ISSN 2545-4366
www.e-mja.finki.ukim.mk

MJA

Macedonian Journal of Anaesthesia

A Journal on Anaesthesiology, Resuscitation, Analgesia and Critical Care

Vol. 9 No 4, December 2025

Journal of the Macedonian Society of Anaesthesiologists
and Macedonian Society of Critical Care Medicine

Publisher:
Department of Anaesthesia and Reanimation Faculty of Medicine,
"Ss. Cyril and Methodius" University, Skopje, R.N.Macedonia

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I.V. Paracetamol

БЕЗБЕДНА АНАЛГЕЗИЈА

менаџирање на болка кога сте загрижени за безбедноста

I.V. paracetamol за прв пат во Европа е применет во 2001 година, а денес поради неговата докажана безбедност и ефикасност е прв од избор **аналгетик и антипиретик.**

Предоперативна и Интраоперативна Аналгезија:
Предоперативна анелгезија е дефинирана како третман кој што започнува пред оперативниот зафат се со цел да се превенира воспоставувањето на централна сензибилизација на болка.
i.v. paracetamol е безбеден, добро толериран лек со докажана ефикасност како **предоперативна и интраоперативна анелгезија** за умерена до средна болка при оперативни зафати.
Голем број на клинички студии ја докажуваат ефикасноста на **i.v. paracetamol** како **преодоперативна и интраоперативна анелгезија**.

КЛИНИЧКА СТУДИЈА:
Ефект од **предоперативен i.v. paracetamol** за постоперативни аналгетски потреби кај пациенти кои се подлежни на оперативни зафати. A Sreenivasulu , R Prabhavathi, 2015
Цел: Да се утврди ефикасноста на **предоперативната употреба на 1000mg i.v. paracetamol** кај постоперативните болки и анелгетски потреби кај пациенти подлежни на хируршки зафати.
Метод: 60 пациенти беа поделени во две рандомизирани групи од по 30 пациенти.
На I. Група им беше администриран**о ампула од 1000mg i.v. paracetamol разредена 0,9%NaCl** р-ор 30 минути пред индукција **(ГРУПА П)**,
На II. Група им беше администрирано **i.v. 0,9% NaCl р-ор 100мл** 30 минути пред индукција **(ГРУПА НС)**
Сите пациенти беа индуцирани со i.v. thiopentone 5mg/kg, i.v. fentanyl 2μg/kg, i.v. vecuronium 0.1mg/kg
Постоперативниот резултат на болка беше мерен со **Визуелна Аналогна Скала (ВАС) од "0-10"**. Исто така беше забележувана и **постоперативната употреба на tramadol** како спасувачки аналгетик. Инциденцата на **постоперативно гадење и повраќање (ПОГП)** и други компликации исто така беа забележувани во пост оперативниот период.
Резултатот на постоперативната болка беше забележуван во интервали 15 мин, 30 мин, 1 час, 2 часа, и 6 часа.

Резултат:

Табела 1: *Споредба на средниот резултат на болка (ВАС) помеѓу двете групи*

Интервали	I Група П	II Група НС	*P вредност*
15 мин	2.06 ± 0.63	2.61 ± 0.56	0.0006
30 мин	2.35 ± 1.17	3.84 ± 1.55	0.0001
1 час	2.42 ± 1.12	2.87 ± 0.99	0.0989
2 часа	2.13 ± 1.06	2.52 ± 0.89	0.1219
6 часа	2 ± 0.52	2.52 ± 0.89	0.0549

Табела 2: *Споредба за потребите од tramadol помеѓу двете групи*

Интервали	I Група П	II Група НС	*P вредност*
До 1 час	4 (12.90%)	15 (50%)	0.0002
1-2 часа	3 (9.68%)	2 (6.45%)	0.64
2-6 часа	1 (3.23%)	3 (9.68%)	0.301
Вкупно	**8 (25.81%)**	**20 (64.52%)**	**0.002**

Табела3: *Споредба на ПОПГ помеѓу двете групи*

ПОГП	
I Група П	II Група НС
0	4

Заклучок: Предоперативна администрација на **1000mg i.v. paracetamol** кај пациенти подлежни на оперативен зафат обезбедува **статистички задоволителна анелегизија**, и ја **намалува постоперативната употреба на tramadol**. Оттука **1000mg i.v. paracetamol** може безбедно да се администитрира како превенција при оперативни зафати.

i.v. Paracetamol + јак опоид	МНОГУ ЈАКА БОЛКА
i.v. Paracetamol + слаб опоид	ЈАКА БОЛКА
i.v. Paracetamol + NSAID i.v. Paracetamol + rescue medicine	УМЕРЕНА БОЛКА
i.v. Paracetamol + rescue medicine	СЛАБА БОЛКА

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- **Ублажување на акутна и хронична болка**

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Macedonian Journal of Anaesthesia

A Journal on Anaesthesiology, Resuscitation, Analgesia and Critical Care

Publisher:
Department of Anaesthesia and Reanimation
Faculty of Medicine
"Ss. Cyril and Methodius" University
Skopje, R. N. Macedonia

Proofreading:
Nikolina Stojanova

Graphic adaptation:
Gavrilo Angeloski (Arbëria Design)

Printing:
Arbëria Design

CONTENT

TINY PATIENTS, BIG DATA: HOW ARTIFICIAL INTELLIGENCE CAN TRANSFORM NEONATOLOGY

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Artificial intelligence (AI) has emerged as a transformative technology, becoming an integral part of our daily lives, particularly in healthcare. It has the potential to harness vast amounts of data, serving as a powerful tool to support clinical decisions, provide personalized care, deliver accurate prognostics, and enhance patient safety.

The term "artificial intelligence" refers to the ability of computing algorithms to replicate human decision-making processes. "Machine learning" (ML) is a subset of AI that encompasses techniques that enable machines to learn from large datasets without explicit programming, primarily aimed at developing predictive models. Both AI and ML can analyze significantly more data than humans can handle, exploring nonlinear relationships and complex interactions among biological, genetic, and environmental factors. Their main focus is on prediction and detection rather than establishing causal relationships. (1)

Neonatology, as a pediatric subspecialty, along with neonatal intensive care, generates significant volumes of multidimensional data. This presents opportunities for both AI and ML to transform neonatology, enhance early diagnostics, improve monitoring processes, and develop targeted treatment strategies.

There has been a significant increase in the number of PubMed citations over the last 15 years on the use of AI in both adults and children. A PubMed search using the combined Medical Subject Headings (MeSH) terms "Artificial Intelligence" or "Machine Learning" and either "Infant, Newborn" or "Intensive Care, Neonatal" for neonates retrieved over 1,000 publications, with a quarter of these published in the last two years.

A recently published systematic review aimed at mapping the current evidence on ML in pediatrics and adolescent medicine found that neonatology was the dominant specialty, accounting for 24% of the 363 articles reviewed. Furthermore, the majority of these studies were conducted in high-income and upper-middle-income countries, whereas low- and lower-middle-income countries (LMIC) were represented in only 3% of the studies. Despite the high academic interest, the implementation of AI in clinical settings remains limited. In addition, the most impactful applications of AI in neonatal medicine will be addressed. (2)

AI Application in Routinely Recorded Neonatal Vital Signs

Continuous real-time monitoring of vital signs—such as heart rate, respiratory rate, and pulse oximetry—is essential in specialized neonatal care. Data collected from multiple sensors provides valuable insights into the infant's clinical status. Vital signs are influenced by complex physiological mechanisms, and any deviations from the normal patterns can be early indicators of potential medical complications. Clinical care is typically influenced by interval assessments

of vital signs, and with periodic assessments, the majority of data on bedside monitors remains unanalyzed. Pre-set alarm thresholds can alert healthcare providers to acute changes in an infant's condition. However, the prevalence of false-positive alarms may lead to alarm fatigue, which can adversely impact clinical decision-making during critical moments when prompt intervention is required. (3)

Recent studies indicate that cumulative analysis of continuously recorded vital sign trends can serve as a valuable tool for predicting imminent clinical deterioration and the onset of pathological conditions such as sepsis. (4)

Late-onset sepsis (LOS) poses a significant burden of morbidity and mortality among preterm infants. Timely recognition, along with prompt initiation of antibiotic therapy, is essential for preventing adverse outcomes in these infants. (4,5) However, due to the subtle and nonspecific signs and symptoms, clinicians often find themselves at a challenging crossroad between early detection and the risks of over-treatment and antimicrobial resistance.

Alterations in heart rate characteristics (HRC), including frequent small accelerations and decelerations, occur as part of the pathophysiologic response to systemic infection. In particular, sepsis is the most significant cause of abnormal heart rate in preterm infants. Since LOS is often associated with variations in vital signs, it offers an ideal opportunity for developing ML models. AI algorithms can help detect LOS before sepsis becomes clinically apparent. (5)

The first commercially available device, called the HeRO (Heart Rate Observation) monitor, was developed to analyze abnormal heart rate characteristics and provide clinicians with a score indicating the risk of an infant developing sepsis within the next 24 hours. (6)

Results from the largest randomized controlled trial to date involving very low-birth-weight (VLBW) infants, including 3,003 participants, showed statistically significant and clinically meaningful outcomes. There was a 22% relative reduction in mortality for infants whose HeRO scores were displayed, translating to one additional survivor for every 48 VLBW infants monitored or for every 23 extremely low birth weight (ELBW) infants monitored, and a 40% reduction of sepsis mortality within 30 days. (7,8)

However, the abnormal HRC is not exclusively indicative of neonatal sepsis; other potential conditions must be considered, as some studies have shown a 10% increase in blood cultures and a 5% rise in antibiotic use. (5) Therefore, by combining physical examination findings, interviewing the attending caregiver, and analyzing trends in the HeRo score, we can significantly enhance the diagnostic accuracy. Ultimately, it is up to the physician to determine the next steps, whether that involves a "wait and watch closely" approach or initiating investigations and empirical treatment.

A recent meta-analysis, including nine articles and twelve prediction models, evaluated the diagnostic accuracy of existing prediction models for sepsis in neonates. Among these, three models demonstrated a sensitivity of at least 95%, with significantly lower specificity and positive predictive value.(9) Consequently, the prediction models should be used as guidance rather than absolute indicators, as most of them have limited diagnostic accuracy. It's essential to always consider the clinical context. Therefore, future research will aim to enhance predictive models by integrating targeted physio and laboratory biomarkers with cardiorespiratory algorithms, as this is likely to have a much greater impact than either strategy alone. Finally, the integration of

validated AI models into wireless monitoring devices has the potential to transform newborn care in terms of comfort, family-centered care, and better outcomes. (10)

AI and Neuromonitoring

Neonatal seizures are a neurological emergency that requires prompt treatment. However, diagnosing seizures is particularly difficult in preterm infants, as over 85% of cases may not exhibit obvious clinical signs, and the events are usually electrographic. Additionally, differentiating neonatal seizures from other physiological or abnormal, but non-epileptic movements in neonates presents a significant challenge. As a result, infants may be undertreated if their condition goes undiagnosed or overtreated if misdiagnosed.

Continuous conventional electroencephalography (cEEG) is the gold standard for diagnosing neonatal seizures. However, its implementation can be expensive and time-consuming. Furthermore, real-time interpretation requires the presence of highly skilled medical personnel 24/7, which may not be feasible, even in high-income countries. (11) A simplified, though less accurate form of EEG monitoring is the amplitude-integrated EEG (aEEG). This method has been used in neonatal units for many years, primarily due to the difficulties in obtaining a conventional EEG.

The majority of AI research using neonatal EEG has focused on developing algorithms for automated seizure detection, achieving impressive detection accuracy comparable to that of human experts.

One of the most impactful studies was a multicenter randomized controlled trial conducted across eight NICUs in Ireland, the Netherlands, Sweden, and the UK. All neonates included in the study underwent EEG monitoring due to clinically suspected seizures or a high risk of seizures. An automated EEG-based seizure detection software, known as the Algorithm for Neonatal Seizure Recognition (ANSeR), was used in real time to assess the diagnostic accuracy of detecting neonatal electrographic seizures, serving as a support tool for clinicians at the bedside. The neonates were randomly assigned (1:1) into two groups: one group received continuous EEG (cEEG) monitoring with ANSeR (the algorithm group), while the other group received routine cEEG monitoring without the algorithm (the non-algorithm group), which is considered standard care at the participating centers. All cEEG recordings were reviewed by two independent expert neurophysiologists. The study's findings revealed a higher percentage of seizure hours correctly identified in the algorithm group. The use of the algorithm was safe and did not lead to an increase in antiseizure medication prescriptions. (12) An additional noteworthy finding was a significant difference in seizure recognition between weekdays and weekends, with seizures being less likely to be recognized during weekends without the support of the algorithm. (12) This implies that in limited resource settings and in centers with less experience in interpreting neonatal EEG there is a potentially greater benefit of using an algorithm.

Ongoing research focuses on developing algorithms that can assess brain maturation, estimate sleep states, and analyze background EEG patterns in conditions such as hypoxic-ischemic encephalopathy (HIE). By applying machine learning algorithms to readily available clinical data, we may be able to accurately identify infants at risk of developing HIE following perinatal asphyxia. This approach could be integrated into bedside decision-support tools, ensuring timely and precise initiation of therapeutic hypothermia for infants who would benefit the most. (13-15)

The multidisciplinary approach is critical to success; thus, a recently funded European Cooperation in Science and Technology (EU COST) AI4NICU Action (https://www.cost.eu/actions/CA20124), to which our university participated, aims to foster the development of AI technologies that detect brain injuries in neonates through such multidisciplinary collaboration.

AI and Neonatal Jaundice

Neonatal jaundice is a prevalent condition, affecting 60-80% of healthy newborns. While it is generally benign, severe hyperbilirubinemia can lead to permanent brain damage, a condition known as "kernicterus," associated with lifelong complications and disabilities. The American Academy of Pediatrics recommends universal screening for bilirubin levels in all newborns prior to discharge, along with a close follow-up for jaundice assessment after 48-72 hours. Since bilirubin levels typically peak around the third postnatal day — when many newborns are already at home — accurately detecting jaundice can be particularly challenging, as it primarily relies on visual inspection. Hyperbilirubinemia presents a prevalent cause of neonatal readmission, particularly in low and LMICs. This can cause considerable stress for newborn mothers and may result in anxiety, depression, or cessation of breastfeeding. Consequently, a need to develop an inexpensive, widely available technology to screen newborns for jaundice globally emerged. Recent studies have introduced innovative methods for assessing neonatal jaundice using digital images and smartphones. Researchers have developed a physics-based system that estimates bilirubin levels from these images using deep learning and machine learning models. In this system, images are captured with a smartphone and color-calibrated using a reference card that matches the skin tone of the area over a newborn's sternum. The calibrated image data is then transmitted via the Internet to a computer server, where it is compared to a large database containing pairs of colors and their corresponding bilirubin levels. (16-18)

Taylor and his group developed BiliCam, a smartphone application, and assessed its accuracy in a diverse sample of newborns at 7 sites across the United States, showing an impressive overall correlation of 0.91 and a sensitivity of 84.6% for identifying newborns in high-risk zones. (17)

Another smartphone application, "Picterus," was developed by researchers at the Norwegian University of Technology and Science. This innovative tool has demonstrated remarkable effectiveness for screening neonatal jaundice, particularly in detecting cases of severe jaundice (total serum bilirubin > 250 μmol/L). The image-derived bilirubin were strongly correlated with total serum bilirubin levels in both Caucasian and non-Caucasian populations in low- and LMICs, including individuals with moderate dark skin tones. (18,19)

We are currently conducting a study to evaluate the accuracy of the Picterus application during phototherapy for neonates hospitalized for jaundice in the Department of Neonatology at the University Children's Hospital. The use of mobile health technology holds great promise for advancing neonatal care, as it allows for a noninvasive alternative to bilirubin monitoring.

Similar approaches could be adapted to support the diagnosis of neonatal conditions, including syndromes, especially when linked with other data, in low and middle-income countries with limited access to genetic screening services. (20)

In conclusion, artificial intelligence will play a crucial role in the future of healthcare, particularly in complex areas such as neonatology and neonatal intensive care. It will enhance clinical decision-making, facilitate efficient and personalized care for newborns, and help minimize avoidable errors. To fully harness the AI capabilities in neonatal care, it is crucial to enhance

digital literacy among healthcare professionals and encourage multi-disciplinary collaboration. AI should be seen as an invaluable tool in the healthcare professionals' toolkit, alongside standardized blood tests and imaging, to provide effective neonatal care in everyday clinical practice.

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ORIGINAL ARTICLE *UDK: 616-006.6-036.81:[616.992:582.282.123.4*

www.doi.org/10.55302/MJA259417m

GALACTOMANNAN ANTIGEN TEST IN RESPIRATORY SAMPLES FOR ASPERGILLOSIS DIAGNOSIS

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Abstract

Introduction: Invasive aspergillosis is an important cause of mortality in patients with malignant diseases, and is an underestimated infection in critically ill patients. Early diagnosis is still challenging, therefore a rapid and more sensitive diagnostic methods could be beneficial.

Aim: the aim of the study was to evaluate the sensitivity and specificity of the galactomannan antigen test in respiratory samples, compared to conventional methods, for early diagnosis of aspergillosis.

Material and methods: Samples of 125 patients divided into 4 groups, classified according to diagnosis and EORTC/MSG criteria, were analysed at the Institute of Microbiology and Parasitology, with culture and galactomannan test in respiratory samples, during a period of two years.

Results: A total of 71 isolates of Aspergillus were confirmed in this study. Culture of respiratory samples revealed Aspergillus in the group of chronic aspergillosis (63.33%), followed by groups of cystic fibrosis (56.67%), primary immune deficiency (51.43%), and the group with prolonged ICU stay (43.33%). Sensitivity and specificity of respiratory samples' culture were: 64.29% and 100%, 59.09% and 100%, 54.55% and 12.5%, 100% and 54.17%, in all four groups, respectively. Sensitivity and specificity of galactomannan in respiratory samples, were: 75% and 57.14%, 86.36% and 62.5%, 81.82% and 0%, 50% and 70.83%, in all 4 groups, respectively.

Conclusion: The results of this study demonstrate that positive galactomannan test in respiratory samples could be a useful diagnostic adjunct in diagnosis of aspergillosis, along with results from conventional mycological analyses, so timely antifungal treatment is administered.

Key words: *Aspergillus, aspergillosis, galactomannan, respiratory tract*

Introduction

The incidence of invasive fungal infections (IFI) has dramatically increased in recent decades. Aspergillosis usually affects the respiratory system causing aspergilloma, chronic pulmonary aspergillosis, allergic bronchopulmonary aspergillosis and invasive aspergillosis (IA), which is the most aggressive form of the infection with these fungi (1,2). IA is mainly caused by Aspergillus fumigatus. Aspergillus can invade the trachea and lungs, resulting in airway colonization, subsequent lung inflammation, and necrotizing pneumonia. They can affect distant organs through hematogenous spread. In the past, IA was recognized as occurring mainly in patients with hae-

matological malignancies, solid organ or hematopoietic stem cell transplants, HIV infection, or in patients receiving long-term immunosuppressive therapy (3). However, it has been found that nonneutropenic patients, like chronic obstructive pulmonary disease (COPD) patients and patients with bronchiectasis, or previous tuberculosis, are also susceptible to pulmonary aspergillosis. Invasive aspergillosis may also be an underestimated infection in critically ill patients treated in intensive care units (ICUs). Despite availability and clinical use of new antifungal drugs, the mortality rate from IA in ICU patients remains high (4). The criteria for IA diagnosis have benefited from the European Organization for the Research and Treatment of Cancer (EORTC) and Mycoses Study Group (MSG) recommendations for defining IFI including aspergillosis (5). To achieve a more favorable prognosis of the life-threatening IA, an early initiation of antifungal treatment is mandatory. It relies on a timely and accurate diagnosis, which is still a big clinical and laboratory challenge, since clinical symptoms and radiological signs of IA are non-specific. Histopathological demonstration of molds in tissue samples or growth of molds on culture media, is still the "gold standard". On the other hand, the procedures for specimen collection are invasive, which can be contraindicated in patients with profound respiratory insufficiency. Conventional mycological methods are also time-consuming and insensitive, since they are positive in less than 30% of cases with IA. Because of these limitations, a significant amount of work has been done in the past few decades regarding the development of non culture-based diagnostic assays for detection of IFI, like fungal biomarkers (5). Galactomannan (GM) is a polysaccharide antigen that exists in the Aspergillus cell walls, which is released into blood and other body fluids even in early stages of invasion (6,7). Levels of this antigen can be determined by enzyme-linked immunosorbent assay (ELISA), which can contribute towards earlier IA diagnosis. Currently, serum GM detection is considered a microbiological diagnostic criterion for fungal infection in neutropenic patients, according to the EORTC/MSG guidelines (5). Recently, GM detection in bronchoalveolar lavage was also strongly recommended in the 2016 Infectious Diseases Society of America guidelines (8) as a test providing high-quality evidence in neutropenic patients, however, its clinical application in nonneutropenic patients lacks evidence and its optimal threshold (9).

The **aim of this study** was to evaluate the sensitivity and specificity of galactomannan antigen test in respiratory samples, compared to conventional method, for early diagnosis of aspergillosis.

Material and Methods

Study Design

A diagnostic study was performed at the Institute of Microbiology and Parasitology, Faculty of Medicine, Skopje, North Macedonia, during a 2-year period, as part of an ongoing PhD study during the 2014-2016 period.

Patient Group and Mycological Analyses

Respiratory tract samples (sputum, tracheal aspirate and BAL) of 125 patients, divided into 4 groups, according to clinical diagnosis and IA risk factors, were analyzed at the Laboratory for diagnosis of fungal infections, at the Institute of Microbiology and Parasitology, Faculty of Medicine, Skopje, North Macedonia. These groups included patients with primary immune deficiency, critically ill patients treated in ICUs, patients with chronic aspergillosis and cystic

fibrosis patients. IA was defined according to the revised definitions by the EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study Group) consensus group (5).

Conventional Mycological Methods

Lower respiratory tract specimens (BAL, tracheal aspirate and sputum) were analyzed with conventional mycological methods, by their inoculation on fungal media (Sabouraud and chromogenic CALB medium (Oxoid)). Identification of Aspergillus on species level was performed with macroscopic analysis of grown mold colonies and further microscopic analysis of fungal conidia with lactophenol cotton blue method. After the specimens were inoculated for culture, all samples were frozen and stored at −70°C for retrospective galactomannan testing.

Galactomannan Antigen Detection

A commercially available sandwich ELISA test for galactomannan antigen detection of Aspergillus species was performed according to the manufacturer's instructions (Platelia Aspergillus protocol: Bio-Rad Laboratories, France) (10). Each sample was tested in duplicate, and the mean value was determined. Three hundred microliters of each respiratory sample and control were pipetted into individual 1.5 ml polypropylene tubes; 100 μL of sample treatment solution was added to each tube, and the tubes were mixed by vortexing. The tubes were then heated for 3 minutes at 100 degrees in a water bath. They were then centrifuged at 10,000xg for 10 minutes. The supernatant was used for detection of the galactomannan antigen. Fifty microliters of the treated respiratory sample supernatant were added to each well. The plate was incubated in a dry microtiter plate incubator for 90±5 minutes at 370C, after which it was washed 5 times. Two hundred microliters of the chromogenic solution were added to each well, avoiding exposure to strong light. The plate was incubated in the dark at room temperature (18-250C) for 30±5 minutes. One hundred microliters of the stop solution were added to each well, in the same order as the chromogenic solution was added. The optical density of each well was read at 450 nm (reference filter 620/630 nm). The microtiter plates were read within 30 minutes after the addition of the stop solution. The optical density (OD) was determined spectrophotometrically with a microplate reader (Bio-Rad, France). The results were interpreted based on the index calculated from the measured OD at a wavelength of 450 nm. Indices ≥ 0.5 were considered positive.

A statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS) for Windows. The results of our study are presented as numbers and percentages. Differences in distribution of proven, probable and possible fungal infections with Aspergillus were compared by Pearson Chi square test. P value less than 0.05 was considered statistically significant.

Results

Respiratory tract samples from 125 patients were divided in 4 groups (first group of patients with primary immune deficiencies, second group with critically ill patients treated in ICUs, third group of patients with chronic aspergillosis and fourth group of patients with cystic fibrosis (CF)). The four groups classification was performed according to primary clinical diagnosis and EORTC/MSG criteria (European Organization for Research and Treatment of Cancer/Mycoses Study group) (Fig. 1).

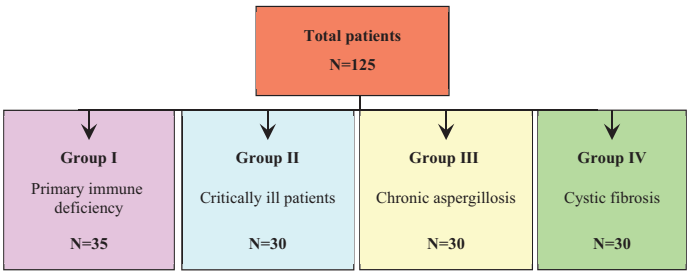

Figure 1: Patient groups classification according to clinical diagnosis and EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study group) criteria

The gender analysis of the study participants revealed that men were more frequently distributed in I, III and IV group (60%, 60%, 53.33% respectively), whereas in the II group, both genders were equally distributed. Average age of patients in all groups were: 40.8±17.7, 59.7±13.3, 64.7±6.3, and 28.9±8.5 years (table 1).

Table 1. Characteristics of patients according to gender and age

Aspergillus				
	Group I N=35	Group II N=30	Group III N=30	Group IV N=30
Gender	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Men 70 (56%)	21 (60%)	15 (50%)	18 (60%)	16 (53.33%)
Women 55 (44%)	14 (40%)	15 (50%)	12 (40%)	14 (46.67%)
	[a]p = 0.81			
Age (years) mean±SD, min-max				
	40.8±17.7 5-69	59.7±13.3 4-78	64.7±6.3 52-76	28.9±8.5 18-52

[a]p(Chi-square test)

The participants' distribution, according to clinical diagnosis for proven, probable and possible fungal infection, with EORTC/MSG criteria (European Organization for Research and Treatment of Cancer/Mycoses Study Group), are presented in figure 2. According to EORTC/MSG criteria, only a small percentage of patients had proven infection with *Aspergillus*. Of these, 20% (7/35) patients had some type of primary deficiency, and 10% (3/30) patients had a prolonged stay in ICU.

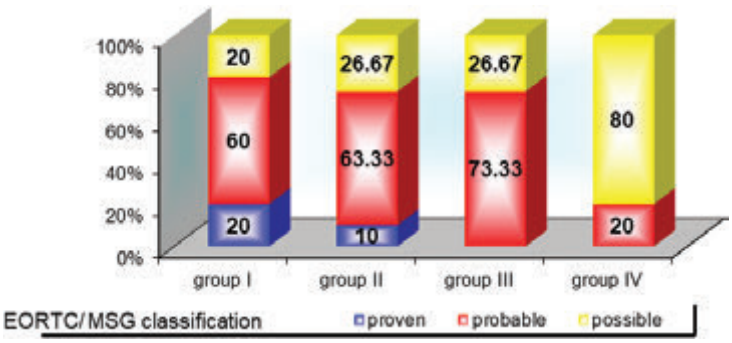

Figure 2. Distribution of fungal infections according to EORTC/MSG criteria in all groups

Differences in distribution of proven, probable and possible fungal infection with Aspergillus were statistically significant between group I versus groups III and IV, and between group II versus groups III and IV (Table 2).

Table 2. Distribution of proven, probable and possible fungal infections according to EORTC/MSG criteria

Aspergillus	group I N=35	group II N=30	group III N=30	group IV N=30
n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
proven 10 (8%)	7 (20%)	3 (10%)	0	0
probable 68 (54.4%)	21 (60%)	19 (63.33%)	22 (73.33%)	6 (20%)
possible 47 (37.6%)	7 (20%)	8 (26.67%)	8 (26.67%)	24 (80%)
	[b]p < 0.001 I vs II p=0.3 II vs III p = 0.345 III vs IV p < 0.001 I vs III p = 0.03* II vs IV p < 0.001 I vs IV p < 0.001			

[a]p(Chi-square test) [b](Fisher exact test) *p<0.05 **p<0.01

The highest rate of *Aspergillus* in respiratory samples culture was registered in the chronic aspergillosis group (63.33%), followed by 56.67% detected in the CF group, 51.43% in the group with primary immune deficiency, and 43.33% in patients hospitalized in ICU. However, the differences in positive respiratory cultures among all groups were insufficient for statistical significance (p=0.46).

The most frequent species (79%) identified in respiratory samples was *A. fumigatus* (53/67). Thirty-two percent of *A. fumigatus* isolates (17/53) originated from samples of patients with chronic aspergillosis, and 26% (14/53) were identified in samples from patients with primary deficiency and cystic fibrosis (Table 3).

Table 3. Culture of respiratory tract samples and identified fungal species

	group I N=35	group II N=30	group III N=30	group IV N=30
Respiratory culture	**n (%)**	**n (%)**	**n (%)**	**n (%)**
negative 58 (46.4%)	17 (48.57%)	17 (56.67%)	11 (36.67%)	13 (43.33%)
positive 67 (53.6%)	18 (51.43%)	13 (43.33%)	19 (63.33%)	17 (56.67%)
	Chi-square: 2.59 p = 0.46			
Identified mold species				
A. fumigatus n=53	14	8	17	14
A. flavus n=11	2	4	2	3
A. terreus n=3	2	1	0	0

p(Chi-square test)

ELISA GM test performed in respiratory samples of patients from the group with primary immundeficiencies was positive in 24 (68.57%) cases. Of these, 6 out of 7 (85.71%) in proven, 15 out of 21 (71.43%) in probable, and 3 out of 7 (42.86%) in possible infections, according to EORTC/MSG criteria. The concentration of GM antigen, in 24 positive samples taken from respiratory samples, ranged from 1.1 to 4.3 pg/ml, with a mean concentration of 2.61±1.1 pg/ml. ELISA GM test in respiratory samples was characterized by 21 true positives, 3 false positives, 4 true negatives, and 7 false negatives; 7 respiratory samples with proven infection were labeled negative by the ELISA GM test, and 3 samples categorized as possible infection were labeled positive by the test. The sensitivity, specificity, PPV and NPV of the GM test in respiratory samples were 75%, 57.14%, 87.5%, 36.36%, respectively.

Results from the comparative diagnostic performance of the conventional method and GM in respiratory samples in the immunodeficiency group are presented in Table 4.

Table 4. Diagnostic performances of culture from RT samples and GM in respiratory samples in the group with primary immunodeficiency

Test	**Se(%)**	**Sp(%)**	**PPV(%)**	**NPV(%)**
Culture from RT samples	64.29	100	100	41.18
Galactomannan in RT samples	75	57.14	87.5	36.36

The ELISA GM respiratory samples test performed to the patients with prolonged hospital stay in ICU from the critically ill group was in 22 (73.33%) of them. GM antigen was detected in all 3 cases categorized as proven infections, 16 of 19 (84.21%) probable, and 3 out of 8 (37.5%) possible, according to EORTC/MSG criteria. The concentration of GM in positive samples ranged from 1.2 to 4.7 pg/ml, with a mean concentration of 2.78±1.04 pg/ml. The ELISA GM respiratory samples test from patients with prolonged hospital stay in ICU was characterized by 19 true positive results, 3 false positives, 5 true negatives, and 3 false negative results. The calculated diagnostic performances were: sensitivity 86.36%, specificity 62.5%, positive predictive value 86.36%, negative predictive value 62.5%.

The results from the conventional method comparative diagnostic performance and GM in respiratory samples in the critically ill patients group with prolonged hospital stay in ICU are presented in Table 5.

Table 5. Diagnostic performances of culture from RT samples and galactomannan in respiratory samples in the group of critically ill patients with prolonged ICU stay

Test	**Se(%)**	**Sp(%)**	**PPV(%)**	**NPV(%)**
Culture from RT samples	59.09	100	100	47.06
Galactomannan in RT samples	86.36	62.5	86.36	62.5

In patients with chronic aspergillosis, GM performed simultaneously with respiratory samples culture detected 26 (86.67%) cases of *Aspergillus* infection, of which, according to the EORTC/MSG criteria, 18 were classified as probable and 8 as possible aspergillosis. The minimum concentration of GM measured in respiratory samples, simultaneously with respiratory samples culture, was 0.8, and the maximum was 2.8, the average concentration was 1.52±0.5. GM as a diagnostic test for *Aspergillus* infection in the chronic aspergillosis group, according to the EO-

RTC/MSG classification, had the following diagnostic performance: sensitivity 81.82%, specificity 0%, positive predictive value 69.23%, negative predictive value 0.82%. The specificity of this test in the chronic aspergillosis group of patients was 0%, i.e., all 8 patients from this group who had a possible *Aspergillus* infection according to the EORTC/MSG had a positive test for GM, i.e., they were marked as false positive results. The test had 4 false negative results, i.e., 4 patients who had a probable infection according to the EORTC/MSG had a negative result for GM in respiratory samples.

The results of the comparative conventional method diagnostic performance and GM in respiratory samples in the chronic aspergillosis group are presented in Table 6.

Table 6. Diagnostic performances of culture from RT samples and galactomannan in respiratory samples in the group of chronic aspergillosis

Test	**Se(%)**	**Sp(%)**	**PPV(%)**	**NPV(%)**
Culture from RT samples	59.09	100	100	47.06
Galactomannan in RT samples	81.82	0	69.23	0

The GM in the respiratory samples in the cystic fibrosis group was positive in 10 (33.33%) patients. Positive findings for GM were obtained in 3 out of 6 (50%) samples in the probable infections group, according to EORTC/MSG, and 7 out of 24 (29.17%) possible infections, according to these criteria. The concentration of GM in the positive samples ranged from 1.3 to 2.4 pg/ml, with a mean concentration of 1.9±0.4 pg/ml. The GM test of the respiratory samples from the cystic fibrosis patients was characterized with 3 true positive results, 7 false positives, 17 true negatives, and 3 false negatives. The calculated diagnostic performances were: sensitivity 50%, specificity 70.83%, positive predictive value 30% and negative predictive value 85%.

The results of the comparative conventional method diagnostic performance and GM in respiratory samples in the cystic fibrosis group are presented in Table 7.

Table 7. Diagnostic performances of culture from RT samples and GM in respiratory samples in the group of cystic fibrosis

Test	**Se(%)**	**Sp(%)**	**PPV(%)**	**NPV(%)**
Culture from RT samples	59.09	100	100	47.06
Galactomannan in RT samples	50	70.83	30	85

Discussion

Invasive fungal infections present an increasing global burden in immunocompromised and critically ill patients. Early fungi identification is crucial for better clinical outcome. Mycological diagnosis of invasive aspergillosis still presents a significant clinical and laboratory challenge (5).

In our study, respiratory samples culture demonstrated growth of Aspergillus most frequently in the chronic aspergillosis group (63.33%), followed by 56.67% patients with cystic fibrosis, 51.43% patients with primary immune deficiency, and 43.33% patients with prolonged stay in intensive care units (ICUs). The sensitivity and specificity of the respiratory samples culture

were: 64.29% and 100%, 59.09% and 100%, 54.55% and 12.5%, 100% and 54.17%, in all groups respectively. Lower sensitivity than in our study was demonstrated in the study of Tashiro and coworkers, where 165 isolates of Aspergillus species were detected in RT sample culture of 139 patients, of which 45% were colonized with Aspergillus but haven't demonstrated clinical symptoms of aspergillosis. Other patients (55%) had some type of pulmonary aspergillosis, which was classified as chronic aspergillosis (48%), aspergilloma (29%), IA (13%) or ABPA (10%).

Due to conventional model's low sensitivity, we evaluated the GM potential in respiratory samples for diagnosis of aspergillosis. ELISA GM test in respiratory samples in the first group demonstrated sensitivity and specificity of 75% and 57.14%, respectively. Similar results have been demonstrated in the study of Lahmer and colleagues, who registered a 70% sensitivity, and higher specificity of 94%, with BAL GM Platelia assay (11). The negative predictive value of the BAL GM Platelia assay was 90%. In a study by Lahmer involving 49 immunosuppressed and ICU-treated patients, 26% had probable invasive aspergillosis, and a positive BAL galactomannan could be detected in 12 of 13 probable cases.

ELISA GM test in respiratory samples in the second group of ICU-treated patients demonstrated a GM test sensitivity and specificity of 86,36% and 62,5%. Different studies of detection of BAL GM have used different cut-off values (from 0.5–1.0), and have demonstrated sensitivities and specificities of 73%–100%, mainly in hematological patients (12), solid organ transplant recipients (13), and non-immunocompromised patients (14). They demonstrated sensitivity in lung transplant recipients (61%), which is significantly lower than the one in other populations (15). All of these studies demonstrate a high negative predictive value, and similar results were obtained in our study, especially among subjects in the first group (NPV 87.5%), however, they do not provide data for analysis between BAL GM results. An exception to this is the study by Maertens and collaborators (16), who reported results from 10 neutropenic and 19 non-neutropenic patients with proven aspergillosis, and a demonstrated higher sensitivity for the detection of GM in BAL. However, comparison between different studies is very difficult, because of differences in the sampling's timing, and because the effect of antifungal treatment has not been defined. Also, the amount of saline administered during the bronchoscopy procedure is different in different studies (12,13).

The GM ELISA test sensitivity and specificity in respiratory samples in chronic aspergillosis patients were of 81.82% and 0% respectively. The specificity of this test was 0, i.e., all 8 patients from this group who were classified as possible Aspergillus infection, according to EORTC/MSG criteria, had a positive ELISA GM test, therefore they were marked as false positive results. Our study also demonstrated a high sensitivity of the GM test in respiratory samples (81.82%), as has been previously demonstrated by Park Seong and colleagues, who obtained a sensitivity of BAL GM test of 92% (17), which suggests that BAL GM test is an effective test for pulmonary aspergillosis diagnosis. However, it should not be forgotten that the GM antigen test is a method for measuring the cell wall antigen of these fungi, and not a test for determining the invasion by these fungi. Nguyen and coworkers (14) compared the BAL GM performance with the GM serum assay in 4 cases of non-invasive pulmonary aspergillosis and found that the BAL GM assay demonstrated higher sensitivity than the GM serum. They obtained a 100% sensitivity for the BAL GM test at a cutoff ≥1.0 (all patients had BAL GM concentrations above 1.18), high specificity (88.1%), and excellent negative predictive value (100%). However, a limitation of the test was a low positive predictive value of 43%, reflecting the low prevalence of pulmonary aspergillosis in this population. Kono and collaborators demonstrated a 85.7% sensitivity for BAL GM test for the chronic aspergillosis diagnosis and ABPA (18). Park and colleagues found that

the BAL GM test sensitivity was 92%, suggesting that BAL GM test is a more useful method for the pulmonary aspergilloma diagnosis (17).

The ELISA GM test in respiratory samples in the fourth group of our cystic fibrosis patients demonstrated a GM test sensitivity and specificity of 50% and 70.83%. Studies in the literature on utility of galactomannan in respiratory samples suggest that the lungs of CF individuals contain abnormally thick mucus that traps Aspergillus conidia and allows them to germinate in large numbers. As a result, large amounts of antigen are released during its growth, which likely contributes to the development of ABPA (19). Although defects in the anatomic barrier make these patients prone to enhanced colonization of the lungs with these fungi, intact immune cell function likely prevents further invasion by conidia. Despite this, it is still possible to assume that GM concentrations in patients colonized with Aspergillus are intermittent, and may only be positive when there is growth of Aspergillus in BAL or sputum culture. We also believe that galactomannan antigenemia may be more frequently present in patients with more frequent positive BAL or Aspergillus sputum cultures over a longer period of time, in contrast to one or two positive intermittent cultures during the year. In the study performed by Baxter and colleagues, 27% (39/146) of the sputa tested were Aspergillus positive by a standard culture. Over a 6-month period, these tests were repeated in 30 patients. Forty-seven percent (68/146) of the samples tested positive for GM. Over a 6-month period, all positive patients remained positive, and additional five patients who were negative became positive. GM demonstrated good reproducibility in CF sputum and therefore can be used to monitor response to antifungal therapy (20).

Despite the possibility for false positive and false negative detection and despite other available biomarkers, such as β-1,3-glucans or the development of a PCR method, the GM remains an unavoidable and useful biomarker for the IA diagnosis and has led to the recent development of new monoclonal antibodies and the lateral flow assay (LFA)-GM technology (21).

Conclusion

Sensitivity and specificity of galactomannan antigen marker detected by ELISA galactomannan test indicate that detection of galactomannan in respiratory samples could be a valuable tool for early IA diagnosis in immunodeficient and nonneutropenic patients.

Although no single method could provide definite etiological aspergillosis diagnosis, ELISA galactomannan test highlights that confirmation of galactomannan in respiratory samples is useful diagnostic adjunct in the aspergillosis diagnosis.

Application of conventional methods and implementation of fungal biomarker tests, as well as appropriate interpretation of results, in collaboration with clinical doctors, is the most important aspect towards accurate and precise etiological aspergillosis. diagnosis and early start of antifungal treatment, to achieve favorable clinical outcome.

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ORIGINAL ARTICLE *UDK: 616.24-002.7-073.756.8:004*

www.doi.org/10.55302/MJA259428d

INTEGRATIVE RADIOLOGICAL AND CLINICAL ASSESSMENT OF COUGH IN PULMONARY SARCOIDOSIS USING HIGH-RESOLUTION CT IMAGING

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Abstract

Introduction: Sarcoidosis is a systemic inflammatory disease of unknown origin, characterized by the formation of non-caseating granulomas in various organs, most commonly the lungs and lymph nodes. The disease can involve multiple organ systems, leading to a wide range of clinical manifestations. Sarcoidosis is often diagnosed through a combination of clinical presentation, radiological findings, and histopathological evidence of granulomatous inflammation.

The aim of the study is to detect HRCT features of pulmonary sarcoidosis and their correlation with cough.

Material and Methods: In the past two years, fifty patients diagnosed with sarcoidosis were treated at our University Clinic for Pulmonology and Allergology -Skopje. Computed tomography with high resolution was conducted on 128 slice CT scanner PHILIPS INCISIVE, using 1 mm thin-slice thickness and a special reconstruction algorithm.

Results: Cough was present in 80% patients, mostly with low intensity (40%). Micronodular changes (1–3 mm), localized peribronchovascularly in the upper and middle lung zones, were observed significantly less often in patients with cough than in those without cough (10% vs 40%, p=0.041). A statistically significant difference between the cough and no-cough groups was identified in the localization of these changes in the peripheral and subpleural regions (p=0.037). The difference was confirmed between the patients with and without cough in terms of the frequency of hypoattenuation findings in the lower peripheral and subpleural zones.

Conclusion: High-resolution computed tomography (HRCT) is the preferred imaging modality for evaluating pathological changes in pulmonary sarcoidosis. It provides detailed visualization of characteristic findings, such as lymphadenopathy, micronodules, and other lesions, along with their distribution patterns and any atypical changes. Despite its utility, further research is needed to better understand the mechanisms underlying cough in patients with sarcoidosis.

Key words:cough; *HRCT; lungs; sarcoidosis.*

Introduction

Sarcoidosis is a systemic inflammatory disease of unknown etiology that can affect any organ system in the body. The most common manifestations involve the lung parenchyma and mediastinal lymph nodes, which are responsible for the majority of morbidity and mortality associ-

ated with the condition. The diagnosis is based on clinical and radiological findings, along with the demonstration of non-caseating granulomas on histopathological examination.

Imaging plays a crucial role in both the diagnosis and follow-up of patients with sarcoidosis. While chest radiography is frequently used as the initial imaging modality, it has several limitations, including relatively low resolution for detecting parenchymal abnormalities and mediastinal lymphadenopathy. In contrast, computed tomography (CT) is more sensitive in terms of detecting both parenchymal disease and lymphadenopathy (1,2).

High-resolution computed tomography (HRCT) offers superior resolution compared to conventional CT, allowing for the detection and detailed assessment of subtle parenchymal lesions and abnormalities in lung structures (3). HRCT is particularly valuable for distinguishing active inflammation, which represents reversible disease, from irreversible lung damage or fibrosis. This capability aids in prognostication and helps guide therapeutic decisions. Additionally, HRCT is essential for diagnosing sarcoidosis in patients with atypical or unusual radiographic presentations and is considered the gold standard for thoracic imaging (4).

Cough is a prevalent and impactful symptom in sarcoidosis, significantly reducing the patients' quality of life. Objective 24-hour cough monitoring has demonstrated that patients with sarcoidosis experience significantly higher cough frequencies compared to healthy controls, with notable diurnal variation. Cough patterns are gender-specific and show racial differences. Importantly, cough frequency correlates with airway inflammation but is not influenced by the radiographic staging of the disease or the degree of airway obstruction (5).

The aim of the study is to detect HRCT features of pulmonary sarcoidosis and their correlation with cough.

Material and Methods

All patients voluntarily participated in the study after providing written informed consent. The study protocol was approved by the Ethics Committee of the Faculty of Medicine in Skopje and was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki of the World Medical Association for research involving human subjects.

A total of 50 patients with a confirmed diagnosis of sarcoidosis were enrolled over a two-year period at the University Clinic of Pulmonology and Allergology in Skopje. All participants underwent high-resolution computed tomography (HRCT) using a 128-slice PHILIPS INCISIVE CT scanner. Scans were performed with a 1 mm thin-slice protocol and reconstructed using a specialized algorithm optimized for thoracic imaging.

Images were reviewed using standard lung and mediastinal window settings. Lymph nodes were classified anatomically as hilar or mediastinal, with enlargement defined as a maximum short-axis diameter (MSAD) greater than 10 mm.

Pulmonary parenchymal abnormalities were categorized as follows: nodules (micronodules 1–3 mm, macronodules >5 mm), reticular opacities, fibrotic lesions, ground-glass opacities, and confluent consolidations. Nodular distribution was further classified into perilymphatic, centrilobular, and random patterns. The predominant localization of lesions within the upper, middle, or lower lung zones was also recorded.

Results

A total of 50 patients diagnosed with sarcoidosis were included in a statistical analysis. The gender structure of the patients is predominantly made up of female patients – 46 (92%) vs 4 (8%).

The patients were aged between 30 and 73, with an average age of 52.6 ± 12.5 years, and a residing mostly in an urban environment – 42 (84%) vs 8 (16%).

Regarding the smoking status, 8 (16%) patients declared themselves as current smokers, 28(56%) as ex-smokers, with an average smoking experience of 14.9 ± 4.8 years.

In the clinical findings, cough was present in 40 (80%) patients, mostly with low intensity – 20 (40%), while in relation to the character of the cough, dry cough was present in more than 50% of patients – 28(56%).

Correlation of HRCT Features of Sarcoidosis with Cough

The HRCT finding of reticular opacities was not significantly associated with cough (p>0.05).

Patients with cough had a finding of reticular opacities in the upper and middle zones insignificantly less often than patients without cough; and in the lower zones peripherally subpleural (15% vs 40%, p=0.097), and (20% vs 40%, p=0.225), respectively, as well as in the lower zones peribronchovascular (20% vs 40%, p=0.225).

Table 1. Distribution of reticular changes in patients with/without cough

			cough		p-level
			yes n (%)	no n (%)	
Reticular opacities					
Upper and middle zones	Peripheral and subpleural	**yes**	6 (15)	4 (40)	p=0.097
		no	34 (85)	6 (60)	
	Peribronchovascular	**yes**	8 (20)	2 (20)	p=1.0
		no	32 (80)	8 (80)	
Lower lobe zones	Peripheral and subpleural	**yes**	8 (20)	4 (40)	p=0.225
		no	32 (80)	6 (60)	
	Peribronchovascular	**yes**	8 (20)	4 (40)	p=0.225
		no	32 (80)	6 (60)	

p (Fisher's exact test)

Patients with cough had findings of micronodular changes with a size of 1 to 3 mm localized peribronchovascularly in the upper and middle zones (10% vs 40%, p=0.041) significantly less often than patients without cough.

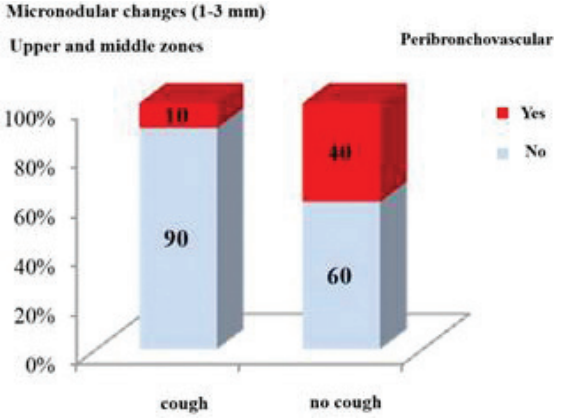
The prevalence of micronodular changes 1 to 3 mm in size in the lower peribronchovascular zones was also less frequent in patients without cough, but without a statistically significant difference (5% vs 20%, p=0.17). In the upper and middle peribronchovascular zones, perilym-

phatic micronodular changes with a size of 1 to 3 mm were seen significantly less often in patients with cough (35% vs 100%, p=0.044). Such changes in the subpleural regions of the lower zones, in the peribronchovascular regions of the upper and middle zones, and in the subpleural regions of the lower zones were seen only in patients with cough, but a statistically significant difference was not manifested between the groups with and without cough (25%, 5%, and 5%, respectively).

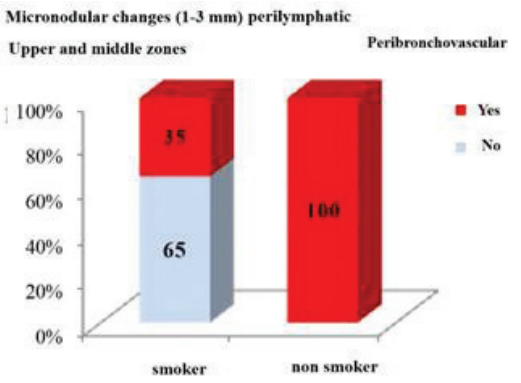
Table 2. Distribution of micron odular changes of 1-3 mm in patients with/without cough

			cough		p-level
			yes n (%)	no n (%)	
Micronodular changes (1-3 мм)					
Upper and middle zones	Centrilobular	**yes**	0	0	
		no	40 (100)	10 (100)	
	Peribronchovascular	**yes**	4 (10)	4 (40)	*p=0.041
		no	36 (90)	6 (60)	
Lower lobe zones	Centrilobular	**yes**	0	0	
		no	40	10	
	Peribronchovascular	**yes**	2 (5)	2 (20)	p=0.17
		no	38 (95)	8 (80)	
Micronodular changes (1-3 мм) perilymphatic					
Upper and middle zones	Peribronchovascular	**yes**	14 (35)	10 (100)	*p=0.044
		no	26 (65)	0	
	Subpleural	**yes**	10 (25)	0	p=0.18
		no	30 (75)	10 (100)	
Lower lobe zones	Peribronchovascular	**yes**	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	
	Subpleural	**yes**	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	

p (Fisher's exact test) *sig p<0.05



Graph-1



Graph-2

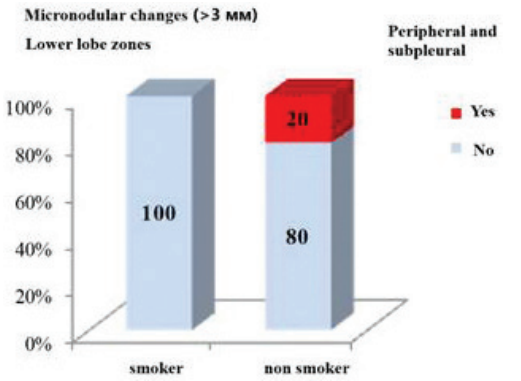
In the groups with and without cough, the representation of patients with findings of micronodular changes greater than 3 mm in the upper and middle lung zones was identical (20%).

In the lower zones, peripheral localization of micronodular shadows larger than 3 mm were detected in 20% of patients without cough, while peribronchovascular localization in 5% of patients with cough. A statistically significant difference between the groups with and without cough was confirmed in the localization of these changes in the peripheral and subpleural regions (p=0.037).

Table 3. Distribution of micronodular changes larger than 1-3 mm in patients with/without cough

			cough		p-level
			yes n (%)	no n (%)	
Micronodular changes (>3 мм)					
Upper and middle zones	Peripheral and subpleural	**yes**	8 (20)	2 (20)	p=1.0
		no	32 (80)	8 (80)	
	Peribronchovascular	**yes**	8 (20)	2 (20)	p=1.0
		no	32 (80)	8 (80)	
Lower lobe zones	Peripheral and subpleural	**yes**	0	2 (20)	*0.037
		no	40 (100)	8 (80)	
	Peribronchovascular	**yes**	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	

p (Fisher's exact test) *sig p<0.05



Graph-3

Localization of opacities seen on HRCT in the central regions of the upper and middle lung zones was significantly less common in patients with cough (5% vs 40%, p=0.011). The remaining localizations of opacities did not differ significantly in patients with and without cough (p>0.055): peripheral and subpleural in the upper and middle zones, and in the lower zones in 5% of patients with cough, central in the lower zones in 25% of patients with cough and 20% of patients without cough. Masses and consolidations in the upper and middle zones with peripheral and subpleural localization were diagnosed in 20% of patients without cough, with a statistically significant difference between the two groups of p=0.037. In 15% of patients with cough and 20% without cough, HRCT showed masses and consolidations in the upper and middle zones centrally, and in the lower zones peripherally and subpleurally, without a statistically significant difference (p=0.65).

Hypoattenuation-type changes were observed in the upper and middle zones only in patients with cough, in the peripheral and subpleural regions in 15%, in the central regions in 20%. For both localizations, the statistical analysis did not confirm a significant difference between the two groups (p>0.05).

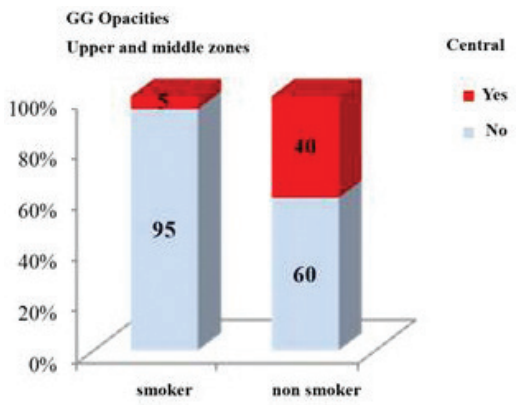
For p=0.041, a statistically significant difference was confirmed between patients with and without cough in terms of the frequency of hypoattenuation findings in the lower peripheral and subpleural zones; such changes were observed significantly less often in patients with cough (10% vs 40%).

Table 4. Distribution of GG opacities, masses and consolidations, and hypoattenuation in patients with/without cough

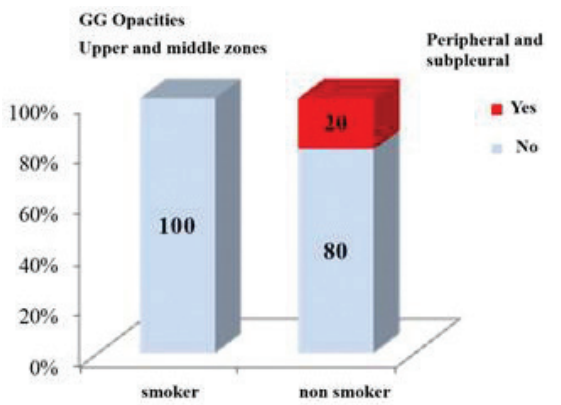
variable			cough		p-level
			yes n (%)	no n (%)	
GG Opacities					
Upper and middle zones	Peripheral and subpleural	**yes**	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	
	Central	**yes**	2 (5)	4 (40)	*p=0.011
		no	38 (95)	6 (60)	
Lower lobe zones	Peripheral and subpleural	**yes**	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	
	Central	**yes**	10 (25)	2 (20)	p=1.0
		no	30 (75)	8 (80)	
Masses and consolidations					
Upper and middle zones	Peripheral and subpleural	**yes**	0	2 (20)	*p=0.037
		no	40 (100)	8 (80)	
	Central	**yes**	6 (15)	2 (20)	p=0.65
		no	34 (85)	8 (80)	
Lower lobe zones	Peripheral and subpleural	**yes**	6 (15)	2 (20)	p=0.65
		no	34 (85)	8 (80)	
	Central	**yes**	0	0	
		no	40 (100)	10 (100)	

Hypoattenuation					
Upper and middle zones	Peripheral and sub-pleural	**yes**	6 (15)	0	p=0.33
		no	34 (85)	10 (100)	
	Central	**yes**	8 (20)	0	p=0.18
		no	32 (80)	10 (100)	
Lower lobe zones	Peripheral and sub-pleural	**yes**	4 (10)	4 (40)	*=0.041
		no	36 (90)	6 (60)	
	Central	**yes**	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	

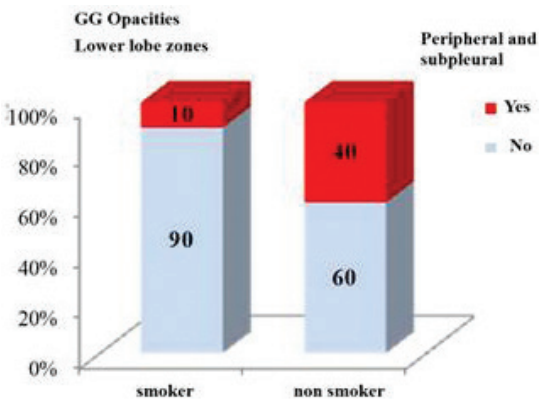
p (Fisher's exact test) *sig p<0.05



Graph-4



Graph-5



Graph-6

The finding of lymphadenopathy was not a significantly different HRCT sign in patients with and without cough. In both groups, bilateral hilar lymphadenopathy was more frequently detected (65% and 80%, patients with and without cough, respectively) and right paratracheal lymphadenopathy (80% of patients in both groups), and conglomerated lymphadenopathy was less frequently seen (20% of patients in both groups).

Calcified nodules were detected only in patients with cough: large focal calcifications in 30%, punctiform in 5%, and scaly in 5%.

Pneumocystis was slightly less common in patients with cough (20% vs 40%, p=0.225) though not significantly, traction bronchiectasis slightly less common in patients with cough (25% vs 40%, p=0.47) though not significantly, fibrosis was slightly less common in patients with cough (30% vs 40%, p=0.71) though not significantly, while honeycomb lung tended to be more common in patients with cough (5% vs 0%, p=1.0), though not significantly.

Table 5. Distribution of lymphadenopathy, calcified lymph nodes, additional findings in patients with/without cough

variable			cough		p-level
			yes n (%)	no n (%)	
Lymphadenopathy	Bilateral Hilar	yes	26 (65)	8 (80)	p=0.47
		no	14 (35)	2 (20)	
	Right paratracheal	yes	32 (80)	8 (80)	p=1.0
		no	8 (20)	2 (20)	
	Others nodal stations	yes	28 (70)	8 (80)	p=0.7
		no	12 (30)	2 (20)	
	Conglomerate lymph nodes	yes	8 (20)	2 (20)	p=1.0
		no	32 (80)	8 (80)	
Calcified Lymph nodes	Focal lymph nodes	yes	12 (30)	0	p=0.09
		no	28 (70)	10 (100)	
	Punctiform lymph nodes	yes	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	
	Egg-shell lymph nodes	yes	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	
Presence of additional finding	Pneumocystis / bullae	yes	8 (20)	4 (40)	p=0.225
		no	32 (80)	6 (60)	
	Traction bronchiectasis	yes	10 (25)	4 (40)	p=0.47
		no	30 (75)	6 (60)	
	Fibrosis	yes	12 (30)	4 (40)	p=0.71
		no	28 (70)	6 (60)	
	Honeycombing	yes	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	

Discussion

Sarcoidosis is a multisystem inflammatory disease of unknown etiology, characterized by the formation of non-caseating granulomas in affected organs. Among its various clinical manifestations, cough is a frequent and significant symptom that can substantially impair the patients' quality of life.

Although the precise mechanisms underlying cough in sarcoidosis remain unclear, current evidence suggests that extensive hilar and mediastinal lymphadenopathy, as well as interstitial lung infiltration, are not solely responsible for its occurrence (6). In our study, neither lymphadenopathy nor reticular opacities were found to be statistically associated with the presence of cough, indicating that other pathological processes may be more relevant.

Recent findings have underscored the predominantly bronchocentric nature of sarcoidosis, wherein granulomatous inflammation targets the airways, potentially contributing to cough. Proposed mechanisms include airway inflammation, mechanical distortion secondary to pulmonary fibrosis, and involvement of the vagus nerve due to compressive effects from enlarged mediastinal lymph nodes (7).

In addition, rare and atypical presentations of sarcoidosis may also provoke cough. These include granulomatous infiltration of the pulmonary veins leading to pulmonary veno-occlusive disease with consequent airway epithelial engorgement, as well as sarcoid involvement of the vagus nerve at the level of the jugular foramen, resulting in vocal cord paralysis and chronic cough (8,9).

In our study, cough was present in 80% of patients, with the majority (40%) reporting symptoms of low intensity. Patients with cough were significantly less likely to exhibit micronodular changes measuring 1–3 mm localized in the peribronchovascular regions of the upper and middle lung zones, compared to those without cough (10% vs. 40%, $p = 0.041$). A statistically significant difference was also observed in the localization of these changes to the peripheral and subpleural regions between the two groups ($p = 0.037$).

Furthermore, a significant difference was identified in the frequency of hypoattenuation findings in the lower peripheral and subpleural zones between patients with and without cough. However, the prevalence of micronodular changes larger than 3 mm in the upper and middle lung zones was identical in both groups (20%). In the lower lung zones, peripheral micronodular shadows larger than 3 mm were detected in 20% of patients without cough, whereas peribronchovascular localization was observed in only 5% of patients with cough.

Lymphadenopathy was not a symptom of a significant statistical difference between patients with and without cough on HRCT. Notably, calcified nodules were detected exclusively in patients with cough. Findings indicative of hypoattenuation, such as pneumoceles, traction bronchiectasis, and honeycombing, were more frequent in patients with cough but did not reach statistical significance.

Hilar and mediastinal lymph node involvement is observed in 50–90% of patients with sarcoidosis (10). Perilymphatic micronodules, a hallmark radiological feature of the disease, are present in over 90% of patients and typically appear symmetrically in the upper and middle lung zones (11–13). These nodules are characteristically well-defined and bilaterally distributed, with predominant involvement of the peribronchovascular interstitium, interlobular septa, and subpleural areas—regions aligned with the pulmonary lymphatic system. Over time, these micronodules may evolve into larger nodular formations. Radiological findings in sarcoidosis can overlap with those of several other diseases, complicating differential diagnosis. Hilar and mediastinal lymphadenopathy, a hallmark feature of sarcoidosis, may also be observed in conditions such as lymphoma, fungal infections, tuberculosis, and certain types of primary lung carcinoma. However, the presence of bilateral hilar and mediastinal lymphadenopathy, particularly in the absence of systemic symptoms typically associated with malignancy or infection—such as unexplained weight loss or persistent fever—strongly favors a diagnosis of sarcoidosis.

The differential diagnosis of perilymphatic nodular distribution on high-resolution computed tomography (HRCT) includes silicosis, coal workers' pneumoconiosis, and lymphangitic carcinomatosis. In sarcoidosis, micronodules are typically well-defined and characteristically distributed along the peribronchovascular interstitium, subpleural regions, and interlobar fissures. In contrast, nodules observed in silicosis and pneumoconiosis are often accompanied by fibrotic changes, and lymph nodes may exhibit coarse or "eggshell" calcification. In such cases, a detailed occupational history is crucial for accurate diagnosis.

In malignant lymphangitic spread, nodules are typically finer and associated with smooth or irregular thickening of the interlobular septa, often lacking the sharply defined and symmetrical distribution seen in sarcoidosis (14).

Conclusion

Pulmonary sarcoidosis demonstrates spontaneous remission in approximately 50% of cases within the first two years, with additional cases resolving over a period of five years. However, in an estimated 20% of patients, the disease follows a progressive and chronic course, often leading to pulmonary fibrosis and significant functional impairment. This progression is associated with a mortality rate of approximately 5%, highlighting the critical need for timely and accurate diagnosis.

High-resolution computed tomography (HRCT) is the imaging modality of choice for assessing pulmonary involvement in sarcoidosis. Given the disease's broad spectrum of radiological manifestations, HRCT plays a vital role in diagnosis and disease monitoring, despite the interpretive challenges it presents. It provides detailed visualization of characteristic features, including lymphadenopathy, perilymphatic micronodules, and other parenchymal abnormalities, along with their distribution patterns and any atypical findings.

HRCT is also essential in guiding treatment strategies by differentiating active granulomatous inflammation from irreversible fibrotic changes. A comprehensive understanding of these imaging features, integrated with clinical symptomatology, enables radiologists to contribute to a more specific and accurate diagnosis of sarcoidosis. Cough is a prevalent and clinically significant symptom in patients with sarcoidosis, often contributing to a substantial reduction in the quality of life. While objective assessments of pulmonary function are essential in evaluating disease severity and treatment response, the subjective burden of cough should also be systematically assessed. The pathophysiology of cough in sarcoidosis is likely multifactorial, with proposed mechanisms including airway hyperresponsiveness, involvement of the upper respiratory tract, cough reflex hypersensitivity, and parenchymal fibrosis. Despite its impact, there are currently no disease-specific guidelines for the management of cough in sarcoidosis. Further clinical and translational research is needed to elucidate the underlying mechanisms and to guide the development of targeted therapeutic strategies.(5)

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ORIGINAL ARTICLE *UDK: 616-001-036-083.98*

www.doi.org/10.55302/MJA259439b

FAST GUIDED INITIAL TRIAGE OF POLYTRAUMA PATIENTS: A PROSPECTIVE EVALUATION OF DIAGNOSTIC TIMELINES

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Abstract

Background: Polytrauma remains a leading cause of mortality worldwide. Rapid triage and timely diagnostic evaluation are essential for improving survival outcomes. Computed tomography (CT) remains the gold standard imaging modality, but logistical limitations often delay diagnosis in resource-limited settings. Focused Assessment with Sonography for Trauma (FAST) enables rapid bedside evaluation and early detection of life-threatening injuries. The objective of this study was to evaluate the impact of FAST on triage timing, diagnostic efficiency, and early management of polytrauma patients.

Material and methods: This prospective study included 40 patients assessed with FAST upon admission. Evaluated variables included demographics, mechanism of injury, FAST duration, diagnostic timings, intervention times, accuracy, ICU admission, complications, and mortality. FAST was performed at five standard anatomical views by a single trained physician. Statistical analysis included descriptive methods and Wilcoxon testing.

Results: Mean FAST duration was 5.12 minutes. FAST did not delay CT imaging nor the total diagnostic process ($p > 0.05$). Accuracy was 92.5% for thoracic trauma and 85% for abdominal trauma. Surgical interventions were required in 42.5% of cases; while the median time to surgery was 2.42 hours. ICU admission was recorded in 55% of patients, and mortality reached 22.5%.

Conclusion: FAST significantly optimized early trauma triage without delaying CT or treatment. Its speed, accuracy, and bedside availability make FAST indispensable in emergency trauma care. The method is particularly beneficial in resource-limited environments. FAST should be integrated as a mandatory component of initial trauma protocols.

Key words: *Diagnostic technologies; Focused Assessment with Sonography for Trauma; Polytrauma patients; Triage.*

Introduction

Polytrauma is a major global health challenge and one of the leading causes of death in patients under 45 years of age (1). The "golden hour" concept emphasizes the urgency of rapid diagnosis and intervention to reduce mortality (2,3). Computed tomography (CT) is the diagnostic gold

standard for trauma assessment due to its precision, but it requires patient transport and radiology resources that may not be immediately available, especially in unstable patients (4,5).

Focused Assessment with Sonography for Trauma (FAST) has emerged as a pivotal bedside diagnostic tool for early identification of hemoperitoneum, hemothorax, pneumothorax, and pericardial effusion (6–9,). It is fast, safe, repeatable, and can be performed within minutes during the primary survey. Its utility is particularly pronounced in systems with limited access to CT imaging.

The aim of this study was to evaluate the duration of initial triage and early management of polytrauma patients using the FAST protocol and to assess its diagnostic value and impact on clinical outcomes.

Material and methods

Study Design and Ethical Considerations

This study was designed as a prospective longitudinal clinical evaluation conducted at the Emergency Center within the University Clinic for Traumatology, Orthopedic Diseases, Anesthesiology, Reanimation, Intensive Care and Emergency Center, "Ss. Cyril and Methodius" University in Skopje. Prior to initiation, the study protocol received ethical approval from the Clinical Research Ethics Committee of the University. Informed consent was obtained from all participants or, when necessary, from legally authorized representatives, with full explanation of the voluntary nature of participation and the right to withdraw without consequences at any time.

Study Population and Eligibility Criteria

The study population consisted of consecutive polytrauma patients admitted to the Emergency Surgical Department. Inclusion criteria were: age ≥ 18 years, admission for polytrauma, and performance of FAST as part of the initial trauma evaluation. Pregnant patients, as well as patients requiring immediate transfer to the operating theater or intensive care unit without the possibility of performing FAST, were excluded.

Initial Patient Assessment and Data Collection

Upon arrival, all patients underwent standardized trauma evaluation following the established A–E protocol (Airway, Breathing, Circulation, Disability, Exposure). Demographic data (age, sex, BMI), mechanism of injury, initial hemodynamic status, and Glasgow Coma Scale (GCS) scores were recorded. Additional clinical variables included the presence of free intraperitoneal or intrathoracic fluid, pneumothorax, thoracic effusions, required interventions, and length of hospitalization.

FAST Protocol

FAST was performed immediately upon admission, at the bedside, and integrated into the primary trauma survey. To minimize operator variability, all FAST examinations were conducted by a single experienced physician trained in emergency ultrasonography. The protocol included visualization of five anatomical regions: the right upper quadrant, the left upper quadrant, the suprapubic region, the subxiphoid cardiac view, and bilateral thoracic views. Time intervals

recorded included arrival-to-triage, triage-to-FAST, FAST-to-completion of diagnostics, and arrival-to-intervention.

Outcome Measures

Primary outcomes included diagnostic timing and time to intervention. Secondary outcomes included FAST accuracy, required interventions, ICU admission rates, complications, and mortality.

Statistical Analysis

The statistical analysis was conducted using STATISTICA version 10 and IBM SPSS 20.0. Descriptive methods assessed proportions, means, medians, and dispersion. Continuous variables were analyzed using Student's t-test or Mann–Whitney U test depending on normality (Shapiro–Wilk). Categorical variables were analyzed with Chi-square or Fisher's exact test. Correlations were explored using Pearson and Spearman coefficients. Multivariable comparisons used ANOVA with Tukey HSD. Significance was set at $p < 0.05$, and results were presented in tables and graphs.

Results

The study included 40 patients, 90% male and 10% female, with a mean age of 40.62 years. The hemodynamic parameters of the cohort are presented in table 1.

Table 1. Hemodynamic parameters (n=40)

Variable	Mean (Median) ± SD	Range
Heart rate (bpm)	107.25 (100) ± 19.44	75–165
Systolic BP (mmHg)	127.25 (130) ± 29.56	67–239
Diastolic BP (mmHg)	80.17 (81.5) ± 19.39	45–115
Mean arterial pressure (mmHg)	95.72 (100) ± 21.7	53–152
SaO_2 (%)	93.0 (93.5) ± 5.09	73–99

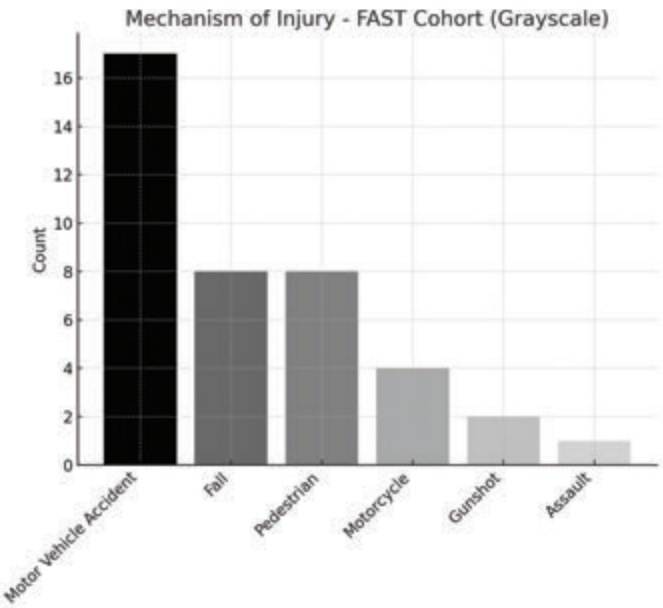
Comprehensive laboratory assessments, including hematological and biochemical markers, are presented in Table 2.

Table 2. Initial Laboratory Findings (n=40)

Variable	Mean (Median) ± SD	Range
Hemoglobin (g/L)	117.67 (124) ± 25.29	73–152
Hematocrit (L/L)	0.35 (0.36) ± 0.09	0.19–0.51
Erythrocytes ($\times 10^{12}$/L)	3.92 (3.94) ± 0.98	2.2–5.7
Platelets ($\times 10^{9}$/L)	248.93 (218) ± 93.75	94–419
Leukocytes ($\times 10^{9}$/L)	15.01 (15) ± 5.96	6.4–31
CRP (mg/L)	10.96 (5.2) ± 12.33	0.2–40

Variable	Mean (Median) ± SD	Range
Glucose (mmol/L)	7.47 (7.05) ± 2.43	3.5–13
LDH (U/L)	427.8 (426.5) ± 121.61	250–665
ALP (U/L)	66.58 (64.5) ± 31.23	22–162
AST (U/L)	87.65 (58.5) ± 66.31	16–237
ALT (U/L)	73.55 (44.5) ± 64.09	20–250
Creatinine (µmol/L)	91.05 (88) ± 26.69	55–184
Urea (mmol/L)	6.27 (6.0) ± 1.83	3.7–10.5
Sodium (mmol/L)	139.18 (139) ± 3.6	130–149
Potassium (mmol/L)	3.79 (3.9) ± 0.48	2.5–4.7
Calcium (mmol/L)	2.05 (2.1) ± 0.22	1.5–2.4
Chloride (mmol/L)	104.55 (105) ± 4.14	94–111

Mechanisms of injury included motor vehicle accidents (42.5%), falls (20%), pedestrian collisions (20%), motorcycle accidents (10%), gunshot wounds (5%), and assaults (2.5%).



Graph 1. Mechanisms of injury

Mean FAST duration was 5.12 minutes. FAST did not delay the total diagnostic process (p = 0.67). Classification of trauma by anatomical region is presented in table 3. Diagnostic accuracy of FAST, reached 92.5% for thoracic trauma and 85% for abdominal trauma, with FAST–CT concordance of 97.5%, presented in table 4.

Table 3. Classification of Trauma by Anatomical Region (n=40)

Type of Trauma	n	%
Thoracic injuries	32	80%
Locomotor system injuries	34	85%

Type of Trauma	n	%
Abdominal trauma	12	30%
Head injuries	12	30%

Table 4. FAST Diagnostic Accuracy (n=40)

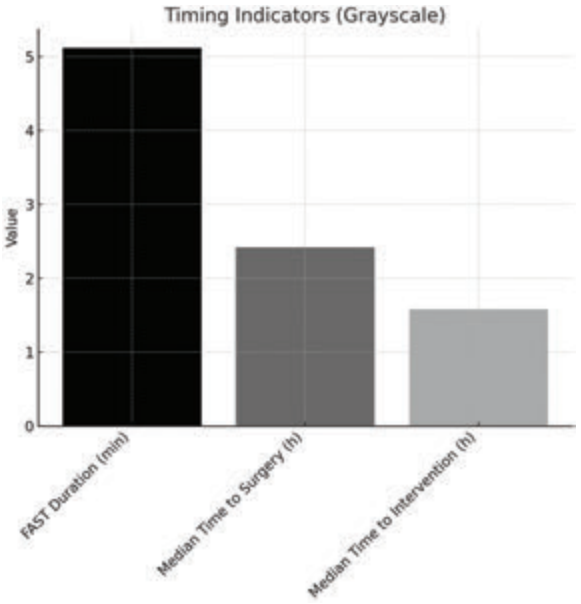
Trauma Type	Accuracy (%)
Thoracic Trauma	92.5
Abdominal Trauma	85.0

Seventeen patients (42.5%) necessitated surgical intervention. The majority of procedures pertained to the locomotor system (n = 9, 22.5%), followed by abdominal surgery (n = 4, 10%) and combined thoracoabdominal interventions (n = 3, 7.5%). Furthermore, one patient (2.5%) received urological surgery.

The duration between admission and surgical intervention demonstrated significant variability. The mean time to surgery was 7.86 hours, with a median of 2.42 hours (range: 1–90.6 hours; SD: 21.37), indicating variability in injury severity and the urgency of necessary interventions.

Non-operative invasive procedures were also commonly conducted. A total of 14 patients (35%) received these therapies. The predominant procedure was unilateral thoracic drainage (n = 15, 37.5%), whereas bilateral thoracic drainage was necessitated in seven individuals (17.5%). Supplementary procedures comprised thoracic drainage with immobilization (n = 1, 2.5%) and nasal tamponade for the management of epistaxis (n = 3, 7.5%).

The timing of these non-surgical therapies was timely and consistent. The average duration from admission to the initial invasive operation was 1.57 hours (median: 1.58 hours; range: 0.87–2.52 hours; standard deviation: 0.41), highlighting the importance of prompt ultrasonographic evaluation in accelerating treatment decisions and prioritizing urgent interventions.



Graph 2. Diagnostic and Intervention Timing Metrics

The cohort exhibited a mean hospitalization duration of 16.82 days (median: 13.5 days; range: 1–53 days; SD: 12.85). This diversity indicates disparities in injury complexity, necessary post-operative care, and clinical recovery pathways.

Discussion

The findings of our inquiry validate previously published data, strengthening existing evidence. The results demonstrated that the male demographic is more often affected by trauma. Literature indicates that trauma primarily affects the male population and younger age groups. The mean age of the patients in our study was 40. This corresponds with previous research suggesting that men are more often subjected to trauma, primarily due to their participation in outdoor activities, vehicular accidents, and other traumas, since fewer women experience accidental traumatic injuries. The higher incidence of younger participants is ascribed to their increased outdoor exercise relative to older adults (10,11).

Despite the significant benefits of FAST, physicians must be aware of its limitations. A negative FAST examination cannot conclusively rule out minor or progressive injuries, particularly those involving hollow organs, retroperitoneal structures, or modest fluid collection. Thus, professional judgment and ongoing evaluations are essential components of trauma management. Literature outlines situations in which FAST may fail to accurately detect certain injuries, such as cases of little hemorrhage, poor acoustic windows, subcutaneous emphysema, obesity, or limited patient mobility (12-15). Technical factors, including probe frequency, resolution, sonographer proficiency, and anatomical variability, may also influence image quality.

The study's findings reveal that specific critically injured patients cannot safely undergo advanced imaging due to hemodynamic instability or time limitations. For these patients, rapid FAST assessment allows physicians to swiftly commence life-saving surgical or procedural procedures, avoiding delays linked to extensive diagnostic imaging. Prompt recognition of intra-abdominal bleeding or thoracic complications is crucial, since timely care greatly affects survival and long-term outcomes.

Time is essential in reducing mortality in these individuals; therefore, it is vital to quickly identify trauma and determine the need for intervention as rapidly as possible. The first sixty minutes following trauma are termed the "golden hour" because of their critical importance in providing timely and suitable medical intervention, hence improving survival rates and reducing the likelihood of long-term complications. To provide timely and effective treatment during this period, rapid assessment, diagnosis, and stabilization are essential (3,16-19). Our study is deficient in data about the duration of the prehospital period owing to numerous affecting factors. The variability of medical history, lack of information due to inadequate victim support, distance to tertiary healthcare, and inter-facility transfers are potential variables.

FAST has become an essential tool in trauma evaluation due to its rapid bedside application. In contrast to traditional imaging methods that require patient transfer, external personnel, and logistical preparations, FAST can be performed immediately upon arrival in the emergency room. This capability is especially beneficial in resource-limited settings, where imaging delays might significantly impact outcomes. FAST enables swift identification of patients requiring immediate care and aids in guiding resuscitation, prioritizing triage, and continuous assessment.

The results of our study demonstrated that the FAST technique neither prolonged the length of stay in the Emergency Surgical Center nor delayed the conclusive diagnosis via CT in trauma patients. The average time of the FAST examination was 5.12 minutes (median 5.08; range 3.92–6.7; SD 0.71). The time to final diagnosis via CT was statistically negligible ($p < 0.05$), suggesting that the use of the FAST technique did not prolong or potentially delay definitive diagnosis and treatment. These results correspond with those documented in the literature (20,21). The mortality rate in our cohort was 22.5 percent.

This study demonstrated that FAST demonstrated a high diagnostic accuracy for traumatic injuries, particularly in thoracic trauma, attaining an accuracy of 92.5%. The identification of abdominal injuries demonstrated a somewhat diminished accuracy of 85%, consistent with earlier published studies (20,22-25). Literature indicates that repeated FAST examinations—one of its primary advantages—can improve diagnostic accuracy to nearly 100%, especially when serial evaluations are performed under continuous hemodynamic monitoring.

A positive FAST scan result requires immediate reporting and intervention, owing to its significant positive predictive value and high specificity. It is prudent to thoroughly assess the suitable course of action, taking into account the method's sensitivity and the incidence of false negatives in 25% of the results (9,20-22). Literature reveals that the sensitivity of the FAST approach varies from 85% to 96%, but its specificity surpasses 98% (20). In trauma patients, the diagnosis demonstrates 100% sensitivity (21, 26). This diagnostic procedure, when performed by proficient clinicians, is accomplished in less than 5 minutes (21). FAST is especially beneficial in healthcare systems with limited resources where access to CT scans may be postponed.

The median duration to surgical intervention (2.42 hours) indicates effective triage enabled by FAST results. Evidence suggests that decreasing time-to-intervention markedly reduces mortality rates (3,25-28). FAST is contingent upon the operator and may overlook injuries that do not result in free fluid. Frequent FAST exams can enhance sensitivity.

Despite these limitations, global statistics consistently validate FAST as a crucial diagnostic tool in trauma care (29,30). The speed, availability, and ability for immediate repetition make it very beneficial for unstable patients. In resource-limited trauma environments, FAST often serves as the primary imaging technique guiding first treatment decisions. The findings of this study align with international experiences, highlighting the importance of FAST in identifying patients requiring urgent intervention, monitoring those at risk of decline, and enabling swift triage decisions (31).

However, the execution of FAST in resource-limited healthcare institutions has specific obstacles. Ensuring ongoing availability of functional ultrasound equipment, preserving high-quality probes, and providing enough training for technicians and doctors are essential. Limited access to formal ultrasound education may hinder wider adoption, underscoring the need for structured training programs and ongoing professional development. Moreover, integrating FAST into emergency procedures requires careful organization. Although FAST can be performed swiftly at the patient's bedside, problems like overcrowding, insufficient workspace, and suboptimal patient flow may impede its effectiveness. Optimal diagnostic efficacy requires proper equipment positioning, explicit protocols, and cohesive collaboration among trauma teams.

The time needed for completing diagnosis and therapy was the main motivation for conducting this research and integrating it into trauma procedures. This assessment, classified as a "point-

of-care" evaluation performed at the patient's bedside, requires no expensive equipment and is easily replicable. FAST evaluation is integrated into trauma protocols worldwide (2,5–7,26,27).

Conclusion

FAST represents a fundamental component of the initial trauma evaluation. Its rapidity, diagnostic accuracy, and non-invasive nature enable timely decision-making without impeding subsequent CT imaging or definitive management. Owing to these advantages, FAST should remain an integral element of early trauma protocols, particularly in resource-limited environments where efficient triage is essential.

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ORIGINAL ARTICLE *UDK: 616.24-002.7-073.756.8:004"2022/2023"*

www.doi.org/10.55302/MJA259449d

HIGH RESOLUTION CT TYPICAL PATTERNS IN PULMONARY SARCOIDOSIS: CORRELATION WITH CLINICAL SYMPTOMS AND RADIOLOGICAL STAGING

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Abstract

Introduction: Sarcoidosis is a multisystemic and often chronic disease that can involve nearly any organ. The lungs and intrathoracic lymph nodes are the most commonly affected structures.

The aim: of the study is to classify the stages of sarcoidosis and analyze their correlation with clinical symptoms.

Material and Methods: A total of 50 patients with sarcoidosis came to our University Clinic for Pulmonology and Allergology-Skopje during 2022-2023 period - a retrospective observational study. A high-resolution computed tomography (HRCT) using a 128-slice PHILIPS INCISIVE CT scanner was performed to all patients, using a 1 mm thin-slice protocol optimized for thoracic imaging. Disease staging was conducted according to the Scadding Score System. Clinical symptoms such as smoking, dyspnea and cough were identified from the MOJ TERMIN medical records and compared with the stage of the disease.

Results: The disease stage did not significantly correlate with the patients' sex and age, but it did significantly correlate with their place of residence. There was a statistically significant difference in the distribution of former smokers across disease stages, driven by the significantly higher proportion of former smokers in stage III compared to stage II. The disease stage had a significant impact on patient hospitalization. The disease stage had a significant impact on the presence of reticular opacities in the upper and middle zones.

Key words: *HRCT; lungs; sarcoidosis; staging; symptoms.*

Introduction

Sarcoidosis is a systemic inflammatory disease of unknown etiology, characterized by the formation of non-caseating granulomas in various organs, most commonly the lungs and intrathoracic lymph nodes. The disease may affect multiple organ systems, resulting in a broad spectrum of clinical manifestations. Diagnosis is typically established through a combination of clinical manifestation, radiologic findings, and histopathological confirmation of granulomatous inflammation.

Imaging plays a central role in both the diagnosis and monitoring of sarcoidosis. While chest radiography is often the first-line imaging modality, it has notable limitations-particularly its lower sensitivity for detecting parenchymal changes and mediastinal lymphadenopathy. In con-

trast, computed tomography (CT) provides greater sensitivity in identifying both pulmonary and nodal involvement (1,2).

High-resolution computed tomography (HRCT) offers even higher spatial resolution than standard CT, allowing for detailed visualization of subtle parenchymal abnormalities and fine structural changes within the lungs (3). HRCT is especially useful in differentiating active inflammatory lesions—representing potentially reversible disease—from irreversible fibrotic changes. This distinction is critical for prognosis and therapeutic decision-making. Moreover, HRCT is invaluable in evaluating atypical or ambiguous radiographic findings and is widely regarded as the gold standard for thoracic imaging in sarcoidosis (4).

This study aims to classify the stages of sarcoidosis and analyze their correlation with clinical symptoms

Material and Methods: A total of 50 patients who came to our hospital with a confirmed diagnosis of sarcoidosis were enrolled over a two-year period at the University Clinic for Pulmonology and Allergology in Skopje- a retrospective observational study. Patients, who have previously signed an informed consent, participated in the study voluntarily. The study was conducted with the consent of the Ethics Commission of the Faculty of Medicine in Skopje and was in accordance with the ethical principles of the Declaration of Helsinki of the World Medical Association for medical research involving human subjects.

A high-resolution computed tomography (HRCT) using a 128-slice PHILIPS INCISIVE CT scanner were performed to all patients, using a 1 mm thin-slice protocol and specialized reconstruction algorithm optimized for thoracic imaging. HRCT images were assessed using standard lung and mediastinal window settings. Lymph nodes were anatomically classified as hilar or mediastinal, and enlargement was defined as a maximum short-axis diameter (MSAD) greater than 10 mm. Disease staging was conducted according to the Scadding Score System: stage 0 – normal; stage I – hilar or mediastinal lymph node enlargement; stage II – lymphadenopathy with parenchymal involvement; stage III – parenchymal disease without nodal enlargement; and stage IV – advanced fibrotic changes indicating end-stage pulmonary disease. Pulmonary parenchymal abnormalities were categorized as nodules (micronodules: 1–3 mm; macronodules: >5 mm), reticular opacities, fibrotic lesions, ground-glass opacities, and confluent consolidations. Nodular distribution was further classified into perilymphatic, centrilobular, and random patterns. Additionally, the predominant localization of pulmonary lesions was documented according to lung zones: upper, middle, or lower. Clinical symptoms such as smoking, dyspnea and cough were identified from the MOJ TERMIN medical records and compared with the stage of the disease.

Results

The statistical analysis of the data obtained from the study was performed using the statistical software SPSS version 23.0.

Categorical (attribute) variables are presented using absolute and relative frequencies. Numerical (quantitative) variables are presented with the mean, standard deviation, minimum, and maximum values.

We used Fisher's exact test to compare the HRCT findings between smokers and non-smokers, patients with and without cough, and among different disease stages.

Statistical significance was defined at a level of $p<0.05$.

The relevant data are presented in tables and graphs.

The disease stage did not significantly correlate with the patients' sex and age ($p = 1.0$ and $p = 0.55$), but it did significantly correlate with their place of residence ($p = 0.023$). All patients in stages III and IV were from urban areas.

Current smokers did not have a significantly different distribution across the four disease stages (16.67% in stage II vs 22.22% in stage IV; $p = 0.81$). However, there was a statistically significant difference in the distribution of former smokers across disease stages ($p = 0.014$), driven by the significantly higher proportion of former smokers in stage III compared to stage II (100% vs. 25%; $p = 0.01$). A statistically significant difference in the frequency of dyspnea was confirmed between patients in stages 1 and 4 ($p = 0.026$).

The disease stage had a significant impact on patient hospitalization ($p < 0.0001$). Pairwise group comparisons showed significant differences between stages I and IV (9.09% vs. 75%, $p = 0.014$), and between stages II and IV (50% vs. 75%, $p = 0.0001$).

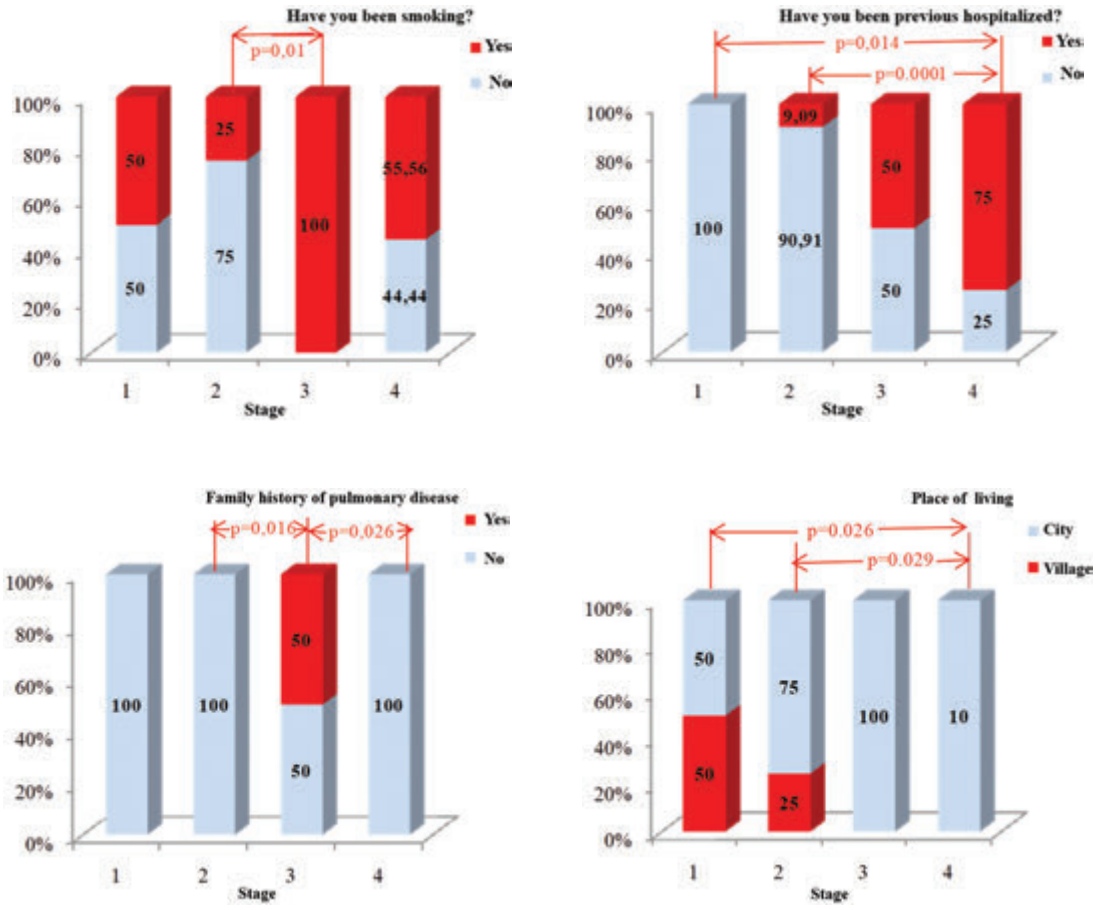
Only 2 out of 4 patients in stage III (50%) had a positive family history of pulmonary disease.

Table 1: Gender Distribution, Residence, Smoking Status, Hospitalizations, and Genetic Predisposition by Sarcoidosis Stage

variable		Stage				p-level
		1 n=4 (%)	**2 n=24 (%)**	**3 n=4 (%)**	**4 n=18 (%)**	
Gender	female	4(100)	22(91.67)	4(100)	16(88.89)	p=1.0
	male	0	2(8.33)	0	2(11.11)	
Place of living	city	2(50)	18(75)	4(100)	18(100)	*p=0.023 1 vs 4 p=0.026 2 vs 4 p=0.029
	village	2(50)	6(25)	0	0	
Do you smoke?	yes	0	4(16.67)	0	4(22.22)	**p=0.81**
	no	4(100)	20(83.33)	4(100)	14(77.78)	
Have you been smoking?	yes	2(50)	6(25)	4(100)	10(55.56)	*p=0.014 2 vs 3 p=0.01
	no	2(50)	18(75)	0	8(44.44)	
Have you been previous hospitalized?	yes	0	2(9.09)	2(50)	12(75)	***p=0.000 1 vs 4 p=0.014 2 vs 4 p=0.0001
	no	4(100)	20(90.91)	2(50)	4(25)	
Family history of pulmonary disease	yes	0	0	2(50	0	**p=0.01 2 vs 3 p=0.016 3 vs 4 p=0.026
	no	4(100)	24(100)	2(50)	18(100)	

p (Fisher's exact test)

*sig p<0.05, **sig p<0.01, ***sig p<0.0001



The stage of the disease was not significantly associated with cough presence or cough intensity ($p = 0.71$); all patients in stages 1 and 3 had cough, as did 75% of patients in stage 2 and 77.78% in stage 4.

Regarding the distribution of patients by stage and cough intensity: mild cough was present in patients across all stages, most commonly in stage 1 (100%). Severe cough occurred only in stage 4 patients (28.57%). There was no statistically significant difference in the distribution of mild, moderate, and severe cough among disease stages ($p = 0.06$).

Shortness of breath was reported by 50% of patients in stage 1, 58.33% in stage 2, and by all patients in stages 3 and 4. A statistically significant difference in the frequency of dyspnea was confirmed between patients in stages 1 and 4 ($p = 0.026$).

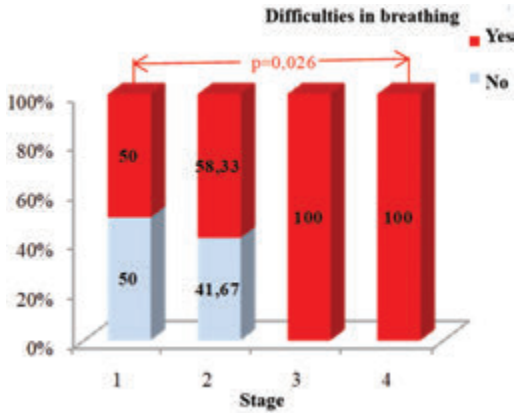
Results from the MRC (Medical Research Council) scale differed significantly across disease stages ($p < 0.0001$):

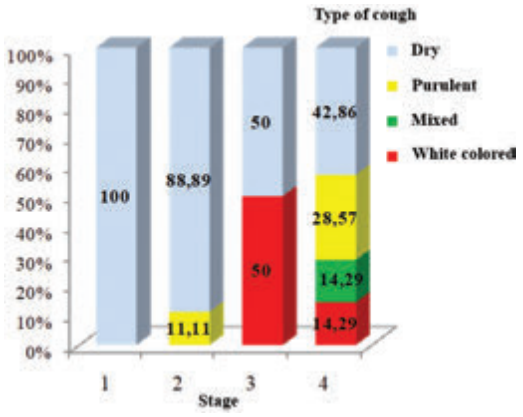
- All stage 1 patients scored MRC 0 (dyspnea only during strenuous exercise);
- Most stage 2 patients had MRC 1 (dyspnea when walking fast on flat ground or climbing a slight hill); this score was also seen in all stage 3 patients;
- Stage 4 patients frequently had MRC 1 and MRC 2 (dyspnea when walking fast on flat ground or climbing a slight hill, and when walking on flat ground for a few minutes)—33.33%.

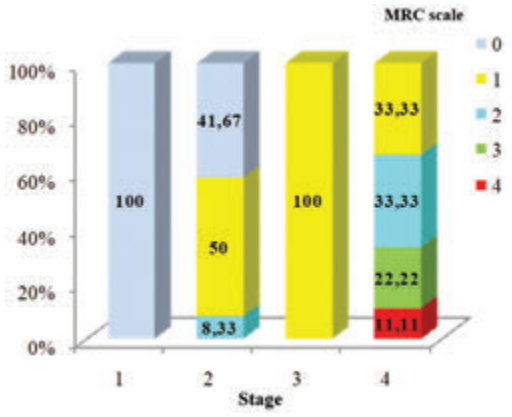
Table 2: Clinical Characteristics of Patients According to Sarcoidosis Stage

variable		Stage				p-level
		1 n=4 (%)	2 n=24 (%)	3 n=4 (%)	4 n=18 (%)	
Do you cough	yes	4(100)	18(75)	4(100)	14(77.78)	**p=0.71**
	no	0	6(25)	0	4(22.22)	
Intensity of cough	mild	4(100)	10(55.56)	2(50)	4(28.57)	**p=0.06**
	moderate	0	8(44.44)	2(50)	6(42.86)	
	severe	0	0	0	4(28.57)	
Type of cough	dry	4(100)	16(88.89)	2(50)	6(42.86)	*p=0.032
	purulent	0	2(11.11)	0	4(28.57)	
	Mixed	0	0	0	2(14.29)	
	White colored	0	0	2(50)	2(14.29)	
Difficulties in breathing	yes	2(50)	14(58.33)	4(100)	18(100)	**p=0.003 1 vs 4 p=0.026
	no	2(50)	10(41.67)	0	0	
MRC scale	0	4(100)	10(41.67)	0	0	***p=0.000
	1	0	12(50)	4(100)	6(33.33)	
	2	0	2(8.33)	0	6(33.33)	
	3	0	0	0	4(22.22)	
	4	0	0	0	2(11.11)	

p (Fisher's exact test) *sig p<0.05, **sig p<0.01, ***sig p<0.0001







The disease stage had a significant impact on the presence of reticular opacities in the upper and middle zones (p = 0.023); 8.33% of stage 2 patients and 44.44% of stage 4 patients had this finding on HRCT, with a statistically significant difference (p = 0.01).

In the lower lung zones, reticular opacities in peripheral and subpleural regions were found in 16.67% of stage 2 patients and 44.44% of stage 4 patients. No statistically significant difference was observed in the frequency of such findings across all four disease stages (p = 0.096).

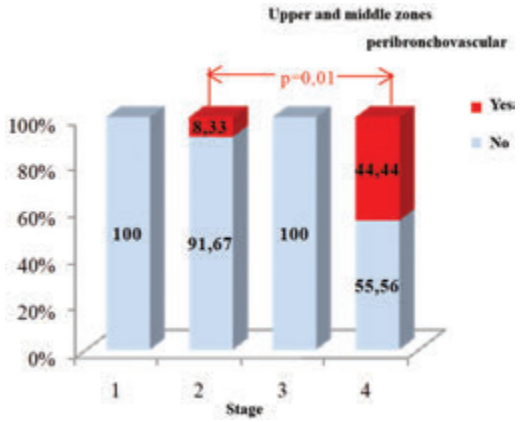
A statistically significant difference in the distribution of patients with and without peribronchovascular reticular opacities in the lower zones was confirmed (p = 0.003). Such opacities were noted in 8.33% of stage 2 patients and 55.56% of stage 4 patients, with a statistically significant difference (p = 0.0014).

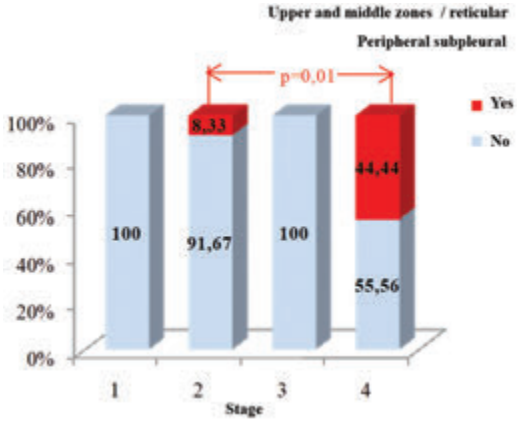
Table 3: Distribution of Reticular Changes According to Sarcoidosis Stage

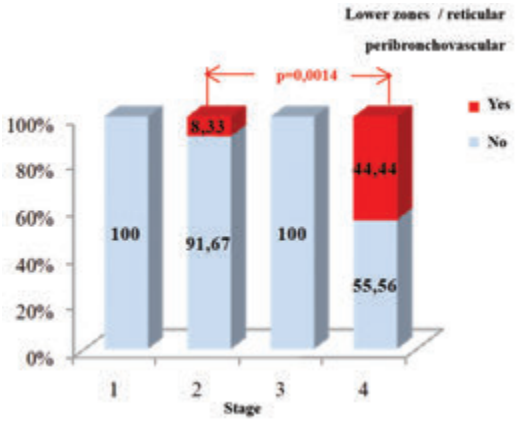
variable			Stage				p-level
			1 n=4 (%)	2 n=24 (%)	3 n=4 (%)	4 n=18 (%)	
Upper and middle zones							
reticular	Peripheral subpleural	**yes**	0	2 (8.33)	0	8(44.44)	*p=0.023 2 vs 4 p=0.01
		no	4 (100)	22(91.67)	4(100)	10(55.56)	
	peribronchovascular	**yes**	0	2 (8.33)	0	8(44.44)	*p=0.023 2 vs 4 p=0.01
		no	4 (100)	22(91.67)	4(100)	10(55.56)	
Lower zones							
reticular	Peripheral subpleural	**yes**	0	4(16.67)	0	8(44.44)	**p=0.096**
		no	4(100)	20(83.33)	4(100)	10(55.56)	
	peribronchovascular	**yes**	0	2 (8.33)	0	10(55.56)	**p=0.003 2 vs 4 p=0.0014
		no	4(100)	22(91.67)	4(100)	8(44.44)	

p (Fisher's exact test)

*sig p<0.05, **sig p<0.01, ***sig p<0.0001







No statistically significant difference was found in the frequency of micronodular changes sized 1–3 mm and >3 mm in the upper and middle lung zones across disease stages ($p > 0.05$). Peribronchovascular micronodular opacities 1–3 mm were most common in stage 2 patients (25%), perilymphatic micronodular opacities 1–3 mm in peribronchovascular regions were most common in stage 4 patients (33.33%), perilymphatic micronodular changes 1–3 mm in subpleural regions were most frequently detected in stage 3 patients (50%), and these stage 3 patients also most often showed micronodular changes >3 mm in peripheral and subpleural regions (50%). Micronodular opacities >3 mm in peribronchovascular regions were most often seen in stage 2 patients (33.33%). In the lower lung zones, peribronchovascular micronodular opacities 1–3 mm were detected in 50% of stage 3 patients and 11.11% of stage 4 patients; this HRCT finding showed a statistically significant difference across disease stages ($p = 0.018$). Other localizations of micronodular changes in the lower lung zones

Table 4: Distribution of Micronodular Changes by Sarcoidosis Stage

Micronodular opacities			**Stage**				**p-level**
			1 n=4 (%)	**2 n=24 (%)**	**3 n=4 (%)**	**4 n=18 (%)**	
Upper and middle zones							
Micronodular opacities (1-3 мм)	Centrilobular	**yes**	0	0	0	0	
		no	4(100)	24(100)	4(100)	18(100)	
	Peribroncho-vascular	**yes**	0	6(25)	0	2(11.11)	p=0.46
		no	4 (100)	18(75)	4(100)	16(88.89)	
Micronodular opacities (1-3 мм) Perilymphatic	Peribroncho-vascular	**yes**	0	6(25)	2(50)	6(33.33)	p=0.45
		no	4 (100)	18(75)	2(50)	12(66.67)	
	Subpleural	**yes**	0	4(16.67)	2(50)	4(22.22)	p=0.33
		no	4 (100)	20(83.33)	2(50)	14(77.78)	
Micronodular opacities (>3 мм)	Periferal and subpleural	**yes**	0	6(25)	2(50)	2(11.11)	p=0.21
		no	4 (100)	18(75)	2(50)	16(88.89)	
	Peribroncho-vascular	**yes**	0	8(33.33)	0	2(11.11)	p=0.18
		no	4 (100)	16(66.67)	4(100)	16(88.89)	

Lower zones							
Micronodular opacities (1-3 мм)	Centrilobular	**yes**	0	0	0	0	
		no	4(100)	24(100)	4(100)	18(100)	
	Peribroncho-vascular	**yes**	0	0	2(50)	2(11.11)	*p=0.018 2 vs 3 p=0.016
		no	4(100)	24(100)	2(50)	16(88.89)	
Micronodular opacities (1-3 мм) perilymphatic	Peribroncho-vascular	**yes**	0	2 (8.33)	0	0	p=0.65
		no	4(100)	22(91.67)	4(100)	18(100)	
	Subpleural	**yes**	0	2 (8.33)	0	0	p=0.65
		no	4(100)	22(91.67)	4(100)	18(100)	
Micronodular opacities (>3 мм)	Peripheral and subpleural	yes	0	0	0	2(11.11)	p=0.65
		no	4(100)	24(100)	4(100)	16(88.89)	
	Peribroncho-vascular	yes	0	2 (8.33)	0	0	p=0.65
		no	4(100)	22(91.67)	4(100)	18(100)	

p (Fisher's exact test)
*sig p<0.05

Enlarged lymph nodes were detected in patients at stages 1, 2, and 4. A statistically significant difference was confirmed among the four disease-stage groups in the prevalence of bilateral hilar lymphadenopathy ($p = 0.003$), right paratracheal lymphadenopathy ($p = 0.001$), and other nodal stations ($p < 0.0001$). Bilateral hilar lymphadenopathy was detected in 100% of stage 1 patients 83, 33% of stage 2 patients and 55, 56% of stage 4 patients with pairwise comparisons showing statistically significant differences between stages 1 and 3 ($p = 0.019$) and between stages 2 and 3 ($p = 0.0034$). Right paratracheal lymphadenopathy was seen in 100% of stage 1 patients 91, 67% of stage 2 patients and 77, 78% of stage 4 patients with significant differences found between stages 1 and 3 ($p = 0.019$), stages 2 and 3 ($p = 0.007$), and stages 3 and 4 ($p = 0.0096$).

Table 5: Distribution of Lymphadenopathy, Calcified Lymph Nodes, and Additional Findings by Sarcoidosis Stage

variable			Stage				p-level
			1 n=4 (%)	2 n=24 (%)	3 n=4 (%)	4 n=18 (%)	
Lymphadenopathy	Bilateral hilar	**yes**	4(100)	20(83.33)	0	10(55.56)	**p=0.003 1vs3 p=0.019 2vs3 p=0.0034
		no	0	4(16.67)	4(100)	8(44.44)	
	Right paratracheal	**yes**	4(100)	22(91.67)	0	14(77.78)	**p=0.001 1vs3 p=0.019 2vs3 p=0.0007 3vs4 p=0.0096
		no	0	2(8.33)	4(100)	4(22.22)	
	Other nodal stations	**yes**	4(100)	22(91.67)	0	10(55.56)	***p=0.000 1 vs 3 p=0.0014 2 vs 3 p=0.0007 2 vs 4 p=0.01
		no	0	2(8.33)	4(100)	8(44.44)	
	Conglomerate lymphnodes	**yes**	2(50)	6(25)	0	2(11.11)	p=0.21
		no	2(50)	18(75)	4(100)	16(88.89)	

Calcified lymphnodes	Focal calcificates	**yes**	0	10(41.67)	0	2(11.11)	p=0.053
		no	4(100)	14(58.33)	4(100)	16(88.89)	
	Punctiform	**yes**	0	2(8.33)	0	0	p=0.65
		no	4(100)	22(91.67)	4(100)	18(100)	
	Scaly	**yes**	0	2(8.33)	0	0	p=0.65
		no	4(100)	22(91.67)	4(100)	18(100)	
Additional finding	Pneumocyst/bullae	**yes**	0	4(16.67)	0	8(44.44)	p=0.096
		no	4(100)	20(83.33)	4(1003)	10(55.56)	
	Traction bronchiectasis	**yes**	0	0	0	14(77.78)	***p=0.000
		no	4(100)	24(100)	4(100)	4(22.22)	
	Fibrosis	**yes**	0	0	0	16(88.89)	***p=0.000
		no	4(100)	24(100)	4(100)	2(11.11)	
	Honeycombing	**yes**	0	0	0	2(11.11)	p=0.42
		no	4(100)	24(100)	4(100)	16(88.89)	

p (Fisher's exact test)

*sig p<0.05, **sig p<0.01, ***sig p<0.0001

Discussion

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. Pulmonary involvement is the most common manifestation of the disease, with interstitial and granulomatous changes of varying location, intensity, and expression, depending on the stage of the disease. Staging of the disease is still performed according to established radiological criteria based on conventional chest radiography, despite the high sensitivity of HRCT (high-resolution computed tomography) in detecting subtle changes in the lungs that are not visible on standard radiographs. According to Lynch, conventional chest radiography detects only 50–60% of enlarged lymph nodes and 30–40% of parenchymal abnormalities found with HRCT. Only in a few cases have patients with biopsy-confirmed sarcoidosis shown a normal HRCT scan. (5)

Involvement of the hilar and mediastinal lymph nodes is observed in 50–90% of patients, most commonly bilaterally. The disease affects both sexes, with a slight predominance in women, in whom a second incidence peak may be seen after the age of 50 (notably in Japan). Although the etiology remains unknown, certain occupations appear to increase the predisposition to this disease. These include nurses, cleaning staff, administrators in the chemical industry, dispatchers, and firefighters. It primarily occurs in non-smokers and typically manifests symptoms of dry cough and dyspnea. Perilymphatic distribution of pulmonary granulomas is consistently detected on HRCT.

The 2010 study by Herreaz, notes that the most common characteristic finding is the presence of small, well-defined nodules ranging in size, from 2 to 5 mm, with a lymphangitic distribution. Although these lesions are seen in the central lung zones—typically with a peribronchovascular and centrilobular distribution—they are more frequently observed in the peripheral lung fields, commonly showing a centrilobular and subpleural distribution, along the fissures. (6)

The 2005 study by Akira et al., which included 40 patients with a 7-year follow-up period, reports that additional findings in sarcoidosis, such as ground-glass opacities and consolidations, most commonly progress into cystic lung changes. In contrast, abnormalities in the form of micro- and macronodular changes typically resolve or decrease in size. Fibrotic changes do not disappear and are associated with a worse prognosis, as well as increased mortality and morbidity (7). Traction bronchiectasis, architectural distortion of the lungs, and cystic lung changes are irreversible alterations.

In this study, the patients were predominantly female—46 (92%) compared to 4 (8%) male—aged between 30 and 73 years, most of whom lived in urban areas. Regarding smoking status, 8 patients (16%) declared themselves as current smokers, while 42 (84%) were non-smokers; however, 28 (56%) of the non-smokers had a history of smoking.

Regarding the distribution of patients by sarcoidosis stage, 4 patients (8%) were in stage 1, 24 (48%) in stage 2, 4 (8%) in stage 3, and 18 (36%) were diagnosed with stage 4 sarcoidosis.

In the study by Peeyush (8), aanalyzed a group of predominantly male 40 patients with pulmonary sarcoidosis, with most cases detected in stages 2 and 3 of the disease. In contrast, our patients were predominantly female, most commonly in stages 2 and 4. Bilateral hilar lymphadenopathy was present in 76% of our patients, with calcifications detected in 17%. Lesion distribution was predominantly in the upper and middle lung zones (78%), while diffuse distribution affecting the lower zones was seen in 22% of patients (8).

Clinically, cough was present in 80% of the patients, most often of mild intensity, and predominantly dry in 56% of cases.

Breathing difficulties were reported in 76% of the patients, with dyspnea lasting between 3 and 24 months, while fatigue was reported by 14 patients (28%).

Overall, reticular opacities were detected in 44 (88%) patients, similarly distributed in the upper/middle and lower lung zones—20 (40%) and 24 (48%) respectively—which corresponds to the larger number of patients diagnosed in stage 4 of the disease.

The stage of the disease was not significantly associated with the presence or intensity of cough. Regarding cough intensity, mild cough was reported by patients across all stages, most frequently in stage 1, while severe cough was observed only in patients with stage 4 disease.

As previously noted, sarcoidosis is a multisystem granulomatous disease of unknown etiology, with pulmonary involvement being the most common presentation. According to general literature, most patients are in stage 1, followed by stage 2, which includes pulmonary involvement and lymphadenopathy. In this study, most patients were found in stages 2 and 4. This variation, as well as the predominance of female patients, is likely due to the relatively small sample size, as well as the socioeconomic status of patients in our country, where health awareness is generally low.

Involvement of the hilar and mediastinal lymph nodes is seen in 50–90% of patients. (9)

The study by Miller BH et al. found that up to 90% of patients with sarcoidosis have pulmonary involvement at some stage of the disease, where lung imaging plays a key role in disease detection, diagnosis, and management. In the same study, thoracic lymphadenopathy was present in over 85% of patients, with bilateral lymph node involvement seen in up to 95% of those with

thoracic nodal disease (10). Parenchymal involvement includes perilymphatic micronodules (up to 5 mm), larger nodules, ground-glass opacities, consolidations, reticulations, and fibrosis (11).

Lymphadenopathy in sarcoidosis is non-necrotizing and typically bilateral and symmetrical—this is a classic pattern of sarcoidosis and is consistent with our findings. Symmetrical lymphadenopathy is an important diagnostic marker for sarcoidosis, as symmetry is uncommon in many differential diagnoses, such as tuberculosis or lymphoma (12). In a high percentage of cases, the lymph nodes may appear conglomerated.

According to Nishino M. and colleagues, as well as Ors F. and colleagues, perilymphatic micronodules on HRCT are found in more than 90% of patients, typically distributed symmetrically in the middle and upper lung zones.

The perilymphatic distribution of micronodules is a characteristic feature of sarcoidosis. These nodules are usually well-defined, with bilateral and generally symmetrical distribution, predominantly involving the upper and middle lung fields (9, 13, 14).

According to Starshinova et al. It has been hypothesized that components of atmospheric particulate matter or infectious causes could serve as immunogenic triggers, causing a systemic granulomatous response. In our study, as well as in the study in USA by Hannah H. Nam et.al, a significantly higher proportion of sarcoidosis patients was found to live in urban areas. (15)

A recent case-control study from India examining 100 newly diagnosed sarcoidosis patients reported that the study showed no change in the clinical presentation or the severity of disease in sarcoidosis patients with a history of smoking.(16) In our study, current smokers did not have a significantly different distribution across the four disease stages, but there was a statistically significant difference in the distribution of former smokers across disease stages, driven by the significantly higher proportion of former smokers in stage III compared to stage II . It is uncertain whether nicotine or other components of cigarette smoke alone or in combination change the clinical manifestation of sarcoidosis.(17)

In our study, the disease stage had a significant impact on the patient hospitalization. Pairwise group comparisons showed significant differences between stages I and IV. This is because in stage 4 of the disease, where pronounced fibrotic changes affect the lung parenchyma, dyspnea and fatigue become the dominant clinical symptoms, significantly impacting the patients' daily activities, and in the most severe cases, necessitating oxygen support and hospitalization.

Conclusion

Although the radiological staging of sarcoidosis is traditionally based on the Scadding Score System, High-Resolution Computed Tomography (HRCT) is the imaging modality of choice and represents the gold standard for evaluating thoracic sarcoidosis. It accurately depicts the characteristic features of parenchymal nodules and lesions, their distribution, associated changes, as well as atypical findings. Moreover, HRCT plays a crucial role in guiding appropriate therapy by distinguishing active inflammatory lesions from irreversible fibrotic changes. Although sarcoidosis generally occurs predominantly in non-smokers, the role of nicotine in patients with sarcoidosis is still not fully understood. Cough is a common and prominent clinical symptom in sarcoidosis patients, although the precise mechanism behind its development remains unclear.

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ORIGINAL ARTICLE *UDK: 616.24-002.2-085.816.2*

www.doi.org/10.55302/MJA259461a

IMPACT OF THE ECONOMIC AVAILABILITY OF LONG-TERM OXYGEN THERAPY ON THE HEALTH STATUS OF PATIENTS WITH COPD: A CROSS-SECTIONAL STUDY

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition characterized by persistent airflow limitation, chronic inflammation, and represents a significant burden globally. Long-term oxygen therapy (LTOT) improves survival, reduces exacerbations, and enhances health-related quality of life (HRQoL) among patients with severe hypoxemia. However, economic constraints in many health systems restrict access to LTOT, potentially exacerbating symptom burden and the overall functional decline. This study evaluates whether economic inaccessibility to LTOT is associated with differences in symptoms and perceived health status among COPD patients who meet clinical criteria for LTOT.

Material and methods: A cross-sectional study was conducted involving 60 adults with COPD who met physiological criteria for LTOT. Participants were divided into two groups: LTOT users (n = 30) and LTOT non-users (n = 30) who could not obtain therapy due to financial limitations. Symptoms and health status were assessed using the COPD Assessment Test (CAT). Statistical analyses included t-tests, Mann–Whitney U tests, chi-square tests, and Cohen's d.

Results: Patients without access to LTOT demonstrated higher CAT scores, indicating worse symptom burden and lower health status. Although the mean difference did not reach statistical significance, the effect size suggested a small-to-moderate clinically meaningful trend favoring LTOT users. A higher proportion of LTOT non-users fell into the very high impact CAT severity band.

Conclusion: Economic barriers to LTOT access may contribute to poorer symptom control and diminished quality of life in COPD patients who meet established criteria for oxygen therapy. Addressing financial constraints through policy reforms may improve equity in COPD care and reduce disease burden.

Keywords: *Chronic obstructive pulmonary disease; Long-term oxygen therapy; Chronic obstructive pulmonary disease Assessment Test.*

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airflow limitation, airway inflammation, and structural lung changes (1). Globally, COPD remains a leading cause of morbidity and mortality, driven largely by tobacco exposure, environmental pollutants, and population aging (2,3). The disease is associated with reduced functional capacity, increased healthcare utilization, and substantial economic cost.

Patients in advanced COPD stages frequently develop chronic hypoxemia, a condition linked to higher mortality, cognitive deficits, reduced exercise capacity, and poorer HRQoL (4). Long-term oxygen therapy (LTOT) is an evidence-based intervention recommended for patients with severe resting hypoxemia, demonstrating improvements in survival, physiological stability, and daily functioning (5,6). International guidelines emphasize LTOT as a cornerstone treatment for advanced COPD (7).

Despite its benefits, LTOT access varies widely across socioeconomic groups. Financial constraints, partial reimbursement, or out-of-pocket expenses often prevent eligible patients from obtaining home oxygen equipment (8,9). Socioeconomic disadvantage—including low income, limited education, and inadequate social support—further reduces the likelihood of LTOT initiation or adherence (10-12).

The COPD Assessment Test (CAT) is a validated patient-reported outcome measure widely used to quantify symptom burden and health status. Higher CAT scores correlate with worse HRQoL, increased exacerbation risk, and greater mortality (13-15).

Given the important role of LTOT in symptom control and functional stability, understanding whether economic inaccessibility affects symptom burden among clinically eligible patients is an urgent research priority. This study compares CAT-measured symptom severity between LTOT users and financially constrained non-users to evaluate the impact of economic barriers on COPD health status.

Material and methods

Study Design

A cross-sectional comparative design was employed to assess differences in symptom severity between COPD patients receiving LTOT and those unable to access LTOT due to financial limitations.

Study Population

Sixty adults with confirmed COPD were consecutively recruited from an outpatient pulmonary clinic.

Inclusion Criteria

- Age ≥ 40 years
- Spirometry-confirmed COPD (post-bronchodilator $FEV_1/FVC < 0.70$)
- Documented LTOT indication per international guidelines (PaO_2 <7,3 kPa or $SaO_2 \leq$ 88%, or PaO_2 8 kPa with cor pulmonale/polycythemia) (7,16)
- Clinical stability for ≥4 weeks

Exclusion Criteria

- Recent exacerbation (<4 weeks)
- Cognitive impairment
- Other chronic lung diseases
- Declined consent

Group Allocation

- Group A: LTOT users (n = 30)
- Group B: LTOT non-users (n = 30) unable to afford oxygen equipment

Data Collection

Primary outcome:

- Symptom burden measured by CAT (0–40 scale) (13)

Secondary variables:

- Age, gender
- Economic status (low/middle/high)
- Smoking history (pack-years)
- Comorbidities

CAT severity categories:

- 0–9 low impact
- 10–20 medium
- 21–30 high
- 31–40 very high (14)

Statistical Analysis

- Descriptive statistics: mean ± SD, frequencies
- Group comparisons: independent t-test, Mann–Whitney U, chi-square
- Normality testing: Shapiro–Wilk
- Effect size: Cohen's d
- Significance: $p < 0.05$
- Software: SPSS v26

Results

Demographic Characteristics

Table 1. Demographic Characteristics

Variable	LTOT Yes (n = 30)	LTOT No (n = 30)
Age (years)		
– Mean ± SD	67.3 ± 10.2	68.2 ± 9.5
– Age range	51–69	56–73

Variable	LTOT Yes (n = 30)	LTOT No (n = 30)
Gender, n (%)		
– Male	18 (60.0%)	22 (73.3%)
– Female	12 (40.0%)	8 (26.7%)
Economic status, n (%)		
– Low	17 (56.7%)	19 (63.3%)
– Middle	11 (36.7%)	10 (33.3%)
– High	2 (6.7%)	1 (3.3%)
Smoking history, median (IQR)**	44 (35–55)	46 (38–58)
Comorbidities, n (%)		
– Cardiovascular disease	13 (43.3%)	16 (53.3%)
– Anxiety/Depression	9 (30.0%)	11 (36.7%)
– Osteoporosis	6 (20.0%)	5 (16.7%)
– Chronic kidney disease	5 (16.7%)	4 (13.3%)
– Hypertension	14 (46.7%)	15 (50.0%)
– GERD	7 (23.3%)	6 (20.0%)

Sixty COPD patients were analyzed. Age and gender distributions were similar between groups. Most participants reported low-to-middle economic status. Smoking exposure and comorbidity patterns did not differ meaningfully.

CAT Scores

LTOT users reported lower symptom burden (CAT mean 24.2 ± 8.5) than non-users (27.8± 9.1). Although the p-value (0.11) did not reach statistical significance, the effect size (Cohen's d = 0.41) suggested a small-to-moderate clinically relevant difference.

Non-users were overrepresented in the very high impact band (46.7% vs. 30%).

Table 2. CAT Scores in LTOT Users and Non-Users

CAT Variable	LTOT Yes (n = 30)	LTOT No (n = 30)
CAT total score, mean ± SD	24.2 ± 8.5	27.8 ± 9.1
Range (min–max)	10–39	12–40
CAT severity categories, n (%)		
– Low impact (0–9)	1 (3.3%)	0 (0%)
– Medium impact (10–20)	7 (23.3%)	5 (16.7%)
– High impact (21–30)	13 (43.3%)	11 (36.7%)
– Very high impact (31–40)	9 (30.0%)	14 (46.7%)

Table 2 summarizes the distribution of CAT scores among patients who use LTOT and those who do not. LTOT users demonstrated a slightly lower mean CAT total score (24.2 ± 8.5) compared with non-users (27.8 ± 9.1), suggesting a trend toward a less severe symptom burden in

the LTOT group. The score ranges were comparable between groups, with LTOT users scoring between 10 and 39 and non-users between 12 and 40.

Table 3. Between-group comparison of CAT scores in LTOT users and non-users

Variable	LTOT Yes (n = 30) Mean ± SD	LTOT No (n = 30) Mean ± SD	Mean difference (No − Yes)	95% CI for mean difference	Statistical test	p-value	Cohen's d
CAT total score	24.2 ± 8.5	27.8 ± 9.1	3.6	−0.9 to 8.1	Independent samples t-test	0.11	0.41

Table 3 presents the comparison of total CAT scores between patients who use long-term oxygen therapy (LTOT Yes) and those who do not use LTOT despite having indications (LTOT No). The mean CAT score was lower in the LTOT group (24.2 ± 8.5) compared with the non-LTOT group (27.8 ± 9.1), indicating a trend toward less severe symptom burden among LTOT users.

Discussion

This study found that COPD patients using LTOT reported lower symptom burden and better perceived health status compared with those who could not obtain LTOT due to financial constraints. Although the difference in mean CAT scores was not statistically significant, the effect size and severity distribution suggest that the lack of LTOT access may contribute to clinically meaningful impairment.

These findings are consistent with extensive literature showing that LTOT improves survival, HRQoL, exercise tolerance, and dyspnea in patients with chronic hypoxemia (1-4). Studies by Ringbaek et al. and Jones et al. further demonstrate improvements in patient-reported outcomes when oxygen therapy is appropriately used (17,18).

The present results highlight the impact of socioeconomic inequalities in COPD management. Numerous investigations have shown that socioeconomic deprivation reduces the likelihood of LTOT initiation or adherence, even among clinically eligible patients (10-12). Economic barriers appear to shape disease burden beyond physiological severity.

International studies reveal that limited access to essential COPD treatments—including medication and oxygen therapy—is associated with higher CAT and SGRQ scores, worse functional outcomes, and increased psychological distress (19-21).

Higher CAT scores also predict exacerbations, hospitalizations, and mortality (15,22). Thus, the greater symptom burden among LTOT non-users may have long-term prognostic implications.

Improving financial accessibility to LTOT—through reimbursement reforms, equipment subsidies, or national oxygen programs—may substantially improve HRQoL and reduce disease progression among vulnerable COPD populations (7,23).

Limitations of the Study

This study has several limitations that should be considered when interpreting the results. First, the cross-sectional design does not allow for establishing causal relationships between LTOT

use and symptom burden. Although differences in CAT scores were observed, the temporal direction of these associations cannot be confirmed.

Second, the sample size was relatively small (n = 60), which may limit the statistical power to detect modest but clinically relevant differences between groups. The non-significant p-value in the CAT comparison may partially reflect limited statistical power rather than the absence of a true effect.

Third, the study relied on a single symptom-related measure (CAT) without including additional validated HRQoL tools such as the SGRQ or mMRC dyspnea scale. The use of multiple instruments might have provided a more comprehensive assessment of health status.

Fourth, although key demographic and clinical variables were comparable between groups, the lack of detailed physiological measurements (e.g., PaO_2, $PaCO_2$, spirometric severity, oxygen saturation profiles) limits the ability to adjust for potential clinical confounders that could influence symptom scores independently of LTOT use.

Fifth, the group of patients not receiving LTOT consisted of individuals who lacked access due to financial constraints, which introduces possible socioeconomic confounding. Economic hardship is known to correlate with worse health outcomes, reduced access to other treatments, poorer nutrition, and lower adherence to medical advice, all of which may have influenced CAT results independently of LTOT status.

Sixth, the study did not evaluate exacerbation frequency, hospitalization history, or treatment adherence, variables that are strongly associated with CAT scores and overall disease burden. Their absence limits the depth of interpretation regarding disease control.

Finally, the study was conducted at a single center, which may affect generalizability. COPD populations in other regions may differ in demographic characteristics, access to care, or patterns of LTOT use.

Recommendations for Future Research

Future studies should build upon these findings through more robust and comprehensive research designs. First, longitudinal or prospective cohort studies are needed to clarify the temporal relationship between LTOT use and changes in symptom burden, functional capacity, and health-related quality of life. Tracking patients over time would allow for stronger inferences regarding the causal effect of LTOT.

Second, future research should include larger and more diverse samples, enabling improved statistical power and greater generalizability across different healthcare settings. Multi-center studies would help validate these results in broader COPD populations, including patients from different socioeconomic backgrounds and healthcare systems.

Third, forthcoming investigations should integrate detailed physiological and clinical parameters, such as arterial blood gases, oxygen saturation trends, spirometry (including FEV_1 decline), and desaturation during exertion. Adding these measures would enable a more comprehensive assessment of disease severity and help disentangle the independent contribution of LTOT from other clinical determinants.

Fourth, the inclusion of multiple validated patient-reported outcome measures (e.g., SGRQ, EQ-5D, mMRC) would provide a more nuanced understanding of how LTOT affects dyspnea, activity limitation, psychosocial functioning, and overall quality of life. Combining patient-reported outcomes with objective measurements such as 6-minute walk distance or actigraphy could further enrich the evidence.

Fifth, it would be valuable to examine exacerbation frequency, hospitalization rates, and healthcare utilization in relation to LTOT accessibility. Understanding whether economic limitations contribute to higher exacerbation risk or increased clinical burden could have important health policy implications.

Sixth, future studies should investigate adherence patterns to LTOT, including barriers related not only to economic limitations but also to stigma, device characteristics, mobility restrictions, and patient perceptions. Qualitative or mixed-methods research could provide insight into patient experiences and identify practical strategies to improve adherence and acceptance of LTOT.

Lastly, given the significant role of economic barriers identified in this study, future research should incorporate health economics analyses, including cost-effectiveness evaluations, modeling of long-term outcomes and healthcare savings, and assessment of reimbursement strategies that could improve equitable access to LTOT.

Conclusion

COPD patients with an established indication for LTOT who lack access to therapy due to financial constraints exhibit a higher symptom burden and poorer perceived health status. Although statistical significance was not reached, clinically relevant differences suggest that economic inaccessibility may contribute to worsened HRQoL. Strengthening health policies aimed at equitable access to LTOT may significantly improve outcomes in this high-risk population.

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ORIGINAL ARTICLE *UDK: 616.441-076*

www.doi.org/10.55302/MJA259469s

DIAGNOSTIC VALUE OF FINE-NEEDLE ASPIRATION BIOPSY IN PATIENTS WITH THYROID CANCER AND HASHIMOTO THYROIDITIS

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Abstract

Introduction: Thyroid nodules are a common finding in clinical practice, with prevalence ranging from 2-6% on physical examination, 19–35% on ultrasound, and 8–65% in autopsy studies. Their incidence increases with age and is more frequent in women, individuals with iodine deficiency, and those previously exposed to ionizing radiation. Hashimoto's thyroiditis may alter cytological interpretation and affect diagnostic accuracy.

Methods: This retrospective study included 80 patients with thyroid nodules and Hashimoto's thyroiditis who underwent fine-needle aspiration biopsy (FNAB), followed by surgical thyroid resection. Diagnostic accuracy parameters were calculated based on histopathological findings as the reference standard.

Results: FNAB demonstrated high sensitivity, indicating effective detection of malignant lesions. The positive predictive value was 100%, confirming the strong reliability of FNAB in identifying malignancy when cytology is positive. However, false-negative results occurred predominantly in Bethesda categories I and II.

Conclusion: FNAB remains a key and highly accurate preoperative diagnostic method for evaluating thyroid nodules. The exceptionally high positive predictive value supports its diagnostic strength. Nevertheless, the presence of false-negative cases underscores the need for close clinical and ultrasound follow-up in patients with benign cytology, particularly due to the possibility of microcarcinoma or slow-growing thyroid carcinoma.

Keywords: *Hashimoto's thyroiditis; thyroid carcinoma; fine-needle aspiration biopsy (FNAB)*

Introduction

Thyroid nodules are a common finding in everyday clinical practice. Studies show that their prevalence is 2–6% on physical examination, 19–35% when detected by ultrasound, and 8–65% in autopsy studies. Their frequency increases with age and is higher in women, in populations

with iodine deficiency, and in individuals previously exposed to ionizing radiation (1–3). Although the majority of thyroid nodules are benign, approximately 5% are malignant, making thyroid carcinoma the most common endocrine malignancy. Globally, it ranks as the seventh most common cancer in women and the fifteenth in men (4–6).

A major clinical challenge is to ensure accurate preoperative diagnosis of malignancy. The diagnostic approach includes physical examination, measurement of thyroid-stimulating hormone (TSH), ultrasonography, and fine-needle aspiration biopsy (FNAB). Among all available methods, FNAB is considered the most accurate, efficient, and cost-effective technique and represents a key tool for identifying patients who require surgical treatment (7,8). Introduced in the 1950s, FNAB revolutionized the diagnostic evaluation of thyroid nodules, owing to its simplicity, minimal invasiveness, and low cost (9). It enables reliable preoperative assessment and helps avoid unnecessary surgery in benign nodules. Additionally, FNAB is safe as an outpatient procedure with an exceptionally low complication rate (10).

Despite its numerous advantages, FNAB has certain limitations. The most significant challenge is distinguishing between follicular adenoma and follicular carcinoma, as cytological analysis cannot assess capsular or vascular invasion criteria determined exclusively through histopathology (11,12). Moreover, FNAB may yield nondiagnostic or indeterminate results, often requiring repeat biopsy or additional evaluation.

To improve standardization, the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was introduced in 2007 and revised in 2017. TBSRTC categorizes cytological findings into six clearly defined diagnostic groups, each associated with a specific risk of malignancy and recommended management (13). This system has significantly improved communication between clinicians and pathologists and enhanced consistency in the diagnostic process (14). Histopathology remains the "gold standard" for diagnosing thyroid lesions. It provides a detailed analysis of architectural and cellular characteristics, assessment of capsular and vascular invasion, lymph node infiltration, and precise tumor subtype identification (15,16). The histopathological diagnosis is essential for definitive classification, particularly in lesions with follicular morphology and in cases with atypical cytological results.

Numerous studies report that the sensitivity and specificity of FNAB in detecting thyroid malignancies range from 80% to 98%, depending on the quality of the specimen, operator expertise, and institutional protocols. However, false-positive and false-negative results still occur, emphasizing that cytological findings should always be correlated with histopathology, particularly in atypical FNAB categories (17,18). FNAB may also yield false-negative results in patients with multinodular goiter (MNG), whereas its accuracy is higher in solitary nodules. Additional controversy exists regarding the accuracy of FNAB in nodules <1 cm and >4 cm in size (19). Hashimoto thyroiditis (HT) is the most common autoimmune thyroid disease and a leading cause of hypothyroidism. Many studies indicate that thyroid carcinoma frequently coexists with HT, with tumors often showing inflammatory immune-cell infiltration (20,21). HT is characterized by lymphocytic infiltration, progressive destruction of thyroid tissue, and fibrotic changes leading to hypothyroidism (22). Its incidence is 1–4% annually, with 3–6 cases per 10,000 population per year. It is the second most common thyroid disorder after endemic goiter and is significantly more frequent in women. HT typically presents with diffuse goiter, whereas the development of solitary or dominant nodules is relatively uncommon. In the preoperative setting, differentiating whether nodules are a consequence of HT or represent malignancy associated with the disease remains a clinical challenge. Numerous studies have suggested an association between

HT and thyroid neoplasia, indicating that HT may be a risk factor for carcinoma development (23, 24, 25). This study aimed to evaluate the diagnostic value of FNAB in detecting thyroid carcinoma in patients with Hashimoto thyroiditis.

Materials and Methods

This retrospective study included 80 patients with thyroid nodules and Hashimoto thyroiditis who underwent fine-needle aspiration biopsy (FNAB) followed by surgical resection of the thyroid gland. Patients were selected at the Institute of Pathophysiology and Nuclear Medicine, Faculty of Medicine in Skopje, during the period from 2021 to 2024. Data on age, sex, FNAB cytology, and histopathological findings were recorded for all patients.

Inclusion criteria: patients of all age groups with a thyroid nodule diagnosed by ultrasound; patients with a confirmed diagnosis of Hashimoto thyroiditis who underwent FNAB followed by surgical resection; availability of both FNAB and histopathological reports for comparison; and confirmed final histopathological diagnosis of thyroid carcinoma.

Exclusion criteria: inadequate or unsatisfactory FNAB samples; patients who did not undergo surgical excision; incomplete medical documentation; incomplete FNAB or histopathological data.

FNAB was performed using a 22–25 G needle under ultrasound guidance with a Samsung V8 device equipped with a 15 MHz linear probe and appropriate thyroid navigation software. For each biopsy, 20 mL Beroject syringes were used. Smears were stained with hematoxylin and eosin (H&E), the standard method at the Institute of Pathological Anatomy, Faculty of Medicine in Skopje.

Cytological diagnoses were classified according to The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). All patients underwent thyroidectomy (total or partial), and the specimens were processed using routine histopathological methods. Tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at a thickness of 4–5 μm, and stained with H&E.

Results

1. Demographic distribution A total of 80 patients were included in the study, of whom 8 (10%) were male and 72 (90%) female. The predominant age groups were 41–50 years (30%) and >60 years (30%), while the least predominant age group was 21–30 years (5%) (Table 1).

Table 1. Demographic characteristics of patients

Age group (years)	Male (n)	Female (n)	Total (n)	Percentage (%)
21–30	0	4	4	5
31–40	3	5	8	10
41–50	3	21	24	30
51–60	1	19	20	25
>60	1	23	24	30
Total	**8**	**72**	**80**	**100**

The majority of FNAB findings were categorized as Bethesda category V (37.5%) and category IV (23.75%), while the lowest proportion belonged to category I (7.5%) (Table 2).

Table 2. Distribution of FNAB results according to the Bethesda system

Bethesda Category	Number of cases (n)	Percentage (%)
I – Nondiagnostic/unsatisfactory	6	7.5
II – Benign	7	8.75
III – Atypia of undetermined significance (AUS)	10	12.5
IV – Follicular neoplasm/Suspicious for follicular neoplasm	19	23.75
V – Suspicious for malignancy	30	37.5
VI – Malignant	8	10
Total	**80**	**100**

3. Histopathological findings. Histopathological examination of the 80 patients revealed the following distribution:

- 59 cases (73.75%) of papillary thyroid carcinoma (PTC)
- 3 cases (3.75%) of follicular thyroid carcinoma (FTC)
- 18 cases (22.5%) of the follicular variant of papillary thyroid carcinoma (FVPTC)

Table 3. Distribution of histopathological diagnoses

Diagnosis	Number of cases (n)	Percentage (%)
Papillary thyroid carcinoma (PTC)	59	73.75
Follicular thyroid carcinoma (FTC)	3	3.75
Follicular variant of papillary thyroid carcinoma (FVPTC)	18	22.5
Total	**80**	**100**

4. Correlation between FNAB and final histopathology

Table 4. Distribution of FNAB categories and final histopathological diagnoses

FNAB (Bethesda)	PTC	FTC	FVPTC
I – Nondiagnostic	3	1	2
II – Benign	7	0	0
III – AUS	6	0	4
IV – Follicular neoplasm/Suspicious FN	14	1	4
V – Suspicious for malignancy	25	0	5
VI – Malignant	8	0	0
Total	**63**	**2**	**15**

The strongest correlation was observed for Bethesda categories V and VI, where all cytological findings corresponded to malignant histopathology. Categories I and II included several cases

with malignant histology, indicating potential false-negative FNAB results. Categories III and IV demonstrated partial diagnostic uncertainty, consistent with expectations based on Bethesda criteria.

5. Diagnostic performance of FNAB

Table 5. Diagnostic performance of FNAB

Parameter	Percentage (%)
Sensitivity	83.8
Specificity	Not calculable
Positive predictive value (PPV)	100
Negative predictive value (NPV)	0
Diagnostic accuracy	83.8

The sensitivity was high, indicating that FNAB identified the majority of malignant cases. The positive predictive value was extremely high (100%), confirming FNAB as a reliable method for diagnosing malignant nodules when results are positive. The low NPV and inability to calculate specificity are attributable to the fact that all patients in the study had confirmed malignancy, with no histopathological benign cases included.

Discussion

Thyroid nodules are a common finding in clinical practice, and distinguishing benign from malignant lesions is crucial to avoid unnecessary surgical interventions and to ensure timely treatment of thyroid malignancies. Fine-needle aspiration biopsy (FNAB) cytology is widely used as a first-line diagnostic tool for the evaluation of thyroid nodules because it is simple, minimally invasive, cost-effective, and provides rapid results (1). In our study of 80 patients, there was a predominance of female participants (90%) with the highest representation in the age groups 41–50 years and >60 years. These findings are consistent with global epidemiological data indicating that thyroid disorders—particularly nodular and autoimmune diseases—are more common in women (4,5).

FNAB proved to be an important method for preoperative assessment of malignancy. The majority of FNAB findings were categorized as Bethesda IV and V, which showed a strong correlation with malignant histopathology. However, categories I and II included several cases with histologically confirmed carcinoma, indicating the presence of potential false-negative FNAB results. This phenomenon aligns with published data showing that incidental carcinoma rates among presumably benign FNAB findings range from 12% to 16% (26, 27).

Our diagnostic performance metrics demonstrated high sensitivity (83.8%) and an excellent positive predictive value (100%), supporting the effectiveness of FNAB in identifying malignant lesions. Specificity was 100%, and the negative predictive value was 53.85%, underscoring the importance of careful follow-up in patients with benign FNAB findings, especially considering the possibility of microcarcinomas or slow-growing thyroid cancers. The overall diagnostic accuracy of 83.8% further confirms the clinical value of FNAB.

Our findings reinforce the central role of FNAB in identifying patients who require surgical intervention but also highlight the importance of meticulous selection of biopsy sites, particularly in multinodular goiters or large nodules (>2 cm), as well as the potential need for multiple sampling to increase diagnostic accuracy (32,33). In accordance with current literature, ultrasound-guided FNAB remains the method of choice, while additional techniques such as elastography, PET/CT, and tumor biomarkers may improve preoperative precision in suspicious or indeterminate cases (28–31). This study also confirms the predominance of papillary thyroid carcinoma (73.75%), followed by the follicular variant (22.5%) and follicular carcinoma (3.75%), which is consistent with global epidemiological data on thyroid cancer. Overall, our results emphasize the diagnostic reliability of FNAB in evaluating thyroid nodules while reminding clinicians of the need for diligent follow-up of patients with benign or indeterminate FNAB categories.

Conclusion

FNAB remains a key and highly accurate method for the preoperative evaluation of thyroid nodules. Our findings demonstrated a high positive predictive value, confirming its capability to reliably identify malignant nodules. However, the presence of false-negative cases in Bethesda categories I and II highlights the importance of cautious follow-up of patients with benign FNAB results, particularly due to the possibility of microcarcinomas or slow-growing thyroid cancers.

In practice, FNAB should continue to be used as the first-line evaluation method for thyroid nodules, combined with careful selection of biopsy sites and periodic monitoring of benign lesions to optimize diagnostic accuracy and improve patient outcomes.

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ORIGINAL ARTICLE *UDK: 618.391-036.88(497.7)*

www.doi.org/10.55302/MJA259477bi

PREMATURE BIRTH AND COMPLICATIONS OF PREMATURE BIRTH ARE LEADING CAUSES FOR INCREASED NEONATAL MORTALITY

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Abstract

Introduction: Neonatal mortality (NNM) is a mortality in newborns in within the first 28 days after birth. Prematurity and the complications from prematurity are the leading cause for higher NNM rates. A premature newborn is born less than 37 gestational weeks of pregnancy. Low birth weight and low gestational age at delivery and their complications are the leading causes of NNM.

Aim of the study: The aim of this paper is to present our results gathered from the material of the newborns treated at the Neonatal Intensive Care Unit (NICU) at the University Clinic of Gynecology and Obstetrics in Skopje (UGOC- Skopje), demonstrating that prematurity and complications of prematurity have been the main causes of increased mortality among newborns, in the analyzed period of 9 months.

Material and methods: The study is a cross-sectional prospective research that included 445 newborns who were transferred to the NICU for resuscitation, monitoring and treatment after birth, over a period of 9 months or the period from May 1, 2019 to January 31, 2020, at the University Clinic of Gynecological and Obstetric (UGOC) in Skopje. In this paper, we focused on prematurity and complications of prematurity, which had a significant impact on the NNM of newborns in the NICU, in the analyzed period.

Results: The study shows that the leading causes for NNM at UGOC- Skopje were prematurity and complications from prematurity: low gestational age at birth, low birth weight, asphyxia, ARDS, NEC, intracranial hemorrhage, sepsis, congenital anomalies etc. Cesarean delivery, prenatal administration of corticosteroids, higher APGAR score in the 1st and 5th minutes, have a significant impact on the survival of newborns and reduction of mortality in newborns.

Conclusion: For a long period of time N. Macedonia was a country with one of the highest NNM rates in Europe. Prevention of prematurity and complications from prematurity, improved health and prenatal service, all this reduce the prematurity and NNM. The reasons for higher NNM are preventable and need programs for health care and education of patients, and better public health service.

Key words: *Acute respiratory distress syndrome; gestational week; intracranial hemorrhage; low birth weight; neonatal intensive care unit, neonatal mortality; necrotizing enterocolitis.*

Introduction

Neonatal mortality (NNM) is a mirror of a country's health system. The care for mothers, newborns, and children is among the highest priorities in the health policies of all countries in the modern world (1).

The neonatal period is the most sensitive period in human life and mortality is highest during this period of life, in the first 28 days after birth (2).

Neonatal mortality is the percentage of newborn deaths of live births, in the neonatal period in the first 28 days after birth, or born after 22 weeks of gestation and with a birth weight greater than 500 g, per thousand live births (3) (4).

In 2023, 2.3 million newborns died in the neonatal period globally, or 6500 newborns per day. The neonatal mortality rate stood at 17 newborns per 1000 live births globally, representing a significant decrease in the NMR rate, from 37 neonatal deaths per 1000 live births in 1990 (5). More than 90% of neonatal deaths occur in developing countries, especially in sub-Saharan Africa and Southeast Asia (5) (6). Japan, Iceland, Singapore, Finland, and Slovenia have the lowest neonatal mortality rates in the world, with 1 neonatal death per 1,000 live births (7).

For many years after gaining independence in 1990, N. Macedonia was among the countries in Europe with the highest neonatal mortality rate. It was often at the top or near the top, right after countries such as Turkey, Albania, Kosovo, and Moldova **(Picture 1)**. N. Macedonia was a European country with a high rate of neonatal mortality, among the highest in Europe, and in 2017, with 7.4 neonatal deaths per 1,000 live births, it was the second country with the highest rate of neonatal mortality in Europe, right after Moldova (8).

Picture 1. Neonatal mortality in N. Macedonia from 1982- 2018

From 2012 to 2017, there was an increasing trend that ranged from 7 to 9.5 neonatal deaths per 1000 live births, while a new decreasing trend of 7-9.5 ‰ was observed from 2018 and 2019 to the present (7). From 2020, the NNM rate in N. Macedonia began to further decrease and approach the European average and was reduced to 2 ‰ in 2022.

The Neonatal Intensive Care Unit (NICU) at the University Clinic of Gynecology and Obstetrics in Skopje (UGOC-Skopje) is the largest neonatal and perinatal center in N. Macedonia, where about 70% of these newborns are cared for, since the largest percentage of these complicated and pathological pregnancies and newborns from the entire country are treated and cared for in this Clinic (9).

The participation of the Clinic's NNM in the total NNM of the country, accounts for about 70% or 2/3, and makes this Clinic the most relevant center for research and studies related to NNM (9).

A lower gestational age at delivery and a low birth weight (LBW) are two of the most important factors that increased NNM rate(10).

Prematurity accounts for 12% or more in developing countries and 9% in developed countries. Prematurity is also high in some developed countries, such as the USA, but the survival rate of premature infants is higher in highly developed countries, than in developing countries. Leading causes of death in developing countries are prematurity, LBW, and infections, while in developed countries are congenital anomalies (10).

Premature newborns are divided into two groups: premature by gestational week and premature by birth weight. A premature newborn or a premature child, is a newborn born between 22-37 weeks of gestation or with a birth weight greater than 500 g at birth (11) (12) . Low birth weight (LBW) infants are at higher risk of neonatal mortality and morbidity, and up to 60% of all neonatal mortality is associated with low birth weight (LBW) (13) (14).

According to birth weight, newborns are divided into: Newborns with extremely low birth weight - less than 1000 g. (from 500 to 999 g.); newborns with very low birth weight - less than 1500 g. (from 1000-1499 g.); newborns with low birth weight - less than 2500 g. (from 1500-2499 g.) and newborns with a weight greater than 2500 g. (11) (13) (15).

According to gestational age at the time of delivery, premature newborns can be divided into several groups: born at 22-27 weeks of pregnancy - extremely premature, the highest risk group; born at 28-32 weeks of pregnancy - very premature, a risk group of premature babies; born at 33-36 weeks of pregnancy - moderately to late premature, a lower risk group of premature babies; born over 37 weeks of pregnancy - term newborns, the group where the neonatal mortality rate is the lowest (11) (16) (17).

The purpose of this paper is to presents the results from our material gathered at the UGOC – Skopje, which show that prematurity and complications of prematurity have been the main causes of increased mortality among newborns at the clinic, and throughout the country for many years. The study was conducted in a transitional year and during a period when the situation with NNM rates at the Clinic and in the country was starting to significantly improve in 2019/20. The study extensively examined a significant number of reproductive, maternal, neonatal, and socio-demographic factors, which collectively have an impact on NNM rates and the main reasons which increase it, both at the Clinic and in the country (9).

In this paper, we focus only on prematurity and complications of prematurity, as the most important factors for increasing the NNM rate.

Material and methods

The study is a cross-sectional prospective research that included 445 newborns, who were transferred to the NICU for resuscitation, monitoring and treatment, over a period of 9 months or the period from May 1, 2019 to January 31, 2020. at the University Clinic of Gynecological and Obstetric (UGOC) in Skopje. For the study, all mothers of newborns signed consent and completed a questionnaire about the course of pregnancy and childbirth, and hospital histories of the mothers and newborns who were transferred to the NICU were also used for data. In this paper, we focused, on the results that are related to prematurity and complications of prematurity, which had a significant impact on the NNM rates of newborns in the NICU, in the analyzed period.

Results

In the analyzed period of 9 months at the UGOC in Skopje, there were a total of 3453 live births. 445 (12.9%) of theese newborns were transferred and treated at NICU. Of all newborns treated at NICU, 368 (82.7%) of newborns remained alive and 77 (17.3%) were neonatally deceased newborns in the first 28 days after birth (Fig.1).

Prematurity in newborns was the main reason for transferring newborns at NICU and accounted for 93% of the total number of newborns transferred for treatment, or 414 premature newborns, out of the total number of 445 newborns treated at NICU.

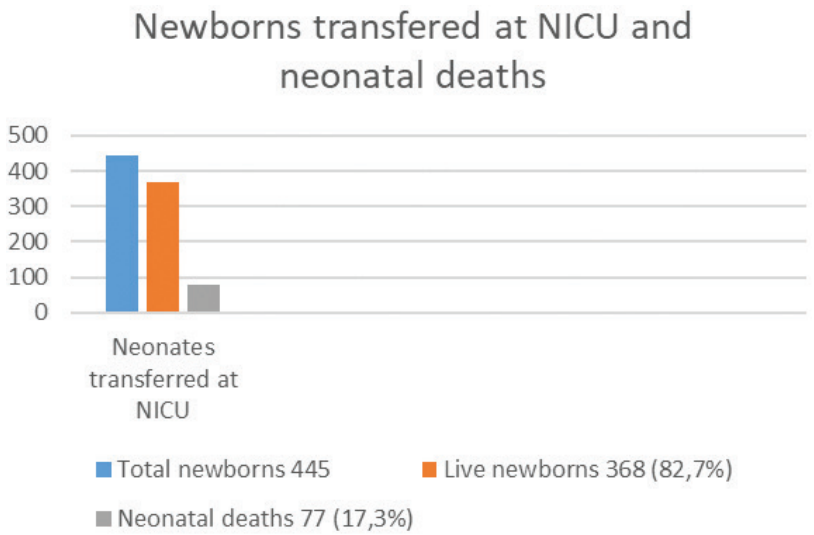

Fig. 1. Neonates transferred at NICU/ UGOC- Skopje and neonatal deaths

The highest mortality rate was identified in the group of extremely preterm newborns, where 88% of newborns died during NICU treatment, followed by the group of 28-32 gestational weeks, where the mortality rate was significantly reduced to 12% and the survival rate in this group of newborns was greatly improved, compared to previous years. The group of late preterm infants consisted of a smaller number of newborns transferred to the NICU, and in this group, the mortality rate was higher due to insufficiently monitored pregnancies, delivery complications such as placental abruption and other bleeding, or due to undetected serious congenital anomalies prenatally **(Fig.2)**.

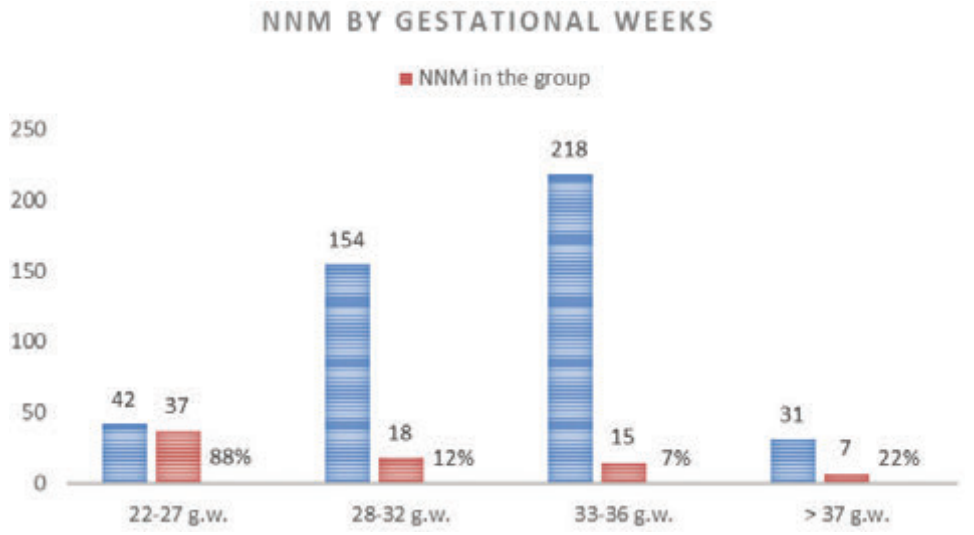

Fig. 2. Presentation of the neonatal mortality rate by gestational age at NICU/ UGOC- Skopje

In relation to low birth weight, the results showed a higher mortality rate among newborns born with a low birth weight, as well as with lower gestational age. The highest mortality rate was among newborns weighing less than 1000 grams - 77.8%, and the mortality rate decreased as the weight of newborns increased. Premature newborns and newborns with lower birth weight are more fragile and their adaptation and survival after birth are much riskier, compared to those born with higher weight and higher gestational age **(Table 1).**

Table. 1. Birth weight and neonatal mortality at NICU/ UGOC- Skopje

Neonatal deaths	500-999 gr.	100-1499 gr.	1500-2499 gr.	>2500 gr..	Total new-born
1- 7 day NNM	30	12	8	6	56
8-28 day NNM	12	3	3	3	21
Total NNM	42 (77,8%)	15 (18%)	11 (4,3%)	9 (17,65%)	77 (17,3%)
Survived newborns	12 (22,2%)	68 (82%)	246 (96%)	42 (82,35%)	368 (82,7%)

Premature newborns are born with lower APGAR scores at birth, due to their immaturity and are more likely to be exposed to RDS, NEC, asphyxia and brain hemorrhage, infections and sepsis, compared to term newborns.

On the other hand, the method of delivery and administration and prenatal maturation with corticosteroids also had a significant impact on the survival of these newborns.

In relation to the APGAR score obtained in the 1st and 5th minute after birth in newborns, the mortality rate of newborns with a lower APGAR score at birth was significantly higher. With an APGAR score < 3 in the 1st minute after birth, the mortality rate was 75%. With an APGAR

score of 4-6 in the 1st minute after birth, the mortality rate in newborns was 20% and with an APGAR score of 7-10, the mortality rate was the lowest at 4.4% **(Fig.3)**.

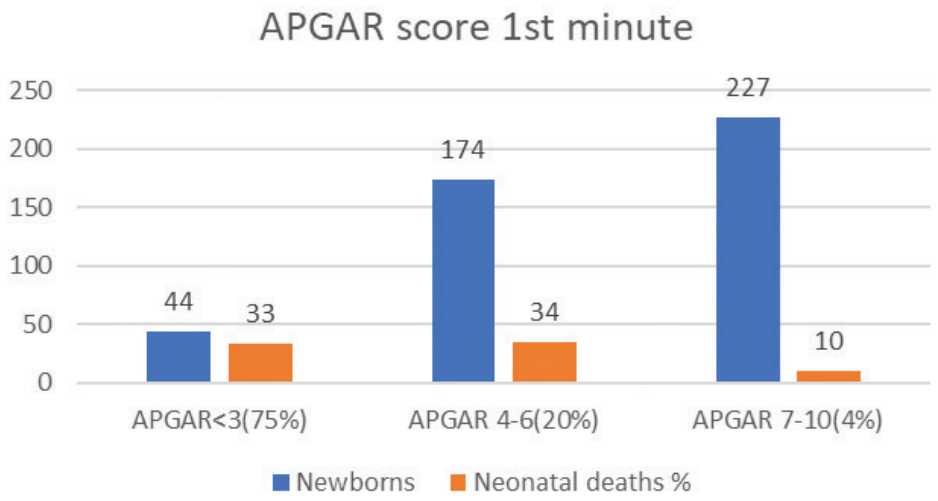

Fig. 3. APGAR score at 1st minute and NNM at the NICU/ UGOC- Skopje

The mortality rate of newborns is even higher with a lower APGAR score at the 5th minute after birth, when the newborn does not accept the initial adaptation and resuscitation after birth and the APGAR score remains low. A low APGAR score < 3 at 5th minute, led to a mortality rate of 89% in newborns; an APGAR score of 4-6 at 5th minute resulted in a fatal outcome in 31% of newborns; and with an APGAR score of 7-10 at 5 minutes, the mortality rate of newborns was significantly lower at 7% **(Fig.4).**

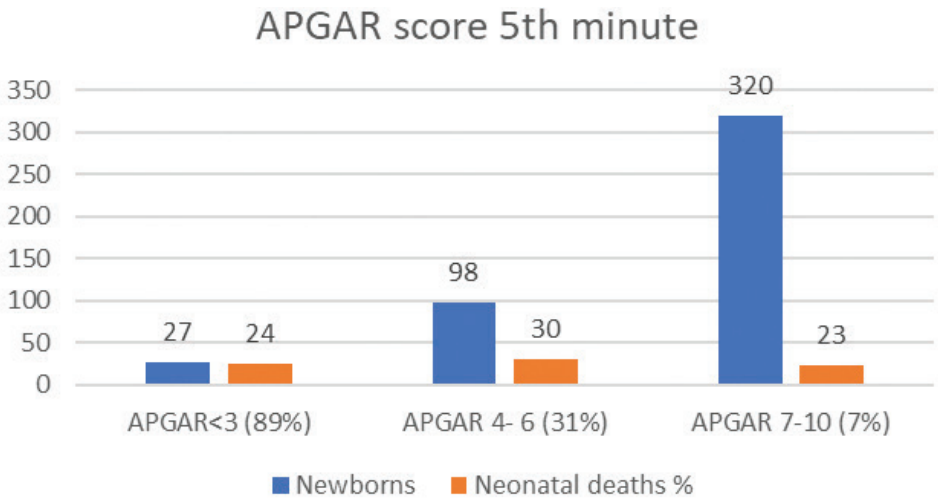

Fig. 4. APGAR score at 5th minute and NNM at the NICU/ UGOC- Skopje

Regarding ARDS (acute respiratory distress syndrome) and asphyxia in newborns who were transferred to the NICU during this period, an increased mortality rate was also observed after birth in newborns who developed ARDS or had asphyxia during birth. Out of 445 newborns transferred to the NICU, 343 newborns developed mild or severe ARDS, and 69 newborns died, or 20.11% of the total number with ARDS **(Fig.5).**

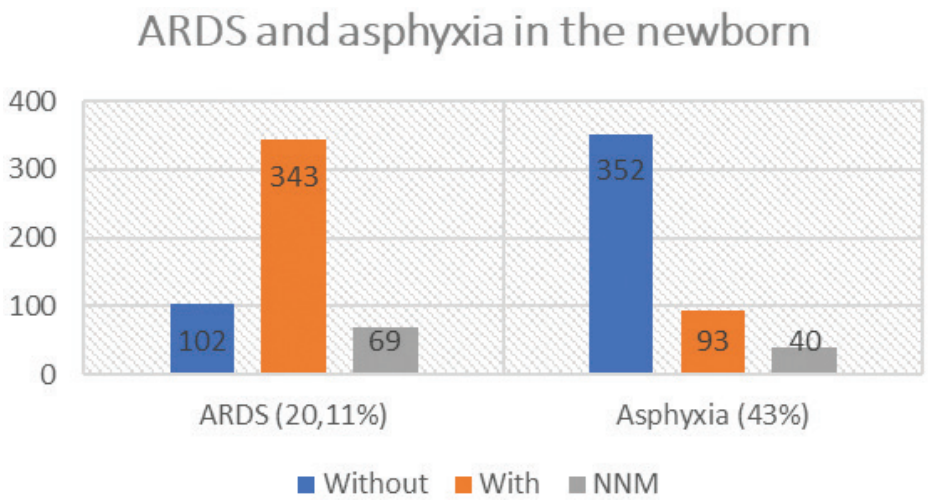

Fig. 5. ARDS and asphyxia in newborn at the NICU/ UGOC- Skopje

Of the total number of newborns transferred to the NICU during this period, 93 newborns from all gestational groups and newborns of different birth weights had asphyxia during delivery. Of these, 40 newborns died, or a high 43% of all newborns with asphyxia transferred to the NICU.

The neonatal mortality rate was the highest in the group of neonates who developed NEC (necrotizing enterocolitis) after delivery, which most often occurs in the group of extremely premature neonates up to 28 weeks of age. Of the 25 neonates who developed NEC after delivery and were transferred to the NICU, 22 (88%) of the neonates died in the neonatal period **(Fig.6).**

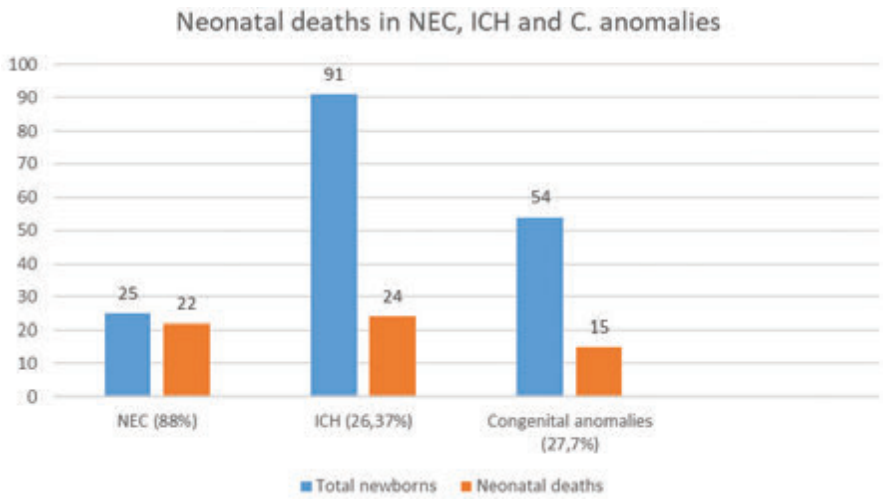

Fig. 6. Neonatal deaths in NEC, ICH and cong. anomalies at the NICU/ UGOC- Skopje

Intracranial hemorrhages (ICH) occurred in 91 newborns out of a total of 445 transferred to the NICU during this period, while 24 newborns from all gestational groups died from ICH, or 26.37% of all newborns who had intracranial hemorrhages (Fig.6).

54 newborns transferred to the NICU had complex or single congenital anomalies, most of which belonged to late premature newborns over 32 weeks of gestation, and 15 of those newborns or 27.7% died (Fig.6).

Many of the 445 neonates transferred to the NICU during this period developed neonatal infections and mild or more serious septic conditions. Of the total number of neonates transferred to the NICU, 321 (72.1%) did not develop sepsis, while 124 (27.7%) developed mild or more serious symptoms of sepsis. Of these, 124 neonates who developed symptoms of sepsis, 32 neonates or 25.8% died in the NICU within the first 28 days after birth **(Fig.7).**

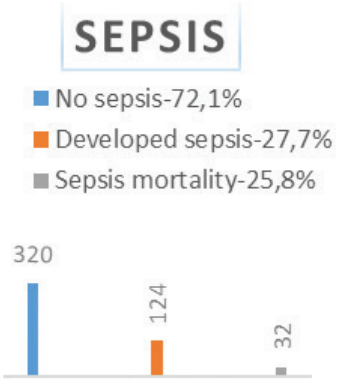

Fig. 7. Neonatal deaths caused by sepsis at the NICU/ UGOC- Skopje

Newborns at risk of preterm birth who had successfully completed maturation with corticosteroids at least 24 hours before delivery had a higher chance of survival in the group of newborns transferred to the NICU. From 279 premature newborns which received corticosteroids for pulmonal maturation before delivery, only 28 (10%) of the newborns died, and 251 (90%) survived. It was not possible to perform prenatal maturation with corticosteroids in 166 newborns, and of these, 49 or 29.5% of them died. The mortality rate in the group where prenatal maturation with corticosteroids was not performed was three times higher than the mortality rate of the newborns who received prenatal maturation with corticosteroids **(Fig.8).**

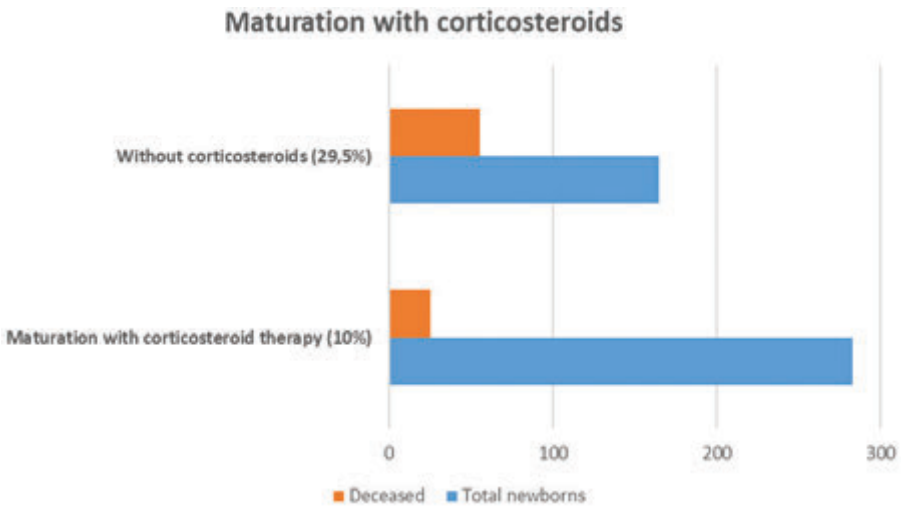

Fig. 8. Maturation with corticosteroids and neonatal deaths at the NICU/ UGOC- Skopje

The way of delivery of these newborns - spontaneous, with intervention (vacuum, forceps) or by cesarean section, also showed a significant impact on the survival pate of newborns. The chances of injury to the mother and the newborn are the lowest during a cesarean section delivery. This was also demonstrated by the examined group of newborns transferred to the NICU

during this period, i.e., the mortality rate was lower among those delivered by a cesarean section (13,6%), unlike newborns delivered spontaneously (26%), where the mortality rate was higher.

Discussion

The study concluded that prematurity and complications of prematurity and low birth weight, such as: lower APGAR score at birth, RDS, NEC, cerebral hemorrhage, infections and sepsis, are the main factors for increasing the NNM rate in newborns transferred to the NICU at the UGOC in Skopje. The study also determined that the neonatal mortality rate is lower in newborns who received prenatal maturation with corticosteroids and in those born by a caesarean section. Each of these factors individually affects the increase in the NNM rate in newborns in the group, and of course the combination of multiple factors together affects the increase in NNM in the group (9).

The mortality rate of newborns transferred at the NICU during the study period is high. Of the 445 newborns transferred at NICU, 77 (17.3%) died. There are studies that have concluded that are very high mortality rates of newborns in Neonatal Intensive Care, with 58.8% neonatal deaths of treated newborns in Ethiopia (18) and with low mortality rates of 4% and 6% in Canada and Brazil (19) (20). A large proportion of newborns born in less developed countries are born out-of-hospital settings (often at home), 20-60% who were then transferred to hospitals. In our study, all analyzed newborns transferred and treated at the NICU were born in hospital.

Prematurity is the main reason for treating newborns in the NICU and of all 445 treated newborns, 414 (93%) were premature, born before 37 weeks of gestation. The majority of extremely premature newborns, less than 28 weeks of gestation, treated in the NICU died, almost 88% of them, as well as newborns with extremely low birth weight under 1000 grams, almost 78% of them. The significant survival rate of newborns born between 28-32 weeks of gestation is notable, with only 12% of newborns treated in the NICU dying, as well as significantly lower mortality rate among newborns born with weight over 1000 grams.

The survival rate of premature infants varies greatly between developed and developing countries. A study conducted by the American College of Obstetricians and Gynecologists, in the United States as a highly developed country as of 2020, reported a survival rate in extremely premature infants at 24 weeks of age in more than 60% of infants, the survival rate of 80% in infants born at 26 weeks of age, more than 90% survival rate in infants born at 28 weeks of age, and about 99% survival rate in infants over 30 weeks of age (21).

The APGAR score at 1st minute <3 and at 5th minute less than 7 has a significant association with the survival rate in newborns. Many studies refer to the APGAR score at 1 and 5 minutes as a direct factor, which has a significant association with the NNM rate. The predictive role of a higher APGAR score at 1 minute, in the survival rate of newborns and in reducing the NNM rate was also demonstrated in the study of Worku B. at al.(22). The predictive role of a higher APGAR score at 5 minutes, in the survival rate of newborns and reducing the NNM rate was found in several other studies (18-20) (24).

Asphyxia in newborns showed a significant association with the NNM rate. Newborns with birth asphyxia have an increased mortality rate, especially in the first 24 h. after birth and in the early neonatal period of up to 7 days after birth, during which period 88% of newborns with

signs of asphyxia died. In a considerable number of studies, asphyxia is associated with a low APGAR score in the 1st and especially with an APGAR score in the 5th minute <7 (18-20). Asphyxia plays one of the most significant roles in the NNM rate, as well as terms of the morbidity and the consequences it leaves in newborns who survive (18-20) (22).

Our study also demonstrated that ARDS - acute respiratory distress syndrome the second leading reason for transferring newborns to the NICU, following prematurity. Of the 445 treated newborns at the NICU, 343 (77.10%) had signs of mild or severe ARDS. The study showed that ARDS had a significant association with the NNM rate. All studies that analyze ARDS confirm that it plays a significant role in the NNM rate and the transfer of newborns to Intensive Care Units, especially in developing countries, with a participation of 27% to 94.5% (57-61). The most common complications of ARDS are intracranial hemorrhage, pneumothorax, bronchopulmonary dysplasia, NEC, sepsis, and death (9) (13) (14) (22).

Our research demonstrated that NEC (necrotizing enterocolitis) had a significant association with the NNM rate. Of the 25 infants who developed NEC, 22 infants died. NEC has been identified as a predictive factor for increased neonatal mortality rate, which other studies have highlighted (9) (13) (23). Intracranial hemorrhages play a significant role in increasing the neonatal mortality rate. Congenital anomalies play a leading role in the neonatal mortality rate in developed countries compared to other causes, unlike in developing countries (19-20).

During the newborns' treatment at the NICU, the clinical and laboratory signs of sepsis were developed in 124 newborns, out of a total of 445 treated newborns during this period, and 32 (25,8%) newborns died. Sepsis is one of the leading causes of neonatal mortality in developing countries, with a share of 30-50% in neonatal mortality shown in several studies (9).

Newborns who received prenatal corticosteroids had a significantly lower risk of NNM compared to newborns who did not receive prenatal corticosteroids, at a ratio of 1:3. Prenatally prescribed corticosteroids showed a predictive role for reducing the NNM rate in this study.

A Japanese multicenter study conducted by JSOG, in 133 level-3 hospitals in Japan, reported an 80% survival rate for premature infants born at 24 weeks of gestation and a birth weight > 500 g. There was a significant difference in the survival rate between infants delivered by a cesarean section and those delivered vaginally at 24–31 weeks of age, favoring cesarean section. In the same study, prenatal corticosteroids and a high 5-minute APGAR score significantly influenced the survival rate of infants (24).

ACOG makes the same recommendations for deliveries at 24 weeks of gestation and beyond, for termination of labor by a cesarean section, use of tocolysis to induce antenatal maturation with corticosteroids, use of antibiotics in PROM, and use of magnesium sulfate as a neuroprotectant (21).

Prematurity and low birth weight, as well as complications of prematurity, are responsible for over 60% of neonatal mortality worldwide (10).

Concluusion

The decline in the NNM rate in N. Macedonia and in the UGOC - Skopje in recent years is largely due to the increase in the survival rate among newborns in the group of 28-32 weeks of

gestation. N. Macedonia still does not have an effective mechanism to increase the survival rate of extremely premature newborns, born during 24-27 weeks of gestation.

Further activities to reduce the NMR rate should be directed towards: prevention of prematurity; strengthening the antenatal primary health care; detection of maternal comorbidities in high-risk pregnancies and timely referral to tertiary centers; proper treatment of infections during pregnancy, childbirth and postpartum in mothers and newborns; as well as reducing complications during childbirth and choosing the most appropriate mode of delivery. The goal of all of these is to obtain a more vital and healthy newborn at birth, who will not need to receive or will receive minimal neonatal care after delivery.

The neonatal mortality rate is a mirror of the health system of a country that sublimates the work, and the functionality in primary, secondary and tertiary health care. The reasons for the increase in the NNM rate are always multifactorial and come from antenatal care, maternal comorbidities, the mode of delivery and the hospital treatment of newborns after delivery. Most of the causes of NNM are preventable.

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www.doi.org/10.55302/MJA259489i

GENETIC RISK IN CARDIOVASCULAR DISEASE: HOW CLOSE ARE WE TO CLINICAL TRANSLATION?

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Abstract

Cardiovascular disease (CVD) remains the leading global cause of morbidity and mortality, influenced by a complex interplay of genetic and environmental factors. By many, medicine is entering the era of personalized management approach, in one direction because of the advances in genomics, particularly genome-wide association studies (GWAS). Monogenic disorders such as familial hypercholesterolemia, driven by mutations in *LDLR, APOB,* and *PCSK9,* illustrate the profound impact of single-gene defects on lipid metabolism and coronary artery disease (CAD) risk. In contrast, polygenic risk scores aggregate multiple variants to refine individual risk prediction for multifactorial diseases such as CAD, though their predictive utility remains modest when added to conventional clinical models. Beyond protein-coding genes, non-coding RNAs (miRNAs, lncRNAs) and endothelial nitric oxide synthase (eNOS) polymorphisms have emerged as key regulators of vascular function and inflammation, offering novel insights into disease mechanisms. However, the clinical translation of genetic testing is hindered by limited predictive accuracy, ethnic bias in genomic research, and challenges in interpreting variants of uncertain significance. Ethical considerations, including psychological impact and data privacy, further complicate its application. Future directions emphasize integrating multi-omics data, diversifying genetic studies, and advancing gene-based therapies such as CRISPR-mediated *PCSK9* editing and RNA silencing approaches. Ultimately, while genetic testing holds promise for precision medicine in cardiovascular care, its implementation must be accompanied by improved risk modeling, equitable population representation, and rigorous clinical validation.

Key words: *Atherosclerosis, Cardiovascular disease, Genomic medicine, Precision cardiology.*

Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, with complex interactions between genetic predisposition and environmental factors driving its development and progression. By many, medicine is entering the era of personalized management approach (1), in one direction because of the advances in genomics, particularly genome-wide association studies (GWAS). Over the past few decades, advances in genetic research have significantly improved our understanding of the inherited components of CVD, identifying numerous genetic variants that contribute to disease susceptibility, modify its clinical course, and shape the individual response to therapeutic interventions. GWAS and large-scale sequencing efforts have uncovered both common and rare genetic variants that play key roles in critical biological pathways such as lipid metabolism, inflammation, vascular homeostasis, and thrombosis.

A major advancement in cardiovascular genetics has been the identification of polygenic risk scores, which aggregate the effects of multiple genetic variants to predict an individual's overall risk of developing conditions such as coronary artery disease (CAD). While these scores enhance risk stratification, particularly when combined with traditional risk factors, their predictive power remains limited by factors such as population-specific genetic variability and the complex interplay between genes and lifestyle. Additionally, monogenic disorders such as familial hypercholesterolemia (FH) have provided insights into the impact of single-gene mutations on CVD risk, highlighting the role of genes such as *LDLR*, *APOB*, and *PCSK9* in cholesterol metabolism and atherosclerosis.

Beyond protein-coding genes, non-coding elements of the genome, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have emerged as critical regulators of gene expression in cardiovascular health and disease. These non-coding RNA molecules modulate processes such as lipid metabolism, endothelial function, and inflammation, offering potential therapeutic targets for precision medicine. Furthermore, genetic variability in endothelial nitric oxide synthase (eNOS) has been linked to vascular dysfunction, further underscoring the molecular complexity underlying CVD.

Despite these achievements, challenges regarding the full clinical translation of genetic discoveries remain. The functional outcomes of many identified genetic variants often remain unclear, and the majority of GWAS studies have been conducted in populations of European ancestry, limiting their applicability across diverse groups. Moreover, there is concern about the clinical utility of genetic testing, as some studies question whether genetic risk prediction significantly improves upon traditional risk models based on lifestyle and clinical factors.

Future research efforts must focus on refining genetic risk prediction through multi-omics approaches, expanding studies in underrepresented populations, and developing targeted therapies that harness genetic insights for personalized treatment strategies. As our understanding of the genetic architecture of cardiovascular diseases continues to evolve, integrating genetic data with environmental and lifestyle factors will be essential for advancing precision medicine and improving patient health outcomes.

The aim of this literature review is to provide a concise overview of the current status of genetic research in cardiovascular diseases, highlighting both its potential and its limitations. This review will examine key genetic associations with CVD, including polygenic risk scores, monogenic disorders such as familial hypercholesterolemia (FH), and the role of non-coding RNAs in disease regulation. In addition, it will explore the impact of endothelial nitric oxide synthase (eNOS) on vascular function and discuss how genetic variations contribute to cardiovascular risk stratification, disease progression, and therapeutic response.

Furthermore, this review will critically assess the clinical utility of genetic testing in cardiovascular diseases, addressing concerns regarding its predictive power, applicability across diverse populations, and integration into existing clinical risk models. By incorporating findings from recent genome-wide studies (GWAS) and functional genomics, this analysis aims to clarify the advantages and limitations of genetic testing in improving patient health outcomes. Finally, future directions in cardiovascular genetics will be explored, including the potential of multi-omics approaches, the expansion of genetic studies to underrepresented populations, and the development of targeted genetic-based therapies. The expected outcome of this review is to provide a balanced perspective on the role of genetic research in cardiovascular disease, guiding future

studies and informing clinical decision-making in the era of precision medicine.

Familial Hypercholesterolemia (FH) and Monogenic Disorders

Familial hypercholesterolemia (FH) is one of the best-characterized monogenic disorders that affect lipid metabolism. FH is primarily caused by mutations in the *LDLR* (low-density lipoprotein receptor), *APOB* (apolipoprotein B), and *PCSK9* (proprotein convertase subtilisin/kexin type 9) genes, which lead to significantly elevated levels of LDL cholesterol and an increased risk of premature atherosclerosis and CAD (coronary artery disease). Individuals with heterozygous FH (1 in 250 people) have a lifetime risk of CAD that is up to 20 times higher than that of the general population, while those with homozygous FH (1 in 160,000 to 1 in 300,000 people) often develop severe CAD in childhood (2). Genetic testing for FH has been successfully implemented in clinical settings, enabling cascade screening of family members and the early initiation of lipid-lowering therapy, which significantly reduces cardiovascular events (3).

Hypertrophic and Dilated Cardiomyopathy

Cardiomyopathies, including hypertrophic cardiomyopathy and dilated cardiomyopathy, also have a strong genetic basis. Hypertrophic cardiomyopathy is primarily caused by mutations in sarcomeric genes such as *MYH7* (beta-myosin heavy chain) and *MYBPC3* (myosin-binding protein C), which account for approximately 80% of genotyped cases (4). Dilated cardiomyopathy, on the other hand, shows greater genetic heterogeneity, with pathogenic variants identified in *TTN* (titin), *LMNA* (lamin A/C), and DSP (desmoplakin), among others (5). Genetic testing for cardiomyopathy has helped refine diagnosis and identify relatives at high risk, but its ability to guide therapeutic decisions remains limited (6).

Mutations in non-sarcomeric genes, such as FHOD3, are considered to be associated with hypertrophic cardiomyopathy in 0.5–2% of patients with a known genetic etiology of hypertrophic cardiomyopathy (7). However, the study by Vodnjov (8) determined that a common variation of FHOD3 c.1646+2T>C is responsible for genetically confirmed hypertrophic cardiomyopathy in 16% of the subjects of Balkan origin. This variation has been confirmed as the second most common cause of hypertrophic cardiomyopathy among individuals tested with Balkan ancestry, after the c.913_914del variant of MYBPC3.

Polygenic Risk Scores and Coronary Artery Disease

Unlike monogenic disorders, CAD (coronary artery disease) is a polygenic disease, which means that it is influenced by the cumulative effects of multiple genetic variants, each having a small individual impact. At present, through GWAS, 350 genetic loci have been associated with CAD (9). Of these, one locus stands out with significant and consistently replicated associations, located on the short arm of chromosome 9, specifically at 9p21.3 (10).

Interestingly, most of the polymorphisms at 9p21.3 are located in non-coding regions and show the strongest association with altered expression of the antisense long non-coding RNA (lncRNA) in the INK4 locus, *ANRIL* (see below in the text). The association between 9p21.3 variants

and CAD appears to be independent of conventional risk factors for atherosclerosis (11). Pechlivanis et al. (12) found that polymorphisms of the 9p21.3 chromosome have a more significant association with coronary artery calcification in men compared to women.

Polygenic risk scores aggregate multiple variants to provide a quantitative estimate of an individual's inherited risk for CAD. Patel et al. (13) introduced *GPS Mult*, a multi-ancestry polygenic risk score that incorporates genetic data from over 1.4 million individuals. *GPS Mult* demonstrated strong associations with both prevalent and incident CAD, identifying individuals with up to three times higher risk compared to those with an average genetic risk.

However, although the polygenic risk score improves genetic risk stratification, its additional predictive value beyond traditional risk models remains a subject of further investigation. Tada et al. (14) and Natarajan et al. (15) found that the polygenic risk score only modestly improves risk prediction when added to clinical algorithms based on age, LDL cholesterol levels, hypertension, and smoking status.

Given that lifestyle and environmental factors also play key roles in the development of CAD, the clinical impact of polygenic risk scores remains a topic of ongoing research.

Atrial Fibrillation (AF)

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and genetic studies have identified a strong hereditary component in its development. Genome-wide association studies (GWAS) have identified more than 100 loci associated with AF, many of which involve genes linked to ion channel function, atrial structure, and cardiac development (16). Mutations in genes such as *PITX2* and *ZFHX3* have been particularly strongly associated with AF susceptibility.

Although AF is a complex disorder influenced by both genetic and environmental factors (such as hypertension, obesity, and sleep apnea), genetic testing is beginning to contribute to risk stratification and the identification of individuals predisposed to early-onset or familial AF. However, the translation of genetic insights into therapeutic strategies remains in its early stages, with current clinical management still relying primarily on traditional risk factors and rhythm-control strategies.

Telomeres and Cardiovascular Disease

Telomeres, the repetitive nucleotide sequences at the ends of chromosomes, play a critical role in maintaining genomic stability. Shortening of telomeres has been associated with cellular aging and the pathogenesis of various cardiovascular diseases. Studies have shown that individuals with shorter leukocyte telomere length have a higher risk of developing coronary artery disease, heart failure, and stroke (17).

Genetic studies have identified variants in genes involved in telomere maintenance, such as *TERT* and *TERC*, that are linked to telomere length and cardiovascular risk (18). However, whether telomere shortening is a causal factor in cardiovascular disease or merely a marker of cumulative exposure to environmental and biological stress remains a subject of debate.

While telomere biology offers an intriguing link between aging and cardiovascular disease, its clinical application as a biomarker for risk prediction is still limited. Additional research is needed to clarify the causal mechanisms and to determine whether therapeutic interventions targeting telomere maintenance could provide benefits in cardiovascular disease prevention and treatment.

Nitric Oxide and Endothelial Function

Nitric oxide (NO) is a key regulator of vascular tone, platelet aggregation, and endothelial function. Genetic variations in the gene for endothelial nitric oxide synthase *(eNOS)*, also known as NOS3, have been associated with cardiovascular disease risk. Polymorphisms such as Glu-298Asp (rs1799983) and 4a/4b VNTR in intron 4 have been linked to altered NO production, endothelial dysfunction, and increased susceptibility to conditions such as hypertension, atherosclerosis, and myocardial infarction (19). Additionally, genetic variations that affect the bioavailability of nitric oxide (NO) may interact with traditional risk factors such as hypertension and smoking, further increasing the risk of atherosclerosis and thrombosis.

In a study by Macedonian researchers involving 36 young individuals with coronary artery disease, variants of the gene encoding eNOS 786 T>C were found in 42%, eNOS 894T in 39%, while eNOS 786 T>C variants were rare, with a frequency of 19% (20).

Non-coding RNA and Cardiovascular Regulation

Non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have emerged as critical regulators of gene expression in cardiovascular diseases, influencing key biological processes such as cholesterol metabolism, endothelial function, and inflammation.

Among the various miRNAs, specific molecules such as *miR-33* and *miR-92a* have shown a significant role in the modulation of cardiovascular health. *miR-33*, for example, inhibits cholesterol efflux by targeting the ATP-binding cassette transporter A1 (*ABCA1*), which is a key transporter in reverse cholesterol transport, thereby contributing to dyslipidemia and the progression of atherosclerosis (21). *MiR-92a* is associated with endothelial dysfunction and the promotion of atherosclerosis through its influence on vascular integrity and inflammatory responses.

Long non-coding RNAs (lncRNAs) also contribute to the pathogenesis of cardiovascular diseases, and ANRIL is one of the most extensively studied. *ANRIL* is associated with the risk of coronary artery disease (CAD) due to its regulatory effects on the proliferation of vascular smooth muscle cells and inflammatory pathways (22). Dysregulation of lncRNAs such as *ANRIL* affects atherogenesis by altering cellular homeostasis within the arterial walls, leading to the formation and progression of atherosclerotic plaques.

Although the therapeutic potential of ncRNA-based interventions is being explored increasingly, their clinical application remains in its early stages. While preclinical studies suggest that targeting specific ncRNAs could offer new strategies for the treatment of CAD and other cardiovascular conditions, significant challenges regarding delivery mechanisms, adverse effects, and validation in large human populations remain.

Further research is necessary to fully understand the mechanistic roles of ncRNAs and to develop safe and effective therapies that harness their regulatory functions for precision medicine in cardiovascular diseases.

Limitations of Genetic Testing in Cardiovascular Diseases

Despite the significant achievements in genetic research and their application in cardiovascular diseases, genetic testing still faces several important limitations that hinder its wide clinical acceptance.

One of the main concerns is the incomplete predictive power of genetic testing, especially in the case of polygenic risk scores (23). Although polygenic risk scores have shown certain usefulness in identifying individuals with increased genetic risk for conditions such as coronary artery disease (CAD), they cover only a part of the total risk. Cardiovascular diseases are influenced by a complex interaction between genetic, environmental, and lifestyle factors, including diet, physical activity, smoking, and socio-economic conditions. The current risk models, which include traditional factors such as cholesterol level, blood pressure, and family history, already provide strong predictive power. Research suggests that adding genetic testing often offers only marginal improvement in risk stratification. This raises concerns about the real usefulness of polygenic risk scores, especially when considering the costs and accessibility of genetic testing for large populations.

Ethnic Bias in Genomic Research

Another significant limitation is the ethnic bias in genome-wide association studies (GWAS). Most large genetic studies have been conducted mainly in populations of European origin, which has led to the development of genetic risk scores that are less applicable to individuals of non-European descent. Since allele frequencies and genetic risk variants can differ significantly among populations, applying risk scores based on European data to individuals of African, Asian, or Latin American origin can lead to errors and misclassification of risk. This problem not only reduces the accuracy of genetic predictions but also worsens existing health inequalities, as individuals from underrepresented populations may receive less accurate assessments of genetic risk. Although there are efforts to include diverse populations in genetic research, there still exists a significant gap in ensuring that genetic findings are equitably applicable to various ethnic groups.

Variants of Uncertain Significance (VUS) and Challenges in Interpretation

Additionally, the presence of variants of uncertain significance (VUS) represents a major challenge for the interpretation of genetic testing. Many genetic variants identified through sequencing still lack well-established functional consequences, which makes it difficult to determine whether they contribute to disease risk or are merely benign variations. In clinical settings, identification of VUS can create uncertainty for both patients and healthcare providers, leading to difficulties in making informed decisions about treatment and preventive measures.

The lack of standardized guidelines for VUS interpretation, as well as the constantly evolving nature of genetic databases, further complicate this issue. Until more research is conducted to clarify the functional impact of these variants, clinicians must be extremely cautious when integrating genetic findings into patient management (24).

Ethical and Psychological Aspects

The psychological burden of genetic risk information must not be overlooked. Individuals who are identified as high-risk based on polygenic risk scores may experience anxiety, stress, or a false sense of inevitability regarding disease development. Additionally, concerns about genetic discrimination and data privacy represent an ethical challenge that must be addressed (25).

Concerns Regarding Direct-to-Consumer (DTC) Genetic Testing

The emergence of DTC genetic tests has made genetic risk information more accessible. However, their reliability and clinical utility remain subjects of debate. The American College of Medical Genetics and Genomics has warned against the unregulated use of DTC genetic testing, emphasizing the need for professional genetic counseling (26). Given these limitations, genetic testing in cardiovascular diseases should be viewed as a complementary tool, rather than a replacement for traditional methods of risk assessment. Although genetic insights can offer valuable information, they must be interpreted in the context of existing clinical risk factors and the overall medical history of the patient. Integration of genetic testing into clinical practice will require continuous refinement of risk models, improved representation of diverse populations in genetic research, and stronger validation of genetic markers before they can be confidently used for clinical decision-making in prevention and treatment of cardiovascular diseases.

Future Directions in Cardiovascular Diseases Genetic Research

To improve the clinical use of genetic testing in cardiovascular diseases, future research must address current limitations and explore new approaches that integrate genetic data with other molecular and clinical factors. One promising direction is the refinement of polygenic risk assessments through integration of multi-omics data. By including not only genetic variants but also proteomic, metabolomic, and epigenomic data, researchers can develop more complex risk models that provide deeper understanding of disease mechanisms (27). Multi-omics approaches have the potential to improve the predictive accuracy of genetic testing by identifying dynamic interactions between genes and biological pathways that contribute to cardiovascular diseases (28).

Another critical area for future research is expanding genetic studies to include more diverse populations. As discussed earlier, the overrepresentation of European ancestry in GWAS limits the applicability of current genetic risk assessments to other ethnic groups. Increasing the representation of African, Asian, and Indigenous populations in genetic research is essential for developing risk models that are more broadly applicable. Large international collaborations and biobanks that prioritize diversity, such as the "All of Us Research" program in the U.S., are already taking steps to bridge this gap. However, continued efforts are needed to ensure that future genetic discoveries benefit all populations equally.

Additionally, the development of targeted therapies based on genetic profiles represents an exciting perspective in cardiovascular medicine. Advances in gene-editing technologies such as CRISPR-Cas9 have opened new possibilities for direct modification of disease-causing genetic variants (29). For example, current studies are exploring how CRISPR-based interventions could be used to inactivate genes such as *PCSK9*, with the aim of lowering LDL-cholesterol levels and reducing atherosclerosis risk (30). Similarly, RNA-based therapies, including siRNA (small interfering RNA) and antisense oligonucleotides, are being investigated as potential tools for modulating gene expression in cardiovascular diseases. Inclisiran was developed; it reduces the production of PCSK9 through messenger ribonucleic acid (mRNA) silencing. The inclisiran administration twice a year reduces LDL-C by over 50% in a range of patient groups. (31). Although these approaches are still in early stages of development, they hold significant potential for precision medicine strategies tailored to individual genetic profiles.

In conclusion, the future of genetic research in cardiovascular diseases will depend on the ability to overcome current limitations while leveraging new technologies to improve risk prediction, expand population applicability, and develop innovative therapeutic approaches (32). As research advances, genetic testing has the potential to evolve from an academic tool into a routine part of cardiovascular risk assessment and personalized medicine. However, realizing this potential will require continuous interdisciplinary collaboration among geneticists, cardiologists, bioinformaticians, and public health experts to translate genetic innovations into meaningful improvements in patient care.

Conclusion

While genetic testing has potential in the field of cardiovascular medicine, especially for certain hereditary conditions, its limitations require a careful and informed approach. It is crucial to emphasize that accurately interpreting genetic findings is essential for reliably distinguishing between pathogenic mutations, benign variants, and variants of uncertain significance. To support wider adoption in the population, standardized protocols may be necessary. Healthcare professionals should provide comprehensive counseling for patients to understand the possible outcomes, benefits, and limitations of genetic testing. Continuous research and refinement of genetic testing methods are essential for increasing their predictive accuracy and clinical usefulness in the treatment of cardiovascular diseases.

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CASE REPORT *UDK: 616.33-006.6-089.87*

www.doi.org/10.55302/MJA2594100e

ANAESTHETIC MANAGEMENT FOR TOTAL GASTRECTOMY IN A PATIENT WITH PREVIOUS ASCENDING AORTIC DISSECTION REPAIR

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Abstract

Introduction: Total gastrectomy remains the gold standard for gastric adenocarcinoma treatment. The procedure poses significant anesthetic challenges due to its complexity and the physiological stress associated with major abdominal surgery. These challenges are further amplified in patients with a history of other diseases, especially those affecting the cardiovascular system, who require careful hemodynamic management and tailored perioperative strategies in the operating room. Case Presentation: This case report presents the perioperative management of a 62-year-old male diagnosed with gastric adenocarcinoma who underwent total gastrectomy. The patient had undergone surgical repair of an ascending aortic dissection three years earlier. Preoperative transthoracic echocardiography was obtained to assess cardiac function and graft integrity. Anesthetic induction was performed with carefully titrated agents to maintain hemodynamic stability. Invasive arterial blood pressure monitoring was employed throughout the procedure to allow real-time hemodynamic management. Analgesia was provided via a thoracic epidural catheter, with a continuous infusion of low-concentration bupivacaine (0.125%) administered to minimize sympathetic blockade and maintain stable blood pressure. The patient reported minimal discomfort and did not require additional analgesics during the recovery period. He was discharged in good general condition on postoperative day eight.

Conclusion: Patients with prior ascending aortic dissection repair undergoing major abdominal surgery pose significant anesthetic challenges. With appropriate monitoring and individualized management, good outcomes can be achieved.

Introduction

Gastric cancer represents a significant global health challenge, ranking as the fifth most common cancer worldwide and the third leading cause of cancer-related mortality. (1) Despite advances in the field of medical and radiation oncology, surgical resection is a crucial intervention and remains the mainstay of the gold standard treatment (2). Total gastrectomy is a major

abdominal surgery often associated with significant hemodynamic fluctuations, blood loss, and postoperative pain management challenges.

Patients with prior ascending aortic dissection repair may represent a higher-risk subgroup in noncardiac surgery, due to altered vascular compliance, graft hemodynamics leading to altered autonomic/sympathetic regulation, and potential for hemodynamic lability when exposed to surgical stress, although direct evidence is limited.

The perioperative literature offers limited guidance for anesthetic management in this particular intersection of aortic disease and extensive abdominal surgery. In accordance with the evidence-based perioperative management for total gastrectomy and contemporary guidelines for the perioperative management of cardiac patients undergoing noncardiac surgery, we adopted a multimodal, evidence-based anesthetic approach tailored to this patient's unique cardiovascular and surgical risk profile. The perioperative strategy—including hemodynamic optimization, analgesic planning, and anesthetic management—was designed to minimize physiologic stress and maintain cardiovascular stability. The details of this individualized approach are presented in this case report.

Case Presentation

A 62-year-old male patient, 172 cm in height and weighing 84 kg (BMI: 28.5 kg/m^2), smoker, classified as ASA class 3, with a diagnosis of gastric adenocarcinoma confirmed by gastroscopic biopsy, was admitted to the University Clinic for Abdominal Surgery in Skopje for surgical management. He had significant medical history related to ascending aortic dissection, for which he underwent sternotomy and surgical repair three years earlier, including replacement of the ascending aorta and aortic arch with a prosthetic graft.

Regular medications included bisoprolol and aspirin, with aspirin being withheld two days before surgery. Airway evaluation demonstrated adequate mouth opening, Mallampati class II, and normal neck mobility. Routine laboratory investigations, coagulation profile, and chest radiography were all within normal limits. The ECG showed normal sinus rhythm with heart rate of 75 bpm, and inverted T wave in precordial leads.

Considering the patient's cardiovascular history, a preoperative transthoracic echocardiographic evaluation was conducted to assess cardiac function and the integrity of the aortic graft. The examination demonstrated a left ventricular ejection fraction of 55% with preserved systolic and diastolic function. Mild left atrial enlargement was observed, measuring 55 mm (normal reference value for males: <40 mm). The valvular assessment confirmed normal function of both the mitral and tricuspid valves, while the prosthetic graft and aortic dimensions appeared intact and within normal limits.

The planned anesthetic technique involved general endotracheal anesthesia (GETA) in combination with epidural analgesia for perioperative pain management. The associated risks and procedures were thoroughly discussed, and a written informed consent was obtained.

On the day of surgery, the patient continued his prescribed morning dose of bisoprolol and was premedicated with 500 mL of intravenous crystalloid solution, intravenous famotidine, metoclopramide, and appropriate antibiotic prophylaxis in accordance with institutional protocol.

Standard ASA recommended monitoring was established, which included ECG, non-invasive blood pressure (NIBP), and oxygen saturation (SpO_2). The baseline parameters recorded were: blood pressure of 180/90 mmHg, heart rate of 80 beats per minute, and SpO_2 at 98%. After explaining the procedure once again, and achieving anxiolysis by slow iv administration of 2 mg of midazolam, a thoracic epidural catheter was placed at T8–T9 for analgesia.

After preoxygenation with 100% oxygen via facial mask with a fresh gas flow of 7 L/min for 2 minutes, anesthesia induction was then achieved with the following medications: fentanyl (1 mcg/kg/BW), lidocaine (0.6 mg/kg/BW), propofol (2 mg/kg/BW). Rapid sequence intubation was performed using succinylcholine (1mg/kg) to ensure prompt airway control while minimizing the risk of aspiration. After successful first attempt intubation, muscle paralysis was achieved with rocuronium (0.6 mg/kg). Anesthesia maintenance was achieved with Sevoflurane at 0.6 MAC. Mechanical ventilation was initiated in pressure-controlled volume-guaranteed mode, with a tidal volume set at 6 mL/kg of predicted body weight and a positive end-expiratory pressure (PEEP) of 5 cm H_2O, and respiratory rate set to achieve end tidal CO2 between 35-45 mmHg.

After induction, the patient remained hemodynamically stable. Invasive blood pressure monitoring was managed by catheterizing the left radial artery. Analgesia was provided via a continuous epidural infusion of Bupivacaine 0.125% delivered at a rate of 8ml/h.

Intraoperative fluid therapy was carefully titrated to maintain euvolemia, guided by continuous monitoring of hemodynamic parameters, urine output, and serial arterial blood gas analyses. Additional analgesia included intravenous administration of 1 g of paracetamol and 1.5 g of magnesium sulfate. The patient remained hemodynamically stable throughout the procedure, with minimal estimated blood loss. The total surgical duration was three and a half hours. At the conclusion of the procedure, residual neuromuscular blockade was reversed, and the patient was uneventfully extubated in the operating room. Afterwards, the patient was transferred to the PACU where his stay was uneventful.

Postoperatively, the patient received antibiotic prophylaxis, antiemetic therapy, and anticoagulation with enoxaparin (1 mg/kg). Analgesia was maintained with epidural administration of morphine three times a day, supplemented with intravenous paracetamol and metamizole. Vital signs and urine output were closely monitored, with supported diuresis as clinically indicated. The patient remained hemodynamically stable throughout the postoperative period and was discharged on the eighth postoperative day. At three-month follow-up, he remained clinically stable with no deterioration in cardiac function and was undergoing adjuvant chemotherapy.

Discussion

Aortic dissection, though uncommon, is a catastrophic vascular disorder characterized by a tear in the intimal layer of the aorta, leading to the separation of the aortic wall layers. Blood enters between the intima and media, propagating the dissection either proximally or retrograde, resulting in compromised blood flow to vital organs. Acute aortic dissection carries extremely high mortality rates, with many patients dying before reaching emergency care. (3) The International Registry of Acute Aortic Dissection is a consortium a 21 large referral centers around the world. This registry's data have shown that the in-hospital mortality of patients with ascending aortic disease is approximately 27% in those who undergo timely and successful surgery. (4)

In vivo studies have revealed that the introduction of an aortic graft augments systolic and pulse pressure (PP), alters waveforms and increases ventricular afterload (5,6,7). It was also found that aortic arch repair can cause shorter inflection time, leading to an increased systolic pressure in comparison to an age-matched control. In combination, these hemodynamic alterations may contribute to subsequent cardiovascular complications such as hypertension, myocardial infarction and coronary heart disease. The proximal graft increased aortic systole and pulse pressure to a greater degree than a distal aortic graft. The proximal graft pulse pressure percent change was twice as high as the distal graft pulse pressure percent change. (5)

Given these considerations, it is understandable that the literature on perioperative management of patients following this type of surgical repair is limited, and that managing potential complications during surgery can be particularly challenging, especially for complex procedures such as total gastrectomy. Accordingly, the anesthetic plan and perioperative management were developed in accordance with evidence-based perioperative management for total gastrectomy, as well as contemporary guidelines for the perioperative care of cardiac patients undergoing noncardiac surgery.

Following the patient's history and physical examination, a preoperative cardiovascular risk assessment was performed using the 2019 AUB-HAS2 Cardiovascular Risk Index, which indicated an intermediate risk (11%) of adverse events within the 30-day postoperative period. In accordance with current recommendations, a transthoracic echocardiographic evaluation was subsequently conducted, confirming normal cardiac function as well as intact graft integrity. (8,9) The risk of perioperative complications is influenced by factors such as the presence of comorbidities, the patient's pre-surgery health status, and the urgency, scale, type, and length of the surgical procedure. (10)

In accordance with the latest 2024 AHA/ACC/ACS/ASNC/HRS/SCA/SCCT/SCMR/SVM Guideline for Perioperative Cardiovascular Management of Patients Undergoing Noncardiac Surgery, which states that abrupt discontinuation of beta-blockers prescribed for long-term indications is harmful and should be avoided (11,12), perioperative beta-blocker therapy should be carefully titrated based on clinical judgment and continued throughout hospitalization and at discharge unless contraindicated. Therefore, the patient's beta-blocker therapy was maintained perioperatively.

Hemodynamic monitoring and management are cornerstones of perioperative care. The goal of hemodynamic management is to maintain organ function by ensuring adequate perfusion pressure, blood flow, and oxygen delivery to prevent perioperative complications – that remain as high as almost 20% in patients having elective non-cardiac surgery. (13, 14). Continuous arterial pressure monitoring allows detecting arterial pressure changes in real-time and can thus help reduce arterial pressure fluctuations and hypotension. (15, 16,17)

In this patient, analgesia was administered via a thoracic epidural catheter—an evidence-based approach, demonstrating the benefits of regional techniques in major abdominal surgery in patients with significant cardiovascular comorbidities. Continuous thoracic epidural analgesia provides effective pain control, reduces perioperative stress responses, and minimizes the need for systemic opioids, thereby promoting earlier mobilization and improved pulmonary function. Moreover, in patients with cardiovascular disease, epidural analgesia has been shown to contribute to greater hemodynamic stability and reduced myocardial oxygen demand. (18). Meanwhile, perioperative cardiovascular guidelines underscore the importance of tailored re-

gional techniques that minimize hemodynamic stress and optimize pain control in patients with vascular or cardiac disease. (19, 20).

Another major challenge encountered was the intraoperative and postoperative fluid management. The combined effects of surgical blood and fluid loss, thoracic epidural analgesia, and general anesthesia often contribute to signs of relative hypovolemia in the immediate postoperative period. Conversely, excessive water and sodium administration increases the risk of respiratory complications and delays the return of bowel function. Current perioperative evidence supports a goal-directed approach to fluid therapy aimed at achieving near-zero fluid balance, even if the temporary use of low-dose vasopressors is required to manage epidural-related hypotension (21). Therefore, intraoperative and postoperative fluid therapy was carefully titrated, guided by continuous hemodynamic monitoring, urine output, and serial arterial blood gas analyses.

Close postoperative surveillance was essential to detect early signs of hemodynamic instability, graft complications, or cardiac ischemia. Analgesic titration continued under vigilance to maintain hemodynamic balance while allowing early mobilization, pulmonary hygiene, and gut recovery. The patient's favorable recovery in this case underscores the value of meticulous planning, multimodal monitoring, and guideline-informed decision making.

Conclusion

This case highlights the complex perioperative challenges in managing a patient with a history of ascending aortic dissection repair undergoing major abdominal surgery. Applying evidence-based perioperative strategies and cardiovascular risk optimization enabled individualized hemodynamic management, balanced fluid therapy, and effective pain control through thoracic epidural analgesia. Careful coordination among surgical, anesthetic, and critical care teams ensured hemodynamic stability and facilitated an uncomplicated recovery. Our experience underscores the importance of a multidisciplinary, guideline-informed approach for patients with significant cardiovascular history undergoing noncardiac surgery.

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CASE REPORT *UDK: 616.12-08984-089.5-053.2*

www.doi.org/10.55302/MJA2594107kgj

WALKING THE TIGHTROPE: NAVIGATING ANESTHETIC CHALLENGES IN A PEDIATRIC CARDIAC SURGERY CASE WITH PORTAL HYPERTENSION AND SEVERE THROMBOCYTOPENIA

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Abstract

Background: Anesthetic management of pediatric patients for corrective cardiac surgery is highly complex when portal hypertension, severe thrombocytopenia and inherited thrombophilia coexist. The interplay between bleeding and thrombotic risks requires meticulous planning.

Case report: We present the case of a 5-year-old child with congenital heart disease and severe thrombocytopenia who was scheduled for corrective cardiac surgery. The child was hospitalized for the first time 6 months earlier because of a sudden abdominal pain and hematemesis, leading to the diagnosis of portal hypertension and inherited thrombophilia. At the time he presented for surgery, the child had very low platelets, 36x10^9/L with no other abnormalities in the laboratory results. Anesthetic management focused on balancing hemorrhage and thrombosis, optimizing coagulation with viscoelastic testing, goal-directed transfusion therapy and maintaining stable hemodynamics. Surgery was completed successfully, with close postoperative monitoring in the pediatric cardiac ICU.

Conclusion: This case highlights the challenges of managing a child with combined bleeding and thrombotic risks. Individualized anesthetic strategies and multidisciplinary approach are essential to achieve safe outcomes in such high-risk background.

Key words: *congenital cardiac surgery, portal hypertension, thrombocytopenia, thrombophilia*

Introduction

Portal vein thrombosis (PVT) is a rare but serious condition leading to impaired hepatic blood flow, specifically obstruction in the blood flow of the splenic and superior mesenteric veins. To date, the pathogenesis of PVT in children still remains unexplained, yet it is major cause of portal hypertension in children and adolescents. (1) In pediatric patients, portal vein thrombosis can result from underlying prothrombotic disorders, abdominal infections or surgical complications, and may be manifested by abdominal pain, vomiting or gastrointestinal bleeding. Hereditary thrombophilias that are known to predispose to venous thrombosis and PVT include certain mutations of the prothrombin, factor V Leiden or methylenetetrahydrofolate reductase genes or deficiency of one of the natural anticoagulant proteins C and S. (1) In our patient, there were mu-

tations in several thrombophilic genes and a deficiency of anticoagulant protein C, but this result was obtained less than 3 months after the diagnosis of portal vein obstruction, therefore, falsely low levels related to active thrombosis are not excluded. Another test in further time was not done.

PVT often manifests with symptoms like splenomegaly, hepatomegaly or ascites, that result from ensuing portal hypertension (PH). Due to the obstruction in the portal vein and the increased hepatic venous pressure, a net of portosystemic collaterals is formed, resulting in increased flow in splenorenal, paraumbilical or gastric and esophageal veins. (2)

Anesthesia in patients with portal hypertension is really challenging. The anesthetist must carefully balance hemodynamics, choose drugs with minimal hepatic metabolism and be prepared for significant bleeding risk. The patients with portal hypertension often have low systemic vascular resistance and high cardiac output. (3) This makes them very sensitive to anesthetic agents, which can further lower blood pressure. In our patient with coarctation of the aorta, there is a severe afterload mismatch: the upper body is hypertensive, while the lower body is hypoperfused. It is therefore essential to maintain adequate proximal perfusion pressure without compromising distal circulation (kidney, gut, liver).

Sometimes, there are respiratory considerations too. For instance, if there is an ascites, it can cause reduced lung volumes, increase risk of hypoxemia and impaired ventilation under anesthesia. Massive ascites increases the intra-abdominal pressure, predisposing the patient to reflux and aspiration during induction. (4)

Also, sudden increases in venous pressure (e.g. from intubation, coughing or fluid overload) may precipitate variceal bleeding. (5) Often there is thrombocytopenia due to splenic sequestration and hypersplenism. Impaired liver function reduces synthesis of coagulation factors. Anesthesia must minimize fluctuations in venous pressure and be prepared for massive transfusion (6).

Case Presentation

A 5-year-old child, weighting 17kg, with coarctation of the aorta was admitted for elective surgery, reconstruction of the aorta with end-to-end anastomosis. Six months prior, the patient had experienced sudden abdominal pain and hematemesis, prompting investigations that revealed extrahepatic portal vein thrombosis due to inherited mutations of several thrombophilic genes. Given that the obstruction was not complete, i.e., tunnels, so-called cavernomas, were created in the thrombus itself, surgical creation of a shunt to bypass the portal vein was not necessary. The patient underwent antegrade transvenous embolization of the varicose fundal gastric veins 2 months prior to surgery in Turkey, but on his last checkup, he had another enlarged gastric varices on top of splenomegaly and severe thrombocytopenia, which are associated with continued persistence of portal hypertension.

On admission, laboratory evaluation showed severe thrombocytopenia (platelets:36x10^9/L), coagulation parameters were otherwise normal, and unremarkable renal and hepatic function except for evidence of portal hypertension confirmed by ultrasound.

Preoperatively, the anesthetic team conducted a detailed risk assessment, focusing on balancing the risk of bleeding and thrombotic complications and multidisciplinary collaboration with hematology, cardiology and surgical teams to formulate a perioperative plan.

In consultation with the hematology and transfusion specialists, we treated the thrombocytopenia with steroids and immunoglobuline, but the platelet count did not improve during treatment. Following bone marrow biopsy, a normal count of blood elements was found with no pathological cells, so it was confirmed that the thrombocytopenia was the result of increased sequestration of platelets in the portal circulation and spleen. The same conclusion was confirmed by the resistance to an increased platelet count following platelet transfusion.

We suggested that the surgery should be delayed untill splenectomy or embolization of the splenic artery is performed, but due to the severity of the coarctation, impossibility to implant a stent to the stenotic area and the unsafe use of antiplatelets drugs, the surgical team insisted that there is an urgent need for open surgery.

On the day of surgery, the patient was transfused with a unit of platelets (six pooled platelets following apheresis of donor whole blood, approximately 10ml/kg) two hours prior to surgery. The rechecked platelet count immediately before surgery was 62x10^9/L. He was also anemic with a haemoglobin level of 87g/L. The preoperative international normalized ratio (INR) was 1.14 and activated partial thromboplastin time (aPTT) was 24 seconds (21-36 sec).

The induction of anesthesia was done with titrating doses of propofol and rocuronium. In patients with coarctation of the aorta, propofol provides rapid and reliable induction; however, its vasodilatory and negative inotropic effects may precipitate hypotension, thereby reducing coronary, cerebral and systemic perfusion distal to the coarctation site. Therefore, careful titration is essential to avoid abrupt decreases in systemic vascular resistance, and adequate intravascular volume status should be ensured (7). Although rocuronium is mainly eliminated by the liver, it can be safely used in patients with portal hypertension if the hepatic function is preserved (8).

After induction of anesthesia, the central venous access and arterial line were established carefully to minimize trauma, with ultrasound guidance to avoid inadvertent vascular injury and bleeding. Standard ASA monitors were applied, including invasive arterial pressure, central venous pressure and continuous ECG. Regarding hemodynamic management, we inserted two arterial lines - one pre-ductal (right arm) to demonstrate perfusion to brain/heart and one post-ductal (femoral) to demonstrate distal perfusion. Therefore, blood pressure was closely monitored (beat-to-beat) and maintained around 85-95 mmHg systolic, to optimize perfusion without increasing portal pressures and reduce the risk of variceal bleeding. We also did not insert nasogastric tube to avoid trauma of the gastric mucosa.

Following initiation of surgery and during the chest opening, another unit of platelets was transfused and one unit of 350ml packed red blood cells as well. Intraoperatively, we administered 15mg/kg (~250mg) bolus dose of tranexamic acid followed by continuous infusion 5mg/kg/h. We also monitored the blood gases every 30 min for signs of bleeding and used ROTEM for real-time guidance and to maintain hemostatic balance while avoiding overcorrection that could exacerbate thrombosis risk. ROTEM analysis had not shown abnormal results preoperatively or postoperatively. During clamping of the aorta we did not use heparin because of the risk of bleeding, while the total cross clamping time was less than 15 minutes.

Surgery was completed successful and the patient was transferred to the pediatric cardiac ICU with ongoing hemodynamic and coagulation monitoring. Postoperative platelet count was 67x10^9/L, thus no further platelet transfusions was administered. The tranexamic acid infusion was continued in the first 24 hours after surgery. Early extubation in the first six hours after

surgery was done with careful monitoring of hypertension and bleeding.

A single thoracic drain was placed intraoperatively, with postoperative drainage amounting to 20ml of blood within the first 24 hours.

Two months after surgery, the patient platelet count was moderately low, 58x10^9/L, so despite the thrombophilic genetic background he was not recommended any antithrombotic drugs.

Discussion

Preoperative thrombocytopenia could be associated with an increased risk of bleeding. Excessive bleeding leads to increased mortality, morbidity, transfusion requirements and reintervention. (9) Platelet thresholds in pediatric cardiac surgery are not always uniform, but there are widely accepted practice ranges. The general principle is that platelet count should be >= 100x10^9/L before major surgery involving cardiopulmonary bypass (CPB). If there is a moderate thrombocytopenia (50-100x10^9/L), surgery can still be performed with availability of platelet transfusion and point-of-care coagulation monitoring (ROTEM/TEG). In case of severe thrombocytopenia (<50x10^9/L), elective cardiac surgery is considered unsafe and correction with platelet transfusion or addressing the underlying cause is generally recommended before proceeding (10).

Children tolerate thrombocytopenia somewhat differently than adults, but CPB amplifies platelet dysfunction, making higher counts desirable. Fortunately, the corrective cardiac surgery in our patient did not require CPB. The platelet function (qualitative) can be just as important as the absolute count, so viscoelastic testing (ROTEM/TEG) is increasingly used to guide transfusions. (11)

There have been some reports where splenectomy was performed in an attempt to improve platelet counts pre-cardiac surgery and also the use of off-pump cardiac surgery to reduce post-operative bleeding. There is one case report that suggests that safe and successful cardiac surgery is feasible in a group of patients despite a very low platelet count (< 20 × 109/L). (12) In this group of patients, coagulopathy should be promptly treated in the immediate postoperative phase and management could be guided by point-of-care TEG analysis and this may be possible in the future with a more reliable point-of-care platelet function assessment kit.

Genetic thrombophilia predisposes to arterial and venous thrombosis. In cardiac surgery, the risk is heightened due to altered hemostasis and endothelial activation during CPB, surgical manipulation of the aorta which brings risk of clot formation at repair site and postoperative reduced mobility and central lines. (13) These patients often require carefully titrated anticoagulation, both intraoperatively and postoperatively. Standard heparinization 400IU/kg is used for CPB; ACT monitoring is essential. If surgery is done without CPB (such as ours) heparin bolus is still usually given to reduce clot risk. We did not proceed with this because the surgeons were convinced that they will be finished with the aortic repair in less than 15 minutes. A blessing in disguise was that our patient had low platelet count, so he did not require long- term postoperative coagulation or antithrombotic prophylaxis. Thrombosis involving the aortic arch or stenotic coarctation segment is rare in children; most published reports are isolated neonatal/infant cases or thrombotic complications after stent/graft placement. (14-17)

Two months after surgery the child is recovering well, with no evidence of rethrombosis and stable hemodynamic status. Importantly, although thrombocytopenia persists (platelet count 53x10^9/L on last checkup), there has been no clinically significant bleeding or deterioration. The absence of new thrombotic events in the early postoperative period is reassuring, considering the prothrombotic background associated with portal hypertension.

Long-term follow up will be essential to monitor vascular patency, control of portal hypertension and the evolution of thrombocytopenia in this patient.

Overall, this case demonstrates that with meticulous perioperative management, excellent outcomes are achievable, even in high risk pediatric patients with coexisting hematologic abnormalities and congenital cardiovascular malformations.

Conclusion

This case underscores the complexity of anesthetic management in children with combined bleeding and thrombotic risks. Portal hypertension and splenomegaly contribute to severe thrombocytopenia and increased risk of bleeding during surgery, while thrombophilia predisposes to intraoperative and postoperative clot formation. Multidisciplinary coordination, goal-directed transfusion strategies and vigilant intra and postoperative monitoring are essential to ensure safe outcomes.

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CASE REPORT *UDK: 616.31-089.5:616.831-009.11]-053.2*

www.doi.org/10.55302/MJA2594113k

ANESTHETIC MANAGEMENT OF A 6-YEAR-OLD CHILD WITH CEREBRAL PALSY UNDERGOING DENTAL SURGERY

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Abstract

Cerebral palsy (CP) is a group of non-progressive neurological disorders affecting posture and movement, mostly resulting from perinatal intrauterine disorders to the developing infant brain.

A 6-years old, male patient with spastic cerebral palsy (CP), which predominantly affected the right extremities more than the left ones, required dental surgical treatment of multiple tooth extractions and restorations, under general anesthesia. He received allogenic umbilical cord derived mesenchymal stem cells treatment one time, 6 months before the dental intervention.

The intervention under general anesthesia lasted approximately one hour and concluded successfully. Muscle relaxants were purposely avoided. The anesthesia was reversed and the patient was extubated successfully without complications and there was no sign of any adverse reactions postoperatively.

Key words: *Cerebral palsy, dental surgery, disabilities, general anesthesia, mesenchymal stem cells, pediatric patient*

Introduction

Cerebral palsy (CP) is a group of non-progressive neurological disorders affecting posture and movement, mostly resulting from perinatal intrauterine insult to the developing infant brain. Most cerebral palsy cases result from factors occurring before birth (antepartum). Conditions such as birth asphyxia, perinatal lack of oxygen, congenital abnormalities, bleeding within the brain's ventricles, and infections during pregnancy, all play a role in the development of CP. In developed countries, the rate of cerebral palsy in the general population is approximately 1 per 500 live births. Various CP-associated conditions often necessitate surgical procedures that require careful anesthetic management. Intraoperative challenges such as low blood volume, decreased body temperature, muscle spasms, seizures, and prolonged recovery can complicate anesthesia in these patients. A detailed preanesthetic assessment is essential for improving both intraoperative and postoperative care (1-5).

Historically, interventions for cerebral palsy have largely centered on medical and physical approaches, though evidence supporting their effectiveness has often been limited. By incorporat-

ing outcome measures that focus on quality of life and participation, treatments are now being developed that provide greater value and relevance to individuals with cerebral palsy and their caregivers (6).

For many years, cerebral palsy (CP) was primarily categorized based on a patient's resting muscle tone, such as hypertonic (spastic), dyskinetic, ataxic, or mixed types. However, this simplistic classification has been replaced by more comprehensive systems that consider a patient's motor function, level of physical activity, and psychosocial capabilities. These updated classifications allow clinicians to plan daily care strategies to better meet the unique needs of each patient (7).

The clinical manifestation can vary widely, from mild monoplegia with normal intellectual function to severe full-body spasticity accompanied by intellectual disability. The shared characteristic is a motor impairment caused by a non-progressive brain lesion or abnormality that appears early in life (8).

Children with cerebral palsy (CP) often require specialized care during preoperative preparation and assessment to anesthesia approach due to underlying neurological, respiratory, and musculoskeletal issues. Anesthetic management for these patients requires attention to specific physiological considerations and potential medication interactions with the underlying disease (9).

Case report

This article presents a case report of a 6-year-old male patient with spastic cerebral palsy (CP), which predominantly affected the right extremities more than the left ones, who required dental treatment of multiple tooth extractions and restorations under general anesthesia. Our patient had a stroke in the early postpartum period, affecting the left cerebral hemisphere, resulting in weakness in the right arm and leg. He has undergone various diagnostic procedures and treatments, including rehabilitation. Six months before, he received allogenic umbilical cord derived mesenchymal stem cells for cerebral palsy with intrathecal, intravenous, and intramuscular administration at the Regenerative Medicine and Stem Cell Production Center under general anesthesia, which have provided partial improvements.

The child was born following a normal and well-monitored pregnancy, delivered at term, spontaneously in a cephalic presentation, with a birth weight of 4100 grams and length of 56 cm, and with a 9/10 Apgar score. Soon after birth, skin color changes and respiratory issues were noted, suspected to be related to possible aspiration of amniotic fluid. The child was placed on oxygen, and a chest X-ray showed slight changes in the lungs. During the night, the child experienced apnea episodes, wheezing, and movements of the right arm resembling spasms. The condition progressed to body stiffness and cyanosis, while a cranial ultrasound showed no signs of bleeding. An EEG was immediately performed, revealing changes over the left hemisphere, prompting the initiation of therapy to stabilize the EEG findings. Later, an MRI revealed a thrombus measuring 6 mm in the middle region of the left hemisphere. Seizures began 7 hours after birth, and a central thrombus was diagnosed in this early postpartum period, leading to a diagnosis of CP. Since then, over the following six months, the patient was placed on levetiracetam (Keppra) for seizure prevention and has been receiving regular follow-up care. The family history is unremarkable. He had developmental follow-up, physical therapy, and exercises monitored by a pediatric neurologist.

The child was brought in for an anesthesia examination and consultation for dental surgery. On the examination, the patient was a 6-year-old child weighing 20 kg, with a normal outward appearance, cheerful and curious demeanor, good facial expression, well-nourished and well-cared-for. The head was normocranial, the bulbi was normopositioned, there was no nystagmus, pupils were isochoric with preserved visual motor reflexes (VMR). There were no clear signs of facial muscle weakness at rest or during activity. He showed weakness of the orofacial musculature: right-sided hemiparesis with increased muscle tone (MTR) and hyperreflexia, with a predominance of flexor muscles in the right upper extremity and extensor muscles in the left upper extremity. The patient had no control over sphincters. Occasionally, minimal cognitive blocks were observed. There were obstacles in the sensory integration.

The child sits independently, crawls, and walks with support. It was deemed that the caries would develop rapidly due to the patient's poor oral hygiene status and that performing dental procedures on multiple teeth using local anesthesia would be difficult due to the patient's lack of ability to cooperate. As a result, general anesthesia was chosen for the purpose of behavior management. His parents were well informed about the method, process, and side effects of the anesthesia and dental procedures. Then, a consent form was signed prior to the inpatient general anesthesia procedure. A preoperative complete blood examination was performed. At this time, the patient was not taking any medications.

The patient received a prophylactic dose of antibiotic, administered via intravenous drip over 15 minutes, one hour prior to the procedure. In the operating room, the patient was positioned supine, and standard monitoring equipment for SpO_2, noninvasive blood pressure, and electrocardiogram was attached. Suction devices were prepared to manage potential regurgitation or aspiration. The patient's head was elevated to a 30°–40° angle, and oxygen was delivered at a flow rate of 8 L/min. A mask was gently placed over the mouth and nose, ensuring no additional pressure, and oxygen was inhaled continuously for 5 minutes. After administering oxygen therapy, the induction of anesthesia was performed with 1 mg midazolam and 40 mg propofol titrated to loss of consciousness (we didn't use a higher dose up to 3.5 mg/kg because he wasn't on chronic anticonvulsants to have enzyme induction). A cuffed endotracheal tube of size 4.0 was used for intubation. Correct tube placement was verified using a capnograph and auscultation. Anesthesia was maintained with 2% sevoflurane and fentanyl, ensuring there was no patient movement or spontaneous respiration during the procedure. Muscle relaxants were not used. The patient received 500 ml of intraoperative fluids. The surgery lasted approximately one hour and concluded successfully. The patient was extubated without complications and showed no adverse reactions postoperatively. After the dental procedure, the patient was discharged home the same day in stable condition, with no signs of postoperative complications.

Discussion

Individuals with cerebral palsy often face complex dental challenges due to issues such as poor lip seal, higher rates of malocclusion, temporomandibular joint disorders, and swallowing difficulties. Motor dysfunction conditions such as cerebral palsy causing uncontrolled tremors often require general anesthesia to facilitate keeping the mouth open for dental procedures. Maintaining the airway during anesthesia induction can be challenging due to excessive secretions. Responses to anesthetic agents may vary, and patients may show resistance to non-depolarizing muscle relaxants. In our case we didn't use muscle relaxants. Clinicians can minimize risks while

optimizing outcomes in these patients by avoiding benzodiazepines and muscle relaxants in anesthesia and careful consideration to ensure patient safety by adhering to principles of safe anesthesia (10).

The severity of cerebral palsy before surgery seems to be closely linked to the risk of complications after the procedure. Wass CT, et al. in their study aimed to evaluate the prevalence of perioperative morbidity and mortality in patients with cerebral palsy undergoing anesthesia through a systematic review of the Mayo Database. The risk for perioperative adverse events was 63.1% (95% confidence interval 59.8%-66.5%). Notably, hypothermia and clinically significant but non–life-threatening hypotension accounted for 80% of these complications. Excluding these two events, the incidence of adverse perioperative outcomes was 13.1% (95% confidence interval: 10.8%-15.5%). Factors contributing to higher risk included an ASA (American Society of Anesthesiologists) physical status score of 2 or higher, a history of seizures, upper airway hypotonia, undergoing general surgery, and being an adult. These results provide valuable insight for counseling patients with cerebral palsy, their families, and caregivers about the risks associated with general anesthesia. In our case, the patient underwent ambulatory anesthesia uneventfully, with a stable axillary body temperature of 36.0 °C (11).

In the coming years, stem cells are expected to play an increasingly significant role in the treatment of neurodevelopmental disorders such as cerebral palsy (CP). Stem cell therapies hold great promise due to their remarkable regenerative capabilities and immunomodulatory properties. However, discrepancies in clinical studies regarding the route of administration, cell sources, and dosing protocols make it challenging to establish standardized practices that optimize therapeutic benefits while minimizing side effects. A critical and intriguing area of focus is the long-term safety and effectiveness of stem cell therapies for CP. Current knowledge remains limited, particularly regarding long-term outcomes in pediatric patients, as most clinical trials have relatively short follow-up periods. Further research is essential to thoroughly evaluate the sustained safety and efficacy of these treatments in children. In this case, six months before the dental procedure, our patient received allogenic umbilical cord derived mesenchymal stem cells for cerebral palsy with intrathecal, intravenous, and intramuscular administration at the Regenerative Medicine and Stem Cell Production Center under general anesthesia, which have provided partial improvements (12).

Escanilla-Casal, et al. in their comparative study between two groups, one of healthy children and the other of children with cerebral palsy, who underwent dental treatment under general anesthesia, compared and determined oral pathology, frequency, severity and postoperative complications in pediatric patients with and without an underlying disease who undergo a dental treatment under general anesthesia. It was concluded that as for postoperative complications recorded on the questionnaire after the first day, the CP group experienced more bleeding and showed higher sleepiness ($p<.05$). On the contrary, our patient experienced neither bleeding nor reported any sleep-related issues (13).

Conclusion:

Cerebral palsy presents unique perioperative challenges that require careful anesthetic planning, individualized technique selection, and vigilant intraoperative and postoperative monitoring. Effective collaboration with the patient and caregivers is essential to ensure optimal

preparation and management, particularly when standard agents such as benzodiazepines and muscle relaxants are avoided. A tailored, safety-focused, and patient-centered approach can lead to successful anesthesia outcomes even in complex cases, underscoring the importance of flexibility and multidisciplinary coordination in care.

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CASE REPORT *UDK: 616.47-006.48-089.853*

www.doi.org/10.55302/MJA2594118tp

PERIOPERATIVE ANESTHETIC MANAGEMENT OF A PATIENT UNDERGOING CAROTID BODY TUMOR REMOVAL: FOCUS ON HEMODYNAMICS

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Abstract

Background: Carotid body tumors (paragangliomas) are uncommon neuroectodermal neoplasms, constituting roughly 1–2% of all head and neck cancers. Their proximity to the carotid vessels and cranial nerves presents considerable perioperative anesthetic problems, especially regarding the danger of hemodynamic instability during tumor manipulation.

Case presentation: We detail the perioperative anesthetic care of a 68-year-old female with a left-sided carotid body tumor, who experienced flushes, palpitations, and headaches. Preoperative imaging confirmed the diagnosis, while the preoperative assessment identified a potentially difficult airway and the need for invasive monitoring. General anesthesia was administered with invasive arterial and central venous monitoring. During tumor dissection, the patient experienced recurring bouts of vagally mediated bradycardia, which resolved upon cessation of manipulation and the administration of atropine and low-dose adrenaline infusion. Hemodynamic stability and sufficient cerebral perfusion were preserved during the surgery. The postoperative recovery was unremarkable, and the patient was discharged on the third day after surgery.

In conclusion: Meticulous hemodynamic monitoring, prompt intervention for vagal reactions, and thorough multidisciplinary collaboration are crucial for the safe administration of anesthesia during carotid body tumor removal.

Key words: *glomus caroticus, glomus caroticus tumor, neck tumors.*

Introduction

Only a small proportion, approximately 1-2%, of the tumors originating from the neuroectodermal tissue are glomus caroticus tumors, which are also known as paragangliomas. These tumors are typically observed as solitary masses, but in 3-10% of the cases, multiple tumors may be present and often in conjunction with other neuroendocrine conditions such as neurofibromatosis type 1, MEN 2, and Von Hippel-Lindau syndrome. (1) Gender and inherited genetic mutations have well-known contributions to the development of glomus caroticus tumors; de novo

mutations can also arise at any stage of life. Paragangliomas are most frequently diagnosed in individuals aged 40-60, with a notable predominance in females at a ratio of 4:1. These tumors are classified according to the scale of Shamblin, based on their relationship to the carotid artery in 3 groups (2). Type I tumors are small tumors confined to the carotid bifurcation, with minimal attachment to the carotid vessels, while type II are larger tumors that partially surround the carotid vessels. Type III tumors are large, encasing tumors that significantly involve the carotid arteries, making their resection and extirpation very challenging. Symptomatology and clinical presentation in these cases is largely determined by the anatomical location of the tumor. Lesions which involve the middle ear are most commonly associated with pulsatile tinnitus, conductive hearing loss, aural fullness, otorrhea or otorrhagia, and the presence of a bluish-red mass visible through the tympanic membrane. In contrast, tumors affecting cranial nerves typically present with facial nerve paralysis, dysphonia, significant sensorineural hearing loss, and otalgia. In general, neurological symptoms are manifested subsequently after occurrence of otologic symptoms (3,4) On the other hand, rare functional CBT may produce neuroendocrine secretions causing catecholamine-related symptoms, such as palpitations, headaches, hypertension, tachycardia, or flushing (5). When considering carotid body tumors, surgical resection of the tumor remains the treatment of choice, which is usually considered a definitive therapy (6). However, the surgical procedure by itself is complex and risky due to the close proximity of the tumor to significant neurovascular structures and great vessels in the neck, leading to significant surgical and anesthetic risks such as major blood loss, airway compromise, or hemodynamic instability due to carotid body stimulation which can arise during the surgical intervention. Managing cases of carotid body tumors could be very challenging to both the surgeon and the anesthetist, as the tumor is highly vascular and the cranial nerves IX, X, XI, and XII in the carotid sheath are close. (7). Therefore, a perioperative rise in blood pressure coupled with the vascular nature of the tumor could result in massive blood loss. This case report is presented to bring to the fore the anesthetic challenges encountered during the perioperative management and the steps taken to overcome them. Adequate preoperative evaluation, including assessment of potential airway difficulties, is essential, as neck masses may distort normal anatomy and increase the risk of difficult intubation. Cardiovascular assessment should focus on identifying hypertension, arrhythmias, or signs suggestive of possible catecholamine secretion. Also, routine laboratory testing, coagulation studies, and detailed imaging such as CT or MRI determine the extent of vascular involvement and guide perioperative planning, playing a crucial role in planning safe anesthetic management.

Case presentation

We present a 68-year-old female patient, 62 kg in weight and 165 cm in height, on chronic antihypertensive therapy, whose laboratory findings and hemostasis tests were within normal ranges. She was admitted to our department for thoracic and vascular surgery with a left-sided neck tumor and symptoms such as flushing, headaches, and palpitations. Preoperatively, the diagnosis was confirmed by contrast-enhanced CT of the neck region. Before induction, her vital parameters were monitored; her blood pressure was 130/70 mmHg, heart rate 60/min, and saturation 98% while spontaneously breathing room air. Proper premedication, aimed at achieving anxiolysis, hemodynamic stability, and attenuation of stress response, is equally important and contributes significantly to minimizing intraoperative cardiovascular instability while enhancing overall anesthetic safety. After preoxygenation for 3 minutes with 8L/min oxygen, the patient was premedicated with 2mg Midazolam i.v, 0.1mcg Fentanyl and inducted to general anesthesia with 100 mg Propofol. Inhalational anesthesia was maintained with continuous use of sevoflurane and

adequate muscular relaxation with rocuronium. The patient presented with a difficult airway, leading to a difficult intubation. The patient was intubated with video laryngoscope and an ETT number 7 was placed. An arterial line was placed in the right radial artery and invasive blood pressure was monitored continuously. A central venous line was inserted in the right internal jugular vein to provide reliable venous access for vasoactive drugs and continuous monitoring of central venous pressure (CVP). CVP measurements offered valuable insight into the patient's intravascular volume status and right-sided cardiac filling pressures during the procedure. After induction and intubation, the patient had stable vital parameters, with a slight decrease in blood pressure, which was 100/65 mmHg, no change in heart rate, with oxygen saturation of 100%. The stability of parameters was maintained throughout the whole surgical intervention, and they were in the range of 100-130 mmHg for systolic pressure and 60-80 mmHg for diastolic, while maintaining adequate MAP above 70 mmHg. The heart rate was in the range of 35-80 beats per minute, and blood oxygenation was 99-100%, with monitored capnography that showed ETCO2 from 32 to 36. Intraoperatively, we administered an ampoule of Dexamethasone 8mg i.v, with adequate gastroprotective therapy with Famotidine 20mg and Metoclopramide 10 mg. Due to vagal stimulation during surgery, the patient necessitated intermittent administration of atropine ampoules, in accordance with the patient's heart rate values. Episodes of bradycardia occurred intraoperatively. The bradycardia that occurred during tumor manipulation resolved when the manipulation or handling was discontinued, but hemodynamic insufficiency responded well to intravenous atropine, adrenaline, and intravenous fluids. Continuous infusion of adrenaline at a dose of 0.01 mg prevented sudden hemodynamic disturbances in the patient. Non-opioid multimodal analgesia was provided with acetaminophen 1 g iv. Fluid replacement was with 1500 ml NaCl 0.9%. After three hours of surgery, the patient awoke and was transferred to the recovery room, in good condition and pain-free. Postoperative pain management was conducted with nonsteroid analgesics, antibiotics, gastroprotective therapy, and anticoagulant therapy. The postoperative period was uneventful, and after 3 days, the patient was discharged from the hospital.

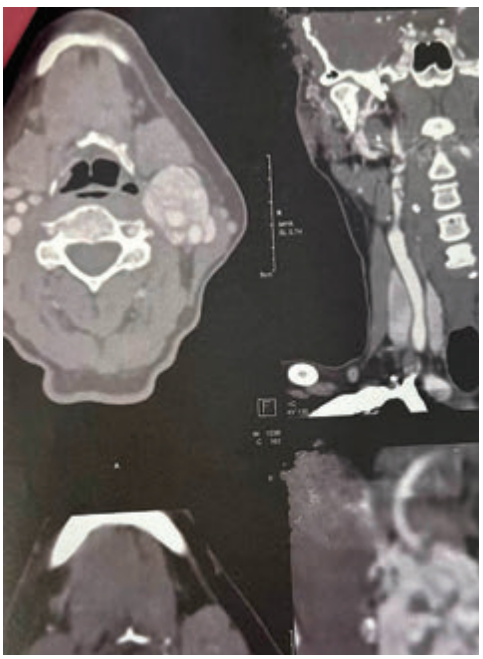

Figure 1. Contrast-enhanced CT scan of the neck demonstrating a well-defined, intensely enhancing hypervascular mass located at the left carotid bifurcation, situated between the external and internal carotid arteries. The lesion measures approximately 32 × 29 × 52 mm and produces characteristic splaying of the carotid vessels ("lyre sign"), consistent with the appearance of a carotid body paraganglioma.

Discussion

Despite the fact that cervical ultrasound is the first diagnostic tool usually applied in cases where the existence of carotid body tumors is suspected, a comprehensive patient history, physical examination, and adequate imaging techniques also must be considered in the diagnostic algorithm (7). Several radiologic modalities, including computerized tomography (CT), magnetic resonance imaging (MRI), angiography, and magnetic resonance angiography, are available to determine the existence of carotid body tumors (7). High resolution and contrast-enhanced computed tomography is a preferred diagnostic modality because it is considered superior in demonstrating the extent of the disease and possible tumor erosion of the skull base (7). Removing the carotid body tumors through surgery brings specific anesthetic perioperative challenges because of the tumor's proximity to the nerves and great blood vessels, as well as the possibility of catecholamine release due to tumor manipulation and resection, which can cause significant hemodynamic disturbances. The risk of intraoperative hemorrhage represents a central anesthetic and surgical concern during carotid body tumor resection because tumors are hypervascular, receiving extensive arterial supply from branches of the carotid artery that significantly increases the risk of bleeding upon dissection. The anesthetic strategy must incorporate volume optimization, readiness for prompt transfusion, and the capacity for rapid titration of vasoactive agents. Similar considerations have been discussed in the Macedonian Journal of Anesthesia, where the management of hormonally active tumors has been shown to require careful preoperative optimization and vigilant intraoperative hemodynamic control.(12) General anesthesia is the most preferred modality for CBT removal, as it allows optimal control of airway, ventilation, and hemodynamics throughout the procedure (8). Since surgery occurs at the place of bifurcation of the carotid artery, anesthesiologists must ensure maintaining optimal hemodynamics, adequate MAP, and cerebral perfusion pressure in order to prevent cerebral hypoperfusion and brain injury (9). This procedure was implemented in our case report and resulted in a favorable outcome due to maintaining optimal hemodynamics. Continuous intraoperative monitoring and hemodynamic optimization are necessary for stable cerebral perfusion and the absence of any postoperative neurological deficits. Continuous cervical plexus block could be considered as another alternative anesthetic modality, which might have many advantages, but also disadvantages when compared to general anesthesia. Faster postoperative recovery and a shorter in-hospital stay as far as hemodynamic stability was observed as one of the benefits of choosing cervical plexus block over general anesthesia when performing a CBT removal (10). Performing this surgical intervention with cervical block as a sole anesthetic technique could sometimes be disadvantageous due to unsecured airway and possible hypoxia related to loss of consciousness due to hypoperfussion and hemodynamic instability. Regardless of the type of anesthesia, continuous invasive hemodynamic monitoring via arterial line and central venous line placement has become a mainstay and a standard of care in this type of surgeries since both can guide the anesthesiologist when tailoring fluid and vasoactive medication administration in case of sudden episodes of hypotension, hypertension, tachycardia or bradycardia. Likely due to tumor manipulation, several episodes of bradycardia were observed in our case, which were well managed and resolved by giving an intermittent injection of atropine and a continuous infusion of adrenaline intraoperatively. Recently, mild hypothermia has been recognized and considered as a beneficial intervention during surgery because of hypothermia-related reduced cerebral metabolic rates and consumption of oxygen (11). In our case report, hypothermia was not used as a particular intervention. Postoperative intensive monitoring ensures prompt detection of cardiovascular and neurological complications and their adequate and on-time resolution. With detailed preoperative assessment and intraoperative vigilance, the anesthetic management of

CBT removal can be safely accomplished without any unfavorable outcomes.

Conclusion

Carotid body tumor removal surgery requires invasive and close monitoring of the hemodynamics with vigilant and complex anesthetic management. Maintaining systemic hemodynamics within the normal ranges as well as cerebral perfusion preservation are crucially important and the main goals in order to diminish complications arising from tumor removal. With careful consideration of the risks, anticipation of unfavorable intraoperative events, planning and collaboration among a multidisciplinary team, the adequate anesthetic management can significantly reduce the occurrence of complications and help achieve successful surgical outcomes during carotid body tumor removal.

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CASE REPORT *UDK: 618.19-006.6-091.8*

www.doi.org/10.55302/MJA2594124l

INVASIVE DUCTAL CARCINOMA IN AN ELDERLY PATIENT: HOW SOCIOECONOMIC BARRIERS INFLUENCE DIAGNOSTIC DELAY AND TREATMENT PATHWAYS

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Abstract

Invasive breast carcinoma is the most common malignant breast tumor and remains a major global public health challenge, with high morbidity and mortality rates among women worldwide. Early diagnosis relies on clinical assessment, imaging, and histopathological evaluation, while treatment requires a multidisciplinary approach. Invasive ductal carcinoma (IDC) accounts for approximately 70–80% of invasive cases, most frequently metastasizing to regional lymph nodes and distant organs via lymphatic and hematogenous pathways.

We present a case of a 78-year-old female with a palpable retro areolar mass in the right breast, accompanied by nipple retraction, erythema, and peau d'orange appearance. Imaging, including mammography, CT, and ultrasound, demonstrated an irregular, multilobulated, hypoechoic lesion consistent with malignancy, while fine-needle aspiration biopsy confirmed invasive ductal carcinoma. Immunohistochemistry revealed strong estrogen receptor positivity (ER 90%) and weak progesterone receptor expression (PR 2%), suggesting a hormonally driven tumor subtype with therapeutic implications.

This case highlights the diagnostic value of multimodal imaging and histopathology in elderly patients, where delayed presentation, comorbidities, and low socioeconomic status may complicate both the diagnostic process and access to timely treatment. It underscores the importance of early detection, sustained clinical suspicion, and a coordinated multidisciplinary approach to optimize outcomes in invasive breast carcinoma.

Keywords: *invasive ductal carcinoma; multimodal imaging; peau d'orange; ER positive breast cancer.*

Introduction

Invasive breast carcinoma remains one of the leading causes of cancer-related mortality among women worldwide, with a lifetime risk estimated at approximately one in eight women (1,2). It most commonly arises from epithelial cells of the ductal-lobular system and is characterized by stromal invasion and metastatic potential via lymphatic and hematogenous pathways (3,4). Histologically, invasive ductal carcinoma (IDC) comprises 70–80% of cases, while invasive lobular carcinoma accounts for 10–15% (3).

The biological behavior and treatment approach are strongly influenced by molecular subtype, particularly the expression of estrogen (ER), progesterone (PR), and HER2 receptors, which guide targeted therapy and correlate with prognosis (5). Established risk factors include genetic predisposition (BRCA1/2 mutations), hormonal influences, ionizing radiation, and lifestyle factors (5).

Clinical presentation varies from asymptomatic disease detected on screening to palpable masses, nipple changes, or "peau d'orange" appearance due to lymphatic obstruction. Definitive diagnosis requires histopathology supported by imaging modalities such as mammography, ultrasound, MRI, and CT (3,4).

Elderly patients often present with diagnostic challenges due to delayed clinical evaluation, comorbidities, and atypical or advanced disease at presentation, complicating staging and treatment decisions.

The aim of this case report is to present a case of a 78-year-old female patient with invasive ductal carcinoma, which emphasizes the role of multimodal imaging, pathological evaluation, and clinical considerations in elderly patients.

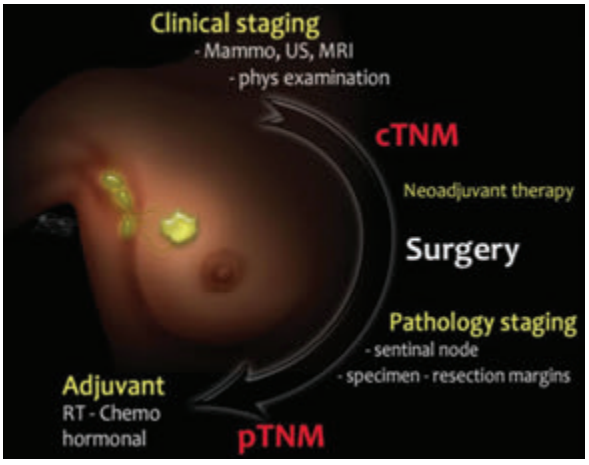


Figure 1. Clinical and pathological staging pathway in breast cancer, illustrating the diagnostic sequence from cTNM evaluation to surgery and pTNM classification, guiding adjuvant therapy (6).

Case Presentation

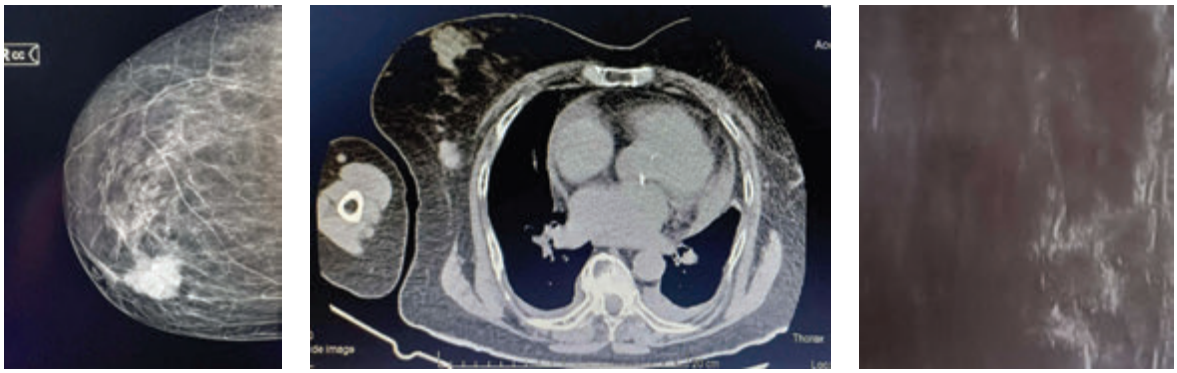
A 78-year-old female patient with comorbidities of epilepsy and chronic heart failure presented with a firm palpable mass above the right nipple, which she noticed on self-examination. Due to her comorbidities and socioeconomic limitations, the patient was unable to fully care for her health. Upon clinical examination by her general practitioner, a firm, immobile retroareolar mass was confirmed, along with an enlarged right axillary lymph node (approximately the size of a walnut).

The overlying skin was shiny and taut, with areas resembling 'orange peel,' moderate erythema, and nipple retraction. The patient underwent the following laboratory and imaging investigations:

- Complete blood count, ESR, CRP, tumor markers (CA15-3, CEA)
- Chest X-ray

- CT scan
- Breast ultrasound
- Fine-needle aspiration biopsy (FNAB)

Laboratory results, including tumor markers, were within normal limits. Chest radiography revealed cardiomegaly. Mammography showed a retroareolar hyperdense multilobulated mass (Figure 2.a). Ultrasound confirmed a hypoechoic subcutaneous irregular lesion consistent with malignancy (Figure 2.c). CT imaging showed no abnormalities in the brain or skull. Left-sided pleural and pericardial effusions were present, with evidence of cardiomyopathy (Figure 2.b). Histopathological examination revealed a malignant epithelial neoplasm composed of atypical tumor cells with moderate nuclear pleomorphism forming tubular, cribriform, and focally papillary structures. Sparse intratumoral lymphocytic infiltration was noted. Immunohistochemistry showed strong nuclear positivity for estrogen receptors (ER 90%) and weak positivity for progesterone receptors (PR 2%). The final diagnosis was invasive breast carcinoma.



a. b. c.

Figure 2. (a). Mammography showed retroareolar hyperdense multilobulated mass; (b.) Thoracic CT showed left-sided pleural and pericardial effusions, with evidence of cardiomyopathy; (c.) ultrasound confirmed a hypoechoic subcutaneous irregular lesion.

Discussion

Invasive breast carcinoma remains the most common malignant breast tumor among women worldwide and continues to be a significant public health concern due to its high morbidity and mortality (1,2). Early diagnosis and treatment are crucial for improving outcomes, as prognosis is strongly influenced by tumor biology, stage at presentation, and timely initiation of therapy (3,5). In this case, a 78-year-old female presented with a palpable retroareolar mass, skin retraction, erythema, and a "peau d'orange" appearance—clinical features strongly suggestive of locally advanced breast carcinoma.

Diagnosis was established through multimodal imaging and fine-needle aspiration biopsy, confirming invasive ductal carcinoma, the most common histopathologic subtype of invasive breast cancer (3). The tumor demonstrated strong estrogen receptor expression (ER 90%) and weak progesterone receptor positivity (PR 2%), suggesting a hormonally driven subtype. However, low PR expression may correlate with more aggressive behavior and reduced response to endocrine therapy, commonly associated with luminal B biology (5). This highlights the importance

of molecular profiling in guiding therapeutic decisions.

A unique aspect of this case is the patient's advanced age, comorbidities, and limited health-seeking behavior, contributing to delayed presentation. Older patients often face diagnostic and therapeutic challenges, including reduced access to screening, limited social support, and higher treatment-related risks (7). These factors frequently result in late-stage presentation and restricted management options, despite evidence that breast cancer incidence remains significant in elderly populations (2,4).

Importantly, due to her socioeconomic circumstances and personal limitations, the patient did not undergo surgical or oncological consultation following biopsy confirmation, and therefore no definitive treatment was initiated. This introduces a critical perspective: timely diagnosis alone is insufficient without access to treatment pathways. The gap between diagnosis and therapy reflects systemic barriers that disproportionately affect elderly individuals, especially those with limited financial, social, or logistical support. Such disparities may influence survival rates independent of tumor biology, underscoring the need for public health strategies aimed at improving healthcare accessibility for vulnerable populations (8,9).

Conclusion

Overall, this case highlights not only the diagnostic value of multimodal imaging and histopathology in suspected breast malignancy but also the real-world challenges in managing elderly patients with limited access to care. It emphasizes the necessity of multidisciplinary coordination and social support interventions to ensure that diagnosis leads to meaningful treatment and improved outcomes. These findings highlight the need for targeted public health strategies aimed at vulnerable elderly populations, improved screening accessibility, and interventions that address social disparities in cancer care. Ultimately, multidisciplinary coordination and personalized treatment planning remain essential to improving outcomes in older patients with breast malignancies.

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CASE REPORT *UDK: 618.14-089.87-034:611.671]-06*

www.doi.org/10.55302/MJA2594129bb

TRANSVAGINAL INTESTINAL EVISCERATION AFTER HYSTERECTOMY

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Abstract

Transvaginal intestinal evisceration is an exceptionally rare and insufficiently documented complication of vaginal hysterectomy, requiring rapid recognition and surgical management to avoid serious outcomes such as bowel ischemia, perforation, and sepsis. We report the case of a 70-year-old woman who had undergone vaginal hysterectomy fourteen months before she presented with acute abdominal pain accompanied by a substantial segment of small bowel protruding through a defect in the vaginal vault. She was immediately taken to the operating room, where the abdominal cavity was opened and the bowel was manually reinserted into the abdominal cavity, and the vaginal defect was closed with a medical stapler. Several surgical strategies—including laparoscopic, abdominal, transvaginal, and combined approaches—have been described, each demonstrating comparable results. Consequently, the choice of technique should be individualized based on the patient's clinical condition.

Keywords: *Hysterectomy; transvaginal intestinal evisceration.*

Introduction

Transvaginal intestinal evisceration is a rare yet potentially fatal surgical emergency, with only a small number of cases documented in the literature, which limits accurate estimation of its true incidence (1-2). Its etiology is understood to be multifactorial, with several predisposing factors contributing to its development. Clinically, the condition most commonly presents as herniation of the small intestine through the vaginal canal, frequently resulting in intestinal obstruction. (3,4,). Diagnosis is usually established through imaging modalities or incidentally during exploratory laparotomy. In exceptionally uncommon and dramatic presentations, large segments of small bowel may prolapse externally through the vagina, placing the patient at substantial risk for intestinal compromise and loss of viability (5,6,7). Such a presentation occurred in the current case, in which the patient arrived with abrupt onset of severe abdominal pain and spontaneous transvaginal evisceration of the small intestine, necessitating immediate surgical intervention to mitigate further complications. This report is prepared in accordance with CARE Guidelines (8).

Case report

A 70-year-old woman was admitted on April 4, 2025, as an emergency due to a prolapsed vaginal cuff with eviscerated small intestine protruding through the vagina (Image 1). She reported sudden severe abdominal pain, weakness, and dizziness, while denying constipation, coughing, or recent trauma—common precipitating factors for increased intra-abdominal pressure—making their absence clinically notable. Her obstetric history included two full-term vaginal deliveries, and she had no prior diagnosis of chronic uterine prolapse. Fourteen months before presentation, she had undergone hysterectomy, and across the same period she subsequently required three separate surgical procedures for recurrent partial vaginal prolapse of the small intestine, two performed by gynecologists and one by an abdominal surgeon, illustrating the recurrent and complex nature of her condition. Her medical history included well-controlled arterial hypertension and diabetes mellitus.

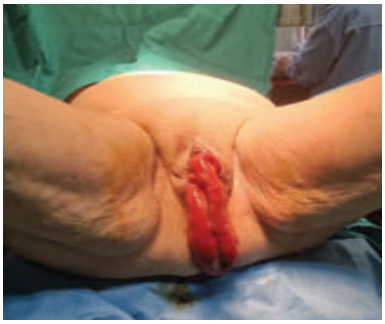

Image 1. (Pre op image of Transvaginal intestinal evisceration)

On admission, the patient appeared significantly compromised. Physical examination revealed pallor of the skin, a pulse of 100 beats per minute, and blood pressure of 125/80 mmHg. Abdominal evaluation demonstrated pronounced lower-quadrant tenderness and hypoactive bowel sounds, indicative of reduced intestinal motility and possible obstruction. Perineal examination revealed that approximately 40–50 cm of small bowel had prolapsed through the vaginal canal. The exposed segment was edematous, thickened, and discolored in a manner suggestive of impaired perfusion, though without overt necrosis. Laboratory results showed anemia (hemoglobin 100 g/L) and elevated inflammatory markers, including leukocytosis (14.7×10^9/L), C-reactive protein (48 mg/dL), and fibrinogen (5.4 g/L), consistent with acute inflammation and possible infection. KT tomography was made and indicated transvaginal intestinal evisceration (image 2 and 3)

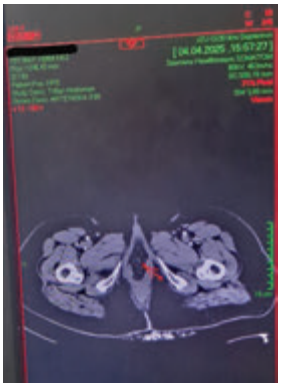

Image 2.

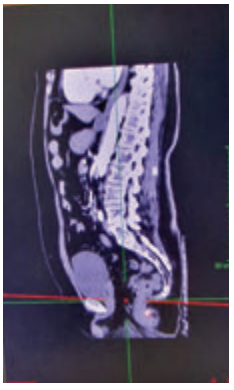

Image 3.

After brief preoperative stabilization, the patient underwent mid-to-lower laparotomy. Upon entering the abdominal cavity, ileus-altered small intestine was found incarcerated through the vaginal defect, and the associated mesentery appeared dusky and ecchymotic, indicating compromised venous return. The bowel was manually reduced, and the vaginal defect was closed using a stapling device, followed by meticulous hemostasis and copious abdominal lavage (image 4). Postoperative management included fluid resuscitation and prompt initiation of intravenous broad-spectrum antibiotics.

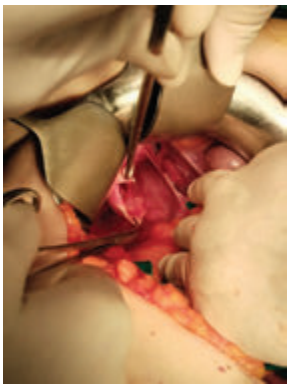

Image 4.

The patient recovered uneventfully and was discharged on April 14, 2025, in good general condition, with recommendations for one month of rest and avoidance of strenuous physical activity for four months.

Discussion

Transvaginal intestinal evisceration is a rare but serious surgical emergency first described by McGregor in 1907 and remains infrequently reported in the literature. Most commonly, it affects postmenopausal women and those with a history of pelvic surgery, particularly hysterectomy (9–10). The incidence is difficult to determine due to its rarity, but several anatomical and physiological factors have been proposed, including weakening of the pelvic floor, vaginal atrophy caused by estrogen deficiency, and surgical disruption of support structures (11). In approximately two-thirds of reported cases, vaginal cuff dehiscence occurs following hysterectomy, often in the context of increased intra-abdominal pressure or trauma (12,13). Our patient's presentation is consistent with this pattern, with transvaginal evisceration occurring fourteen months after hysterectomy; however, her case is further complicated by multiple recurrent episodes requiring surgical intervention.

Notably, the patient denied experiencing common precipitating factors such as coughing, straining, or trauma, which are frequently implicated in the pathogenesis of evisceration through sudden increases in intra-abdominal pressure (14). The absence of such triggers highlights the possibility that persistent structural weakness of the vaginal cuff combined with compromised tissue integrity—potentially exacerbated by previous surgeries—played a central role in her presentation. Recurrent prolapse of small bowel segments through the vaginal canal, as observed in this patient, is exceptionally uncommon and has been described in only a handful of reports, emphasizing the complexity of her underlying pelvic floor dysfunction (15).

Clinically, transvaginal intestinal evisceration typically presents as acute abdominal pain associated with visible bowel protrusion, constituting a true surgical emergency given the high risk of bowel ischemia, necrosis, and subsequent sepsis. In this case, the identification of edematous and discolored small bowel loops, along with hypoactive bowel sounds and elevated inflammatory markers, indicated evolving bowel compromise. Although no frank necrosis was present, the dusky and ecchymotic appearance of the mesentery at laparotomy was consistent with impaired venous return and imminent risk of ischemia, underscoring the need for rapid operative management. Current literature strongly advocates immediate surgical intervention, including reduction of the eviscerated bowel, assessment of viability, and secure repair of the vaginal defect, as delays significantly increase morbidity and mortality (16,17).

The surgical approach taken—mid-to-lower laparotomy with manual reduction, thorough inspection of bowel viability, closure of the vaginal defect using stapling techniques, and extensive peritoneal lavage—aligns with recommendations from previous case series and reviews. Ensuring hemostasis and initiating early broad-spectrum antibiotics are also emphasized in the literature as essential components of postoperative care to reduce the risk of intra-abdominal infection and recurrence (18).

The patient's favorable postoperative recovery and discharge in good condition demonstrate the effectiveness of prompt recognition and timely surgical management. However, her history of recurrent prolapse underscores the importance of considering long-term preventive strategies. Several authors suggest that reinforcing the vaginal cuff, addressing pelvic floor weaknesses, and optimizing postoperative rehabilitation may help reduce recurrence risk, particularly in individuals with multiple prior surgeries or other predisposing factors (19,20).

Overall, this case adds to the limited body of evidence on recurrent transvaginal intestinal evisceration and highlights the need for heightened clinical vigilance in patients with previous hysterectomy and repeated pelvic surgeries. Early diagnosis and emergent surgical repair remain crucial to preventing bowel ischemia, sepsis, and life-threatening complications.

Conclusion

Transvaginal intestinal evisceration thus represents an exceptionally uncommon but severe surgical emergency, and early recognition combined with urgent operative management is critical to preventing bowel ischemia and subsequent sepsis. When the eviscerated intestinal segment is non-viable, resection with primary anastomosis is required to restore bowel continuity. Optimal management should be individualized and undertaken by a multidisciplinary team to ensure the best possible clinical outcomes.

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CASE REPORT *UDK: 616.33-007.41-089.819-053.8*

www.doi.org/10.55302/MJA2594134z

MESENTEROAXIAL GASTRIC VOLVULUS IN AN ADULT

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Abstract

We present the case of a 58-year-old female with mesenteroaxial gastric volvulus secondary to a large paraesophageal hernia. The patient underwent successful surgical treatment via median laparotomy, including adhesiolysis, gastric detorsion, cruroplasty, and Nissen fundoplication. Her postoperative recovery was uneventful. This case highlights the importance of early recognition, cross-sectional imaging, and timely surgical intervention in preventing morbidity and mortality associated with gastric volvulus.

Keywords: *Case report; Computed tomography; Gastric volvulus; Mesenteroaxial volvulus; Nissen fundoplication; Paraesophageal hernia.*

Introduction

Gastric volvulus is a rare but potentially life-threatening condition characterized by abnormal rotation of the stomach along its anatomical axes, leading to obstruction and potential ischemia. It is classified into organoaxial, mesenteroaxial, and mixed subtypes. Mesenteroaxial volvulus involves rotation along the short axis, resulting in the antrum being displaced above the gastroesophageal junction. Recent case reports confirm its presence across a wide age range, including adults, and highlight diagnostic difficulties due to nonspecific symptoms (1-4). Early diagnosis using CT or upper gastrointestinal contrast studies is essential to prevent complications such as strangulation, necrosis, and perforation (5).

Case Presentation

A 58-year-old female reported a 4-year history of upper abdominal discomfort, nausea, intermittent vomiting, and reduced appetite. She experienced significant unintentional weight loss of over 10 kg from March to September 2023. During the preceding three years, she underwent three gastroscopies, the most recent in March 2023, which described a paraesophageal hernia with displacement of the antropyloric region into the thoracic cavity.

Due to worsening symptoms—persistent vomiting, inability to tolerate oral intake, and marked abdominal distension—the patient was admitted to hospital in September 2023. Laboratory tests demonstrated anemia (Hb 113 g/L) and elevated urea (15.5 mmol/L) and creatinine (229.6 μmol/L).

Contrast-enhanced CT demonstrated a large paraesophageal hernia with mesenteroaxial gastric volvulus, with the antropyloric region positioned superior to the fundus within the thoracic cavity, consistent with recent imaging characteristics described in the literature (1,5). (Fig. 1, 2)

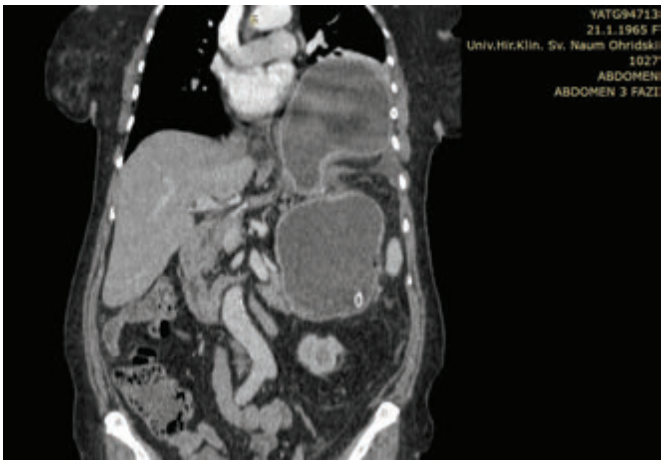

Figure 1. Presentation of the paraesophageal hernia containing the antropyloric part on contrast-enhanced CT in coronal plane.

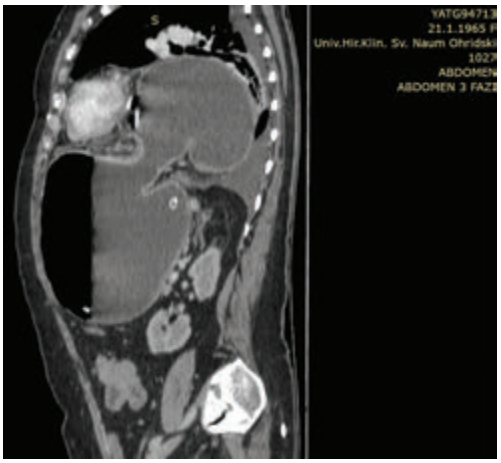

Figure 2. Presentation of the mesenteroaxial volvulus of the stomach on contrast-enhanced CT in sagittal plane with the antropyloric part positioned superiorly and gastro-esophageal junction positioned inferiorly.

Nasogastric tube (NGT) placement aspirated approximately 6 liters of stagnant gastric content and resulted in temporary clinical improvement. Two days later, recurrent distension prompted repeat CT imaging showing similar findings. Gastroscopy demonstrated inversion of the antropyloric segment with mucosal erosions.

Given persistent volvulus and failure of conservative management, surgical intervention was performed on September 13, 2023. A median laparotomy revealed an incarcerated paraesophageal hernia caused by adhesions of the greater omentum to the left diaphragmatic crus and a mesenteroaxial volvulus, in accordance with intraoperative findings described in recent case reports (3,4). Adhesiolysis, gastric detorsion, cruroplasty, and Nissen fundoplication were performed. Postoperative CT confirmed normal anatomical positioning of the stomach beneath the diaphragm (fig.3).

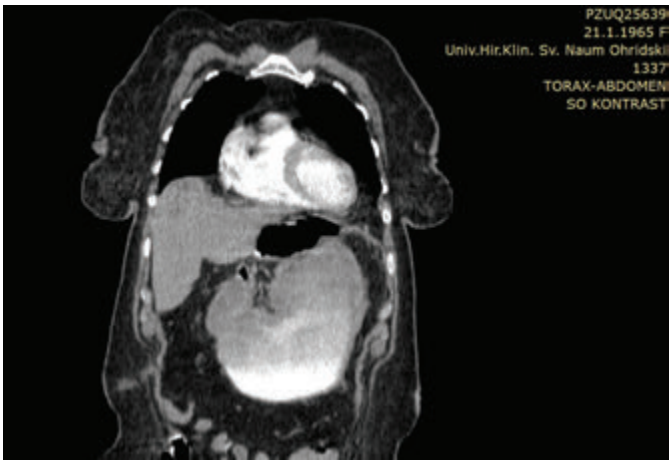

Figure 3. Postoperatively, a follow-up CT

Discussion

Mesenteroaxial gastric volvulus in adults is uncommon and often presents diagnostic challenges due to its intermittent and nonspecific course. Recent literature further supports its association with paraesophageal hernias as a major predisposing factor (1,2,5).

Based on the imaging and intraoperative findings, the patient presented with a Type III paraesophageal hernia, which represents a mixed form in which both the gastroesophageal junction and the fundus of the stomach herniate into the thoracic cavity. In the standard hiatal hernia classification, Type I refers to a sliding hernia with migration of the gastroesophageal junction alone, while Type II describes a true paraesophageal hernia in which the gastroesophageal junction remains in its normal position and the fundus herniates alongside the esophagus. Type III, as seen in this patient, combines features of both Type I and II. This was evidenced by the intrathoracic displacement of the antropyloric portion and the superior position of the herniated stomach relative to the fundus on CT imaging. Additionally, Type IV hernias, the most complex form, involve herniation of other abdominal organs such as colon, spleen, or small bowel, which were not present in this case. The intraoperative finding of an incarcerated hernia with adhesions involving the greater omentum further supports the Type III classification. Type III hernias are strongly associated with secondary gastric volvulus, consistent with the mesenteroaxial rotation identified in this case.

NGT decompression may provide temporary symptom relief but rarely resolves the volvulus. Endoscopic detorsion may be considered, particularly in patients without evidence of ischemia or in high-risk surgical candidates, as demonstrated in contemporary endoscopic case reports (6). However, in this case, the presence of an incarcerated paraesophageal hernia made surgical intervention necessary.

Cross-sectional imaging remains the gold standard for diagnosis, as confirmed in recent radiological studies of gastric volvulus (5). Surgical management aims to reduce volvulus, repair the diaphragmatic defect, and stabilize the stomach using gastropexy or fundoplication. Acute gastric volvulus carries a complication rate of 30–50% if untreated, with gastric necrosis occurring in 10–20% of cases. Mortality in untreated volvulus historically reaches 30–50%, primarily due to strangulation and perforation (7). With prompt surgical treatment, mortality

decreases to 10–15%, and elective or minimally invasive repair in stable patients has mortality rates below 5%.

Conclusion

This case underscores the importance of considering mesenteroaxial gastric volvulus in patients with chronic upper gastrointestinal symptoms and paraesophageal hernias. Early CT-based diagnosis and timely surgical correction remain essential to reducing morbidity and preventing life-threatening complications.

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CASE REPORT *UDK: 616-056.7-053.31*

www.doi.org/10.55302/MJA2594138n

ALDOSTERONE SYNTHASE DEFICIENCY FROM HOMOZYGOUS CYP11B2 MUTATION PRESENTING WITH SALT-WASTING CRISIS AND FAILURE TO THRIVE IN AN INFANT

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Abstract

Introduction: Aldosterone synthase deficiency (ASD) is a rare autosomal recessive disorder caused by pathogenic variants in the CYP11B2 gene, leading to impaired aldosterone synthesis and life-threatening salt-wasting. We present a case of an infant with failure to thrive, dehydration, and electrolyte imbalance, diagnosed through next-generation sequencing.

Material and Methods: mitted with persistent vomiting, constipation, and a10% weight loss. Laboratory evaluation showed severe hyponatremia (116 mmol/L), hyperkalemia (6.5 mmol/L), hypochloremia (87 mmol/L), and metabolic alkalosis. Differential diagnosis included gastrointestinal loss, renal salt-wasting, cystic fibrosis, celiac disease, and congenital adrenal hyperplasia. Normal 17-hydroxyprogesterone excluded classical CAH. Next-generation sequencing was performed.

Results: A homozygous pathogenic variant c.554C>T (p.Thr185Ile) in CYP11B2 confirmed ASD. Treatment with fludrocortisone and sodium supplementation resulted in rapid correction of electrolytes and improved growth. Follow-up at 3.5 years showed normal growth (14.5 kg, 103 cm), stable electrolytes, and normal development, with only mild transient hyponatremia during illness.

Conclusion: ASD should be considered in infants with vomiting, dehydration, and combined hyponatremia–hyperkalemia when CAH is excluded. Early diagnosis and mineralocorticoid therapy prevent complications and support normal development.

Key words: *aldosterone synthase deficiency; CYP11B2; infant; hyperkalemia; hyponatremia; fludrocortisone.*

Introduction

Aldosterone synthase deficiency (ASD) is a rare autosomal recessive disorder caused by pathogenic variants in the CYP11B2 gene, which encodes aldosterone synthase—the mitochondrial

enzyme responsible for the final steps of aldosterone synthesis (1). Aldosterone plays a crucial role in sodium and potassium regulation, extracellular fluid balance, and blood pressure homeostasis. Impaired synthesis leads to salt-wasting, dehydration, vomiting, failure to thrive, and potentially life-threatening electrolyte disturbances, most commonly hyponatremia and hyperkalemia (2).

Although ASD is extremely uncommon, with fewer than one hundred reported cases worldwide, its clinical presentation overlaps with more prevalent neonatal and infantile conditions such as congenital adrenal hyperplasia (CAH), renal tubular disorders, gastrointestinal salt loss, cystic fibrosis, and endocrinological abnormalities (3). Because CAH is often the first diagnostic consideration in infants presenting with hyponatremia and hyperkalemia, ASD may remain unrecognized until severe metabolic derangements occur or until genetic testing is performed (3,4). Early distinction between these disorders is essential, especially in critically ill infants with combined hyponatremia and hyperkalemia but normal cortisol and 17-hydroxyprogesterone levels.

ASD is classified into two biochemical subtypes: type I, characterized by defective conversion of corticosterone to aldosterone; and type II, characterized by partial enzymatic activity with insufficient aldosterone production (1,4). Both types may present in infancy with episodes of vomiting, dehydration, hypotension, and poor weight gain, often precipitated by physiological stress or decreased oral intake (5). Without timely recognition and appropriate mineralocorticoid replacement, affected infants are at risk for cardiovascular collapse, arrhythmias due to severe hyperkalemia, and significant long-term morbidity.

The availability of next-generation sequencing has substantially improved the ability to diagnose rare adrenal disorders such as ASD (4,5). This case report describes an infant with persistent salt-wasting, metabolic derangements, and growth failure, ultimately diagnosed with ASD following extensive clinical and genetic evaluation. The case emphasizes the importance of considering mineralocorticoid synthesis defects in infants presenting with unexplained hyponatremia and hyperkalemia, particularly when CAH has been excluded. We present a rare case of aldosterone synthase deficiency caused by a homozygous CYP11B2 mutation, presenting with severe salt-wasting crisis and failure to thrive.

Material and method

A 9-month-old male infant was admitted to the Pediatric Department at Acibadem Sistina Clinical Hospital due to persistent vomiting, constipation, reduced oral intake, and poor weight gain. He was born full-term with a birth weight of 4100 g, and was exclusively breastfed until 5 months of age, after which complementary feeding was introduced. The parents reported normal growth and feeding in the early months of life, with progressive onset of symptoms after transition to mixed nutrition. There was no history of fever, diarrhea, respiratory infection, or previous hospitalizations.

On admission, the infant appeared lethargic and clinically dehydrated. Vital signs were: heart rate 168/min, respiratory rate 42/min, blood pressure 75/45 mmHg, and capillary refill >3 seconds. Physical examination revealed dry mucous membranes, decreased skin turgor, mild hypotonia, and reduced subcutaneous fat tissue. His weight was below the 3rd percentile for age, with a documented weight loss of approximately 10% over several weeks.

Initial laboratory investigations showed severe electrolyte imbalance with serum sodium 116 mmol/L, potassium 6.5 mmol/L, chloride 87 mmol/L, and metabolic alkalosis (pH 7.51). Renal function tests were within normal limits for age. Blood glucose was normal. Stool examination showed no pathological findings. Abdominal ultrasound and chest radiograph revealed no abnormalities. Urine analysis demonstrated no glycosuria or proteinuria, while urine sodium was low, suggesting renal salt loss.

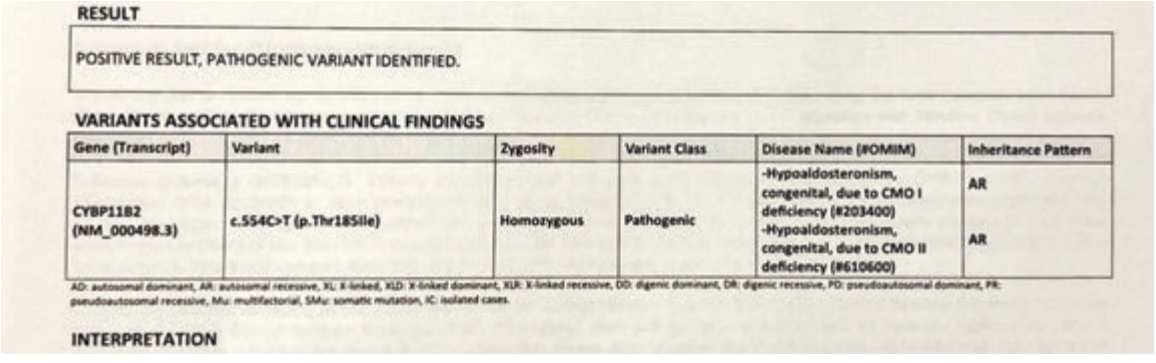
Given the clinical picture of dehydration, hyponatremia, and hyperkalemia, congenital adrenal hyperplasia (CAH) was initially suspected. However, serum 17-hydroxyprogesterone levels were normal, ruling out classical CAH. Differential diagnosis additionally included cystic fibrosis, celiac disease, metabolic disorders, and primary renal tubular dysfunction; all were excluded through targeted laboratory and imaging investigations.

Despite fluid resuscitation and partial correction of electrolytes, the etiology of the persistent salt-wasting remained unclear. Because the infant presented with hyponatremia, hyperkalemia, and metabolic alkalosis without elevation of adrenal androgens, a mineralocorticoid synthesis defect was suspected. Next-generation sequencing (NGS) using a targeted adrenal gene panel was performed.

Genetic analysis revealed a homozygous pathogenic variant c.554C>T (p.Thr185Ile) in the CYP11B2 gene, confirming the diagnosis of aldosterone synthase deficiency. Both parents were clinically healthy and declined carrier genetic testing.

Results

Following initial stabilization with intravenous fluids and careful correction of hyponatremia, the infant was started on fludrocortisone therapy (0.1 mg/day), accompanied by oral sodium supplementation adjusted to clinical response (2–4 mEq/kg/day). Within 48 hours, serum sodium levels began to rise, potassium decreased, and the clinical signs of dehydration improved. The child became more alert, with improved feeding and activity levels.



RESULT

POSITIVE RESULT, PATHOGENIC VARIANT IDENTIFIED.

VARIANTS ASSOCIATED WITH CLINICAL FINDINGS

Gene (Transcript)	Variant	Zygosity	Variant Class	Disease Name (#OMIM)	Inheritance Pattern
CYBP11B2 (NM_000498.3)	c.554C>T (p.Thr185Ile)	Homozygous	Pathogenic	-Hypoaldosteronism, congenital, due to CMO I deficiency (#203400) -Hypoaldosteronism, congenital, due to CMO II deficiency (#610600)	AR AR

AD: autosomal dominant, AR: autosomal recessive, XL: X-linked, XLD: X-linked dominant, XLR: X-linked recessive, DD: digenic dominant, DR: digenic recessive, PD: pseudoautosomal dominant, PR: pseudoautosomal recessive, Mu: multifactorial, SMu: somatic mutation, IC: isolated cases.

INTERPRETATION

By day 5 of hospitalization, laboratory values showed near-normalization of electrolytes, with sodium 130 mmol/L and potassium 4.8 mmol/L. Metabolic alkalosis resolved, and steady weight gain was recorded during hospitalization.

Genetic testing using next-generation sequencing identified the homozygous pathogenic variant c.554C>T (p.Thr185Ile) in the CYP11B2 gene, confirming the diagnosis of aldosterone

synthase deficiency.

Figure 1. *Next-generation sequencing (NGS) chromatogram demonstrating the homozygous c.554C>T (p.Thr185Ile) pathogenic variant in the CYP11B2 gene.*

Outpatient follow-up demonstrated sustained clinical improvement. Electrolytes remained stable with continued fludrocortisone therapy and sodium supplementation. Growth parameters progressively normalized.

At the most recent follow-up at 3 years and 6 months of age, the child showed appropriate growth (weight 14.5 kg, height 103 cm) and normal psychomotor development. Laboratory monitoring demonstrated low but stable aldosterone levels (3.75 ng/dL in February 2023; 6.55 ng/dL in October 2023). Occasional mild hyponatremia (Na 132 mmol/L) during intercurrent infections resolved without hospitalization.

No further episodes of dehydration, vomiting, or salt-wasting were recorded. The family received genetic counseling, although parental carrier testing was declined.

Discussion

Aldosterone synthase deficiency (ASD) is an uncommon but important cause of salt-wasting in infancy. Its rarity and overlapping clinical features with more prevalent endocrine and renal disorders frequently delay recognition and treatment (1). The typical biochemical profile—hyponatremia, hyperkalemia, dehydration, and metabolic derangements—often leads clinicians to initially suspect congenital adrenal hyperplasia (CAH), particularly 21-hydroxylase deficiency, which remains the most common etiology of life-threatening salt-wasting crises in infants (2,3). In the present case, normal 17-hydroxyprogesterone levels effectively excluded classical CAH, prompting further evaluation.

ASD results from pathogenic variants in the **CYP11B2** gene, which encodes aldosterone synthase, the enzyme responsible for the final steps of aldosterone biosynthesis (1,4). The homozygous c.554C>T (p.Thr185Ile) mutation identified in our patient has been previously described as a disease-causing variant associated with reduced enzymatic activity and impaired aldosterone production (5,6). Reduced aldosterone synthesis leads to renal sodium loss, volume depletion, and reduced potassium excretion, which collectively produce the characteristic biochemical abnormalities (7).

Clinical manifestations of ASD typically arise during the neonatal period or early infancy. Symptoms include vomiting, poor feeding, dehydration, hypotension, and failure to thrive, which can quickly progress to life-threatening crises if unrecognized (8,9). In many cases, symptoms are precipitated by physiological stress, reduced oral intake, or intercurrent illness. Our patient presented at nine months of age, later than typical for ASD, highlighting the variable and occasionally subtle onset of the disorder.

The diagnostic challenge lies in the clinical overlap with more frequent conditions. Besides CAH, differential diagnosis includes renal tubular disorders, pseudohypoaldosteronism, cystic fibrosis, and gastrointestinal salt loss (3,10). Normal renal function, absence of gastrointestinal symptoms, and low urine sodium in our case supported a renal salt-wasting state driven by

mineralocorticoid deficiency rather than tubular dysfunction. Routine hormonal testing cannot definitively distinguish isolated aldosterone deficiency; therefore, genetic confirmation is essential, especially when clinical suspicion is high and alternative etiologies have been excluded (11).

The widespread availability of next-generation sequencing (NGS) has significantly improved diagnostic accuracy for rare adrenal disorders, allowing early identification and precise classification of CYP11B2 variants (4,12). Early diagnosis is crucial, as prompt mineralocorticoid replacement prevents severe complications and supports normal growth and neurodevelopment.

Fludrocortisone remains the mainstay of therapy, acting as a synthetic mineralocorticoid that enhances sodium reabsorption and potassium excretion (13). Sodium supplementation is frequently required in infancy due to physiologically reduced renal responsiveness to mineralocorticoids (2). In our patient, combined therapy resulted in rapid correction of electrolytes, resolution of vomiting and dehydration, and subsequent catch-up growth.

Long-term outcomes in ASD are generally favorable when treatment is initiated early and electrolyte balance is maintained (8,14). Consistent with the literature, our patient demonstrated normal growth, stable electrolyte values, and no recurrent salt-wasting crises during follow-up. Mild hyponatremia during intercurrent infections is common and reflects increased physiological stress and transiently increased sodium requirements.

This case underscores the importance of considering ASD in infants with persistent hyponatremia and hyperkalemia, particularly when CAH has been excluded and no renal or gastrointestinal pathology is identified. Increased awareness among clinicians, combined with access to genetic testing, enables timely diagnosis and improves clinical outcomes.

Conclusion

Aldosterone synthase deficiency is a rare but clinically significant cause of salt-wasting in infancy. Because its presentation overlaps with more common endocrine, renal, and gastrointestinal disorders, the condition is frequently misinterpreted, leading to delayed diagnosis. Persistent hyponatremia and hyperkalemia in the absence of elevated adrenal androgens should raise suspicion for an isolated mineralocorticoid synthesis defect. Genetic confirmation using next-generation sequencing enables precise diagnosis and guides appropriate treatment. Early initiation of fludrocortisone therapy and sodium supplementation results in rapid clinical improvement and supports normal growth and development. This case highlights the importance of maintaining awareness of aldosterone synthase deficiency in infants with unexplained electrolyte disturbances and underscores the value of timely genetic evaluation in achieving favorable long-term outcomes.

Acknowledgment

The authors extend gratitude to the pediatric medical and nursing staff at Acibadem Sistina Clinical Hospital for their dedicated care, continuous support, and professional engagement in the management of this patient.

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CASE REPORT *UDK: 616.133-003.7-085.8*

www.doi.org/10.55302/MJA2594144b

THE ROLE OF SHOCKWAVE INTRAVASCULAR LITHOTRIPSY IN THE TREATMENT OF HEAVILY CALCIFIED CORONARY ARTERY LESIONS: OUR FIRST EXPERIENCE

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Abstract

Introduction: Coronary artery disease (CAD) is typically a chronic, progressive, inflammatory disease of the coronary arteries caused by coronary atherosclerosis. Moderate-to-severe calcification is present in up to 30% of patients undergoing coronary angiography (CA). Calcified coronary artery lesions are one of the most complex and challenging lesion subsets in interventional cardiology. Shockwave intravascular lithotripsy (IVL) is a recently introduced calcium-modifying technique for the treatment of concentric, eccentric and nodular calcifications.

Case presentation: We present a clinical case of a 73-year-old male complaining of intermittent chest pain. He was a non-smoker with a positive familiar history for CVD. He had previous myocardial infarction and stenting of the right coronary artery (RCA), previous CVI, paroxysmal atrial fibrillation, insulin-dependent type 2 diabetes, heart failure with mildly reduced ejection fraction (HFmrEF) and chronic kidney disease (CKD) stage II/IIIa. CA revealed heavily calcified CAD. A calcified lesion of the left anterior descending artery (LAD) was treated using a 3.0/12 mm Shockwave IVL balloon; and calcium cracks and fractures were confirmed by optical coherence tomography (OCT). We proceeded with an NC balloon and finally treated the lesion with a 3.5/15 mm drug-coated balloon (DCB). The calcified lesion of the RCA was treated with conventional techniques using guiding catheter extension, NC balloons and drug-eluting stent (DES).

Conclusion: Heavily calcified coronary artery lesions remain one of the biggest challenges for interventional cardiologists. Shockwave IVL is designed for treatment of all types of heavily calcified lesions using acoustic waves (shock waves). IVL is safe and effective technique that will definitely strengthen the armamentarium for modern treatment of heavily calcified lesions.

Keywords: *Calcified lesion, coronary artery disease, calcium-modifying technique, Shockwave IVL.*

Introduction

Coronary artery disease (CAD) is a typically chronic, progressive and inflammatory disease of the coronary arteries caused by coronary atherosclerosis that leads to coronary artery stenosis and clinical manifestation of either chronic coronary syndrome (CCS) or acute coronary syndrome (ACS). The main substrate of the atherosclerotic CAD is atherosclerotic coronary plaque that may contain different amount of calcium. Coronary artery calcification is associated with

age and some risk factors and comorbidities such as male sex, smoking, hypertension, diabetes and chronic kidney disease (1). It has been widely accepted that coronary artery calcification is a true marker of coronary atherosclerosis. Nevertheless, atherosclerotic lesions that contain only spotty calcifications are often unstable and more frequently lead to plaque rupture, which is clinically manifested as an ACS. On the contrary, lesions that contain higher amount of calcium are usually more stable and are related to CCS (2). Heavily calcified atherosclerotic lesions cause decreased vessel elasticity and increased artery stiffness. According to different authors, calcified atherosclerotic lesions may be present in 18-60% of patients, but moderate-to-severe calcification is present in up to 30% of patients undergoing coronary angiography and percutaneous coronary interventions (PCIs) (1-4). There are mainly two types of vascular calcifications: intimal and medial. Intimal calcifications are generally related to atherosclerosis (and its pathogenesis includes inflammation and subintimal lipid deposition) whereas medial calcifications are more associated with diabetes, chronic kidney disease and dialysis where serum hyperphosphatemia plays a main role (5-7).

Although revolutionary advances in the calcium modification technology have been recently achieved, heavily calcified coronary artery lesions may still be a challenge in interventional cardiology. They may prolong the total procedural time, increase the rate of intraprocedural complications (such as dissection, rupture), hinder stent delivery, and may be the main reason for suboptimal stent expansion and malapposition, thus increasing the risk for in-stent thrombosis and restenosis and poor clinical outcomes (8-11).

Coronary artery calcifications can appear as concentric (involving most of the circumferential arc or whole arc), eccentric or as calcific nodule.

Visualization of the coronary artery calcification. Visualization of the coronary artery calcifications can be obtained by several non-invasive and invasive imaging modalities. Non-invasive assessment of the coronary artery calcification can be performed by determining the so-called coronary artery calcium score (CACS, Agatston score), which is a specific marker of atherosclerosis. It is calculated by using non-contrast computed tomography (CT) and it is generally applied in asymptomatic patients to predict their cardiovascular risk (12). Agatston score >400 is associated with a significant CAD and carries an increased risk of major adverse cardiac events (MACE) (13). Coronary angiography (CA), as an invasive procedure, can also detect moderate to severe coronary artery calcifications, but with low sensitivity. Moderate to severe coronary calcifications appear as linear shadows or radio-opaque deposits of various intensity, clearly seen before contrast injection, which usually follows the contour of the coronary vessel wall (tram-track appearance). Heavily calcified atherosclerotic plaques that grow intraluminally can be detected by intracoronary contrast injection as areas of haziness or even as a filling defect if calcified nodule is detected. The latter appearance can often create diagnostic challenges in differentiating it from thrombi, especially in patients with an ACS (10, 14-16).

Intravascular imaging modalities like intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have the highest sensitivity and specificity in detection of coronary artery calcifications (Figure 1). IVUS allows detailed assessment of the circumferential (360-degree arc) and longitudinal extension of the coronary artery calcifications. Due to its high penetration power, IVUS can discriminate superficial from deep calcium. Coronary artery calcifications are visualized as hyperechoic areas with consecutive acoustic shadows. But IVUS cannot assess the real thickness of the coronary artery wall calcification. This imaging modality can serve as a PCI-guiding modality in terms of planning of the procedure and selection of sizes of the bal-

loons and stents (10, 12, 14, 15).

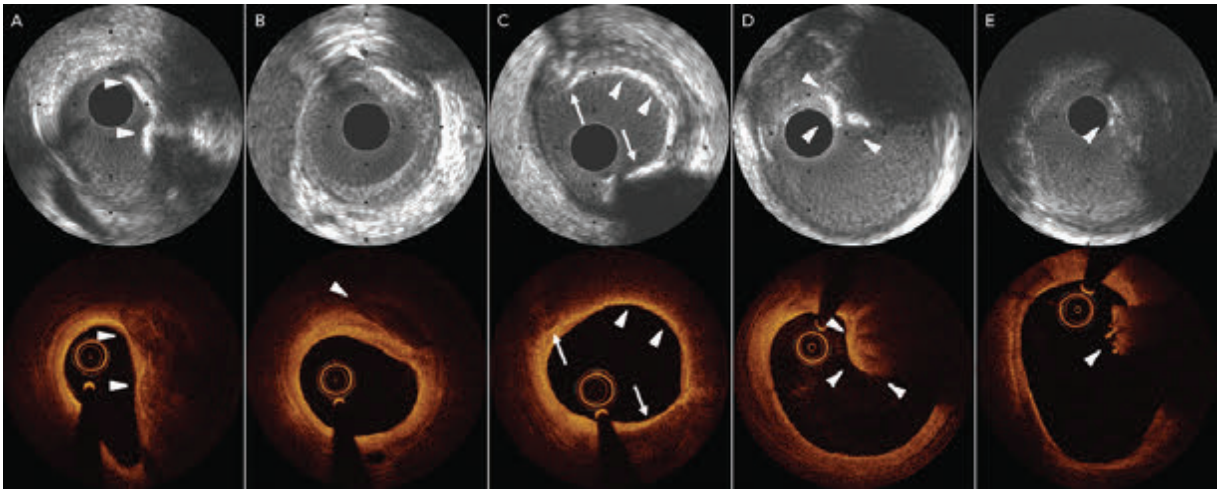


Figure 1. Images of calcified plaque by intravascular ultrasound (upper panel) and optical coherence tomography (lower panel). A. superficial calcium with arrowheads, B. deep calcium with arrowheads, C. IVUS reveals hyperechogenic tissue without shadows (arrowheads) between spotty calcium (arrows), suggesting dense fibrous plaque or a thin layer of calcium; OCT reveals fibrous tissue with no evidence of calcium (arrowheads), D. calcified nodule (arrowheads), E. OCT depicts irregular mass protruding into the lumen (could be misinterpreted as red thrombus), IVUS shows hyperechogenic mass with shadowing suggesting calcified nodule; IVUS, intravascular ultrasound; OCT, optical coherence tomography (Adapted from Interventional Cardiology Review 2019;14(3):164–8)

OCT has higher resolution than IVUS and it can easily and accurately detect and assess coronary artery calcifications, with sensitivity and specificity approaching 100%. Coronary artery calcification on OCT appears as heterogeneous or low-intensity signal area which is clearly delineated. OCT can precisely calculate the thickness of the calcified lesion and determine its circumferential and longitudinal distribution. In addition, it can be also used for intravascular guidance of the complex PCI procedures. However, the penetration power of OCT is lower than that of IVUS, which may result in deep calcification if assessed by OCT (10, 12, 15-17).

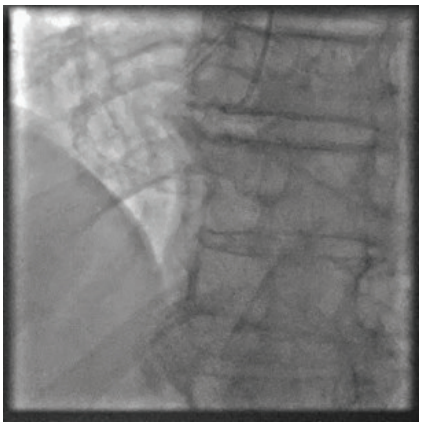
Intravascular imaging can be used to guide PCIs and to assess the risk for suboptimal stent expansion regarding extent of coronary artery calcification. Moreover, there are two risk scores, IVUS-derived and OCT-derived, which can predict the risk for stent underexpansion based on certain criteria. IVUS-derived calcium risk score includes 4 criteria (360-degree arc of calcium, >270-degree of calcium with length >5 mm, calcified nodule and vessel diameter <3,5 mm) and coexistence of at least 2 of them (2 points). According to Zhang et al. it can predict suboptimal stent expansion. Similarly, Fujino et al. presented an OCT-derived calcium risk score for prediction of suboptimal stent expansion based on 3 parameters (maximal calcium angle >180 degrees, maximal calcium thickness >0,5 mm and longitudinal calcium length >5 mm) (Figure 2). It is of great importance to underline the fact that these calcium risk scores are primarily intended for patients with CCS and coronary artery calcifications. Their application in patients with an ACS need further validation, as calcium and thrombi can coexist in this clinical setting (10, 11, 15, 18).

OCT-based calcium score		
Maximal calcium angle (°)	≤180°	0 points
	>180°	2 points
Maximal calcium thickness (mm)	≤0.5 mm	0 points
	>0.5 mm	1 point
Calcium length (mm)	≤5 mm	0 points
	>5 mm	1 point
IVUS-based calcium score		
360° arc of calcium	Absence	0 points
	Presence	1 point
>270° arc of calcium with length > 5 mm	Absence	0 points
	Presence	1 point
Calcified nodule	Absence	0 points
	Presence	1 point
Vessel diameter (mm)	≥3.5 mm	0 points
	<3.5 mm	1 point

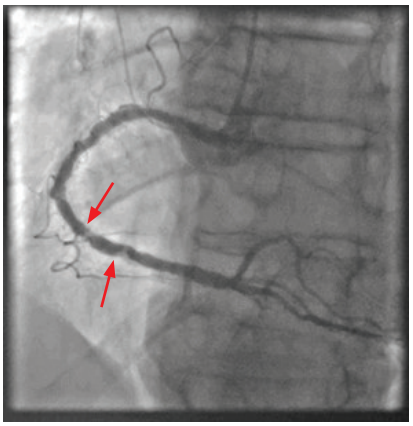
Figure 2. Intravascular imaging-based calcium scores. Each score is calculated by adding the points assigned to each parameter. Lesion with an OCT-based score of 4 and/or an IVUS-based score ≥ 2 is more likely to result in stent underexpansion, highlighting the need for adequate lesion preparation. IVUS, intravascular ultrasound; OCT, optical coherence tomography (Adapted from Percutaneous Revascularization of Thrombotic and Calcified Coronary Lesions. J. Clin. Med. 2025, 14, 692).

Case presentation

We present a clinical case of a 73-year-old male complaining of intermittent chest pain that had started several months ago. The patient had typical effort angina that was worsening over time. He was a non-smoker with positive familiar history for CVD and BMI 27,4 kg/m2. He had a previous myocardial infarction and stenting of the right coronary artery (RCA) in 2011, a previous ischemic CVI in 2013, episodes of paroxysmal atrial fibrillation, insulin-dependent type 2 diabetes, heart failure with mildly reduced ejection fraction (HFmrEF, LVEF 45%) and chronic kidney disease (CKD) stage II/IIIa. His ascending aorta was dilated and measured 48 mm by echocardiography. The patient was treated with optimal medical therapy including bisoprolol, valsartan, empagliflozin, furosemide, spironolactone, rivaroxaban, atorvastatin, and proton-pump inhibitor. Diabetes was therapeutically managed with insulin, metformin and empagliflozin. Recent laboratory findings revealed HbA1c of 8,4% and lipid profile as follows: total cholesterol 2,1 mmol/l, LDL-c 0,94 mmol/l, HDL-c 0,73 mmol/l, and triglycerides 1,27 mmol/l. The ECG on admission was unremarkable, showing sinus rhythm with leftward axis deviation and left anterior hemiblock. The patient has already underwent coronary angiography 3 months ago, which revealed diffusely and heavily calcified CAD. He was now scheduled for repeated elective coronary angiography with the aim of treating the heavily calcified right and left coronary arteries with Shockwave intravascular lithotripsy (IVL) – a novel calcium-modifying technique for treatment of all types of heavily calcified coronary lesions (Figures 3-6).

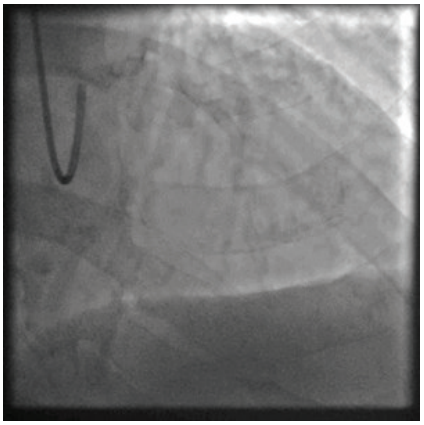


Figures 3

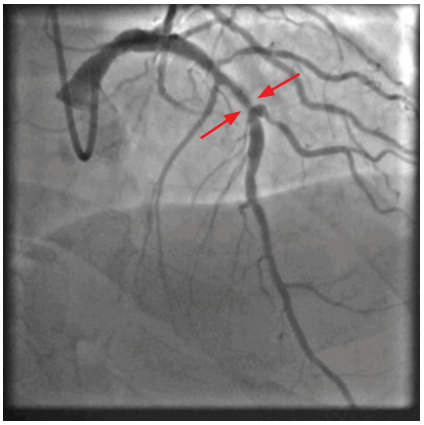


Figures 4

Figures 3 & 4. Heavily calcified right coronary artery on coronary angiography seen prior to contrast injection (Fig. 3) (tram-track appearance) and during contrast injection (Fig. 4). Red arrows show calcified coronary lesions that lead to a significant coronary artery stenosis.



Figures 5



Figures 6

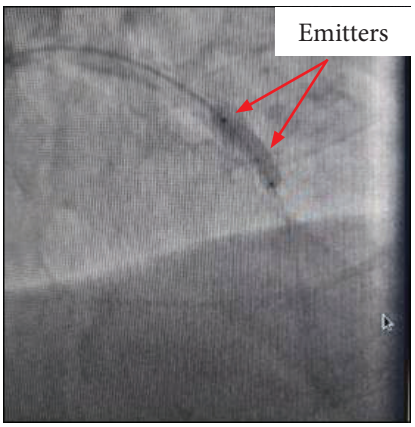
Figures 5 & 6. Heavily calcified left coronary artery on coronary angiography seen prior to contrast injection (Fig. 5) and during contrast injection (Fig. 6). Red arrows show calcified coronary lesion that leads to a significant coronary artery stenosis

Repeated coronary angiography confirmed diffusely and heavily calcified coronary arteries causing significant coronary artery stenosis at mid segment of the LAD and mid-to-distal segment of the RCA. After initial anticoagulation with 100 IU/kg unfractionated heparin (UFH), we initiated the interventional procedure with canulation of the left anterior descending artery (LAD) using EBU 3.5 catheter and placement of standard coronary BMW wire. Then we proceeded with positioning of the IVL balloon, its expansion to 4 atm, and further application of 40 pulses from the Shockwave system. Figure 7 shows the IVL balloon catheter with its emitters during pulse application. After that we performed an OCT pullback of the LAD which clearly showed cracks and fractures of the heavily calcified coronary artery lesion (Figure 8). We continued with further lesion preparation using NC balloon, achieving solid lumen gain. The final step was treating the lesion with paclitaxel drug-coated balloon (DCB) 3,5/15 mm on 7 atm, achieving solid angiographic result with no significant residual stenosis, no dissection and TIMI 3 flow (Figure 9). RCA was treated using Amplatz right guiding catheter (AR 2), standard BMW coronary wire and a guiding catheter extension to increase support and enhance preparation of the

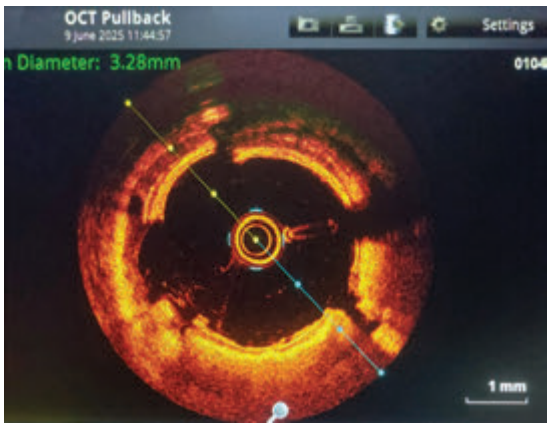
calcified coronary artery lesion. Lesion preparation was performed using standard NC balloons with different sizes. The procedure was completed with implantation of one 3,5/24 mm DES into the mid-to-distal segment of the RCA achieving optimal angiographic result (Figure 10).

During the procedure, the patient remained asymptomatic, with stable vital signs and excellent tolerability of the novel therapeutic tool. We completed the interventional procedure successfully with no periprocedural complications. The loading dose of Clopidogrel 600 mg was given to the patient right upon completing the procedure.

This clinical case reflects our very first experience of using Shockwave IVL in the treatment of heavily calcified CAD at the University Clinic of Cardiology in Skopje, N. Macedonia. We believe that this tool may become one of the preferred treatment modalities for heavily calcified CAD concerning the ease of use, the safety profile and the effectiveness of the treatment.

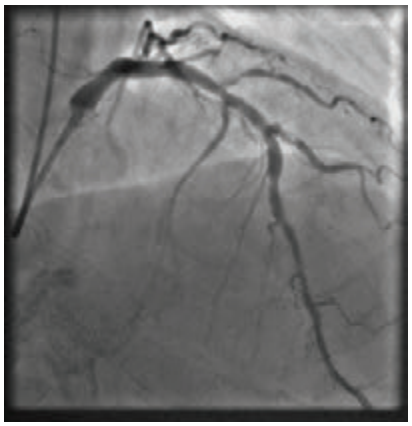


Figures 7

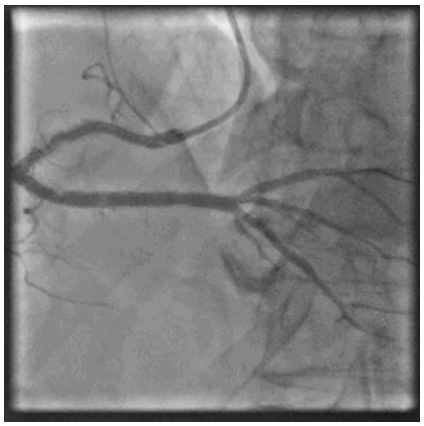


Figures 8

Figures 7 & 8. Shockwave IVL balloon catheter showing its emitters that are responsible for generation of the acoustic waves (Fig. 7). Cracks and fractures of the heavily calcified coronary artery lesion caused by Shockwave IVL and detected by OCT pullback (Fig. 8); IVL, intravascular lithotripsy; OCT, optical coherence tomography.



Figures 9



Figures 10

Figures 9 & 10. Final result of the left anterior descending artery after Shockwave IVL, NC balloon and final treatment with DCB (Fig. 9). Final result of the right coronary artery after implantation of one 3,5/24 mm DES (mid to distal segment). (Fig. 10); DES, drug-eluting stent; IVL, intravascular lithotripsy; NC, non-compliant; DCB, drug-coated balloon.

Discussion

Calcified coronary artery lesions are one of the most complex and challenging subsets of lesions in interventional cardiology. Every single heavily calcified coronary artery lesion has to be appropriately prepared, which usually means applying a proper debulking and/or calcium-modifying technique.

Generally speaking, the preparation of the heavily calcified lesions can be performed by plaque (calcium) debulking (ablative) techniques and plaque (calcium) modifying (balloon-based) techniques. The former involves atherectomy devices like rotational atherectomy (rotablation), orbital atherectomy and laser atherectomy (excimer laser coronary atherectomy, ELCA) and they can debulk/decrease the thickness of the calcium, however, unfortunately, they do not increase vessel compliance/elasticity. The latter includes semi-compliant (SC) balloons, non-compliant (NC) balloons, specialized high-pressure balloons (OPN), cutting and scoring balloons, and intravascular lithotripsy (IVL)(15). These techniques do not change the thickness of the calcium, but rather lead to crack and/or fracture of the calcium, thus increasing the vessel compliance/elasticity. All balloon-based techniques rely on mechanical high-pressure treatment except shockwave IVL, which relies on acoustic waves and utilizes an external source of energy. However, it is worth mentioning that IVL-based techniques beside shockwave IVL include the recently introduced LithiX Hertz Contact IVL (HC-IVL) that does not require an external source of energy. It utilizes a balloon catheter with several metallic hemispheres that deliver focus stress on the calcified plaque with no impact on the surrounding soft tissue (mechanical IVL) (19). Any of these techniques can be used for the treatment of calcified coronary lesions as a single technique or in combination, depending on the lesion characteristics.

Shockwave IVL is one of the most recently introduced techniques for treatment of this lesion subset. The whole system includes a generator, a connector cable, and a semicompliant balloon (Figure 11).

Figures 11 **Figures 12**

Figures 11 & 12. (Fig. 11) Shockwave IVL system consisting of a generator, a connector cable and a semicompliant balloon; IVL, intravascular lithotripsy. (Fig. 12) Balloon for Shockwave IVL containing 2 emitters; IVL, intravascular lithotripsy (Adapted from https://shockwavemedical.com/en-eu/products/shockwave-c2-plus/)

The balloon contains two emitters that generate acoustic pressure waves (shockwaves). The first (distal) emitter is positioned 4 mm from the distal balloon marker and the second (proximal) emitter is positioned 6 mm proximally to the distal one (Figure 12). As a general rule, it is rec-

ommended to select a 1:1 balloon size and position the IVL balloon so that the emitters face the most heavily calcified region of the plaque in order to have most efficient interaction with calcium. Then, it is inflated at 4 atm and the button for energy generation and transmission is pressed. It is now not recommended to inflate the balloon to 6 or more atmospheres because of the highe risk of balloon rupture (15). Energy delivery can start with 10 shockwave pulses per location. When the shockwave pulse interacts with the calcium, it transfers energy that is usually equal to 50 atm pressure, which is achieved with a conventional balloon technique. The first generation original IVL balloon catheters were designed to deliver the total of 80 pulses (C2), while the new ones called C2+ can deliver up to 120 pulses per balloon catheter. Shockwaves interact with the superficial and the deep calcium of the atherosclerotic lesion; while soft vascular tissues remain untouched, which makes this modality safe (20).

If properly used, this technique is completely safe, and the risk of complications is typically below 0,5%. The main indications for Shockwave IVL usage are all types of calcified atherosclerotic lesions, including concentric, eccentric, and nodular. There are currently 4 commercially available balloons with sizes 2.50, 3.0, 3.50, and 4.0 mm over 12 mm length (20).

Shockwave IVL has received CE marking for official use in Europe in 2017, following the results from the Disrupt CAD I study (21). The Disrupt CAD I study was the first prospective, multicenter, single-arm, pre-market study in a series of studies that successfully demonstrated the safety and the efficient performance of the Shockwave IVL in treating heavily calcified coronary lesions in 60 patients followed for 6 months. The results of this study showed that the rate of vessel perforation, abrupt vessel closure, slow flow and no reflow was 0,0% for each event separately. The rate of 30-day MACEs was 5%, whereas the rate of 6-month MACE was 8,3% (20, 22). The next study, Disrupt CAD II, was a prospective, multicenter, single-arm, post-approval study encompassing 120 patients with heavily calcified coronary lesions between May 2018 and March 2019. It achieved similar results like Disrupt CAD I, in terms of vascular complications and MACEs. The effectiveness of Shockwave IVL was confirmed by optical coherence tomography (OCT) (20, 23). Disrupt CAD III was a prospective, single-arm, pivotal study demonstrating the safety, effectiveness and ease of use of Shockwave IVL, designed for regulatory approval of coronary IVL. The results from 384 patients in this study treated with Shockwave IVL showed that 92,2% of them were free from MACEs at 30 days after the procedure, whereas the rate of vessel perforation (0,3%), abrupt closure (0,3%) and slow flow/no reflow (0,0%) remained low. This study also demonstrated the ease of use of the device, simultaneously achieving Shockwave IVL crossing and therapy delivery in 98% of lesions (20, 24). The results from this study led to obtaining the approval from the US FDA for the use of Shockwave IVL in treating severely calcified CAD in 2021 (25). The latest from this series of studies is the Disrupt CAD IV, a prospective, multicenter study specifically designed for Japanese regulatory approval of the Shockwave coronary IVL. It was conducted on 64 patients with severely calcified CAD, achieving a high degree of procedural success (93,8%), with low rates of MACEs at 30-day (6,3%) and 1-year follow up (9,4%) and no vascular complications, including vessel perforation (0%), abrupt vessel closure (0%), slow flow/no reflow (0%) and major dissections (0%) (26). As a conclusion, the Disrupt CAD IV study demonstrated a high procedural success rate with low MACEs of Shockwave IVL in heavily calcified lesions in a Japanese population.

The direct comparison of Shockwave IVL to conventional lesion preparation in heavily calcified CAD, regarding procedural and target vessel failure (TVF) was studied in the BALI trial (200 patients) and the results were announced at the most recent EuroPCR Congress 2025 in Paris. This study showed that in patients with severely calcified CAD, IVL significantly re-

duced the incidence (35,4% vs 51,5%) of primary endpoint (procedural failure or TVF) compared to conventional lesion preparation (RR 0.69; 95% CI 0.48–0.97; p=0.02) (27).

But maybe one of the most interesting trials conducted in this field was the ICARE trial, comparing Shockwave IVL to rotational atherectomy (RA) in 169 patients with heavily calcified CAD. This was a prospective, randomized, multicenter trial that investigated the efficacy of IVL in comparison to RA assessed by minimal stent area measurements (MSA) with optical frequency domain imaging (OFDI), and the safety of IVL in comparison to RA in terms of MACEs at 30 days. The results confirmed that IVL was non-inferior to RA in achieving optimal stent expansion. Moreover, RA was associated with a significantly higher rate of periprocedural myocardial infarction compared to IVL (5,8% in RA vs 0,0% in IVL, p=0.06) (28, 29).

We are now awaiting results of the last and most important clinical trial – the ISAR WAVE trial. This trial tests whether IVL is superior to other calcium debulking or modifying techniques (atherectomy devices, super high-pressure balloons) in de novo heavily calcified coronary artery lesions. It is a multicenter, randomized clinical trial which plans to include 666 patients (30).

Conclusion

Heavily calcified coronary artery lesions remain one of the biggest challenges for interventional cardiologists. There are currently many useful tools and techniques designed for appropriate lesion preparation. Shockwave IVL is one of the most recently introduced technique for handling all types of heavily calcified lesions using acoustic waves (shock waves) that are capable of plaque modification without risk of soft vascular tissue injury. They crack the superficial and deep calcium, allowing improvement of the vessel compliance and elasticity, which in return enhances further treatment of the lesion with high-pressure balloons (NC and OPN) and final treatment with DCB or DES. This step is critical since it leads to optimal lesion preparation and eventually optimal stent expansion and apposition, which significantly reduces the rate of subsequent adverse events like in-stent thrombosis and restenosis. Many clinical trials and meta-analyses confirmed its safety and efficacy in the fight against calcium. Shockwave IVL will definitely strengthen the armamentarium for modern treatment of heavily calcified lesions.

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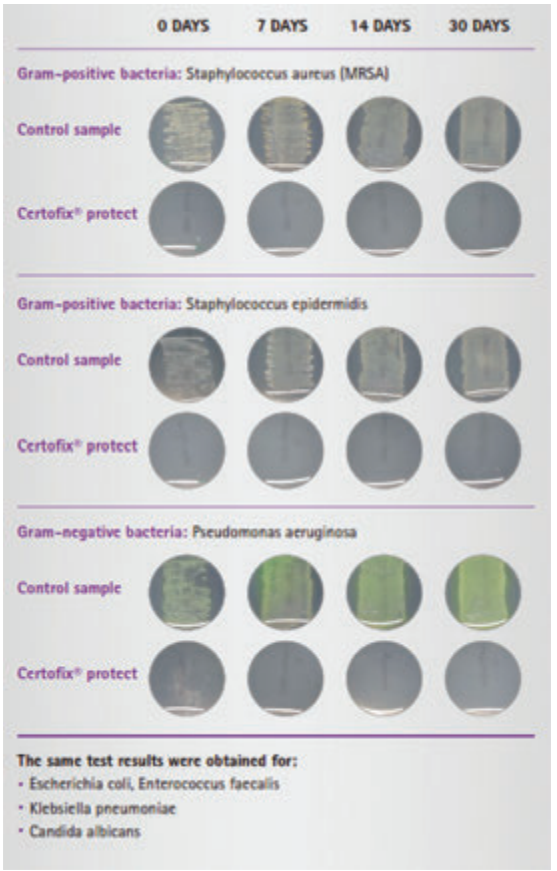

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