ISSN 3029-3472 (Online)

SaMJ Sarajevo MEDICAL Journal

Volume 1 • Number 1 • July 2024

LIJEČNIČKA - LJEKARSKA
KOMORA
KANTONA SARAJEVO

SARAJEVO MEDICAL JOURNAL
Official Publication of the Medical Association of Sarajevo Canton Bosnia and Herzegovina

ISSN 3029-3472 (Online); ISSN 3029-3464 (Print)

Editor's Note

Dear Colleagues,

Working with patients, if not accompanied by a scientific-research component, can eventually become routine for clinicians. Scientific and research work compels us to learn something new every day, to seek out the unexpected, and to continuously push the boundaries of our practice and knowledge. This drive motivated the Medical Chamber of the Canton of Sarajevo and a group of like-minded individuals to embark on a new project, the establishment of the "Sarajevo Medical Journal."

The process of collecting manuscripts, finding reviewers, revising (often repeatedly), and the subsequent editing and formatting is indeed time-consuming. However, participating in this process is profoundly meaningful, as it feels like working towards a worthwhile goal. Investing in continuous education and functioning as a team is essential for the development of a medical healthcare system, and it is through this collaborative effort that true progress is made.

You now hold the inaugural issue of the "Sarajevo Medical Journal." I hope that after reading it, you will agree that initiating this journal was worthwhile and that we are on the right track.

I invite you to become part of this endeavor. The success of the journal relies on your support and involvement.

Sincerely,

Prof. Edin Begic MD, PhD

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Tel.: +387 33 219 272, Fax: +387 33 219 493 ;
Email: sarajevomedicaljournal@gmail.com; web site: www.samj.ba
DTP by: ZeForge Solutions;
Printed by:

SARAJEVO MEDICAL JOURNAL
Official Publication of the Medical Association of Sarajevo Canton Bosnia and Herzegovina

SARAJEVO MEDICAL JOURNAL
Official Publication of the Medical Association of Sarajevo Canton, Bosnia and Herzegovina

Volume 1, Number 1, August 2024

Free full-text online at: www.samj.ba

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EDITORIAL

Precision Medicine: Trends In Perinatal Gynecology

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Pages: 1-4 / Published online: 19 August 2024

Cite this article: Kurjak A.Precision Medicine: Trends In Perinatal Gynecology.Sar Med J. 2024; 1(1): Online ahead of print. DOI: 10.70119/0001-24

Original submission: 14 March 2024; **Revised submission:** 06 June 2024; **Accepted:** 10 July 2024

Abstract

The Kurjak Antenatal Neurodevelopmental Test (KANET) has revolutionized prenatal care and fetal neurology by providing a non-invasive method to assess fetal neurodevelopment using four-dimensional ultrasound (4D US). Over the past ten years, KANET has been widely implemented across various clinical settings, enabling the early detection of neurodevelopmental disorders. This early identification is crucial for timely intervention and improved long-term outcomes. KANET standardizes the assessment of fetal neurological function, offering a structured and objective approach that enhances our understanding of fetal behavior and its implications for postnatal development. While KANET demonstrates high specificity and a low false-negative rate, its sensitivity in detecting specific conditions like cerebral palsy (CP) remains limited. The test's widespread use has not only informed clinical management strategies but also promoted further research into prenatal neurodevelopment and potential prenatal interventions. Recent studies highlight differences in fetal behavior in pregnancies complicated by gestational diabetes, suggesting the potential for KANET to inform future neurodevelopmental outcomes. Continued research and refinement of KANET are essential to enhance its predictive accuracy and ensure comprehensive postnatal follow-up.

Keywords: fetal development, screening, prognosis.

Significance of the Kurjak Antenatal Neurodevelopmental Test

The introduction of the Kurjak Antenatal Neurodevelopmental Test (KANET) has significantly impacted clinical practice, particularly in prenatal care and fetal neurology (1-8). According to our opinion, the key aspects of its significance and importance are (1):

- early detection of neurodevelopmental disorders
- non-invasive assessment,
- enhanced understanding of fetal behavior,
- standardization in fetal neurology,
- guidance for clinical management,
- promoting research and innovation.

KANET has enabled healthcare providers to detect potential neurodevelopmental disorders much earlier than by traditional methods. By using four-dimensional ultrasound

(4D US) to assess fetal behavior and movements, KANET offers a window into the developing fetal nervous system, allowing clinicians to identify abnormalities that could indicate future neurological issues (1-8). This early detection is crucial for timely intervention and management (7).

As a non-invasive procedure, KANET provides a safe way to assess fetal development without posing risks to the mother or fetus (4-6). This aspect is particularly valuable in prenatal care, where minimizing risks is a priority.

KANET has contributed to a deeper understanding of fetal behavior and its correlation with postnatal neurodevelopment (9). It has highlighted that certain patterns in fetal movements and behavior can be early indicators of conditions like developmental delays (among them cerebral palsy) (1-9).

The development of KANET represents a significant step towards standardizing the assessment of fetal neurodevelopment (9). Before KANET, assessment of fetal behavior by two-dimensional ultrasound (2D US) was less standardized and more subjective. The test provides a structured and objective method to evaluate fetal neurological function, making it possible to compare results across different clinical settings and studies (1, 4, 5).

The results from KANET can inform clinical decisions and management strategies (1-9). For instance, identifying a fetus at high risk for neurological issues allows healthcare providers to plan for appropriate monitoring and interventions postnatally, potentially improving long-term outcomes for the child (9).

KANET has spurred further research into prenatal neurodevelopment and the factors that influence it (1). It has opened up new avenues for exploring how prenatal interventions might mitigate or prevent neurodevelopmental disorders (1-9).

Ten Years of Wide Clinical Use of KANET

Based on the detailed review of the investigation which has been conducted for almost ten years, here are the most important points regarding the use of KANET over the mentioned period (1-9):

- development and purpose of KANET,
- clinical findings and reliability,
- postnatal outcomes.

KANET was developed to provide a standardized method to evaluate fetal neurodevelopment using four-dimensional ultrasonography (4D US) (9). This test assesses fetal behavior and general movements to identify potential neurodevelopmental disorders early, even before birth.

The test has been widely used across multiple centers, with numerous published papers reporting over 3,709 fetuses assessed (1). The findings revealed that abnormal or borderline KANET scores are more prevalent in high-risk pregnancies (1-11).

KANET demonstrated high specificity and a low false-negative rate, indicating that a normal KANET score strongly correlates with normal postnatal development (1). However, its sensitivity, particularly in detecting conditions like cerebral palsy (CP), remains limited (1).

Of the infants assessed postnatally, a vast majority (98.3%) had normal development. Abnormal KANET scores were associated with a higher incidence of severe developmental delays and conditions like CP (1). However, even among those with abnormal KANET scores, a significant number still developed normally postnatally (1).

Challenges and Limitations of KANET

While KANET has significant benefits, it also has limitations, such as its sensitivity in detecting specific conditions like CP (1). Despite these limitations, its high specificity and positive predictive value make it a valuable tool in prenatal screening and diagnosis (1).

In summary, the introduction of KANET into clinical practice has been a groundbreaking development in prenatal medicine. It has enhanced the ability of clinicians to detect and understand neurodevelopmental issues

early in life, offering significant potential for early intervention and better outcomes for affected individuals (1-9).

The accuracy of KANET in predicting neurodevelopmental outcomes, particularly for conditions like CP, is constrained by the test's limited sensitivity (1). Additionally, the diverse intrauterine environment complicates the interpretation of fetal neurobehavioral data.

Promising Long-Term Investigations Post-KANET Scoring

Recent studies have explored the correlation between KANET scores and long-term neurodevelopmental outcomes, especially in cases involving pregnancies complicated by gestational or pregestational diabetes (10,11). Research, including a PhD thesis focused on assessing fetal behavior via 4D US in pregnant women with gestational diabetes, has shown significant differences in fetal movements between complicated and uncomplicated pregnancies (10-12). Higher HbA1c levels were associated with altered fetal behavior (12). Preliminary findings indicate that children with lower KANET scores as fetuses tend to perform worse on neurodevelopmental tests at ten years of age. These promising results warrant further investigation.

Recommendations for Future Use of KANET

It could be suggested that while KANET is a valuable tool for early detection of potential neurodevelopmental issues, it should not replace comprehensive postnatal assessments.

KANET is the first neurological test that very successfully separates healthy children from those with suspected cerebral palsy, and soon for some other neurodevelopmental diseases. After attending a week-long education (we have centers in Zagreb, Sarajevo and Athens) attendees are awarded a KANET diploma.

At the moment, our groups are ready to submit a research project related to Screening for cerebral palsy with KANET test and artificial intelligence. We believe that KANET is an ideal test for screening procedures. In the meantime, all groups in collaborative studies are trying to assess scientifically reliable sensitivity, specificity and accuracy of the new test. Until now, 14 PhD thesis were defended in Croatia, Greece, Romania, Bosnia and Herzegovina, Saudi Arabia, Indonesia, Qatar, Egypt, Libya, and India.

Acknowledgment: Thank you to all the colleagues who have worked for years on the development and use of KANET in clinical practice.

Author Contribution: Conceptualization, Formal Analysis, Methodology, Writing – Original Draft, and Writing – Review & Editing were carried out by Asim Kurjak.

Financial support and sponsorship: There was no funding.

Conflict of interest: The authors have nothing to disclose.

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ORIGINAL RESEARCH

Tonsillectomy and the Risk of Post-Tonsillectomy Hemorrhage: A Retrospective Cross-Sectional Study

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Pages: 5-10 / Published online: 19 August 2024

Cite this article: Krkalic A, Mandra H, Joguncic A. Tonsillectomy and the Risk of Post-Tonsillectomy Hemorrhage: A Retrospective Cross-Sectional Study. Sar Med J. 2024; 1(1): Online ahead of print.
DOI: 10.70119/0002-24

Original submission: 15 March 2024; **Revised submission:** 07 June 2024; **Accepted:** 11 July 2024

Abstract

Intorduction. Aim of article was to retrospectively reviewed occurrence of post-tonsillectomy hemorrhage (PTH) in a population with a wide age range and assessing the association between patients' age, time of PTH, and the need for surgery to control bleeding.

Methods. A retrospective cross-sectional study of 240 patients who underwent a tonsillectomy, tonsilloadenotomy or adenectomy in our Department. Demographic parameters, indication, complication, performed operation and PHD were analyzed in patients.

Results. A total of 240 patients with a mean age of 12.29 years, a median age of 8 years and an interquartile range of 5 to 15 years. In relation to the age limit of 16 years, 181 (75.4%) patients were 16 or younger, and 59 (24.6%) were over 16. 9 (5%) children had PTH, primary in 2.2%, and secondary in 2.8%. 8 adults (13.6%) had secondary PTH. Patients older than 16 had a 2.73 times higher risk of bleeding than patients younger than 16 (RR=2.73; p=0.030). In terms of gender, 9 male patients (8%) and 8 female patients (6.3%) experienced bleeding. There was no significant statistical difference (p=0.529).

Conclusion. The risk of PTH has increased with age. In terms of gender, there was no difference.

Keywords: tonsillectomy, demographic, complication, hemorrhage, treatment.

INTRODUCTION

According to the American Academy of Otolaryngology – Head and Neck Surgery, tonsillectomy is defined as a "surgical procedure performed with or without adenoidectomy that completely removes the tonsil, including its capsule, by dissecting the peritonsillar space between the tonsil capsule and the muscular wall." Depending on the context in which it is used, it may indicate tonsillectomy with adenoidectomy, especially in relation to sleep *breathing* diseases (SBD) (1).

It is one of the most common operations during childhood and the majority of studies so far have been conducted on the children's population. Obstructive sleep apnea (OSA), chronic tonsillitis with *or without* adenoides vegetationes are most common reasons for

surgery (2). Post-tonsillectomy hemorrhage (PTH) is the most common and most serious complication. It may occur at any time in postoperative period, usually in the first postoperative week. PTH is often divided into primary (within 24 hours of surgery) and secondary (24 hours after surgery). *Complications of tonsillectomy include sore throat, postoperative nausea, vomiting, dehydration, otalgia, Eustachian tube dysfunction, pneumothorax and fatality* (3).

After a long history of tonsillectomy, its necessity is still controversial. *Treatment* or outcomes of PTH were shown only in a few studies. No PTH management guidelines currently exist (4).

Primary objective of this study was to show our experience with tonsillectomy and retrospectively reviewed PTH in a population with a wide age range, and to assess the association between patients' age, time of PTH, and the need for surgery to control bleeding.

METHODS

Patients and study design

A retrospective cross-sectional study was conducted of 240 patients who underwent a tonsillectomy, tonsilloadenotomy or just adenectomy in our Department of Otolaryngology and Maxillofacial Surgery of the Cantonal Hospital Zenica, in the period from 01/01/2020 to 12/31/2022. This study was approved by the Ethics *Committee* of the Cantonal Hospital Zenica (No:00-03-35-166-5/23).

Methods

All patients had preoperative examination and normal coagulation parameters. They were examined postoperatively, before discharge from the hospital and 15 days after discharge or earlier in case of bleeding. All patients were operated using the cold method with electrocoagulation hemostasis, under general or local anesthesia by six surgeons.

We divided all patients into two groups. All patients under 16 were defined as pediatric group, and 16+ patient age groups were defined as adults.

All patients who underwent tonsillectomy with or without adenectomy and myringotomy at the Department of Otorhinolaryngology in the period from January 1, 2020 until December 31, 2022 were included in the analysis.

Patients who were indicated for tonsillectomy or adenectomy and did not consent, patients who were indicated for tonsillectomy or adenectomy and did not undergo preoperative preparation, and patients in whom only myringotomy was performed were excluded.

Data were collected by searching the medical records of the patients included in the research. Data were collected on age, gender, existing comorbidities, clinical diagnosis, surgical procedure, type of anesthesia, intraoperative and postoperative complications, the method of their management, whether the removed tissue was sent for pathohistological analysis, and final pathohistological findings.

Statistical Methods

Results are presented in tables and graphs, with a *significant* level of $p<0.05$. Statistical analysis was performed with IBM SPSS v27.0. Distribution of data among examined groups was tested using Chi square test. When expected cells had the value of 0 or 20% or more, and when their value was less than 5, Fisher's exact test was used.

RESULTS

The study included data from 240 patients with a mean age of 12.29 years, a median age of 8 years, and an interquartile range of 5 to 15. In relation to the age limit of 16 years, 181 (75.4%) patients were 16 or younger, and 59 (24.6%) were over 16. The distribution of respondents by gender in relation to the age limit did not show a signifi-

cant difference (x2=0.286; p=0.593). Table 1 shows indications for surgery. PTH was the most common complication with *frequency* of 7%. Patients older than 16 had a 2.73 times higher risk of bleeding than those younger than 16 (RR=2.73; p=0.030). In terms of gender, 9 male patients (8%) and 8 female patients (6.3%) experienced bleeding. There was no significant statistical difference (p=0.529) (Table 2). PTH occurred in average on the 4th day, with mean of 4.41. Median value was 5 days, with interquartile range from 2 to 6 days.

Regarding the type of anesthesia used, 225 (93.7%) operations were performed under general anesthesia, and 15 (6.3%) under local anesthesia. One patient had a reaction to the anesthesia, resulting in heart failure with pulmonary oedema, and heart infection.

Analyzing the co-morbidities of operated patients, arthritis was presented in 0.4%, asthma in 0.8%, bronchitis in 2.1% of patients, and allergic rhinitis was presented in 2.5% of operated patients. Neurological diseases were presented in 1.2% of cases, and syndromes affecting development were presented in 0.8% of cases. Comorbidities on heart as aberrant chords or hypertension, or valve insufficiency were present in 2.8% of patients. There was no significant difference in the incidence of cardiovascular or neurological diseases between the sexes or age groups. Also, when *hemorrhage* was compared to the comorbidities, it was observed that 14 (82.35%) patients with PSH did not have any comorbidity. Among three patients with comorbidities, one patient had psoriasis, one had Down syndrome, and one patient had *hypothyroidism.*

Table 1. Distribution of patients based on the indication for surgery, by age

Diagnosis	Indication for surgery					
	Total		≤16 years		>16 years	
	N	%	N	%	N	%
Focalosis	1	0.42	1	0.55	0	0.00
Secretory otitis media	1	0.42	1	0.55	0	0.00
Tonsilitis chronica	69	28.75	15	8.29	54	91.53
Tonsilitis chr et vegetatio adenoides epypharngis	139	57.92	139	76.8	0	0.00
Tumor	6	2.50	1	0.55	5	8.47
Vegetatio adenoides epyohsringis	20	8.33	20	11.05	0	0.00
Vegetatio adenoides epyohsringis, secretory otitis media	4	1.67	4	2.21	0	0.00

N - number of patients; %- percentage

DISCUSSION

Tonsillectomy and/or adenotomy is the most performed surgery at the Otorhinolaryngology Clinic, and one of the most performed surgeries in childhood and adolescence. However, numerous studies attempt to analyze the necessity of its performance. Tonsillectomy is also associated with postoperative complications. PTH is one of the most common complications. Incidence of PTH is the main objective of this study. However, we also analyzed indication, surgical procedures, pathohistological evaluation and other postoperative complications in patients who underwent tonsillectomy and/or adenotomy.

The main finding of this study, which included 240 patients, was mean PTH rate of 7%. In childhood, PTH was found in 5% patients. Also, our study showed PTH in 13.6%

Table 2. Distribution of postoperative complications

Complications	Presented	?16 years		16+ years		Fisher's exact test
		N	%	N	%	
Bleeding	In 24 hours	4	2.2 %	0	0.0 %	0.08
	After 24 hours	5	2.8 %	8	13.6 %	
Heart failure and pulmonary edema	No	181	100.0 %	58	98.3 %	0.245
	Yes	0	0.0 %	1	1.7 %	
Heavy breathing	No	180	99.4 %	59	100.0 %	0.999
	Yes	1	0.6 %	0	0.0 %	

N - number of patients; %- percentage

adult patients. It was found that patients older than 16 had a 2.73 times higher risk of bleeding than those under 16 (RR=2.73; p=0.030). In terms of gender, there was no significant statistical difference. We did not note any fatal cases.

240 patients were included, 113 male and 127 female, and average age was 12.29 years. 181 patients were under 16 (children), and 59 patients were older (adults). All patients under 16 were prepared for surgery by a pediatrician. Adults were prepared by an internist. Tonsillectomy is more common in childhood than in adults, according to literature (5).

We found chronic tonsillitis with adenoiditis as the most common ailment. Tonsilloadenotomy was the most often performed surgical procedure. Results can be comparable to those of Šumilo et al. (6). Our findings are not similar to those of De Benedeto et al. who observed that OSA was the most common ailment. Discrepancy in the results can be related to the practice of performing preoperative polysomnography and diagnosis of OSA. We did not perform polysomnography preoperatively in our study. Maybe we should change our practice and take a role in pediatric OSA through polysomnography and surgery as the literature recommends (7). Also, effects of tonsillectomy on IgA nephropathy should be considered (8,9).

In adults, chronic tonsillitis was found as the most common ailment, and tonsillectomy was the most performed surgical procedure. These results are similar to those of Zagolski et al. (10). However, several studies showed that tonsillectomy could be considered in adult patients with OSA with medium to large tonsils and normal soft palate (11,12).

Suspicion of tonsillar malignancy was found in six patients. Five of them were older than 16. Tonsil specimens were sent for histopathological evaluation only in case of suspected malignancy (13). Studies showed lower risk of malignancy in children (14). There was only one malignancy suspicion in children's population, and histopathological evaluation found chronic tonsillitis. Four adults had squamous cell carcinoma. Our findings are similar to results of other studies which showed squamous cell carcinoma as the most common tonsillar malignancy in adults (15).

Our study found that PTH and tonsillectomy occurred in 5% of children. 2.2% of PTH was primary, and 2.8% secondary. Four patients were reoperated due to primary PTH, and only one after secondary PTH. David et al. found PTH frequency of 4.9% (16). Other studies showed cases of primary hemorrhage accounted for approximately 33.70%, and secondary hemorrhage occurred in 66.30% of cases (17). Alvo et al. showed that the overall PTH rate was 3.6% (0.23% occurring within the first 24 hours (primary) and 3.4% after 24 hours (secondary)). Mean time to PTH was 6.6 ± 3 days (18). Overall, primary PTH occurrence was found to be 2.2%, and secondary PTH accounting for 0.78% and 1.34% (19). PTH was found as the most common reason for revisit, and 5th postoperative day was the median revisit time. The higher risk of revisits was associated with older children. (20). In a study of case day tonsil surgery, 5.7% patients experienced hemorrhage, and 4.1% were readmitted (17).

On the other hand, PTH and associated utilization after tonsillectomy occurred in more than 13.6% of adults. All of them were revisited. Only one (1.6%) patient required second surgery. Inuzuka et al. found in their study, which included 325 adult patients who underwent a tonsillectomy, that PTH in 21.8% of patients and 1.5% of patients required the second surgery for hemostasis (22). A study which included 193 adult patients showed PTH in ten (5.18%) adult patients of whom seven (70%) were male.

The risk of postoperative complications

We did not find that comorbid diseases could increase the risk of postoperative complications in children. Demir et al. findings are similar (23).

There are different limitations of this study. We do not have a national health system

register which would contain information on all citizens. Data were collected by searching the medical records of the patients included in this study. Information were insufficient and posed limits on the assessment and variables.

The retrospective design of this study limited the variables and the ability of control for confounders. In this study, we were not able to control risk factors such as surgeon's level of experience or change in surgery techniques from cold to hot. Also, we did not investigate other risk factors. We were not allowed to control speculative PTH confounders like excessive weight, medicine use, pre and post operative medications, recent upper respiratory infection, smoking habits, or alcohol consumption.

This study predominantly included young population. However, obstructive sleep apnea was not diagnosed in our study. Sometimes, short-lived PTH with minimal bleeding could be managed at home with observation and ice per os but patients were usually readmitted to the hospital. This may have an impact on indication or PTH incidence in our study.

CONCLUSION

PTH has low incidence rates, and the risk increases with age. It should be given more attention in preparations for surgery. Conclusively, surgeons should prepare and choose a conservative or surgical approach to PTH management. I recommend careful preoperative counseling with patients and their families in order to set the PTH expectations.

Acknowledgment: None.

Declaration of patient consent: Informed consent was obtained from all participants in the study.

Authors' Contributions: Conceptualization: Amel Krkalic. Formal analysis: Amel Krkalic, Harun Mandra, Anes Joguncic. Project administration: Amel Krkalic, Harun Mandra, Anes Joguncic. Visualization: Amel Krkalic, Harun Mandra, Anes Joguncic. Writing – original draft: Amel Krkalic, Harun Mandra, Anes Joguncic. Writing – review & editing: Amel Krkalic, Harun Mandra, Anes Joguncic.

Financial support and sponsorship: There was no funding.

Conflict of interest: The authors have nothing to disclose.

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ORIGINAL RESEARCH

Comparison of Postoperative Morbidity Between Two Tension-Free Hernioplasty Techniques: With Mesh versus Without Mesh

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Pages: 11-17 / Published online: 19 August 2024

Cite this article: Kulo A, Kulo D, Sukic-Karalic R, Hodzic E, Holjan S, Sarajlic L, et al. Comparison of Postoperative Morbidity Between Two Tension-Free Hernioplasty Techniques: With Mesh versus Without Mesh. Sar Med J. 2024; 1(1): Online ahead of print. DOI: 10.70119/0003-24

Original submission: 19 March 2024; **Revised submission**: 16 June 2024; **Accepted**: 18 July 2024

Abstract

Introduction. Although inguinal hernia surgery is the most common surgical procedure worldwide, the best surgical method is still not universally accepted. The Lichtenstein technique is considered the gold standard, although it also has its limitations. Therefore, there is still a need for new techniques, such as the Desarda technique. The aim of this article is to evaluate and compare the postoperative morbidity of two tension-free techniques for inguinal canal plastic surgery with and without the use of mesh.

Methods. This prospective randomized clinical study was conducted at the Clinic for General and Abdominal Surgery of the Clinical Center of the University of Sarajevo from January 2017 to December 2022. The study included 60 patients with primary inguinal hernia who met the predefined inclusion and exclusion criteria and were randomly allocated into two equal groups: 30 patients operated on by the Desarda technique and 30 patients operated on by the Lichtenstein technique.

Results: The following parameters showed a statistically significant difference in favor of the Desarda operative technique: shorter hospitalization, lower level of postoperative pain, faster achievement of early physical activity, lesser amount of analgesic consumption, earlier return to regular daily and work activities, and absence of chronic inguinal pain. Postoperative morbidity was more frequent in the Lichtenstein group, but likely due to the small sample size, this difference remained statistically insignificant.

Conclusion: Patients operated on by the Desarda method exhibited significantly lower levels and frequencies of postoperative pain, faster postoperative recovery, and return to usual daily and work activities.

Keywords: hernia, inguinal, treatment, prognosis.

INTRODUCTION

The development of inguinal hernia surgery spans centuries and can be considered the history of hernia treatment and surgery (1). The era of modern tension-free hernioplasty extends from the mid-20th century to the present day (1,2). Lichtenstein was

among the pioneers who popularized tension-free hernioplasty with prosthetic material, achieving exceptionally good results in terms of morbidity and recurrence (3). Until the Desarda technique, tissue repair techniques were tension-based along the suture line, resulting in pain and recurrences (4). Advances in surgical techniques have led to the quality of life and postoperative chronic inguinal pain becoming the most important considerations in hernia repair. Revision surgery rates, postoperative morbidity, including chronic inguinal pain, are key indicators used to evaluate the success of hernia repair treatment. Despite various techniques, there is still a need for new techniques to reduce recurrence rates and improve patient quality of life (4). The Lichtenstein technique of inguinal canal plastic surgery has become one of the most popular and common surgical procedures, but postoperative morbidity continues to burden this technique (4). There is a high incidence of chronic inguinal pain associated with the Lichtenstein technique, ranging from 28.7% to 43.3% (2-4). Chronic surgical site infection after repair with prosthetic mesh requires complete removal of the mesh to treat the infection (4). Possible damage to the elements of the spermatic cord and nerve entrapment due to extensive fibrosis raise concerns about the use of this technique. Inguinal hernia surgery is the most common surgical procedure worldwide (4). The quest for the ideal surgical technique without the use of alloplastic material, which will provide excellent results even when performed by less experienced general surgeons, continues. In the Desarda operative technique, there is no displacement of muscles and the sutures are tension-free during muscle contraction (4). The aim of the article is to evaluate and compare the postoperative morbidity of two tension-free inguinal canal plastic surgery techniques with and without the use of mesh and to access the advantages and disadvantages of these methods regarding postoperative morbidity and their true indication area.

METHODS

Patients and Study Design

This study was prospective-retrospective, and was conducted at the Clinic for General and Abdominal Surgery, Clinical Center of the University of Sarajevo, from January 2017 to December 2022. It aimed to compare the outcomes of two tension-free surgical techniques for treating primary inguinal hernias: the traditional Lichtenstein technique and the newer Desarda technique. The study involved 60 patients, aged 18 to 65 years, of both genders. Patients were randomly assigned to one of the two techniques by drawing sealed envelopes containing the name of the surgical method. Demographic data were collected throughout the study. Ethical approval was granted by the Ethical Committee of the Clinical Center of the University of Sarajevo.

Methods

The source of data was the medical records of patients operated on at the Clinic for General and Abdominal Surgery of the University Clinical Center. Basic laboratory tests were performed preoperatively on all patients as part of routine preparation for surgery. Additional laboratory tests were conducted during the postoperative course of patients, as needed. Preoperatively, all patients underwent chest X-ray, electrocardiogram, and internal medicine examination. Patients were advised to resume routine activities on the third postoperative day. Data were collected intrahospital and then on an outpatient basis on the eighth day, first month, and six months after surgery. All surgical procedures were performed under general endotracheal anesthesia. In patients of the Lichtenstein group, a Vypro II (polypropylene + polyglactin) semi-resorbable mesh measuring 6x11 cm was placed and secured with Vicryl (polyglactin 910) 2.0 sutures, while in patients of the Desarda group, PDS 1 (polydioxanone) suture was used for hernioplasty. Antibiotic prophylaxis was administered to all participants, including

preoperative administration of intravenous 2 grams of Cefazolin 30 to 60 minutes before incision. Prophylactic anticoagulant therapy was prescribed subcutaneously in a single evening dose to all patients during hospitalization. Parenteral analgesia was administered to all patients in the 24 hours after surgery, followed by oral or parenteral analgesia only as needed. Patients were encouraged to mobilize 4-6 hours after surgery and to be discharged from the hospital when they could go to the toilet independently. Six months after the treatment, pain was assessed using the Visual Analog Scale (VAS).

Statistical Methods

Standard descriptive and inferential statistical methods were employed. Data were presented based on their nature: absolute numbers, percentages, arithmetic means with standard deviations for normally distributed data, and medians with interquartile ranges for non-normally distributed data. The normality of continuous numerical variables was assessed using the Shapiro-Wilk test, and comparisons were made using the non-parametric Mann-Whitney U test due to the lack of normal distribution. Categorical variables were compared using the chi-square test, with Fisher's exact test applied for 2x2 tables and Yates' correction used for small sample sizes. A significance level of 95% ($p < 0.05$) was set for all tests. Results were reported both textually and through tables and graphs.

Results

At the Clinic for General and Abdominal Surgery, Clinical Center of the University of Sarajevo, a prospective-retrospective randomized study was conducted from January 2017 to January 2022, involving a group of 60 patients who underwent surgery for primary inguinal hernia. Patients were randomized into two equal groups. In the first group were patients operated on using the Desarda technique, while in the second, the control group, patients were operated on using the Lichtenstein technique. Analysis of the results revealed a significantly higher prevalence of inguinal hernia among male patients (93.3%), and both groups had an equal representation of male patients (28 or 93.3% of cases each) and female patients (2 or 6.7% of cases each).

Analysis of the age structure of patients in relation to the examined groups shows certain variations, but they are not statistically significant ($p>0.05$). According to the average age, the examined groups of patients did not differ significantly ($p=0.599$).

The analysis of age structure in relation to the examined groups shows certain variations, but they are not statistically significant ($p > 0.05$).

Postoperative morbidity

Surgical site infection was diagnosed in 4 (13.3%) patients from the Lichtenstein group and in 1 (3.3%) patient from the Desarda group. Surgical site infections were managed with local wound treatment and parenteral antibiotic administration, and removal of the prosthetic material was not necessary. Seroma occurred in 3 (10.0%) patients from the Lichtenstein group, while there were no seromas in the Desarda group. Hematoma occurred in 2 (6.6%) patients from the Lichtenstein group, while there were no hematomas in the Desarda group. Scrotal swelling occurred in 5 (16.6%) patients from the Lichtenstein group and in 1 (3.3%) patient from the Desarda group. Although postoperative morbidity is more common with the Lichtenstein technique, it is presumed that due to the small sample size, the differences were not statistically significant. Urinary tract infections and urinary retention were not observed in any patient.

Postoperative Recovery Rate

Postoperative recovery, or the time to return to usual daily activities after a surgi-

cal procedure, was statistically significantly shorter in the group treated with the Desarda technique compared to the Lichtenstein technique (p = 0.0156). The mean time to return to daily activities was statistically significantly shorter in the Desarda group (4.13 ± 1.85 days) compared to the Lichtenstein group (6.90 ± 3.39 days) (p < 0.001) (Table 1).

Table 1. Return to daily activities

Return to daily activities /days/	Desarda technique (n=30)		Lichtenstein technique (n=30)		Total	
	Number of Patients	%	Number of Patients	%	Number of Patients	%
<4 days	14	46.7	10	33.3	24	40.0
5-7 days	15	50.0	8	26.7	23	38.3
8-10 days	1	3.3	8	26.7	9	15.0
11-13 days	0	0.0	3	10.0	3	5.0
14-16 days	0	0.0	1	3.3	1	1.7
>17 days	0	0.0	0	0.0	0	0.0
Total	30	50.0	30	50.0	60	100.0
$\overline{X}$ ± SD	4.13 ± 1.85		6.90 ± 3.39		5.52 ± 3.05	

SD standard deviation $\overline{X}$=12.242; p=0.0156

The time required to return to daily activities was significantly shorter for patients treated with the Desarda technique compared to those treated with the Lichtenstein technique (p < 0.05) (Table 2). All patients were evaluated for the time taken to resume work, measured by the number of days needed to recover sufficiently. Patients in the Desarda group had a shorter recovery period before returning to work, typically ranging from two to four weeks. A statistically significant difference was found between the two groups (p = 0.0221). However, these results should not be viewed as absolute, as not all patients are equally motivated to return to work and some may choose to use the full duration of sick leave provided by their health fund.

Table 2. Return of patients to work activities

Return to work activities /days/	Desarda technique (n=30)		Lichtenstein technique (n=30)		Total	
	Number of Patients	%	Number of Patients	%	Number of Patients	%
<14 days	14	46.7	8	26.7	22	36.7
15-30 days	12	40.0	10	33.3	22	36.7
31-45 days	3	10.0	5	16.7	8	13.3
46-50 days	1	3.3	5	16.7	6	10.0
>60 days	0	0.0	1	3.3	1	1.7
>80 days	0	0.0	1	3.3	1	1.7
Total	30	50.0	30	50.0	60	100.0
$\overline{X}$ ± SD	17.13 ± 10.06		32.73 ± 22.49		24.93 ± 18.98	

SD standard deviation $\overline{X}$=16.985; p=0.0221

Return to work activities was statistically significantly shorter in the group treated with the Desarda technique compared to the Lichtenstein technique (p < 0.05).

Chronic Inguinal Pain

Neuralgic postoperative pain in the inguinal region was present one month after the surgery in 16 (53.3%) patients in the Lichtenstein group, with the highest frequency of pain intensity being 6 in 6 (20.0%) patients, while 3 (10.0%) patients had pain intensity of 8, which they described descriptively as disturbing and severe. In the Desarda group, as many as 26 (86.6%) patients were without any postoperative neuralgia, while in 4 (13.3%) patients, there was some discomfort, which they described descriptively as discomfort during prolonged standing and walking.

Statistical analysis shows that the frequency and intensity of postoperative neuralgia on the 30th postoperative day are statistically significantly lower in the group treated with the Desarda technique compared to the Lichtenstein technique (p = 0.006).

The average level of postoperative neuralgia one month after the surgical procedure was statistically significantly lower in the Desarda group (0.40 ± 1.07) compared to the Lichtenstein group (3.00 ± 3.05), p < 0.001.

The rate of postoperative neuralgia was significantly lower in patients treated with the Desarda technique compared to those who underwent the Lichtenstein technique (p < 0.05). One month after surgery, the average level of postoperative neuralgia was markedly lower in the Desarda group (0.40 ± 1.07) compared to the Lichtenstein group

(3.00 ± 3.05), with a p-value of <0.001. Six months post-surgery, no patients (0%) in the Desarda group experienced postoperative neuralgia, whereas 10 patients (33.3%) in the Lichtenstein group reported neuralgia, with 6 (20.0%) finding it bothersome during physical activities and 2 (6.6%) describing it as severe, constant pain with a VAS score of 8. Statistical analysis revealed a significant difference in the occurrence of chronic inguinal pain between the two groups (p = 0.017) (Table 3).

Table 3. Chronic inguinal pain six months after surgery

Chronic inguinal pain six months after surgery	Desarda technique (n=30)		Lichtenstein technique (n=30)		Total	
	Number of Patients	%	Number of Patients	%	Number of Patients	%
0	30	100.0	20	66.7	50	83.3
4	0	0.0	2	6.7	2	3.3
5	0	0.0	3	10.0	3	5.0
6	0	0.0	3	10.0	3	5.0
8	0	0.0	2	6.7	2	3.3
Total	30	50.0	30	50.0	60	100.0
$\bar{x}$ ± SD	0.00 ± 0.00		1.90 ± 2.85		0.95 ± 2.21	

SD standard deviation $\bar{x}$=12.000; p=0.017

DISCUSSION

Inguinal hernias are the most common surgical condition, with an average lifetime risk of 27% in males and 3% in females (5). Before 2009, there were no established protocols for treating inguinal hernias. That year, the European Hernia Society (EHS) released recommendations based on literature reviews and clinical study outcomes. According to the EHS guidelines, the Lichtenstein technique and endoscopic mesh placement are considered the gold standard treatments (6).

If there is a need to deviate from the tension-free technique using mesh, the Shouldice tissue repair technique is considered the preferred alternative. It is important to note that protocols should remain open to innovations, and further research is necessary to evaluate new methods. Additionally, the potential influence of the pharmaceutical industry, which often favors mesh procedures, should be taken into account. Consequently, the strong recommendation of the EHS protocol for mesh use needs re-evaluation. Although the Lichtenstein technique is regarded as the gold standard, it has limitations, including sensations of a foreign body, surgical site infections, spermatic cord fibrosis, and chronic postoperative pain. Surgical site infections with symptoms persisting for years are more common with mesh use. The intense chronic inflammatory response to the foreign body reaction around the mesh can lead to the formation of meshomas or pseudo-tumors. Moreover, using mesh increases surgical costs. There are also reports that reproduction and sexual function can be significantly affected when mesh is used in the surgical treatment of inguinal hernias. Robinson and colleagues have documented 252 complications, including infection (42%), postoperative pain (9%), foreign body reactions (8%), intestinal complications (7%), adhesions (6%), seroma (4%), erosion (2%), and other issues (4%) (7). Mesh repair may lead to male infertility and sexual dysfunction (8). Additionally, it can result in chronic inguinal pain due to nerve entrapment (9). These postoperative complications have prompted many researchers to explore new techniques. An example of such efforts is the Desarda surgical technique, which was presented in 2001 and became the first tension-free tissue-based method for repairing inguinal hernias. In recent years, the focus of inguinal repair has shifted rapidly to chronic postoperative pain. New studies have shown that the Lichtenstein technique may be associated with postoperative pain. The Desarda technique provides a physiologically dynamic posterior wall of the inguinal canal (10). The aging process in the body is minimal in tendons and aponeuroses, so the strip segment, which is tendon-aponeurotic, is the best alternative to mesh (11). Desarda published the results of the first study in 2001, which included 400 patients (12). The results were excellent, with only one recurrence and one postoperative complication in terms of hydrocele. In 2006, the author published the results of a second study involving 860 patients, which also yielded outstanding

results, with no recurrences or postoperative neuralgia (12). In our study, homogeneity was observed among the investigated groups in terms of age and gender distribution, associated diseases, as well as local findings related to the type, localization, and classification of hernias. Patients in the Desarda group had better physical activity, reflected in earlier and easier mobilization. Although postoperative morbidity was more present in the Lichtenstein method, it is presumed that due to the small sample size, the differences were not statistically significant. Complete postoperative recovery was significantly shorter in the Desarda group. We also found a significant difference in the persistence of neuralgic pain. After six months, none of the patients (100%) in the Desarda group had chronic inguinal pain. Postoperative neuralgia was present in 10 patients (33.3%) in the Lichtenstein group, with 6 patients (20.0%) reporting pain during physical activities, while 2 patients (6.6%) experienced constant severe pain independent of activity. Chronic pain diminishes and impairs quality of life.

The Desarda surgical technique could soon be recognized not only as an alternative to the Shouldice technique but also as a substitute for current protocols that favor open and laparoscopic mesh techniques. Research generally suggests that the Desarda technique is at least comparable to the Shouldice technique in terms of recurrence rates and postoperative pain (13-18). Due to the simplicity of the procedure, which does not require foreign material or complex dissection of the inguinal canal floor, the learning curve for the Desarda technique is shorter than that of the Shouldice technique. It has demonstrated excellent results, with virtually no recurrences (13-15). The Desarda surgical technique is a physiological repair that primarily restores the normal physiology of the inguinal canal. The Desarda technique is safe and effective even for large defects and cases with a compromised posterior wall of the inguinal canal. It is easy to perform, has a short learning curve, and is cost-effective. Compared to the Desarda technique, the Lichtenstein surgical method is associated with significantly higher postoperative pain, a greater incidence of surgical site infections, hematomas, and seromas, as well as scrotal swelling. These complications are likely due to the direct contact of the mesh with the spermatic cord and nerve branches, leading to tissue edema and extensive fibrosis. The results of this study suggest that the Desarda technique could increase the overall proportion of tissue-based repairs of the inguinal canal in the future.

CONCLUSION

Patients who undergo the Desarda technique experience significantly lower postoperative pain, faster recovery times, and quicker return to daily and work activities. The use of the Desarda technique helps to avoid complications associated with mesh repairs, such as chronic inguinal pain and foreign body sensation. This technique is particularly advantageous for younger patients and those with infected or strangulated inguinal hernias.

Acknowledgment: None.

Declaration of patient consent: Informed consent was obtained from all patients in the study.

Authors' Contributions: Conceptualization: Adnan Kulo, Edin Hodzic, Sandin Holjan, Salem Bajramagic. Formal analysis: Adnan Kulo, Diela Kulo, Ramajana Sukic-Karalic, Lana Sarajlic, Edin Hodzic, Sandin Holjan, Salem Bajramagic. Project administration: Adnan Kulo, Diela Kulo, Ramajana Sukic-Karalic, Lana Sarajlic. Visualization: Adnan Kulo, Edin Hodzic, Sandin Holjan, Salem Bajramagic. Writing – original draft: Adnan Kulo, Diela Kulo, Ramajana Sukic-Karalic, Lana Sarajlic, Edin Hodzic, Sandin Holjan, Salem Bajramagic. Writing – review & editing: Adnan Kulo, Diela Kulo, Ramajana Sukic-Karalic, Lana Sarajlic, Edin Hodzic, Sandin Holjan, Salem Bajramagic.

Financial support and sponsorship: There was no funding.

Conflict of interest: The authors have nothing to disclose.

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ORIGINAL RESEARCH

THE IMPORTANCE OF VACCINATION AGAINST COVID-19 ON THE OUTCOME OF CRITICALLY ILL COVID-19 PATIENTS

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Pages: 18-24 / Published online: 19 August 2024

Cite this article: Pasalic H, Gojak H, Gojak R, Baljic R. Importance of Covid-19 Vaccination on the Outcome of Critically Ill Covid-19 Patients. Sar Med J. 2024; 1(1): Online ahead of print. DOI: 10.70119/0004-24

Original submission: 12 March 2024; **Revised submission:** 11 June 2024; **Accepted:** 19 July 2024

Abstract

Introduction. The development of the coronavirus disease 2019 (COVID-19) vaccine marked the beginning of the end of the pandemic and the understanding of the disease as something that is part of clinical practice. The aim of this study was to investigate, assess, and demonstrate the significance of vaccination on the outcome of severely ill patients treated in intensive care units.

Methods. A retrospective study was conducted on a sample of patients hospitalized at the Clinic for Infectious Diseases of the Clinical Center of the University of Sarajevo during 2022.

Results. Participants who were vaccinated against COVID-19 had a lower mortality rate and a higher chance of survival compared to unvaccinated participants. Additionally, disease outcomes were significantly influenced by oxygen saturation and platelet count at admission.

Conclusion. COVID-19 vaccination significantly reduced the mortality rate, with vaccinated participants having a higher chance of survival compared to unvaccinated participants.

Keywords: Coronavirus disease 2019, vaccination, treatment, prognosis.

INTRODUCTION

The clinical manifestation of coronavirus disease 2019 (COVID-19) is not specific and is very similar to other viral infections (1). After an incubation period of around 4 to 14 days, the infection can develop with mild to severe symptoms, which can also be fatal. COVID-19 is clinically classified as mild to moderate illness (without pneumonia or with pneumonia), severe illness (dyspnea, respiratory rate above 30/min, oxygen saturation below 93%, partial pressure of oxygen in arterial blood (PaO2)/ inspiratory oxygen concentration (FiO2) ratio less than 300, and/or lung infiltrates covering 50% of the lung surface within 24 to 48 hours), and critical illness (respiratory failure, multi-organ failure, sepsis) (2-4). All patients who experienced a severe clinical course of the disease had chronic conditions such as cardiovascular diseases, pulmonary pathology, chronic kid-

ney disease, or were oncology cases (5-9). COVID-19 vaccines that have been analyzed or approved for clinical studies include inactivated vaccines, live attenuated vaccines, vector vaccines, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), protein subunit-based vaccines, and virus-like particle vaccines (10,11). The primary goal of the vaccine was to prevent the development of severe clinical disease, i.e., to reduce mortality and morbidity rates and to slow the spread of the virus (11). After the first vaccines were approved and vaccination began, it was observed that the spread of this severe infection slowed down (11). Clinicians noticed that vaccinated patients, compared to unvaccinated patients, had a milder course of the disease, shorter hospital stays, and a lower percentage of fatal outcomes in the vaccinated population (11).

The aim of the study was to determine the vaccination status of critically ill COVID-19 patients admitted to intensive care units (ICU), to assess the significance of vaccination on the outcome of critically ill COVID-19 patients, to establish the average values of vital parameters at admission in patients admitted to ICUs, to determine the average values of non-specific inflammation and blood count parameters, and to assess their significance on the outcome of critically ill COVID-19 patients, as well as to compare independent predictors at admission on the outcome of critically ill COVID-19 patients.

METHODS

Patients and study design

The study utilized data obtained from clinical data records, temperature charts, laboratory findings, and discharge letters. A total of 110 patients (57 male, 53 female) hospitalized in the ICU at the Clinic for Infectious Diseases of the Clinical Center of the University of Sarajevo (CCUS) between January 1, 2022, and December 31, 2022, were included in the study. The analyzed variables were: gender, age, comorbidities, vaccination status (number of doses and vaccine manufacturer), assessment of the patient's general condition, vital parameters (oxygen saturation (sO2), blood pressure, heart rate), laboratory parameters (values of leukocytes, neutrophils, erythrocytes, hemoglobin, hematocrit, platelets, C-reactive protein (CRP)), duration of treatment (in days), and disease outcome.

Methods

The study was designed as a retrospective cohort study. Approval for the review and processing of data from patients was obtained from the Institute for Scientific Research at CCUS. The study was conducted in accordance with the Convention on Human Rights (Oviedo Convention), the Helsinki Declaration on the Rights of Patients in Biomedical Research and its latest revision, as well as national laws on patient rights (Law on the Rights, Obligations, and Responsibilities of Patients of the Federation of Bosnia and Herzegovina, Law on the Protection of Personal Data of Bosnia and Herzegovina, and the Rulebook on Regulations and Records in the Field of Health Care of the Federation of Bosnia and Herzegovina).

Statistical Methods

Upon completion of the study, statistical data analysis was performed. The statistical analysis of the data was conducted using the SPSS for Windows software package (version 19.0, SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel (version 11, Microsoft Corporation, Redmond, WA, USA). The Kolmogorov-Smirnov test was used to determine the distribution of continuous variables (for a sample size greater than 50 participants). For variables that showed a statistically significant deviation from normal distribution, average values were presented using the median and interquartile range (25th-75th percentile), and the Mann-Whitney U test was used for their comparison. Binary logistic regression was applied to

examine whether independent predictors/variables in the study had an influence on the disease outcome univariately. Subsequently, multivariate regression analysis was used to assess the combined influence of variables that were identified as statistically significant predictors in univariate analysis. The Chi-square test of independence was employed to examine the dependency of disease outcomes on the vaccination status of participants. A significance level of $\alpha=0.05$ was set for statistical analysis. Decisions to accept or reject hypotheses in the relevant tests were made based on the p-value of the statistical test (if $p \geq \alpha$, the hypothesis was accepted; if $p < \alpha$, the hypothesis was rejected). The results were thoroughly detailed and documented, presented in absolute numbers, relative numbers, and statistical values using statistical indicators, and displayed in simple and understandable tables and graphs.

RESULTS

The average age of participants hospitalized in the ICU during this period was 75.5 (67.75-83), with the youngest participant being 22 years old and the oldest 93 years old. The average age of male participants was 76.0, while the average age of female participants was 75.0, and no statistically significant difference in age between genders was found (p=0.434). The most common pre-existing cardiorespiratory risk factors were present in 74 participants (63.7%), followed by endocrinological pathology in 34 participants (30.9%), urological pathology in 23 participants (20.9%), and gastrointestinal pathology in 3 participants (2.7%). Regarding vaccination status, a larger number of participants, 59 (53.6%), were unvaccinated, while 51 (46.4%) were vaccinated. Among the 51 vaccinated participants, four had received one dose, 37 had received two doses, and 10 participants had received a booster—a third dose. The majority of participants had a moderately severe clinical presentation, 73 (66.4%), while 30 participants (27.3%) had a severe clinical presentation, and 7 participants (6.4%) were in critical condition upon admission. The average oxygen saturation level of participants was 91% (86-95%), with a minimum value of 60% and a maximum of 99%.

The average systolic blood pressure was 125 mmHg (110-135.25 mmHg), and the average diastolic blood pressure was 76 mmHg (69.75-85 mmHg). The average heart rate was 84 beats/min (76-97), with a minimum of 36 and a maximum of 150 beats/min. Table 1 shows the values of non-specific inflammatory and blood parameters.

The average value of CRP was 86 mg/L (29.75-137 mg/L), with a minimum of 1 mg/L and a maximum of 310 mg/L. The average leukocyte count was 7.2 x 10^9/L (5.275-10.275 x 10^9/L), with a minimum of 1 x 10^9/L and a maximum of 38 x 10^9/L. The average erythrocyte count was 4.3 x 10^{12}/L, with a minimum of 2 x 10^{12}/L and a maximum of 22.6 x 10^{12}/L. The average hemoglobin level was 127 g/L, with a minimum of 57 g/L and a maximum of 166 g/L.

Table 1. Average values of non-specific inflammatory and blood parameters

	N	Minimum	Maximum	Percentiles		
				25th	50th (Median)	75th
C-reactive protein (mg/L)	110	1	310	29.75	86.00	137.50
Leukocytes x 10^9/L	110	1.0	38.0	5.275	7.200	10.275
Erythrocytes x10^{12}/L	110	2.0	22.6	3.700	4.300	4.700
Hemoglobin g/L	110	57	166	107.00	127.00	140.25
Hematocrit L/L	110	3	58	34.00	39.00	42.25
Thrombocytes x10^9/L	110	13	525	129.00	168.00	220.25
Neutrophiles %	71	11	94	64.40	75.80	85.50

N - number of data

Table 2. The impact of participants' vaccination status on disease outcome

		B	Wald	Df	p	Exp (B)	95.0%C.I.for Exp (B)	
							Lower	Upper
Step 1 (a)	Vaccination status	1.390	8.161	1	0.004	4.016	1.547	10.424
	Constant	0.448	2.817	1	0.093	1.565		

B – estimated logit coefficient; Wald –Wald test; Df – Degrees of freedom; p-level of significance; Exp(B)- odds ratio; CI - Confidence Interval

The average duration of treatment for participants in the ICU was 7 days (5-10 days), with a minimum duration of one (1) day and a maximum of 21 days. Out of the total number of participants included in the study, 30 (27.3%) had a fatal outcome, while 80 (72.7%) had a positive outcome, meaning they recovered. Univariate binary logistic regression was used to examine the influence of independent predictors on disease outcome (survived - 1; did not survive - 0), with age and gender of the participants not proving to be statistically significant predictors of survival (p>0.5). The presence or absence of pre-existing comorbidities also did not have a statistically significant predictive value (p>0.05).

Univariate binary logistic regression was used to examine the impact of vaccination status on disease outcomes. Vaccination status was found to be a significant predictor (p=0.004, Exp(B)= 4.0) of disease outcome (Table 2). Vaccinated participants had a fourfold greater chance of survival compared to unvaccinated participants, with the survival chance in this population ranging from 1.5 to 10 times higher. The univariate binary logistic regression also demonstrated that oxygen saturation (O2%) upon admission had a statistically significant impact on disease outcome (p=0.019, Exp(B)=1.07). For every one percent increase in oxygen saturation at admission, the chance of survival increased by 7% in our sample, with the range in such a population being between 1% and 14%. The impact of systolic and diastolic blood pressure, as well as heart rate, was also examined using univariate binary logistic regression, but no statistically significant influence on disease outcome was found (p>0.05). Values of non-specific acute inflammation markers such as CRP, leukocytes, and the percentage of neutrophils at admission did not show a statistically significant impact on disease outcome (p>0.05). However, platelet count was found to be a significant predictor (p=0.009, Exp(B)=1.08) of disease outcome. If the platelet count at admission was higher by 10 ($x10^9$/L), the chance of survival increased by 8% in our sample, with the survival chance in such a population ranging between 2% and 14%. Multivariate logistic regression was used to examine the impact of independent predictors (which were found to be significant in the univariate analysis) on disease outcomes. Multivariate regression analysis showed that all three independent factors had a statistically significant impact on disease outcomes (p<0.05). Among them, platelet count at admission had the greatest impact (Wald=6.69), followed by vaccination status (Wald=5.58) and peripheral oxygen saturation percentage (Wald=4.58). The Hosmer

Table 3. The impact of independent predictors (vaccination status, peripheral oxygen saturation, and platelets) on disease outcomes at admission

	B	Wald	Df	p	Exp(B)	95.0% CIfor EXP(B)	
						Lower	Upper
Vaccination status (yes/no)	1.222	5.589	1	0.018	3.392	1.232	9.340
O2 saturation %	0.072	4.583	1	0.032	1.075	1.006	1.148
Thrombocytes x 109/L	0.085	6.699	1	0.010	1.089	1.021	1.161
Constant	-7.337	5.440	1	0.020	0.001		

B – estimated logit coefficient; Wald – Wald test; Df – Degrees of freedom; p-level of significance; Exp(B)- odds ratio; CI - Confidence Interval

and Lemeshow test supports the assertion that the model is a good fit, with a χ^2 value of 9.115 and p=0.329. Out of 59 unvaccinated participants, 36 (61%) survived, while 23 (39%) had a fatal outcome. In the vaccinated group (n=51), 44 (86.3%) survived, and 7 (13.7%) had a fatal outcome. The chi-square test of independence showed a significant association between treatment outcome and vaccination status (χ^2=8.7, p=0.003).

DISCUSSION

In our study, data were analyzed for 52% male patients and 48% female patients. Compared to similar studies, our study had a similar gender distribution (12) as the retrospective cohort study by Nachtigall et al. in Germany (2021), which included 51% male and 49% female participants (12). Other studies showed different gender distributions, such as Kautzky-Willer et al. (2022) in Austria, which included 65% male and 35% female patients (13), or Jirak et al. (2022), also in Austria, which included 72% male and 28% female participants (14). The average age of our participants was 75.5 (67.75-83), similar to the study by Jung et al. (2021), where the average age was 75 (15). Other studies showed different age structures, such as Bruni et al., where the average age was 65 (16). The age structure by gender in our study was 76 for males and 75 for females, which is similar to the study by Meijis et al., where the age structure was 64 for females and 66 for males (17). Among the participants in our study, the most common comorbidities were cardiorespiratory, affecting 67.7% of patients, followed by endocrine (30.9%), urological (20.9%), and gastrointestinal (2.7%) comorbidities. Our study had similar comorbidities compared to other studies of similar design (17,18). In our sample of 110 patients in the intensive care unit, 46.4% were vaccinated against COVID-19, while 53.6% were unvaccinated. Among those vaccinated, 7.8% received one dose, 72.5% received two doses, and 19.7% received a booster dose. In contrast, Bruni et al. (2022) in Italy found that 41% of participants were vaccinated, with 38% receiving two doses and 62% receiving a booster dose (16). Lorenzoni et al. (2022) in Italy reported that 18% of patients in the intensive care unit were vaccinated, 8% were partially vaccinated, and 74% were unvaccinated. Vaccinated patients were more likely to be over 80 years old compared to partially vaccinated and unvaccinated patients (19). Uzun et al. (2022) found 53.1% unvaccinated and 46.9% vaccinated participants, with 12.5% receiving one dose, 74.2% receiving two doses, and 13.3% receiving a booster dose (20). In our study, vaccination status was a significant predictor of disease outcome. Vaccinated participants had a fourfold increased chance of survival compared to unvaccinated participants, with chances ranging from 1.5 to 10 times higher in our population. Conversely, Lorenzoni et al. found that vaccinated patients received their second dose on average 5 months before admission to the intensive care unit, while partially vaccinated patients waited for their second dose. They observed a significant increase in admissions to the intensive care unit only among unvaccinated patients. Their data also indicated higher mortality among vaccinated compared to unvaccinated patients, and a higher proportion of patients over 80 years old among the vaccinated (19). Uzun et al. demonstrated that vaccination reduces the severity of the disease and, consequently, the mortality rate among vaccinated compared to unvaccinated patients (20). For every 10(x 10^9/L) increase in platelet count upon admission, the chance of survival increased by 8% in our sample. In contrast, Wang et al. (2021) found that a higher leukocyte value was associated with higher mortality rates. They observed that 23% of patients had a white blood cell count below the normal range, 12% had a count above the normal range, and about 50% had a reduced lymphocyte count (21). Aly et al. also demonstrated that lymphocyte count, platelet count, neutrophils, and CRP

are significant predictors of disease outcome in their sample (22). Data suggest that thrombocytopenia and lymphopenia in COVID-19 patients are associated with prolonged hospitalization and worse outcomes. Patients with SARS have a higher percentage of lymphopenia (68-90%) and thrombocytopenia (20-45%) compared to those with COVID-19. Thrombocytopenia and lymphopenia have previously been associated with increased mortality risk in patients with COVID-19 (22). The limitations of the study are a small patient sample, not differentiating patients based on vaccine type, and lack of virus strain analysis, therefore a larger sample size, differentiation of patients based on vaccine type, and analysis of the infective strain could provide more significant conclusions.

CONCLUSION

It has been found that in critically ill COVID-19 patients, vaccination status has significant effects on the course of the disease**.** It was discovered through statistical research that patients who were vaccinated have a higher chance of survival compared to non-vaccinated patients. Besides the vaccination status, the patient's platelet count upon admission, followed by their immunization history and, finally, their oxygen saturation %, have the most statistical relevance on the disease's course.

Acknowledgment: None.

Declaration of patient consent: Informed consent was obtained from all patients in the study.

Authors' Contributions: Conceptualization: Refet Gojak, Rusmir Baljic. Formal analysis: Refet Gojak, Hajrudin Pasalic, Hena Gojak, Rusmir Baljic. Project administration: Refet Gojak, Rusmir Baljic, Hena Gojak. Visualization: Refet Gojak, Hajrudin Pasalic, Rusmir Baljic. Writing – original draft: Refet Gojak, Hena Gojak, Hajrudin Pasalic, Rusmir Baljic. Writing – review & editing: Refet Gojak, Hena Gojak, Hajrudin Pasalic, Rusmir Baljic.

Financial support and sponsorship: There was no funding.

Conflict of interest: The authors have nothing to disclose.

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ORIGINAL RESEARCH

Predictors Of Marketing Authorization Status Of Dipyrone Within A Country

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Pages: 25-31 / Published online: 20 August 2024

Cite this article: De Avellar Ramos I, Jankovic S. Predictors Of Marketing Authorization Status Of Dipyrone Within A Country. Sar Med J. 2024; 1(1): Online ahead of print. DOI: 10.70119/0005-24

Original submission: 16 March 2024; **Revised submission:** 08 June 2024; **Accepted:** 12 July 2024

Abstract

Introduction. Although there are numerous data about increased risk of bone marrow toxicity with dipyrone when compared to other nonsteroid anti-inflammatory drugs, it continues to be marketed in many countries. The aim of this study was to identify currently unknown putative predictors of dipyrone having marketing authorization in a country.

Methods. The study was designed as secondary research of a cross-sectional type. The data were collected from web pages of relevant international and national entities. The main outcome variable of the study was dipyrone marketing authorization status within a country. The data were analyzed by both uni- and multi-variate statistics, including logistic regression.

Results. The following factors showed significant influence on marketing authorization status of dipyrone: Current Health Expenditure per capita ($p = 0.02$), Gross Domestic Product per capita ($p = 0.02$), Incarceration Rate (per 100.000 population) ($p = 0.04$), and overall Global Innovation Index ($p = 0.04$). However, after adjustment, the multivariate analysis showed that the most important predictor was Current Health Expenditure per capita ($p = 0.01$).

Conclusion. The use of medications already considered by many to be obsolete and even dangerous due to their low benefits/harm ratio seems related to the underdevelopment of a country. There is a need for further research into ways to help these countries make better choices about the use of potentially harmful drugs and other health technologies.

Keywords: dipyrone, bone marrow toxicity, marketing authorization, predictors.

INTRODUCTION

Dipyrone, or metamizole, is a well-known analgesic, anti-inflammatory, antipyretic and spasmolytic medication (1) released in the drug market in 1922 (2), belonging to class of nonsteroid anti-inflammatory drugs (NSAIDs). However, it is surrounded by controversy when it comes to safety issues (3). It has been prohibited in various countries, such as the United States of America and the United Kingdom (2), for its potential life-threatening damage to the bone marrow. It may cause agranulocytosis (3), which consists in a neutrophil count of less than 500 cells per microliter of blood (2). A report from EudraVigilance pharmacoviligance database, using data mostly from Germany and Switzerland

between 1985 and 2017, registered 1,478 cases of agranulocytosis in the reporting period, marking forty-three percent of those as life-threatening and sixteen percent as fatal. Nonetheless, the authors also state the difficulty in getting a true incident rate for this event since it is underreported and there are a lot of opposing data reported by different countries, like Germany, that estimates a rate of 7.9 cases per million prescriptions, and Sweden stating 1 case per 1,400 outpatients based on ten spontaneous reports and data from drug sales (2).

The marketing ban on this medication is mostly due to the aforementioned controversial occurrence of agranulocytosis that may come with its use (4). However, in contradiction to those that have banned this drug for decades now, there are many countries that still rely on metamizole daily. As a result, dipyrone is still largely produced and utilized in many Central and South American, European, Asian and African countries (5). It is also illegally sold due to higher efficacy when compared to other NSAIDs (5), being referred to as the "Mexican aspirin" (6) and commonly used by families whose countries of origin still allow it (5), creating sometimes a family pattern of agranulocytosis (6). There are certain authors who associate its marketing clearance with the nations classified by some as the "Third World" (7).

Although occasionally mentioned, social-economic variables are still understudied as a contributing factor to this drug's marketing clearance. A study conducted in San Diego, California, stated that dipyrone use in low-income Hispanic people is a problem, but added that the use of the medication, and its possible fatal side-effects, may not be limited to low-income people and even warrants the need for a social-economic overview of the matter (6). Against this backdrop, and given that many developed nations still allow it, the aim of our research was to identify currently unknown putative predictors of dipyrone having marketing authorization in a country.

METHODS

Patients and study design

The study was designed as secondary research of a cross-sectional type. The data were collected from web pages of World Health Organization (Global Health Expenditure Database) (8), United Nations (9), Trading Economics (10), International Monetary Fund (11,12), the World Population Review (13,14), UNESCO database (15), Global Report of Human Development Index (16) and Global Innovation Index Report (17). Certain variables that could not be found at the web pages of these entities were searched for in publications from medical journals, using the MEDLINE database.

Methods

The data were searched for and extracted from the above-mentioned web pages by a junior author, and the senior author checked the quality of the search and extraction. The literature search and data extraction were conducted from July 2, 2024 to July 11, 2024.

The population of the study were countries as political entities. The sample of the countries was taken as a convenience sample, i.e., the countries with all necessary accessible data were selected. The sample size was calculated based on binary logistic regression, where the outcome was whether dipyrone is allowed for use or not by a country's health authorities. With power of the study being 80%, probability of statistical error type one being 0.05, expected odds ratio of 0.05, expected R2 value of 0.1 and assuming normal distribution, minimum sample size was 23 countries. The calculation of the sample size was made by G*power software, version 3.1.9.7.(18).

The main outcome variable of this study was dipyrone status within a country (whether having marketing authorization or not), and putative predictors were: Cu-

rrent Health Expenditure (CHE) as % Gross Domestic Product (GDP), Current Health Expenditure (CHE) per capita in US$, Gross Domestic Product (GDP) per capita in US$, population (in thousands) (8), unemployment rate (10), General Country Gross Debt (% of GDP) (11), inflation rate, average consumer prices (annual percent change) (12), completion rate, upper secondary education, both sexes (%) (15), Human Development Index (HDI – composite index calculated from data on life expectancy, education (length of schooling), and per capita income) (16), Crime Index (per 100.000) (13), Incarceration rate (per 100.000 population) (14), Overall Global Innovation Index (the average of a country's innovation input and output, with 81 parameters involved in calculation) (17), developed/developing status according to the UN classification of nations (9) and continent where a country is situated.

Statistical analysis

The extracted data were first tabulated and checked for errors or inconsistencies. The values of continuous variables were described according to the groups defined by dipyrone status using measures of central tendency (mean and median) and variability (standard deviation and interquartile range), and values of categorical variables by frequences and percentages. Normality of data distribution was checked by the Kolmogorov-Smirnov test. The differences among the study groups were tested for statistical significance by the Mann-Whitney U test (for continuous variables) or by Chi square of the Fischer exact test (categorical variables). Multivariate data analysis was made by binary logistic regression, using forward addition method for building the regression model. Validity of the model was checked by the Hosmer-Lemeshow test and explaining potential of the model by Cox and Snellen and Nagelkerke R2. The results of the analysis were shown by odds ratio and 95% confidence intervals.

RESULTS

The total of 23 countries were included with complete data available over the Internet; thirteen countries – the Russian Federation, Mexico, Brazil, Israel (19), Egypt, Serbia (20), South Africa (21), New Zealand (22), China (23), Austria, Portugal, (24), Argentina (25) and Spain (26) – still allow the use of dipyrone, which currently possesses marketing authorization. Meanwhile, ten countries – Sweden, USA, Japan, Iran, Australia (19), UK, France, Canada (23), Nigeria (27) and Ireland (28) – banned its use and/or withdrew marketing authorizations granted in the past. Values of various indicators of socioeconomic status or investment in healthcare per country according to whether dipyrone is allowed for use or not are shown in Table 1.

When multivariate analysis of variables associated with dipyrone status in a country (allowed or not allowed) was made using binary logistic regression, the acceptable model included only two variables, Current Health Expenditure (CHE) per Capita in US$ and Human Development Index (Hosmer-Lemeshow test Chi Square = 9,725, dr = 8, p = 0.285; Cox & Snell R Square = 0.469, Nagelkerke R Square = 0.629). Only CHE per capita was significantly associated with dipyrone being allowed for use, but in reverse, acting as a protective factor: Odds Ratio (OR) = 0.998 (95% Confidence Interval = 0.0015), p = 0.01.

DISCUSSION

After univariate analysis of our data, the following factors showed significant influence on marketing authorization status of dipyrone: Current Health Expenditure (CHE) per capita in US dollars, Gross Domestic Product (GDP) per capita in US dollars, Incarcerated Rate (per 100.000 population) and overall Global Innovation Index (GII). However, after adjustment, the multivariate analysis showed that the most important predictor was Current Health Expenditure (CHE) per capita in US dollars.

Table 1. Values of the study variables according to status of dipyrone (expressed as mean ± standard deviation, median [interquartile range]) in the study sample of countries.

Variable		Dipyrone allowed (n = 13)	Dipyrone not allowed (n = 10)	Statistical significance of difference (p)
Current Health Expenditure (CHE) as % of Gross Domestic Product (GDP)		7.63 ± 1.93, 8.62 [3.59]	9.25 ± 3.39, 9.48 [3.59]	0.10
Current Health Expenditure (CHE) per capita in US$		1464.32 ± 1401.85, 712.28 [2730.74]	3899.8 ± 2486.96, 4318.49 [2730.74]	0.02
Gross Domestic Product (GDP) per capita in US$		17,141.28 ± 14,211.67, 9,756.13 [29,545.14]	37,327 ± 20,249.34, 42,291.6 [20,545.14]	0.02
Population (in thousands)		160,570.64 ± 365,563.96, 45,518.3 [119,565.42]	97,583.98 ± 96,156.26, 64,967.7 [119,565.42]	0.69
Unemployment rate		0.08 ± 0.07, 0.06 [0.02]	0.05 ± 0.01, 0.04 [0.02]	0.48
General Country Gross Debt (% of GDP)		0.73 ± 0.24, 0.75 [0.73]	0.95 ± 0.69, 1.04 [0.73]	0.78
Inflation rate, average consumer prices (annual percent change)		0.24 ± 0.68, 0.04 [0.12]	0.09 ± 0.13, 0.02 [0.12]	0.28
Completion rate, upper secondary education, both sexes (%)		0.76 ± 0.09, 0.76 [0.34]	0.8 ± 0.17, 0.88 [0.34]	0.23
Human Development Index (HDI)		0.83 ± 0.07, 0.82 [0.09]	0.87 ± 0.13, 0.92 [0.09]	0.07
Crime Index (per 100.000)		47.62 ± 15.31, 47 [18]	43,07 ± 17.94, 46.9 [18]	0.87
Incarcerated rate (per 100.000 population)		191.46 ± 88.25, 173 [131]	156.81 ± 152.81, 109 [131]	0.04
Overall Global Innovation Index		43 ± 23.23, 49 [36]	29.22 ± 34.71, 15 [36]	0.04
UN classification of nations	Developing	6 (46,2%)	2 (20%)	0.379
	Developed	7 (53,8%)	8 (80%)	
Continent	Europe	5 (38,5%)	4 (40%)	0.963
	North America	1 (7.7%)	2 (20%)	
	Asia	1 (7.7%)	1 (10%)	
	Middle East	1 (7.7%)	1 (10%)	
	Africa	2 (15,4%)	1 (10%)	
	Oceania	1 (7.7%)	1 (10%)	
	South America	2 (15,4%)	0 (0%)	

Individually speaking, the CHE in USD reflects the amount spent on healthcare per person in each population, using the American currency as a unit of measurement, and aiming to enable a comparison between nations (29). This has been shown to be a protective factor, therefore, the higher its value, the less likely it is that a country will still allow dipyrone to be marketed. A higher value of this variable indicates more considerable investment in the health system. Consequently, it is possible to infer that there is a more developed medical infrastructure in the country, not only in the clinical aspect, but also in pharmacovigilance and in the sectors responsible for authorizing the sale of medications. In this way, there is a better assessment of the balance between risk and benefit of a drug, as in the case of metamizole. A Chinese study similarly associated fiscal spending on health and the pharmaceutical industry's stock index, concluding that by controlling the former it is possible to achieve sustainable management of the latter, characterizing a directly proportional relationship between them (30).

The variable GDP demonstrates the wealth of population in a given country in US dollars, and is comparable internationally (31). It is an indicator that acts in a very similar way to the CHE on the marketing authorization status of dipyrone. It also plays a protective role and is associated with the existence of drug regulatory agencies with greater funding and more rigorous process of granting marketing authorization. An African study showed that for an effective pharmacovigilance system to ensure the

safety and control of medications, adequate funds are also necessary, or this function cannot be guaranteed (32).

Regarding the Incarceration Rate, it consists of the number of people arrested in proportion to its total population, being measured per 100,000 inhabitants and illustrating part of the criminal reality of a country due to the influence it suffers from the number of crimes, the policing and prosecution rates, time served in prison, etc. (33). In this case, it was found to be a risk factor for the marketing authorization of metamizole as it could reflect economic and social problems that also affect the health sector and the quality of its services. The literature pointed out that the effects of mass incarceration in the health area affect not only the families of those arrested, but the community and the country as a whole (34).

The GII uses around 80 indicators from different areas, from political and environmental, to technological and educational, to try to rank the most innovative economies in the world and monitor their position and progress or regression, comparing them internationally (35). In this way, it also behaved as a protective factor against the marketing authorization of dipyrone as it represented greater access and incentive to technology, medical advances and, consequently, more modern and regulatory pharmacovigilance. Similarly, a Brazilian study that correlated the health system with innovations in the pharmaceutical industry declared a favorable repercussion derived from this relationship (36).

Furthermore, the Human Development Index (HDI) is based on data from three major areas: health, education and economy. To assess health, life expectancy at birth is used. For education, the average years of study for adults and expected years of study for children are analyzed. Finally, the economy is illustrated by gross national income per capita. The final number after logarithmic transformation varies between 0 and 1, with 1 being the best possible value (37). Countries with a higher HDI are more likely to have better health and pharmacovigilance systems and a population with higher level of knowledge, contributing to the prohibition of metamizole and acting as a protective factor. Although in our study its influence did not reach statistical significance, there was a clear tendency.

When it comes to study limitations, there are two factors to be considered: small sample size and choice of variables. The first was due to unavailability of information about the study variables for many countries, which is why important predictors may have been lost in the process due to the small statistical power of the study. The second factor is present because information on some potentially important variables was not publicly available, e.g., the political stability of a country, etc.

CONCLUSION

The use of medications already considered by many to be obsolete and even dangerous due to their low benefits/harm ratio seems related to the underdevelopment of a country, not only in an economic context, but also in educational, cultural, scientific and social contexts in general. There is a need for more research into ways to help these countries make better choices about the use of potentially harmful drugs and other health technologies.

Acknowledgment: None.

Declaration of patient consent: Not applicable.

Authors' Contributions: Slobodan Janković devised the main idea of the study, designed the study plan and protocol, performed statistical analysis and wrote the paper. Isabella de Avellar Ramos participated in the study design, searched the literature, collected the study data and tabulated it, participated in the statistical analysis and wrote the paper.

Financial support and sponsorship: None.

Conflict of interest: None.

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REVIEW ARTICLE

Artificial Intelligence in Perinatal Medicine and Human Reproduction: Is it "The End of the Beginning" or "The Beginning of the End"?

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Pages: 32-37 / Published online: 20 August 2024

Cite this article: Stanojevic M, Kurjak A, Medjedovic E. Artificial Intelligence in Perinatal Medicine and Human Reproduction: Is it "The End of the Beginning" or "The Beginning of the End"?. Sar Med J. 2024; 1(1): Online ahead of print.. DOI: 10.70119/0006-24

Original submission: 17 March 2024; **Revised submission:** 09 June 2024; **Accepted:** 13 July 2024

Abstract

The paper explores the evolving role of Artificial Intelligence (AI) in perinatal medicine and human reproduction, highlighting its potential to transform clinical practices. AI technologies are being utilized to improve diagnostic accuracy, personalize treatment, and enhance patient care, particularly in areas like perinatal ultrasound, fetal heart rate monitoring, and fetal neurology. The Kurjak Antenatal Neurodevelopmental Test (KANET) exemplifies how AI can aid early detection of neurodevelopmental disorders. However, the integration of AI presents challenges such as data quality concerns, algorithmic bias, ethical concerns, and the need for robust regulatory frameworks. The authors argue that while AI offers significant opportunities, its implementation must be carefully managed to avoid over-reliance on technology and ensure equitable healthcare access. The paper concludes that the current state of AI in this field marks not an endpoint but a critical phase of growth and development, necessitating a balanced approach that combines innovation with ethical and practical considerations.

Keywords: artificial intelligence, perinatology, healthcare.

Introduction

Artificial Intelligence (AI) refers to the simulation of human intelligence processes by machines, particularly computer systems (1). These processes include learning (the acquisition of information and rules for using that information), reasoning (using rules to reach approximate or definite conclusions), and self-correction (1). Essentially, AI systems are designed to perform tasks that would typically require human intelligence, such as visual perception, speech recognition, decision-making, and language translation (1, 2). AI was developed to create systems that can perform tasks requiring human intelligence, thereby increasing efficiency, accuracy, and capabilities beyond human limits (1). The primary motivations include automating repetitive tasks, enhancing decision-making, addressing complex problems, and fostering innovation and ad-

vancement (1, 3). AI significantly impacts various aspects of human life, including education, agriculture, retail, e-commerce, manufacturing, entertainment, media, transportation, logistics, environment, sustainability, security, surveillance, human resources, and the non-profit sector (3). AI assists in tackling complex and data-intensive problems beyond human capacity, such as climate modeling, genetic research, and large-scale logistical planning (3). AI's ability to process and analyze vast amounts of data far quicker than humans provides valuable insights and aids decision-making processes across different areas (1, 3).

Medicine and Artificial Intelligence

AI is increasingly utilized in medicine and healthcare, extending beyond primary applications like diagnostics, personalized treatment plans, drug discovery, and patient monitoring (4 - 6). AI plays an extensive and transformative role in healthcare, enhancing clinical practices, operational efficiencies, and patient engagement (4 - 6). It is becoming an integral part of the healthcare ecosystem, offering new possibilities for improved patient outcomes and more efficient healthcare delivery (4 - 6).

Artificial Intelligence in Perinatal Medicine and Reproductive Health

Recent research demonstrates that AI has significant potential to improve the accuracy and timeliness of diagnoses in perinatal medicine and human reproduction, such as advancing perinatal ultrasound techniques, monitoring fetal heart rates during labor, or predicting modes of delivery (4 - 10). The integration of AI with obstetric ultrasound can optimize fetal ultrasound assessments by reducing examination time, improving diagnostic accuracy, and alleviating physician workload (7, 11). As technology advances, AI algorithms are expected to become even more sophisticated, potentially improving patient outcomes, enhancing healthcare efficiency, and enabling individualized care plans (7, 11). However, the successful implementation of AI in perinatal medicine and reproductive health requires addressing challenges related to interpretability and reliability (7, 11). AI can improve the prediction and early diagnosis of pregnancy complications through machine learning by analyzing large datasets to identify risk factors (7, 11). The potential of AI to tailor treatments and interventions based on individual patient data can lead to more personalized and effective care plans for mothers and infants (7, 11). Additionally, AI enhances telemedicine and remote patient monitoring, particularly in managing high-risk pregnancies or providing care access in underserved areas (7, 11). AI is also used in sophisticated robotic systems for performing complex surgical procedures, such as fetal surgery or in vitro fertilization (IVF), offering numerous benefits alongside some risks associated with these technologies (7, 11). The integration of AI in medical practice also impacts the training and education of healthcare professionals, posing challenges for clinicians as educators, as new skill sets and shifts in the role of clinicians are required (7, 11). Further research is necessary to explore areas such as long-term outcomes of AI-assisted interventions and ensuring these technologies benefit all population segments (7, 11). Additionally, the current regulatory landscape governing the use of AI in medicine, potential legal issues, and the need for updated guidelines to ensure the safe and ethical use of AI technologies in perinatal medicine and reproductive health are critical considerations (7, 11). Ethical challenges, including data privacy concerns, the potential for bias in AI algorithms, and the need for transparent and fair use of AI in clinical settings, must also be addressed (7, 11).

The Case of Fetal Neurology: Kurjak Antenatal Neurodevelopmental Test and AI

Investigating fetal neurology and behavior is crucial for understanding neurodevelopmental outcomes and potential neurological con-

ditions post-birth. One significant method in this field is the Kurjak Antenatal Neurodevelopmental Test (KANET) (12 – 20). KANET is a structured assessment tool that evaluates fetal neurobehavioral patterns using advanced ultrasound technology, particularly the four-dimensional (4D) ultrasound (12 – 20). Studies on fetal neurology and behavior, such as those conducted using KANET, can identify abnormal neurological development and potential neurobehavioral disorders early in gestation (12 – 20). This early detection is vital for planning interventions that can improve outcomes or manage conditions postnatally (12 – 20).

KANET focuses on observing fetal movements and behaviors, which are indicators of brain function and maturation (12 – 20). Specific movements, facial expressions, and the complexity of motor activities are associated with the development of the central nervous system (12 – 20). Abnormalities in these patterns can suggest higher risk of developmental delays, other neurological conditions or even cerebral palsy (12 – 20).

The test helps predict neurodevelopmental outcomes after birth by assessing specific neurobehavioral markers during the fetal period (12 – 20). This predictive capability is valuable for healthcare providers and parents, enabling them to anticipate and prepare for potential challenges that might arise post-birth (12 – 20).

In high-risk pregnancies, such as those involving maternal diabetes, preeclampsia, or intrauterine growth restriction (IUGR), KANET provides critical insights into the neurological health of the fetus (12 – 20). This information is essential for making informed decisions about the timing and mode of delivery and postnatal care (12 – 20).

By identifying potential neurodevelopmental issues before birth, KANET can guide early therapeutic interventions, including physiotherapy, occupational therapy, or other specialized care, immediately post-birth, aiming to improve developmental outcomes (15).

The KANET scoring system assesses fetal neurobehavioral development by observing fetal movements and facial expressions (21). AI can facilitate objective assessments of fetal facial expressions (21). A study reported a high accuracy and reliability score for AI in analyzing fetal facial expressions, categorizing them into seven types: eye blinking, mouthing, neutral face, scowling, smiling, tongue expulsion, and yawning (21). However, challenges remain, including the time-consuming nature of observing fetal faces, the lack of consensus among examiners on image classification, and the imperfect classification of fetal facial expressions (21). Moreover, the feasibility of recognizing fetal facial expressions using AI depends on data supervised by experienced examiners. Some datasets, such as those for rare expressions like sucking, remain problematic (21).

KANET offers a non-invasive, accessible, and informative method for evaluating fetal neurobehavior and predicting neurodevelopmental outcomes (12 – 20). Its application can significantly impact clinical decision-making, parental counseling, and planning early interventions, ultimately contributing to better health outcomes for children (12 – 20). The growing body of research supports the continued use and refinement of KANET as a valuable tool in perinatal medicine (12 – 20). However, using AI in conjunction with the KANET test presents challenges, particularly concerning data privacy, potential bias, ethical considerations, and the need for robust regulatory frameworks (21). Addressing these challenges requires a comprehensive approach that balances technological innovation with ethical standards and safeguards, ensuring AI enhances rather than detracts from patient care.

Strengths, Weaknesses, Opportunities, and Threats (SWOT) Analysis of AI Use in Perinatal Medicine and Reproductive Health

Strengths

Artificial Intelligence (AI) offers several significant strengths in perinatal medicine and reproductive health. These strengths

have the potential to revolutionize the field by enhancing diagnostic accuracy, personalizing treatment, improving patient outcomes, and streamlining clinical workflows (22). AI can improve predictive analytics and operational efficiency, which are crucial in managing high-risk pregnancies and optimizing patient care. However, it is essential to address challenges related to data privacy, algorithmic bias, and the need for robust regulatory frameworks to fully realize these benefits while ensuring patient safety and ethical standards.

Weaknesses

Despite its promising applications, AI in perinatal medicine and reproductive health presents several challenges and weaknesses (23):

- Data quality and availability: AI models require large, high-quality datasets. However, data can be sparse, incomplete, or biased, limiting the models' effectiveness.
- Bias and fairness: AI systems can inadvertently incorporate biases from the training data, such as those related to race, socioeconomic status, or gender, potentially leading to unequal healthcare outcomes.
- Lack of interpretability and transparency: AI-driven recommendations may lack transparency, making it difficult for healthcare providers and patients to trust these systems, especially if they do not understand how decisions are made.
- Regulatory and ethical concerns: The lack of clear regulations and ethical guidelines can lead to legal challenges and ethical dilemmas, particularly concerning patient consent and data privacy.
- Technical and integration challenges: Without proper integration into healthcare systems, AI tools may be underutilized or misused, leading to inefficiencies or errors in patient care.
- Over-reliance on technology: There is a risk of healthcare professionals becoming over-reliant on AI, which could lead to a de-skilling of the workforce and weaken patient-doctor relationships.
- Patient acceptance and trust: Low patient acceptance and trust in AI tools can reduce their effectiveness, as patients may be reluctant to follow AI-generated recommendations or share their data.
- Cost and accessibility: Implementing and maintaining AI systems can be expensive, potentially limiting their availability to wealthier institutions or countries.

Addressing these weaknesses is crucial to ensure the safe, fair, and effective implementation of AI in clinical practice. This requires collaboration among technologists, healthcare providers, regulators, and ethicists to develop robust systems, clear guidelines, and transparent practices that protect and benefit patients.

Opportunities

The application of AI in perinatal medicine and reproductive health presents numerous opportunities to enhance care quality, efficiency, and accessibility. AI's capabilities in data analysis, pattern recognition, and automation support healthcare professionals in various aspects of patient management. Key opportunities include (24):

- Improving diagnostic accuracy: AI can analyze medical images and other diagnostic data with high precision, aiding early detection of complications and diseases.
- Personalizing treatment: AI can help tailor treatment plans based on individual patient data, improving outcomes and patient satisfaction.
- Increasing efficiency: AI can streamline administrative tasks and clinical workflows, allowing healthcare providers to focus more on patient care.

- Expanding accessibility: AI-driven tools can enhance access to care, particularly in underserved regions, through telemedicine and remote monitoring.

To fully realize these opportunities, it is essential to ensure data quality, mitigate bias, and maintain transparency and trust in AI systems (22- 24). With careful implementation and ongoing oversight, AI has the potential to transform these fields, improving outcomes for mothers and infants worldwide.

Threats

The integration of AI into perinatal medicine and reproductive health, while promising, also poses several significant threats and challenges (22-24):

- Technical limitations: AI systems are only as good as the data and algorithms they are based on, and technical errors can lead to incorrect diagnoses or treatment plans.
- Ethical considerations: Issues such as data privacy, informed consent, and the potential for AI to perpetuate existing biases are critical concerns that must be addressed.
- Impact on healthcare systems: The widespread adoption of AI may disrupt traditional healthcare delivery models, requiring significant adjustments in training and practice for healthcare professionals.

Concluding Remarks on the Use of AI in Perinatal Medicine and Reproductive Health

Winston Churchill once said, "Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning." This sentiment is echoed in the evolving landscape of AI in perinatal medicine and human reproduction. We are at a significant turning point where AI technologies are becoming integral to clinical practice (5, 6). This phase of maturity involves building on initial developments to create real-world applications and improvements.

However, this progress comes with caution. The rapid advancement of AI in sensitive areas like perinatal medicine and human reproduction raises potential ethical, practical, and societal challenges (7 – 9). Concerns such as over-reliance on technology, potential ethical dilemmas, and the need for robust regulatory frameworks must be carefully considered (7 – 9).

As Stanisław Jerzy Lec wisely noted, "The only fool bigger than the person who knows it all is the person who argues with him." This thought underscores the importance of humility and open-mindedness in our understanding and application of AI. While AI has transformative potential, it is crucial to consider the ethical, legal, and practical challenges it presents. Balancing technological innovation with ethical standards and safeguards will be key to ensuring that AI enhances, rather than detracts from, patient care in perinatal medicine and reproductive health. The future holds both promising advancements and significant challenges in this emerging field.

Acknowledgment: None.

Authors' Contributions: Conceptualization: Milan Stanojevic, Asim Kurjak, Edin Medjedovic. Formal analysis: Milan Stanojevic, Asim Kurjak. Methodology: Milan Stanojevic, Asim Kurjak. Project administration: Milan Stanojevic, Asim Kurjak. Resources: Milan Stanojevic, Asim Kurjak, Edin Medjedovic. Software: Milan Stanojevic, Asim Kurjak, Edin Medjedovic. Supervision: Milan Stanojevic, Asim Kurjak. Visualization: Milan Stanojevic, Asim Kurjak, Edin Medjedovic. Writing – original draft: Milan Stanojevic, Asim Kurjak, Edin Medjedovic. Writing – review & editing: Milan Stanojevic, Asim Kurjak, Edin Medjedovic.

Financial support and sponsorship: There was no funding.

Conflict of interest: The authors have nothing to disclose.

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PHD CORNER

Efficiency of Early Penile Rehabilitation on Erectile Function Recovery after Open Radical Prostatectomy

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Pages: 38-40 / Published online: 21 August 2024

Cite this article: Alic J. Efficiency of Early Penile Rehabilitation on Erectile Function Recovery after Open Radical Prostatectomy. Sar Med J. 2024; 1(1): Online ahead of print.. DOI: 10.70119/0007-24

Original submission: 18 March 2024; **Revised submission:** 10 June 2024; **Accepted:** 14 July 2024

RESEARCH BACKGROUND

Prostate cancer (PC) is one of the most commonly diagnosed malignancies worldwide and the second leading cause of mortality among men (1). Nowadays, radical prostatectomy is considered the primary therapeutic modality for treating patients with localized PC (stage pT2), providing a five-year survival rate of nearly 100% (2). Sexual dysfunction in men associated with PC treatment encompasses three distinct entities: erectile dysfunction (ED) and penile shortening; ejaculatory and orgasmic dysfunction; and psychosexual dysfunction, which pertains to sexual desire, intimacy, and mental health (3). Penile rehabilitation (PR) is defined as the use of any intervention or combination of procedures aimed not only at achieving an erection sufficient for satisfactory sexual intercourse but also at restoring erectile function to its preoperative level (4).

Despite efforts to preserve the neurovascular bundle during radical prostatectomy, ED remains a common outcome. Although prevalence rates of ED after the procedure vary widely, recent studies report rates as high as 85% (5). This is primarily due to the lack of control over factors that significantly influence the erection recovery, such as the patient's age, preoperative erectile function, comorbidities, surgical approach (open, laparoscopic, or robot-assisted), surgical technique (non-, uni-, or bilateral nerve-sparing), and the surgeon's skills and experience. The pathophysiology of postoperative ED is multifactorial. The primary mechanisms are believed to be damage to the cavernous nerves, whether through dissection or neuropraxia, and vascular injury, which includes damage to the accessory pudendal arteries, hypoxia and fibrosis of the endothelium and smooth muscle, resulting in penile shortening (6-8).

Although there is no consensus on the optimal approach to PR, accepted modalities include the use of phosphodiesterase type 5 inhibitors (PDE-5i; such as sildenafil, vardenafil, tadalafil) and vacuum erection devices (VED) or vacuum constriction devices (VCD) as first-line therapies. Second-line treatments involve prostaglandin E1 preparations for intracavernous, or intraurethral (MUSE - "Medicated Urethral System for Erection") administration. The final therapeutic option is the implantation of penile prostheses (3-10).

HYPOTHESIS AND OBJECTIVES

Given the current knowledge, this research is based on the hypothesis that early PR methods are effective and safe in treating erectile dysfunction following open radical prostatectomy. The study aims to determine and compare the effectiveness of the most commonly used modalities, assess their safety profiles, and investigate whether perioperative variables can predict the PR outcomes. It also aims to determine if it is justifiable to persist with PR efforts if erectile function does not initially recover within the first 6 months following surgery.

Additionally, the objectives are to examine the role of preoperative penile ultrasonography in patient selection, establish the correlation between preoperative and postoperative hemodynamic profiles and the degree of erectile function recovery, evaluate the rationale for including patients who underwent a non-nerve-sparing procedure in PR programs, and assess the impact of PR on the quality of life (QoL) of patients following open prostatectomy.

MATERIALS AND METHODS

The study will be conducted in the form of a prospective, placebo-controlled randomized clinical trial, and will include 80 patients treated surgically by open retropubic prostatectomy. Patients are randomized into 4 groups according to the preferred PR modality: A: PDE5i (tadalafil 5 mg, daily), B: VED (daily, for 10 min), C: combination therapy (PDE5i + VED), D: placebo group. The follow-up will last 12 months and the erectile function analysis will be performed preoperatively, then after 3, 6 and 12 months, and after a wash-out period of 2 months, using the International Erectile Function Index - 5 (IIEF-5), Erection Hardness Score (EHS) and Penile Color Doppler ultrasonography. The answers to SEP2 and SEP3 (Sexual Encounter Profile) questions will be used as the main inclusion criteria, and the Global Assessment Question (GAQ) as the patient reported outcome.

The term "recovery of erectile function" is defined as a return to the base IIEF-5 score. A specialized FACT-P questionnaire (Functional Assessment of Cancer Therapy – Prostate) will be used to assess QoL. Penile color Doppler ultrasonography (CDUS) at rest and after intracavernosal administration of vasoactive drug (alprostadil, 20 μg) will register hemodynamic variables (PSV, EDV, RI), on the Mindray DC-70 device (Mindray Bio-Medical Electronics Co. Ltd., Shenzhen, China).

OUTCOMES AND EXPECTED RESULTS

Some patients may not complete the PR program due to decreased sexual desire, treatment complications, or ineffectiveness. Those who complete the program will be divided into the group of responders (those reporting recovery of spontaneous erection) and non-responders. The responders will be divided into complete responders (those achieving full recovery of spontaneous erection sufficient for sexual activity) and partial responders (those with partial recovery, experiencing inadequate erection in less than 50% of sexual attempts).

Significant differences between the two groups are expected concerning age, ASA status, smoking status, and CCI (Charlson Comorbidity Index). Younger non-smokers with a lower ASA score and fewer comorbidities, patients who had a nerve-sparing procedure, specially who underwent bilateral nerve-sparing surgery, are more likely to be in the responder group. No significant difference is expected regarding the status of resection margins. Univariate analysis is expected to show that age and PSA levels are associated with the outcome of erectile rehabilitation. Bivariate analysis may reveal that CCI, ASA status, and Gleason score are linked to poorer rehabilitation prognosis. Smoking, alcohol abuse, higher pT stage, preoperative PSA, and surgical technique are likely to be confirmed as significant predictors of rehabilitation outcomes. Multivariate analysis may demonstrate that age over 65, higher BMI, non-nerve-sparing

surgery, and higher ASA status are associated with worse outcomes.

Patients in group C (PDE-5i+VED) may have an advantage in rehabilitation outcomes and be predominant in the responder group. It is expected that the sexual aspect of QoL, as well as overall QoL, will improve across all groups during the follow-up period, though the placebo group may be slightly behind in this regard. Adverse effects of treatment are expected to be sporadic, mild to moderate in intensity, and are unlikely to lead to discontinuation of the rehabilitation program.

CONCLUSIONS

Following the hypothesis and the expected results, we conclude that early penile rehabilitation modalities are effective and safe in the treatment of erectile dysfunction after open radical prostatectomy. Combination therapy with PDE5i and VED may have an advantage over other modalities. Penile CDUS can play a significant role, both in preoperative patient selection and in monitoring rehabilitation efficacy.

ORIGINAL SCIENTIFIC CONTRIBUTION

Most current knowledge on PR following radical prostatectomy is derived from retrospective studies, which should be interpreted cautiously due to methodological limitations, small sample sizes, and short follow-ups. This study stands out by integrating the latest research methodologies and offering a novel approach. It is the first of its kind in the region, aiming to enhance understanding of post-PC surgery conditions and improve monitoring. A key aspect is analyzing self-reported outcomes alongside objective ultrasonographic assessments, which is unique in this context.

The study will identify factors that differentiate patients likely to benefit from PR from those who might not recover erectile function despite intensive treatment. This is vital due to the high cost of rehabilitation programs and helps in setting realistic expectations and exploring more effective alternatives. In a society where sexual health is often taboo, this research will contribute to better understanding and treatment of ED, and propose a culturally adapted PR protocol for our urological centers.

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CASE REPORT

Transthyretin Amyloid Cardiomyopathy – Setting the Diagnosis Step by Step

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Pages: 41-45 / Published online: 20 August 2024

Cite this article: Mlaco-Vrazalic N, Subo A, Prohic N, Skalonja M, Djozic A, Kurbasic I, et al. Transthyretin Amyloid Cardiomyopathy – Setting the Diagnosis Step by Step. Sar Med J. 2024; 1(1): Online ahead of print.
DOI: 10.70119/0008-24

Original submission: 20 March 2024; **Revised submission:** 14 June 2024; **Accepted:** 17 July 2024

Abstract

Introduction: Transthyretin amyloid cardiomyopathy (ATTR-CM) can be diagnosed in the absence of histology with typical echocardiographic findings and skeletal scintigraphy showing grade 2 or 3 myocardial tracer uptake, when clonal plasma cell dyscrasia is excluded. Aim: To present a patient diagnosed with ATTR-CM, who was hospitalized with clinical signs of congestive heart failure. Case Report: An 84-year-old man was hospitalized with clinical signs of heart failure. Echocardiography showed concentric left ventricular hypertrophy (LVH) with reduced systolic function, along with impaired LV global longitudinal strain (GLS) with apical sparing (-9.9%). Serum and urine protein electrophoresis with immunofixation were obtained and were negative for plasma cell dyscrasia. Bone scintigraphy showed similar radiotracer uptake in the myocardium and ribs (Perugini grade 2). The diagnosis of ATTR-CM was confirmed. Conclusion: ATTR-CM is an underdiagnosed condition and should be suspected in patients with heart failure and unexplained LVH.

Keywords: amyloidosis, cardiomyopathies, diagnosis, rare diseases.

Learning Objectives

- To consider infiltrative cardiomyopathy in patients with "red flag" signs related to transthyretin amyloid cardiomyopathy (ATTR-CM), including LV hypertrophy.
- To understand the ATTR-CM diagnostic approach.
- To understand that ATTR-CM can be diagnosed in daily clinical practice via non-invasive means.
- Early diagnosis of ATTR-CM is a key to improving patient outcomes.

INTRODUCTION

Transthyretin amyloid cardiomyopathy (ATTR-CM) can be diagnosed in the absence of histology with typical echocardiographic findings (or cardiac magnetic resonance findings) when skeletal scintigraphy with 99mTc-pyrophosphate (PYP), 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), or 99mTc-(hydroxy) methylene diphosphonate ((H)MDP) shows grade 2 or 3 myocardial tracer uptake, and clonal plasma cell dyscrasia is excluded (1-3). ATTR-CM is often an unrecognized pathology, and it has been found in 25% of people aged over 85 years in autopsy studies (1-3). It was reported in up to 16% of patients with aortic stenosis who underwent transcatheter aortic valve implantation, and 13% of patients with heart failure with preserved ejection fraction (HFpEF) (4). Echocardiography is the primary diagnostic test for cardiac amyloidosis, revealing infiltration of the ventricular walls characterized by a speckled appearance of the myocardium (5). The hallmark echocardiographic feature of cardiac amyloidosis is the relative apical sparing of longitudinal strain (5-7). There is a discrepancy between LV (left ventricular) wall thickness and electrocardiogram (ECG) voltage (4). The aim of the case report was to present a patient diagnosed with ATTR-CM, who was admitted initially due to clinical manifestations of heart failure and exhibited pleural effusions, ascites, and free fluid in the pelvic cavity.

CASE PRESENTATION

An 84-year-old man was admitted to the hospital presenting clinical symptoms of congestive heart failure, including dyspnea and peripheral edema. His past medical history included permanent atrial fibrillation (AF), hypertension, chronic kidney disease (CKD) grade IV, megaloblastic anemia and periurethral adenoma. The initial chest X-ray upon admission revealed bilateral pleural effusions. A pulmonologist was consulted, and a thoracocentesis was performed for diagnostic and therapeutic purposes. The analysis of the pleural fluid indicated it was a transudate. Abdominal ultrasound confirmed congestive hepatopathy with ascites. The ECG revealed atrial fibrillation alongside the left bundle branch block and low voltage. Transthoracic echocardiography revealed concentric left ventricular hypertrophy (LVH) with global hypokinesia and reduced systolic function (left ventricular ejection fraction (LVEF) of 36%, assessed using the Simpson biplane method). Cardiac chamber sizes were normal, with right ventricular free wall hypertrophy (13mm). Mild mitral regurgitation and moderate tricuspid regurgitation were detected, along with moderate pulmonary hypertension. The inferior vena cava (IVC) diameter was 2.5cm with inspiratory collapse of less than 50%. Subsequent analysis of global longitudinal strain (GLS) showed GLS reduction (-9.9%) with an apical sparing pattern ('cherry on top'). We suspected infiltrative cardiomyopathy and obtained serum and urine protein electrophoresis with immunofixation and the kappa/lambda ratio, which were negative for clonal plasma cell dyscrasia. The next diagnostic modality was bone scintigraphy with 99Tc MDP, which showed similar radiotracer uptake in the myocardium and ribs (Perugini grade 2) with a region of interest (ROI) ratio of 1.54. Additionally, a rest myocardial perfusion scan with 99m-technetium methoxy isobutyl isonitrile (99mTc MIBI) was performed, and an irreversible perfusion defect of the inferolateral wall was detected.

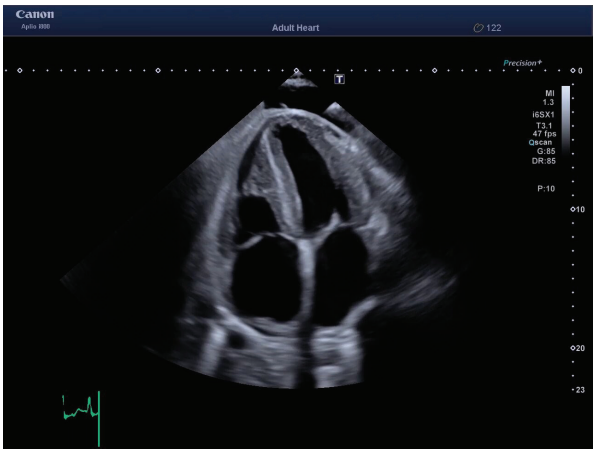

Figure 1. Assessment of cardiac muscle by transthoracic echocardiography

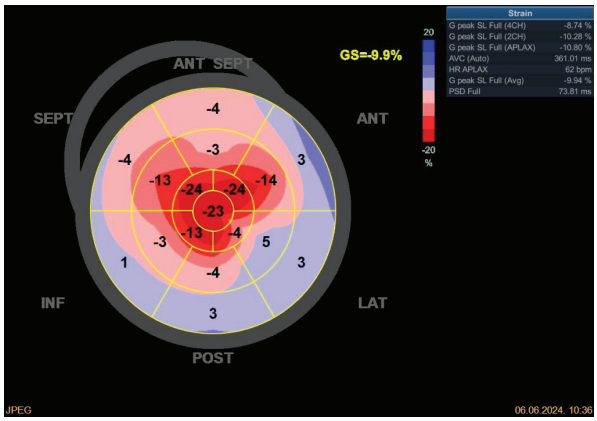

Figure 2. Apical sparing pattern (global longitudinal strain of left ventricle)

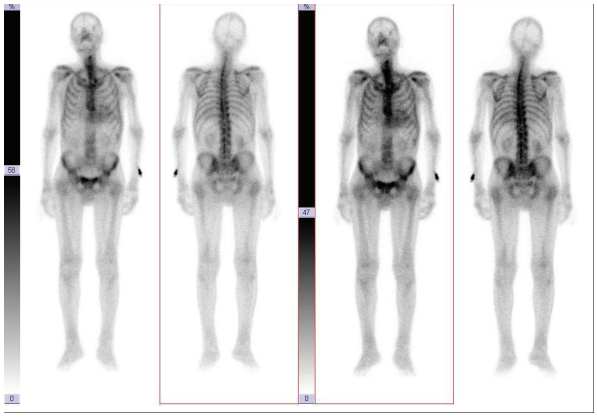

Figure 3. Perugini grade 2 on skeletal scintigraphy

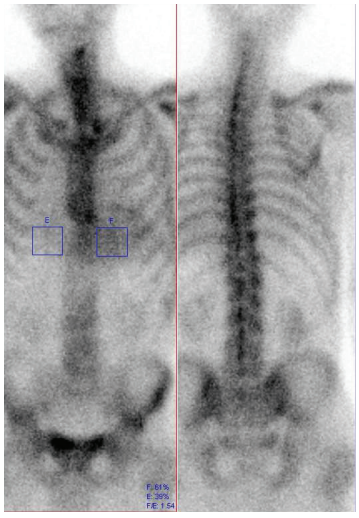

Figure 4. ROI ratio 1.54

DISCUSSION

Unexplained LVH, especially in patients with HFpEF, should raise suspicion for cardiac amyloidosis (3, 5). It is important to differentiate amyloid light chain (AL) amyloidosis which causes the deposition of misfolded immunoglobulin light chains, produced by a plasma cell clone, and ATTR amyloidosis which causes deposition of the transthyretin (TTR), a protein produced by the liver (3). ATTR amyloidosis can be hereditary (variant type, ATTRv) or acquired (senile or wild-type, ATTRwt) (3). Systolic function can be impaired in earlier stages of amyloidosis, reduced end-diastolic volume decreases the stroke volume (6). LVEF is preserved until the end-stage disease, but we commonly diagnose patients when LVEF is already mildly reduced (3, 6). Extracardiac signs and symptoms can be helpful in earlier detection of the disease, they vary among the types of amyloidosis. ATTR amyloidosis primarily involves the heart and peripheral nervous system (3). ATTRwt is associated with bilateral carpal tunnel syndrome (often precedes cardiac manifestations by 10 years), biceps tendon rupture and spinal canal stenosis. ATTRv is associated with peripheral sensorimotor neuropathy and autonomic dysfunction including gastrointestinal dysautonomia and orthostatic hypotension (3). Our patient did not present with classic extracardiac manifestations. He was previously diagnosed with CKD, which was described by a nephrologist as cardio-renal syndrome type 2. Our diagnosis was suspected based on echocardiography. Echocardiographic findings in ATTR amyloidosis are non-specific and include infiltration of the ventricular walls, which produces the appearance of pseudohypertrophy (wall thickness ≥12mm; relative wall thickness (RWT)≥ 0,42) with increased LV mass (5). Pericardial effusion, enlarged atria, thickening of the atrioventricular valves and interatrial septum are common (5, 6). Amyloid deposition can cause 'granular speckling' of the myocardium, however, it is a non-specific finding commonly seen in other infiltrative cardiomyopathies and end-stage renal disease (3, 6). Reduction in GLS with relative apical sparing has high sensitivity (93%) and specificity (82%) for cardiac amyloidosis (1). Apical sparing in the bulls-eye plot with an apex:base ratio of > 2.1 helps distinguish cardiac amyloidosis from other causes of LV hypertrophy (such as hypertensi-

on, Fabry disease and Friedreich's ataxia) (5). In suspected cases, serum and urine protein electrophoresis with immunofixation should be performed first to exclude AL (3). If a monoclonal protein was identified by these tests, the patient would need a referral to a hematologist, bone marrow biopsy or other tissue biopsies may be required (1). If monoclonal protein is not identified, as in our case, we proceed to bone scintigraphy. Bone scintigraphy showing myocardial uptake equal to or greater than in ribs (Perugini score 2 or 3), coupled with a lack of evidence of plasma cell dyscrasia, is sufficient to diagnose cardiac ATTR amyloidosis and tissue biopsy is not required (9). The role of cardiac magnetic resonance (CMR) depends largely on local accessibility, it is indicated if echocardiographic findings are inconclusive and if there is a broader differential diagnosis (4, 10). ATTR amyloidosis typically demonstrates transmural late gadolinium enhancement (LGE), whereas AL amyloidosis shows subendocardial LGE (4). T1 mapping detects the combined signal of myocytes and extracellular matrix. Native T1 signals are increased in regions with amyloid deposits or diffuse fibrosis. T2 signals are increased in AL compared to ATTR and the general population (10). Genetic testing is recommended to distinguish ATTRv from ATTRwt (3).

CONCLUSION

Cardiac amyloidosis is an underdiagnosed disease and should be included in differential diagnosis for patients presenting with heart failure and increased LV wall thickness on echocardiography. In suspected cases, negative serum and urine protein electrophoresis, with bone scintigraphy showing a Perugini score of 2 or 3, are sufficient to diagnose ATTR amyloidosis.

Acknowledgment: None.

Declaration of patient consent: The patient gave consent after being informed of the case report.

Authors' Contributions: Conceptualization: Nejra Mlaco-Vrazalic, Edin Begic, Anela Subo, Nejra Prohic. Formal analysis: Nejra Mlaco-Vrazalic, Edin Begic, Ada Djozic, Anela Subo, Izeta Kurbasic, Ada Djozic, Mirza Skalonja, Sejla Biscevic. Project administration: Nejra Mlaco-Vrazalic, Edin Begic, Nejra Prohic. Resources: Nejra Mlaco-Vrazalic, Edin Begic, Anela Subo, Mirza Skalonja, Ada Djozic, Sejla Biscevic. Software: Edin Begic, Mirza Skalonja. Supervision: Edin Begic. Visualization: Nejra Mlaco-Vrazalic, Edin Begic, Anela Subo, Mirza Skalonja, Sejla Biscevic. Writing – original draft: Nejra Mlaco-Vrazalic, Anela Subo, Nejra Prohic, Mirza Skalonja, Ada Djozic, Izeta Kurbasic, Sejla Biscevic, Edin Begic. Writing – review & editing: Nejra Mlaco-Vrazalic, Anela Subo, Nejra Prohic, Mirza Skalonja, Ada Djozic, Izeta Kurbasic, Sejla Biscevic, Edin Begic.

Financial support and sponsorship: There was no funding.

Conflict of interest: The authors have nothing to disclose.

Consent: The authors have obtained written consent from the patient to submit and publish this case report, including images and accompanying text, in accordance with COPE guidelines.

Funding: None declared.

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CASE REPORT

Valsalva Aneurysm of Right Sinus: A Case Report and Review of Literature

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Pages: 46-51 / Published online: 25 Jul 2024

Cite this article: Begic E, Mladenovic Z, Aziri B, Hondo Z, Hujdur M. Valsalva Aneurysm of Right Sinus: A Case Report and Review of Literature, Sar Med J. 2024; 1(1): Online ahead of print. DOI: 10.70119/0009-24

Original submission: 23 March 2024; **Revised submission:** 15 June 2024; **Accepted:** 21 July 2024

Abstract

In this case report, we describe the diagnostic modality of sinus of Valsalva aneurysm (SOVA) in combination with congenital cardiac defect, aortic valve involvement, and conduction abnormality in a 19-year-old patient. Aim of article was to understand the importance of clinicians being cautious about SOVA presenting in young patients, despite cases being rare, and that SOVA requires a thorough SOVA diagnostic approach. We further provide a review of literature highlighting and comparing the treatment options for both unruptured and ruptured SOVAs. The patient presented for examination due to tachycardia and palpitations. A murmur was heard, and the patient was found to have an atrioventricular nodal reentry tachycardia. Echocardiographic evaluation, magnetic resonance imaging, and computed tomography angiography confirmed an aneurysmally dilated aortic root, aortic regurgitation, and ventricular septal defect. Surgical intervention was indicated; however, the patient refused to undergo surgery.

Keywords: sinus of valsalva, aneurysm, treatment, cardiac surgical procedures.

Learning Objectives

- To understand the importance of clinicians being cautious about SOVA presenting in young patients, despite cases being rare
- To understand the SOVA diagnostic approach
- To understand to that timely intervention for SOVA in combination with VSD is imperative, due to likelihood of rupture
- To understand the adequate therapeutic modality for sinus of Valsalva aneurysm coexisting with congenital cardiac defects, aortic valve involvement, or conduction abnormalities

INTRODUCTION

In this case report, we describe the diagnostic modality of sinus of Valsalva aneurysm (SOVA) in combination with congenital cardiac defect, aortic valve involvement, and conduction abnormality in a 19-year-old patient. We further provide a review of literature highlighting and comparing the treatment options for both unruptured and ruptured

SOVAs. The main take-home message from this article is to understand the importance of clinicians being cautious about SOVA presenting in young patients, despite cases being rare, and that SOVA diagnosis requires a thorough approach. Moreover, timely intervention for SOVA in combination with VSD is imperative, due to likelihood of rupture. Understanding the adequate therapeutic modality for sinus of Valsalva aneurysm coexisting with congenital cardiac defects, aortic valve involvement, or conduction abnormalities on a case-by-case basis carries prognostic implications.

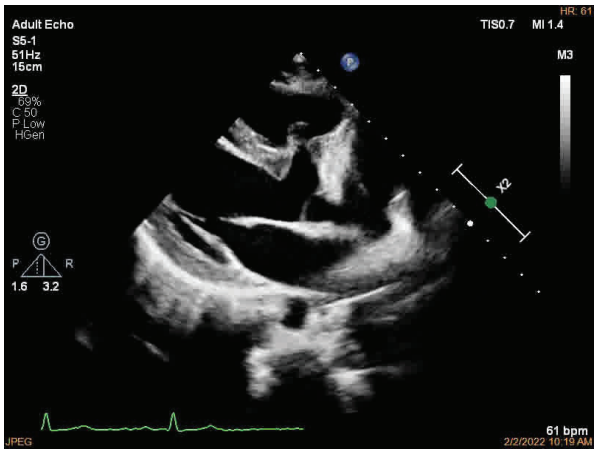

Figure 1. The parasternal long axis view (PLAX).

CASE PRESENTATION

A 19-year-old patient (body weight 70 kg, body height 175 cm) came for an examination due to tachycardia and palpitations, which occurred regardless of effort. A decrescendo diastolic murmur of intensity 2/6, according to Levine, was heard at the left upper sternal border, around the 2nd and 3rd intercostal spaces. Two attacks of atrioventricular nodal reentry tachycardia (AVNRT) with a maximum heart rate of 188 beats per minute were verified on 24-hour electrocardiogram (ECG) Holter monitoring. Per anamnesis, the father died of sudden cardiac death at the age of 52 and the brother at the age of 32. Physical exam was otherwise unremarkable.

On transthoracic echocardiogram (TTE), left and right heart cavities were with regular dimensions, along with a saccular formation that floats in the area of the distal membranous part of the interventricular septum, with an aneurysmally altered aortic root and membranous part of the septum (Figure 1).

Transesophageal echocardiography (TEE) showed aortic valve morphologically three-leaflet (with fused raphe of right and left cusp-functionally bicuspid), with an altered annulus in the form of aneurysm involving the right Valsalva's sinus (covering 30% of the circumference of the annulus), forming a triangular formation measuring 2.7x2.0 cm. On the lateral wall, there were two saccular formations of 1x0.8 cm and 1.1x0.9 cm in dimension, with the effect of filling and emptying during contractions. The entire lateral wall of this formation was of scatter structure. The mentioned formation expanded towards the membranous part of the interventricular septum and formed a channel 1.8 cm long and 0.8 cm wide (Figure 2).

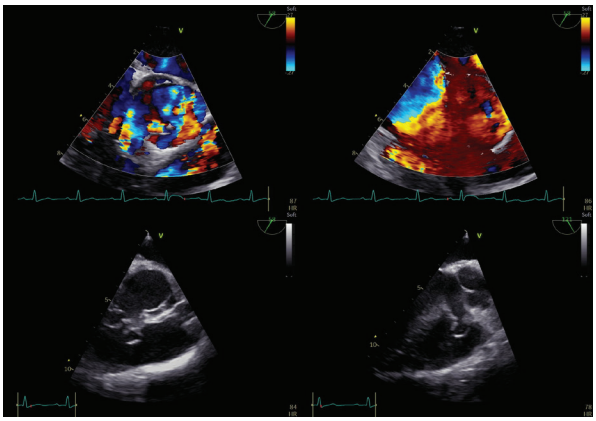

Figure 2. Altered aortic annulus in a form of aneurism, involving the right Valsalva's sinus.

The hemodynamics of the described formation was independent of the pressures in the left and right cavities. The flow from the mentioned aneurysm entered the dilated sinus of Valsalva and communicated with the left ventricle through the formed channel, along with the right ventricle (ventricular septal defect). Moderate aortic regurgitation (AR) of central type was registered, independent of the flow in the described formation, vena contracta was 0.6 cm, and aortic regurgitation/left ventricular outflow tract was 39%. Diastolic flow in descending aorta

was with peak aortic jet velocity (AV Vmax) 0.13 m/s, which corresponded to the picture of mild to moderate AR, along with an empty left atrial appendage (Figure 3). Aneurysmically altered right sinus of Valsalva is verified by aortography, as well as with cardiac magnetic resonance imaging (MRI). Computed tomography (CT) angiography of the aorta confirms the diagnosis (Figure 4). On the CT scan, an aneurysmal expansion consisting of two changes in the saccular form, measuring 9.98x8.2 mm and 10.3x9.4 mm, is described on the lateral wall of a separate compartment (area up to 3.66 cm^2), and the space, in addition to communication with the left ventricle, further communicates with the right ventricle through a tubular form with a diameter of up to 0.78 mm, a length of 18.4 mm. Aortic valve circumference is up to 110.1 mm, and total area is up to 870.1 mm^2.

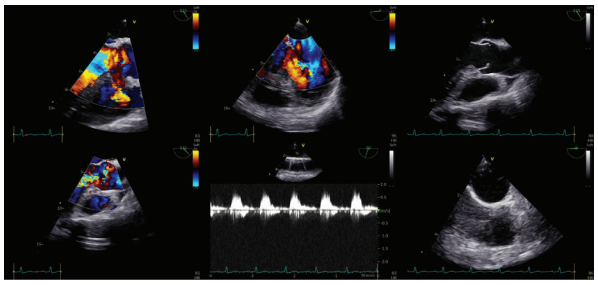

Figure 3. Moderate aortic regurgitation.

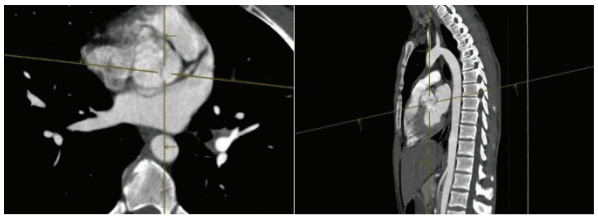

Figure 4. Computed tomography angiography of aorta.

DISCUSSION

The incidence of SOVA is 0.09% percent in the general population, 0.5% - 3% of all congenital heart defects (in 75–90% affected by RCC), occurring four times more often in men and in the Asian population (6). In the majority of cases, SOVA is discovered incidentally during cardiac imaging (2). SOVA represents dilatation of the aortic root located between the aortic valve annulus and the sinotubular junction and may be associated with the existence of connective tissue diseases (6). Our patient had no history of infections associated with acquired SOVA (syphilis, bacterial endocarditis, and tuberculosis), no Marfan syndrome or Ehlers-Danlos syndrome (or any connective tissue disorder) in the family, and the patient's rheumatological and ophthalmological findings were neat.

In 30% to 50% of cases it is associated with aortic regurgitation, VSD is associated with aneurysm in 30-60% (most often with bicuspid AV) (6). Supracrystalline VSD (frequent rupture) is more common in Asians, and perimembranous in Western populations (7). Our patient presents with an aneurysm of the right sinus of Valsalva with perimembranous VSD, functionally bicuspid AV, and moderate AR, which is an uncommon combination of congenital cardiac abnormalities, whereby the role of timing of surgery is of utmost importance.

VSD is associated with aneurysm in 30-60% (most often with bicuspid AV), and the association with VSD brings a higher risk of rupture (4). Rupture can occur spontaneously due to trauma or endocarditis (in 60% of RV); most often sudden, in previously undiagnosed cases, before the age of 40 (4,6). Also, the occurrence of rhythm disorders is something that should be taken into account. Our patient also has verified AVNRT, which represents an additional problem in understanding the therapeutic modality.

An important consideration is that it may be challenging to differentiate the sinus of Valsalva aneurysm associated with perimembranous VSD from membranous septal aneurysm, owing to the close anatomical location.

Surgical treatment of SOVA is widely acknowledged and associated with low mortality, the choice of technique depending on the presence of VSD (8). Operative treatment goes in two directions. The first option is transcatheter closure (Rashkind umbrella, septal occluder device, ductal occluder,

Table 1: Case reports of SOVA originating from right coronary sinus with associated perimembranous VSD and aortic valve disease in young adults (age group 18-25 years old)

Reference	Age, sex	Presentation	SOVA	Associated conditions	Mode of diagnosis	Changes on ECHO	Treatment	Outcome
Udora et al. (2023) (1)	24-year-old, female	Chest pain, SOB, generalized body swelling, weight loss, cough, paroxysmal nocturnal dyspnea, orthopnea, palpitation, dizziness; grade 4/6 pansystolic murmur at the left mid-sternal border, loud, nonsplitting pulmonary component of S2	Unruptured	Grade 2 AR, bidirectional perimembranous VSD 1.1 cm	TTE	N/A	N/A	N/A
Mhanna et al. (2022) (2)	23-year-old, female	Palpitations, exertional dyspnea; continuous murmur; HR 110 bpm	Ruptured	AR	TEE	Ruptured 1.8 cm SOVA of the non-coronary cusp to the right ventricle, with significant left-to-right shunt and pulmonary hypertension	Surgical correction	Significant resolution of the shunt, pulmonary pressure was normalized
Kumar et al. (2016) (3)	24-year-old, male	Gradually progressive SOB and palpitations on exertion; grade 3/4 early diastolic murmur over the aortic area, wide pulse pressure with presence of peripheral aortic run off; two previous syncope episodes	Unruptured, dissecting into IVS	Severe AR, perimembranous VSD	TTE TEE	LVEF 40%, LVEDD of 5.4 cm, LVESD of 4.0 cm; aortic annulus dilated 3 cm; severe AR without evidence of leak into any of the chambers	Repair and closure of the right SOVA with Dacron patch	Completely healed and thrombosed aneurysmal sac within the IVS
Hyung Rae Kim et al. (2015) (4)	20-year-old, male	Chest pain, HF symptoms, history of VSD	Ruptured	Perimembranous VSD 1 cm	TTE Exercise treadmill test TEE	LVEDD of 52 mm, LVESD of 31 mm, Qp/Qs 1.2; RV enlargement with depressed function, preserved LV function; elongated right SOVA with ruptured tip	Open heart surgery - ruptured aneurysm and perimembranous VSD were closed with Dacron patch	Uneventful postop period, without residual shunt
Kumar et al. (2015) (5)	21-year-old, male	Progressively worsening effort dyspnea, long early diastolic murmur heard best over the third left intercostal space, prolonged PR interval	Ruptured, through the IVS into LV cavity	AR, cardiac conduction abnormality	TTE Right heart catheterization Aortic root angiography	Ruptured aneurysm with flow arising from the right sinus of Valsalva, traversing the IVS into the LV; LV dilatation and global hypokinesia	Right aortic sinus defect was successfully repaired with a Dacron patch	Uneventful postop period, symptomatically improved

AR: aortic regurgitation; HR: heart rate; HF: heart failure; IVS: interventricular septum; LV: left ventricle; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; N/A: not available; RV: right ventricle; SOB: shortness of breath; SOVA: sinus of Valsalva aneurysm; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography; VSD: ventricular septal defect

Amplatzer vascular plug (AVP II)), which has emerged as an effective alternative in carefully selected patients, revealing promising results (9). However, it is worth noting that, due to the thickness of the non-coronary cusp (NCC) and its proximity to the AV conduction system, occurrence of complete heart block after transcatheter closure of perimembranous VSD has been reported as a perturbing complication; however, a good response to high-dose steroids has been observed in such cases (9). Another option is surgical intervention, in case of rupture or without rupture, if there is a ventricular septal defect or significant aortic valve regurgitation (6). Options for surgical treatment

are the Bentall procedure, or preserving the valve with an aortic valve suture annuloplasty technique involving external stabilization of the annulus following the remodeling of the aortic root, although there is no clear evidence that preserving the valve should be an option before the classic replacement of both the aortic root and valve (10). In current practice, for specific isolated ruptured sinus of Valsalva aneurysm cases or those including a combination with perimembranous VSD, percutaneous closure employing modified double-disk occluders (which are easily retrievable, repositioned, flexible, non-space occupying, without affecting aortic valve function) is a compelling alternative to surgery; in fact, percutaneous closure has been found to be more therapeutically advantageous than surgical closure due to the avoidance of extracorporeal circulation, intensive care unit stay, and blood transfusion, as well as a shorter hospital stay and minimal invasiveness (10). In patients with mechanical aortic valve, transcatheter closure of ruptured sinus of Valsalva aneurysm with double-disc (shorter in length) perimembranous VSD occlude is a viable method for successfully repairing ruptured sinus of Valsalva aneurysms; compared with the Amplatzer Duct Occluder, thus avoiding iatrogenic right ventricular outflow tract (RVOT) obstruction (8,9). On the whole, ruptured SOVA has a poor prognosis with high mortality (3.6%) unless timely intervention is undertaken (6).

CONCLUSION

Clinicians ought to remain cautious about sinus of Valsalva aneurysm in young patients presenting with signs and symptoms of cardiac conduction abnormalities or myocardial ischemia and heart failure. The most conspicuous physical finding is a new continuous murmur, prompting urgent echocardiography to enable timely diagnosis and treatment of the aneurysm. Unruptured aneurysm of the right coronary sinus of Valsalva cases in young patients are rare and detected incidentally. Surgery is indicated when SOVA is in conjunction with a VSD and aortic valve involvement, due to likelihood of rupture. In the event of a ruptured SOVA with perimembranous VSD, treatment modalities include not only surgical repair, but also transcatheter closure in carefully selected patients. Yet, the prognosis is poor if no prompt diagnosis is made.

Acknowledgment: We thank our colleagues Alden Begic, Nihad Kukavica, and Fuad Zukic for their assistance in the diagnostic evaluation of the patient.

Declaration of patient consent: The patient gave consent after receiving information about writing the case report.

Authors' Contributions: Conceptualization: Edin Begic, Zorica Mladenovic. Formal analysis: Edin Begic, Zorica Mladenovic, Buena Aziri, Zorica Hondo, Mirad Hujdur. Methodology: Edin Begic, Zorica Mladenovic. Project administration: Edin Begic, Zorica Mladenovic. Resources: Edin Begic, Zorica Mladenovic. Software: Buena Aziri. Supervision: Zorica Mladenovic. Visualization: Edin Begic, Zorica Mladenovic, Zorica Hondo. Writing – original draft: Edin Begic, Zorica Mladenovic, Buena Aziri, Zorica Hondo, Mirad Hujdur. Writing – review & editing: Edin Begic, Zorica Mladenovic, Buena Aziri, Zorica Hondo, Mirad Hujdur.

Financial support and sponsorship: There was no funding.

Conflict of interest: The authors have nothing to disclose.

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Images in Medicine

Malposition of the Aortic Valve After TAVI with Consequent Severe Aortic Regurgitation

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Pages: 52-53 / Published online: 9 Jul 2024

Cite this article: Milic G, Mladenovic Z. Malposition of the Aortic Valve After TAVI with Consequent Severe Aortic Regurgitation. Sar Med J. 2024; 1(1): Online ahead of print. DOI: 10.70119/0010-24

Original submission: 24 March 2024; **Revised submission:** 17 June 2024; **Accepted:** 24 July 2024

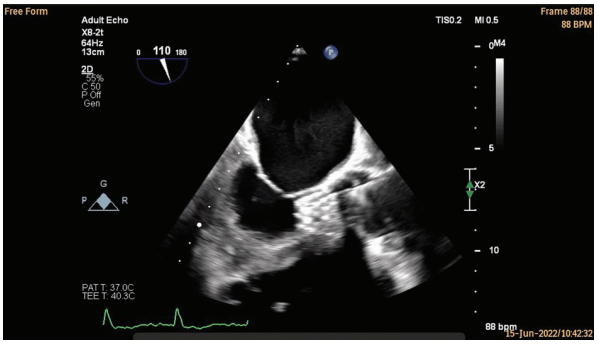

Figure 1. 2D transoesophageal echocardiography – Long axis (LAX) aortic bioprostheses malposition with displacement towards left ventricular outflow tract (LVOT)

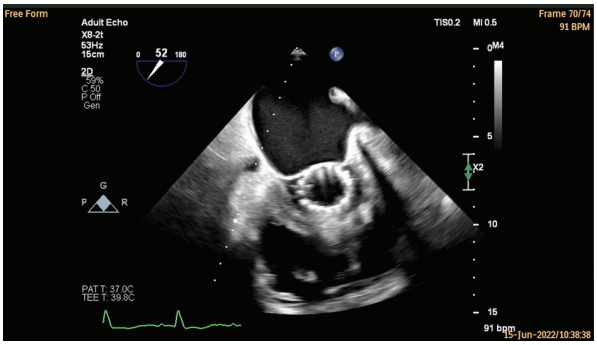

Figure 2. 2D transesophageal echocardiography – Short axis (SAX) aortic bioprothesis dehiscence

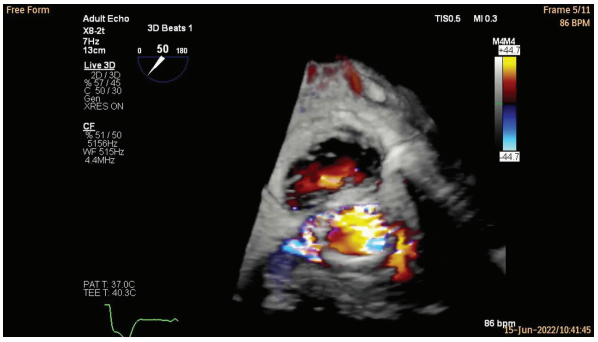

Figure 3. 3D Color transesophageal echocardiography – SAX visualization of paravalvular leak

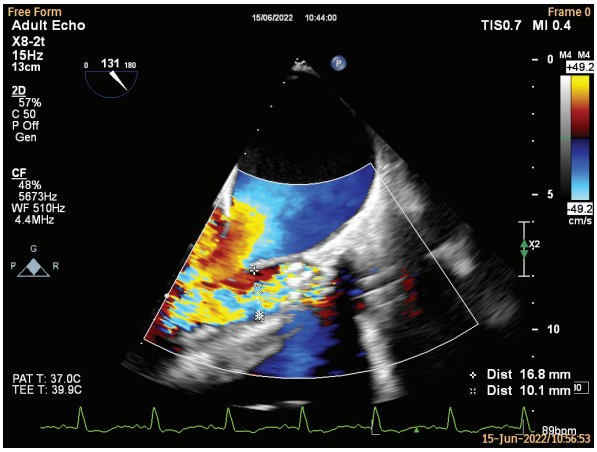

Figure 4. 2D Color transoesophageal echocardiography – LAX moderate to severe aortic regurgitation due to aortic bioprostheses malposition (AR/LVOT 60%)

Male, 63 years old, with a long-term history of ischemic heart disease. After an myocardial infarction 20 years ago, a surgical revascularization was performed with left interior mammary artery (LIMA) - left anterior descending (LAD) bypass. Elective percutaneous coronary intervention (PCI) with the implantation of one bare metal stent in the circumflex artery was done 4 years ago. During this procedure, an indication for transcatheter aortic valve implantation (TAVI) was set due to the progression of stenosis gradient in the bicuspid aortic valve.

Immediately after the TAVI procedure, the patient developed symptoms and signs of acute heart failure due to the malposition of the aortic valve and consequent severe aortic regurgitation (AR)(1).

The images depict a transesophageal echocardiographic examination after TAVI (Figure 1-4). Severe AR with paravalvular jets is the result of the malposition of the biological valve after TAVI, where the valve partially occupies the left ventricular outflow tract. The inadequately positioned aortic valve was surgically removed, followed by the implantation of a mechanical aortic valve. Subsequently, as the patient was dependent on a temporary pacemaker, a permanent dual-chamber pacemaker was implanted. Following the surgical treatment, the patient recovered successfully (2,3).

Consent: The authors have obtained written consent from the patient to submit and publish this case report, including images and accompanying text, in accordance with COPE guidelines.

Authors' Contributions: Gordana Milic and Zorica Mladenovic participated in the conceptualization, methodology, formal analysis, visualization, writing (original draft), and review & editing of the paper.

Conflict of interest: None declared.

Funding: None declared.

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Images in Medicine

Contrast-Enhanced Ultrasound (CEUS) for Evaluating Indeterminate Liver Lesions During Pregnancy: A Case Report

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Pages: 54-55 / Published online: 9 Jul 2024

Cite this article: Smajlovic A. Contrast-Enhanced Ultrasound (CEUS) for Evaluating Indeterminate Liver Lesions During Pregnancy: A Case Report. Sar Med J. 2024; 1(1): Online ahead of print. DOI: 10.70119/0011-24

Original submission: 26 March 2024; **Revised submission:** 19 June 2024; **Accepted:** 28 July 2024

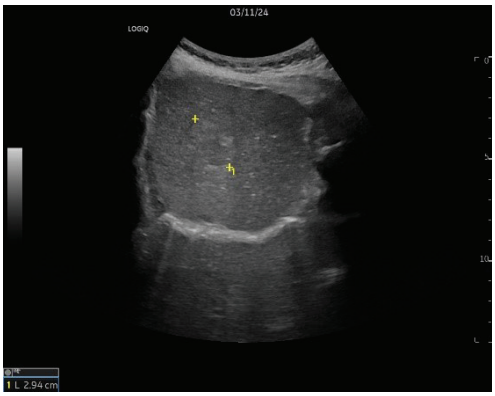

Figure 1. Detected liver lesion

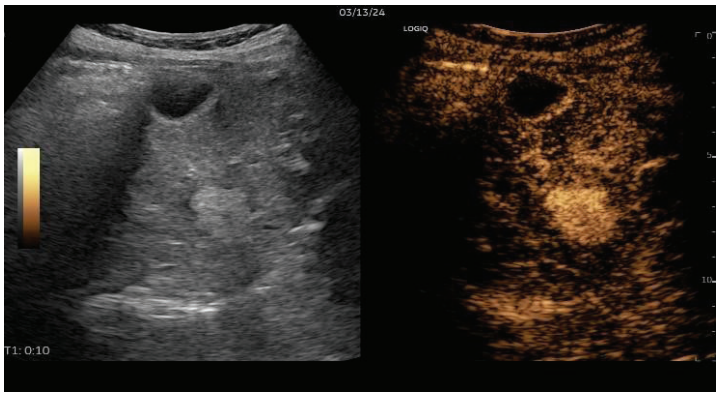

Figure 2. Arterial phase (10 seconds)

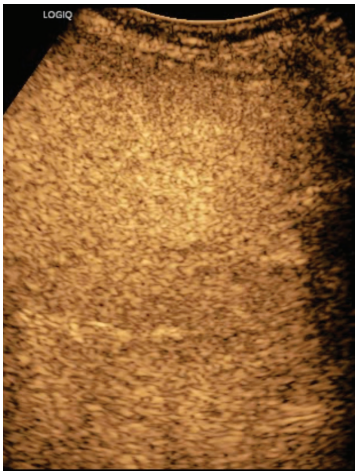

Figure 3. Delayed phase (120 seconds)

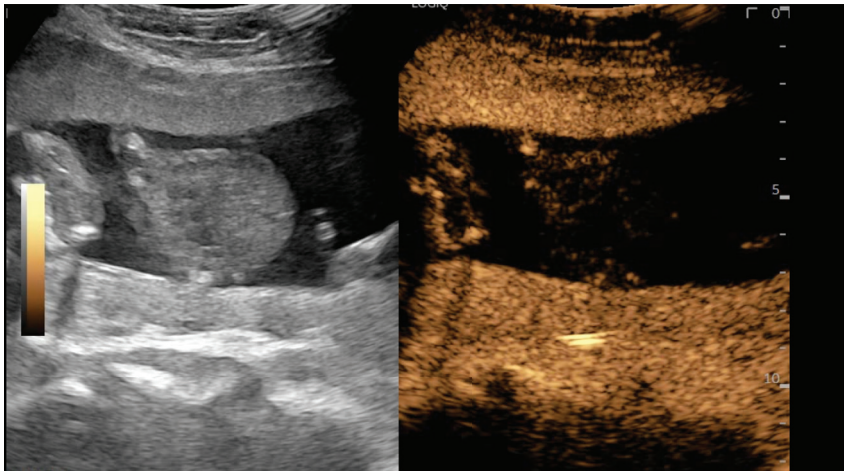

Figure 4. No contrast in baby (artifact is from bones)

We report a case of a 34-year-old woman diagnosed with HER2-positive breast cancer at 12 weeks of pregnancy. The oncology team opted for neoadjuvant chemotherapy while continuing the pregnancy. To exclude metastatic liver disease, CT was not feasible due to radiation risks, and liver MRI was avoided due to concerns about gadolinium deposition in the fetal basal ganglia.

At 16 weeks of pregnancy, an abdominal ultrasound revealed an indeterminate liver lesion in segment VIII, measuring 30mm and

mostly isoechoic (Figure 1). To further evaluate the lesion, we performed a contrast-enhanced ultrasound (CEUS) using 1,8ml of a microbubble contrast agent intravenously.

Current evidence suggests that microbubble contrast agents do not cross the placental barrier (1).

To our knowledge, only two studies have been conducted on eleven patients. Although off-label, this data supports the safety and efficacy of microbubble contrast agents in pregnancy (2,3).

During the arterial phase, the lesion showed quick centrifugal enhancement (Figure 2), and in the portovenous and delayed phases, there was no washout (Figure 3), suggesting a benign lesion typical of focal nodular hyperplasia (FNH). No other liver lesions were detected. The baby was briefly checked afterwards, with no contrast beyond placenta and normal heartbeat (Figure 4).

Consent: The authors have obtained written consent from the patient to submit and publish this case report, including images and accompanying text, in accordance with COPE guidelines.

Author Contribution: Conceptualization, Formal Analysis, Methodology, Writing – Original Draft, and Writing – Review & Editing were carried out by Ajdin Smajlovic.

Conflict of interest: None declared.

Funding: None declared.

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