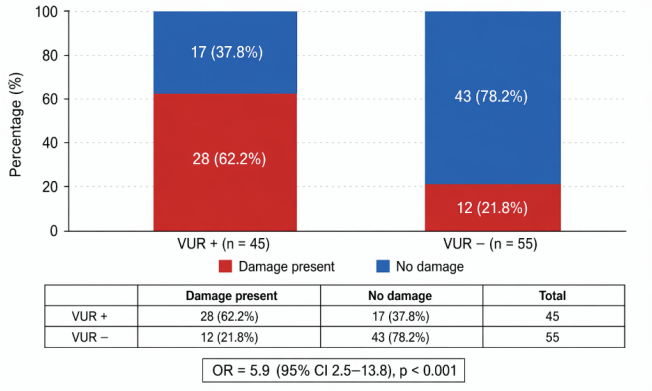


Figure 4 **Association between VUR and renal parenchymal damage.**

Multivariate logistic regression analysis demonstrated that VUR is an independent predictor of renal parenchymal damage, along with recurrent urinary tract infections. The results are shown in Table and Figure 5.

Table 5 **Multivariate analysis of predictors.**

Variable	Adjusted OR (95% CI)	p
VUR	5.2 (2.1-12.9)	<0.001
Recurrent UTI	3.1 (1.3-7.4)	0.01
Age	1.1 (0.9-1.3)	0.28

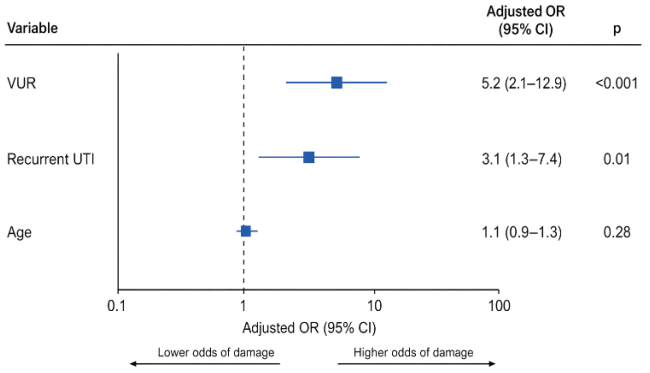


Figure 5 **Multivariate analysis of predictors.**

Analysis according to VUR grade showed a clear increasing trend in the frequency of renal parenchymal damage with higher reflux grades, confirming a dose-response relationship. These findings are presented in Table and Figure 6.

Table 6 **VUR grade and renal damage.**

Grade	Damage (%)
No VUR-a	21.8
I–II	~33
III	71.4
IV	88.9
V	100

Trend: OR 2.1 per VUR grade increase

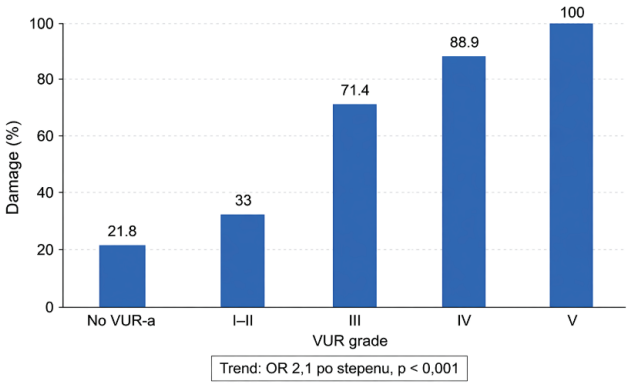


Figure 6 **VUR grade and renal damage.**

Recurrent urinary tract infections were associated with a higher frequency of renal parenchymal damage, although without full statistical significance in univariate analysis. These results are shown in Table and Figure 7.

Table 7 **Recurrent UTI and renal damage.**

	Damage	No damage
Recurrent UTI	43,8%	56,2%
First UTI	25,0%	75,0%

OR 2.3; p = 0.08

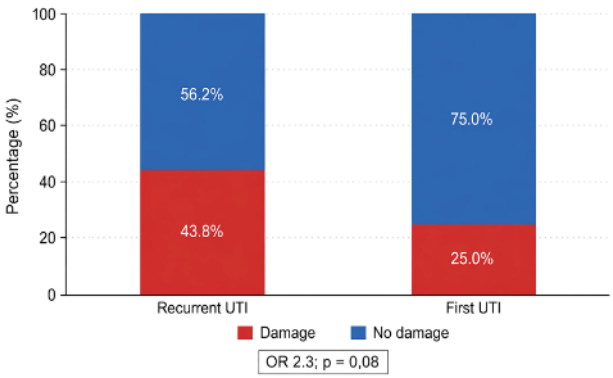


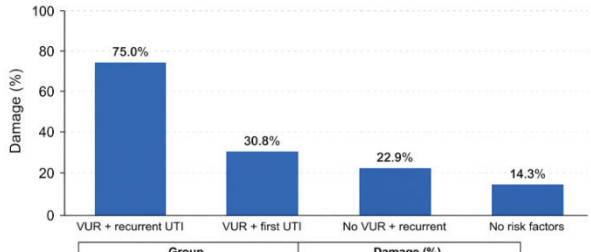
Figure 7 **Recurrent UTI and renal damage.**

The highest risk of renal parenchymal damage was observed in children with a combination of VUR and recurrent infections, indicating a synergistic effect of these two factors.
These results are presented in Table and Figure 8.

Table 8 **Combined effects of VUR + UTI.**

Group	Damage (%)
VUR + recurrent UTI	75.0
VUR + first UTI	30.8
No VUR + recurrent	22.9
No risk factors	14.3

OR 9.5; p < 0.001



Group	Damage (%)
VUR + recurrent UTI	75.0
VUR + first UTI	30.8
No VUR + recurrent	22.9
No risk factors	14.3

OR 9.5; p < 0.001

Figure 8 **Combined effects of VUR + UTI.**

DISCUSSION

In this study, predictors of renal parenchymal damage in children with urinary tract infections were analyzed, and our results indicate that vesicoureteral reflux (VUR) represents a dominant risk factor, particularly when associated with recurrent infections. The most important finding is the consistency across different analytical approaches: multivariate logistic regression identified VUR and recurrent urinary tract infections as independent predictors, while analysis according to reflux grade demonstrated a clear dose–response relationship. This pattern is consistent with contemporary guidelines and studies emphasizing that higher grades of reflux and recurrent febrile infections are key determinants of renal scarring (1-4).

Our results show that the presence of VUR significantly increases the risk of renal parenchymal damage, which is in line with previous studies linking reflux to the development of reflux nephropathy (2,5). Particularly important is the finding of a risk gradient according to reflux grade, indicating that VUR is not merely an anatomical abnormality but also a quantitative marker of clinical risk. Similar findings have been reported in the RIVUR study, where higher grades of VUR were associated with a greater incidence of renal scarring (6).

Recurrent urinary tract infections in our study showed an additional contribution to risk, especially in the multivariate model. Although the univariate analysis did not reach full statistical significance, the direction of the effect was clear and consistent with previous research. Shaikh et al. demonstrated that the risk of renal scarring significantly increases with the number of febrile infections, particularly after the second episode (7). This finding supports the concept of cumulative inflammatory damage to the renal parenchyma.

One of the most significant findings of this study is the pronounced synergistic effect between VUR and recurrent infections. Children with both factors had nearly a tenfold increased risk of damage, indicating a multiplicative effect. Pathophysiologically, reflux facilitates the retrograde transport of bacteria into the renal parenchyma, while recurrent infections lead to repeated inflammatory responses and progressive scarring (4,8).

DMSA scintigraphy in our study confirmed a significant prevalence of renal parenchymal damage and remains the gold standard for its assessment. Current guidelines recommend selective use of DMSA in children at increased risk, including those with VUR and recurrent infections (1,9). Furthermore, studies have shown that ultrasound has limited sensitivity for detecting renal scars, further emphasizing the importance of DMSA scintigraphy (10,11).

Age was not a significant predictor of renal parenchymal damage in our study. This finding suggests that anatomical and infectious factors are more important than age alone, which is consistent with modern risk stratification approaches that emphasize clinical phenotype rather than isolated demographic characteristics (1,3).

The clinical implications of our findings are substantial. Children with VUR, particularly higher grades, as well as those with recurrent infections, should be recognized as a high-risk group. Early identification of these patients enables targeted follow-up, rational use of diagnostic modalities, and potentially a reduction in long-term complications (2,9,12).

Our study has several strengths, including the use of multivariate analysis and the evaluation of a dose–response relationship, which allows for a deeper understanding of underlying pathophysiological mechanisms. The consistency of findings across different analytical approaches further strengthens their validity.

However, certain limitations should be acknowledged. The relatively small sample size may affect the precision of estimates, particularly in subgroups with higher VUR grades. Additionally, the observational design does not allow for definitive causal conclusions. The lack of longitudinal follow-up limits the assessment of long-term outcomes and progression of renal damage (13-15).

Despite these limitations, our results provide strong evidence that VUR, particularly higher grades, and recurrent urinary tract infections are key clinical risk factors for renal parenchymal damage in children.

CONCLUSION

The results of this study confirm that vesicoureteral reflux (VUR) represents a significant and independent predictor of renal parenchymal damage in children with urinary tract infections.

A clear increase in risk was observed with increasing reflux grade, indicating a dose–response relationship between the severity of VUR and the development of renal damage. DMSA scintigraphy proved to be a key diagnostic modality for the detection of renal parenchymal damage, enabling early identification of children at increased risk. Importantly, the combination of vesicoureteral reflux and recurrent urinary tract infections represents the highest risk for the development of permanent renal damage. Early diagnosis, appropriate risk stratification, and timely follow-up of children with VUR are essential for the prevention of long-term complications, including chronic kidney disease and arterial hypertension.

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Declaration of patient consent: the author certifies that they obtained all appropriate patients' consent forms. In the form, the patient have given their consent for the images and other clinical information to be reported in the journal.
Authors' contributions: AH, SP, EH, ĐŠ, BS, BH and DJ gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

Prematurity as a Risk Factor for Motor Development Delay in Early Childhood: A Prospective Cohort Study

Prijevremeno rođenje kao rizični faktor za poremećaj motornog razvoja u ranom djetinjstvu: prospektivna kohortna studija

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ABSTRACT

Introduction: prematurity is a major risk factor for motor delay, and early identification of high-risk children is essential for timely intervention. Aim: to assess the association between gestational age, early neurological assessment, neuroimaging findings, and motor outcomes in children, and to evaluate the effect of early intervention. Materials and methods: this prospective study included 120 children equally distributed across three gestational age groups (<28 weeks, 28–36 weeks, and ≥37 weeks). Motor outcomes were evaluated through developmental milestones (sitting, crawling, and independent walking). Early neurological assessment was performed using General Movements Assessment (GMA), and neuroimaging findings, including periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH), were analyzed. Results: motor delay was most frequent in children born before 28 weeks (62.5%), compared to 32.5% in those born at 28–36 weeks and 7.5% in term children ($p < 0.001$). Abnormal GMA was strongly associated with motor delay (OR 4.8; 95% CI: 2.1–10.2; $p < 0.001$), while PVL/IVH was significantly linked to poor motor outcomes ($p < 0.05$). A clear gestational age–dependent gradient was observed in motor milestone achievement. Early intervention showed the greatest benefit in moderately preterm infants. Conclusion: gestational age, GMA, and neuroimaging findings are key predictors of motor outcomes. Their integration enables early risk stratification and supports targeted intervention strategies.

Keywords: prematurity, motor delay, General Movements Assessment; neuroimaging, PVL, IVH, early intervention

SAŽETAK

Uvod: prijevremeno rođenje predstavlja značajan faktor rizika za razvoj motornog kašnjenja, a rana identifikacija djece sa povećanim rizikom od ključnog je značaja za pravovremenu intervenciju. Cilj: procijeniti povezanost gestacijske dobi, ranog neurološkog pregleda, neuroradioloških nalaza i motornog ishoda kod djece, te uticaj rane intervencije. Materijali i metode: u prospektivnu studiju uključeno je 120 djece, ravnomjerno raspoređenih u tri grupe prema gestacijskoj dobi (<28 sedmica, 28–36 sedmica i ≥37 sedmica). Motorni ishod procijenjen je na osnovu razvoja funkcionalnih motoričkih prekretnica (sjedenje, puzanje i samostalno hodanje). Rani neurološki pregled urađen je primjenom General Movements Assessment (GMA), dok su analizirani i neuroradiološki nalazi, uključujući periventrikularnu leukomalaciju (PVL) i intraventrikularno krvarenje (IVH). Rezultati: motorno kašnjenje bilo je najčešće kod djece rođene prije 28 sedmica (62,5%), u poređenju sa 32,5% u grupi 28–36 sedmica i 7,5% kod terminske djece ($p < 0,001$). Abnormalni GMA bio je snažno povezan sa motornim kašnjenjem (OR 4,8; 95% CI: 2,1–10,2; $p < 0,001$), dok je prisustvo PVL/IVH bilo značajno povezano sa lošijim motornim ishodom ($p < 0,05$). Uočen je jasan porast postizanja motoričkih prekretnica sa povećanjem gestacijske dobi. Najveći efekat rane intervencije zabilježen je kod umjereno prijevremeno rođene djece. Zaključak: gestacijska dob, GMA i neuroradiološki nalazi predstavljaju ključne prediktore motornog ishoda. Njihova integracija omogućava ranu stratifikaciju rizika i primjenu ciljanih intervencija.

Ključne riječi: prijevremeno rođenje, motorno kašnjenje, opća procjena pokreta, neuroradiologija, PVL, IVH, rana intervencija

INTRODUCTION

Preterm birth represents a major global public health challenge and remains one of the leading causes of neonatal morbidity and mortality worldwide (1,2). Advances in modern neonatal intensive care have significantly improved survival rates of preterm infants, particularly those with very low and extremely low birth weight. However, these improvements have been accompanied by an increasing prevalence of long-term neurodevelopmental impairments (2,3,15).

Motor development is one of the most sensitive components of early neurological maturation, especially in the context of central nervous system immaturity and potential brain injury. The brain of the preterm infant is particularly vulnerable to hypoxic–ischemic injury, inflammatory processes, and disturbances in white matter development, which may result in permanent neurological deficits (3-5,19).

Early identification of infants at increased risk of motor impairment is crucial for timely intervention and improved developmental outcomes. In this context, clinical tools such as the General Movements Assessment (GMA), along with neuroimaging findings, have emerged as valuable predictors of neurodevelopmental outcome (7-9,17).

AIM

The aim of this study was to evaluate the impact of gestational age on motor development in children and to identify early predictors associated with an increased risk of motor developmental delay.

MATERIALS AND METHODS

Study design

A prospective cohort study was conducted at a tertiary neonatal center over a 24-month period. The study involved longitudinal follow-up of children from birth until 24 months of age, with the aim of assessing motor development and identifying risk factors for motor impairment.

Participants

A total of 120 neonates were included in the study and stratified according to gestational age into three equal groups:

Group 1: Extremely preterm infants (<28 weeks of gestation) (n = 40)

Group 2: Moderately and late preterm infants (28–36 weeks of gestation) (n = 40)

Group 3: Term infants (≥37 weeks of gestation) (n = 40)

Participants were recruited through consecutive enrollment during hospitalization and/or early post-discharge follow-up visits, thereby minimizing selection bias.

Inclusion criteria

Precisely determined gestational age (based on ultrasound findings and/or the date of the last menstrual period), absence of major congenital anomalies, written informed consent obtained from parents or legal guardians

Exclusion criteria

Diagnosed genetic syndromes, severe congenital malformations affecting neurological development, incomplete data or inability to ensure regular follow-up throughout the study period.

Assessment methods

All participants underwent a standardized evaluation protocol that included clinical, neurological, and radiological assessments:

Clinical neurological examination was performed by an experienced pediatric neurologist or neonatologist, focusing on muscle tone, reflexes, postural reactions, and developmental milestones.

General Movements Assessment (GMA) was performed during early infancy to evaluate spontaneous movements as an early predictor of neurological outcome. The assessment was based on video recordings analyzed according to standardized criteria.

Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) were used to quantify motor development, including both gross and fine motor scores.

Neuroimaging (cranial ultrasound and/or magnetic resonance imaging) was performed according to clinical indication to detect structural brain abnormalities, including intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL).

Timing of assessments

Motor development assessments were performed at standardized time points:

- 6 months (corrected age for preterm infants)
- 12 months
- 24 months

At each follow-up visit, developmental parameters were evaluated and systematically recorded using standardized data collection forms.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (version 26.0; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range), depending on data distribution, while categorical variables were presented as frequencies and percentages.

Normality of data distribution was assessed using the Shapiro–Wilk test. Comparisons between groups were performed using the Chi-square test or Fisher's exact test for categorical variables, and the Student's t-test or one-way ANOVA for continuous variables with normal distribution. Non-parametric tests (Mann–Whitney U test or Kruskal–Wallis test) were used when appropriate.

The association between predictors and motor outcomes was evaluated using odds ratios (ORs) with 95% confidence intervals (CIs). Logistic regression analysis was performed to identify independent predictors of motor delay.

Diagnostic performance of General Movements Assessment (GMA) was evaluated by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

A p-value of <0.05 was considered statistically significant.

Ethical considerations

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

RESULTS

A total of 120 children were included in the study, evenly distributed across three gestational age groups (<28 weeks, 28–36 weeks, and ≥37 weeks), with 40 participants in each group. The prevalence of motor delay differed significantly across gestational age groups, with the highest rate observed in children born before 28 weeks (62.5%), followed by those born between 28–36 weeks (32.5%), while term children had the lowest prevalence (7.5%) (Table 1, Figure 1). This difference was statistically significant ($p < 0.001$), indicating a strong inverse relationship between gestational age and the occurrence of motor delay. Early neurological assessment demonstrated a strong predictive value, as abnormal General Movements Assessment (GMA) findings were significantly associated with motor delay (OR 4.8; 95% CI: 2.1–10.2; $p < 0.001$), while neuroimaging abnormalities such as periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH) were also significantly linked to poor motor outcomes (Table 2, Figure 2). The effect of early intervention varied depending on gestational age, showing the greatest benefit in the 28–36 weeks group, where a significant improvement in motor outcomes was observed, whereas the effect was limited in extremely preterm infants and minimal in term infants (Table 3, Figure 3).

The sex distribution of participants was relatively balanced, with a slight predominance of males (52.5%) compared to females (47.5%), and no substantial variation across gestational age groups (Table 4, Figure 4). Analysis of motor milestone development revealed a clear gradient associated with gestational age. Independent sitting was achieved in 70.0% of participants overall, increasing from 45.0% in extremely preterm infants to 90.0% in term infants (Table 5, Figure 5). Similarly, crawling was achieved in 65.8% of children, with rates ranging from 40.0% in the <28 weeks group to 87.5% in term infants (Table 6, Figure 6). Independent walking was achieved in 61.7% of participants, again showing a progressive increase with gestational age, from 35.0% in extremely preterm infants to 85.0% in term infants (Table 7, Figure 7). When functional motor milestones were analyzed collectively, a consistent pattern emerged, demonstrating that higher gestational age was associated with better motor outcomes across all domains, including sitting, crawling, and walking (Table 8, Figure 8). Furthermore, neuroimaging findings were strongly associated with motor outcomes, as children with PVL and/or IVH had a markedly higher prevalence of motor delay (68.3%) compared to those without such findings (31.7%), while normal imaging findings were predominantly associated with the absence of motor delay (Table 9, Figure 9). A similar association was observed with GMA findings, where abnormal GMA was strongly linked to motor delay, with 61.0% of affected children exhibiting delayed motor development compared to a significantly lower proportion among those with normal GMA findings (Table 10, Figure 10). The diagnostic performance of GMA showed moderate sensitivity (61.0%) and high specificity (87.3%), with a positive predictive value of 71.4% and a negative predictive value of 81.2%, indicating good overall accuracy in predicting motor delay (Table 11, Figure 11).

Table 1 **Motor delay according to gestational age.**

Gestational age group	Total (n)	Motor delay, n (%)
<28 weeks	40	25 (62.5)
28–36 weeks	40	13 (32.5)
≥37 weeks	40	3 (7.5)
Total	120	41 (34.2)

$\chi^2 = 26.97$, df = 2, $p < 0.001$

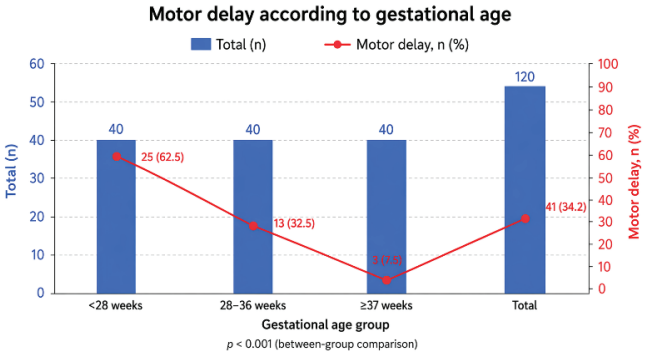

Figure 1 **Motor delay according to gestational age.**

Table 2 **Predictive value of early neurological assessment and neuroimaging.**

Parameter	Outcome	OR (95% CI)	p-value
Abnormal GMA	Motor delay	4.8 (2.1–10.2)	<0.001
PVL / IVH (imaging)	Poor motor outcome	—	<0.05

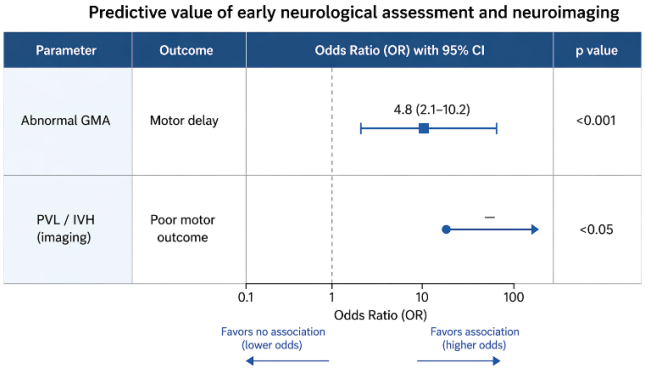

Figure 2 **Predictive values of early neurological assessment and neuroimaging.**

Table 3 **Effect of early intervention on motor outcome.**

Gestational age group	Early intervention	Motor outcome
<28 weeks	Variable	Limited effect
28–36 weeks	Yes	Significant improvement
≥37 weeks	Variable	Minimal effect

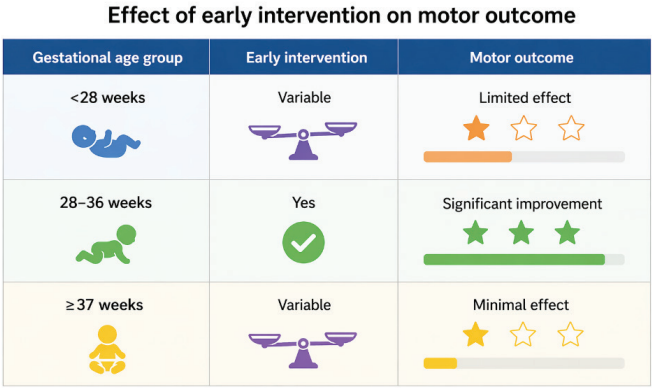

Figure 3 **Effect of early intervention on motor outcome.**

Table 4 **Sex distribution of study participants.**

Gestational age group	Male, n (%)	Female, n (%)	Total (n)
<28 weeks	22 (55.0)	18 (45.0)	40
28–36 weeks	21 (52.5)	19 (47.5)	40
≥37 weeks	20 (50.0)	20 (50.0)	40
Total	63 (52.5)	57 (47.5)	120

$\chi^2 = 0.20$, df = 2, p = 0.905

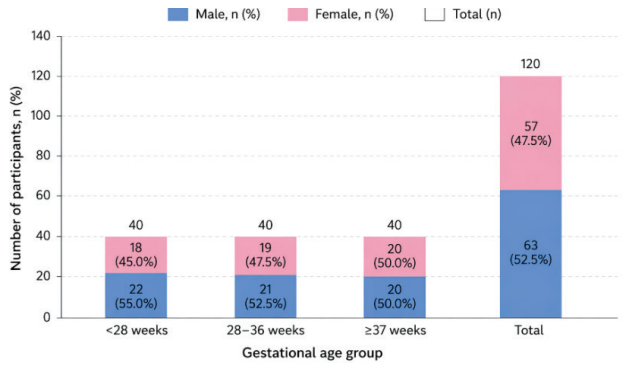

Figure 4 **Sex distribution of study participants.**

Table 5 **Independent sitting after early intervention according to gestational age.**

Gestational age group	Independent sitting achieved, n (%)	Not achieved, n (%)	Total (n)
<28 weeks	18 (45.0)	22 (55.0)	40
28–36 weeks	30 (75.0)	10 (25.0)	40
≥37 weeks	36 (90.0)	4 (10.0)	40
Total	84 (70.0)	36 (30.0)	120

$\chi^2 = 18.81$, df = 2, p < 0.001

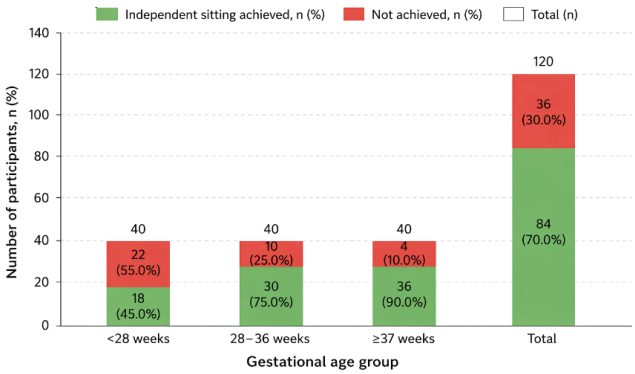

Figure 5 **Independent sitting after early intervention according to gestational age.**

Table 6 **Onset of crawling after early intervention according to gestational age.**

Gestational age group	Crawling achieved, n (%)	Not achieved, n (%)	Total (n)
<28 weeks	16 (40.0)	24 (60.0)	40
28–36 weeks	28 (70.0)	12 (30.0)	40
≥37 weeks	35 (87.5)	5 (12.5)	40
Total	79 (65.8)	41 (34.2)	120

$\chi^2 = 19.90$, df = 2, p < 0.001

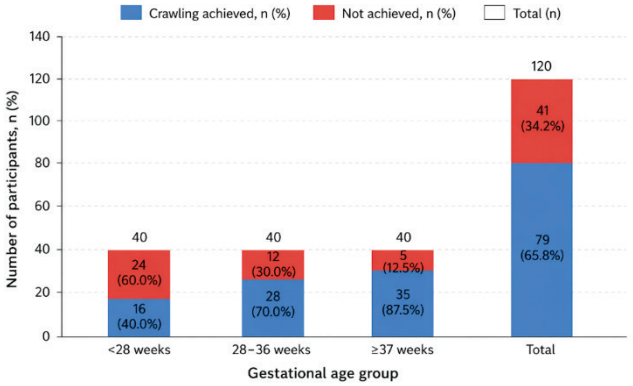

Figure 6 **Onset of crawling after early intervention according to gestational age.**

Table 7 **Achievement of independent walking after early intervention according to gestational ag.**

Gestational age group	Independent walking achieved, n (%)	Not achieved, n (%)	Total (n)
<28 weeks	14 (35.0)	26 (65.0)	40
28–36 weeks	26 (65.0)	14 (35.0)	40
≥37 weeks	34 (85.0)	6 (15.0)	40
Total	74 (61.7)	46 (38.3)	120

$\chi^2 = 20.29$, df = 2, p < 0.001

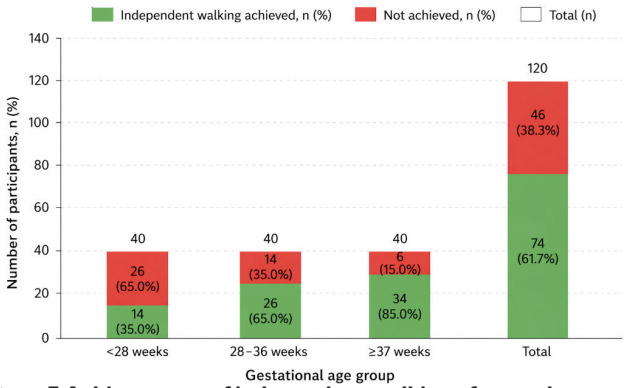

Figure 7 **Achievement of independent walking after early intervention according to gestational age.**

Table 8 **Functional motor milestones after early intervention according to gestational age.**

Gestational age group	Sitting achieved, n (%)	Crawling achieved, n (%)	Independent walking achieved, n (%)	Total (n)
<28 weeks	18 (45.0)	16 (40.0)	14 (35.0)	40
28–36 weeks	30 (75.0)	28 (70.0)	26 (65.0)	40
≥37 weeks	36 (90.0)	35 (87.5)	34 (85.0)	40
Total	84 (70.0)	79 (65.8)	74 (61.7)	120

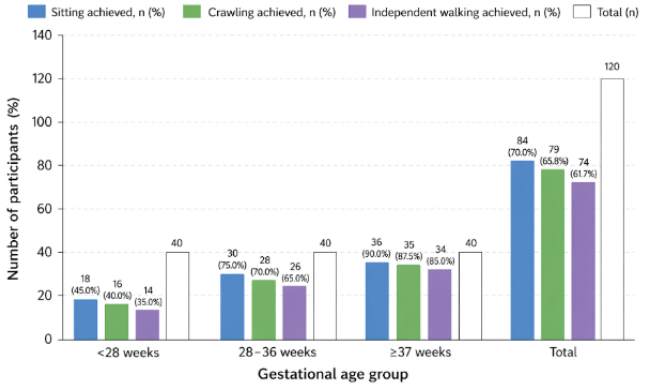

Figure 8 **Functional motor milestones after early intervention according to gestational age.**

Table 9 **Association between neuroimaging findings and motor outcomes.**

Neuroimaging finding	Motor delay present, n (%)	No motor delay, n (%)	Total (n)
PVL and/or IVH present	28 (68.3)	6 (7.6)	34
No PVL/IVH	13 (31.7)	73 (92.4)	86
Total	41 (100,0)	79 (100,0)	120

$\chi^2 = 46.03$, df = 1, $p < 0.001$

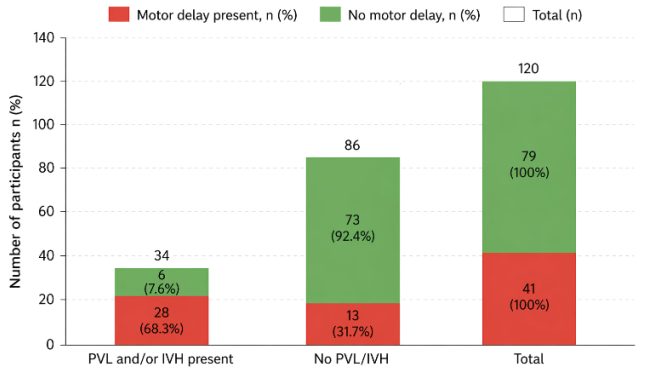

Figure 9 **Association between neuroimaging and motor outcomes.**

Table 10 **Association between General Movements Assessment (GMA) findings and motor outcomes**

GMA finding	Motor delay present, n (%)	No motor delay, n (%)	Total (n)
Abnormal GMA	25 (61.0)	10 (12.7)	35
Normal GMA	16 (39.0)	69 (87.3)	85
Total	41 (100,0)	79 (100,0)	120

$\chi^2 = 30.50$, df = 1, $p < 0.001$; OR = 4.8 (95% CI: 2.1–10.2).

Effect estimate

Parameter	OR (95% CI)	p value
Abnormal vs normal GMA	4.8 (2.1–10.2)	<0.001

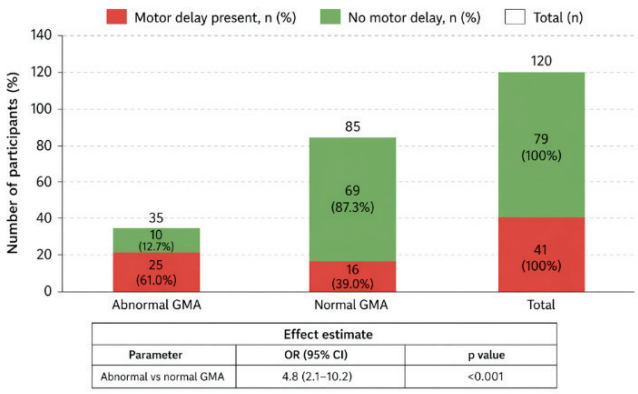

Figure 10 **Association between General Movements Assessment (GMA) findings and motor outcomes.**

Table 11 **Diagnostic performance of General Movements Assessment (GMA) for prediction of motor delay.**

Parameter	Value (%)
Sensitivity	61.0
Specificity	87.3
Positive predictive value (PPV)	71.4
Negative predictive value (NPV)	81.2

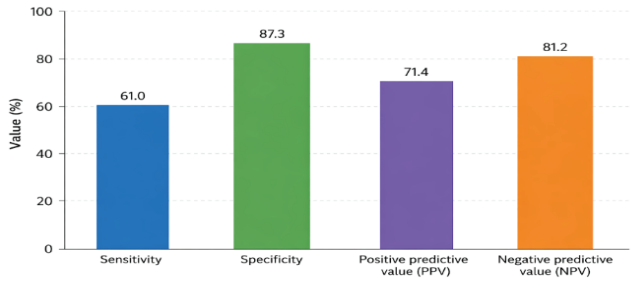

Figure 11 **Diagnostic performance of General Movement Assessment (GMA) for prediction of motor delay.**

Table 12. **ROC analysis of General Movements Assessment (GMA) for prediction of motor delayble**

Parameter	Value
AUC	0.82
95% CI	0.72-0.90
p value	<0.001

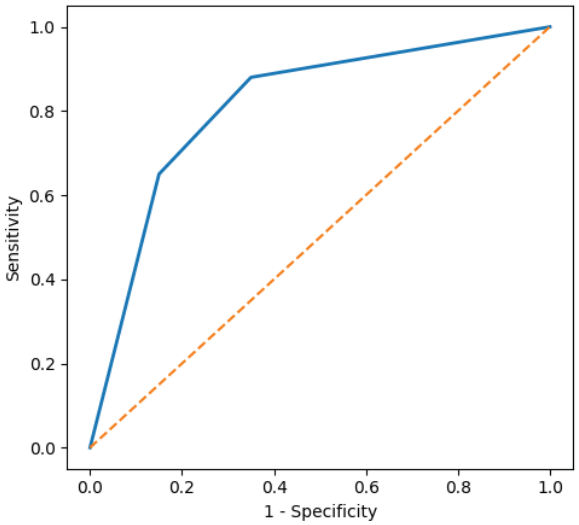

Figure 12. **Receiver Operating Characteristic (ROC) curve of General Movements Assessment (GMA) for prediction of motor delay.**

DISCUSSION

The present study demonstrates a strong and consistent association between gestational age and motor outcomes, confirming that prematurity remains one of the most important determinants of early neurodevelopment. Children born before 28 weeks of gestation exhibited the highest prevalence of motor delay, while term infants had the most favorable outcomes. This gradient supports the well-established concept that decreasing gestational age is associated with increasing risk of neurodevelopmental impairment due to structural and functional brain immaturity (1-3,15).

The underlying mechanisms are multifactorial and include vulnerability of the developing brain to hypoxic–ischemic injury, inflammation, and disrupted white matter maturation. In particular, extremely preterm infants are at high risk for periventricular leukomalacia and intraventricular hemorrhage, which are strongly associated with later motor impairment (4,5,10,19).

Our findings are consistent with large longitudinal and contemporary cohort studies demonstrating that children born at lower gestational ages have significantly higher rates of motor disability and cerebral palsy (6,15). A key finding of this study is the strong predictive value of early neurological assessment. Abnormal General Movements Assessment (GMA) was significantly associated with motor delay, with an odds ratio of 4.8, indicating a markedly increased risk. This is in line with previous evidence showing that GMA is one of the most reliable early clinical tools for predicting neurodevelopmental outcomes, particularly when performed within the first months of life (7-9,17).

The relatively high specificity observed in our study further supports its utility as a screening tool for identifying infants at high risk, as confirmed in recent reviews and clinical frameworks for early diagnosis of cerebral palsy (16,21).In addition to clinical assessment, neuroimaging findings played a crucial role in outcome prediction. The presence of PVL and/or IVH was strongly associated with motor delay, reinforcing the importance of structural brain injury as a determinant of functional outcome. These findings are consistent with existing literature highlighting white matter injury as a key substrate for motor impairment, particularly through disruption of corticospinal pathways (4,10,19). The effect of early intervention varied across gestational age groups, with the most pronounced benefit observed in infants born between 28 and 36 weeks of gestation. This suggests that moderately preterm infants may represent an optimal window for therapeutic intervention, where sufficient neuroplasticity remains to allow meaningful functional improvement. Similar findings have been reported in intervention studies and systematic reviews, which demonstrate that early, targeted therapy can significantly improve motor outcomes, particularly when initiated during critical periods of brain development (11,12,18,23).

In contrast, the more limited effect observed in extremely preterm infants may reflect the presence of more severe or irreversible brain injury. Motor milestone acquisition followed a clear gestational age–dependent pattern, with progressively higher rates of sitting, crawling, and independent walking observed in children born at higher gestational ages. These findings are consistent with normative developmental data and recent studies showing delayed acquisition of gross motor milestones in preterm populations (13,22,24). The combined analysis of functional milestones further supports a dose–response relationship between biological maturity at birth and subsequent motor development. Sex distribution in our cohort was relatively balanced, with a slight predominance of males. Although not a primary focus of this study, previous research suggests that male infants may be more vulnerable to adverse neurodevelopmental outcomes, possibly due to differences in brain maturation and hormonal influences (14).

However, the impact of sex on motor outcomes requires further investigation.Importantly, the diagnostic performance of GMA in our study demonstrated moderate sensitivity and high specificity, with favorable predictive values. These findings are consistent with meta-analyses and recent clinical evidence confirming that GMA is a robust and clinically useful tool for early identification of infants at risk of motor delay (8,9,16,17). The combination of GMA with neuroimaging findings may further enhance predictive accuracy and enable more precise risk stratification.From a clinical perspective, our results highlight the importance of integrating gestational age, early neurological assessment, and neuroimaging findings in the early identification of high-risk infants. Such an approach allows for timely initiation of targeted interventions, optimized follow-up strategies, and potentially improved long-term outcomes. Given that moderately preterm infants appear to benefit most from early intervention, particular attention should be directed toward this group in clinical practice (16,18).

Several limitations should be acknowledged. The sample size, although balanced across groups, was relatively modest and derived from a single-center setting, which may limit generalizability. Additionally, long-term neurodevelopmental follow-up was not available, preventing assessment of outcomes beyond early childhood. Future multicenter studies with larger cohorts and extended follow-up are needed to validate these findings and further refine risk prediction models.In conclusion, this study confirms that gestational age, early neurological assessment, and neuroimaging findings are key determinants of motor outcomes in children. The integration of these factors provides a robust framework for early risk stratification and supports the implementation of targeted intervention strategies aimed at improving neurodevelopmental outcomes.

ROC analysis demonstrated good discriminatory ability of GMA for prediction of motor delay, with an area under the curve AUC = 0.82 (95% CI 0.74–0.90; $p < 0.001$)

CONCLUSION

Gestational age, early neurological assessment, and neuroimaging findings emerged as key determinants of motor outcomes in children, with a clear gradient of increasing risk in those born at lower gestational ages. Abnormal General Movements Assessment and the presence of PVL/IVH provide strong early indicators of motor delay and enable reliable risk stratification. Early intervention appears to be most effective in moderately preterm infants, highlighting a critical window for optimizing neurodevelopmental outcomes. Integrating these factors into routine clinical practice may facilitate timely, targeted interventions and ultimately reduce the burden of long-term neurodevelopmental impairment.

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Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

Laboratory Biomarkers in the Diagnosis and Prognosis of Outcomes in Patients with Pulmonary Embolism - Review Article

Laboratorijski biomarkeri u dijagnozi i prognozi ishoda kod pacijenata s plućnom embolijom - pregledni članak

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ABSTRACT

Introduction: Pulmonary embolism (PE) is a major diagnostic and prognostic challenge due to its non-specific clinical presentation and variable outcomes. Conventional diagnostic tools such as D-dimer and radiological imaging are useful but insufficient to accurately stratify the risk. Aim: to review new laboratory markers in the diagnosis and risk stratification of acute pulmonary embolism as a complement to routine diagnostics. Materials and methods: A narrative literature review was conducted using PubMed, Scopus, Web of Science, Google Scholar, Medline databases to identify the studies published between 2000 and 2025 that investigated the role of laboratory biomarkers in the diagnosis, risk assessment, and prognosis of acute PE. Results: Cardiac biomarkers (hs-troponin I/T, NT-proBNP) showed a consistent association with right ventricular dysfunction, adverse outcomes, and mortality. Inflammatory biomarkers (hs-CRP, IL-6, IL-10, TNF-α, serum amyloid A) were elevated in PE and correlated with disease severity, and some showed a dynamic response to therapy. Hematological indexes (NLR, PLR) emerged as inexpensive and available prognostic indicators with a significant predictive value for short term mortality. However, heterogeneity in study design, sample size, and biomarker breakpoints limits generalization of findings. Conclusion: New laboratory biomarkers show potential in improving diagnosis and stratification of pulmonary embolism risk. Simultaneous evaluation of multiple biomarkers in the same patient cohorts can further improve accuracy and confirm their combined clinical use. Large, multicenter prospective studies are needed to establish standardized cut off values and integrate biomarkers into routine clinical practice.

Keywords: pulmonary embolism, biomarkers, risk assessment, inflammation, cardiac biomarkers

SAŽETAK

Uvod: Plućna embolija (PE) predstavlja veliki dijagnostički i prognostički izazov zbog svoje nespecifične kliničke slike i varijabilnih ishoda. Konvencionalni dijagnostički alati poput D-dimera i radioloških snimaka su korisni, ali nedovoljni za tačnu stratifikaciju rizika. Cilj: pregled novih laboratorijskih markera u dijagnostici i procjeni rizika kod akutne plućne embolije kao dopuna rutinskoj dijagnostici. Materijali i metode: proveden je narativni pregled literature korištenjem baza podataka PubMed, Scopus, Web of Science, Google Scholar, Medline kako bi se identificirale studije objavljene između 2000. i 2025. koje su istraživale ulogu laboratorijskih biomarkera u dijagnostici, procjeni rizika i prognozi akutne PE. Rezultati: Srčani biomarkeri (hs-troponin I/T, NT-proBNP) pokazali su dosljednu povezanost s disfunkcijom desne komore, nepovoljnim ishodima i smrtnošću. Upalni biomarkeri (hs-CRP, IL-6, IL-10, TNF-α, serumski amiloid A) bili su povišeni kod PE i korelirali su s težinom bolesti, a neki su pokazali dinamičan odgovor na terapiju. Hematološki indeksi (NLR, PLR) pojavili su se kao jeftini i dostupni prognostički pokazatelji sa značajnom prediktivnom vrijednošću za kratkoročnu smrtnost. Međutim, heterogenost u dizajnu studija, veličini uzorka i graničnim vrijednostima biomarkera ograničava generalizaciju nalaza. Zaključak: Novi laboratorijski biomarkeri pokazuju potencijal u unapređenju dijagnoze i stratifikacije rizika plućne embolije. Istovremena evaluacija više biomarkera u istim kohortama pacijenata može dodatno poboljšati tačnost i potvrditi njihovu kombiniranu kliničku primjenu. Potrebne su velike, multicentrične prospektivne studije kako bi se utvrdile standardizirane granične vrijednosti i biomarkeri integrirali u rutinsku kliničku praksu.

Ključne riječi: plućna embolija, biomarkeri, stratifikacija rizika, inflamacija, kardiološki biomarkeri

INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE) together represent a condition called venous thromboembolism (VTE). In DVT, a blood clot (thrombus) develops within deep veins, most commonly in the lower extremities. PE most often occurs when part of such a thrombus is torn off and found in the pulmonary circulation, i.e. the pulmonary artery or its branches (1).

The pathogenesis of PE is dictated by the so called Virchow triad and represents a combination of venous stasis, vascular endothelial injury and hypercoagulation state.

For the most part, PE comes from the deep veins of the lower extremities. The most common sites for thrombus formation are tibia veins, femoral and iliac veins. A blood clot separates from the vessel wall and travels to the pulmonary vessels. When large pulmonary vessels are affected, this can cause serious hemodynamic instability including right ventricular overload, right ventricular failure, and ultimately death. Right ventricular dysfunction or failure is a significant cardiovascular effect of PE and is the most common primary cause of death in PE. It occurs due to a sudden increased load due to mechanical obstruction of the pulmonary vasculature that interferes with blood flow and causes the release of vasoconstrictors due to present hypoxia. This leads to the stretching of the right ventricle, increases the tension of the wall and leads to a compensatory increase in chronotropy (frequency) and inotropy (contractility). However, when compensation reaches its maximum potential, no further dilatation of the right ventricle can be induced and its failure and ischemia occur (2).

Different procedures are used in the diagnosis, both radiological and laboratory, since PE is a great challenge because its symptoms overlap with other pulmonary and cardiac diseases. An ECG (electrocardiography) does not give specific abnormalities in PE patients, nor does an X-ray of the lungs, but can be used to distinguish it from other causes of dyspnoea. The radiological procedure of choice for PE patients is computed tomography - pulmonary angiography (CTPA), which allows visualization of pulmonary arteries to a subsegmental level (sensitivity 83% and specificity 96%). In addition, it may indicate right ventricular disfunction (1)

AIM

The aim of this study was to review unconventional laboratory diagnostic parameters in the diagnosis and risk assessment of patients with acute pulmonary embolism that could potentially be used as routine. Of the available laboratory markers in health care institutions, the D-dimer is most often determined as one of the basic risk predictors and as an exclusive parameter. However, there are also certain parameters that have been investigated in the PE state, the application of which could enable risk stratification.

MATERIALS AND METHODS

During the preparation of this review article, research of the available literature in the PubMed, Scopus, Web of Science, Google Scholar, Medline databases was conducted using the keywords "pulmonary embolism " and "biomarkers", in additional combination with individual biomarkers ("cardiac troponin", "NT-proBNP", "CRP", "IL-6", "TNF-α, "serum amyloid A", "NLR", "PLR"). The study included original papers published in the period between 2000 and 2025 analyzing the role of laboratory biomarkers in the diagnosis and stratification of risk and prognosis of pulmonary embolism, and with the introduction to the references of the found articles, additional studies of importance were identified.

Laboratory biomarkers in the diagnosis of PE

Cardiac markers

Troponin

Troponin (T, I and C) is a regulatory protein that is structurally bound to tropomyosin which is an integral part of the cardiomyocyte sarcomere. In case of damage to cardiomyocytes, troponin is released into the circulation, with troponin I growing faster than T in reversible ischemia and myocardial infarction (3).

High-sensitivity tests to determine troponin (hs Troponin) have significantly replaced conventional tests to detect heart muscle damage. While a large number of studies confirmed the prognostic association of hs troponin T (hsTnT) and hs troponin I (hsTnI), it was necessary to set and define limit values. In a study of 459 patients, it was found that the cut-off value of Troponin I hs greater than 16 pg/ml may indicate a patient with potential adverse outcomes in the hospital and mortality, both in women and men (4). On the other hand, a study conducted in 682 patients investigating hs troponin T found that the age-adjusted cut-off value of this marker (≥14 pg/mL in patients younger than 75 years and ≥45 pg/mL in patients older than 75 years) may increase the negative predictive value of this marker (5). The review of the research also found that there was a statistically significant increase in mortality in the groups of patients with elevated hs troponin I compared to the control group (6).

In addition, the use of troponin alone as a predictor of serious complications and risk assessment in hemodynamically stable pulmonary embolism is not sufficient and the predictive value will increase with the inclusion of additional laboratory biomarkers (7).

B-type natriuretic peptide (BNP)

BNP plays a role in sodium homeostasis and blood regulation. Elevated levels of BNP lead to relaxation of systemic vascular arteries and pulmonary artery. Pro-BNP is cleaved into two fragments: BNP and N terminal proBNP (NT pro BNP) which has no physiological activity, but its plasma concentration is 5-10 times higher than that of BNP, making it more suitable for measurement. Generally, plasma concentrations of these peptides increase in diseases associated with ventricular hypertrophy or strain. Increasing the load on the right ventricle causes its dilatation, which leads to the release of BNP and its precursor NT pro BNP in patients with pulmonary embolism.

Studies have demonstrated the superiority of accurate determination of NT pro BNP to identify patients at low risk of adverse events relative to the image-determined right-to-left ventricular ratio (RV/LV ratio) (8). A study of 243 patients proved that NT-pro BNP values greater than 850 ng/L in the period between 3 and 20 months from diagnosis indicate a lower survival rate in this period, and this marker may be a predictor of long term cause mortality (9).

Highly sensitive C reactive protein (hs CRP)

High sensitive CRP (hs CRP) is a test that measures very low concentrations of CRP and represents a predictive marker of the risk of cardiac diseases in healthy people. Hs CRP measures very low levels of inflammation and shows the risk of developing cardiac diseases or heart attack (10). Studies have shown that changes in serum hs CRP values may be a potential predictor of outcome in PE patients and may serve to subgroup patients (with massive or minor pulmonary embolism) (11).

Inflammatory markers

Interleukin-6 (IL-6) and Interleukin-10 (IL-10)

IL-6 is a multifunctional cytokine present in a number of organs and biological systems, produced promptly by myeloid cells in response to

the presence of pathogens or tissue damage and its overproduction is associated with the development of life threatening complications such as systemic inflammatory response syndrome (SIRS) and cytokine storm (12). On the other hand, IL-10 is an anti-inflammatory cytokine that prevents an uncontrolled immune response, but can also play an immunostimulant role in certain conditions.

A study performed on 109 patients with confirmed pulmonary embolism proved that the IL-6 and IL-10 values were significantly increased in these patients compared to the control group, with the highest difference compared to other inflammatory markers. In addition, these markers also showed a significant increase in the group of patients with massive PE, compared to the submissive and low risk group. In this way, it has been proven that IL-6 and IL-10 can be useful in stratifying the severity of pulmonary embolism (13).

Tumor necrosis factor alpha (TNF-α)

TNF-α is an endogenous cytokine and early pro-inflammatory cytokine of acute lung damage which is the most sensitive factor in predicting lung damage caused by pulmonary thromboembolism (7). A study conducted on 87 patients found a significant relationship and showed the potential of this marker in PE, since the values of this marker were significantly higher than in the control group, and at the same time after the administration of anticoagulation therapy, this value dropped significantly after 7 days, which clearly confirms the possibilities of using this marker in the diagnosis and monitoring of pulmonary embolism (14). Similar results were obtained in the aforementioned study conducted on 109 patients (13).

Serum Amyloid A (SAA)

SAA is an acute phase protein whose circulating values rise up to 1000-fold during an inflammatory response analogous to CRP. There are 4 isotypes of SAA, and studies have proven that its elevated values are probably related to blood coagulability and that additional studies are needed to prove whether SAA is a potential biomarker in patients with deep vein thrombosis and pulmonary thromboembolism (15,16). Specifically, the SAA-1 isotype showed 81.8% specificity and 83.7% sensitivity to optimal cut off value (1.26 ug/ml), however, it did not show a significant benefit in high-risk pulmonary embolism. Additionally, the SAA can provide additional information on the presence of the underlying inflammatory process (15).

Neutrophils/lymphocytes (NLR) to platelets/lymphocytes (PLR) ratio

NLR and PLR are markers associated with a number of inflammatory conditions, and are increasingly used as prognostic markers in predicting heart disease and cancer risk. Their big advantage is that they are available in routine work. Given the proven infiltration of neutrophils and macrophages in acute pulmonary embolism, as well as the formation of procoagulant and pro-inflammatory microparticles from platelets, leukocytes and endothelium, there was a need to examine these relationships in patients with acute PE (17,18). A study of 321 patients proved that NLR has a significant impact on short-term (30-day) mortality. For every single unit increase in NLR values, mortality risk increased by 13% (17). In addition, a study performed on 191 patients also demonstrated the importance of these markers in the assessment of all-cause mortality as well as risk assessment, where PLR was significantly higher in the low risk group than in other groups, and NLR was significantly higher in the group of surviving patients compared to non survivors (18).

The reviewed studies indicate that cardiac biomarkers consistently correlate with hemodynamic load and adverse outcomes, while inflammatory biomarkers reflect the intensity of systemic inflammation and thus the severity of the clinical picture. On the other hand, hematological parameters, although nonspecific, may represent practical and readily available parameters with a notable prognostic value. Combined, these markers show significant potential in a comprehensive risk assessment and clinical approach to patients with acute pulmonary embolism.

Table I **Studies related to the use of biomarkers in the diagnosis and prognosis of pulmonary embolism.**

Author (year)	Design / Population	Biomarker	Cut off / finding	Main results	Conclusion
Ebner M, et al., 2020 (n=459)	Normotensive PE patients	hs-Troponin I	>16 pg/mL	Associated with adverse outcomes and mortality	Useful for risk stratification
Kaeberich A, et al., 2015 (n=682)	PE patients	hs-Troponin T	≥14 pg/mL (<75 age), ≥45 pg/mL (≥75 age)	Increases negative predictive value	Important in risk assessment by age
Alonso-Martínez JL, et al., 2015 (n=243)	PE, follow up 3–20 months	NT-proBNP	>850 ng/L	Lower survival rate, predictor of long term mortality	Useful in long term follow up
Araz O, et al., 2016 (n=85)	PE patients	hs-CRP	Elevated	Outcome predictor, distinguishes massive/minor PE	Can be used to stratify patients
Bontekoe E, et al., 2021 (n=109)	PE Patients vs Control	IL-6, IL-10, TNF-α	Elevated in PE, especially massive	IL-6 most elevated, IL-10 and TNF-α also significant	All markers useful in stratifying the severity of PE
Yang P, et al., 2021 (n=87)	PE patients before and after therapy	TNF-α	Elevated in PE, declining after therapy	The most sensitive marker of lung damage	Diagnostic marker and for therapeutic monitoring
Han B, et al., 2021; Deguchi H, et al., 2013	PE and VTE PATIENTS	SAA	Cut off 1.26 μg/mL	Associated with coagulability, high sensitivity and specificity	Potential biomarker, further research needed
Ma et al., 2016 (n=321)	PE patients	NLR	Elevated	Each unit of NLR elevation increases mortality risk by 13%	Predictor of 30 day mortality
Phan T, et al., 2020 (n=191)	PE patients	NLR, PLR	Elevated	NLR higher in survivors, PLR higher in low risk group	Useful for stratification and prognosis

DISCUSSION

Acute pulmonary embolism presents a significant clinical challenge, both diagnostically and therapeutically, due to the non-specificity of its symptoms and variability in the clinical course. Standard, so far used diagnostic tools (D-dimer and radiological techniques), play a significant role in the initial treatment, but they are insufficient in accurately stratifying the risk and predicting the outcome of this disease. Therefore, a significant focus of research in recent years has been based on the identification of unconventional laboratory biomarkers that could be used for these purposes.

Cardiological biomarkers, especially highly sensitive troponins and NT-proBNP show, in several studies, a consistent association with adverse outcomes, where troponins indicate myocardial damage, while NT-proBNP indicates right ventricular dysfunction, and hs-CRP values are significantly related to the outcome of the disease. The increased value of these biomarkers indicates the presence of ischemia and dilatation of the right ventricle due to an acute increase in pressure in the pulmonary circulation, which makes these markers very useful in hemodynamically stable patients.

On the other hand, inflammatory biomarkers offer an additional dimension in understanding this disease. Namely, while cytokines (IL-6, IL-10) show a significant role in stratifying the severity of the disease, TNF-α stands out as a marker that not only reflects the presence of inflammation, but can also serve to monitor the effectiveness of treatment, given their dynamic decline after applied therapy.

Hematological indices (NLR, PLR) attract additional attention because they are inexpensive and easily measurable and in everyday laboratory practice available biomarkers, and at the same time show great prognostic significance in terms of mortality and risk stratification. The lack of standardization in the case of these biomarkers is what future research should be based on.

Although, individually, these biomarkers provide insight into certain aspects of the disease, their clinical value becomes more significant when viewed as related parts of the same pathophysiological process. Namely, while cardiological markers speak of hemodynamic consequences of the resulting obstruction, inflammatory markers simultaneously indicate endothelial damage, increased coagulation and cytokine activation, and hematological markers speak of a globally present immune response. By integrating these indicators, a significant and comprehensive insight into the severity of the disease and the risk of complications of the disease is obtained, which leads to the possibility of creating combined biomarker panels with an even higher predictive value than the individual marker offers. This could potentially enable earlier identification of high risk patients and a personalized clinical approach.

In general, although available studies indicate the potential role of the above biomarkers in the diagnosis and prognosis of PE, some limitations remain. Namely, these are often studies on relatively small samples, different methods of determining biomarkers and often uneven cut off values. This makes it difficult to compare the results and generalize them. Also, prospective, randomized studies that would integrate these laboratory biomarkers into validated clinical algorithms are lacking. Further research should focus on the simultaneous determination of multiple biomarkers on the same cohort of patients. This would obtain their direct comparability, validation of combined panels and standardization of biomarker panels for clinical use, and integration into standard guidelines. In addition, a personalized approach to treatment and optimization of the allocation of health resources would be provided.

CONCLUSION

Pulmonary embolism, as a clinically challenging condition with significant morbidity and mortality, is an entity for which timely diagnosis and risk assessment are crucial for optimal treatment outcome. While traditionally used biomarkers have their place in the diagnostic algorithm, the introduction of new laboratory biomarkers, not often used in the routine practice of this disease, would significantly help in additional insight into pathophysiological processes and better risk stratification, especially parameters that are easily available and lower priced. However, additional research, multicenter, prospective studies on a larger number of samples, are needed to standardize cut off values and further validate the clinical application of these biomarkers. The combination of laboratory biomarkers with existing clinical and radiological parameters could enable a personalized approach to treatment, better identification of high risk patients and reduction of mortality from pulmonary embolism.

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Authors' Contribution: DŠ and TB contributed substantially to the conception or design of the article and the acquisition. Each author contributed in analysis and interpretation of data for the work. Each author had a role in the article drafting and the revision process. Each author gave final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.
Financial support and sponsorship: nil.
Conflict of interest: There are no conflicts of interest.

Paliperidone Palmitate vs. Risperidone Long-Acting Injection: Effects on Cognitive Symptoms in Patients with Schizophrenia

Paliperidon palmitat u odnosu na dugodjelujući risperidon: efekti na kognitivne simptome kod pacijenata koji boluju od shizofrenije

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ABSTRACT

Schizophrenia is a severe psychiatric disorder characterized by positive symptoms, negative symptoms, and significant cognitive impairment. Cognitive deficits, particularly in attention, working memory, executive functioning, and processing speed, are major determinants of long-term functional outcomes. Long-acting injectable (LAI) antipsychotics are frequently used to improve treatment adherence and maintain stable therapeutic drug levels. Among these agents, risperidone long-acting injection (RLAI) and paliperidone palmitate (PP) are widely prescribed second-generation antipsychotics with similar pharmacodynamic mechanisms but different pharmacokinetic properties. This review examines available evidence regarding the comparative effects of PP and RLAI on cognitive symptoms in patients with schizophrenia. Current findings suggest that paliperidone palmitate may offer modest advantages in certain cognitive domains, particularly attention and processing speed, potentially due to more stable plasma concentrations and reduced pharmacokinetic variability. However, available studies remain limited, often involving small sample sizes or open-label designs. Larger randomized controlled trials focusing specifically on cognitive outcomes are required to clarify whether clinically meaningful differences exist between these two long-acting formulations.

Keywords: schizophrenia, cognitive impairment, long-acting injectable antipsychotics

SAŽETAK

Shizofrenija je ozbiljan psihijatrijski poremećaj karakteriziran pozitivnim i negativnim simptomima, kao i značajnom kognitivnom deterioracijom. Kognitivni deficit, naročito u domenu pažnje, radne memorije, izvršnih funkcija i brzine obrade informacija predstavljaju ključne determinante dugoročnog funkcionalnog ishoda. Dugodjelujući ampularni antipsihotici (LAI) često se koriste u cilju poboljšanja adherencije i održavanja stabilnih terapijskih koncentracija lijeka. Među ovim lijekovima, dugodjelujući risperidon i paliperidon palmitat su široko propisivani antipsihotici druge generacije sa sličnim farmakodinamskim mehanizmima, ali različitim farmakokinetičkim osobinama. Ovaj rad razmatra dostupne naučne dokaze o komparativnim efektima paliperidon palmitata i dugodjelujućeg risperidona na kognitivne simptome kod pacijenata koji boluju od shizofrenije. Trenutni nalazi ukazuju da paliperidon palmitat može imati blage prednosti u određenim kognitivnim domenima, naročito u pažnji i brzini obrade informacija, što se potencijalno može objasniti stabilnijim koncentracijama u plazmi i manjom farmakokinetičkom varijabilnošću. Ipak, dostupne studije su ograničene, često sa malim uzorcima ili otvorenim dizajnom. Potrebna su veća randomizirana kontrolisana istraživanja usmjerena na kognitivne ishode kako bi se utvrdilo postoje li klinički značajne razlike između ove dvije dugodjelujuće formulacije.

Ključne riječi: shizofrenija, kognitivni deficit, dugodjelujući ampularni antipsihotici

INTRODUCTION

Schizophrenia is a chronic and disabling psychiatric disorder affecting approximately 1% of the global population (1). It is characterized by positive symptoms such as hallucinations and delusions, negative symptoms including social withdrawal and affective flattening, and a broad range of cognitive impairments (2). Cognitive deficits are now recognized as a core feature of schizophrenia and are among the strongest predictors of long-term functional outcomes, including employment, social functioning, and quality of life. The cognitive domains most frequently affected include attention, working memory, processing speed, verbal learning, and executive functioning (3). Importantly, these deficits often persist even when positive symptoms are well controlled, suggesting partially independent neurobiological mechanisms (4). Despite advances in antipsychotic therapy, current pharmacological treatments provide only modest improvements in cognitive functioning, leaving cognitive impairment a major unmet therapeutic need (5).

Long-acting injectable antipsychotics were developed to improve treatment adherence and ensure more stable plasma drug concentrations. Poor adherence to oral antipsychotic medication is a common problem in schizophrenia and is associated with relapse, hospitalization, and worsening functional outcomes (6). By providing sustained drug delivery, LAIs may reduce fluctuations in dopamine receptor occupancy and potentially stabilize clinical and cognitive symptoms (7). Risperidone long-acting injection and paliperidone palmitate are among the most commonly used second-generation LAI antipsychotics. Both medications primarily exert their therapeutic effects through antagonism of dopamine D- and serotonin 5-HT-A receptors (8). Paliperidone is the primary active metabolite of risperidone (9-hydroxyrisperidone), but differences in metabolism, pharmacokinetics, and formulation may influence clinical outcomes (9). Although both medications demonstrate comparable efficacy for positive symptoms, their relative effects on cognitive symptoms remain less well understood. Understanding these differences is clinically relevant, given the central role of cognition in functional recovery for patients with schizophrenia.

AIM

The aim of this review paper was to examine current evidence comparing the effects of paliperidone palmitate and risperidone long-acting injection on cognitive functioning in patients with schizophrenia.

Chemical Structure and Pharmacological Characteristics

Paliperidone Palmitate

Paliperidone palmitate is a long-acting injectable ester prodrug of paliperidone (9-hydroxyrisperidone). The addition of a palmitate ester chain increases lipophilicity and allows slow hydrolysis following intramuscular injection, enabling sustained drug release over several weeks (10). Once administered, paliperidone palmitate is gradually converted to paliperidone, which acts primarily as a dopamine D2 receptor antagonist and serotonin 5-HT2A receptor antagonist. Additional activity includes interactions with α1-adrenergic and H1 histamine receptors (11).

Risperidone Long-Acting Injection

Risperidone LAI (Risperdal Consta) uses biodegradable polymer microspheres to encapsulate risperidone, enabling extended release after intramuscular administration. The formulation typically requires injections every two weeks and often includes oral supplementation during the initial treatment period due to delayed drug release (12). Risperidone shares a similar pharmacodynamic profile with paliperidone, including antagonism at dopamine D2 and serotonin 5-HT2A receptors, which contributes to its antipsychotic effects (13).

Pharmacokinetic Differences

Despite similar receptor targets, the pharmacokinetic properties of paliperidone palmitate and risperidone LAI differ significantly. Paliperidone palmitate is administered once monthly and reaches steady-state concentrations relatively quickly after loading doses (14). Its metabolism is minimal and largely independent of hepatic cytochrome P450 enzymes, which may reduce interindividual variability in drug levels (15). In contrast, risperidone LAI requires biweekly administration and undergoes hepatic metabolism through CYP2D6 to form paliperidone (16). This metabolic pathway may contribute to variability in plasma concentrations and therapeutic response. More stable pharmacokinetic profiles may theoretically benefit cognitive functioning by reducing fluctuations in dopamine receptor occupancy that could affect cortical neurotransmission involved in cognition (17).

Cognitive Impairment in Schizophrenia

Cognitive dysfunction is present in approximately 70-80% of patients with schizophrenia and often precedes the onset of psychotic symptoms. These deficits affect several domains:

- Processing speed
- Working memory
- Attention and vigilance
- Verbal learning and memory
- Executive functioning

The MATRICS Consensus Cognitive Battery (MCCB) is commonly used in research settings to evaluate these domains and has become a standard tool in schizophrenia cognition studies (18,19).

Comparative Evidence on Cognitive Outcomes

Randomized and Controlled Studies

One of the few direct comparisons between risperidone LAI and paliperidone palmitate was conducted in a six-month open-label randomized pilot trial. In this study, patients stabilized on risperidone LAI were either maintained on the same therapy or switched to paliperidone palmitate. The results suggested that patients treated with paliperidone palmitate demonstrated greater improvements in attention and processing speed compared with those continuing risperidone LAI (20).

Switching Studies

Naturalistic studies examining patients switched from risperidone to paliperidone palmitate have provided additional insights. In one observational study, switching to paliperidone palmitate was associated with improvements in several cognitive domains, including processing speed, working memory, visual memory, and attention after six months of treatment (21). Another analysis reported improvements in cognitive performance at three and six months following the transition from risperidone to paliperidone palmitate (22). These findings suggest that the pharmacokinetic stability of paliperidone palmitate may contribute to cognitive improvements in some patients (23,24,25,26)

Potential Mechanisms for Cognitive Differences

Several mechanisms may explain potential cognitive advantages associated with paliperidone palmitate.

Pharmacokinetic Stability

Monthly administration produces relatively stable plasma concentrations, potentially reducing dopamine receptor occupancy fluctuations that could impair cognitive processes.

Neuroprotective Effects

Experimental studies suggest paliperidone may exert neuroprotective effects through modulation of inflammatory pathways and oxidative stress, although these findings require further validation in clinical populations (27).

Reduced Relapse and Symptom Instability

Improved adherence and reduced relapse risk associated with LAI formulations may indirectly support cognitive functioning by maintaining clinical stability.

Limitations of Current Evidence

Despite emerging evidence, several limitations remain:

- Many studies involve small sample sizes
- Few randomized controlled trials directly compare cognitive outcomes between LAIs
- Cognitive domains are measured using heterogeneous neuropsychological batteries
- Some studies report neutral or modest cognitive effects of antipsychotics overall.

Consequently, conclusions regarding superiority of one LAI over another remain tentative.

Clinical Implications

When selecting a long-acting injectable antipsychotic, clinicians should consider several factors:

- treatment adherence history
- side-effect profiles
- dosing frequency
- patient preference
- metabolic and pharmacokinetic characteristics

Although paliperidone palmitate may offer advantages in convenience and pharmacokinetic stability, evidence for superior cognitive benefits remains limited. Treatment decisions should therefore be individualized based on the patient's clinical profile (28).

CONCLUSION

Cognitive impairment represents a central determinant of long-term disability in schizophrenia. Long-acting injectable antipsychotics play an important role in improving treatment adherence and maintaining symptom stability. Current evidence suggests that paliperidone palmitate may provide modest improvements in certain cognitive domains compared with risperidone long-acting injection, particularly attention and processing speed. However, existing studies are limited by small sample sizes and methodological constraints. Further large-scale randomized controlled trials focusing specifically on cognitive outcomes are necessary to determine whether these differences are clinically meaningful.

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Authors´ Contributions: NH and GS contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved..
Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest

Therapeutic Challenges in the Treatment of Negative Symptoms of Schizophrenia

Terapijski izazovi u liječenju negativnih simptoma shizofrenije

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ABSTRACT

Negative symptoms of schizophrenia remain one of the most difficult aspects of the disorder to treat in everyday clinical practice. Despite substantial progress in understanding the neurobiology of schizophrenia and the development of newer antipsychotic agents, therapeutic options for negative symptoms are still limited. Symptoms such as avolition, anhedonia, alogia, blunted affect, and asociality are strongly associated with poor functional outcome and often persist even when positive symptoms are adequately controlled. During the past decade, increasing attention has been directed toward pharmacological and non-pharmacological strategies specifically targeting primary and persistent negative symptoms. The aim of this paper was to review current challenges in the treatment of negative symptoms of schizophrenia, with particular emphasis on pharmacological approaches and emerging therapeutic mechanisms. Special attention is given to dopamine D3-preferring agents such as cariprazine, novel compounds with non-dopaminergic mechanisms including roluperidone and TAAR1 agonists, as well as neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), which have shown potential benefit in selected patient populations.

Keywords: schizophrenia, antipsychotics, neuromodulation

SAŽETAK

Negativni simptomi shizofrenije predstavljaju jedan od najtežih izazova za liječenje u svakodnevnoj kliničkoj praksi. Uprkos značajnom napretku u razumijevanju neurobiologije shizofrenije i razvoju novih antipsihotika, efikasne terapijske mogućnosti za negativne simptome i dalje su ograničene. Simptomi kao što su avolicija, anhedonija, alogija, zaravnjen afekt i asocijalnost snažno su povezani sa lošim funkcionalnim ishodom i često perzistiraju čak i nakon adekvatne kontrole pozitivnih simptoma. Tokom posljednje decenije sve veća pažnja usmjerena je na farmakološke i nefarmakološke strategije koje ciljaju primarne i perzistentne negativne simptome. Cilj ovog rada je prikazati savremene izazove u liječenju negativnih simptoma shizofrenije, sa posebnim osvrtom na farmakološke intervencije i nove terapijske mehanizme. Poseban naglasak stavljen je na dopamin D3-preferirajuće lijekove, kao što je kariprazin, nove spojeve sa nedopaminskim mehanizmima djelovanja, uključujući roluperidon i agoniste TAAR1 receptora, kao i neuromodulacijske metode poput repetitivne transkranijalne magnetne stimulacije (rTMS) i transkranijalne direktne strujne stimulacije (tDCS), koje su pokazale potencijalnu korist kod odabranih grupa pacijenata.

Ključne riječi: shizofrenija, antipsihotici, neuromodulacija

INTRODUCTION

Schizophrenia is a chronic psychiatric disorder with a complex and heterogeneous clinical presentation that includes positive, negative, and cognitive symptoms (1,2). While positive symptoms usually respond to antipsychotic treatment, negative symptoms remain considerably more difficult to manage and are among the main determinants of long-term disability. In many patients, these symptoms persist even after remission of acute psychosis and are closely related to impaired social functioning, reduced occupational capacity, and poor overall quality of life (3,4). The pathogenesis of negative symptoms is multifactorial and involves interactions between neurobiological vulnerability, psychological factors, and environmental influences. In clinical practice, assessment is further complicated by the fact that negative symptoms frequently overlap with depressive features, cognitive deficits, medication side effects, and social withdrawal. This overlap makes it difficult to determine whether symptoms represent the core deficit of the disorder or secondary phenomena, which in turn has important implications for treatment selection.

AIM

The aim of this review paper was to examine current evidence and analysis of relevant data on newer treatment methods for negative symptoms of schizophrenia.

MATERIALS AND METHODS

The research was conducted by searching multiple databases and scientific sources. The searches were performed in the following databases:

1.PubMed;
2. Google Scholar;
3. Articles published in other scientific journals;
4. Available literature

Negative Symptoms of Schizophrenia: Concept and Classification

Negative symptoms are traditionally defined as a reduction or loss of normal emotional and behavioral functions. Contemporary models, however, suggest that negative symptoms are not a single construct but consist of at least two partially independent dimensions (5,6). The first includes motivational and hedonic deficits, such as avolition, anhedonia, and asociality, while the second refers to diminished emotional and verbal expression, including blunted affect and alogia. This distinction has important clinical implications, as accumulating evidence indicates that motivational deficits are more strongly associated with functional impairment and tend to respond less consistently to currently available treatments.

Primary and Secondary Negative Symptoms

A clinically relevant distinction is made between primary and secondary negative symptoms. Primary negative symptoms are considered part of the core psychopathology of schizophrenia, whereas secondary symptoms may arise from other factors, including depression, anxiety, social deprivation, persistent positive symptoms, or adverse effects of antipsychotic medication.

In everyday clinical practice, differentiating between these two forms can be difficult, yet it is essential for treatment planning. Secondary negative symptoms often improve when the underlying cause is adequately treated, while primary symptoms tend to be more persistent and less responsive to standard pharmacological interventions (7).

Mechanisms Underlying Negative Symptoms

The neurobiology of negative symptoms is less clearly defined than that of positive symptoms and likely involves several interacting neurochemical and neurocircuitry abnormalities. Rather than being explained by a single neurotransmitter dysfunction, current models suggest that negative symptoms reflect disturbances in multiple systems, particularly those involved in motivation, reward processing, and executive control.

Dopaminergic Dysfunction Outside the Mesolimbic System

The classical dopamine hypothesis of schizophrenia primarily relates positive symptoms to hyperactivity of the mesolimbic dopaminergic pathway. In contrast, negative symptoms have been linked to reduced dopaminergic activity in the mesocortical pathway, especially in the prefrontal cortex. Hypodopaminergia in these regions may contribute to deficits in motivation, initiative, and emotional responsiveness, which represent key clinical features of negative symptoms. This model also helps explain why strong D2 receptor blockade, particularly with first-generation antipsychotics, may worsen secondary negative symptoms in some patients (8).

Glutamatergic hypofunction and NMDA receptors

In addition to dopaminergic abnormalities, growing evidence supports a role for glutamatergic dysfunction in the pathophysiology of negative symptoms. The NMDA receptor hypofunction hypothesis proposes that reduced activity of NMDA receptors leads to impaired cortical integration and secondary dysregulation of dopaminergic pathways. Such disturbances may be particularly relevant for persistent negative symptoms that remain present independently of acute psychotic episodes and are closely related to deficits in motivation, cognition, and social functioning (9).

Kynurenine Pathway and NMDA Dysfunction

The kynurenine pathway of tryptophan metabolism has received increasing attention as a potential link between neuroinflammation, glutamatergic dysfunction, and the development of negative symptoms. This metabolic pathway produces several neuroactive compounds, among which kynurenic acid (KYNA) is of particular interest because it acts as an endogenous antagonist at NMDA receptors as well as α7 nicotinic acetylcholine receptors. Elevated KYNA concentrations have been reported in the cerebrospinal fluid and brain tissue of patients with schizophrenia and have been associated with more pronounced negative symptoms and cognitive impairment. Increased activation of the kynurenine pathway, possibly driven by inflammatory processes, may contribute to functional NMDA receptor hypofunction in the prefrontal cortex and thereby interfere with neural circuits involved in motivation, affect regulation, and goal-directed behavior. These findings have important therapeutic implications, and pharmacological strategies targeting enzymes of the kynurenine pathway or inflammatory mechanisms that regulate this pathway are currently being explored, although most remain at an experimental stage (9,10).

Neuroinflammation and Neurodegenerative Processes

There is increasing evidence that inflammatory and neurodegenerative mechanisms may contribute to the clinical expression of schizophrenia, particularly in patients with prominent negative symptoms. Elevated levels of pro-inflammatory cytokines and signs of microglial activation have been reported in several studies and appear to correlate with greater symptom severity and poorer functional outcome. Although the causal relationship remains uncertain, these findings support further investigation of anti-inflammatory and neuroprotective treatment strategies as possible adjunctive approaches in patients with treatment-resistant negative symptoms (11).

Challenges in the assessment of negative symptoms

Accurate assessment of negative symptoms remains a major difficulty both in clinical practice and in research settings. Traditional rating scales, such as the Positive and Negative Syndrome Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS), have been widely used but show important limitations, particularly in distinguishing primary negative symptoms from other psychopathological domains. In response to these limitations, newer instruments such as the Brief Negative Symptom Scale (BNSS) and the Clinical Assessment Interview for Negative Symptoms (CAINS) were developed in order to provide a more precise evaluation of the two main domains of negative symptoms and to improve sensitivity to treatment-related change. Despite these advances, interpretation of treatment effects remains challenging, since apparent improvement in negative symptoms may reflect changes in secondary factors, such as depression, sedation, or extrapyramidal side effects, rather than a true effect on the core deficit of the disorder (12,13,14).

Pharmacological Treatment of Negative Symptoms of Schizophrenia

Antipsychotics and negative symptoms

Antipsychotic medication remains the foundation of schizophrenia treatment, but its direct effect on negative symptoms is generally modest. In many cases, improvement observed during treatment reflects indirect effects, such as better control of positive symptoms, reduction of distress, or adjustment of medication-related side effects. First-generation antipsychotics, because of their strong dopamine D2 receptor blockade, may even contribute to secondary negative symptoms through extrapyramidal adverse effects, emotional blunting, or sedation. Second-generation antipsychotics appear somewhat better tolerated, but their advantage in treating primary negative symptoms remains limited.

Cariprazine

Cariprazine, a partial agonist at dopamine D2 and D3 receptors with preferential affinity for D3 receptors, has attracted particular interest because of the role of D3 receptors in reward processing, motivation, and cognitive function. In a randomized double-blind study involving patients with predominant negative symptoms, cariprazine demonstrated greater improvement compared with risperidone, along with a modest but clinically relevant benefit in functional outcome. Although these findings represent one of the few positive results in this field, the overall effect size remains moderate, and careful dose titration is often required due to the risk of akathisia and other adverse effects related to partial dopamine agonism (15).

Roluperidone

Roluperidone represents a different pharmacological approach, as it lacks significant dopamine D2 receptor blockade. Its mechanism involves antagonism at serotonin 5-HT2A and sigma-2 receptors, which may influence cortical neurotransmission without producing typical antipsychotic side effects. Clinical trials in stable patients with schizophrenia have shown improvement in negative symptoms with a favorable tolerability profile and minimal extrapyramidal adverse effects. However, results across studies have not been entirely consistent, and further confirmation is required before its role in routine clinical practice can be clearly defined (16,17).

Glutamatergic and other novel pharmacological approaches

The hypothesis of NMDA receptor hypofunction has led to the development of several compounds targeting the glutamatergic system. Early studies with glycine reuptake inhibitors and related agents suggested a possible benefit for negative symptoms, but later phase III trials failed to demonstrate consistent clinical efficacy. More recently, interest has shifted toward drugs with alternative mechanisms, including TAAR1 receptor agonists and agents with potential anti-inflammatory or neuroprotective effects. Although these approaches remain experimental, they reflect the growing recognition that negative symptoms are unlikely to be explained by dopaminergic dysfunction alone (18).

Augmentation strategies

Augmentation of antipsychotic therapy with antidepressants has been explored as a possible strategy for patients with prominent negative symptoms, particularly when depressive features are also present. Meta-analytic data suggest a small but statistically significant effect; however, the clinical relevance of this benefit remains uncertain, and routine use cannot be recommended without careful patient selection. In practice, augmentation strategies are most useful when negative symptoms are suspected to be secondary rather than primary (18,19).

Neuromodulation in the Treatment of Negative Symptoms of Schizophrenia

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) has been increasingly investigated as an adjunctive treatment for negative symptoms of schizophrenia, particularly in patients with stable illness and insufficient response to pharmacotherapy. Most studies have focused on high-frequency stimulation of the left dorsolateral prefrontal cortex, a region involved in motivation, executive functioning, and emotional regulation. Meta-analyses of randomized controlled trials suggest a modest but statistically significant effect of rTMS compared with sham stimulation. However, interpretation of these findings is limited by substantial heterogeneity across studies, including differences in stimulation parameters, treatment duration, and patient selection. It remains unclear which subgroup of patients is most likely to benefit, although some evidence suggests that individuals with predominantly negative symptoms and low levels of positive psychopathology may respond better (20,21).

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) represents a technically simpler and more accessible neuromodulation method that modulates cortical excitability using low-intensity electrical currents. Several randomized studies and meta-analyses have reported small but potentially clinically meaningful improvements in negative symptoms when tDCS is used as an adjunct to standard treatment. Nevertheless, effect sizes are generally modest, and methodological limitations such as small sample sizes, short follow-up periods, and variability in stimulation protocols make it difficult to draw firm conclusions. At present, tDCS should be considered an experimental or adjunctive option rather than a standard treatment (21).

DISCUSSION

The treatment of negative symptoms of schizophrenia remains one of the most challenging areas in contemporary psychopharmacology. Despite advances in the understanding of underlying neurobiological mechanisms, currently available interventions provide only limited and often inconsistent benefit. Several factors contribute to these difficulties, including the heterogeneity of negative symptoms, the frequent presence of secondary symptoms, and methodological problems in clinical trials. Recent research has focused on compounds with mechanisms beyond dopamine D2 receptor blockade. Pimavanserin, a selective 5-HT2A inverse agonist, has been investigated as an augmentation strategy in

patients with predominant negative symptoms. Because it does not directly block dopamine receptors, this agent may avoid some of the limitations associated with conventional antipsychotics, particularly worsening of secondary negative symptoms. Randomized controlled trials have shown a statistically significant but moderate improvement compared with placebo, with a favorable safety profile. However, the clinical relevance of these findings remains a matter of debate, and further studies are needed to clarify its role in routine treatment. Among currently available medications, cariprazine has shown the most consistent evidence of benefit in patients with predominant negative symptoms, although the magnitude of improvement is still limited. Novel agents such as roluperidone and drugs targeting glutamatergic or inflammatory pathways represent promising directions, but the available data are not yet sufficient to support widespread clinical use. These findings suggest that negative symptoms are unlikely to respond to a single pharmacological mechanism and that future progress will probably depend on a more individualized approach. Combining pharmacological treatment with psychosocial interventions, cognitive remediation, and neuromodulation may be necessary in order to achieve meaningful functional improvement in many patients.

CONCLUSION

Negative symptoms of schizophrenia continue to represent a major therapeutic challenge with significant clinical and social consequences. Although recent research has improved understanding of the neurobiological basis of these symptoms, effective treatment options remain limited. The development of drugs with novel mechanisms of action, together with better characterization of primary and secondary negative symptoms, may improve future treatment strategies. At present, the most realistic approach involves individualized treatment that integrates pharmacological, psychosocial, and neuromodulation-based interventions, with the primary goal of improving functional outcome and quality of life rather than achieving complete symptom remission.

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Authors' contributions: ZŠ-A and GS contributed substantially to the conception or design of the article and the acquisition, analysis, and interpretation of data for the work. Each author had a role in article drafting and the revision process. Each author gave final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

The Impact of Extracorporeal Low-Intensity Shockwave Therapy in the Treatment of Erectile Dysfunction - A Systematic Review

Uticaj niskointenzivne ekstrakorporalne terapije udarnim talasima u liječenju erektilne disfunkcije - sistemski pregled literature

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ABSTRACT

Introduction: Erectile dysfunction (ED) is a common condition that significantly impairs quality of life. Although phosphodiesterase type 5 inhibitors (PDE5i) remain the first-line therapy, a substantial proportion of patients, particularly those with vasculogenic ED, fail to achieve an adequate therapeutic response. Low-intensity extracorporeal shockwave therapy (LI-ESWT) has emerged as a potential regenerative treatment targeting the underlying pathophysiology of ED. Aim: to evaluate the efficacy and safety of LI-ESWT in the treatment of erectile dysfunction. Materials and methods: A systematic review was conducted in accordance with PRISMA guidelines. Electronic database searches were performed in PubMed/MEDLINE, Scopus, and Web of Science for studies published between January 2015 and December 2025. After removal of duplicates and screening of titles, abstracts, and full texts, 21 clinical studies met the inclusion criteria. Primary outcomes included changes in erectile function assessed using validated instruments such as the International Index of Erectile Function (IIEF-EF), Sexual Health Inventory for Men (SHIM/IIEF-5), and Erection Hardness Score (EHS). Due to substantial heterogeneity among studies, a qualitative synthesis was performed. Results: Most included studies demonstrated moderate improvement in erectile function following LI-ESWT therapy, particularly in patients with mild to moderate vasculogenic ED. The therapeutic effect appeared to be more consistent in studies using focused LI-ESWT devices. However, several sham-controlled randomized trials failed to demonstrate statistically significant differences compared with placebo treatment. Short-term improvement was most commonly observed within 3-6 months after therapy, while long-term efficacy remained uncertain. LI-ESWT demonstrated a favorable safety profile, with no serious adverse events reported. Conclusions: LI-ESWT may represent a promising minimally invasive therapeutic option for selected patients with erectile dysfunction, especially those with vasculogenic disease and inadequate response to PDE5 inhibitors. Nevertheless, current evidence remains limited by heterogeneity in study design and treatment protocols. Additional high-quality sham-controlled randomized trials with long-term follow-up are required before routine clinical implementation can be recommended.

Keywords: erectile dysfunction, LI-ESWT, shockwave therapy, vasculogenic ED

SAŽETAK

Uvod: Erektilna disfunkcija (ED) predstavlja čest poremećaj koji značajno narušava kvalitet života. Iako inhibitori fosfodiesteraze tipa 5 (PDE5i) predstavljaju terapiju prve linije, značajan broj pacijenata, posebno onih s vaskulogenom erektilnom disfunkcijom, ne postiže adekvatan terapijski odgovor. Niskointenzivna ekstrakorporalna terapija udarnim talasima (LI-ESWT) posljednjih godina se izdvaja kao potencijalna regenerativna terapija usmjerena na osnovne patofiziološke mehanizme erektilne disfunkcije. Cilj: procijeniti efikasnost i sigurnost LI-ESWT terapije u liječenju erektilne disfunkcije. Materijali i metode: Sistematski pregled literature proveden je u skladu sa PRISMA smjernicama. Pretraga elektronskih baza podataka PubMed/MEDLINE, Scopus i Web of Science obuhvatila je studije objavljene u periodu od 2015. do 2025. godine. Nakon uklanjanja duplikata i pregleda naslova, sažetaka i punih tekstova, kriterije uključenja ispunila je 21 klinička studija. Primarni ishodi uključivali su promjene erektilne funkcije procijenjene validiranim instrumentima kao što su International Index of Erectile Function (IIEF-EF), Sexual Health Inventory for Men (SHIM/IIEF-5) i Erection Hardness Score (EHS). Zbog značajne heterogenosti uključenih studija provedena je kvalitativna analiza rezultata. Rezultati:Većina uključenih studija pokazala je umjereno poboljšanje erektilne funkcije nakon primjene LI-ESWT terapije, naročito kod pacijenata s blagom do umjerenom vaskulogenom erektilnom disfunkcijom. Terapijski efekat bio je konzistentniji u studijama koje su koristile fokusirane LI-ESWT uređaje. Međutim, nekoliko sham-kontrolisanih randomiziranih studija nije pokazalo statistički značajnu razliku u odnosu na placebo tretman. Kratkoročno poboljšanje najčešće je zabilježeno tokom prvih 3–6 mjeseci nakon terapije, dok dugoročna efikasnost ostaje nedovoljno razjašnjena. LI-ESWT je pokazao povoljan sigurnosni profil bez prijavljenih ozbiljnih neželjenih događaja. Zaključak: LI-ESWT može predstavljati obećavajuću minimalno invazivnu terapijsku opciju za odabrane pacijente s erektilnom disfunkcijom, posebno kod vaskulogene etiologije i pacijenata s nedovoljnim odgovorom na PDE5 inhibitore. Međutim, postojeći dokazi ograničeni su heterogenošću studija i terapijskih protokola. Potrebna su dodatna visokokvalitetna sham-kontrolisana randomizirana istraživanja s dugoročnim praćenjem prije preporuke za rutinsku kliničku primjenu.

Ključne riječi: erektilna disfunkcija, LI-ESWT, terapija udarnim talasima, vaskulogena ED

INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent or recurrent inability to achieve and/or maintain an erection sufficient for satisfactory sexual intercourse. The prevalence of ED increases with age and is associated with numerous risk factors, including cardiovascular disease, diabetes mellitus, dyslipidemia, and smoking (1). It is estimated that more than 150 million men worldwide suffer from some form of erectile dysfunction (2).

Vasculogenic erectile dysfunction represents the most common form of this disorder and is closely associated with endothelial dysfunction and reduced blood flow within the penile cavernous tissue (3). Since endothelial dysfunction is considered an early marker of systemic vascular disease, ED may often precede the onset of cardiovascular events (4).

Although phosphodiesterase type 5 inhibitors (PDE5i) remain the first-line therapy, approximately 30-40% of patients fail to achieve a satisfactory therapeutic response (5,6). Limitations of current pharmacological treatment have led to the development of novel regenerative therapeutic approaches targeting the underlying pathophysiological mechanisms of erectile dysfunction.

In recent years, low-intensity extracorporeal shockwave therapy (LI-ESWT) has attracted considerable attention as a potential regenerative treatment for vasculogenic erectile dysfunction. LI-ESWT is believed to stimulate angiogenesis, improve endothelial function, and enhance microcirculation within the cavernous tissue, thereby contributing to improved erectile function (7). Although current international guidelines recognize LI-ESWT as a promising therapeutic option, its routine clinical application remains under investigation due to the heterogeneity of available studies and the lack of standardized treatment protocols (8,9).

Given the growing number of clinical studies and the still inconsistent findings in the available literature, there is a need for a systematic evaluation of current evidence regarding the efficacy and safety of LI-ESWT in the treatment of erectile dysfunction.

Mechanism of Action

LI-ESWT delivers low-energy acoustic waves to penile tissue, stimulating biological processes without causing significant tissue damage (7). Experimental and clinical evidence suggests that LI-ESWT promotes angiogenesis through increased expression of vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS), while also improving endothelial function and microcirculation within the cavernous tissue (1,3,10).

In addition to its angiogenic effects, LI-ESWT is believed to stimulate activation of endogenous stem cells and regenerative processes within cavernous tissue, further contributing to the improvement of erectile function (3,7). In recent years, several studies have also investigated combination therapeutic approaches, including LI-ESWT combined with pharmacological therapy or platelet-rich plasma (PRP), with some reports demonstrating potentially superior therapeutic outcomes compared with monotherapy (10-13).

Available evidence indicates that LI-ESWT has a favorable safety profile, with no serious adverse events reported in the majority of clinical studies (4,7).

AIM

The aim of this systematic review was to critically evaluate the available clinical evidence regarding the efficacy and safety of low-intensity extracorporeal shockwave therapy (LI-ESWT) in the treatment of erectile dysfunction, with particular emphasis on randomized controlled, prospective, and observational clinical studies.

MATERIALS AND METHODS

This study was designed as a systematic review conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (5,6,14).

Literature Search Strategy

A systematic literature search was performed in the electronic databases PubMed/MEDLINE, Scopus, and Web of Science for studies published between January 2015 and December 2025. The following keywords and search terms were used:

- "erectile dysfunction"
- "low-intensity shockwave therapy"
- "LI-ESWT"
- "shockwave therapy"
- "vasculogenic erectile dysfunction"

Keywords were combined using the Boolean operators AND and OR. In addition, the reference lists of included studies were manually screened to identify potentially relevant publications.

Inclusion and Exclusion Criteria

Randomized controlled, prospective, and observational clinical studies involving adult patients with erectile dysfunction treated with LI-ESWT were included in the review. Eligible studies were required to report relevant clinical outcomes related to erectile function assessment, including the International Index of Erectile Function (IIEF-EF), Sexual Health Inventory for Men (SHIM/IIEF-5), and Erection Hardness Score (EHS).

Review articles, meta-analyses, umbrella reviews, case reports, animal studies, studies without available full text, and articles not published in English were excluded from the review.

Study Selection

A total of 412 records were identified through the database search. After duplicate removal, titles and abstracts were screened, followed by full-text assessment of potentially eligible studies. Ultimately, 21 clinical studies were included in the qualitative synthesis. Full-text articles were excluded due to insufficient outcome data, inappropriate study design, unavailable full text, or non-English language. The study selection process was illustrated using a PRISMA flow diagram (Figure 1).

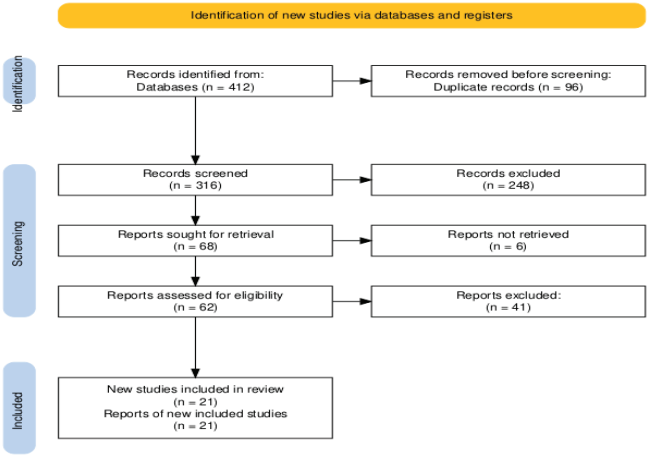

Figure 1 **PRISMA flow diagram of the study selection process for inclusion in the systematic review.**

Data Extraction

The following data were extracted from the included studies:

- author and year of publication,
- study design,
- sample size,
- patient characteristics,
- device type and treatment parameters,
- treatment protocol,
- treatment application site,
- follow-up duration,
- clinical outcomes and safety data.
- Quality Assessment and Risk of Bias

The methodological quality of the included studies was assessed according to study design and key methodological characteristics. Risk of bias assessment included evaluation of randomization, the presence of sham/placebo control, blinding, sample size, follow-up duration, completeness of outcome data, and objectivity of outcome measurements.

Due to substantial heterogeneity among the included studies regarding treatment protocols, patient populations, and measured outcomes, a quantitative meta-analysis was not performed. Instead, the results were synthesized using a qualitative descriptive analysis.

RESULTS

Study Selection

A total of 412 records were identified through systematic database searching. After duplicate removal and screening of titles and abstracts, full-text assessment of potentially relevant studies was performed. Ultimately, 21 clinical studies were included in the qualitative synthesis. The study selection process was illustrated using a PRISMA flow diagram.

Characteristics of Included Studies

The main characteristics of the included studies are presented in Table 1. The included studies comprised randomized controlled, prospective, and observational clinical studies. Sample sizes ranged from 33 to 150 participants.

Most of the studies included patients with mild to moderate vasculogenic erectile dysfunction. In addition, specific patient subgroups were analyzed, including diabetic erectile dysfunction, post-prostatectomy erectile dysfunction, and patients with inadequate response to PDE5 inhibitors.

Table 1 **Characteristics of included studies.**

Author (year)	Study design	N	Population
Fojecki GI, et al. (2017)	Double-blind sham-controlled randomized controlled trial (RCT)	126	Patients with mixed-etiology erectile dysfunction
Olsen AB, et al. (2015)	Randomized placebo-controlled study	105	Patients with mild erectile dysfunction
Kitrey ND, et al. (2018)	Randomized controlled study	58	PDE5i non-responders
Srini VS, et al. (2015)	Prospective study	150	Patients with vasculogenic erectile dysfunction
Vinay J, et al. (2021)	Randomized double-blind sham-controlled study	76	PDE5i non-responders
Ladegaard PBJ, et al. (2021)	Randomized placebo-controlled study	120	Post-prostatectomy erectile dysfunction
Shendy WS, et al. (2021)	Randomized controlled study	42	Diabetic erectile dysfunction
Lei Q, et al. (2021)	Comparative randomized study	80	Patients with mixed-etiology erectile dysfunction
Geyik S. (2021)	Prospective comparative study	70	Patients with erectile dysfunction
Palmieri A, et al. (2021)	Multicenter clinical study	100	Patients with vasculogenic erectile dysfunction
Gallo L, et al. (2022)	Prospective randomized study	100	Patients with vasculogenic erectile dysfunction
Kalyvianakis D, et al. (2022)	Double-blind sham-controlled RCT	70	Patients with moderate erectile dysfunction
Kennady EH, et al. (2023)	Randomized crossover sham-controlled study	33	Patients with organic erectile dysfunction
Bocchino AC, et al. (2023)	Prospective study	50	Patients with erectile dysfunction
Rubino M, et al. (2024)	Observational study	65	Patients with arteriogenic erectile dysfunction
Goldstein SW, et al. (2024)	Randomized clinical study	60	Patients with vasculogenic erectile dysfunction
Özsoy E, et al (2024)	Prospective study	60	Patients with vasculogenic erectile dysfunction
Pyrgidis N, et al. (2024)	Prospective study	72	Patients with erectile dysfunction
Lange M, et al. (2024)	Long-term follow-up study	60	Patients with erectile dysfunction
Kalyvianakis D, et al. (2024)	Double-blind randomized controlled study	90	Patients with severe erectile dysfunction

Table 2 **Treatment protocols and clinical outcomes.**

Author (year)	Device type	EFD (mJ/mm²)	Pulses	Treatment protocol	Application site	Follow-up	Main findings
Fojecki GI, et al. (2017)	Focused LI-ESWT	Not reported	Not reported	2 sessions weekly for 5 weeks	Penile shaft	3 months	No significant difference versus sham
Olsen AB, et al. (2015)	Focused LI-ESWT	0.09	3000	5 weeks	Penile shaft	6 months	Moderate improvement in erectile function
Kitrey ND, et al. (2018)	Focused LI-ESWT	0.09	3000	6 weeks	Cavernous tissue	6 months	Improved response in PDE5i non-responders
Srini VS, et al. (2015)	Focused LI-ESWT	Not reported	Not reported	12 weeks	Penile shaft	12 months	Longer-lasting therapeutic effect
Vinay J, et al. (2021)	Focused LI-ESWT	0.09	5000	1 session weekly for 4 weeks	Penile shaft and crura	6 months	Significant improvement in IIEF-EF score
Ladegaard PBJ, et al. (2021)	Focused LI-ESWT	0.09	1500–3000	5 weeks	Penile shaft and crura	3–6 months	Limited therapeutic effect
Shendy WS, et al. (2021)	Focused LI-ESWT	Not reported	Not reported	2 sessions weekly for 3 weeks	Cavernous tissue	3 months	Improvement in IIEF-5 score
Lei Q, et al. (2021)	Focused LI-ESWT	0.09	1500–2000	6 weeks	Penile shaft	1–3 months	Comparable efficacy to sildenafil
Geyik S. (2021)	Radial LI-ESWT	Not reported	Not reported	6 weeks	Penile shaft	6 months	Better outcomes with PRP combination
Palmieri A, et al. (2021)	Focused LI-ESWT	0.09	3000	6–12 weeks	Penile shaft and crura	3–6 months	Increased efficacy in combination therapy
Gallo L, et al. (2022)	Focused LI-ESWT	0.09	3000	6–12 weeks	Penile shaft and crura	12 months	Long-term improvement in erectile function
Kalyvianakis D, et al. (2022)	Focused LI-ESWT	0.096	5000	2 sessions weekly for 6 weeks	Cavernous tissue and crura	3 months	Clinically significant improvement
Kennady EH, et al. (2023)	Focused LI-ESWT	0.10	3000	2 sessions weekly for 3 weeks	Cavernous tissue	6 months	Improvement in SHIM score
Bocchino AC, et al. (2023)	Focused LI-ESWT	Not reported	Not reported	6 weeks	Penile shaft	6 months	Improvement in erectile function
Rubino M, et al. (2024)	Radial LI-ESWT	Not reported	Not reported	6 weeks	Cavernous tissue	6 months	Improvement in IIEF-5 score
Goldstein SW, et al. (2024)	Focused LI-ESWT	0.09	3000	6–12 weeks	Penile shaft and crura	3–6 months	Improvement in IIEF and ultrasound parameters
Özsoy E, et al. (2024)	Focused LI-ESWT	0.09–0.15	1500–3000	6–8 weeks	Penile shaft and crura	3 months	Significant improvement in erectile function
Pyrgidis N, et al. (2024)	Focused LI-ESWT	Variable	Variable	Variable	Variable	6 months	Moderate therapeutic effect
Lange M, et al. (2024)	Focused LI-ESWT	Variable	Variable	Variable	Variable	12 months	Reduction in treatment effect over time
Kalyvianakis D, et al. (2024)	Focused LI-ESWT	0.10	5000	2 sessions weekly for 6 weeks	Penile shaft and crura	6 months	Better outcomes combined with PDE5 inhibitors
Schuh MF, et al. (2025)	Focused LI-ESWT	0.09	1500–3000	6–8 weeks	Penile shaft and crura	3 months	Significant improvement in IIEF-EF score

Treatment Protocols

Treatment protocols and clinical outcomes of the included studies are presented in Table 2. Most studies used focused LI-ESWT devices, whereas a smaller number of studies used radial devices. Energy flux density (EFD) most commonly ranged between 0.09 and 0.10 mJ/mm², while the number of shockwave pulses varied from 1,500 to 5,000 per treatment session.

Treatment protocols ranged from 3 to 12 weeks, with different application regimens and anatomical treatment sites.

Clinical outcomes

Most randomized and prospective studies demonstrated statistically significant improvement in erectile function following LI-ESWT therapy, assessed using validated instruments such as IIEF-EF, SHIM/IIEF-5, and Erection Hardness Score (EHS) (5,6,14).

The most pronounced therapeutic effect was observed in patients with mild to moderate vasculogenic erectile dysfunction (5,6,15). Several studies also reported improved therapeutic response in patients who had previously shown inadequate response to PDE5 inhibitors (10,11).

However, some sham-controlled studies failed to demonstrate statistically significant differences between active treatment and placebo groups (16-18).

Studies using focused LI-ESWT devices generally demonstrated more consistent therapeutic effects compared with studies using radial devices (16,17).

The greatest improvement in erectile function was observed within the first 3-6 months following therapy, whereas several studies reported gradual decline in therapeutic effect after 12-24 months of follow-up (5,6,18).

Safety Profile

LI-ESWT demonstrated a favorable safety profile in the majority of included studies. No serious adverse events were reported, while the most commonly observed adverse effects were mild and transient, including local discomfort and mild erythema during treatment (5,6,18,19).

Risk of Bias Assessment

Risk of bias assessment is presented in Table 3. Most randomized sham-controlled studies were assessed as having low risk of bias, whereas prospective and observational studies generally demonstrated moderate risk of bias due to the absence of randomization and sham control. None of the included studies was assessed as having high risk of bias.

Table 3 **Risk of bias assessment.**

Study	Randomization	Sham/placebo control	Blinding	Follow-up	Risk of bias
Fojecki GI, et al., 2017	Yes	Yes	Double-blind	3 months	Low
Olsen AB, et al., 2015	Yes	Yes	Double-blind	6 months	Low
Kitrey ND, et al., 2018	Yes	No	Not clearly reported	6 months	Moderate
Srini VS, et al., 2015	No	No	Not reported	12 months	Moderate
Vinay J, et al., 2021	Yes	Yes	Double-blind	6 months	Low
Ladegaard PBJ, et al., 2021	Yes	Yes	Double-blind	3–6 months	Low
Shendy WS, et al., 2021	Yes	No	Not reported	3 months	Moderate
Lei Q, et al., 2021	Yes	No	Not reported	1–3 months	Moderate
Geyik S, 2021	No	No	Not reported	6 months	Moderate
Palmieri A, et al., 2021	No	No	Not reported	3–6 months	Moderate
Gallo L, et al., 2022	Yes	No	Single-blind	12 months	Moderate
Kalyvianakis D, et al., 2022	Yes	Yes	Double-blind	3 months	Low
Kennady EH, et al., 2023	Yes	Yes	Double-blind	6 months	Low
Bocchino AC, et al., 2023	No	No	Not reported	6 months	Moderate
Rubino M, et al., 2024	No	No	Not reported	6 months	Moderate
Goldstein SW, et al., 2024	Yes	No	Not clearly reported	3–6 months	Moderate
Özsoy E, et al., 2024	No	No	Not reported	3 months	Moderate
Pyrgidis N, et al., 2024	No	No	Not reported	6 months	Moderate
Lange M, et al., 2024	Yes	Yes	Sham-controlled	12 months	Low
Kalyvianakis D, et al., 2024	Yes	No	Double-blind	6 months	Moderate
Schuh MF, et al., 2025	Yes	Yes	Double-blind	3 months	Low

DISCUSSION

The findings of this systematic review suggest that low-intensity extracorporeal shockwave therapy (LI-ESWT) may provide moderate improvement in erectile function, particularly in patients with mild to moderate vasculogenic erectile dysfunction (2,5,6,15,20,21). Most included studies demonstrated positive changes in validated clinical parameters such as IIEF-EF, SHIM/IIEF-5, and Erection Hardness Score (22). Nevertheless, despite the growing number of published studies, current evidence remains inconsistent and methodologically heterogeneous, which limits the strength of available conclusions (2,23,24).

The proposed therapeutic effect of LI-ESWT is primarily based on its regenerative potential. Experimental evidence suggests that low-intensity shockwaves may stimulate angiogenesis, improve endothelial function, and enhance microvascular circulation within cavernous tissue through increased expression of angiogenic mediators such as vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS) (1,3,23). However, although these biological mechanisms appear plausible, the translation of experimental findings into consistent clinical benefit remains insufficiently established (23,24). Several randomized sham-controlled studies failed to demonstrate statistically significant superiority of LI-ESWT over placebo treatment, indicating that the observed clinical improvement may partly reflect placebo response, patient expectation, or natural fluctuation of erectile function over time (19,25,26).

One of the major limitations of the current literature is the substantial heterogeneity of treatment protocols. Included studies differed considerably regarding device type, energy flux density, number of pulses, treatment duration, treatment frequency, and anatomical application sites. Such variability significantly complicates direct comparison between studies and prevents clear identification of optimal treatment parameters. Even among studies reporting positive outcomes, therapeutic protocols varied from 3 to 12 weeks, while the number of delivered shockwaves ranged from 1,500 to 5,000 per session. Consequently, it remains unclear whether observed differences in clinical efficacy are attributable to treatment intensity, protocol duration, patient selection, or device characteristics (16,23,24).

An additional source of inconsistency relates to the use of focused versus radial LI-ESWT devices. Most studies demonstrating favorable outcomes used focused devices, whereas studies using radial devices generally reported less consistent therapeutic effects (16,17). Focused LI-ESWT allows deeper and more localized energy penetration within

cavernous tissue, which may explain the more reproducible outcomes observed in several randomized studies. In contrast, radial shockwave therapy produces more superficial energy dispersion and may therefore have limited biological efficacy in erectile tissue. Nevertheless, currently available comparative evidence remains limited, and additional head-to-head trials are necessary before definitive conclusions regarding device superiority can be established (16,17,24).

Patient selection also appears to play a crucial role in treatment response (27). The most favorable outcomes were consistently observed in patients with mild to moderate vasculogenic erectile dysfunction and relatively preserved vascular integrity (3,5,15). Conversely, patients with severe erectile dysfunction, diabetes mellitus, advanced endothelial dysfunction, or post-prostatectomy erectile dysfunction generally demonstrated less pronounced therapeutic benefit (2,18,28). These findings suggest that LI-ESWT may be more effective in earlier stages of vascular impairment, whereas advanced structural or neurogenic damage may limit regenerative potential (1,3). However, many included studies enrolled heterogeneous patient populations without adequate stratification according to ED severity or etiology, further limiting interpretation of results (23,24,29).

Another important limitation of the current evidence is the relatively short duration of follow-up in most available studies (2,29,30). Although short-term improvement within 3-6 months after therapy was commonly reported, several studies demonstrated gradual decline in therapeutic effect after 12 months of follow-up (5,14,18). This raises important questions regarding the long-term durability of LI-ESWT and whether repeated treatment cycles or maintenance protocols may be required. At present, there is insufficient evidence to determine the optimal retreatment interval or long-term sustainability of therapeutic benefit (2,23,29).

The role of combination therapy remains another emerging but still insufficiently clarified area. Several studies suggested that LI-ESWT combined with phosphodiesterase type 5 inhibitors, L-arginine supplementation, or platelet-rich plasma (PRP) may provide superior outcomes compared with monotherapy (8,10–13). However, because these studies frequently lacked adequate sham control or included relatively small sample sizes, the true additive value of combination therapy remains uncertain. Furthermore, the use of concomitant therapies complicates isolation of the independent therapeutic contribution of LI-ESWT itself (13,23,24).

Despite these limitations, LI-ESWT demonstrated a highly favorable safety profile across nearly all included studies. No serious adverse events were reported, while observed side effects were generally mild and transient, including local discomfort, erythema, or temporary penile sensitivity during treatment (1,7,20,30). This favorable safety profile represents one of the main advantages of LI-ESWT compared with more invasive therapeutic options (2,5,6,14,18,19).

Several methodological limitations of this systematic review should also be acknowledged. First, substantial clinical and methodological heterogeneity among included studies prevented quantitative meta-analysis. Second, several included studies involved relatively small sample sizes and moderate risk of bias due to lack of blinding or sham control. Third, publication bias cannot be excluded, since studies reporting positive therapeutic outcomes may be more likely to be published than studies demonstrating neutral findings. Finally, the absence of standardized LI-ESWT protocols currently limits reproducibility and broader clinical applicability of available evidence (2,16,23,24,29).

Future research should focus on large multicenter randomized sham-controlled trials with standardized treatment protocols and longer follow-up duration. Particular emphasis should be placed on defining optimal energy settings, treatment schedules, patient selection criteria, and long-term maintenance strategies. Additional comparative studies evaluating focused versus radial devices and monotherapy versus combination therapy are also required to clarify the most effective therapeutic approach (16,23,24,29).

Overall, current evidence suggests that LI-ESWT may represent a promising minimally invasive therapeutic option for carefully selected patients with vasculogenic erectile dysfunction, particularly those with mild to moderate disease and inadequate response to PDE5 inhibitors. However, due to persistent heterogeneity, inconsistent sham-controlled evidence, and limited long-term data, routine clinical implementation should still be approached with caution pending further high-quality evidence (2,9,23,29).

CONCLUSION

Available clinical evidence suggests that LI-ESWT may represent a safe and potentially effective therapeutic option for patients with mild to moderate vasculogenic erectile dysfunction. The most pronounced therapeutic effects were observed in patients with preserved vascular function and during short-term follow-up. However, heterogeneity of treatment protocols and the limited number of high-quality randomized sham-controlled studies highlight the need for further standardized research before wider routine clinical application of LI-ESWT can be recommended.

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Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

Feasibility of Single-Session Surgery for Combined Duodenal Atresia and Anorectal Malformation in a Neonate: A Case Report

Izvodljivost hirurškog liječenja u jednom operativnom aktu kod kombinovane duodenalne atrezije i anorektalne malformacije kod neonatusa: prikaz slučaja

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ABSTRACT

The coexistence of duodenal atresia and anorectal malformation as an isolated association is exceedingly rare. We report a case of a preterm male neonate with a clinically suspected anorectal malformation, which was confirmed postnatally. Abdominal radiography demonstrated findings consistent with duodenal atresia. An emergency surgical procedure was performed during a single operative session, consisting of sigmoid colostomy and excision of the duodenal membrane with duodenoplasty. Such combinations of congenital anomalies present significant diagnostic and therapeutic challenges, requiring a multidisciplinary approach and careful surgical planning. This case highlights the feasibility of a single-session surgical approach in selected patients.

Keywords: duodenal atresia, anorectal malformation, preterm neonate, intestinal obstruction, case report

SAŽETAK

Udruženost duodenalne atrezije i anorektalne malformacije kao izolirane kombinacije izuzetno je rijetka. Prikazujemo slučaj prijevremeno rođenog muškog novorođenčeta s klinički suspektnom anorektalnom malformacijom, koja je potvrđena postnatalno. Radiografski pregled abdomena pokazao je nalaz u skladu s duodenalnom atrezijom. Hitni hirurški zahvat izveden je u okviru jednofazne hirurgije, a sastojao se od sigmoidne kolostomije i ekscizije duodenalne membrane s duodenoplastikom. Ovakve kombinacije kongenitalnih anomalija predstavljaju značajan dijagnostički i terapijski izazov, zahtijevajući multidisciplinarni pristup i pažljivo hirurško planiranje. Ovaj slučaj ističe izvodljivost hirurškog pristupa u jednoj sesiji kod odabranih pacijenata.

Ključne riječi: duodenalna atrezija, anorektalna malformacija, prijevremeno rođeno dijete, crijevna opstrukcija, prikaz slučaja

INTRODUCTION

Duodenal atresia is a congenital intestinal obstruction that can cause bilious or non-bilious vomiting within the first 24-38 hours of neonatal life, typically following initial feeding. It may be associated with polyhydramnios in utero and is one of the most common causes of fetal bowel obstruction. Duodenal atresia is commonly associated with trisomy 21 and congenital heart defects, and less frequently with other gastrointestinal malformations or the VACTERL association (1,2).

Anorectal malformations (ARM) are a spectrum of congenital anomalies characterized by abnormal development of the distal rectum and anal opening, frequently occurring in association with anomalies of the genitourinary, cardiovascular, gastrointestinal, skeletal, and spinal systems (3-5).

The coexistence of duodenal atresia ARM is extremely rare as an isolated combination, with duodenal atresia reported in approximately 0.9% of patients with ARM (6). To the best of our knowledge, this is a rare presentation of isolated duodenal atresia associated with ARM. This case report has been reported in line with the SCARE Criteria (7).

CASE REPORT

A 1-day-old preterm male neonate, the first child of a regularly monitored pregnancy complicated by early first-trimester vanishing twin syndrome (twin I), was delivered by emergency cesarean section at 36 + 5 weeks of gestation. His birth weight was 2250 g and his length was 48 cm. Prenatal imaging raised suspicion of ARM.

Postnatal examination revealed a flattened anal pit and mild abdominal distension, predominantly in the upper abdomen. An invertogram confirmed a high ARM (Figure 1A). Plain abdominal radiography demonstrated the characteristic "double bubble" sign, suggestive of duodenal atresia. This finding was further supported by a contrast study, which showed minimal passage of contrast into the distal duodenum (Figure 1B).

Postnatal ultrasonographic evaluation of the heart and central nervous system revealed no associated structural abnormalities.

Based on these findings, emergency surgical intervention was indicated. Under general endotracheal anesthesia and standard sterile preparation, the patient was placed in the supine position. A left parainguinal laparotomy was performed, and the sigmoid colon was divided, with the proximal segment matured as a sigmoid colostomy and the distal segment as a mucous fistula.

Subsequently, a right supraumbilical transverse laparotomy was carried out. Intraoperatively, the cecum was noted to be in a non-rotated position. The proximal duodenum was markedly dilated, with a transition to a narrowed distal segment. Following irrigation with normal saline, only minimal passage into the distal duodenum was observed. The atretic segment was identified within the intraperitoneal portion of the duodenum.

A longitudinal duodenotomy was performed across the transition zone. An intraluminal membrane (Figure 1C) causing near-complete obstruction

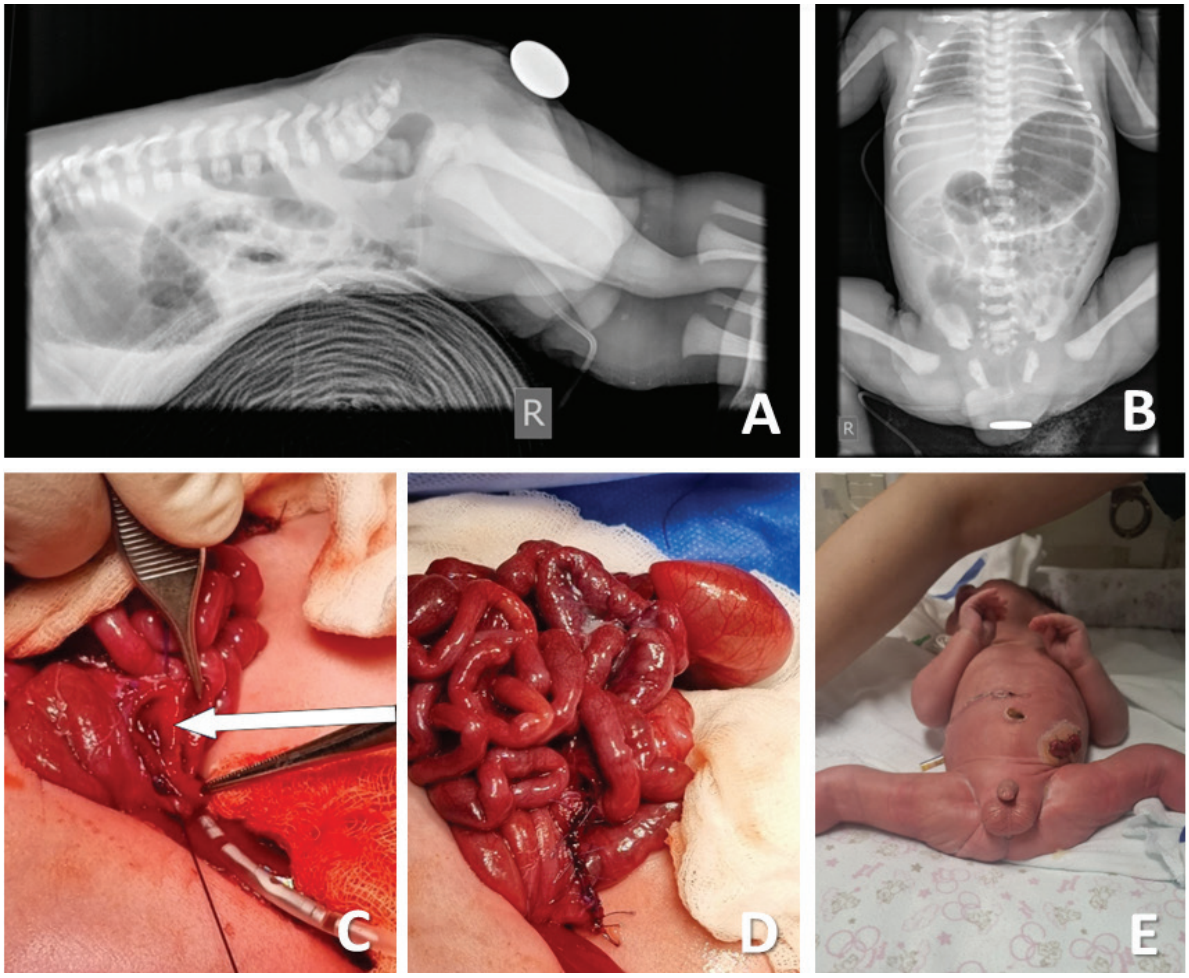

Figure 1 **Composite image.**

A) Invertogram showing findings consistent with a high anorectal malformation; (B) Abdominal radiograph showing a double bubble sign; C) Intraoperative view of duodenal atresia with a membranous obstruction; (D) Duodenoplasty; (E) Postoperative view of the neonate with a visible sigmoid colostomy.

DISCUSSION

We present a preterm neonate with a rare isolated combination of duodenal atresia and ARM. Duodenal atresia is a rare congenital intestinal obstruction occurring in approximately 1 in 5,000-10,000 live births (1) and is frequently associated with other congenital anomalies, particularly trisomy 21 and congenital heart defects, which are reported in up to 30-40% of cases (1,2).

ARM occur in approximately 1 in 4,000-5,000 live births (4), and more than half of affected infants present with at least one associated anomaly, most commonly involving the genitourinary, cardiovascular, and spinal systems (4,5).

Although both anomalies are individually associated with multisystem congenital abnormalities, their simultaneous occurrence is rare and only sporadically described in the literature (6,8). The coexistence of multiple congenital anomalies can pose significant diagnostic and therapeutic challenges, often requiring a multidisciplinary approach and careful surgical planning (6).

In contrast to previously reported cases, our patient presented with an isolated combination of these two anomalies without evidence of additional systemic malformations or syndromes, making this presentation particularly uncommon (6,8).

A similar case has been reported by Dardanelli et al., in which duodenal atresia, ARM, and intestinal malrotation were managed in a single operative session with definitive repair of all anomalies, including posterior sagittal anorectoplasty (PSARP) and duodenal reconstruction (6). Intestinal malrotation was addressed by division of Ladd bands (6), whereas no corrective procedure for malrotation was performed in our patient.

Takeuchi et al. reported a case of oesophageal, duodenal, and anorectal atresia managed through a multi-stage surgical approach. Gastrostomy was performed on day 0, followed by oesophageal and duodenal repair and colostomy on day 6, and delayed PSARP in later infancy (9).

In our case, a single operative session was used for initial management of both anomalies, while definitive anorectal reconstruction is planned in a staged manner.

The presence of ARM associated with signs of intestinal obstruction should prompt consideration of additional gastrointestinal anomalies (10, 11). As reported in previous studies, some associated atresias may only be identified intraoperatively, highlighting the importance of careful surgical exploration and a high index of suspicion in these complex cases. A thorough intraoperative evaluation is recommended in patients with ARM, particularly when radiological findings suggest a proximal obstruction (12).

These reports highlight the rarity of such anomalies and the variability in surgical management strategies for complex congenital conditions. This case emphasizes the importance of individualized surgical planning in neonates with multiple congenital anomalies and demonstrates that selected complex cases may be safely managed with an initial single operative session, while definitive reconstruction can be staged depending on clinical condition.

CONCLUSION

Although both duodenal atresia and ARM are well-recognized congenital anomalies, their isolated coexistence is uncommon. When deciding on the approach to surgical treatment, there is a dilemma about simultaneous surgery on both malformations, which was given priority in our case and resulted in a positive outcome. In similar cases, the possibility of treatment in stages can be considered, which is described in some case reports.

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Authors' contributions: AJ, AT, AZ, AK, SH, AM and ZZ gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial support and sponsorship: nil.

Conflict of interest: there are no conflicts of interest.

Retroperitoneal Squamous Cell Carcinoma of the Right Iliac Region - Case Report

Retroperitonealni skvamocelularni karcinom desne ilijačne regije - Prikaz slučaja

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ABSTRACT

A 44-year-old female patient was hospitalized for a planned myomectomy due to an ultrasonographically diagnosed intramural fibroid and a right-sided intraligamentary fibroid. During surgery, palpation of the retroperitoneal space in the right iliac region, at the site corresponding to the previously described intraligamentary fibroid, revealed a tumor mass measuring approximately 6 cm in diameter, with irregular margins and in close proximity to the major iliac blood vessels and the ureter. Histopathological analysis of the tumor tissue confirmed a squamous cell carcinoma. Immunohistochemical analysis demonstrated diffuse p16 positivity. Further management of the patient is being conducted under oncological supervision, with the treatment outcome currently unknown. Retroperitoneal localization of squamous cell carcinoma is rare, with poorly understood pathophysiology and clinical presentation. This case report highlights the potential association with human papillomavirus (HPV) infection and, through a review of the available literature, aims to suggest possible therapeutic approaches.

Keywords: retroperitoneal squamous cell carcinoma, HPV infection, p16 biomarker, Iliac region

SAŽETAK

Pacijentica stara 44 godine je hospitalizirana radi planirane miomektomije, ultrazvučno opisanog intramuralnog mioma i intraligamentarnog mioma desno. Tokom operacije, palpacijom retroperitonealnog područja desne ilijačne regije, na mjestu ultrazvučno opisanog intraligamentarnog mioma, palpira se tumorska masa promjera 6 cm, neravnih zidova, u intimnom kontaktu sa velikim krvnim sudovima ilijačne regije i sa ureterom. Patohistološka analiza tumorskog tkiva potvrđuje skvamocelularni tumor. Imunohistohemijska analiza uzorka pokaže pozitivan blok p16. Daljni tok liječenja bolesti pacijentice odvija se pod nadzorom onkologa, za sada nepoznatog ishoda liječenja. Retroperitonealna lokalizacija skvamocelularnog karcinoma je rijetka i nedovoljno razjašnjene patofiziologije i kliničke manifestacije bolesti. Ovim prikazom slučaja dovodimo infekciju HPV-om sa mogućim razvojem bolesti i pregledom dostupne literature uputiti na potencijalni terapijski pristup.

Ključne riječi: retroperitonealni skvamocelularni karcinom, HPV infekcija, p16 biomarker, ilijačna regija.

INTRODUCTION

Squamous cell carcinoma (SCC) with primary localization in the retroperitoneal space is extremely rare, accounting for only 0.1-0.2% of all malignant tumors (1). Only a few cases of SCC arising in the retroperitoneum with an unknown primary site have been described in the literature. These cases are most commonly associated with a history of prior hysterectomy of unclear indication and human papillomavirus (HPV) infection, although in the majority of cases the primary tumor site remains unidentified. Retroperitoneal SCC, as a distinct clinical entity, lacks clearly defined diagnostic and therapeutic guidelines. Surgical resection is most commonly employed, typically followed by adjuvant chemotherapy and radiotherapy (2). Available studies indicate the effectiveness of locoregional treatment combined with chemotherapy, with reported five-year survival rates ranging from 27% to 74% (9). The limited understanding of the tumor's pathophysiology and clinical presentation restricts the development of standardized diagnostic and therapeutic protocols. In this report, we present a case of retroperitoneal SCC associated with HPV infection in a patient with a normal Papanicolaou (Pap) smear result.

CASE REPORT

A 44-year-old female patient was admitted for an elective surgical procedure, myomectomy. The admission diagnosis was Myoma uteri per magnum (intramurale et intraligamentarum). The patient reported long-term ultrasonographic follow-up of uterine fibroids and a history of two unsuccessful in vitro fertilization (IVF) attempts. She described her menstrual cycles as heavy, lasting 5-7 days.

Ultrasonographic examination at admission revealed a uterus measuring 103 × 88 × 64 mm, with an intramural, partially subserosal fibroid located on the posterior uterine wall, measuring 70 × 51 mm, deforming the uterine cavity. Lateral to the right ovary, a suspected intraligamentary fibroid measuring 71 × 44 mm was identified. The Papanicolaou (Pap) smear result was normal.

The patient's surgical history included cervical conization performed in 2014 for cervical intraepithelial neoplasia grade III (CIN III), followed by reconization in the same year, as well as a prior myomectomy in 2021.

Histopathological findings (2014 conization specimen): Microinvasive squamous cell carcinoma (Carcinoma squamocellulare microinvasivum, focus approximately 3 × 5 mm) of the vaginal portion of the cervix (portio vaginalis cervicis uteri). AJCC TNM classification: pT1a1 Nx Mx; FIGO stage IA1.

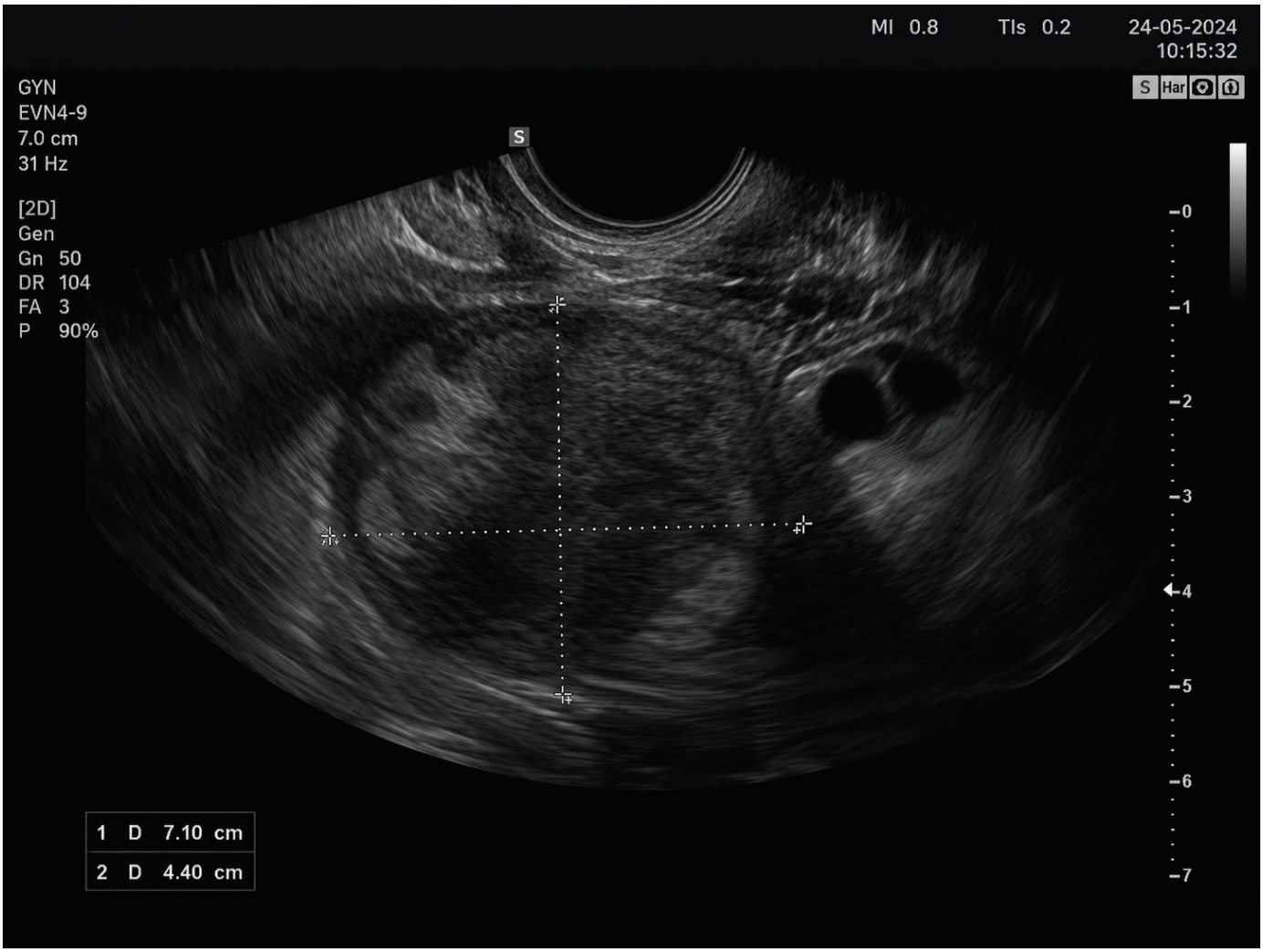

Figure 1 **Ultrasound examination: Right ovary with suspected intraligamentary fibroid measuring 71 × 44 mm.**

Resection margins: Severe dysplastic changes were identified at a distance of less than 1 mm from the endocervical and basal resection margins (quadrants III and IV).

Histological findings included mild dysplasia (CIN I – quadrants I–IV), moderate dysplasia (CIN II - quadrant IV), and severe dysplasia with carcinoma in situ (CIN III/CIS - quadrants III and IV) of the squamous epithelium of the vaginal portion of the cervix. Additionally, squamous metaplasia with severe dysplasia and carcinoma in situ (CIN III/CIS) was present in the cervical glandular epithelium (quadrants III and IV). Chronic cervicitis was also noted.

Histopathological findings (2014 reconization specimen): Microscopic examination of the submitted tissue sections, corresponding to the vaginal portion of the cervix following prior conization, showed no identifiable transformation zone (the junction between the squamous epithelium of the ectocervix and the columnar epithelium of the endocervix), nor endocervical glands containing the previously described microinvasive carcinoma with glandular involvement.

An elective surgical procedure consisting of hysterectomy with bilateral adnexectomy was subsequently performed. The uterus was enlarged to approximately 10 cm and exhibited multiple adhesions to adjacent structures. The adnexa were positioned horizontally and fixed to the pelvic wall.

During surgery, a retroperitoneal mass was palpated in the right iliac region, characterized by irregular margins, firm adherence to the major iliac blood vessels and the ureter, and indistinct borders. With the assistance of a vascular surgeon, the apical portion of the tumor firm and avascular was resected and submitted for histopathological evaluation.

Histopathological findings of the uterus and adnexa: Uterine leiomyoma and adenomyosis.

Histopathological analysis of the resected retroperitoneal tumor from the right iliac region revealed HPV-associated squamous cell carcinoma. Immunohistochemical analysis demonstrated diffuse (block-type) positivity for p16, positivity for cytokeratin (AE1/AE3), heterogeneous positivity for p63, focal positivity for CK5/6, and negativity for synaptophysin, chromogranin, and p40.

The progression biomarker p16 is a sensitive marker for HPV infection, as HPV-infected cells produce high levels of this protein. HPV-associated tumors frequently exhibit p16 overexpression; therefore, immunohistochemical staining for p16 is routinely performed by pathologists to support the diagnosis.

DISCUSSION

Retroperitoneally localized squamous cell carcinoma (SCC) represents a rare tumor entity. Its pathophysiology remains poorly understood, which explains the absence of standardized protocols for diagnosis, staging, treatment, and overall management. A review of the literature reveals only a limited number of relevant publications. The reported incidence of retroperitoneal SCC accounts for approximately 0.1-0.2% of all malignant tumors (1). In a study by Jin H, et al., describing a 56-year-old patient with a 5 cm pelvic mass identified by ultrasound in the left pelvic region, intraoperative findings confirmed a retroperitoneal tumor, which was histopathologically verified as squamous cell carcinoma positive for HPV-18 (3).

A study by Pandey A, et al. (2), reviewing available literature on retroperitoneal SCC, identified fourteen cases across seven relevant articles. These cases described intra-abdominal masses developing similarly to sarcomas, with HPV infection most frequently suggested as a potential etiological factor underlying the squamous histological phenotype. The role of HPV in carcinogenesis and its therapeutic implications are more clearly established in the head and neck region than in the pelvis. Consequently, in cases of retroperitoneal tumors associated with HPV infection, the effectiveness of targeted radiotherapy remains uncertain (4). However, metastatic pelvic squamous cell carcinoma of unknown primary origin with diffuse p16 positivity has demonstrated favorable responses to palliative radiotherapy and immunotherapy (5).

In patients presenting with retroperitoneal tumors of unknown primary origin and normal gynecological examination and Papanicolaou (Pap) smear findings, p16 positivity has been reported in up to 100% of cases. Treatment with palliative chemotherapy and radiotherapy has shown variable outcomes, ranging from complete remission to disease progression and death (6).

Across seven reported case series, the average diameter of retroperitoneal tumor masses was approximately 6.2 cm. Six out of seven patients presented with pelvic pain as the primary symptom. Diagnostic approaches included image-guided needle biopsy (ultrasound or CT) in three cases, while four patients underwent exploratory laparotomy for diagnostic and cytoreductive purposes (1).

The prognosis of retroperitoneal SCC of unknown primary origin remains insufficiently defined, although available data suggest generally poor outcomes. The rarity of this histological subtype limits the establishment of clear clinical guidelines. Tumors of unknown primary origin are typically managed with aggressive multimodal treatment strategies.

A retrospective study of patients with SCC of unknown primary origin categorized cases into isolated (single-site) and multiple-site disease. Among 227 patients, 36 had retroperitoneal SCC, of whom 22 presented with isolated disease and 14 with multiple-site involvement. Isolated disease was further classified into favorable and unfavorable subgroups. Favorable cases included those with metastases confined to inguinal lymph nodes or the head and neck region, demonstrating better prognosis and response to localized treatment (7).

In contrast, no standardized therapeutic approach exists for unfavorable isolated SCC. Complete surgical resection of retroperitoneal tumor masses is associated with improved prognosis; however, it is often limited by the tumor's close proximity to major blood vessels and neural structures. Adhesions to these structures may result in neurological deficits and necessitate vascular reconstruction (8).

In our case report, we suggest a potential association between HPV infection and the development of retroperitoneal SCC of unknown primary origin. The intraoperative finding of a tumor mass measuring up to 6 cm is consistent with previously reported data, which indicate an average tumor size of approximately 6.2 cm (1). The therapeutic course in our case has not yet been completed; however, diffuse p16 positivity strongly supports a link between HPV infection and the development of retroperitoneal SCC in the right iliac region.

CONCLUSION

Retroperitoneal squamous cell carcinoma of unknown primary origin may be associated with HPV infection. The etiology and clinical manifestations of this disease remain unclear due to the limited number of reported cases, which also contributes to the absence of standardized treatment protocols. Available studies suggest that combined treatment approaches including chemotherapy, radiotherapy, and surgical resection or cytoreduction may yield favorable outcomes; however, evidence remains limited due to small sample sizes.

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Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

Atypical Granular Cell Tumor of the Breast Mimicking Malignancy: A Case Report

Atipični Granular cell tumor dojke koji imitira malignitet: prikaz slučaja

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ABSTRACT

Granular cell tumors (GCTs) are rare neoplasms of Schwann cell origin that can occur throughout the body, with breast involvement representing approximately 15% of cases. Although typically benign, GCTs of the breast (GCTB) often mimic invasive carcinoma clinically and radiologically, leading to potential misdiagnosis and overtreatment. We report a case of a 31-year-old female presenting with a left breast lesion classified as BI-RADS 4c/5. Core needle biopsy revealed a granular cell tumor with immunohistochemical positivity for S100 and CD68, while epithelial markers were negative. Surgical excision confirmed an atypical GCT, with infiltrative growth and one Fanburg-Smith criterion for malignancy. This case highlights the diagnostic challenge of GCTB and underscores the importance of combining radiology, histopathology, and immunohistochemistry to guide appropriate management.

Keywords: granular cell tumor, breast neoplasms, Schwann cell neoplasm, surgical excision

SAŽETAK

Granularni ćelijski tumori (GCT) su rijetke neoplazme porijeklom iz Švanovih ćelija (engl. Schwann cells) koji se mogu pojaviti u različitim dijelovima tijela, pri čemu se u dojci javljaju u približno 15% slučajeva. Iako su uglavnom benigni, GCT dojke (GCTB) često klinički i radiološki oponašaju invazivni karcinom, što može dovesti do pogrešne dijagnoze i nepotrebnog liječenja. U ovom radu opisujemo slučaj 31-godišnje pacijentice sa promjenom u lijevoj dojci, radiološki klasificiranom kao BI-RADS 4c/5. Sržna biopsija iglom otkrila je granularni ćelijski tumor s imunohistohemijskom pozitivnošću za S100 i CD68, dok su epitelni markeri bili negativni. Hirurškom ekscizijom te naknadnom PH dijagnostikom potvrđen je atipični GCT s infiltrativnim rastom i jednim Fanburg-Smith kriterijem maligniteta. Potpuno uklanjanje postignuto je dodatnom radikalizacijom. Ovaj slučaj ističe dijagnostički izazov GCTB i naglašava važnost kombinovanja radiologije, histopatologije i imunohistohemije za pravilno vođenje liječenja.

Ključne riječi: granularnocelularni tumor, neoplazme dojke, Schwannova ćelijska neoplazma, hirurška ekscizija

INTRODUCTION

Granular cell tumors (GCTs) were first described by Abrikossoff in 1926(1). Their source was determined to be derived from perineural Schwann cells between the lobular breast tissue (2). These tumors can occur in any part of the body, but are commonly observed in the skin, oral cavity, digestive tract, and subcutaneous tissue.

The overall incidence of GCTs in surgical specimens is approximately 0.03%, with breast involvement reported in about 15% of cases (3,4).

Approximately 1–2% of these lesions are malignant, which is associated with a poor prognosis and limited curative options, with surgery remaining the mainstay of treatment (5). GCT of the breast (GCTB) can mimic breast carcinoma both clinically and radiologically, making it difficult to distinguish from breast malignancies. In order to improve the understanding of GCTB and prevent misdiagnosis and overtreatment, we report a patient with GCTB, who was admitted to our hospital.

Though usually benign, these tumours mimic scirrhous breast carcinoma not only clinically and radiologically but also on frozen section. This can lead to misdiagnosis and further unnecessary radical treatment. Hence, the diagnosis of this tumour can be made by a combination of core biopsy and immunohistochemistry, as we demonstrate in this case report.

CASE REPORT

A 31-year-old woman presented with a newly identified tumor mass in the left breast, which prompted further diagnostic workup including clinical examination and imaging. Ultrasound examination revealed an anechoic area measuring 12 × 13 mm in the lower medial quadrant of the left breast, with partially irregular margins and without pathologically enlarged axillary lymph nodes.

Due to the suspicious characteristics of the lesion, an additional radiological assessment with magnetic resonance imaging was performed, classifying the lesion as BI-RADS 4c/5, indicating a high suspicion of malignancy.

A core needle biopsy of the lesion in the left breast was requested. The core biopsy of the left breast lesion showed cylinders of fibroadipose tissue containing a tumor composed of nests and cords of cells with abundant eosinophilic granular cytoplasm. The nuclei were uniform, without marked pleomorphism, and mitotic activity was not prominent. No necrosis was observed.

Immunohistochemically, the tumor cells showed diffuse positivity for S100 protein and CD68 (Figure 1), while CK, EMA, and desmin were negative. The findings suggested a granular cell tumor and were classified as a B3a lesion.

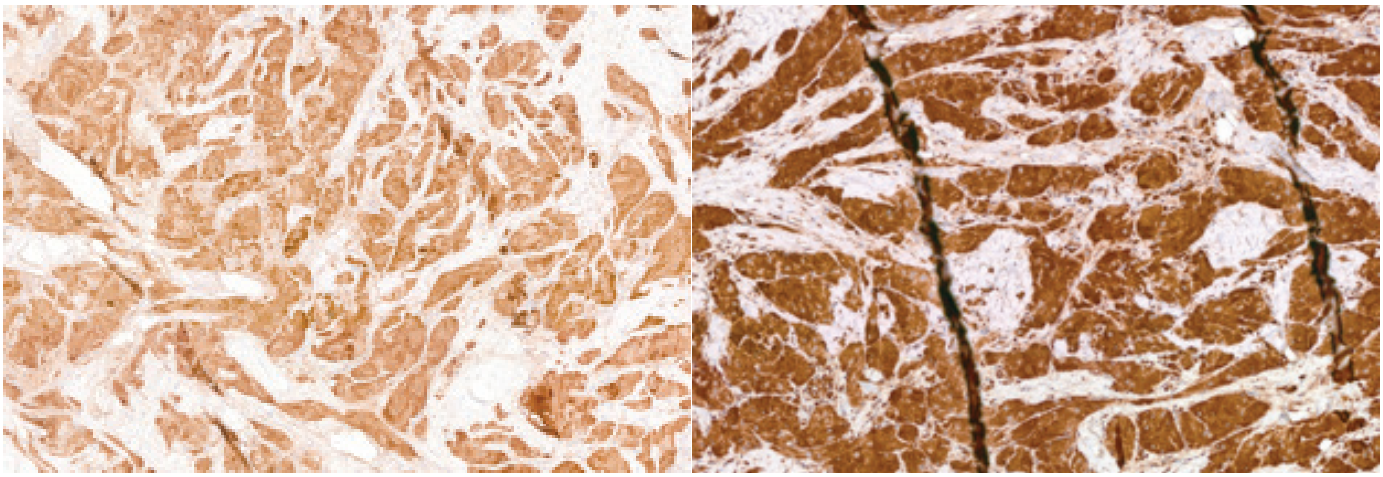

Figure 1 **Immunohistochemical findings of the breast lesion.**
(A) Tumor cells show diffuse strong nuclear and cytoplasmic positivity for S100 protein.
(B) Tumor cells show diffuse cytoplasmic positivity for CD68.

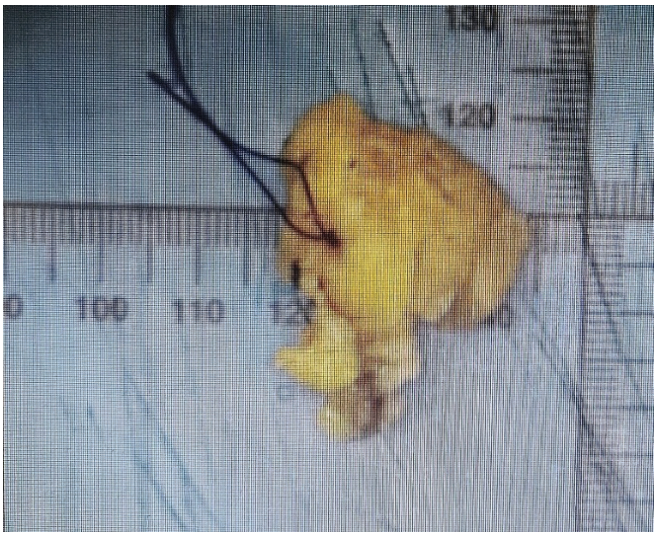

Figure 2 **Macroscopic view of the tumor mass.**

Given the significant discrepancy between the radiological findings, which were highly suspicious for malignancy, and the histopathological findings, which indicated a benign nature of the tumor, surgical excision of the lesion was indicated for definitive diagnosis.

Surgical excision yielded a breast specimen measuring 40 × 35 × 32 mm, containing a solid, whitish tumor measuring 33 × 23 × 20 mm, which was completely excised with negative margins (Figure 2).

Microscopic analysis showed that the tumor lesion was composed of polygonal to round cells arranged in nests, trabeculae, and solid sheets, infiltrating the surrounding fibrous and adipose tissue of the breast. Tumor cells had abundant eosinophilic granular cytoplasm, with cytoplasmic granules corresponding to lysosomes The nuclei were centrally located, round to oval, with vesicular chromatin and occasionally prominent nucleoli. Nuclear pleomorphism was mild, mitotic figures were absent, and necrosis was not present. The stroma showed a mild fibrous reaction, and the tumor exhibited infiltrative growth between lobules and ducts of the breast (Figure 3).

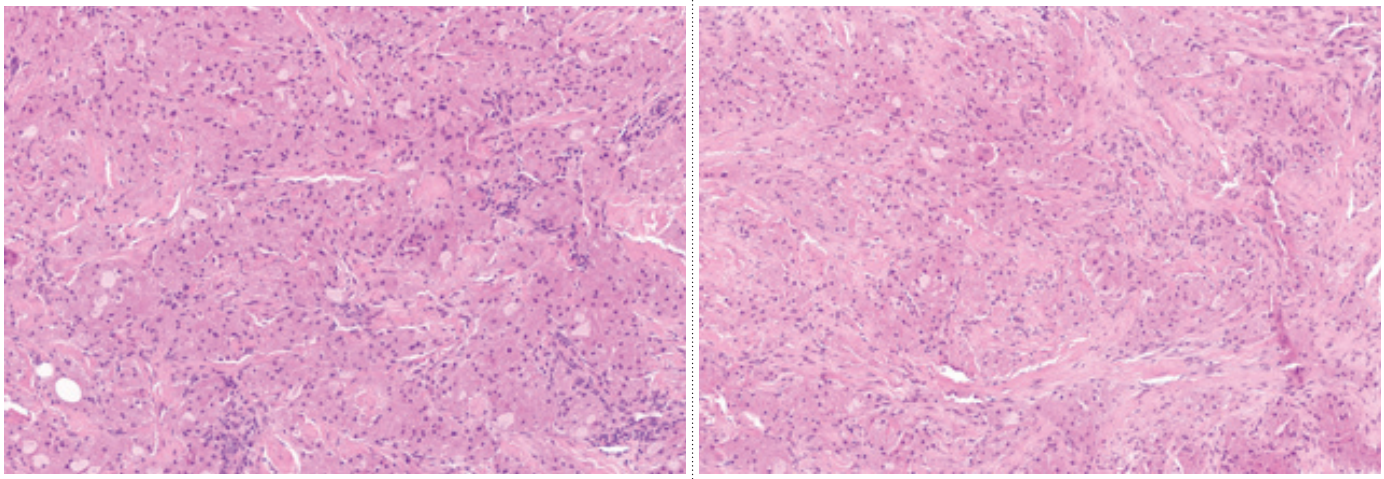

Figure 3 **(A & B). Microscopic analysis of the breast tumor.**

The immunohistochemical profile was consistent with the biopsy findings, showing diffuse positivity for S100 and CD68 and negativity for epithelial markers.

Assessment of malignant potential was performed according to the Fanburg-Smith criteria (6). In this case, only one criterion was present, namely vesicular nuclei with prominent nucleoli, while other criteria, including necrosis, increased mitotic activity, marked pleomorphism, spindle cell formation, and high nuclear-to-cytoplasmic ratio were absent. Based on this, the tumor was classified as an atypical granular cell tumor.

In the specimen, following additional radicalization, a complete resection was achieved with no residual tumor present R0.

DISCCUSION

Granular cell tumor (GCT) of the breast is a rare neoplasm, accounting for less than 1% of all breast tumors, and originates from Schwann cells of peripheral nerves, as confirmed by its characteristic immunohistochemical positivity for S100 protein (7,8). Although the majority of cases are benign, their clinical and radiological appearance often mimics breast carcinoma, which can lead to diagnostic dilemmas and a more aggressive therapeutic approach (9).

In the presented case, the pronounced discrepancy between the radiological finding, which was highly suspicious for malignancy (BI-RADS 4c/5), and the histopathological result of the core needle biopsy, which indicated a granular cell tumor, represents a typical diagnostic challenge described in the literature. GCT of the breast often demonstrates irregular contours, infiltrative growth, and absence of a capsule on imaging, making it difficult to distinguish from invasive carcinoma (2,10) For this reason, core biopsy may be insufficient for a definitive diagnosis, especially in cases where there is discordance between clinical, radiological, and histopathological findings.

Classification of the lesion as B3a further emphasizes this diagnostic uncertainty. B3 lesions represent a heterogeneous group of changes of uncertain malignant potential, where there is a risk that the initial biopsy may not be fully representative of the entire lesion. Although B3a implies the absence of cytological atypia, additional diagnostic evaluation or excision is recommended, particularly in the presence of suspicious radiological features (11). In this case, the decision to perform surgical excision was justified and in accordance with literature recommendations.

The definitive diagnosis was established after tumor excision and detailed histological analysis. The tumor displayed typical morphological features of a granular cell tumor, including abundant eosinophilic granular cytoplasm and infiltrative growth into surrounding tissue. The immunohistochemical profile, with positivity for S100 and CD68 and negativity for epithelial markers, further confirmed the diagnosis (12,13).

Assessment of malignant potential was performed according to the Fanburg-Smith criteria, which are most commonly used to differentiate benign, atypical, and malignant forms of GCT (6). In this case, only one criterion of malignancy was present, corresponding to the category of atypical granular cell tumor. Atypical GCT occupies an intermediate position between benign and malignant forms and, although it generally behaves in a benign manner, requires careful follow-up due to the risk of local recurrence (14).

Surgical excision with negative resection margins (R0) represents the treatment of choice for granular cell tumor of the breast (9,15). Lymphadenectomy is not routinely recommended due to the rare occurrence of metastases, except in cases of histologically confirmed malignant GCT (7).

This case further underscores the importance of a multidisciplinary approach in the diagnosis of breast lesions, particularly when there is discordance between different diagnostic modalities. Timely decision for surgical excision allowed for definitive diagnosis and appropriate management of the patient.

CONCLUSION

Granular cell tumors of the breast are rare and may closely resemble malignant breast lesions on imaging, potentially leading to unnecessary aggressive interventions. Core biopsy combined with immunohistochemistry is essential for accurate diagnosis, particularly in cases with discordant clinical and radiological findings. Surgical excision with negative margins remains the definitive treatment, and careful follow-up is recommended for atypical lesions due to the risk of local recurrence. Multidisciplinary evaluation is crucial to ensure appropriate diagnosis and management.

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Declaration of patient consent: the authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his/her consent for his/her images and other clinical information to be reported in the journal.

Authors' Contributions: EB, SH, SP, VD, MS, EB-F, TK and AC gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author had role in article drafting and in process of revision. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial support and sponsorship: nil.

Conflict of interest: there are no conflicts of interest.

Molar-Incisor Hypomineralization (MIH): The Importance of Early Diagnosis - A Case Report

Molarno incizivna hipomineralizacija - MIH, važnost rane dijagnostike - prikaz slučaja

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ABSTRACT

Molar-incisor hypomineralization (MIH) is a developmental enamel defect affecting first permanent molars and frequently permanent incisors. It is characterized by insufficient enamel mineralization, resulting in teeth that are sensitive, fragile, and more prone to caries. These changes may also lead to emotional disturbances in young patients and a loss of self-confidence. We present a case of a 12-year-old boy who attended our clinic due to pain in the upper right first permanent molar (tooth 16). Clinical examination confirmed MIH, with changes observed in molars and incisors, as well as gingival alterations. A radiographic examination of tooth 16 was performed, and extraction was indicated. Further treatment planning and rehabilitation of the remaining teeth were carried out. Therapeutic limitations were observed due to the delayed dental visit. Patients with MIH require an individualized approach immediately after tooth eruption, along with an appropriate treatment and rehabilitation plan. Additionally, it is necessary to inform mothers during pregnancy about potential risk factors, emphasizing the importance of collaboration between gynecologists, pediatricians, and pediatric dentists.

Keywords: MIH, molars, incisors, early detection

SAŽETAK

Molarno-incizivna hipomineralizacija (MIH) je razvojni poremećaj gleđi koji zahvata prve stalne molare i često stalne sjekutiće. Karakteriše je nedovoljna mineralizacija gleđi, zbog čega su zubi osjetljivi, krhki i skloniji karijesu. Promjene mogu dovesti do emocionalnih promjena kod mladog pacijenta I gubitak samopouzdanja. Prikazujemo slučaj dvanaestogodišnjeg dječaka, koji dolazi u ambulantu zbog bola gornjeg prvog desnog molara (16). Kliničkim pregledom dijagnostikujemo MIH, promjene na molarima i incizivima, kao i promjene na gingivi. Uradimo rtg zuba 16 i odlučujemo se za extrakciju zuba 16. Uradimo dalji plan terapije i sanacije ostalih zuba. Uvidimo ograničenost u terapijskom djelovanju zbog kasnije posjete stomatologu. Pacijenti sa MIH-om zahtijevaju individualni pristup odmah po nicanju zuba, adekvatan plan sanacije i terapije zuba. Takođe je potrebno informisati majke u toku trudnoće o mogućim rizicima u trudnoći, što uključuje saradnju ginekologa, pedijatra I pedodonta.

Ključne riječi: MIH, molari, incizivi, rano otkrivanje

INTRODUCTION

Molar-incisor hypomineralization (MIH) is a developmental enamel defect affecting first permanent molars and frequently permanent incisors (1). It is characterized by insufficient enamel mineralization, with less defined cuspal margins and crystals, increased interprismatic spaces, and wider dentinal tubules (2,3). As a result, teeth are sensitive, fragile, and prone to caries.

Due to the porous enamel surface, there is increased susceptibility to biofilm retention (4) and chronic gingivitis (1). The risk of caries progression increases due to dental hypersensitivity, as children may neglect oral hygiene out of fear of pain (3). These dental changes may also lead to emotional disturbances and behavioral difficulties during dental visits (5).

The etiology of MIH is multifactorial, including local, systemic, genetic, or idiopathic factors (6,11). Major contributing factors include low birth weight, maternal illness, and psychological stress during pregnancy (2). Additional factors include perinatal complications, dioxins in breast milk, smoking, alcohol consumption during pregnancy, asthma, pneumonia, respiratory infections, otitis media, tonsillitis, varicella, and early exposure to amoxicillin (2).

Vitamin D deficiency during pregnancy and early childhood has also been identified as a risk factor (2). Recent studies have demonstrated an association between gestational diabetes, acute fetal distress, and MIH (6). Maternal hyperglycemia during pregnancy can compromise fetal health, leading to respiratory deficits. Fetal distress or neonatal hypoxia, often caused by maternal conditions such as hypertension or gestational diabetes, results in reduced oxygen supply through the placenta, affecting ameloblast function and increasing the risk of enamel defects (6).

Etiological factors may act individually or synergistically during pregnancy, delivery, or the first three years of life, corresponding to enamel formation, mineralization, and maturation. For first permanent molars, this process begins around the 20th week of intrauterine life, while for permanent incisors it occurs between 3 and 12 months of age (3). These processes continue for approximately three years until crown formation is complete.

According to the European Academy of Paediatric Dentistry (EAPD) guidelines, MIH is diagnosed based on clearly demarcated opacities on occlusal and buccal surfaces, white or yellow-brown discolorations, defects of at least 1 mm in diameter, hypersensitivity, atypical restorations, and the need for tooth extraction (2).

The global prevalence of MIH ranges from 9.8% to 40.2% and is increasing (4,10). Based on opacity, MIH is classified as white, yellow, or brown, while according to severity it is classified as mild, moderate, or severe (3).

Posteruptive breakdown is more pronounced in boys than in girls, and this difference appears to be increasing. Additionally, maxillary molars are more severely affected than mandibular molars (7).

MIH represents a significant challenge in dentistry due to enamel porosity, structural breakdown, rapid caries progression, hypersensitivity, reduced effectiveness of local anesthesia, poor patient cooperation, restoration failure, aesthetic concerns in anterior teeth, and reduced self-confidence in young patients (8). Early detection and prevention are key to minimizing damage (3).

CASE REPORT

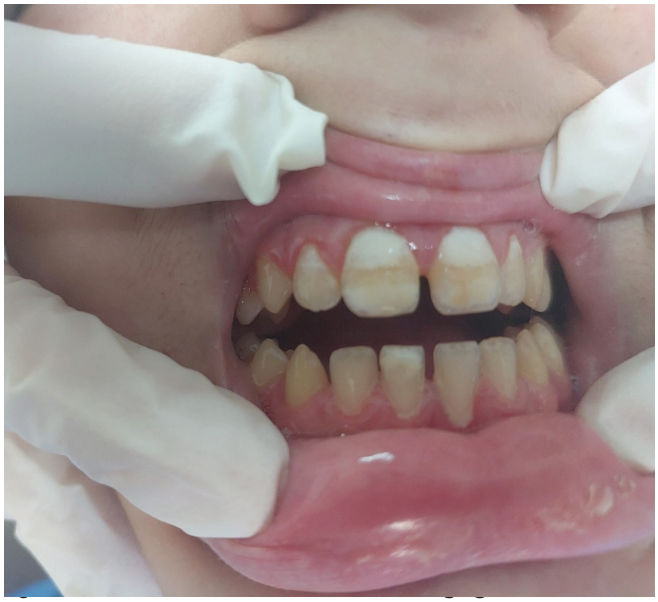
A 12-year-old boy presented to our clinic with pain in the upper right first permanent molar (tooth 16). Medical history revealed significant dental anxiety due to previous interventions, hypersensitivity during tooth brushing and food intake, and reduced self-confidence due to aesthetic issues on the incisors.

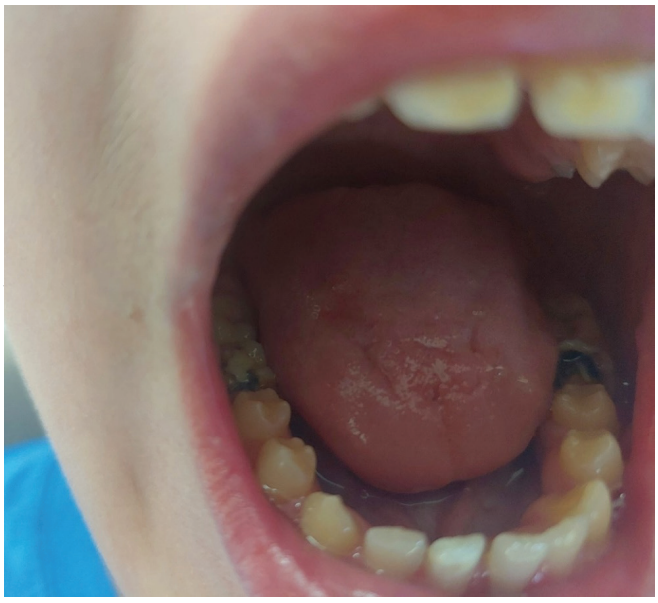
The mother reported frequent respiratory infections and antibiotic use. The child had no systemic diseases or allergies. The mother reported smoking during pregnancy and breastfeeding.

Differential diagnosis included dental fluorosis, amelogenesis imperfecta, and enamel hypoplasia, which were excluded based on the location, appearance, and distribution of affected teeth.

Clinical examination revealed changes in first permanent molars and incisors, as well as gingival changes consistent with chronic gingivitis caused by dental plaque and poor oral hygiene (Figure 1). Clearly demarcated opacities were observed—white on incisors and yellow-brown to brown on molars (Figure 2), along with hypersensitivity and an indication for extraction.

A diagnosis of severe MIH was established. Tooth 16 exhibited complete crown destruction and was painful on palpation and percussion. Radiographic examination (Figure 3) revealed a large carious lesion, its relationship with the maxillary sinus, and root positioning. Extraction of tooth 16 was performed without complications.





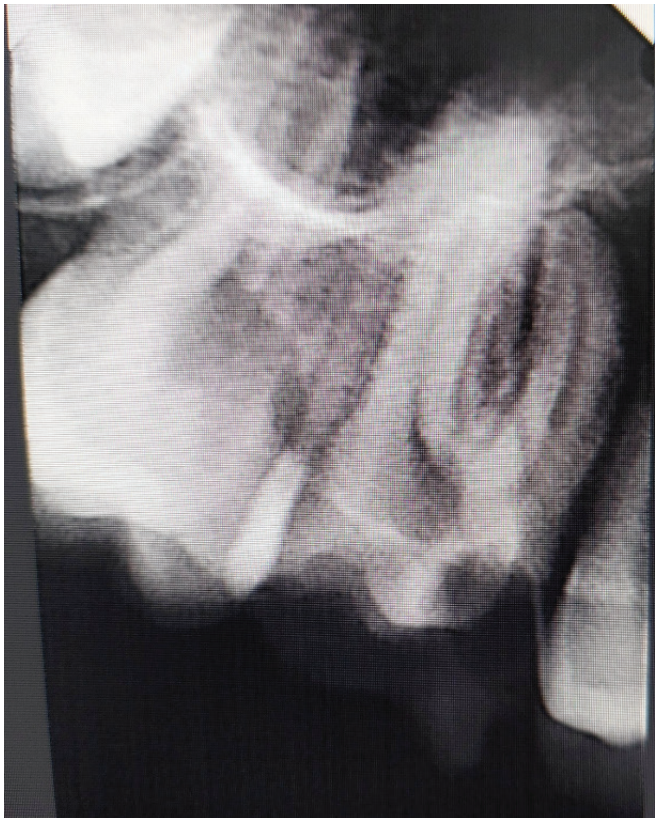


Figure 3 **Radiographic image of the upper right first molar (tooth 16).**

The patient was referred for further preventive care. Oral hygiene instructions included tooth brushing with toothpaste containing at least 1000 ppm fluoride, and nightly use of casein phosphopeptide-amorphous calcium phosphate (CPP-ACP). Proper brushing technique and dental floss use were demonstrated to improve gingival health.

Further treatment included restoration of remaining molars using composite resins or stainless steel crowns, and management of incisor defects through microabrasion or resin infiltration. Treatment requires a multidisciplinary approach involving orthodontists, prosthodontists, and implantologists.

Delayed diagnosis significantly limited therapeutic options.

DISCUSSION

This case highlights the challenges associated with late diagnosis, which restricts therapeutic options. Treatment of pediatric patients is further complicated by fear, poor cooperation, restoration failure, and reduced effectiveness of local anesthesia.

Management of MIH involves multiple approaches, with prevention as the cornerstone. Immediate protection of teeth after eruption is essential, including the use of desensitizing and remineralizing agents. Daily use of fluoride toothpaste (≥1000 ppm) is recommended to enhance remineralization and resistance to demineralization (2). Fluoride provides a reservoir for the formation of fluoroapatite.

Nightly use of CPP-ACP-based products strengthens enamel, reduces sensitivity, and promotes remineralization (9). These products are contraindicated in patients with milk protein allergy, but not in those with lactose intolerance.

Restoration of molars is complex and should begin immediately after eruption. Affected molars are fragile, hypersensitive, and difficult to anesthetize. Glass ionomer cement (GIC) and resin-modified GIC restorations may be used as temporary fillings due to their ease of application, fluoride release, chemical bonding, and hydrophilicity in conditions of poor moisture control. Due to their limited mechanical properties, they should be replaced with resin-based materials once full eruption and adequate moisture control are achieved. Stainless steel crowns are recommended for long-term protection (12).

In the management of incisors, microabrasion is used as a treatment method, involving the removal of a superficial enamel layer, followed by the application of CPP-ACP paste to enhance remineralization, although this approach is limited to shallow defects. Resin infiltration may be effective; however, its use is limited due to uneven material penetration. Composite resins and veneers are used in older patients, where pulp chambers are smaller and gingival contours are more stable (2,13).

CONCLUSION

Patients with MIH require an individualized and preventive approach immediately after tooth eruption. Adequate and individualized treatment planning is essential to alleviate symptoms and improve patient outcomes. Early intervention reduces hypersensitivity, improves oral hygiene, and enhances self-confidence in young patients. Early detection and structured management are key to successful treatment. Timely education of mothers regarding potential risk factors during pregnancy is essential and requires collaboration between gynecologists, pediatricians, and pediatric dentists.

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Declaration of patient consent: the authors certify that they have obtained all appropriate patient's consent forms. The photographs used in this case report were taken with the verbal consent of the children's parents.

Authors' Contributions: HG, ŠP and HG gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author had role in article drafting and in process of revision. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial support and sponsorship: nil.

Conflict of interest: there are no conflicts of interest.

Hematuria in Children and a Case Report

Hematurija kod dece i prikaz slučaja

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ABSTRACT

Introduction: hematuria in children may represent a transient finding, but it can also be an important indicator of kidney or urinary tract disease. Although in most children with isolated hematuria the abnormal urinary finding usually disappears upon repeated testing, persistent microscopic hematuria (MH) is considered a significant risk factor for the development of progressive chronic kidney disease. Aim and Differential Diagnosis: this paper analyzes the wide spectrum of causes of hematuria, including infections, hypercalciuria, urinary tract anomalies, and glomerular diseases such as IgA nephropathy. Variants in genes encoding type IV collagen (COL4A3, COL4A4, and COL4A5) account for up to 30% of genetic diagnoses in patients with MH, highlighting the importance of genetic testing even in the absence of a positive family history. Case report: we present the case of a 4.5-year-old girl with asymptomatic persistent MH. During two and a half years of follow-up, despite treatment with ACE inhibitors, an increase in proteinuria was observed. Instead of performing a kidney biopsy, whole-exome sequencing was carried out, which identified a de novo pathogenic variant in the COL4A5 gene, confirming the diagnosis of X-linked Alport syndrome (XLAS). Conclusion: in children with persistent hematuria of unclear etiology, genetic testing is crucial for establishing an accurate diagnosis, determining prognosis, and providing counseling regarding the risk for future offspring, given the high probability of transmission of XLAS to subsequent generations.

Keywords: hematuria; children; differential diagnosis; Alport syndrome (X-linked, XLAS); genetic testing.

SAŽETAK

Uvod: hematurija kod dece može biti tranzitorni nalaz, ali i važan indikator bolesti bubrega ili urinarnog trakta. Dok kod većine dece sa izolovanom hematurijom patološki nalaz u urinu obično iščezne prilikom ponovljenog testiranja, perzistentna mikroskopska hematurija (MH) smatra se značajnim faktorom rizika za nastanak progresivne hronične bubrežne slabosti. Cilj i diferencijalna dijagnoza: rad analizira širok spektar uzroka hematurije, uključujući infekcije, hiperkalciuriju, anomalije urinarnog trakta i glomerulske bolesti poput IgA nefropatije. Ističe se da varijante u genima za sintezu kolagena tipa IV (COL4A3, COL4A4 i COL4A5) čine i do 30% genetičkih dijagnoza kod pacijenata sa MH, što naglašava važnost genetičkog testiranja čak i kod negativne porodične anamneze. Prikaz slučaja: Prikazan je slučaj devojčice uzrasta 4,5 godine sa asimptomatskom perzistentnom MH. Tokom dvoipogodišnjeg praćenja, uprkos terapiji ACE inhibitorima, došlo je do porasta proteinurije. Umesto biopsije bubrega, primenjeno je sekvencioniranje celog egzoma kojim je identifikovana de novo patogena varijanta u genu COL4A5, čime je potvrđena dijagnoza X-vezanog Alportovog sindroma (XLAS). Zaključak: kod dece sa perzistentnom hematurijom nejasne etiologije, genetičko testiranje je ključno za postavljanje tačne dijagnoze, prognozu i informisanje o rizicima za buduće potomstvo, s obzirom na visoku verovatnoću prenošenja XLAS na naredne generacije.

Ključne riječi: hematurija, deca, diferencijalna dijagnoza, Alportov sindrom (X-vezani, XLAS), genetičko

INTRODUCTION

The presence of blood in the urine may represent a normal, transient finding in children, usually associated with nonspecific symptoms of a viral infection (1). However, more importantly, this finding may also indicate disease of the kidneys or urinary tract. Macroscopic hematuria, as well as the incidental finding of microscopic hematuria, is a frequent cause of concern for parents who bring their children to a pediatrician. The etiology of hematuria includes a wide range of conditions; therefore, the evaluation of its cause may be extensive, costly, and sometimes unnecessary, since most children with isolated hematuria do not have significant kidney disease and the abnormal urinary finding usually disappears upon repeated testing. On the other hand, persistent microscopic hematuria may be an indicator of significant glomerular disease associated with an increased risk of developing end-stage renal disease (ESRD). Pediatricians are faced with the task of first clearly establishing the presence of hematuria, indicating the necessary diagnostic evaluation, and recognizing when it is necessary to urgently refer the patient to a pediatric subspecialist, either a pediatric nephrologist or urologist (2). Hematuria is most commonly defined as the presence of ≥3 erythrocytes (RBCs) per high-power field on microscopic examination of the sediment of centrifuged urine, or ≥5 RBCs/mm^3 in non-centrifuged urine (3). Even when the urine appears red or dipstick testing detects the presence of occult blood in the urine, erythrocytes may not be present; therefore, microscopic examination is necessary to confirm hematuria. Hematuria may be visible to the naked eye (macroscopic hematuria) or detected only by urinalysis (microscopic hematuria). Based on duration, hematuria can be classified as intermittent or persistent, and according to the presence of symptoms as asymptomatic or symptomatic. Asymptomatic microscopic hematuria is considered clinically significant if it persists in three or more urine sediment examinations performed at approximately two-week intervals (within a period of one to three months).

Causes of hematuria in children

The causes of hematuria in children are numerous, and the broad differential diagnosis may range from infections to hypercalciuria, nephrolithiasis, vascular abnormalities such as nutcracker syndrome, acute and chronic glomerular diseases, congenital anomalies of the kidneys and urinary tract, and tumors. The differential diagnosis depends on whether the hematuria is glomerular or non-glomerular and whether comorbidities such as pain are present (4). Glomerular hematuria (originating from the glomeruli, renal tubules, or renal interstitium) is usually reddish-brown in color, often described as cola-colored or tea-colored urine, does not contain blood clots, and is characterized by the presence of dysmorphic erythrocytes or erythrocyte casts. It may also be associated with proteinuria (≥2+ on dipstick testing, ≥1 g/24 hours), hypertension, and impaired renal function (Table 1, according to reference 4).

Macroscopic hematuria

Macroscopic hematuria accompanied by pain is most commonly non-glomerular hematuria, usually caused by infection, urolithiasis, or structural abnormalities of the kidneys and urinary tract, whereas hematuria of glomerular origin is most often painless. A urinary tract infection should be considered in the presence of fever and/or lower urinary tract symptoms such as dysuria, urgency, frequency, and painful urination. In the case of sharp flank or lumbar pain (so-called renal colic) accompanied by macroscopic hematuria, urinary stones should be suspected first, or, much more rarely, renal vein thrombosis. Additionally, some cases of nutcracker syndrome may be associated with pain and macroscopic hematuria. Hypercalciuria may cause recurrent episodes of macroscopic or microscopic hematuria even in the absence of evident urolithiasis. Rarely, tumors of the kidneys and urinary tract may be a cause of macroscopic hematuria in children, typically presenting with a palpable abdominal mass (5). The most common causes of glomerulonephritis are immunoglobulin A nephropathy (IgAN) and post-streptococcal glomerulonephritis (PSGN). The occurrence of macroscopic hematuria in a patient with an upper respiratory tract infection (within one week) suggests IgA nephropathy, whereas hematuria developing in a patient whose infection occurred somewhat earlier (approximately two weeks previously), particularly with history of streptococcal pharyngitis, suggests the development of post-streptococcal a glomerulonephritis.

Table 1 **Causes of hematuria in children.**

Glomerular		Non-glomerular
Kidney related	Systemic	
PSGN/PIGN	Systemic lupus erythematosus	Hypercalciuria
IgAN	IgA vasculitis (HSPN)	Urinary tract infections
TBMD	Hemolytic-uremic syndrome	Tubulointerstitial nephritis
MPGN/C3 glomerulopathy	Granulomatosis with polyangiitis	Congenital Anomalies of the Kidney and Urinary Tract
FSGS	Goodpasture syndrome	Vascular malformations (thrombosis)
Alport syndrome	Polyarteritis nodosa	Nutcracker syndrome
Other chronic glomerulonephritis	Sickle cell nephropathy	Nephrolithiasis
		ADPKD
		Trauma
		Tumors
		Coagulopathy
		Urethral hemorrhage
		Exercise-induced hematuria

PSGN - post-streptococcal glomerulonephritis; PIGN - post-infectious glomerulonephritis; IgAN - immunoglobulin A nephropathy; TBMD - thin basement membrane disease; MPGN – membranoproliferative glomerulonephritis; C3 - complement component 3; FSGS - focal segmental glomerulosclerosis; HSPN – Henoch-Schönlein purpura nephritis; ADPKD - autosomal dominant polycystic kidney disease.

Microscopic hematuria with clinical symptoms

In cases of persistent microscopic hematuria, associated clinical symptoms such as fever (which may also be absent), malaise, abdominal or flank pain, hypertension, and edema may indicate glomerulonephritis. Lower urinary tract (UT) symptoms such as urinary frequency, dysuria,

and nocturia most commonly suggest urinary tract infection (UTI), hypercalciuria, or nephrolithiasis, while other non-urinary symptoms, such as rash, purpura, joint pain, or joint swelling, may indicate systemic diseases such as systemic lupus erythematosus (SLE) or IgA vasculitis nephritis.

Asymptomatic persistent microscopic hematuria

Asymptomatic persistent microscopic hematuria (MH) in children and adolescents has an estimated prevalence of 0.5-2% (6). Although it was previously considered a benign finding, persistent MH has, over the past decade, been recognized as a significant risk factor for the development of progressive chronic kidney disease (CKD) (7,8). Glomerular nephropathy resulting from genetic defects in the COL4A3/4/5 genes, including classic Alport syndrome, is the second most common inherited kidney disease characterized by persistent hematuria that progresses to the need for renal replacement therapy. Recent medical literature on Alport syndrome in 2025 emphasizes a shift to "Alport spectrum" terminology, earlier genetic screening, and proactive nephroprotective treatment (9). Variants in genes encoding the α chains of type IV collagen of the glomerular basement membrane (COL4A3, COL4A4, and COL4A5) are most commonly associated with MH and account for up to 30% of genetic diagnoses in this group of patients (10). In a study of pediatric patients (6) presenting with unexplained MH, 68% of those tested had a pathogenic or likely pathogenic variant in the COL4A3–5 genes, while only 49.5% had a positive family history. This finding further emphasizes the importance of genetic testing in children with persistent MH even in the absence of a positive family history. In children with pathogenic or likely pathogenic variants in the COL4A3–5 genes and microhematuria, regular monitoring of microalbuminuria every 1-4 years starting from the age of 4–6 years is recommended (11). Non-glomerular causes predominantly include hypercalciuria, nephrolithiasis, congenital anomalies of the kidneys and urinary tract, and nutcracker syndrome; however, in many cases, a clear underlying cause cannot be identified (4).

Evaluation of Children with Hematuria

Medical History

To identify the origin of hematuria, a detailed description of urine color and the possible presence of blood clots is essential. It is also important to record recent trauma, fever, intense physical exercise, recent respiratory or skin infection, the presence of a menstrual cycle, and other relevant factors at the time of urinalysis. Particular attention should be paid to the presence of oliguria, rapid weight gain over a short period of time, lower urinary tract symptoms, flank pain, as well as associated non-renal symptoms such as rash, joint pain, abdominal pain, blood in the stool, hearing problems, and ophthalmologic abnormalities (2).

Physical Examination

During the physical examination of a child with hematuria, special attention should be given to measurement of blood pressure, body height, and body weight, as well as the presence of localized or generalized edema, purpura/rash, or joint swelling. Patients with a family history of kidney disease should be referred for additional audiological and ophthalmological evaluations (2).

Urinalysis

Dipstick tests use a chromogenic reaction to detect the presence of heme proteins in urine. A finding of ≥1+ on dipstick testing for occult blood is considered a positive result. This test may also be positive in cases of hemoglobinuria or myoglobinuria (2). False-negative hematuria may occur due to the presence of reducing agents in the urine, such as ascorbic acid or formalin, as well as in cases of diluted urine. False-positive hematuria may occur in hemoglobinuria or myoglobinuria, and in cases of highly concentrated urine (specific gravity >1010). Confirmation of the presence of erythrocytes (RBCs) in urine requires microscopic examination of the urine sediment. Based on sediment analysis, it is possible to determine the morphology of erythrocytes, the presence of casts, and possible crystals. The presence of dysmorphic erythrocytes (>30%), acanthocytes (>5%), or erythrocyte casts indicates a glomerular origin of hematuria. Erythrocyte casts rapidly disintegrate in alkaline urine and acquire a granular appearance. The presence of crystals, particularly calcium oxalate crystals, suggests non-glomerular hematuria in cases of hypercalciuria (3).

Additional Tests in the Evaluation of a Child with Hematuria

Based on the results of the initial evaluation, when glomerular hematuria is suspected, in addition to routine biochemical analyses, the following tests are indicated: complement components C3 and C4, antinuclear antibodies (ANA), anti–double-stranded DNA antibodies, anti-neutrophil cytoplasmic antibodies (ANCA), hepatitis B virus antibodies and antigens, kidney biopsy, and genetic testing (4). In light of the most recent evidence, and according to the 2024 guidelines for the diagnosis, monitoring, and treatment of individuals with the spectrum of Alport syndrome, the indications for genetic testing have been significantly expanded (9) and now include children with isolated persistent glomerular hematuria. When non-glomerular hematuria is suspected, it is necessary to perform ultrasound examination of the urinary tract with Doppler, abdominal computed tomography, cystoscopy, and genetic testing when indicated.

CASE REPORT

A 4.5-year-old girl was referred to a nephrologist for evaluation of asymptomatic persistent microscopic hematuria, which had lasted for at least 8 months and was incidentally discovered during a routine check-up. Previous urine sediment analyses showed numerous shriveled and pale erythrocytes (RBCs) with sterile urine cultures. A urinary tract ultrasound was performed and was normal. On physical examination, the child was healthy, normotensive, and had a normal physical exam. Personal history: Healthy, normal psychomotor development, history of enuresis. Family history: Negative for hereditary kidney disease; has a younger healthy brother.

First follow-up (after 1 month): Family urines: normal. Serum biochemistry: normal. Urine tests: Protein/Creatinine (Prt/Cr) 23.75 mg/mmol, Microalbumin/Creatinine (MAU/Cr) 4.78 mg/mmol, Calcium/Creatinine (Ca/Cr) 0.25 mmol/mmol, Immunological analyses: C3, C4, ANA, ANCA, anti-DNA antibodies all normal, IgA: 2.35 g/L (slightly elevated; normal up to 1.9 g/L). Treatment: Omega-3 capsules, one capsule twice daily.

Second follow-up (after 8 months): Urine sediment varied from 2-3 fresh RBCs, 2-3 shriveled RBCs to numerous fresh and shriveled RBCs. During infection (ear inflammation), macroscopic hematuria was observed. Morning urine: MAU/Cr 5.25 mg/mmol, Prt/Cr 17.25 mg/mmol (Figure 1), 24-hour urine: Microalbuminuria 38.1 mg/day, Proteinuria 110.6 mg/day. Treatment adjustment: ACE inhibitor Enalapril 1×2 mg, continued Omega-3 capsules, one capsule twice daily.

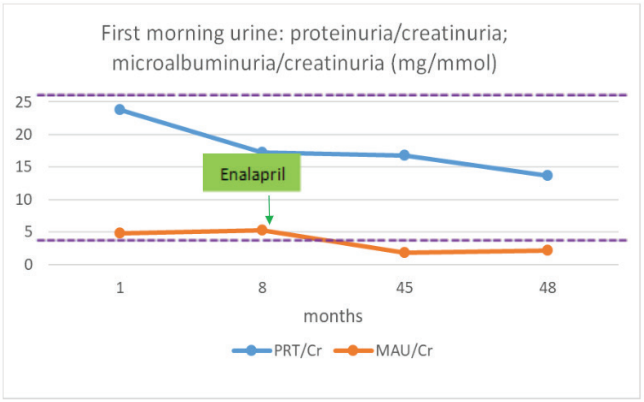

Figure 1 **First morning urine proteinuria/creatinuria (PRT/Cr) and microalbuminuria/creatinuria (MAU/Cr).**

Due to elevated serum IgA, a celiac disease screen was performed and was negative. Over 2.5 years of follow-up by the nephrologist, despite the introduction and gradual increase of ACE inhibitor therapy, proteinuria increased: albuminuria 98 mg/day and proteinuria 274 mg/day (Figure 2).

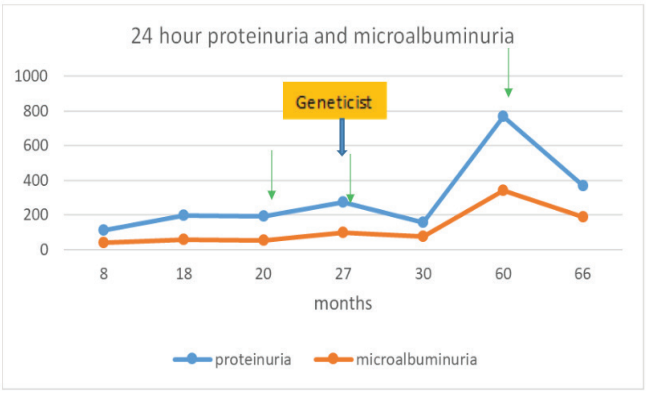

Figure 2 **24 hour proteinuria and microalbuminuria.**

Instead of a kidney biopsy, genetic testing was indicated. Whole-exome sequencing revealed a heterozygous, likely pathogenic variant in the COL4A5 gene, c.989del (frameshift). Targeted parental testing showed that the variant was not inherited from either parent; it arose de novo in the child, confirming a diagnosis of X-linked Alport syndrome (XLAS). Testing of the healthy younger brother with a normal urine analysis was not required, as the COL4A5 variant was absent in both parents. Future implications for the patient's offspring: 50% risk that a male child will inherit likely severe Alport syndrome (hemizygous for the COL4A5 variant) and 50% risk that a female child will inherit Alport syndrome with variable expression (heterozygous for the COL4A5 variant). Genetic counseling is recommended for the patient at 16 years of age regarding options for prenatal or preimplantation genetic diagnosis. The reason for this is that the risks for disease occurrence in girl`s offspring will be highly elevated: 50% for a male child to suffer from a possibly severe form of Alport syndrome and 50% for a female child to inherit Alport syndrome with the possibility of variable expression.

DISCUSSION

Etiological diagnosis of hematuria in children represents a significant clinical challenge due to the wide range of possible causes, which vary from benign and transient conditions to serious progressive glomerulopathies. While isolated microscopic hematuria (MH) was previously often considered a benign finding, modern literature recognizes it as a significant risk factor for the development of progressive chronic kidney disease (7, 8). In the presented case of a 4.5-year-old girl, the initial clinical picture of asymptomatic persistent MH with slightly elevated serum IgA and an episode of macroscopic hematuria during the infection initially led to the suspicion of IgA nephropathy (IgAN). According to the literature, IgAN and poststreptococcal glomerulonephritis are the most common causes of glomerular hematuria in children (1). A key moment in this presentation is the decision to perform genetic testing (Whole Exome Sequencing - WES) instead of an invasive kidney biopsy. Nevertheless, according to the ERKNet 2024 guideline, genetic testing is now recommended as a primary diagnostic tool in children with isolated persistent glomerular hemathuria that can often replace invasive renal biopsy (9). The literature supports this approach, stating that variants in the COL4A3, COL4A4, and COL4A5 genes account for up to 30% of all genetic diagnoses in MH patients (10). The identified de novo pathogenic "frameshift" variant in the COL4A5 gene (c.989del) of our patient, confirmed the diagnosis of X-linked Alport syndrome (XLAS). Our case highlights an important fact from the literature: although Alport syndrome is a hereditary disease, a negative family history does not exclude this diagnosis (9). Studies show that as many as 50% of children with pathogenic COL4A3-5 variants do not have a positive family history of the disease, underscoring the importance of genetic analysis in children with unclear MH (5). According to the recommendations, in children with confirmed variants in the COL4A3-5 genes, it is necessary to regularly monitor albuminuria every 1 to 4 years (9), starting from the age of 4-6 years, which was fully implemented in this case. Finally, the 2024 ERKNet guideline specifically emphasizes the importance of genetic counseling (9). Although heterozygous female patients with XLAS are sometimes mistakenly considered only "carriers", they are actually part of the AS spectrum at risk of progression and require lifelong follow-up. Accurate genetic diagnosis in this case enables timely information on the risks for the offspring (50% probability for a severe form of the disease in male children) and provides the opportunity for future prenatal or preimplantation diagnostics, which is the highest standard of modern pediatric nephrology.

CONCLUSION

The causes of hematuria in children are numerous. Once its presence and persistence are confirmed (i.e., detected in at least three separate urine samples over a two-week period), it is essential to perform a detailed medical history, physical examination, and further laboratory and radiological investigations. Children with findings suggestive of glomerulonephritis (proteinuria, hypertension, impaired kidney function, reduced complement component C3), a positive family history of kidney disease, or congenital or acquired structural abnormalities of the kidneys should be referred to a pediatric nephrologist. Children with acute obstruction and development of hydronephrosis due to urolithiasis should be referred as soon as possible to a pediatric urologist. In children with persistent hematuria of unclear etiology, genetic testing is crucial for establishing an accurate diagnosis, determining prognosis, and informing families about risks for future offspring as is the case with Alport syndrome.

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Authors' contributions: BS, AP, IG and MC gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Financial support and sponsorship: nil.
Conflict of interest: there are no conflicts of interest.

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