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REVIEW

Genomic Sequencing in Precision Medicine: Applications, Interpretation and Limitations

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Abstract

Genomic sequencing (GS) has become a cornerstone in precision medicine (PM), facilitating the identification of genetic variants linked to disease susceptibility, diagnosis, and treatment customization. Leveraging next-generation sequencing technologies, including whole-exome sequencing (WES) and whole-genome sequencing (WGS), GS provides unparalleled insights into genetic underpinnings of rare diseases, cancers, and multifactorial conditions. WES focuses on protein-coding regions, efficiently identifying pathogenic variants, while WGS offers comprehensive genomic coverage, enabling the detection of structural and non-coding variants. Despite its transformative potential, GS faces limitations such as variant interpretation challenges, lack of exhaustive annotation for non-coding regions, and variability in clinical significance assessment. The integration of variant databases like ClinVar and GnomAD, alongside machine learning-driven annotation, has improved variant prioritization and clinical applicability. However, the implementation of GS in clinical practice remains hampered by knowledge gaps among healthcare providers and inconsistencies in defining actionable mutations. Emerging techniques such as spatial transcriptomics and single-cell genomics, coupled with multi-omics data integration, promise to address these challenges, enhancing the precision and utility of GS in PM. This review highlights GS's clinical applications, including early disease risk detection, targeted therapeutics, and oncogenomic advancements, while addressing its interpretive and operational barriers. Future directions emphasize technology innovations and interdisciplinary strategies to maximize GS's clinical impact, positioning it as a critical tool in the era of personalized healthcare.

Keywords: Precision Medicine, Next Generation Sequencing, Rare Diseases, Oncogenomic, Spatial Transcriptomics

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INTRODUCTION

Precision medicine (PM) is a relatively new approach in modern medicine. It is used to categorise individuals or demographics based on disease susceptibility or treatment response (1). PM is generally seen as the future of medicine because it offers a holistic approach and integrates omics, electronic health records, and environmental data, to provide diagnosis. PM has grown tremendously due to novel tools and techniques, such as genomic sequencing (GS) and computational algorithms for omics analysis.

The precision and cheapness of next-generation sequencing (NGS) played a vital role in the rise of PM. There are certain diseases that the conventional diagnostic approaches are unable to identify, whereas GS can be used to identify disease-causing gene variants to provide a targeted therapeutic approach or personalised medicine. For example, rare diseases are almost exclusively of genetic origins (2). These diseases, such as cystic fibrosis, are often identified by genetic testing. Genetic testing is often beneficial in these situations because it can be used to identify inherited mutations. However, GS detects disease-causing mutations with no observable phenotypes or inheritance patterns, offering a wider scope.

This review explores the applications, limitations, challenges, and interpretation of GS in PM. Also, the future direction of the technique is discussed.

Genomic Sequencing

GS detects the arrangements of DNA nucleotides in the genome. NGS allows for the sequencing of numerous genes via a single test. NGS has been widely adopted in clinical settings and could replace existing genetic testing methods (3). GS is preferred because it can be used to test and generate hypotheses (4). The common GS types are discussed below.

Targeted Sequencing (TS)

TS targets specific genetic regions and can detect insertion-deletions (INDELs), duplications, and single-nucleotide variation (SNV) associated with known phenotypes (5). The various targeted gene panels available on the market are due to population-wide studies performed using whole-genome sequencing (WGS)/whole-exome sequencing (WES). TS is the most cost-effective technique while offering a high sequencing depth. However, TS offers the least genomic coverage. Additionally, due to its design, adding new genes to the panel is difficult.

Whole-exome Sequencing

WES is focused on the genomic coding region, where most of the disease-causing variants exist (5,6). In PM, WES is advantageous because it can be used to query approximately 20,000 protein-coding regions for copy number variation (CNV), INDEL and SNV simultaneously (5). WES offers advantages, such as high sequencing depth and mitochondrial mutation detection, at a cheaper rate. Furthermore, fewer variants are identified, so, interpretation is not usually difficult. Conversely, WES offer less genomic coverage, so, detecting rare-disease-causing variants is difficult.

Whole-genome Sequencing

WGS is used to produce the entire DNA sequence of an individual. WGS is useful in oncology, rare disease genetics, genome assembly, and population genetics (7). Due to its coverage, WGS can detect single-nucleotide polymorphisms (SNPs), INDELs, and structural variations (SV) (4). The numerous information WGS provides makes it useful in PM (8). Potentially, WGS can be used to identify sequence repeats and mitochondrial mutations.

The challenge with WGS is that not all the genetic variants detected will have clinical significance (9). WGS data is bound to contain variants of unknown significance (VUS). To tackle this problem, for example, for cancer, there are databases containing VUS, variants with disease association, and variants with drug discovery or implication (10). These databases will help improve our knowledge of VUS and their potential disease associations. Additionally, the sequencing depth is somewhat lower, making WGS less sensitive to detecting genetic variants of low frequency.

WGS can be done using short-read or long-read protocols. Short-read protocols are characterised as having a few hundred base pairs (bp). Long-read protocols, on the other hand, have reads that span between 10 k bp to megabases (8). In population screening for rare diseases, long-read WGS is the preferred method because it can be used to identify haplotypes, sequence repeats, and SV (11). Short-read sequencing is useful when aiming for

high sequence depth and precision – making it relevant for expression analysis (11). The choice of which protocol to employ often depends on the objectives of the study.

The process involved in WGS data generation for precision medicine is triphasic, namely primary, secondary and tertiary. The primary phase involves DNA extraction, DNA library preparation, and sequence quality control. The secondary phase deals with filtration and sequence alignment, specifically to the annotated human genome. The tertiary phase involves variant calling and annotation, then interpretation.

In PM, WES/WGS are diagnostic tools for detecting already known disease-causing variants and genes. However, for WGS to properly detect pathogenic variants in non-coding regions, exhaustive annotation of said region is vital. In many clinical settings, WES and WGS are used in conjunction.

Interpreting Variants Observed in GS Analysis
Candidate Variant Annotation and Prioritisation

Before a causal link between a variant and a disease trait can be established, function annotation and prioritisation must be done. Variant annotation is achieved by integrating Human Phenotype Ontology terms into the VC (Variant Classification) data. Afterwards, algorithms focused on mutation tolerance and architecture can be used to candidate genetic variants associated with disease phenotypes (12).

Variant Databases and Frequency Analysis

Variant databases are another useful analytic tool for elucidating the correlation between genetic variants and diseases. The frequency analysis alongside other annotations for genetic variants are uploaded to these databases. To conclude that a variant is pathogenic, the frequency of that specific variant must be known. Although frequency analysis alone is not sufficient to ascribe pathogenicity to a variant, it can still be used to prove a plausible relationship between a variant and disease phenotype (13). Examples of variant databases are ClinVar, dbSNP, HGMD, and GnomAD.

Significance of Variants in Medical Practice

The last and most important step in genetic testing is to determine the medical significance and pathogenic/non-pathogenic nature of variants. Before a variant can be categorised as pathogenic, there must be sufficient evidence in the variant database at the segregation, functional, computational, and population levels. So, variants with little information are categorised as VUS (13). Additionally, in silico techniques can be used to predict variant phenotypic relevance via machine learning (14).

The American College of Medical Genetics and Genomics (ACMG) Classification of Variants

The interpretation of observed variants in WGS analysis culminates with the proper categorisation of said variants. The ACMG categorised variants into five distinct groups: VUS, likely benign (LB), benign (B), likely pathogenic (LP), and pathogenic (P) (15). The ACMG categories only account for disorders or diseases that follow a Mendelian inheritance pattern. However, some diseases are multifactorial and multilocus, and may not follow Mendelian genetics. Furthermore, although the ACMG categorisation makes room for unknown significance, there are yet variants that would not fit into the benign-pathogenic dichotomy (16). Some improved variant classifications include the causal-predisposing method (17) and the ABC system (18). The ABC system is still under research and development and is not yet a standardized approach.

Current Applications of Sequencing in PM

A few studies reported that WES was used in clinical settings to obtain diagnoses 25-50% of the time, although the rate was lower in adults (19-21). A study comparing the diagnostic rate of WES to gene panels reported that WES improved the rate from 22-38% (22). Additionally, WES was used to detect rare Mendelian diseases in 13/57 children (23). FANCM was identified as a risk for triple-negative breast cancer via WES (24). Similarly, unreported mutations in CCNF, ACCS, TH, XCR1, DLL1, SPPL3, and SRL were linked the breast cancer occurrence through WES (25). Interestingly, a mutation (in SF3B1) was discovered to have an anti-oncogenic effect, making it a potential drug target, by using WES and WGS (26).

Although BRCA1/BRCA2 are popular genes associated the breast cancer predisposition, their mutations only account for about 24% of cancer mutations (27). Thus, making it difficult to detect breast cancers in individuals

with non-BRCA1/BRCA2 mutations. WES, however, has been successfully used to discover significant locus heterogeneity in cancer patients who do not present with BRCA1/BRCA2 mutations (28).

WGS can be used to prophylactically address disease-causing or -predisposing genes in infants. Essentially, WGS allows for early disease discovery. In oncogenomics, WGS has been used in the early identification of somatic variants in tumours, with a significant risk of cancer development (29). Furthermore, WGS was used to diagnose Glut1 deficiency syndrome, BRCA1/BRCA2 mutations, and CTPS1 mutation in old and young patients (2). WGS has also been used to identify 2,000 loci associated with common diseases, of which over 90 risk loci are linked with breast cancer (30).

User Cases of GS in PM

In a study of 108 individuals, where chromosomal microarray and WES techniques did not yield any diagnosis, however, it was reported that WGS provided a diagnosis in 7 cases by identifying variants in ADAT3, PHOX2B, TPM3, SLC35A2, and TSC2 (31). Vassy et al. used WGS as a screening tool where to find unidentified disease risk (loci) in 11/50 adults, pharmacogenomic allelic variants in 48/50, and those with high risk for 8 cardiometabolic conditions (32). These reports suggest that, in most cases, WGS has proven useful in disease detection over WES.

Targeted treatments involving modelling treatment based on disease genome have proved beneficial in treating cancer patients. Patients with ovarian, melanoma, pulmonary, and colorectal cancer who were administered treatments based on their cancer's mutation showed a better response rate (22% more than the control) and survival (lived 4 months longer than those who did not receive sequence-specific treatment) (33). Similarly, patients who received cancer therapy based on the disease's CNV or mRNA levels had higher progression-free survival (37 days) than those who did not (34).

In early disease risk discovery, WGS was used to identify novel mutations, a nonsense mutation in MLKL and a point mutation in OR51G1, associated with Alzheimer's disease (35). Additionally, WGS was used to detect unreported common and rare variants in long non-coding RNA, TENM3 and PARK7 genes associated with age-related macular degeneration (36).

Challenges and Limitations of GS in PM

The difference between sequence-based and non-sequence-based treatment cohorts in PM makes it difficult to assess the benefits (33). For instance, certain cancers present with a high mutation rate and targetable mutations, while some cancers may not. Also, what is the delineation scale for targetable mutation? There are instances where patients with targetable mutations are unable to receive sequence-based treatment simply because they did not meet a criterion (37). Many studies that claim sequence-based treatment targeting mutations offers therapeutic benefits are often vague in their definition of targetable mutation. Another challenge of GS implementation in PM is the inability of some physicians to interpret genomic data. Bryce et al. reported that 52% of oncologists were either mildly uncomfortable or totally uncomfortable interpreting GS results (38), which would prevent patients from exploring this option.

Sometimes using WGS alone is insufficient to obtain a diagnosis, especially when the condition has a complicated genetic and epigenetic basis (32). Non-Mendelian disease phenotypes are such examples. This limitation can be overcome through trio testing (32). Another limitation of is WGS the difficulty in determining the clinical significance of non-coding variants. This knowledge gap prevents the complete utility of WGS in clinical practice. Some pathogenic variants are often flagged as false positives because they have a low penetrance. However, these variants are actually pathogenic. By increasing the statistical power of WGS-based association studies and accounting for linkage disequilibrium, this limitation could be overcome (27).

These challenges and limitations highlight the issues that need to be addressed for the complete utilisation of GS in clinical diagnostics. Although the data produced by GS is large, expertise is needed for correct interpretation, as misinterpretation can cause grave medical errors.

Future Directions of GS

Utilising novel technologies such as spatial transcriptomics, nanopore sequencing, and single-cell genomics, can expand the usefulness of WGS to precision medicine. These technologies can be used to get robust details on gene expression and the resulting metabolomics. Additionally, more information on the pathogenesis and tissue molecular structure of the resulting

disease phenotype can be obtained (39, 40). Integration of WGS data with multi-omics data into an extensible multimodal framework will help interpret the aspects of WGS data that are yet unexplained (41, 42).

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Abbreviations list

GS: Genomic sequencing
PM: Precision medicine
WES: Whole exome sequencing
WGS: Whole genome sequencing
NGS: Next generation sequencing
DNA: Deoxyribonucleic acid
RNA: Ribonucleic acid
TS: Targeted sequencing
INDELs: Insertion-deletions
SNV: Single nucleotide variation
SNPs: Single nucleotide polymorphisms
SV: Structural variations
VUS: Variants of unknown significance
CNV: Copy number variation
VC: Variant classification

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ORIGINAL ARTICLE

Assessment of Fever Phobia and Fever Management in Mothers of Febrile Children Admitted to Hospitals in Northwestern Syria: A Fever Phobia Survey Study

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Abstract

Background: Childhood fever is a natural, positive biological strategy developed by the body to protect the child from potentially harmful foreign agents. Complaint of fever that worries families because it causes discomfort to children and is externally recognizable, and it is one of the most common reasons for presentation to pediatric emergency departments.

Methods: This study was conducted on the mothers of children aged 0-6 years admitted to the emergency departments of Cobanbey and Azaz Vatan Hospitals using the face-to-face interview technique.

Results: Over half of the mothers chose to administer antipyretic syrup as a first line of treatment, while one-third of the mothers initiated antibiotic therapy without seeking medical advice when their children had a fever. In addition, the decision to lower the body temperature was based on concerns that the child might have a seizure and/or be harmed due to high temperatures.

Conclusion: Education for mothers can improve care for children with fever and reduce unnecessary emergency room visits and the use of antibiotics and antipyretics. It may be useful for civil society organizations and state-based institutions to create opportunities for access to education and information in humanitarian aid activities in these and similar regions.

Keywords: Antipyretic, Body Temperature Changes, Hyperthermia, Syria.

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INTRODUCTION

Childhood fever is a natural, positive biological strategy developed by the body to protect the child from potentially harmful foreign agents. Fever provides some survival benefits to the child but has a significant metabolic cost (1-3). Fever is a coordinated increase in body temperature following infectious disease, inflammation, malignancy, immunization, or administration of certain medications (4-7). Febrile diseases can also cause morbidity and mortality in children (8,9). In this case, fever is perceived by caregivers not as a symptom or sign of an underlying disease, but as a dangerous disease (10,11). Caregivers' perception that all fevers are harmful has been termed fever phobia, fever anxiety (12), or fever turmoil (2). This phobic behavior is common among parents, other caregivers, and even healthcare providers (4,7,13-15). This perception can lead to inappropriate medication practices, the waste of scarce resources, and the overuse of already overburdened healthcare facilities (13,16,17). In fact, worries families because it causes discomfort to children and is externally recognizable. It is one of the most common reasons for presentation to pediatric emergency departments (17-20).

It is not uncommon for families to employ inappropriate and potentially harmful methods for reducing fever, often driven by unwarranted fear and panic. The practice of alternating or combining antipyretics during a fever attack can result in irrational use. Such practices may result in confusion, inaccurate dosing, toxicities, and, in rare cases, mortality (14, 16, 17). The irrational use of antibiotics is also a common feature of this lack of knowledge and can result in concomitant risks such as antimicrobial resistance, antibiotic-associated diarrhea, and inflammatory diseases, including atopy associated with late-onset dysbiosis (17). Furthermore, inadequate knowledge of families regarding fever and its treatment, low maternal education, the number of children in the family, and the living environment have been identified as factors influencing maternal approaches to febrile children (18, 19, 21). While unnecessary and excessive use of antibiotics highlights antibiotic resistance, overuse of emergency departments increases the risk of emergency department crowding and the spread of infectious diseases. In areas such as Syria, where public health control is currently difficult, the use of uncontrolled health facilities and medicines may complicate the effective use of humanitarian aid. In particular, the characteristics of the mother who has assumed the role of primary caregiver for a child also influence the perception outcome in low-income countries. In the northern Syrian region, characterized by low income and a post-conflict environment with ongoing civil unrest, early marriage, and limited educational opportunities represent significant challenges for mothers assuming care roles. However, a considerable number of children in this region are brought to the emergency department with complaints of fever. The objective of this study is to ascertain the approach of mothers in the region to their febrile children; their level of knowledge regarding fever; their fear of fever; and their methods of management when fever occurs.

MATERIALS AND METHODS

Study Design

This study, using the face-to-face interview technique, was conducted on the mothers of children aged 0-6 years admitted to the emergency departments of Cobanbey and Azaz Vatan Hospitals. A total of 203 participants who accepted the survey and met the inclusion criteria were included in the study. The study was approved by the Ethics Committee of Hatay Mustafa Kemal University for Noninterventional Research (Meeting date: 06/05/2021, Number of decisions: 15); the relevant hospital administrations. In addition, the study was conducted in accordance with the "Declaration of Helsinki" by the World Medical Association on Ethical Principles of Helsinki.

The study was conducted at Cobanbey and Azaz Vatan Hospitals. The hospitals were established by Türkiye in 2018 and 2020 as part of its humanitarian aid program (22-24). Local Syrian doctors and healthcare professionals are employed at these hospitals, while Turkish healthcare professionals provide consultancy services (25). Patients are admitted to these two hospitals from the Cobanbey and Azaz Vatan centers and surrounding small settlements.

Participant Selection

The study included mothers of children aged 0-6 years admitted to Cobanbey and Azaz Vatan Hospitals Emergency Department, and subsequently hospitalized. Mothers who declined to participate in the survey or

who had a known mental disability or psychiatric disorder were excluded from the study. In cases where the child patient was admitted to the hospital, the biological mother was included in the study as part of a polygamous family. Those who agreed to participate in the survey were coded with the initials of their first and last names and the last two digits of their identification number (ID) numbers. This ensured participant confidentiality and prevented participant duplication.

Data Collection

The questionnaire was prepared in Turkish following a comprehensive review of the existing literature on fever phobia and subsequently translated into Arabic by sworn translators. To assess their appropriateness, simplicity, and importance, the questions were evaluated by Syrian specialist physicians selected according to their experience and competence in the relevant subjects. Following a pilot study involving twenty individuals, the necessary corrections were implemented, and the questionnaire was finalized. The questionnaire was intended to ask questions that would allow deeper information to be obtained. However, after the pilot study, questions that differed between the intended queries and participants' understanding were removed from the questionnaire. The first section of the questionnaire pertains to the sociodemographic characteristics of the participants, while the second section comprises an 11-item instrument designed to assess maternal knowledge and attitudes regarding fever. The sociodemographic data form included inquiries regarding the participants' age, gender, educational status, income, number of children, place of residence, home, and family type. The second part of the questionnaire addressed knowledge of fevers, methods of measurement, and attitudes towards fevers.

Statistical Analysis

Since there was no similar study in the region and the number of mothers was not clear, no sample calculation could be made. However, in order to reach as many mothers as possible, after obtaining ethics committee and administrative permissions, it was planned to administer the questionnaire to all mothers who visited emergency departments for a full calendar year and who agreed to be surveyed and accepted that they understood the questions and could answer them without hesitation

The statistical analysis of the study was conducted using the Statistical Package for Social Sciences (SPSS) software, version 28.0 for Windows (IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp., USA). The descriptive statistics for the variables are presented as median (minimum-maximum) and n (%).

RESULTS

A total of 203 mothers who met the established inclusion criteria and agreed to participate in the survey were included in the study. Two hundred mothers (98.5%) were married, while three (1.5%) were not. The mean age of the mothers was 30 years, with the youngest aged 15 years and the oldest aged 57 years. The median age at which the mothers gave birth for the first time was 19 years. The youngest mother was 14 years old, while the oldest was 33 years old. However, the age at first motherhood was predominantly concentrated between 16 and 20 years (n=147, 72.4%). A total of 58 participants (28.6%) had no formal education, 53 (26.1%) had completed primary school, 35 (17.2%) had completed middle school, 21 (10.3%) had completed high school, 25 (12.3%) had completed an associate degree, 9 (4.4%) had completed an undergraduate degree, and 2 (1.0%) had completed a postgraduate degree.

Of the participants, 60 (29.6%) resided in urban areas, 80 (39.4%) in rural counties, and 59 (29.1%) in rural villages. Of the mothers who participated in the study, 157 (77.3%) indicated that they resided in their place of origin, 25 (12.3%) in regular encampments, and 20 (9.9%) in irregular encampments. While 92 (45.3%) of the families of febrile children presenting to hospitals had a nearby health institution in the region where they lived, 111 (54.7%) did not.

Of the families in question, 129 (63.5%) were identified as nuclear families, while 72 (35.5%) were classified as extended families. Only 2 (1.0%) mothers lived alone. The mean monthly income of the families was 750 Turkish Lira (approximately 100 US dollars), with a minimum of 100 Turkish Lira (approximately 13.3 US dollars) and a maximum of 8000 Turkish Lira (approximately 1066.7 US dollars).

The mean number of children per mother is 3, with a minimum of 1 and a maximum of 8. The mean age of the children was 8 years, with a minimum age of 2 months and a maximum age of 40 years.

Twenty-five families (12.6%) had children who died due to the disease shortly after birth.

Evaluation of the responses provided by the mothers in the questionnaire regarding fever determined that 177 (88.1%) of mothers were aware of their children's fever status by feeling with their hands, 23 (11.4%) by using a thermometer, and 1 (0.5%) by employing both methods (Figure 1). With regard to thermometers, 61 (48.4%) of the mothers indicated that they had used a mercury manual thermometer, 62 (49.2%) had used a digital thermometer, and 3 (2.4%) had used an electronic thermometer (Figure 2).

In response to the question of where they measured their children's fever, 90 mothers (44.3%) indicated that they most frequently measured it on the skin, 37 (18.2%) at the mouth, 15 (7.4%) at the ear, 32 (15.8%) at the armpit, and 8 (3.9%) at the rectum. "62 (31.6%) of the mothers accepted 37 °C and above as fever, 73 (37.2%) accepted 38 °C and above as fever, 45 (23.2%) accepted 39 °C and above as fever, and 16 (8.2%) accepted 40 °C and above as fever.". The majority of participants (n=196, 99.0%) indicated that the fever should be lowered, while a smaller proportion (n=2, 1.0%) stated that it did not require lowering.

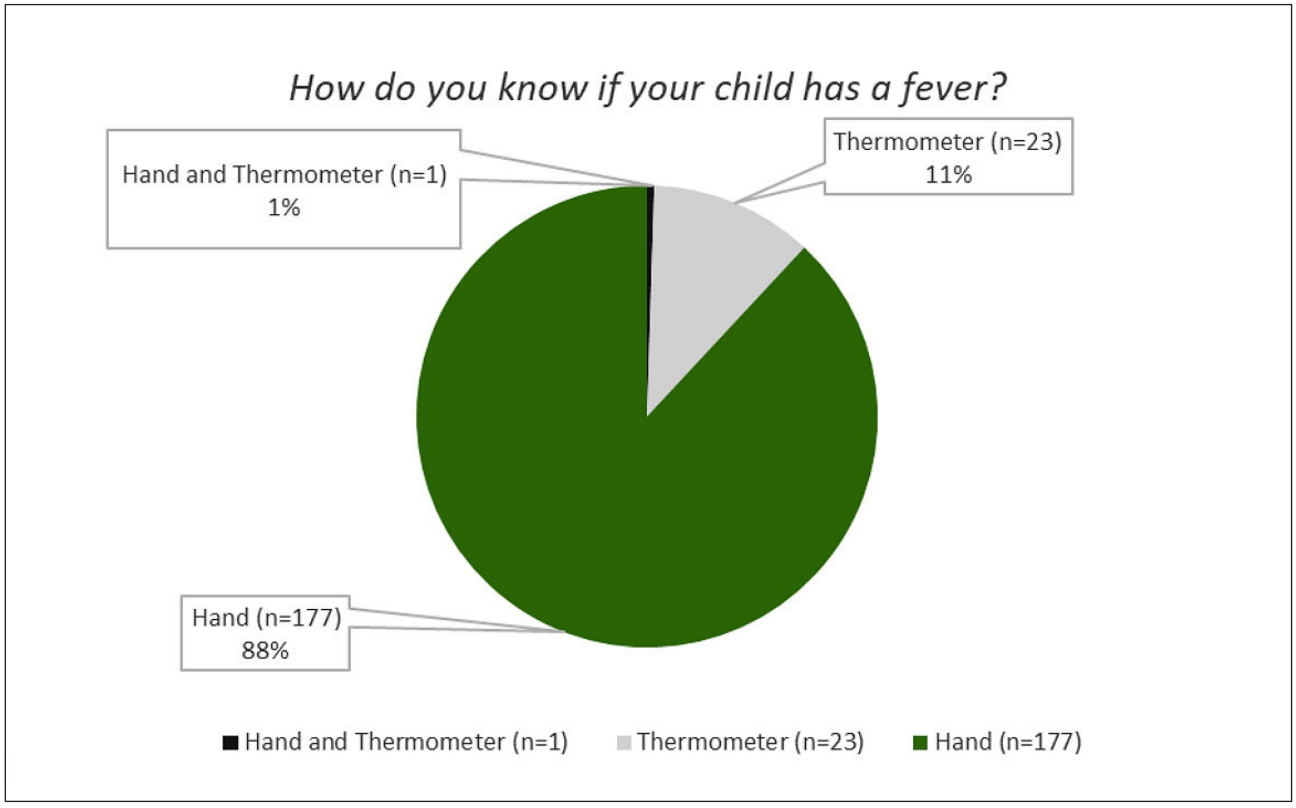

Figure 1: Distribution of participants' responses to the question "How do you know if your child has a fever?"

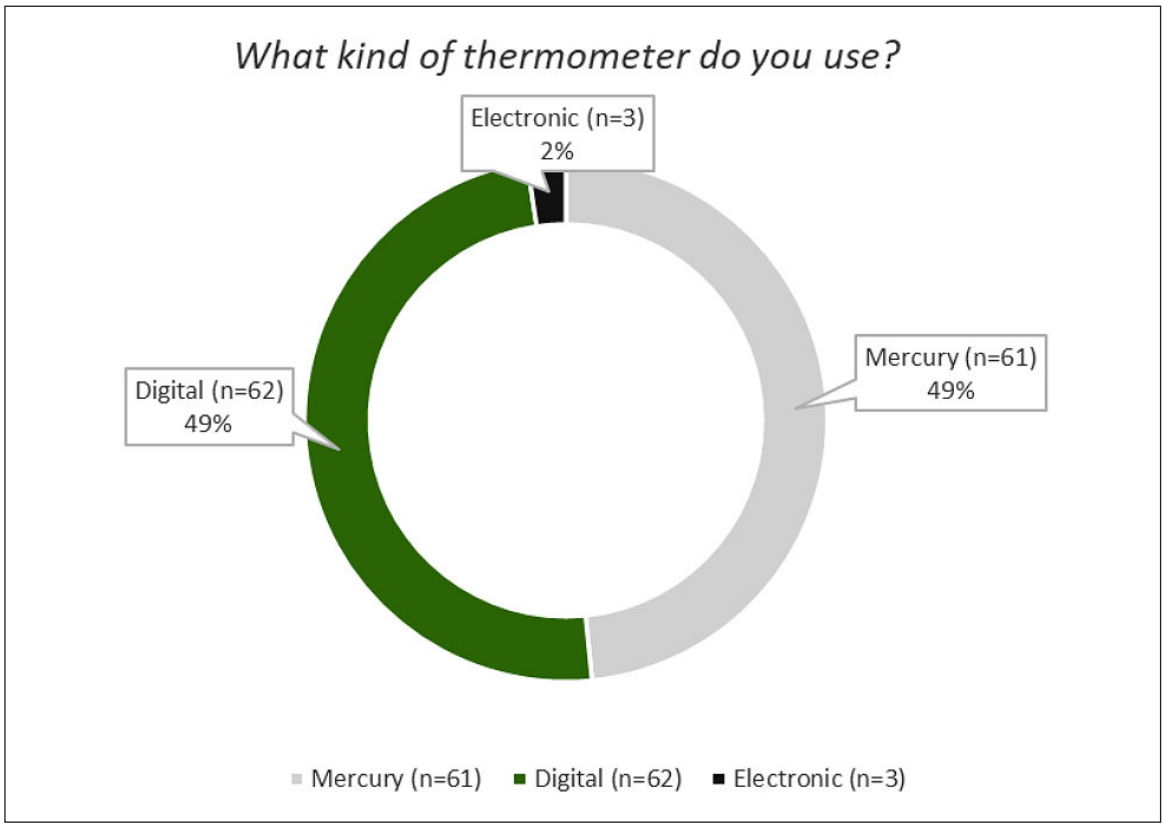

Figure 2: Distribution of participants' responses to the question "Which thermometer do you use?"

When the mothers were questioned about their actions when the child's fever began to rise, 82 (40.4%) stated that they took a lukewarm shower, 38 (18.7%) took a cold shower, 12 (5.9%) waited without taking any action, 13 (6.4%) covered the child, and 108 (53.2%) administered antipyretics.

When the attitudes of the participants were questioned in order to reduce the child's fever, 128 (63.1%) stated that they would give antipyretic syrup, 21 (10.3%) would take the child to the hospital immediately, 21 (10.3%) would call the doctor, 21 (10.3%) would use water with vinegar, 22 (10.8%) would take a warm shower, 34 (16.7%) would apply cold, and 1 (0.5%) would wait. 132 (65.3%) of the mothers stated that they used paracetamol, and 46 (22.8%) stated that they used ibuprofen.

Among the mothers of febrile children admitted to hospitals in Northwest Syria, 65 (32.5%) reported initiating antibiotic treatment without consulting a medical professional, while 135 (67.5%) stated that they did not. When asked why the fever should be reduced, 21 (10.3%) of the participants stated to prevent organ damage, 19 (9.4%) to prevent brain damage, 69 (34.0%) to prevent convulsions, and 104 (51.2%) to prevent the disease. With regard to the sources of information about fever in children, 130 (64.0%) of the mothers indicated that they received information from their families, 30 (14.8%) from doctors, 41 (20.2%) from midwives/nurses, 8 (3.9%) from television, 2 (1.0%) from radio, and 4 (2.0%) from social media.

The mean difference between the age of the mothers in the study and the age of their oldest child was 20 years (12–42 years). The minimum age difference between the mothers and their eldest child was 12 years, and the maximum was 42 years. In this case, it was determined that some mothers who participated in the survey gave birth to their first child under the age of 14, as reported by them. The average age difference between the mothers and their youngest child was 27 (12-46) years. The minimum age difference between the mothers and their youngest child was 12 years, and the maximum age difference was 46 years.

Table 1. Distribution of participants' answers about level of education, age at first birth and information about their children, and their preferences regarding information about fever and care for a febrile child.

Survey Questions	**n(%)**
Education level	
Illiterate	58(28.6)
Primary School	53(26.1)
Middle School	35(17.2)
High School	21(10.3)
Associate Degree	25(12.3)
Undergraduate Degree	9(4.4)
Post-Graduate Degree	2(1.0)
Age at first motherhood, Median (Min-Max)	*19(14-33)*
14	3(1.5)
15	9(4.4)
16	19(9.4)
17	28(13.8)
18	24(11.8)
19	32(15.8)
20	44(21.7)
21+	44(21.7)
How many children do you have, Median (Min-Max)	*3(1-8)*
1	39(19.2)
2	29(14.3)
3	45(22.2)
4	29(14.3)
5	32(15.8)
6	13(6.4)
7	8(3.9)
8	8(3.9)

Average age of your children	*8(2months-40 years)*
Did you experience the death of a child after birth?	
Yes	25(12.6)
No	174(87.4)
*If yes, cause of death**	
Diarrhea, fever	2(9.1)
Birth-related causes	11(49.9)
Hepatitis	4(18.2)
Cardiac Failure	1(4.5)
Consuming chemical substances	1(4.5)
Respiratory Distress	1(4.5)
Traffic Accident	2(9.1)
Which do you often prefer to take your child's temperature?#	
Mouth	37(18.2)
Ear	15(7.4)
Armpit	32(15.8)
Rectal	8(3.9)
Skin	90(44.3)
According to you, how many °C body temperature is considered fever?	
37 °C and above	62(31.6)
38 °C and above	73(37.2)
39 °C and above	45(23.0)
40 °C and above	16(8.2)
Should the fever be lowered?	
Yes	196(99.0)
No	2(1.0)
What do you do when your child's temperature starts to rise?	
Lukewarm shower	82(40.4)
Apply cold	38(18.7)
Wait	12(5.9)
Cover the child	13(6.4)
Administer antipyretics	108(53.2)

When your child has a fever, what do you do to reduce it?	
Administer antipyretic syrup	128(63.1)
Take the child to the hospital immediately	21(10.3)
Contact medical professional	21(10.3)
Use water with vinegar	21(10.3)
Lukewarm shower	22(10.8)
Apply cold	34(16.7)
Wait	1(0.5)
Other	2(1.0)
What is the antipyretic medicine you often use?	
Paracetamol	132(65.3)
Ibuprofen	46(22.8)
No	24(11.9)
Do you begin to give your child antibiotics without consulting your doctor?	
Yes	65(32.5)
No	135(67.5)
What is your reason for wanting to reduce the fever?	
Prevent organ damage	21(10.3)
Prevent brain damage	19(9.4)
Prevent convulsions	69(34.0)
Cure the disease	104(51.2)
Other	20(9.9)
Where did you learn about fever in children?	
Family	130(64.0)
Doctor	30(14.8)
Midwife/Nurse	41(20.2)
Television	8(3.9)
Radio	2(1.0)
Social media	4(2.0)

Min-Max: Minimum-Maximum. #: Multiple options can be checked. *Missing values are not included in the % calculation. Valid percent values are used.

DISCUSSION

The study revealed that approximately one-third of the mothers were unaware of the threshold for fever, with the majority seeking to lower the fever. Over half of the mothers chose to administer antipyretic syrup as a first line of treatment, while one-third initiated antibiotic therapy without seeking medical advice when their children had a fever. Additionally, the rationale for the decision to reduce the body temperature was the concern that the child would experience a seizure and/or suffer harm as a result of the elevated temperature. It was observed that more than half of the mothers had acquired the information that formed the basis for such attitudes and behaviors from their families, while the remaining portion had obtained the information from doctors, nurses, midwives, and mass or social media.

Encountering a new phenomenon can cause anxiety because of human nature. Mothers encounter many new situations with their first child. The mother may experience anxiety in response to either normal or abnormal situations involving the child. A lack of life experience and emotional maturity on the part of the mother may contribute to an increase in anxiety levels (26). As time progresses and society progresses, the age at which women give birth for the first time has also increased, and in many countries the average age is now over 28 years old (27, 28). However, due to significant socioeconomic inequalities between countries, the timing of the first birth varies considerably between different national contexts. At the national level, social norms and family policies may have an impact on the timing of the first birth. Societies have established norms regarding the optimal age for becoming a parent, which is often perceived as either premature or delayed (26). The European Social Survey revealed that the perceived ideal age for first birth is 25.3 years in France and 24.2 years in Great Britain (29). Consequently, contemporary trends are increasingly marginalizing early entry into motherhood, particularly during adolescence. This is particularly evident in Western countries, where adolescent motherhood is perceived as problematic not only for the mother but also for her child and society as a whole (29). Some studies in the existing literature indicate that the age at which women give birth for the first time varies according to their level of education. In the study by Rendal et al. evaluating developed countries, it was demonstrated that the age at first birth increased in accordance with the level of education, for the 1950s, and this phenomenon was even more pronounced in the subsequent years (30). Concurrently, Tomkinson et al. discovered that involvement in higher education had a detrimental impact on the likelihood of becoming a first-time parent (29). In the existing literature, socioeconomic status is also identified as a factor associated with the age at first motherhood. A low level of socioeconomic status is associated with a younger age at first motherhood; moreover, this low level may be related to a higher incidence of adolescent pregnancies (31). Furthermore, Rendal et al. demonstrated that the age of first childbirth was influenced by the employment status of women (30). The findings of Özel et al. (32) indicate that the age at pregnancy among Syrian immigrants in Türkiye is notably younger, with a significantly higher prevalence of adolescent pregnancies compared to Turkish pregnant women. In a more recent study, it was demonstrated that the aforementioned circumstances persisted in Syrian pregnant women who had resided in their current country for a minimum of 10 years (33). Sayili et al. investigated pregnant women in Turkey, and the mean age at first pregnancy in Syrian immigrant pregnant women was found to be 20.6 years, which was lower than the mean age at first pregnancy in Turkish pregnant women (34). In a further study conducted in Lebanon, it was determined that the majority of adolescent pregnancies were among Syrian immigrants (35). In a further study conducted in Aleppo as a sample from Syria, the age at first motherhood was found to be 18.9 years in women who had experienced violence and 20.3 years in women who had not experienced violence (36). In this study, the median age at first motherhood was found to be 19 years (range 14-33 years), consistent with the findings of previous literature. The age at first motherhood was found to be concentrated between 16 and 20 years.

Although modern thermometers are now used to detect fever, half a century ago the literature suggested that thermometers were not superior to hand contact measurement (37). In the following years, this situation was addressed with quantitative studies that demonstrated thermometers to be superior, but also showed that the success rate in detecting fever improved with greater experience in attempting to detect fever by hand measurement (38).

After 1980, subjective methods used by mothers to detect fever were evaluated in the literature, and it was found that 86% of mothers used measuring temperature by hand. In particular, when taking temperature from the trunk and abdomen by hand, the rate of correct detection of fever in the child was 71.4%, while 93.3% of mothers were able to detect the absence of fever in a child (39). In this study, it was determined that 88.1% of mothers knew that their child had a high fever by measuring it with their hands, 11.4% by using a thermometer, and 0.5% by using both methods, in line with the literature.

While the fact that the contact method is preferred over thermometers in half a century of literature reveals the importance of physical examination, it may suggest that spot fever measurement methods and devices may still need development.

Due to the risk of internal conflict and terrorism, neutral observers in home settings do not have the opportunity to observe mothers' practices and attitudes regarding fever management. The study did not include mothers who visited other private institutions or who could not come to the hospital. Direct verbal communication between the researchers and the participants could not be established, and communication was limited to interviewers and interpreters. For this reason, the participants were asked to select answers to direct questions in the study. This may have limited the participants' ability to freely provide more information.

The implementation of public education initiatives targeting mothers caring for febrile children could potentially lead to improved care for children with high fever and a reduction in unnecessary emergency admissions, antibiotics, and antipyretic use. It may be useful for civil society organizations and state-based institutions to create opportunities for access to education and information in humanitarian aid activities in these and similar regions. In these trainings, we believe that repeatedly explaining the correct fever measurement techniques to every mother visiting health units during pregnancy and teaching the correct use of thermometers can improve the care of children with fever and prevent unnecessary emergency admissions and drug use.

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Abbreviations list

ID: Identification number
SPSS: Statistical Package for Social Sciences

Ethics approval and consent to participate

This study was approved by the Non-Interventional Clinical Trials Ethics Committee of Hatay Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine on 06.05.2021 with decision number 16.

Consent for publication

Informed consent was obtained from all individual adult participants included in this study.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

All authors contributed at all stages.

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ORIGINAL ARTICLE

Comparison of Telescopic and Balloon Dissection Techniques in Total Extraperitoneal Inguinal Hernia Repair: A Retrospective Analysis

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Abstract

Background: Totally extraperitoneal (TEP) inguinal hernia repair involves creating a preperitoneal space with balloon dissection (BD) or telescopic dissection (TD). This study aimed to compare the outcomes of TD and BD techniques in TEP inguinal hernia repair in male patients.

Methods: A retrospective analysis was conducted on male patients who underwent TEP hernia repair by a single surgeon between November 2023 and November 2024. Patients were divided into two groups based on the technique used to create the preperitoneal space: BD or TD. Demographic data, operative outcomes, and postoperative pain scores were compared between the groups. Statistical significance was set at $p < 0.05$.

Results: A total of 49 patients were included, with 31 in the TD group and 18 in the BD group. The BD group had significantly shorter operative times (37.8 ± 15.8 vs. 45.6 ± 17.4 minutes, $p = 0.029$). Postoperative pain at the 3rd hour was significantly lower in the TD group (2.0 ± 2.1 vs. 3.0 ± 1.6, $p = 0.018$). Pain scores at later time points and other parameters, including peritoneal rupture rates and hospital stay duration, were comparable between the groups.

Conclusion: Both TD and BD are safe and effective techniques for TEP hernia repair. BD may reduce operative time, while TD offers superior early postoperative pain control. The choice of technique should be guided by patient characteristics, surgeon expertise, and cost considerations.

Keywords: Total Extraperitoneal Hernia Repair, Balloon Dissection, Telescopic Dissection, Postoperative Pain

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INTRODUCTION

Laparoscopic totally extraperitoneal (TEP) inguinal hernia repair is among the most frequently applied techniques for inguinal hernia (1). One of the critical steps in TEP hernia repair is the creation of an adequate preperitoneal space (PPS). Complications such as epigastric artery bleeding or peritoneal rupture during this step can obscure the surgical field and complicate the procedure (2). In such cases, it may be necessary to convert to a transabdominal preperitoneal (TAPP) approach or open hernia repair (3).

Balloon dissection (BD) is commonly used to create an adequate PPS. However, the blunt dissection caused by BD may lead to bleeding or peritoneal laceration (4). Another method for PPS creation is the telescopic dissection (TD) technique, which is hypothesized to allow for more controlled dissection under direct visualization (5). Recent studies have reported no significant differences in complications between the two techniques (2).

Studies comparing BD and TD in TEP hernia repair have yielded inconclusive results. Therefore, the present study aimed to compare these two techniques for creating an adequate PPS.

MATERIALS AND METHODS

This retrospective study included male patients who underwent TEP inguinal hernia repair performed by a single surgeon between November 2023 and November 2024. The study was approved by the local ethics committee (Gaziantep City Hospital Clinical Research Ethics Committee (2024/88, date: 20.11.2024)). Male patients over 18 years of age who underwent TEP hernia repair for inguinal hernia were included. Patients requiring emergency surgery, those with scrotal hernias, recurrent inguinal hernias, bilateral inguinal hernias, or a history of prior abdominal surgery were excluded. Patients with bleeding disorders and plegic patients were not included in the study. In addition, patients who did not speak Turkish and were illiterate were not included in the study.

Data were collected retrospectively from the hospital information system and patient files. Demographic data, surgical details, Numeric Rating Scale (NRS) pain scores (6), and other relevant information were recorded in an Excel file. Hernia dimensions were recorded according to radiological imaging results. Patients were divided into two groups: those who underwent BD group and those who underwent TD group.

Surgical Technique

A 10-mm incision was made below the umbilicus, and the rectus sheath was incised to lateralize the rectus muscle. In the BD group, a balloon trocar was inserted, inflated, and left for three minutes before removal. A 10-mm trocar was then placed. In the TD group, a 10-mm trocar was directly inserted, and the Retzius space was opened under camera guidance. Once the initial workspace was created, the remaining operational steps were the same for both groups. For both groups, two additional 5 mm working trocars were inserted along the midline, and a 10×15 cm polypropylene mesh was placed over the hernia sites after appropriate dissection. The mesh was fixed with two absorbable tackers to the Cooper ligament at the medial and posterior aspects of the transverse abdominis aponeurosis.

Pain Management

All patients received 1000 mg paracetamol intravenously every 8 hours after surgery. If patients had pain unresponsive to paracetamol, 100 mg tramadol was administered intravenously. Additional dose analgesic application was recorded in the Excel file.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 21. Continuous variables such as age, BMI, operative time, and postoperative NRS pain scores were expressed as mean ± standard deviation and analyzed using the independent sample t test. Categorical variables such as ASA grade and hernia type were analyzed using the Chi-square test or Fisher's exact test, as appropriate. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 49 male patients were analyzed, with 31 in the telescopic dissection group and 18 in the balloon dissection group. The groups had similar results in terms of age (42.8 ± 8.0 vs. 46.0 ± 4.3 years, $p = 0.332$), BMI (25.0 ± 2.8 vs. 25.7 ± 3.1 kg/m², $p = 0.198$), ASA scores, hernia types, hernia sides, and hernia diameters. The mean

operative time was significantly shorter in the balloon dissection group (37.8 ± 15.8 vs. 45.6 ± 17.4 minutes, p=0.029). Peritoneal laceration occurred in 9 patients in the telescopic group and 2 patients in the balloon group (p=0.147). Hospitalization duration was similar between groups (1.1 ± 0.4 vs. 1.0 ± 0.2 days, p=0.188) (Table 1). No complications occurred in any patient.

Postoperative pain at the 3rd hour was lower in the telescopic dissection group (2.0 ± 2.1 vs. 3.0 ± 1.6, p=0.018), while pain scores at the 6th, 12th, and 24th hours showed no significant differences (Table 2).

Table 1: Comparison of characteristics between the groups

Characteristics	Telescopic dissection (n=31)	Balloon dissection (n=18)	P value
Age (years)	42.8 ± 8.0	46.0 ± 4.3	0.332
BMI (kg/m2)	25.0 ± 2.8	25.7 ± 3.1	0.198
ASA score I II III	 21 6 4	 13 5 0	 0.257
Comorbidities Diabetes Hypertension	 4 4	 2 3	 0.854 0.717
Hernia type Medial Lateral Both	 6 22 3	 5 13 0	 0.349
Hernia side Right Left	 18 13	 7 11	 0.161
Hernia diameter (mm)	15.6 ± 5.0	14.8 ± 1.3	0.727
Operative time (minutes)	45.6 ± 17.4	37.8 ± 15.8	0.029
Peritoneal laceration (n)	9	2	0.147
Hospitalization day	1.1 ± 0.4	1.0 ± 0.2	0.188
Need additional analgesics	3	2	0.873

BMI=Body mass index, ASA= American Society of Anesthesiologists

Table 2: Comparison of postoperative pain between groups at 3rd, 6th, 12th and 24th hours			
Timing of the pain	**Telescopic dissection (n=31)**	**Balloon dissection (n=18)**	**P value**
Pain at 3th hour	2.0 ± 2.1	3.0 ± 1.6	0.018
Pain at 6th hour	1.9 ± 1.4	2.0 ± 1.1	0.783
Pain at 12th hour	1.9 ± 1.5	1.9 ± 0.7	0.771
Pain at 24th hour	1.7 ± 1.2	1.2 ± 1.0	0.188

DISCUSSION

This study evaluated the outcomes of telescopic and balloon dissection techniques in male patients undergoing TEP hernia repair. Our findings highlight the distinct advantages and comparable safety profiles of both methods, providing valuable insights for clinical decision-making.

The shorter operative time observed in the balloon dissection group aligns with previous studies emphasizing its efficiency in creating the PPS (7,8). This may be attributed to the occasional displacement of the inferior epigastric vessels and the time required for lateral dissection during PPS creation. Notably, increased peritoneal laceration during TD may narrow the surgical field and prolong operative time (7).

Peritoneal laceration during TEP hernia repair are among the leading causes of conversion to TAPP or open hernia repair (9). For surgeons in the early stages of their learning curve, identifying anatomical structures in a constricted field can be challenging, complicating the TEP procedure (10). The effectiveness of TD heavily depends on the surgeon's familiarity with the PPS. Thus, BD may be a more suitable option for surgeons early in their learning curve (2,11).

The telescopic dissection group demonstrated significantly lower pain scores at the third postoperative hour. However, pain scores between the groups equalized at the sixth postoperative hour and beyond, indicating that both techniques provide comparable mid- to long-term analgesic outcomes. Similar studies have also reported no significant differences in postoperative pain outcomes between BD and TD groups (7,12,13). Early pain control is critical for improving patient satisfaction and facilitating faster recovery, key components of enhanced recovery after surgery protocols (14).

Cost is another significant consideration in the choice of technique. Cost-effectiveness calculations depend on several factors, including the materials used, operative time, and length of hospital stay (15). While some studies have shown that the use of balloon trocars increases costs by over $350, others have reported smaller cost differences (8,16,17). These variations depend on the type of balloon used, with a wide range of brands available. Considering the reduced operative time with BD, debates remain about which technique is more cost-effective (18). Ultimately, cost-effectiveness must be evaluated based on multiple factors.

This research has certain limitations, including a limited sample size. The absence of long-term follow-up inhibits the ability to draw conclusions on hernia recurrence rates or chronic pain outcomes. In addition, the fact that the study was retrospective and did not conduct a cost analysis are other limitations. Subsequent research with larger cohorts, multicenter collaboration, and prolonged follow-up is essential to corroborate these results and evaluate their influence on long-term patient outcomes.

Both telescopic and balloon dissection techniques are safe for TEP hernia repair in male patients, each offering unique advantages. Balloon dissection is associated with shorter operative times, while telescopic dissection may provide better early postoperative pain control. The choice of technique should be tailored to individual patient characteristics, surgeon expertise, and cost considerations.

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Abbreviations list

ASA: American Society of Anesthesiologists
BD: balloon dissection
BMI: body mass index
NRS: numeric rating scale
PPS: preperitoneal space
TAPP: transabdominal preperitoneal
TD: telescopic dissection
TEP: total extraperitoneal

Ethics approval and consent to participate

Informed consent was obtained from all participants.

Consent for publication

It does not contain any personal data.

Availability of data and materials

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ORIGINAL ARTICLE

Effects of Supervised Aerobic Exercise Training on Weight Loss, Functional Capacity, Quality of Life and Depression Level in Patients With Essential Hypertension: A Non-Randomized Controlled Trial

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Abstract

Background: Hypertension is a major risk factor for cardiovascular disease, and aerobic exercise is recommended as complementary therapy for its management. This study aimed to evaluate the effects of a supervised aerobic exercise program on weight loss, functional capacity, quality of life (QoL), and depression level in patients with essential hypertension.

Methods: A non-randomized controlled trial with patient preference allocation was conducted. The participants were assigned to either a supervised aerobic exercise group (n = 91) or a control group (n = 47). The exercise group underwent a six-week supervised aerobic training program (five sessions per week), while the control group maintained their usual lifestyle. Outcome measures, including resting blood pressure, weight, body mass index (BMI), lipid profile, functional capacity (6-minute walk test, 6 MWT), QoL (SF-36), and depression level (Beck Depression Inventory, BDI), were assessed at baseline and after six weeks.

Results: The supervised aerobic exercise group showed significant improvements in the 6 MWT distance, SF-36 subscales (physical function, role physical, vitality, role emotional, and mental health), and reductions in resting systolic blood pressure, weight, BMI, and BDI scores compared to the control group ($p < 0.05$). Within-group comparisons further confirmed significant improvements in physical and mental health measures post-intervention ($p < 0.01$).

Conclusion: A 6-week supervised aerobic exercise program significantly enhanced functional capacity, QoL, and mental health in patients with hypertension. These findings support supervised aerobic exercise as an effective complementary therapy for hypertension, promoting both physical and mental well-being with no reported adverse effects.

Keywords: Supervised aerobic exercise, functional capacity, quality of life, depression level, essential hypertension.

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INTRODUCTION

Hypertension is the most common and modifiable cardiovascular disease (CVD) risk factor for cardiovascular disease due to stroke, myocardial infarction, and sudden death (1). Despite the availability of effective pharmacological treatments and guideline-based management strategies, a sizable portion of the hypertensive population still fails to achieve optimal blood pressure control (2). However, this underscores the need to explore complementary and alternative therapeutic approaches rather than relying solely on traditional methods. While pharmacological interventions remain a cornerstone of hypertension management, incorporating alternative strategies such as supervised aerobic exercise training may offer additional benefits and help address the persistent challenges in achieving satisfactory blood pressure control (2). In contrast, sedentary behavior is positively associated with higher blood pressure levels (3).

Sedentary lifestyles pose significant health risks across all age groups (4, 5). Low physical activity is a strong predictor of future cardiovascular morbidity and mortality in patients with hypertension (6, 7). Many researchers have shown that a single episode of exercise can reduce blood pressure (BP), and physically active individuals have a lower risk of becoming hypertensive than sedentary individuals (8, 9). Physical activity has a positive effect on hypertension by activating the sympathetic nervous system, endothelial function, insulin sensitivity, and renin-angiotensin system (10). Regular exercise, mainly aerobic exercise, is a critical modifiable behavioral determinant of hypertension and is recommended as a complementary therapy for the prevention and treatment of hypertension (1).

A meta-analysis of 26 randomized controlled studies (RCS) concluded that aerobic exercise is effective in reducing clinical BP in hypertensive subjects (-8.3 mmHg, systolic blood pressure (SBP), and- 5.2 mmHg diastolic blood pressure (DBP)) with training sessions conducted 2–3 times per week, lasting 30–45 min, and with moderate intensity (11). Therefore, aerobic exercise is recommended by current American and European hypertension guidelines to reduce BP (12). Previous studies have reported that patients with hypertension have low long-term compliance with exercise programs (13). Poor adherence to exercise as an antihypertensive therapy underscores the need for supervised aerobic exercise training to increase motivation to exercise, which may favorably impact adherence among patients with hypertension (13).

Other benefits of aerobic exercise training in patients with hypertension include positive effects on cardiovascular health, including functional capacity, weight loss, quality of life (QoL), and depression level. A significant factor in the effectiveness of aerobic exercise is its positive effect on functional capacity, which results in improved prognosis and survival after a diagnosis of hypertension (14). Functional capacity following a cardiovascular event is a strong independent predictor of mortality (15). Aerobic training includes interventions specifically addressing weight loss, such as high-calorie energy expenditure exercise training (16-18). A few studies examining the effect of aerobic exercise training on weight and QoL have shown that decreases in body mass index (BMI) also resulted in significant improvements in QoL (17, 19). According to a meta-analysis of 33 studies, the QoL of hypertensive patients is worse than that of normotensive individuals (20). Previous studies have indicated that psychological distress is a significant risk factor for CVD, such as hypertension, and adversely affects recovery after hypertension (17, 21). Many studies have shown that aerobic exercise has potentially positive effects on some psychiatric conditions such as anxiety and depression (19, 22). Although important, the effect of a supervised aerobic exercise training program on weight loss, functional capacity, QoL, and depression level in hypertensive subjects has been poorly investigated (17, 19, 23), and none of the studies have examined all these parameters collectively in the same patient group (24, 25).

The present trial aimed to evaluate the effects of a supervised aerobic exercise training program on weight loss, functional capacity, QoL, and depression level in patients with essential hypertension.

MATERIALS AND METHODS

Study Population

The study included 155 patients who had been diagnosed with controlled arterial hypertension (essential hypertension) more than one year prior and had been taking the same anti-hypertensive medication for a minimum of three months. Essential hypertension was diagnosed according to the criteria outlined (BP ≥140/90) in the Association for the Advancement of Medical Instru-

mentation/European Society of Hypertension/International Organization for Standardization Guidelines (26). The inclusion criteria were as follows: age > 18 years and the absence of concomitant metabolic and cardiovascular diseases. Exclusion criteria were: having suffered an event of ischaemic heart disease (<6 months), secondary hypertension, hypertrophic obstructive cardiomyopathy, congestive heart failure, uncontrolled cardiac arrhythmia, thyroid dysfunction, diabetes mellitus, symptomatic peripheral arterial occlusive disease, aortic insufficiency or stenosis, pulmonary or heart disease with dyspnoea at small or moderate effort, an outbreak of orthopedic problems on hip, knee or ankles, such as arthroplasty, contracture or severe osteoarthritis, using of antidepressant or anxiolytic drugs, pregnancy, cognitive dysfunction. The patients signed an informed consent form before inclusion in the study.

The study was approved by the local ethics committee (No.2016/196), and the Helsinki Declaration was taken into consideration. Written informed consent was obtained from each patient before participation in the study. The study protocol was registered and made public at ClinicalTrials.gov (NCT05987436).

Procedure and Intervention

The participants were followed up for routine management of diet, weight, and BP. No antihypertensive medication changes were made during the study period of 6 weeks. There was no randomization of the type of treatment or of the patients to be chosen. A supervised aerobic exercise training program was administered to patients who were accepted for inpatient treatment for six weeks. Patients who chose the treatment type according to personal preferences were divided into two groups:

1. The supervised aerobic exercise group (Group 1) exercised for six weeks, involving once per day, five sessions per week, under the supervision of a medical doctor and a nurse in the aerobic exercise laboratory. The aerobic exercise training program lasted six weeks, and the patients lived in the hospital for the entire period. Aerobic exercise training was performed on cycle ergometers (Ergoline, Ergoselect II 100/200/Reha, Germany) equipped with a computed ergometer and developed to monitor electrocardiography (ECG), heart rhythm, and BP. Each session consisted of a 5-minute warm-up, followed by 50 min of aerobic exercise with an intensity of 50–70% of heart rate reserve, calculated using the Karvonen formula, and ended with a 5-minute cool-down period (27).

2. The participants assigned to the control group (Group 2) were advised to maintain their dietary habits and physical activity levels, and an aerobic exercise program was provided to them after completing the study. No aerobic exercise program was administered in the control group.

Blood Pressure

After ten minutes of resting in a supine position, office BP was measured from the brachial artery using a mercury sphygmomanometer (ERKA D-83646 Bad Tolz, Kallmeyer Medizintechnik GmbP Co. KG, Germany) by the same physician. Exercise Stress Test All patients in Group 1 performed the exercise test on a treadmill following the Bruce Protocol with continuous 12-lead electrocardiograph recording (Cambridge Heart, Inc. Exercise System CH 2000, GB) before initiating the aerobic training program (28). For each patient, test readings were recorded with 12-derivated ECG at the beginning, every 3 min during the test, and at the 2nd minute of the resting period.

Outcome Measures

A detailed history and physical examination were obtained, including that of the patients in the study. All participants completed the questionnaire, which gathered demographic data (age, sex, marital status, education level, and occupation). Baseline body weight (using calibrated electronic digital scales [Oncomed; SC-105, California, America]) was measured at the pre-treatment period and after post-treatment 6th week for all participants by the same physician.

Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very-low-density lipoprotein (VLDL) cholesterol, and triglycerides were measured using standard enzymatic kits during the pre-treatment and post-treatment periods for all participants. Twelve-hour fasting blood samples were collected between 6.00 am and 10.00 am at baseline and at week 6.

The functional capacity, QoL, and depression level of all the participants were evaluated by the six-minute walk test (6MWT), Short Form-36 (SF-36), and Beck Depres-

sion Inventory (BDI), respectively from face-to-face interviews at the pre-treatment and the post-treatment. These instruments were recorded by the same physician who was blinded to the type of treatment for each patient.

Assessment Of Functional Capacity

The 6 MWT and estimated metabolic equivalents (METs) were performed to evaluate functional capacity. The 6 MWTs were performed along a flat, 30-meter-long hospital corridor with marks at 3 m intervals for all participants. The 6 MWT was supervised by a medical practitioner.

Assessment Of Qol

The SF-36, which was used to evaluate QoL, consists of 36 questions and two components. The physical component summary comprises four domains (physical function, physical role, bodily pain, and general health), and the other four comprise the mental component summary (vitality, emotional role, social function, and mental health). Scores range from 0 to 100, with higher scores indicating a better QoL (29).

Assessment Of Depression Level

The BDI was used to assess participants' depression levels. The BDI is a 21-item self-reporting questionnaire. The questionnaire consisted of four statements. These statements were graded on a scale of 0 to 3 (30). A score higher than 17 indicated the presence of depression.

Statistical Analyses

Kolmogorov-Smirnov normality tests were conducted for all continuous data. Comparisons between pre- and post-treatment values were evaluated using the Student's dependent samples t-test. Nonparametric Mann-Whitney or Chi-square tests (x2) were performed to compare sociodemographic and clinical measures between the two groups. All categorical variables were described as percentages, whereas means and standard deviations were reported for continuous variables. The level of significance was set at $p < 0.05$. All analyses were conducted using IBM SPSS 23.

RESULTS

None of the patients received any treatment other than that described earlier, and no complications were observed. This study included 138 patients (Figure 1). There were 91 patients in group 1 and 47 patients in group 2. There were no statistically significant differences between the two groups in terms of age, sex, marital status, educational level, or occupation. The demographic and clinical characteristics of the patients are presented in Table 1.

Between-Groups

There was a significant difference in total cholesterol, LDL levels, and role physical scores during pre-treatment between the two groups ($p=0.01$, $p=0.002$, and $p=0.007$, respectively). A comparison of resting SBP, resting DBP, resting heart rate, weight, body mass index (BMI), total cholesterol, HDL, LDL, VLDL, triglycerides, and 6 MWT scores between the two groups before and after treatment is shown in Table 2. When the two groups were compared, a significant increase in the 6 MWT distance and SF-36 subscales, including physical function, role physical, physical component summary, vitality, role emotional, mental health, and mental component summary, was found in Group 1 after the post-treatment ($p<0.05$).

Within-Groups

Resting SBP, resting DBP, resting heart rate, weight, BMI, total cholesterol, HDL, LDL, VLDL, triglycerides, and 6MWT scores between pre-treatment and post-treatment sixth week in both groups are shown in Table 2.

There was a significant reduction in resting SBP, weight, BMI, and BDI scores between the pre-treatment and post-treatment groups in Group 1 ($p<0.05$). There was a significant increase in the 6 MWT and SF-36 subscales of physical function, physical role, physical component summary, vitality, emotional role, and mental component summary scores between pre-treatment and post-treatment in Group 1($p<0.05$). There was a significant increase in the SF-36 subscales of role physical and mental health scores between pre- and post-treatment in Group 2 ($p<0.05$).

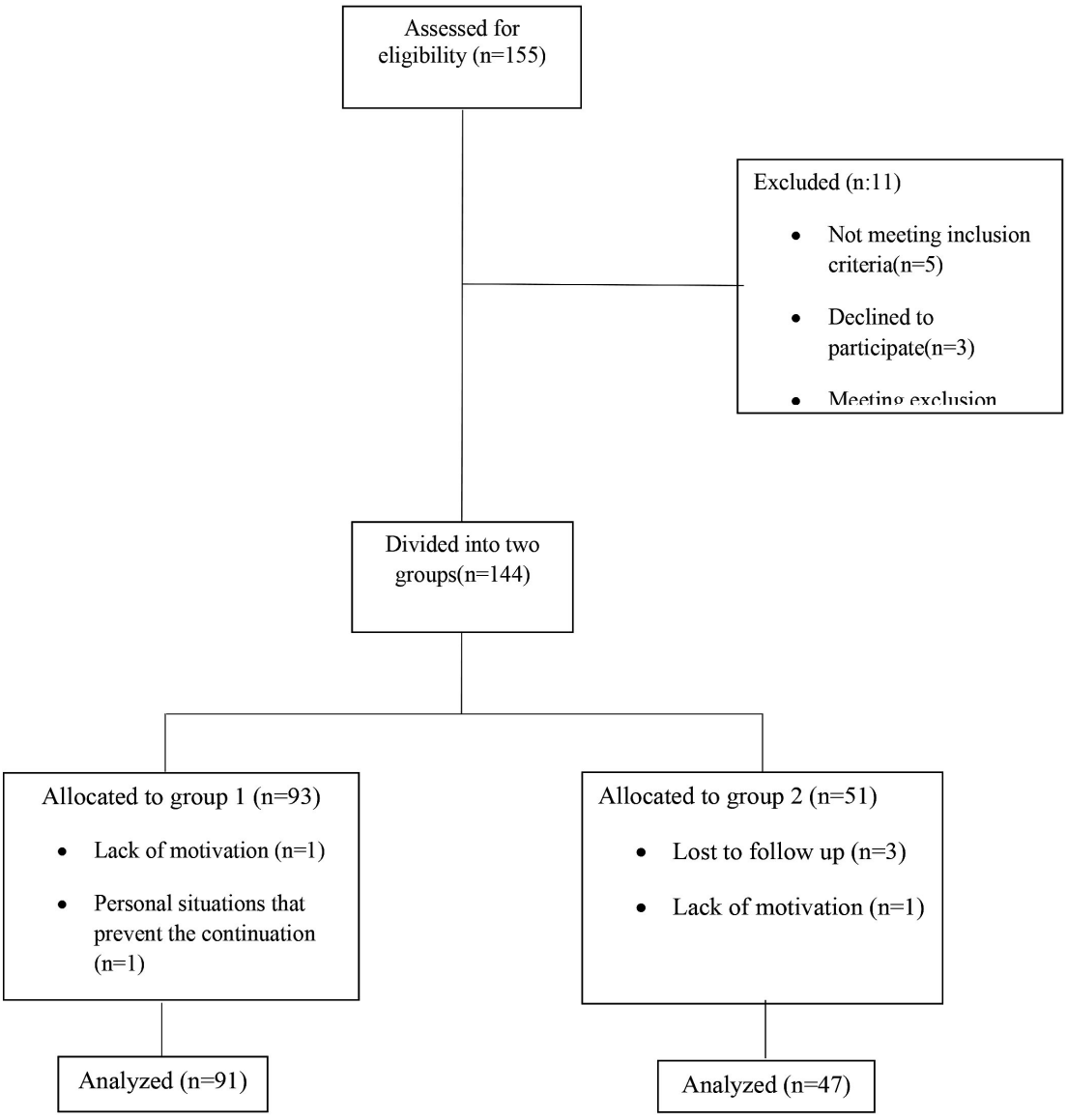

Figure 1: In the flow chart, under the heading 'Excluded', the 3rd premise is incomplete. it should be '- Meeting exclusion criteria (n=3)'.

DISCUSSION

This study has shown that supervised aerobic exercise training for 6 weeks can reduce resting SBP, weight, and depression levels, and increase functional capacity and QoL in patients with essential hypertension. The supervised aerobic exercise training group showed better functional capacity and QoL than the control group among patients with essential hypertension. Collectively, our findings indicate that supervised aerobic exercise should be recommended for its benefits in patients with essential hypertension.

Aerobic exercise is the cornerstone of lifestyle recommendations in current hypertension guidelines (31). A meta-analysis of 28 RCTs concluded a mean reduction in SBP of 12 mmHg, thus supporting the antihypertensive effects of aerobic exercise (32). Tabara et al. (33) found that aerobic exercise could lower the resting SBP by 5–15 mmHg and resting DBP by 4–9 mmHg in patients with essential hypertension. In the present study, we found that the supervised aerobic exercise training of 6 weeks duration reduced resting SBP by 4.4±12.8

Table 1. Demographic characteristics of Group 1 and Group 2

	Group 1 (n=91)	Group 2 (n=47)	P value
Age (years)	59.36±6.22	59.14±7.75	0.861
Gender			0.783
Female	79 (86.8%)	40 (85.1%)	
Male	12 (13.2%)	7 (14.9%)	
Marital status			0.926
Married	73 (80.2%)	37 (78.8%)	
Single	1 (1.1%)	1 (2.1%)	
Widower	16 (17.6%)	8 (17%)	
Divorced	1 (1.1%)	1 (2.1%)	
Education level			0.651
No formal education	17 (18.7%)	9 (19.2%)	
Primary school	67 (73.6%)	34 (72.3%)	
Secondary school	1 (1.1%)	0	
High school	2 (2.2%)	0	
University	4 (4.4%)	4 (8.5%)	
Occupation			0.622
Housewife	83 (91.2%)	45 (95.8%)	
Officer	4 (4.4%)	1 (2.1%)	
Work requiring physical effort	4 (4.4%)	1 (2.1%)	

mmHg and resting DBP 2±12.8 mmHg in patients with hypertension. There was no reduction in resting BP in the control group.

Obesity predisposes all age groups to CVD by increasing blood pressure, plasma lipid levels, and causing a sedentary lifestyle (17, 34). According to previous studies, obese patients may acquire significant health benefits from improvements in physical activity levels and weight changes (17, 35). Weight reduction with aerobic exercise training has significant effects on increasing functional capacity, QoL, and psychological health (17, 19). There is strong evidence in the general population that physical activity is a determining factor for the decrease and maintenance of healthy weight (19). A RCT with a physical activity program of 165-220 min/week with hypertensive patients reported a significant reduction in body weight (-1,8 kg) and BMI (-0,6 kg/m2), results for the present study (-3,2 kg and-1,2 kg/m2, respectively) were better

Table 2. Clinical and functional outcomes after treatments and changes from baseline values

	Group 1 (Aerobic exercise) (n=91)			Group 2 (Control) (n=47)		
	Pre-treatment	Post-treatment	Change	Pre-treatment	Post-treatment	Change
Resting SBP (mm Hg)	119.7±11.9	115.2±6.7	-4.4±12.8[a]	116.3±5.2	117±5	0.6±3.8
Resting DBP (mm Hg)	74.1±11.6	72±6.8	-2±12.8	71±2	71.6±3	0.6±3
Resting heart rate (beats/min)	78.5±9.8	77.1±8.4	-1.3±8.9	76.5±7.8	76.4±7	0±2.2
Weight	87.3±13.9	84.1±13	-3.2±2.1[c]	84.5±11.9	84±11.6	-0.51±1.1
BMI	34.8±5.2	33.5±4.9	-1.2±0.8[c]	32.9±4.8	32.5±4.6	-0.4±0.4
Total cholesterol (mg/dl)	196.5±37.6	192.3±44.5	-4.1±39	213.7±36.3	210.8±37.5	-2.9±21.1
HDL (mg/dl)	44.5±9.8	45.1±9.9	0.6±6.6	44.4±11.2	43.4±9.8	-1±4.2
LDL (mg/dl)	118.8±29.6	117.5±33.6	-1.3±31.8	135.7±33	133,9±33.7	-1.8±16.1
VLDL (mg/dl)	34±18.8	31.3±12.1	-2.7±16.4	33.4±15	31.4±14.1	-2±9.6
Triglycerides (mg/dl)	168.8±95.8	156.3±60.7	-12.5±83.3	162.7±68.8	160.2±72.2	-2.5±43.7
6MWT (m)	376.1±53.4	424.9±76.3	48.7±53.3[c,f]	365.2±57.1	354.5±87.3	-10.7±3.6
SF-36						
Physical function	37.3±21.9	53.4±22.1	16±18.5[c,e]	40.3±21.9	42.6±24.1	2.3±12
Role physical	26.3±37.7	57.6±44.5	31.3±40.4[c,f]	9.5±26.8	19.1±38.3	9.5±26.8[a]
Bodily pain	47.6±21.1	45.9±19.1	-1.7±24.4	45.5±18.7	41.4±13	-4.1±13.1
General health	52.5±15.3	54.1±14.1	1,5±11.8	57.3±9	56.4±10.1	0.8±5.2
Physical component summary	40.9±15.4	52.4±16.6	11.4±12.2[c,f]	40.7±9	42.3±11.5	1.6±6.6
Vitality	46.7±14	51.2±15.4	4.5±13.3[b,d]	45.1±13.3	45.2±12.4	0.1±4.1
Social function	54.5±22.7	56.5±22.2	2±17.7	51±22.2	49.2±18.3	-1.8±8.2
Role emotional	27.4±36.7	59±43.5	31.5±44.2[c,f]	17.7±33.9	19.8±39.1	2.1±37
Mental health	56.7±14.6	58.8±15.1	2±12.2[e]	51.4±10.1	53.5±10.2	1.1±3.1[a]
Mental component summary	46.3±13.4	55.9±16.9	9.5±13[c,f]	43.7±8.5	42,6±12	-1.1±9
BDI	14.9±9.3	10.7±8.2	-4.2±5.2[c]	13.6±10	13.1±9.9	-0.4±1.9

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low density lipoprotein, VLDL: Very-low-density lipoprotein, 6MWT: Six-minute walk test, SF-36: Short Form-36, BDI: Beck Depression Inventory.
Within-group differences: [a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$. Between-group differences (As compared to the pre-treatment and the post-treatment 6th week): [d] $P < 0.05$; [e] $P < 0.01$; [f] $P < 0.001$.

than in that study (33). In this study, while weight reduction in the supervised aerobic exercise training group was 3.6%, there was a 0.6% reduction in body weight in the control group over six weeks. Based on the results of this study, we consider that supervised aerobic exercise training as a physical activity can be more successful in weight loss in patients with hypertension.

Exercise training has also been shown to reduce triglyceride and LDL cholesterol levels and increase HDL cholesterol levels (36, 37). It has not yet been established how much aerobic exercise is required in order to improve lipid levels (38). According to previous studies, the duration of aerobic exercise for improvement of serum lipid levels is mostly eight weeks or more (39). In the present study, we found that supervised aerobic exercise training increased HDL cholesterol by 0,6 mg/dl, and reduced LDL cholesterol and triglycerides by 1,3 mg/dl and 12,5 mg/dl, respectively after 6 weeks. However, these differences were not statistically significant. If the aerobic exercise duration is longer than six weeks, lipid levels can be more positively affected.

Previous studies have shown that an improvement in functional capacity is an important predictive marker of survival in cardiovascular diseases (15, 17). Using the 6 MWT, there was an increase of 48 months (12.8%) in the supervised group at the end of 6 weeks, while there was an increase of 10 months (2.7%) in the control group. According to these results, functional capacity improved approximately five times in the supervised aerobic exercise training group compared to the control group for hypertensive patients. In view of the considerable impact that an increase in functional capacity has on the health of hypertensive patients, supervised aerobic exercise training should be recommended.

Two RCTs with hypertensive patients reported that there is a positive effect of physical activity on QoL (24, 25). Specific designs of physical activity programs aimed at improving QoL and adherence to exercise have been reported, such as counseling, supervision, and group interventions (19). In this study, when the two groups were compared, the benefits of supervised aerobic exercise training on QoL were observed in some domains, such as physical function, role physical, physical component summary, vitality, role emotional, mental health, and mental component summary after six weeks for hypertensive patients. It seems that supervised aerobic exercise training, such as in the present study, has had favorable effects on the QoL of hypertensive patients.

Previous studies show that psychological distress plays an essential role in the pathogenesis and prognosis of CVD (17, 21). Physical activity such as aerobic exercise has potentially beneficial effects on psychological status (19, 22). The sense of well-being associated with aerobic exercise training may be related to the release of neurotransmitters, which act at the brain level and increase the feeling of well-being (19). Weight loss due to aerobic exercise training may contribute to these reduced levels (17). In this study, during 6 weeks, while the reduction in BDI score in the supervised aerobic exercise training group was 4.2±5.2, there was a 0.4±1.9 reduction in the BDI score in the control group in patients with hypertension. Although there was no significant difference between the two groups in terms of depression levels, a noticeable improvement was observed in the supervised aerobic exercise group compared to pre-treatment.

Several potentially important limitations of this study deserve attention. First, there was no randomization of the type of treatment or the patients to be chosen. All patients were allocated to the experimental group according to their desire to participate in the supervised aerobic exercise or control group. This situation has the potential for self-selection bias, as patients choose their treatment groups based on personal preferences. This may have influenced the outcomes and limited the generalizability of our findings. Second, the present study had no long-term follow-up assessments, making it impossible to determine if the observed short-term improvements were maintained in the long term. Third, the comparison groups were subjected to different conditions. Hospitalized patients had a controlled lifestyle, with regular hospital meals and monitored BP. Randomized studies and long-term follow-up assessments may better demonstrate the effectiveness of supervised aerobic exercise training in patients with hypertension.

The findings of this study demonstrate that a 6-week supervised aerobic exercise program provides significant benefits to patients with essential hypertension. Participants in the exercise group experienced a 12.8% increase in the 6-minute walk test distance, substantial improvements in multiple SF-36 subscales related to quality of life, a mean reduction of 4.4 mmHg in resting systolic blood pressure, an average weight loss of 3.2 kg, and a notable decrease in Beck Depression Inventory scores. These results highlight the positive impact

of supervised aerobic exercise on functional capacity, cardiovascular health, weight management, and mental wellbeing. The structured and supervised nature of the program may have contributed to better adherence and improved outcomes than unsupervised interventions. Given the absence of adverse events and their beneficial effects on metabolic outcomes, functional capacity, and overall well-being, supervised aerobic exercise should be recommended as an effective complementary lifestyle therapy for hypertensive patients. These findings also have important implications for the design of exercise programs tailored to patients with hypertension, emphasizing the role of structured exercise interventions in managing the condition.

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Abbreviations list

6-MWT: 6-minute walk test
BDI: Beck Depression Inventory
BMI: Body Mass Index
BP: Blood pressure
CVD: Cardiovascular disease
DBP: Diastolic Blood Pressure
ECG: Electrocardiography
HDL: High-density lipoprotein
LDL: Low-density lipoprotein
QoL: Quality of life
RCS: Randomized Controlled Study
SBP: Systolic Blood Pressure
SF-36: Short form 36
VLDL: Very-low-density lipoprotein

Ethics approval and consent to participate

This study was approved by Selcuk University Faculty of Medicine local ethics committee (No.2016/196). The research protocol adhered to the principles of the Helsinki Declaration. The study protocol was registered on ClinicalTrials.gov (NCT05987436). As this study did not involve animal subjects, no statement on ethical approval for animal research is required.

Consent for publication

Written informed consent was obtained from all participants prior to enrollment.

Availability of data and materials

The physical data collected in the study are securely stored in physical form. Access to the data is provided in accordance with research ethics guidelines and legal regulations concerning the protection of personal data. Data sharing is possible under the condition that the requesting researcher complies with ethical standards and obtains the necessary institutional approvals. Requests for access should be made by contacting the corresponding author.

Competing interests

All of the authors had no conflict of interest.

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Authors' contributions

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ORIGINAL ARTICLE

Foreign Body Aspiration in Children is Time-Sensitive: A Retrospective Analysis of 79 Cases

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Abstract

Background: Foreign body aspiration (FBA) is an important cause of morbidity and mortality in children, especially within the 1-3 year age range. Bronchoscopy is the gold standard diagnostic method in patients with a suspected history of FBA and is also the primary treatment.

Methods: We evaluated pediatric patients who presented with suspected FBA between December 2023 and December 2024. Bronchoscopy was recommended for all patients who might have aspiration, and fiberoptic bronchoscopy (FOB) was done under a laryngeal mask on those who agreed to the procedure.

Results: A foreign body was identified in 43 patients (54.4%). Foreign body extraction was performed by FOB in 2 (2.6%), rigid bronchoscopy in 40 (50.6%), and thoracotomy in 1 (1.3%) of the patients. FBA of organic origin was considerably elevated before schooling compared to post-schooling (p=0.004). The median interval between aspiration and interventional procedure was 8 (min: 5 - max: 45) and 2 (min: 0 - max: 61) days in FBA cases with and without granulation tissue development, respectively. The median interval between aspiration and interventional procedure was significantly longer in those who developed granulation tissue (p=0.002).

Conclusion: FBA is an important health issue in childhood and can lead to morbidity and mortality. Foreign body aspirations should be considered time-sensitive due to the development of granulation tissue and potential accompanying complications.

Keywords: Bronchoscopy, childhood, foreign body aspiration

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INTRODUCTION

Foreign body aspiration (FBA) is an important cause of morbidity and mortality in the pediatric age group, particularly in the 1-3 year age group. In this age group, lack of teeth, weak swallowing reflex, involuntary breathing during laughing and crying, and the habit of putting objects in the mouth are considered the main aetiological factors (1).

FBA may occur with or without witnesses. The most important clue in the diagnosis is anamnesis. In the anamnesis, a history of witnessed aspiration is present in most cases (1). Despite the absence of findings on physical examination and radiological imaging, the number of cases in which FBA is found on bronchoscopy is considerable. Therefore, bronchoscopy is the gold standard diagnostic method in patients with a suspected history of FBA and is also the basic treatment (2).

In our study, we aimed to present the results of our patients who were evaluated for suspected FBA in our clinic during a one-year period between December 2023 and December 2024 in light of the literature.

MATERIALS AND METHODS

Pediatric cases consulted at our clinic with suspicion of FBA between December 2023 and December 2024 were included in the study. Local ethics committee approval was obtained before the study (AEŞH-BADEK-2024-1264), and the study was conducted in accordance with the Helsinki Declaration of Human Rights.

Age, gender, symptoms, physical examination findings, procedure (flexible/rigid bronchoscopy, surgery), type of foreign body (organic, non-organic), complications, mortality, length of hospitalization, and follow-up data were retrospectively evaluated. Patients were categorized into two periods, preschool (<7 years) and post-school (>7 years), due to the prolonged separation from parents/caregivers and increased exposure to a variety of materials with the start of school age.

Patient Management

Bronchoscopy was routinely recommended for all patients with suspected aspiration, and all patients who consented to the procedure were admitted to either the pediatric ward or the intensive care unit based on their clinical condition. No premedication was administered to any patient, and all procedures were initiated following standard anesthesia monitoring, including electrocardiography, peripheral oxygen saturation, and noninvasive arterial blood pressure measurement. Anesthesia induction was performed intravenously with propofol (2–3 mg/kg) in the presence of intravenous access; otherwise, inhalational induction was achieved with sevoflurane (4–5%) in 100% oxygen. Rocuronium (0.6–1.2 mg/kg) was administered as a neuromuscular blocking agent. Following induction, a Class 1 laryngeal mask airway (LMA) of appropriate size was inserted, and the patient was connected to the respiratory circuit via a T-tube. Flexible bronchoscopy was performed through the connection between the T-tube and the LMA. If a foreign body was identified and couldn't be removed with FOB, both the FOB and LMA were removed, and rigid bronchoscopy was initiated (Figure 1).

Figure 1: Foreign body aspirastion bronchoscopy image

The T-tube was connected at one end to the ventilation port of the rigid bronchoscope and at the other end to the respiratory circuit, allowing manual ventilation with 100% oxygen at a flow rate of 8–10 L/min. Anesthesia was maintained using either inhalational anesthesia (sevoflurane 2–5% in 100% oxygen) or total intravenous anesthesia (TIVA) with propofol (100–150 μg/kg/min) and remifentanil (0.1–0.2 μg/kg/min). At the conclusion of the procedure, anesthetic agents were discontinued, and neuromuscular blockade was reversed in

patients who had received muscle relaxants. Manual ventilation with 100% oxygen was provided until sufficient spontaneous respiration was restored. Patients without respiratory distress at the end of the procedure were transferred to the recovery unit, where they were monitored until an Aldrete score of 9 was achieved before being discharged to the ward.

Statistical analysis

All analyses of the study were performed using the SPSS 24.0 software package. Descriptive statistics were presented as the number of units (n), percentage, and median (minimum-maximum) values for age, time between aspiration and procedure, and length of hospital stay. Pearson chi-squared analysis and Fisher's exact test were used to compare the distribution of categorical variables between groups. The Mann-Whitney U test was used for continuous numerical variables without normal distribution. A p-value less than 0.05 was considered statistically significant.

RESULTS

A total of 125 patients who were evaluated with suspicion of foreign body aspiration (FBA) were retrospectively assessed in our clinic. Diagnostic bronchoscopy was recommended to all patients. Forty-six patients who refused the procedure were excluded from the study. In 79 patients, the median month was 20 months (min: 4 - 180), and the median age was 1 year (min: 0 - max: 15). Forty-eight (60.8%) of the patients were male and 31 (39.2%) were female. Of the patients with suspected foreign body aspiration, 63 (79.7%) were diagnosed. Suspected foreign body aspiration was most common in the 1-2 year age range (44.3%). Symptoms, physical examination, and chest x-ray findings are shown in Table 1. Radiopaque foreign bodies were seen in 7 (8.9%) of the chest radiographs. The median time between suspected foreign body aspiration and interventional procedure was 3 (min: 0 - max: 61) days.

Table 1. Patients' Symptom, Physical Examination, Radiology, Procedure, and Complication Data

Parameters	Suspected Foreign Body Aspiration
	Number n (%)
Symptom	
None	2 (%2,5)
Cough	43 (%54,5)
Shortness of breath	23 (%29)
Wheezing	14 (%17,7)
Cyanosis	12 (%15,2)
Sore throat	1 (%1,3)
Flushing	1 (%1,3)
Chest pain	1 (%1,3)
Physical Examination	
Normal	37 (%46,8)
Decreased breath sounds	16 (%20,3)
Rhonchi	14 (%17,7)
Wheezing	4 (%5,1)
Stridor	3 (%3,8)
Coarse breath sounds	3 (%3,8)
Rales	2 (%2,5)

Chest X-ray	
Normal	38 (%48,1)
Increased aeration	33 (%41,7)
Atelectasis	6 (%7,6)
Foreign body	3 (%3,8)
Opacity	1 (%1,3)
Pneumonia	1 (%1,3)
Procedure	
Fiberoptic bronchoscopy (FOB)	38 (%48,1)
Rigid bronchoscopy	40 (%50,6)
Thoracotomy with exploration	1 (%1,3)
Complication	
None	75 (%95)
Pneumothorax	2 (%2,5)
Bronchospasm	2 (%2,5)
Cardiopulmonary resuscitation	1 (%1,3)
Hypoxic brain injury	1 (%1,3)

FOB was performed as standard at the beginning of the procedure (Figure 2). Foreign bodies were detected in 43 patients (54.4%). Foreign body removal was performed by FOB in 2 patients (2.6%), rigid bronchoscopy in 40 patients (50.6%), and thoracotomy in 1 patient (1.3%) (Table 1). Foreign bodies were of organic origin in 36 of 43 patients (83.7%) and of inorganic origin in 7 patients (16.3%). Complications developed in 4 patients (5.1%) and were as follows: pneumothorax in 2 patients (2.5%), bronchospasm in 1 patient (1.3%), bronchospasm, cardiopulmonary arrest, and subsequent hypoxic brain in 1 patient (1.3%) (Table 1). The median length of hospital stay was 3 (min: 0 - max: 23) days. Patients with suspected foreign body aspiration did not experience any pre- or post-procedural mortality. The type and location of the foreign bodies are shown in Table 2. Figure 1 illustrates the discovery of a localized foreign body in both the right lower lobe and the left upper lobe in one patient. It was found that suspicion of a foreign body was more common in the 1-2 and 2-3 age groups, while the likelihood of no significant findings was higher in the 0-1 age group. Thirty-two (74.4%) of the patients with FBA were aged between 1 and 3 years (Figure 3). Seven patients (16.3%) with foreign body aspiration showed granulation tissue development.

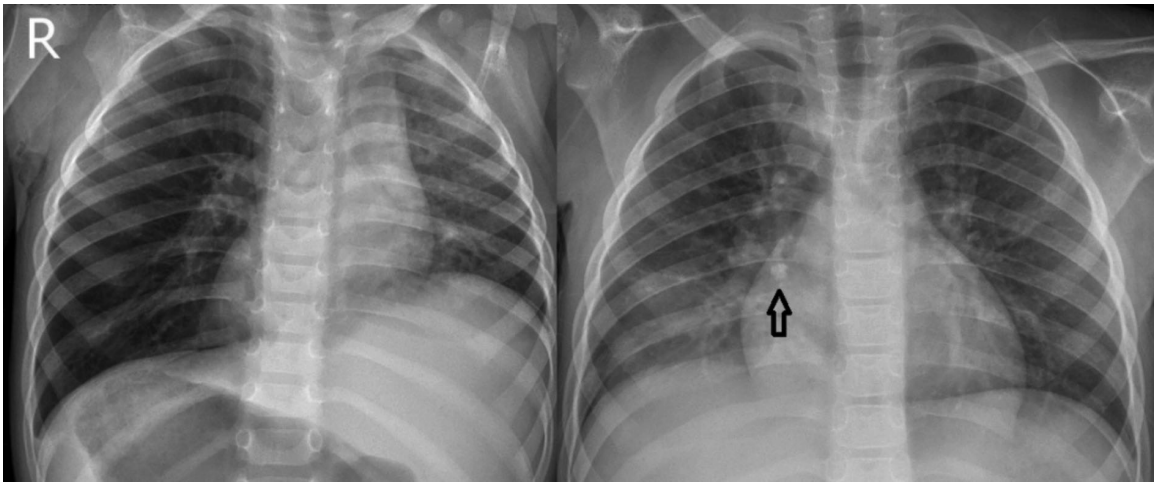

Figure 2: Chest X-ray of foreign body aspiration

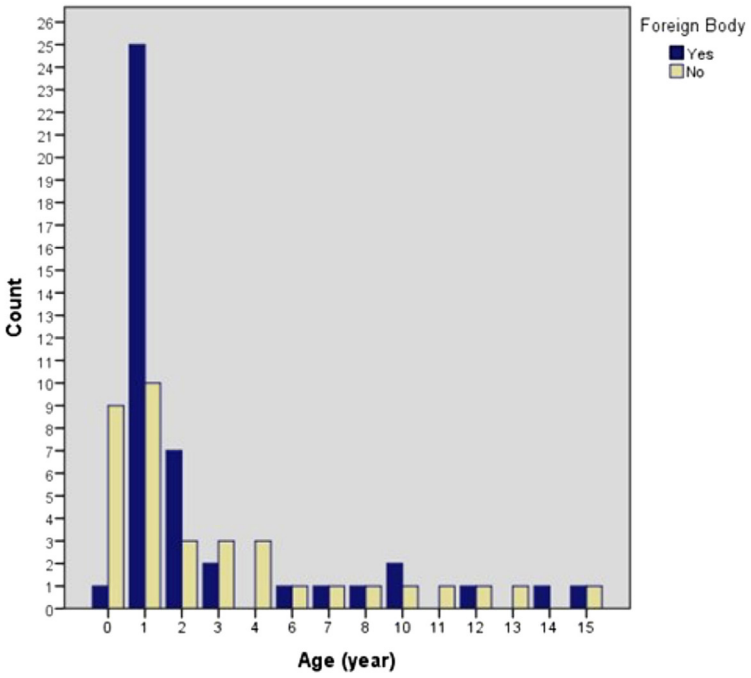

Figure 3: Age distribution graph of foreign body aspirations

We found that FBA of organic origin was significantly higher in preschool age compared to post-school age (p=0.004). The median time between aspiration and interventional procedure was 8 (min: 5 - max: 45) and 2 (min: 0 - max: 61) days in FBA cases with and without granulation tissue development, respectively. We found that those with granulation tissue development had a significantly longer median time (p=0.002).

Table 2. Characteristics of the Foreign Body

Parameters	Suspected Foreign Body Aspiration
	Number n (%)
Type of Foreign Body	
Nut	25 (%58,1)
Food	10 (%16,3)
Tooth	2 (%4,7)
Apple	1 (%2,3)
Plastic piece	1 (%2,3)
Screw	1 (%2,3)
Thumbtack	1 (%2,3)
Stone	1 (%2,3)
Pen cap	1 (%2,3)
Location	
Trachea	3 (%7)
Right	16 (%37,2)
Left	21 (%48,8)
Bilateral	3 (%7)

DISCUSSION

Anamnesis and bronchoscopy are the most important tools in FBA. FBA may cause a wide range of respiratory symptoms, from coughs to severe respiratory distress, and it may be completely asymptomatic. In addition, no radiological findings may be observed. Therefore, bronchoscopy is recommended in patients with suspected FBA even if physical examination and radiology are completely normal (2, 3, 4). In our clinical approach, we recommend bronchoscopy in all patients regardless of physical examination and radiological findings in case of suspicion in the anamnesis. FOB is performed under a laryngeal mask and low-dose anesthesia in order to confirm the diagnosis, and the procedure is terminated in cases in which no foreign body is detected within a few minutes. In our clinic, we found that 2.5% of the patients with foreign bodies were asymptomatic; 2.5% were both asymptomatic and had no physical examination or radiological findings.

Some studies have focused on scoring studies to avoid bronchoscopy in all patients, and negative findings on bronchoscopy have been shown in the literature to be 14-47% (3, 5). In our study, this rate was 45.6%. However, similar to the literature, in our study we did not observe any complications in patients in whom no foreign body was observed and in whom only rapid FOB was performed; therefore, we adopted the principle of bronchoscopy as an approach in cases of clinical suspicion.

In patients with suspected FBA, granulation tissue development due to inflammation within 48 hours and delayed procedures (>3 days) increase the risk of complications. Therefore, delaying the procedure is not recommended in patients with suspected FBA (3, 6-9). In our study, when evaluating the development of granulation tissue among patients, it was found that patients with granulation tissue developed had significantly later procedures. Although the results are similar to the literature, in our clinical approach, if the patients are stable at the time of admission, we choose to perform the procedure on the first day of the next working shift and under conditions where the anesthesia, pediatric intensive care unit, and the whole experienced team of our clinic are present in the hospital in order to minimize complications.

In the literature, complications range from incomplete removal of the foreign body and subsequent repeat bronchoscopy to laryngospasm and associated mortality or hypoxic brain damage (6). The complication rate varies between clinics with rates ranging from 2-15% (2, 3, 10). In our study, no mortality was observed. Laryngospasm was observed in two patients, one of whom had a completely normal follow-up after intubation, while one patient had respiratory and cardiac arrest on the operating table and was resuscitated. Ischemic foci were observed on cranial imaging during ICU follow-up, and the patient was discharged clinically normal after follow-up. At the 3-month follow-up after discharge, the patient continued to be monitored with age-appropriate developmental characteristics and no neurological findings were observed. In one patient, the aspirated foreign body was wrapped with granulation tissue in the distal bronchus and was not removed to avoid complications; surgery was decided. Preoperative chest X-ray of this patient revealed pneumothorax. However, no additional intervention was performed as surgery was planned. In the other patient, a tube thoracostomy was performed, and the lungs were subsequently observed to be fully expanded. No further interventions were required.

Radiological findings in FBA can generally be parallel to physical examination findings. However, particularly in non-occlusive lesions, radiological findings may be absent in 10-50% of cases, while physical examination findings such as wheezing and rhonchi may be present. The rate of radiological findings is high with radiopaque foreign bodies. In the pediatric age group, the foreign body type is predominantly organic. In FBA consisting of organic bodies, the rate of radiological findings directly related to the foreign body is quite low, and parenchymal findings secondary to the foreign body are observed. The literature describes air trapping, atelectasis, infiltration, and pneumonia as the most common radiological findings, particularly in delayed cases (3, 11-18). In our study, 83.7% of foreign bodies were organic, and the most common radiological finding was air trapping (Figure 2). In addition, radiological findings were completely normal in 48.1% of cases.

Although FBA is observed in all pediatric age groups, the literature has shown that FBA is particularly common in the 1-3 year age group and in males. In the literature, the higher incidence in males is thought to be due to both the greater activity levels of boys and the faster developmental growth of girls during early childhood. (1, 11, 13, 19, 20). In our study, a wide range of pediatric patients aged between 4 months and 15 years were eval-

uated, and 74% of these patients were children aged 1-3 years. Similar to the literature, the majority of patients were male.

When the foreign body localization is examined, it is observed that foreign bodies are predominantly localized on the right in the adult age group due to the anatomical structure. However, there are also left-main bronchus-dominant FBA studies in the literature, especially in children because the anatomical angulation difference is not yet fully established (2, 11, 18, 21). However, especially FBAs localized in the trachea are more important in terms of mortality and have a higher life-threatening risk (18). In our study, when FBAs were evaluated in terms of location, it was observed that the location was left dominant. Furthermore, we observed the foreign body at the level of the trachea in 7% of cases.

The value of our study is that the data from an experienced and frequently performed FBA intervention center in the province and throughout the country shows that this procedure can be performed with a very low complication rate in competent hands.

The limitation of our study is that variables such as the time of FBA aspiration may introduce a margin of error due to its retrospective design. In addition, although most of the children were asymptomatic at the time of evaluation, the rate of symptomatic patients is likely to be high because the symptom reported at the first suspicion of aspiration was accepted, as the records were evaluated retrospectively.

In conclusion, FBAs are time-sensitive cases due to the formation of granulation tissue over time and the presence of associated complications. FBA is an important health problem in childhood and can cause morbidity and mortality. However, there is a perception that FBA is underestimated in clinical practice, although it is not uncommon. There is a perceived need to diversify the centers performing procedures for FBA and to perform procedures in multiple centers to prevent complications. Increasing the number of centers performing procedures and using them as a basis for specialist training will be beneficial in preventing one of the health problems.

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Abbreviations list

FBA: Foreign body aspiration
LMA: laryngeal mask airway
TIVA: total intravenous anesthesia

Ethics approval and consent to participate

Local ethical committee approval (AEŞH-BADEK-2024-1264) was taken from Ankara Etlik City Hospital Ethical Commitee and the study was conducted in accordance with the Helsinki Declaration of Human Rights before the study.

Consent for publication

Informed consent was obtained from the legal guardians of patients under the age of 18 for the anonymous use of their data.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

Is There a Relation Between Chorion Frondosum Thickness and Severe Hyperemesis Gravidarum?

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Abstract

Background: Hyperemesis gravidarum (HG) is a pregnancy complication that is characterized by severe nausea, vomiting, weight loss, and dehydration. The current study investigated chorion frondosum (CF) thickness and the relation between placental dysfunction and hyperemesis gravidarum.

Methods: We enrolled 96 participants in this study during their first trimester of pregnancy. We found that 48 of them had hyperemesis gravidarum symptoms and +2/+3 urine ketone levels. The others were taken as controls. Demographic characteristics, blood β-hCG, thyroid hormone levels (TSH, fT3, fT4), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and urine ketone levels were obtained from all participants. The CF thickness of each participant was measured to demonstrate the relation between CF thickness and HG.

Results: The mean gestational age was 8.69 (± 2.15) weeks in the HG group and 8.92 (±2.14) weeks in the control group (p=0.6). The HG group had significantly higher urine ketone levels (+2.7) compared to the control group (+0.1) (p<0.001). The CF thickness was significantly higher in the HG group (16.02 mm) than in the control group (13.50 mm) (p=0.02).

Conclusion: The mean chorion frondosum thickness (CF) was significantly higher in the HG group than the healthy controls. This finding may also constitute clinical prediction, in addition to indicating pathophysiology.

Keywords: Chorion; hyperemesis gravidarum; ultrasonography.

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INTRODUCTION

Hyperemesis gravidarum is a pregnancy-specific clinical condition with nausea and vomiting and it can cause critical weight loss and ketoacidosis in severe cases. The incidence of hyperemesis gravidarum (HG) is 0.3-1.5% of all pregnancies (1). Although emesis gravidarum is a common and pregnancy-specific finding in the Turkish population, HG is the most common reason for hospitalization in the first trimester (2). Women with hyperemesis gravidarum have an increased risk for small gestational age (SGA) as shown in a recent meta-analysis (3). This can be evaluated as a demonstration of the correlation between placental disorders and hyperemesis gravidarum. An abnormal placenta or an abnormal placenta location is related to poor obstetric outcomes like small for gestational age, pre-eclampsia, placental abruption, and stillbirth (4–6). One of the theories is that increased β-hCG levels are caused by inadequate trophoblast invasion and subsequent placental hypoxia (7). There is a relation between imperfect placentation, compensatory growth, and an increased number of pregnancy complications that were linked to HG pathophysiology (8). Besides, there is a positive correlation between β-hCG levels and nausea and vomiting during pregnancy (9). Higher β-HCG levels present as HG in early pregnancy. Later, it occurs as preeclampsia (PE) and early neonatal complications (8). The effects of placental weight on placental function in hyperemesis gravidarum patients were previously investigated and a correlation between a heavy placenta compared to birth weight has been proven (10). Considering the mentioned literature, the present study started with the hypothesis that placental dysfunction is related to hyperemesis gravidarum. According to our hypothesis, this relation affects chorion frondosum (CF) thickness. The current study aimed to reveal the relationship between CF thickness and HG.

MATERIALS AND METHODS

This prospective clinical study with a parallel design was conducted in a tertiary referral center between February 2023 and June 2024. Inclusion criteria were determined as being in the first trimester of pregnancy and having a diagnosis of hyperemesis gravidarum for the study group. Healthy pregnant women who applied to the outpatient clinic in the first trimester of pregnancy were included in the control group. Exclusion criteria were a history of hyperthyroidism, type 1 diabetes mellitus, positive urine culture test, early pregnancy bleeding, smoking, and an elevated liver function test, as they may cause nausea and vomiting or affect urinary ketones, and CF thickness and affect study homogeneity. In the current study, the definition of HG was made as moderate and severe nausea and vomiting accompanied by ketonuria, seen in the first trimester of pregnancy. Based on previous data, we calculated that for a power of 80% and significance of 5%, by taking impact size 1,02, a minimum sample of 46 patients for both groups was required. Taking into consideration possible dropouts, we enrolled 96 participants in the trial (11).

Age, body mass index (BMI), gravida, parity, pregnancy week, and hyperemesis history in prior pregnancy were obtained from the participants at admission. For laboratory tests, blood β-hCG, thyroid hormone levels (TSH, fT3, fT4), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urine ketone levels, and urine culture were checked for all participants at admission. Participants who had a history of hyperthyroidism and high AST or ALT levels were excluded from the study.

Ultrasonographic examinations were performed by the same experienced physician (C.S.) for all patients to prevent the intra-observer difference in measurements. Ultrasonographic examinations were performed using a Voluson E8 ultrasound machine (GE Healthcare, UK) with a Rab 4-8d 4D probe (GE Healthcare, UK). The CF thickness of each participant was measured. The CF thickness, in mm, was measured at the central thickest area. The myometrial and sub-chorionic veins were excluded from the measurement, and all the chorionic measurements were taken during the relaxed phase of the uterus as contractions can suddenly increase the CF thickness. To ensure standardization, three measurements were taken from the thickest part of the CF in the vertical position of the uterus and the average value was recorded (Fig. 1).

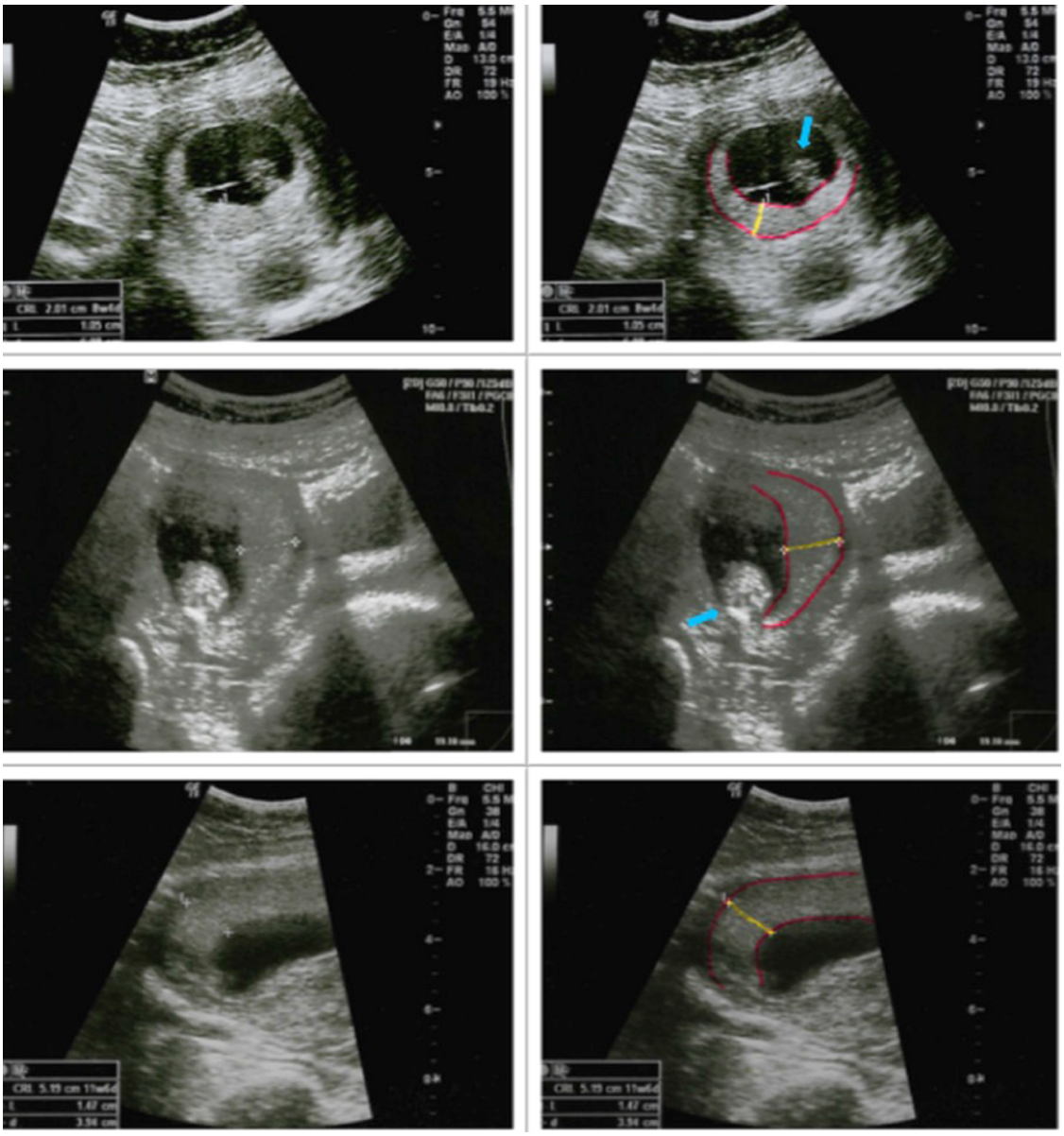

Fig. 1: Measurement of Chorion frondosum (CF) technique. Area of between red lines: CF, Yellow line: CF thickness, Blue arrow: Embryo

Statistical Analyses

The Kolmogorov-Smirnov normality test was used to evaluate the normal distribution of the numeric variables. The mean of normally distributed variables (CF thickness, body mass index (BMI), fT3, fT4, and β-hCG results) was compared using the unpaired t-test, the non-normal distributed variables (rest the of variables) were compared using the Mann-Whitney U test. The Spearman Correlation coefficient was calculated to examine the correlation between the data. p-value < 0.05 were considered statistically significant Statistical analyses were performed using GraphPad Prism version 7.00 (La Jolla, CA, USA).

The local ethics committee of Izmir Bakircay University approved the trial with 865 reference IDs. Written informed consent was obtained from all participants. All procedures performed in the current study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

RESULTS

We enrolled 96 participants who were admitted to our outpatient clinic in their first trimester of pregnancy. A total of 48 participants with hyperemesis gravidarum symptoms and +2/+3 urine ketone levels were enrolled in the study group and 48 healthy pregnant women in the first trimester of pregnancy were enrolled in the control group.

There were no statistically significant differences between the groups in demographic variables (Table 1). The mean gestational age was 8.69 (± 2.15) weeks in the HG group and 8.92 (±2.14) weeks in the control group. There was no statistical difference between the two groups in terms of gestational age (p=0.6). There were 27 patients in the HG group who had HG during a prior pregnancy while only 4 participants in the control group did, providing evidence of its tendency to repeat. It was found that nausea and vomiting started at 6 weeks and 6 days on average for the HG group, and 19 patients had to be hospitalized for treatment during the study period. The symptoms tended to end at the 18th week of pregnancy.

Table 1. Demographic data

	HG Group (mean) (n=48)	*Control Group (mean) (n=48)*	*p Value*
Age	27	25,7	p>0,05
BMI (kg/m2)	24,6	23,84	p>0,05
Pregnancy	1,95	2,29	p>0,05
Parity	0,75	0,85	p>0,05

Urine ketone levels were +2.7 in the HG group but +0.1 in the control group. The HG group had significantly higher urine ketone levels compared with the control group (p<0.001). The HG group's mean TSH levels were determined as 0.99 mU/L, and the control group's mean TSH level was 1.57 mU/L. Mean AST and ALT levels in HG were 19.69 to 19.65 U/L and for the control group, they were 18.22 to 18.22 U/L, respectively. There was no statistical difference between groups in terms of blood AST and ALT levels. TSH was significantly suppressed in the HG group (p=0.0019) but the differences in the fT3 and fT4 levels were not significant between the groups (p=0.07, p=0.49, respectively) (Table 2).

Table 1. Demographic data

	HG Group (mean) (n=48)	*Control Group (mean) (n=48)*	*p Value*
Age	27	25,7	p>0,05
BMI (kg/m2)	24,6	23,84	p>0,05
Pregnancy	1,95	2,29	p>0,05
Parity	0,75	0,85	p>0,05

Ultrasound examination revealed the mean CF thickness was 16.02 mm in the HG group. Conversely, the mean CF thickness was 13.50 mm in the control group. The CF thickness was significantly higher in the HG group than in the control group (p=0.02) (Table 2). Blood Blood-hCG values were also higher in the HG group following the CF thickness at 109620 mlU/ml in the HG group and 99201 mlU/ml in the control group. However, statistical significance was not achieved between the groups in terms of β-hCG levels (p=0.34).

DISCUSSION

Nausea and vomiting were seen as synonymous with the onset of pregnancy. The severity of nausea and vomiting is correlated with β-hCG levels and peaks in the 9th week of pregnancy (12). A diagnosis of hyperemesis gravidarum can be mentioned in cases where the pregnant woman's happiness about the relation between nausea/vomiting and a desired pregnancy is disrupted. Although the etiology of HG is cloudy, it is obvious that the quality of life of pregnant women is significantly decreased by HG (1,13,14). The current study was designed to compare CF thickness between women with HG and healthy controls. Based on our findings, we showed that the mean chorion frondosum thickness (CF) was significantly higher in the HG group compared to the controls. Literature is scarce on the relation between CF thickness and HG. However, researchers proved the link between insufficient placentation, HG, and the compensatory growth of the placenta.

Despite the cause of HG being unknown, its results have been extensively investigated. Bolin et al. showed an association between placental dysfunction and HG via a very large population-based cohort study. According to their research, HG cases in the first trimester had an increased risk of pre-eclampsia. Additionally, in cases presented in the second trimester with HG symptoms, the risk of preterm pre-eclampsia and placental abruption was increased two- to three-fold. These patients also had an increased risk for a small for gestational age birth (15). According to Bolin; HG and high β-hCG levels could be a compensatory mechanism for insufficient placentation. In an observational study, Ali et. al. showed that there was an association between low birth weight with HG. According to their study, there was an increased frequency of term-SGA, and preterm-SGA births in the HG group (8). Our findings are consistent with this study that concluded abnormal placentation may cause hyperemesis gravidarum (15). Thus, hyperemesis gravidarum and increased CF thickness, might be an early pregnancy indicator of a process that results in symptomatic placental dysfunction later. A relationship between low birth weight and HG was also demonstrated in a prospective cohort study with 2252 pregnant participants in Indonesia. However, in that study, they did not find any differences in terms of other placental functional disorders or poor neonatal outcomes (11).

Women with severe HG have a reduced caloric intake and lose nutrients and electrolytes (10). As a result of this, HG often involves ketonuria, which is frequently tested by physicians (9). We found that the HG group had significantly higher urine ketone levels compared with the control group, like the literature.

On the other hand, data indicating that the placental weight reflects the function of the placenta has provided new opportunities in daily practice (16,17). As a result of many observations, clinicians have concluded that maternal undernutrition causes increased placental weight but a decreased birth weight. Despite the inadequate nutrients, the compensatory growth of the placenta presents an explanation for maintaining the necessary nutrient transfer (18). In addition, prior trials have shown that placental efficiency changes in women who are exposed to famine. During the Dutch famine of 1944-45, pregnant women had increased placental weight which suggests compensatory growth where nutrients are inadequate (19). The same compensator mechanism might occur in women with severe hyperemesis gravidarum (11). Vandraas et al. also confirmed that HG has been associated with a high placental weight/birth weight (PW/BW) ratio in another large population-based study. However, the extent of the high PW/BW ratio was limited for women with female fetuses in their trials (10). Compensatory growth of the placenta in women with severe HG might result in increased CF thickness in accordance with our data. However, the explanation for this finding remains unclear.

The strengths of this study are its cross-sectional design and the performance of all the ultrasonic measurements by the same experienced physician to avoid inter-operator variability and bias. Additionally, three measurements were taken for all participants, and the average value was recorded for the standardization of ultrasonographic examinations. However, lack of follow-up for infants is a limitation of the study.

The main new finding of the present study is that the mean CF thickness was significantly higher in the HG group than in the control group. After that, studies can be conducted to express how CF thickness can be used in diagnosing and staging HG.

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Abbreviations list

HG: Hyperemesis gravidarum
CF: Chorion Frondosum
AST: Aspartate Aminotransferase
ALT: Alanine Aminotransferase
SGA: Small for Gestational Age
BMI: Body Mass Index

Ethics approval and consent to participate

The local ethics committee of Izmir Bakircay University approved the trial with 865 reference IDs. All procedures performed in the current study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publication

Written informed consent was obtained from all participants.

Availability of data and materials

Data related to the study is not stored digitally.

Competing interests

The authors declared no conflict of interest.

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Authors' contributions

Idea/Concept: CS Design: SAA, CS. Control/Supervision IK. Data Collection And/or Processing: SAA, CS, IK. Analysis And/or Interpretation: IK. Literature Review: SAA. Writing The Article: SAA. Critical Review: CS, IK.

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ORIGINAL ARTICLE

The Mediating Role of Psychological Distress in the Relationship Between Self-Compassion and Problematic Alcohol Use

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Abstract

Background: Alcohol is a widely consumed psychoactive substance, with significant global prevalence and a major impact on public health. The World Health Organization estimates that approximately 2.6 million deaths occur annually due to alcohol-related causes, highlighting the urgent need to address alcohol use disorders. Self-compassion, defined as being kind and understanding toward oneself in times of suffering or failure, has been linked to better emotional regulation and coping strategies. Understanding the relationship between self-compassion and problematic alcohol use may offer insights into effective intervention strategies.

Methods: This cross-sectional study involved 142 participants aged 18 and older with a history of alcohol use, assessed through the Alcohol Use Disorders Identification Test (AUDIT), the Self-Compassion Scale-Short Form (SCS-SF), and the Patient Health Questionnaire-4 (PHQ-4).

Results: The analysis revealed that individuals with higher self-compassion reported significantly lower levels of psychological distress. Conversely, those experiencing greater psychological distress exhibited higher levels of problematic alcohol use, indicated by elevated AUDIT scores. Mediation analysis demonstrated that psychological distress serves as a significant mediator in the relationship between self-compassion and alcohol use.

Conclusion: The findings emphasize the protective role of self-compassion against psychological distress and maladaptive drinking patterns. This study highlights the potential benefits of integrating self-compassion-based interventions into therapeutic interventions for individuals with alcohol use disorders. Future research should consider longitudinal designs and a broader range of socio-psychological factors to deepen our understanding of these relationships and enhance the effectiveness of treatment strategies.

Key words: Alcohol consumption, Psychological distress, Self-compassion

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INTRODUCTION

Alcohol, a psychoactive and toxic substance, exerts a profound global impact, contributing to the health burden of millions and accounting for approximately 2.6 million deaths annually. According to the World Health Organization (WHO), 7% of individuals aged 15 years and older are affected by alcohol use disorder (1). A significant challenge in the diagnosis and treatment of alcohol-related conditions lies in the conceptual variability among terms such as alcohol use and alcohol use disorders, which complicates the accurate application of diagnostic criteria. The WHO has addressed this complexity through a three-dimensional model that encompasses dependence, harmful use, and risky consumption. In line with this framework, the Alcohol Use Disorders Identification Test (AUDIT) is a widely utilized tool for assessing the severity of individual's alcohol use disorder (2).

Alcohol consumption is influenced by a range of individual, social, and societal factors. Empirical evidence underscores that alcohol use often arises as a coping mechanism in response to stress, relaxation, or socialization pressures (3). Furthermore, motivations such as enhancing social confidence and pursuing pleasure are recognized as additional drivers of alcohol consumption (4). Notably, individuals who exhibit poor stress management skills are more susceptible to alcohol misuse, as highlighted by Demirden and Sarıkoç (5). Psychological distress has been identified as a key correlate of alcohol consumption, further emphasizing the complex interplay between emorional regulation and substance use behaviors (6,7).

In recent years, the concept of self-compassion has garnered considerable attention within the psychological literature, Neff et al. (8) define self-compassion as "*being kind and understanding towards oneself, recognizing that pain and failure are universal human experiences, and maintaining a balanced awareness of one's emotions*." This construct, characterized by a non-judgmental attitude toward one's own shortcomings, has been identified as a protective factor against psychological distress (9,10). Self-compassion is inversely associated with conditions such as depression and shame, both of which are known contributors to problematic alcohol use (10). Emerging evidence suggest that self-compassion, may serve as a positive coping strategy, mitigating the risk of alcohol use and enhancing recovery outcomes in the treatment of alcohol use disorders (11).

The primary objective of this study is to investigate the relationship between alcohol consumption and self-compassion. The secondary aim of this study is to identify the mediating role of psychological distress in the relationship between alcohol consumption and self-compassion. A review of the literature reveals that in previous mediation analyses, the multifaceted construct of self-compassion has often been treated as an independent variable (12). However, when examining the effects of self-compassion on alcohol use, it is important to consider the possibility that these effects may occur indirectly through psychological distress. In this context, a study by Wisener and Khoury found that self-compassion was negatively associated with alcohol-related problems, particularly drinking to cope with anxiety. Specifically, self-compassion was linked to lower drinking motives for both depression and anxiety, with a stronger effect for depression (13). Self-compassion is known to have a negative relationship with components of psychological distress, such as depression, anxiety, and stress, while being positively associated with psychological well-being (14). In contrast, compassion-related therapies have been shown to reduce psychological distress and foster the development of adaptive coping strategies (14,15). Therefore, it can be hypothesized that interventions aimed at enhancing self-compassion may primarily exert their effects by reducing psychological distress and promoting emotional regulation, thereby preventing the activation of maladaptive coping mechanisms such as alcohol or substance use. Gaining an understanding of how psychological distress influences the interaction between self-compassion and alcohol consumption may offer valuable insights into the underlying mechanisms that connect these variables. Specifically, elucidating the role of psychological distress in this relationship holds potential to inform the development of more effective diagnostic and therapeutic strategies.

MATERIALS AND METHODS

Participants and Procedure

The cross-sectional research sample consists of 142 individuals aged 18 and over who consume alcohol, and were assessed through an online survey administered via social media between August 15, 2024, and September 15, 2024. Inclusion criteria are being 18 years of age or older, having a history of alcohol use, consenting to participate

by signing an informed consent form. Exclusion criteria include not having a history of alcohol use and having cognitive issues that would impede fulfilling the study requirements. Approval for the study was obtained from the Toros University Scientific Research and Publication Ethics Committee under decision number 119, dated June 25, 2024. All procedures adhered to the Helsinki Declaration and ethical standards. To prevent duplication, each participant was allowed to complete the survey only once using the same email address. Participants in the study first completed a sociodemographic data form. Following this, they responded to the AUDIT, which assesses alcohol consumption frequency and associated problems, the SCS-SF to determine levels of self-compassion, and the PHQ-4 to assess psychological distress levels. At the outset of the study, 151 participants were initially enrolled; however, 2 were excluded for not consuming alcohol, and 9 were excluded due to discontinuing the survey before completion.

Measures

Alcohol Use Disorders Identification Test (AUDIT), designed by researchers at the World Health Organization for use in primary health care settings was finalized by Babor et al. (16,17). It consists of 10 items rated on a 5-point Likert scale, with each item scored between 0 and 4, aimed at assessing drinking frequency, alcohol consumption, and associated problems. The first three items evaluate risky alcohol use, items 4 through 6 assess signs of dependence, and the last four items measure harmful alcohol use. The total possible score on the scale is 40, with a score of 8 or higher indicating the presence of alcohol-related problems (17). The Turkish validity and reliability study of the scale was conducted by Saatçioğlu et al. (2).

The Self-Compassion Scale-Short Form (SCS-SF) was developed a 12-item short version of the original scale, which includes six subscales: "self-kindness," "self-judgment," "common humanity," "isolation," "mindfulness," and "over-identification." The scale uses a 5-point Likert format, with each item rated from "1 = almost never" to "5 = almost always." The total score ranges from 12 to 60, with higher scores indicating a higher level of self-compassion (18). The Turkish validity and reliability study of the scale was conducted by Barutçu Yıldırım et al. (19).

Patient Health Questionnaire-4 (PHQ-4) developed by Kroenke et al. (20) consists of four items and is designed to briefly measure symptoms related to depression and anxiety. It uses a four-point Likert scale, with responses ranging from "0 = Not at all" to "3 = Nearly every day." The total score ranges from 0 to 12, with higher scores indicating the presence of psychological distress. The Turkish validity and reliability study of the scale was conducted by Demirci and Ekşi (21).

Statistical Analysis

Statistical analysis was conducted using the Jamovi v2.5 software package (22). Continuous variables are presented with means and standard deviations, while categorical variables are summarized as counts and percentages. Normality was evaluated through skewness and kurtosis values, in addition to a visual inspection of histogram plots. The literature suggests that a skewness value ranging from -2 to +2 and kurtosis values between -7 and +7 are indicative of a normal distribution (23). Correlations between variables were assessed using Pearson correlation analysis. Statistical significance was set at $p < .05$ for all tests. Finally, the mediating effect of psychological distress was tested using the Generalized Linear Model (GLM) mediation model of the medmod module within the Jamovi statistical software package (24). This analysis aimed to comprehensively investigate the total, direct, and indirect effects among the variables of interest. To enhance the robustness and reliability of the findings, a bootstrapping approach with 1000 replications was utilized, facilitating the computation of 95% confidence intervals for the mediated effect. This rigorous method not only strengthens the statistical inference but also provides deeper insights into the intricate relationships among the variables under consideration. Although it was considered that psychiatric diagnoses might be associated with the PHQ-4, they were not controlled for during the data analysis due to their categorical heterogeneity and the small sample size within each category.

RESULTS

The mean age of the 142 participants included in the study was 36.50 ± 12.71 years. Of the participants, 53.5% were female, and 85.2% were university graduates. The sociodemographic data of the participants are presented in Table 1.

Table 1. Sociodemographic data of the participants	
Variables	**Participants (n=142)**
Age (mean ± SD)	36.50 ± 12.71
Gender (n(%))	
Female	76 (53.5)
Male	66 (46.5)
Marital status (n(%))	
Single/Divorced	74 (52.1)
Married	68 (47.9)
Education level (n(%))	
University graduate	121 (85.2)
High school graduate	17 (12)
Other	4 (2.8)
Number of employees (n(%))	106 (74.6)
Presence of physical disease (n(%))	29 (20.4)
Presence of psychiatric history (n(%))	36 (25.4)
Presence of suicide attempts (n(%))	4 (2.8)
Cigarette use per day (n(%))	
0	66 (46.5)
1-10	26 (19.3)
10-20	34 (23.9)
>20	16 (11.3)
Presence of substance use (n(%))	5 (3.5)

The mean and standard deviation for the scales were computed, resulting in the following values: PHQ-4 was 6.18 ± 4.89, SFS-SF was 41.39 ± 8.33, and AUDIT was 6.18 ± 4.89. The correlation analysis data among the variables are presented in Table 2. A significant negative correlation was found between the PHQ-4 and SCS-SF scores ($r = –0.521$, $p < .001$), along with a negative correlation between the SFS-SF and AUDIT scores ($r = –0.210$, $p < .05$). Conversely, a significant positive correlation was identified between the PHQ-4 and AUDIT scores ($r = 0.290$, $p < .001$).

In order to examine the relationships among self-compassion, problematic alcohol use and the potential mediator role of psychological distress, a mediation analysis was conducted. The findings are presented in Figure 1. A significant negative correlation was identified between self-compassion and psychological distress ($\beta = -.521$, b=

-.185, 95% CI [-.233, -.138], p < .001). Additionally, a statistically significant positive correlation was found between psychological distress and problematic alcohol use (β = .248, b = .409, 95% CI [.109, .717], p = .008). The total effect of self-compassion on problematic alcohol use was significant (β = -.210, b = -.123, 95% CI [-.228, -0.037], p = .011). Nonetheless, the direct effect did not attain statistical significance (β = -.081, b = -.047, 95% CI [-.148, .048], p = .389). Importantly, the indirect effect of self-compassion on problematic alcohol use, as mediated by psychological distress, was statistically significant (β = -.129, b = -.076, 95% CI [-.147, -.019], p = .013).

Table 2. Correlation analysis and Cronbach alpha values of the scales

Variables	1	2	3	α
1. Patient Health Questionnaire-4	—			.879
2. Self-Compassion Scale-Short Form	-.521**	—		.809
3. Alcohol Use Disorders Identification Test	.290**	-.210*	—	.827

*p < .05, **p < .001

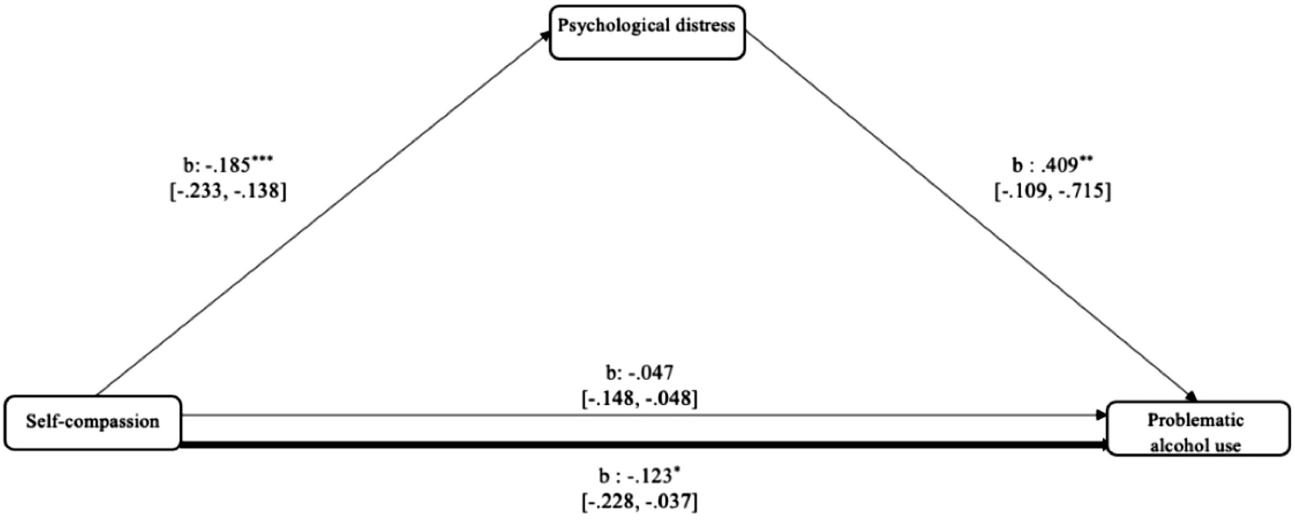

Figure 1: Mediation model of psychological distress in between self-compassion and problematic alcohol use (The unstandardized coefficients were reported, the dark-colored arrow represents the total path, *p<.05, **p<.01, **p<.001)

DISCUSSION

In this study, we investigated the association between self-compassion and problematic alcohol use, with a particular focus on exploring the mediating effects of psychological distress. The findings revealed a statistically significant negative correlation between self-compassion and problematic alcohol use, indicating that individuals with higher levels of self-compassion tend to report lower levels of problematic alcohol consumption. Furthermore, this relationship was mediated by psychological distress, underscoring its role as a significant intermediary in this association.

Psychological distress broadly conceptualized as a state of emotional suffering, encompasses symptoms of depression such as anhedonia, dysphoria, and hopelessness-and symptoms of anxiety, including restlessness and

tension (25). Previous research has firmly established a link between alcohol use disorder and psychological distress, highlighting the critical role of stress the initiation, maintenance and relapse of alcohol consumption (26,27). Self-medication theory suggest that alcohol use serves as a coping mechanism to mitigate psychological stress (28). This theory is particularly relevant in high-stress contexts, such as during the COVID-19 pandemic, where alcohol consumption has been shown to increase as a response to elevated stress levels (29). Consistent with the existing literature, our study identified a significant positive association between psychological distress and alcohol consumption. These findings suggest that heightened psychological distress may predispose individuals to engage in more problematic alcohol use, potentially as a maladaptive coping strategy. This correlation emphasizes the need to address psychological distress in both the prevention and treatment of alcohol use disorders, as it may play a pivotal role in the development and perpetuation of problematic drinking behaviors.

Adopting an attitude aligned with self-compassion is hypothesized to support individual well-being, reduce distress and foster adaptive functioning (27). Numerous studies in both clinical and non-clinical populations have demonstrated a significant negative correlation between self-compassion and various psychopathologies (9). Additionally, self-compassion-focused interventions have been shown to improve psychological outcomes and enhance quality of life, particularly in individuals with chronic illness (30). Consistent with these findings, our study identified a similar negative correlation between self-compassion and psychological distress, indicating that higher levels of self-compassion are associated with lower levels of distress. This reinforces the notion that cultivating self-compassion may serve as a protective factor against emotional suffering.

A growing body of literature has examined the relationship between self-compassion and problematic alcohol use, a maladaptive coping behavior. In a systematic review by Berg et al. (11), which analyzed 18 studies, individuals with higher levels of self-compassion and self-forgiveness demonstrated lower levels of problematic alcohol consumption. Additionally, self-compassion and self-forgiveness were associated with coping-motivated drinking and increased social support. Rendon (31) explored the relationships among alcohol use, self-compassion, mindfulness, and self-esteem in a cohort of 300 psychology students. This study found a negative correlation between alcohol use and both self-compassion and self-esteem, with psychological symptoms partially mediating these relationships. Notably, self-compassion emerged as a stronger predictor of psychological health than mindfulness. Janicki (32) further examined these constructs among individuals in sober recovery and those undergoing treatment for alcohol use disorders. Results indicated that individuals in recovery exhibited higher levels of self-compassion and lower levels of depression and anxiety. It was posited that integrating self-compassion training into alcohol use disorder treatment programs could yield significant benefits. In our study, we obtained findings that align with existing research, revealing a significant relationship between self-compassion and problematic alcohol use. Specifically, individuals with lower levels of self-compassion were more likely to engage in problematic drinking behaviors. These findings suggest that fostering self-compassion may serve as a valuable target for interventions aimed at reducing problematic alcohol consumption.

Upon reviewing the literature, it appears that studies modeling self-compassion as an independent variable are relatively less common, with most research focusing on examining mediating factors in the relationship between self-compassion and psychological distress. For instance, in this context, one study explored the role of perceived stress in the relationships between self-compassion and anxiety as well as depression, demonstrating a partial mediating effect (33). In another study, it was found that rumination had a stronger effect in the relationship between self-compassion and depression, while worry played a more significant role in the relationship between self-compassion and anxiety (34). Additionally, in the relationship between self-compassion and depressive symptoms, the mediating effects of avoidance and activation processes have been identified, with an emphasis on the behavioral model of depression (35). In this study, psychological distress appears to mediate the relationship between self-compassion and alcohol use, indicating that interventions to enhance self-compassion may not only directly reduce alcohol-related behaviors but also alleviate the psychological distress frequently associated with alcohol misuse. The lack of a significant direct effect of self-compassion on problematic alcohol use highlights the multidimensional and complex nature of this relationship. This suggests that mediating factors, such as psychological distress, play a critical role

in shaping a mechanism through which self-compassion indirectly influences alcohol consumption. Therefore, understanding the relationship between self-compassion and alcohol use should not be limited to direct effects, but should also consider how individuals cope with emotional distress and stress. Ultimately, conceptualizing self-compassion as an independent variable provides a novel perspective for a deeper understanding of behavioral issues such as alcohol use, thus holding the potential to enhance the effectiveness of intervention strategies.

It is important to consider the potential influence of socio-cultural factors on these observed relationships. Socio-cultural context plays a crucial role in shaping individuals' emotional regulation, coping strategies, and substance use behaviors. As an example, cultural norms may encourage alcohol use as a social activity or a coping mechanism, while simultaneously influencing how individuals express and cope with their emotional distress (36, 37). In certain cultures, the expression of emotional suffering or personal weaknesses may be stigmatized (38). On the other hand, in cultures where social support systems are more robust, psychological distress is more likely to be met with understanding, and stigma is comparatively lower, the practice of self-compassion may be more readily embraced, which could mitigate psychological distress and reduce the risk of problematic alcohol use.

Exploring the role of socio-cultural factors in how individuals cope with psychological distress and engage in alcohol use would enhance our understanding of these relationships and inform more personalized and contextually relevant treatment approaches. For instance, the effectiveness of self-compassion-based interventions may vary depending on cultural values and the strength of social support networks. Future research should, therefore, take these factors into account, aiming to develop culturally sensitive therapeutic strategies that can improve treatment outcomes across diverse populations.

In conclusion, this study highlights the critical role of self-compassion as an effective coping mechanism that mitigates psychological distress and promotes positive affect, thereby offering protection against problematic alcohol use. These findings underscore the potential value of incorporating self-compassion training into therapeutic interventions for individuals with alcohol use disorders, suggesting that such approaches may play a crucial role in reducing symptoms and improving outcomes in this population.

This study offers valuable insights and contributes to the growing body of literature on the complex association between self-compassion and problematic alcohol use. Nonetheless, several limitations should be acknowledged. First, the cross-sectional design limits the ability to infer longitudinal or causal relationships between the variables of interest. Second, the relatively modest sample size may constrain the generalizability of the findings to broader populations. In the post-hoc evaluation of the sample size for the study, the calculation method proposed by Fritz and MacKinnon (39) was employed, which indicated that approximately 400 participants should have been included in the study. However, due to constraints related to the data collection period and conditions, the sample size obtained in this study was limited to 142 participants. This limitation should be acknowledged as a constraint that may have compromised the statistical power of the study and, consequently, the reliability of the results. Although psychological distress was examined, the study did not account for various socio-psychological factors—such as social support, childhood trauma, or personality traits—that may influence the relationship between self-compassion and problematic alcohol use. The exclusion of these factors could potentially overlook significant variables affecting this association. Furthermore, the homogeneity of the participant demographic may restrict the applicability of the findings to diverse populations or cultural contexts. Finally, the use of self-reported measures, which are susceptible to social desirability bias, and the online participation method are factors that limit the diversity of the sample and affect the generalizability of the findings.

Future research should consider employing longitudinal designs to elucidate the causal relationships between self-compassion, psychological distress, and problematic alcohol use over time. Increasing sample size and enhancing participant diversity would improve the generalizability of the results. Moreover, the inclusion of qualitative methodologies could offer a more nuanced understanding of individuals' experiences with self-compassion and alcohol use. Finally, clinical intervention studies that focus on enhancing self-compassion as a therapeutic strategy may provide critical evidence regarding its efficacy in reducing alcohol misuse in clinical populations.

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Abbreviations list

AUDIT: Alcohol Use Disorders Identification Test
GLM: Generalized Linear Model
PHQ-4: Patient Health Questionnaire-4
SCS-SF: Self-Compassion Scale-Short Form
WHO: World Health Organization

Ethics approval and consent to participate

Permission was obtained from the Toros University Scientific Research and Publication Ethics Committee (Approval no: 25.06.2024/119), and Helsinki Declaration rules were followed to conduct this study. All participants provided informed consent.

Consent for publication

Not applicable

Availability of data and materials

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Competing interests

The authors report no conflict of interest.

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Authors' contributions

CÜ and MKM contributed to the study conception and design. Material preparation, data collection, and analysis were performed by CÜ and MKM. The first draft of the manuscript was written by CÜ and MKM commented on previous versions. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

The Relationship Between Vaginal Microbiome and Infertility: A Descriptive Trend Analysis (1947-2024)

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Abstract

Background: The menstrual cycle and gestational state, as well as other physiological factors, have a substantial impact on the vaginal microbiome, which aids in preventing infections caused by pathogenic microorganisms. Dysbiosis of the vaginal microbiome can cause infertility as well as adverse outcomes in pregnancy. The aim of this study is to examine the studies examining the relationship between vaginal microbiota and infertility in Scopus and WoS databases in terms of different variables and to compare them by revealing their bibliometric profiles.

Methods: We conducted a bibliometric study to determine the scholarly papers published across all journals that addressed the relationship between the vaginal microbiome and infertility. Scopus and Web of Science (WoS) databases were accessed for all the published articles on vaginal microbiome and infertility. The number of publications by year, language, country, institute, author, journal, and impact factors (IF) are reported as bibliometric indicators.

Results: Our findings indicate that the topic is much understudied; only 161 papers met the criteria set forth in our research. But, a striking increase was observed after 2020. The United States, China and Italy drew attention as the countries that contributed the most to the literature.

Conclusion: Prospective and clinical studies on the mechanisms linking the vaginal microbiome of the female reproductive system to reproductive physiology may shed light on infertility treatment.

Key words: Bibliometric analysis; dysbiosis; infertility; vaginal microbiome

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INTRODUCTION

An essential part of human physiological processes like immunity and nutrition is handled by microbiome. In a cooperative relationship, they safeguard the human host from a variety of pathogenic microorganisms in exchange for the host's supply of food and shelter (1). Human Microbiome Project (HMP) and Integrative HMP (iHMP) are collaborative projects that have investigated the skin, gut, vaginal, and oral communities to evaluate the metagenomics, distributions, and characteristics of microorganisms from specific anatomical locations (2). The outcomes of HMP are thought to be important for determining the pathophysiology of disease and the association between changes in the microbiota and the identification of biomarkers for diagnostic purposes (3). The female genital tract also has its own microbiome, which constitutes 9% of all the bacteria in female body (4). The composition of the microbial communities in microbiome has an essential impact for the health status of an individual. The host and the native bacteria in the vaginal environment are considered to coexist in a symbiotic relationship (5). Colonization and domination of lactobacilli, typically by species like *Lactobacillus crispatus, Lactobacillus gasseri, Lactobacillus iners, and Lactobacillus jensenii,* are crucial characteristics of a healthy vaginal microbiome (6). Certain strains of lactobacilli work with the host cells and a woman's genome type to increase the production of the proper mucus and preserve the vagina's acidic environment (7). Recent research, however, has shown that there are more than 200 phylotypes in the female vagina, with the phyla Firmicutes, Bacteroidetes, Actinobacteria, and Fusobacteria being the most prevalent (8). The bacterial communities in the vaginal microflora might vary depending on factors like gestational status, contraceptive use, menstrual cycle, and sexual activity (9,10). According to how metabolic and microbial variables interact, vaginal microbiome dysbiosis can be either physiological or pathogenic. The vaginal microbiome changes significantly during pregnancy. With the dominance of one or more *Lactobacillus* species at the beginning of pregnancy, it becomes more stable and less diverse (11). Aberrant vaginal microbiome is more prevalent in women who experience idiopathic infertility (12). According to in vivo studies, the vaginal microbiome has a significant impact in embryo implantation and the pregnancy's outcome (11).

Bibliometric analyses have emerged as one of the most widely used tools to assess the reliability, scientific value, and significance of scientific research (13). Although it is not a foolproof method, bibliometrics can be a useful tool for funding organizations to use for allocating resources and for spotting possible research deficits in a subject (14). Analyzing the relationships between pertinent research institutions and evaluating the general trend of research activity can be accomplished effectively with bibliometric studies. We conducted a bibliometric study to determine the scholarly papers published across all journals that addressed the relationship between the vaginal microbiome and infertility. In order to define the direction for future investigations, we also thoroughly compared the findings of the most-cited studies. Using the bibliometric analysis method, it was aimed to examine the trends of the studies examining the relationship between "vaginal microbiota and infertility" indexed by Scopus and Web of Science (WOS), to evaluate the results of the most cited studies and to shed light on future studies.

MATERIALS AND METHODS

In December 2024, the Scopus library, ISI Web of Science Core Collection (WoS) and InCites Journal Citation Reports (JCR) were accessed for all the published articles on vaginal microbiome and infertility, also for the citations of these studies. Scopus and WoS were used as the databases because of their broader coverage of journals compared with the other databases. In the research, the bibliometric profile of academic studies on the vaginal microbiome-infertility relationship in WoS and Scopus, which are the two most preferred large databases for researching academic studies, was determined and compared. Thus, the trends, changes and innovations of the studies in both databases were revealed. The aim of the study was to create and compare the bibliometric profiles of academic studies on the vaginal microbiome-infertility relationship in Web of Science (WoS) and Scopus, which are the two most preferred databases for researching academic studies. No time limitation was set for the search, original articles and reviews were included. To ensure a comprehensive coverage of all the available literature, studies pertaining to fields other than medicine, studies on nonhuman subjects, and those without abstracts were also included. We used "vaginal microbiome", "vaginal microbiota" and "vaginal flora"

for topical retrieval and the following search queries in titles, abstracts, and keywords: (vaginal microbiome AND infertility), (vaginal microbiota AND infertility), (vaginal flora AND infertility), (vaginal microbiom AND infertile), (vaginal microbiota AND infertile) and (vaginal flora AND infertile). The search protocol used here was undertaken was restricted to the articles published in English. The number of publications by year, publishing language, country, institute, author, journal, and impact factors (IF) are reported as bibliometric indicators.

Additionally, 15 countries, and 10 scientific publications that received the most citations in the literature are all discussed. The average number of citations per article, the overall number of citations, and the IF of the journals that published the articles are considered when evaluating the quality of publications. The document possessed the article's titles, publication year, document's type, abstract, authors and journals names, author's institution, journal impact factor, author's country, citations, database and language used were exported to VOSviewer software. VOSviewer, a freely available software tool for analysis, was used to make visualization maps in this study. The software primarily performs the following analyses for our study: keyword co-occurrence analysis, author and co-cited author analysis, journal and co-cited journal analysis, and country and institution analysis. A node on the VOSviewer-generated map stands for an item, such as a nation, organization, journal, or author. The number and classification of these objects are indicated by the node's size and color, accordingly. The degree of cooperation or co-citation of the items is shown by the line thickness between nodes. Statistical analysis: Frequency, percentage and arithmetic mean values were calculated in the analysis of the collected data. For statistical calculations, Microsoft Excel (Ver. 2013) was used. The data used in this study are publicly available and contain no protected health information. Therefore, institutional review board approval was not sought. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies.

RESULTS

In this study, based on the search strategy presented in the methods, 161 and 163 articles were found in the Scopus and Web of Science databases between 1947 and 2024, respectively. The first article on vaginal microbiome and infertility was published in 2005, and it did not exceed ten articles per year until the end of the 2010s. In the analysis made according to the year the studies were published, an insignificant increase in the number of articles was observed until 2019, while a striking increase was observed after 2020 (Figure 1). Accordingly, there was a linear increase in the number of citations per article over time. When the studies were evaluated in terms of research subject; the majority of the publications were found in the field of "Obstetrics and Gynecology" (27.9%). This is followed by "Reproductive Biology" (21.7%), "Microbiology" (21.1%), "Immunology" (13.0%), "Medicine General Internal" (8%), "Biochemistry Molecular Biology" (6.2%) and other topics. The international literature currently includes articles from 49 different countries in terms of countries of the published literature on vaginal microbiome and infertility. The United States (US) accounts for 25.4% of all publications, ahead of China, Italy and Spain in terms of the number of publications. Figure 2 shows the top 10 countries by number of publications. Nanchang University in China and Sapienza University in Italy contributed three publications each, providing the most scientific data on vaginal microbiome and infertility. The top ten journals preferred for publication of articles on vaginal microbiome and infertility are listed in Table 1. The IF values of the journals in the list are between 3.1 and 7.0. A total of 45 articles on vaginal microbiome and infertility were published in the top ten journals listed in Table 1. In addition, 20% (n=9) of the retrieved articles were published in the journal "Frontiers in Cellular and Infection Microbiology" (IF = 4.6). The top 10 most cited articles are presented in Table 2. The most cited study was the article "The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases" published in the journal "Nature Communications" (15). When the distribution of the number of citations of the articles by year is evaluated, it is seen that it has increased since 2020 and reached the highest number in 2024 (Figure 1). The network map of the publications on the vaginal microbiome-infertility relationship was displayed using the VOSviewer program. The documents shown on the map were calculated by selecting the minimum citation number as "2". It was seen that there was a complex and intense relationship between these documents on the map (Figure 3). More than one cluster was formed in

different colors between these documents. In addition, the co-citation analysis network map on the vaginal microbiome-infertility relationship was visualized in the VOSviewer program (Figure 4). When the minimum citation number was selected as 20, 45 of the 5569 cited authors met the threshold value. The author with the highest number of co-citations was Moreno I. with 172 citations (16). When the co-citation analyzes of the vaginal microbiota-infertility studies were evaluated, it was seen that the literature was divided into three groups: Moreno I. (endometrial (effect of the microbiome on implantation), Ravel J. (effects of the vaginal microbiome on female physiology) and Haahr T. (effect of bacterial vaginosis in IVF patients) (16-18).

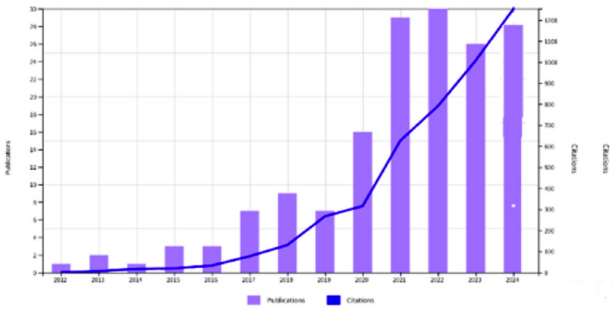

Figure 1: Publication year-specific and citation trends in the quantity of publications research on vaginal microbiome and infertility

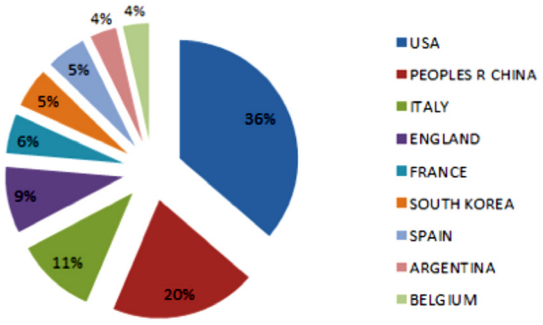

Figure 2: The top ten countries regarding the quantity of publications on vaginal microbiome and infertility

Table 1. The top 10 Journals in terms of publication quantity.

Journal	Number of Publications	Total Citations	Average citation per year	Impact Factor (2023)
Frontiers in Cellular and Infection Microbiology	9	158	19.75	4.6
Journal of Assisted Reproduction and Genetics	6	237	16.93	3.2
American Journal of Reproductive Immunology	4	79	19.88	3.1
Diagnostics	4	33	11	3.5
Frontiers in Endocrinology	4	26	8.67	5.2
International Journal of Molecular Sciences	4	57	14.25	6.2
Journal of Clinical Medicine	4	32	6.4	4.2
Microorganisms	4	58	11.6	4.1
Archives of Gynecology and Obstetrics	3	32	6.4	2.5
Fertility and Sterility	3	422	32.4	7.0

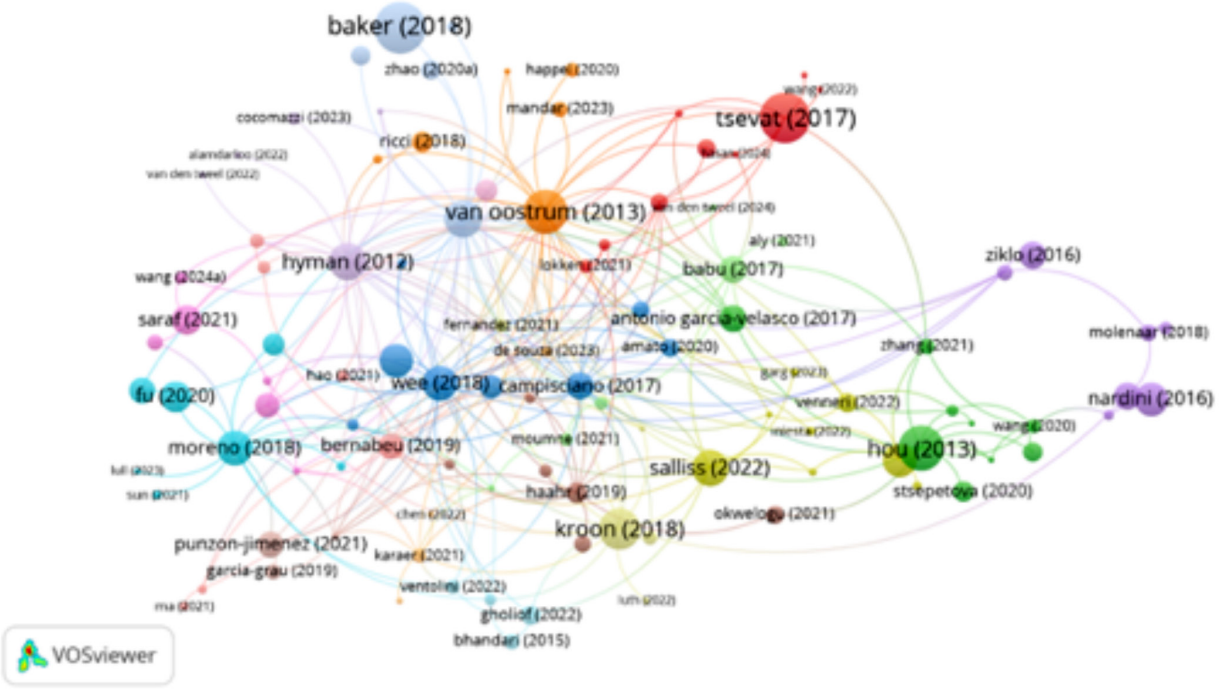

Figure 3: The network map of the publications on the vaginal microbiome-infertility relationship (VOSviewer)

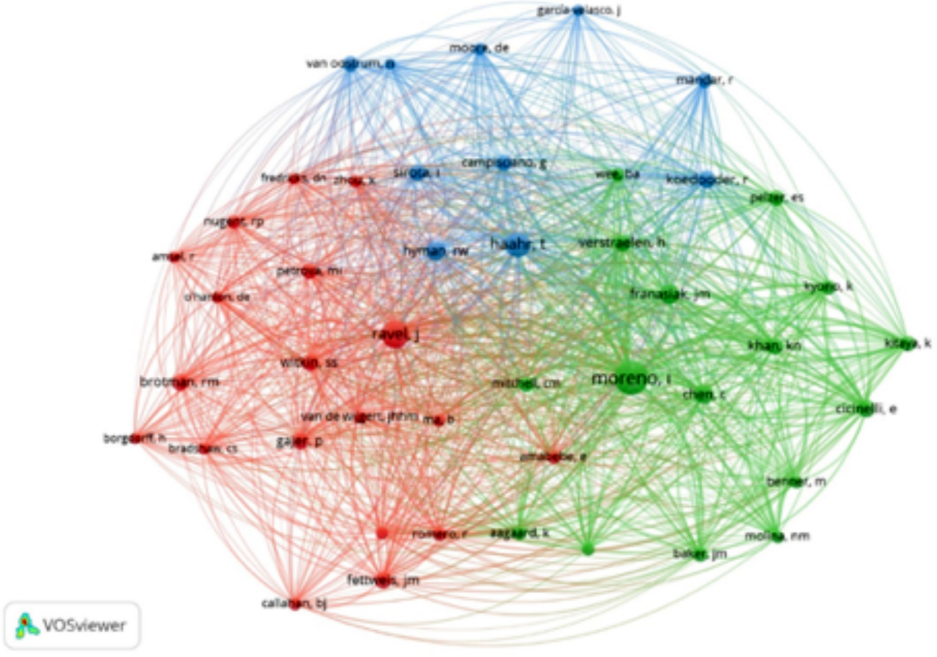

Figure 4: The co-citation analysis network map on the vaginal microbiome-infertility relationship (VOSviewer)

Table 2. The top 10 Studies in terms of citation quantity

Authors	ArticleTitle	Source Title	Year	Country	Journal IF	Times Cited
Chen et al. (15)	The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases	*Nature Communications*	2017	China	14.7	534
Baker et al. (25)	Uterine Microbiota: Residents, Tourists, or invaders?	*Frontiers in İmmunology*	2018	USA	0.95	231
Tsevat et al. (19)	Sexually transmitted diseases and infertility	*American Journal of Obstetrics and Gynecology*	2017	USA	3.4	219
Hou et al. (26)	Microbiota of the seminal fluid from healthy and infertile men	*Fertility and sterility*	2013	USA	2.25	171
vanOostrum et al. (21)	Risks associated with bacterial vaginosis in infertility patients: a systematic review and meta-analysis	*Human reproduction*	2013	Belgium	2.19	163
Kroon et al. (6)	Cervicovaginal microbiota, women's health, and reproductive outcomes	*Fertility and Sterility*	2018	Australia	2,18	144
Sirota et al. (24)	Potential influence of the microbiome on infertility and assisted reproductive technology	*Seminars in Reproductive Medicine*	2014	USA	1,3	121
Hyman et al. (22)	The dynamics of the vaginal microbiome during infertility therapy with in vitro fertilization-embryo transfer	*Journal of assited reproduction and genetics*	2012	USA	0.94	116
Saliss et al. (27)	The role of gut and genital microbiota and the estrobolome in endometriosis, infertility and chronic pelvic pain	*Human reproduction update*	2022	USA	3.62	110
Moreno et al. (16)	Evidence that the endometrial microbiota has an effect on implantation success or failure	*American Journal of Obstetrics and Gynecology*	2016	Spain	2.25	107

DISCUSSION

Chen et al. (15) conducted urogenital system microbiome analyzes of 10 women in a study published in the journal "Nature Communications" with IF 3.13 in 2017 and found that cervical sampling would be sufficient without the need for more invasive sampling due to the similarity between uterine microbiome and cervical microbiome. Furthermore, it has been revealed that bacterial vaginosis is associated with preterm birth and sexually transmitted diseases (STDs), with a high *Lactobacillus* content acting as a protective factor. Moreno et al. (16) examined the effect of vaginal microbiome on implantation in a study published in the "American Journal of Obstetrics and Gynecology" in 2015 with an IF of 3.22. Low *Lactobacillus* content have been shown to be associated with failed implantation (p=0.02) (16). Smith et al. (17) mentioned the effects of vaginal microbiome on female reproductive physiology in the study published in the "Journal of Physiology" with an IF of

6.22 in 2017. Tsevat et al. (19) in the study published in the "American Journal of Obstetrics and Gynecology" with an IF of 3.22 in 2017, it was noted that *Chlamydia trachomatis and Neisseria gonorrhoeae* are absolutely associated with tubal factor infertility and that the microbiome of women of reproductive age is associated with infertility.

Yarbrough et al. (20) in the study published in the journal "Human Reproduction Update" with an IF 3.2 in 2015, it was noted that antimicrobial peptides (AMP) produced by vaginal microbiome components in the female reproductive system are a protective barrier against exogenous pathogens. vanOostrum et al. (21) in a meta-analysis study, published in the journal "Human Reproduction" with an IF of 2.22, in 2013, it was found that bacterial vaginosis was associated with infertility and In vitro fertilization (IVF) failure. Additionally, it was discovered that it only had an impact on preclinical pregnancy loss and not on the incidence of pregnancy. Hyman et al. (22) in a study published in the "Journal of Assisted Reproduction and Genetics" with an IF 0.92 in 2012, the clinical correlation of vaginal microbiome with IVF treatment was investigated. Vaginal sampling of 30 women during IVF and if pregnant, 4th-6th week of pregnancy taken during the week. It has been discovered that the vaginal microbiome influences pregnancy success on the day of embryo transfer and that the bacterial diversity of the vaginal microbiome changes during several hormone cycles.

When the most cited articles were examined, very few studies were found showing the clinical correlation of vaginal microbiota with reproductive physiology and infertility. The role of microbiome in examining the physiology of the reproductive system is undeniable and more screening and sampling is needed in the clinical setting. In the majority of studies, attention is drawn to the importance of *Lactobacillus*, and it emerges as a factor that should be evaluated in the prevention of infections and, accordingly, reproductive failure. Prospective studies evaluating demographic and behavioral factors, the effects of co-infections, and the impact of the vaginal microbiome will provide guidance to unravel the relationship between these pathogens and impaired fertility and adverse pregnancy outcomes.

In human reproduction, the reproductive tract microbiota at the embryo-maternal interface is gaining more interest since it may affect the mother's and the child's health both before and after delivery, in addition to the likelihood of becoming pregnant (4). In a study assessing vaginal and endometrial samples of healthy volunteers, non-infertile patients, and patients receiving in vitro fertilization (IVF) treatment, results showed that the healthy volunteers presented low diversity microbiota (≥90% *Lactobacillus* species), with 25% of the women presenting different taxonomic profiles in endometrial and vaginal samples (23). Researchers links unfavorable pregnancy outcomes following both natural and in vitro fertilization (IVF) conceptions to opportunistic infections in the lower female reproductive tract (18). Thus, it is worth considering whether in vitro fertilization (IVF) outcomes could be influenced by the microbial taxa present in the reproductive tract during infertility treatment (4). In fact, bacterial vaginosis and other variations from the low-diversity vaginal microbiome have been strongly linked to lower post-IVF pregnancy rates (18). As a limitation of our study, we would like to point out that only the studies included in the WoS and Scopus databases were included in our study, and therefore it is insufficient to cover the entire literature.

In this study, 161 original studies, from 1947 to 2024, on the relationship of the vaginal microbiome with infertility were retrieved from the WoS and Scopus databases and analyzed using VOSviewer to generate knowledge maps. This bibliometric analysis reveals a surge in microbiome research over the past three years, with the goal of understanding the role of vaginal microbiome in successful reproduction and proving its value. We also listed the distribution of journals, authors and countries on the subject and highlighted the key features of the vaginal microbiome by examining the most cited articles in databases. The United States, China and Italy drew attention as the countries that contributed the most to the literature. Prospective and clinical studies on the mechanisms linking the vaginal microbiome of the female reproductive system to reproductive physiology may shed light on infertility treatment.

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Abbreviations list

WoS: Web of Science
IF: Impact factor
HMP: Human Microbiome Project
iHMP: Integrative HMP
JCR: Journal Citation Reports
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
STDS: Sexually transmitted diseases
AMP: Antimicrobial peptides
IVF: In vitro fertilization

Ethics approval and consent to participate

The data used in this study are publicly available; contain no protected health information or patient information from the authors' institutions. Neither human nor animal subject data are used in our investigation. Therefore, institutional review board approval was not sought.

Consent for publication

Not applicable since this study contains no protected health information or patient information.

Availability of data and materials

The data used in this study are publicly available. Also, the data that support the findings of this study are available on request from the corresponding author.

Competing interests

None to declare.

Funding

This research received no external funding.

Authors' contributions

Idea/Concept: ME, İK. Desıgn: İK. Control/Supervısıon ME, İK. Data Collectıon And/Or Processıng: ME, İK. Analysıs And/Or Interpretatıon: ME, İK. Lıterature Revıew: ME, İK. Wrıtıng The Artıcle: ME. Crıtıcal Revıew: ME, İK. References And Fundıngs: İK. Materıals: İK.

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ORIGINAL ARTICLE

Tension Band Wiring of AO 34C Patella Fractures: Relationship Between Fracture Subtype and Early-Term Functional Results

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Abstract

Background: Patella fractures account for about 1% of skeletal injuries, leading to pain, limited knee motion, extensor weakness, and difficulty with weight-bearing. This study retrospectively assessed clinical and radiological outcomes of patients with OTA/AO Type 34-C patella fractures treated with tension band wiring, analyzing fracture type and treatment outcomes in relation to daily activities to identify potential correlations.

Methods: Between 2017 and 2024, 28 patients treated for OTA/AO Type 34-C fractures with tension band wiring and attending regular follow-ups were included. Data on age, gender, ASA score, AO fracture type, and fracture side were collected. At six months postoperatively, KOOS, VAS, and knee range of motion (ROM) were assessed.

Results: The 28 participants had an average age of 45 ± 19.65 years. No significant differences were found between males and females in ROM, KOOS scores, or VAS ($p > 0.05$). AO34-C3 fractures were the most common. AO Type C1 fractures had the highest KOOS scores and lowest VAS pain scores, while AO34-C3 fractures had the lowest KOOS scores and highest VAS scores. However, no significant differences were found in ROM, KOOS, or VAS scores across OTA/AO fracture subtypes (C1, C2, C3) or fracture side ($p > 0.05$).

Conclusion: This study highlights that while literature reports poor medium- and long-term outcomes for comminuted, displaced patella fractures, the early period differences in outcomes between subtypes, though not statistically significant, suggest other contributing factors. The prevalence of OTA/AO Type C3 fractures emphasizes the need for tailored treatment protocols for this subtype.

Keywords: Patella fracture, OTA/AO 34-C subtype, early functional results, pain, range of motion.

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INTRODUCTION

The patella plays a critical role in the extensor mechanism by enhancing the mechanical advantage of the quadriceps muscle, which is essential for effective knee extension during walking and other weight-bearing tasks. As a sesamoid bone, the patella links the proximal quadriceps tendon and the distal patellar ligament, contributing to knee joint stability and force transmission. Fractures of the patella can disrupt this mechanism, leading to extensor weakness, reduced knee range of motion (ROM), and long-term complications such as patellofemoral or tibiofemoral arthritis (1-3).

Patella fractures are relatively uncommon, accounting for approximately 1% of all skeletal injuries, and predominantly affect individuals aged 20-50 years, typically occuring due to direct blow or indirectly from forceful quadriceps contraction against a flexed knee. Surgical treatment is commonly indicated in cases of extensor mechanism failure, articular displacement >2 mm, or interfragmentary displacement >3 mm (4). The primary goals of surgical fixation include anatomical reduction, stable fixation capable of withstanding physiological forces during healing, and preservation of extensor mechanism integrity to allow early mobilization. Persistent knee stiffness, extensor lag, and patellofemoral osteoarthritis may arise, especially in cases of comminuted fractures (2).

The AO/OTA classification provides a standardized approach with type 34-C specifically referring to complete articular fractures with varying degrees of comminution. Despite the utility of this classification, limited data exist correlating early postoperative outcomes with specific fracture subtypes within the 34-C category. Our study aims to address this gap by evaluating short-term postoperative physical examination findings, functional outcomes, and pain levels in patients with AO/OTA 34-C patella fracture subtypes, thereby contributing to the existing literature on fracture management and recovery patterns

MATERIALS AND METHODS

After Ethical approval for this study was obtained from Local Ethics Committee of the Tertiary Hospital (28.06.2024,No:2024/351), database records were reviewed retrospectively to identify patients who underwent tension band wiring for OTA/AO Type 3C patella fractures between January 2017 and January 2024 and attended their postoperative six-month follow-up. Patients who had preexisting knee conditions visible on the initial radiographs, patients who had fixation with screws either alone or in combination with tension band wiring and patients with additional ipsilateral lower extremity fractures were excluded from the study. Of the 32 patients treated with tension band wiring, two were lost in follow-up, one patient required implant removal due to symptomatic hardware prominence and another patient underwent implant removal for infection before the completion of postoperative sixth month. Therefore, 28 patients were enrolled in the study. Informed consents had been routinely obtained from all patients before the surgery. Data included age, gender, ASA score, side and the subtype of the fracture were collected (Figure-1). Fracture classification was initially performed by an attending surgeon and subsequently reviewed and revised as needed by a senior orthopedic surgeon. Anteroposterior (Figure 2a) and lateral knee radiographs (Figure 2b) confirming fracture union, knee joint range of motion (ROM), Knee Injury and Osteoarthritis Outcome Score (KOOS) with related subscales and Visual Analogue Scale (VAS) scores at the six-month postoperative follow-up were documented from outpatient clinic records.

In this study, internal fixation had been achieved using a modified tension band technique, in which a metallic cerclage wire was tightened in a figure-of-eight fashion in 16 patient and in circular fashion in 12 patients around vertically placed Kirschner wires (K-wires) to convert tensile forces on the anterior surface into compressive forces at the joint surface as described in the literature (5) (Figure 3a and 3b). Operations were performed by three different surgeons. Reduction quality and fixation stability was assessed by intraoperative flouroscopic images and digital palpation of the patellofemoral articular surface by the attending surgeon. Patients were instructed to wear an adjustable knee brace with full extension for the postoperative first two weeks. After the second week, controlled range of motion exercises were initiated. From the sixth week onward, full weight-bearing and full range of motion exercises were introduced.

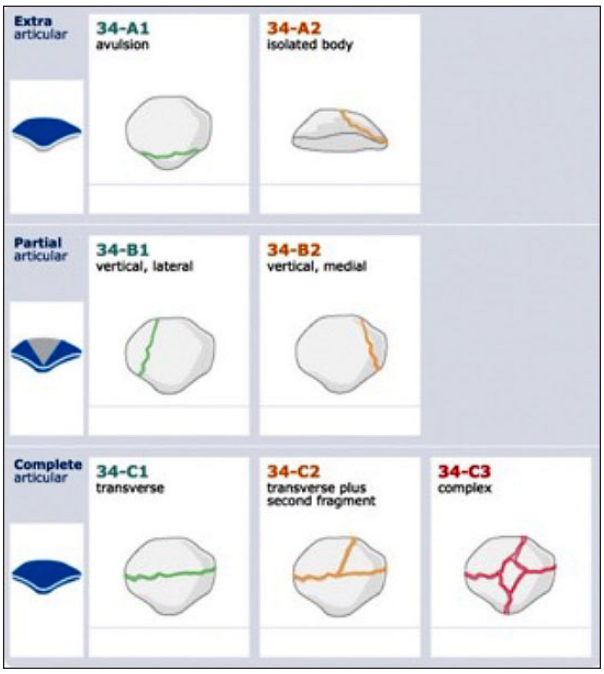

Figure 1: OTA/AO Classification for Patella Fractures: The OTA/AO classification categorizes patella fractures based on fracture morphology by indicating increased complexity. Type 34-A describes extra-articular fractures, Type 34-B includes partial articular fractures, and Type 34-C fractures represent complete articular fractures of the patella, involving disruption of the entire articular surface. They are further divided into: 34-C1: Simple, non-comminuted complete articular fractures. 34-C2: Complete articular fractures with partial comminution. 34-C3: Severely comminuted complete articular fractures with multiple fragments.

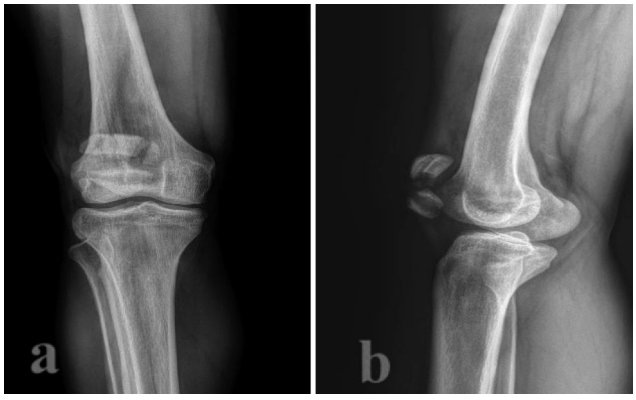

Figure 2a: Anteroposterior (AP) x-ray of OTA/AO Type 3C patella fracture, b. Lateral x-ray of OTA/AO Type 3C patella fracture demonstrating the multiple fracture lines and disrupted articular surface.

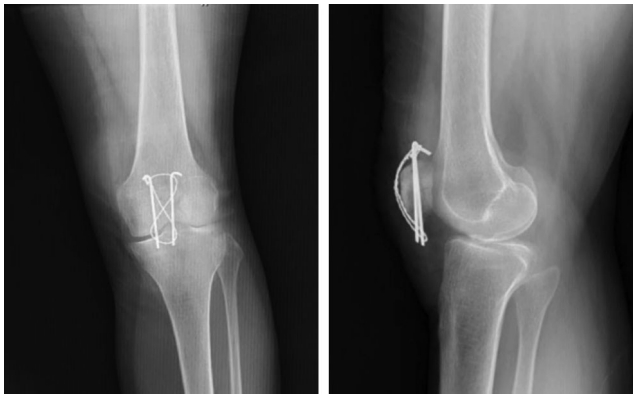

Figure 3a: Anteroposterior (AP) x-ray of tension band wiring b. Lateral x-ray of tension band wiring in figure-of-eight fashion around two vertically placed kirschner wires, performed after anatomical congruity of patellofemoral articular surface was achieved.

Statistical analyses were performed using IBM SPSS version 22.0 (IBM Corporation, Armonk, NY, USA), with a significance level set at $p<0.05$. Continuous variables were presented as mean ± standard deviation, and categorical data as frequencies and percentages. Normality of continuous variables was assessed using the Kolmogorov-Smirnov goodness-of-fit test. For data that did not follow a normal distribution, the Mann-Whitney U test was used. The Kruskal-Wallis test was employed for between-group comparisons of non-normally distributed values.

RESULTS

This study included 28 patients, with 71.4% (n=20) male and 28.6% (n=8) female. The mean age of the patients was 45 ± 19.65 years. The ASA scores were recorded as 28.6% (n=8) ASA 1, 57.1% (n=16) ASA 2, and 14.3% (n=4) ASA 3. The fractures were distributed as follows: 32.1% (n=9) AO 34-C1, 28.6% (n=8) AO 34-C2, and 39.3% (n=11) AO 34-C3. It was observed that 67.9% (n=19) of the fractures were on the right side (Table 1).

Table 1. Demographic data of patients

	n	%		n	%		n	%		n	%
Gender			ASA			Fracture subtype (OTA/AO Classification)			Laterality		
Male	20	71,4	1	8	28,6	34-C1	9	32,1	Dominant	19	67,9
Female	8	28,6	2	16	57,1	34-C2	8	28,6	Non-dominant	9	32,1
Age/year (mean±ss)	45 ± 19,65		3	4	14,3	34-C3	11	39,3			

In male patients, the mean ROM was 129 ± 8.97 degrees for flexion, 3.65 ± 1.30 degrees for extension, mean KOOS symptoms score was 74.05 ± 18.32, KOOS pain score was 84.80 ± 17, activities of daily living score was 82.90 ± 18.09, KOOS sports and recreation score was 61.50 ± 28.88, KOOS quality of life score was 58.50 ± 25.50, KOOS total score was 72.30 ± 19.45, and mean VAS score was 3 ± 3.06. In female patients, the mean ROM was 117.63 ± 18.66 degrees for flexion, 3.25 ± 1.03 degrees for extension, mean KOOS symptoms score was 72 ± 15.91, KOOS pain score was 76.38 ± 31.93, KOOS activities of daily living score was 74.13 ± 27.48, KOOS sports and recreation score was 50 ± 30.35, KOOS quality of life score was 36.13 ± 31.02, KOOS total score was 61.87 ± 23.14, and mean VAS score was 4.38 ± 2.38. No statistically significant difference was found between genders for any of these parameters (p-values: 0.153, 0.306, 0.444, 0.919, 0.541, 0.332, 0.059, 0.284, and 0.222, respectively) (Table-2).

When analyzed based on OTA/AO fracture subtypes (C1, C2, C3), no statistically significant differences were observed for ROM, KOOS symptoms, KOOS pain, KOOS activities of daily living, KOOS sports and recreation, KOOS quality of life, KOOS total score, or VAS scores ($p > 0.05$ for all). However, a trend of lower KOOS scores and higher VAS pain levels was noted as the fracture complexity increased (C1 to C3). KOOS pain and KOOS quality of life scores were more affected in AO 34-C2 and C3 groups compared to the C1 group. VAS scores were also higher in the C2 and C3 subtypes, although not statistically significant.(p-values: 0.306, 0.814, 0.626, 0.191, 0.598, 0.817, 0.536, 0.689, and 0.880, respectively).

No statistically significant difference was found in knee joint ROM, KOOS symptoms, KOOS pain, KOOS activities of daily living, KOOS function sports and recreation, KOOS quality of life, KOOS total score, or VAS score based on whether the fracture was on the domi-

Table 2. Results at postoperative sixth month

	Gender		Fracture type (OTA / AO Classification)			Laterality	
	Male	Female	34-C1	34-C2	34-C3	Right	Left
	mean ±ss	mean±ss	mean±ss	mean±ss	mean±ss	mean±ss	mean±ss
Flexion	129 ±8,97	117,63±18,66	123,67±16,18	126,63±12,63	127,55±11,91	123,53±13,60	130,44±11,63
P	0,153*		0,306**			0,126*	
Extension	3,65 ±1,30	3,25±1,03	3,89±1,26	3,25±1,48	3,45±1,03	3,68±1,25	3,22±1,20
P	0,306*		0,814**			0,310*	
KOOS Functional Scores							
KOOS Symptoms	74,05±18,32	72±15,91	77±14,33	70,13±14,92	73±21,83	71,79±17,57	77±17,50
P	0,444*					0,375*	
KOOS Pain	84,80 ±17	76,38±31,93	90,67±8,78	76,50±26,98	79,91±25,22	82,53±22,85	82,11±21,31
P	0,919*					0,921*	
KOOS Activities of Daily Living	82,90±18,09	74,13±27,48	85,67±17,74	75,38±24,18	79,73±22,08	79,95±21,34	81,33±21,60
P	0,541*		0,598**			0,844*	
KOOS Sports and Recreation	61,50±28,88	50±30,35	62,78±30,32	56,88±24,48	55,45±33,50	55,79±27,65	63,33±33,44
P	0,332*		0,817**			0,570*	
KOOS Quality of Life	58,50±25,50	36,13±31,02	55,67±33,38	49,38±22,87	51,18±30,31	49,79±25,89	57±34,59
P	0,059*		0,536**			0,538*	
KOOS Score	72,30±19,45	61,87±23,14	74,44±16,80	65,50±20,45	67,91±24,50	67,95±19,98	72,22±23,08
P	0,284*		0,689**			0,506*	
VAS Score	3±3,06	4,38±2,38	2,22±2,6	4±3,02	3,82±3,02	2,95±2,89	4,22±2,94
p	0,222*		0,880**			0,315*	
	*Mann-Whitney U Test, ** Kruskal Wallis Test						

nant or non-dominant side (p-values: 0.126, 0.310, 0.375, 0.921, 0.844, 0.570, 0.538, 0.506, and 0.315, respectively).

Our study found that AO 34-C3 fractures were more frequently encountered. There was no significant difference between AO C1-C2-C3 fracture types and KOOS and VAS scores. KOOS scores were highest in AO Type C1 fractures and lower in C2 and C3 fractures. VAS pain scores were higher in AO Type C2 and C3 fractures, with the lowest scores observed in AO Type C1 fractures. No significant difference was observed between fracture types and joint range of motion.

DISCUSSION

The subcutaneous position of the patella and the limited soft tissue coverage over it increase its risk of fracture from impacts. Given the high contact stress experienced by the patellofemoral joint due to its location and function, it is crucial to achieve an optimal distribution of stress by reconstructing the articular surface accurately post-fracture (10).The tension band method is commonly preferred in non-displaced or two-part patellar fractures without fragmentation, etiher alone or combined with cannulated screw fixation, which offers biomechanical advantages. In fractures with significant fragmentation, other methods like mini fragment screws and angular plates are utilized in addition to the conventional tension band technique (11).

Post-fracture complications of patellar fractures include extension weakness, gait disturbances, pain, degenerative changes in the patellofemoral joint surface, and the development of osteoarthritis. Thus, many studies have evaluated the functional outcomes of surgical treatment for patellar fractures over mid and long terms using various radiological and clinical parameters (12-17). While good functional outcomes are reported for non-displaced or minimally displaced patellar fractures treated conservatively, there is a lack of recent studies to support these results (18, 19). However, outcomes for displaced patellar fractures requiring surgical treatment differ. LeBrun and colleagues evaluated the mid-term functional outcomes of 241 patients who underwent tension band or partial patellectomy for displaced patellar fractures, using SF36 and KOOS scoring, and reported poor functional outcomes in the mid-term (10). Vedel and colleagues assessed long-term functional outcomes of surgically treated patellar fracture patients with KOOS, muscle strength measurements, and gait analysis, observing significant reductions in knee extension strength and accelerated osteoarthritis progression in both the patellofemoral and tibiofemoral joints, with a notable decline in health-related quality of life (20). Özdemir and colleagues evaluated mid-term outcomes of patients with operated patellar fractures and reported that nearly half of the patients had moderate or unsatisfactory results (21).

According to the AO classification, patellar fractures are categorized alphanumerically as AO 34, with three main types: Type A (extra-articular fractures), Type B (fractures partially involving the joint surface), and Type C (complete articular fractures). Type C is further subdivided into three subgroups: Type C1 indicates a transverse fracture line, Type C2 includes an additional fracture line in one of the major fragments, and Type C3 represents multifragmentary fractures (22).

In our study group, the most common fracture subtype was OTA/AO C3, a finding consistent with Larsen and colleagues' recent large-scale epidemiological study on patellar fractures, which also identified OTA/AO C3 as the most frequent subtype (23). We found no significant differences were observed between fracture subtypes (C1, C2, C3) in terms of knee joint ROM, KOOS scores, or VAS scores. However, a trend toward lower KOOS scores and higher VAS pain scores was evident in more complex fractures (C2 and C3), despite the absence of statistical significance. These findings align with previous studies highlighting the correlation between increased fracture complexity and poorer functional outcomes (10).

Notably, the KOOS pain and quality of life subscales were lower in the C2 and C3 groups, while the KOOS activities of daily living and KOOS sports and recreation scores were less impacted. Our results suggest that more complex fractures may have a greater impact on pain perception and quality of life rather than functional domains such as activities of daily living or sports participation in the early postoperative period. The lack of statistical significance may be related to the limited sample size, but the clinical relevance of these patterns warrants consideration. Our results suggest that clinicians should be aware that increasing fracture complexity might be associated with reduced pain relief and functional capacity, even in the early postoperative period, emphasizing the need for individualized surgical and rehabilitation strategies for complex fractures. Although poor mid- and long-term outcomes for patellar fractures are attributed to accelerated patellofemoral joint arthrosis due to articular involvement, inadequate reduction, and fixation; our findings indicate that poorer results may also be observed in the early term, even in the absence of arthrosis. This may be explained by the possibility that the degree of fragmentation could affect outcomes and this effect does not necessarily have to be mediated through patellofemoral osteoarthritis. Moreover, demonstrating the impact of fragmentation degree on early outcomes could lead to the adoption of different surgical strategies among complete articular fracture subtypes of patella.

The frequent observation of OTA/AO Type C3 fractures among patellar fractures underscores the need to develop an evidence-based treatment protocol specific to this fracture subtype (23). Several studies suggests locked plates are biomechanically superior and might be more suitable especially for complex fractures (24, 25, 26). However, Bickel et al report that one-year functional outcome does not differ significantly between cerclage wiring and locked plate groups, while the locked plate group is associated with less complications and revision surgeries (27). Poh et al report similar functional outcomes with tension band wiring compared with cannulated screw constructs at postoperative fifth year in their multi-center study, although the latter is associated with less implant-related complications (28). On the other hand, the meta-analysis by Zhang et al conclude that the alternative types of surgery might yield better functional results and pain scores with less complications than tension band wiring (3). Considering the literature and our results in early postoperative period, it could be more appropriate to evaluate alternative surgical techniques as fracture complexity increases, rather than adopting a one-size-fits-all approach.

The primary limitations of this study include its retrospective design, the fact that surgeries were performed by multiple surgeons with varying experience, and the small sample size. The inclusion of only 28 patients may have reduced the statistical power of the analyses, potentially limiting the detection of significant differences between groups. Furthermore, the small sample size could restrict the generalizability of the findings to broader patient populations. Our findings should be confirmed by studies with larger sample sizes and methods that can assess the quality of articular surface reconstruction. In our study, we aimed to investigate the impact of fracture subtypes on functional outcomes in patients operated on with the same surgical technique in the early postoperative period, before the development of patellofemoral osteoarthritis, which is a significant cause of poor functionality and pain after patellar fractures. Therefore, we established the sixth postoperative month as the evaluation point. A noteworthy limitation is the lack of long-term data to determine whether the early outcomes observed at this time point correlate with long-term results. Future studies should aim for larger cohorts and longer follow-up durations to better establish the relationship between fracture complexity and functional recovery.

As conclusion, in patients treated with tension band wiring for AO Type 34-C patella fractures, no significant difference was found in functional outcomes or pain levels at the sixth month based on gender, fracture subtype, or fracture side. AO Type C3 fractures were the most common, but functional outcomes were similar across fracture subtypes, with a slight improvement tendency observed in AO Type C1 fractures, although this was not statistically significant. Compared to non-displaced simple patellar fractures, multifragmentary patellar fractures are generally associated with poorer mid- to long-term outcomes, which are often linked to accelerated development of patellofemoral joint osteoarthritis. Our findings suggest that early functional outcomes may be influenced by factors other the development of osteoarthritis.

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Abbreviations list

ROM: range of motion
VAS: visual analogue scale
K-wires: kirschner wires
KOOS: knee ınjury and osteoarthritis outcome score
AP: anteroposterior

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Gülhane Faculty of Medicine (Decision No: 2024/351). Written informed consent was obtained from all participants prior to surgery.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request. No restrictions apply to data availability.

Competing interests

All authors of the study titled "Tension Band Attachment of AO 34C Patella Fractures: Relationship Between Fracture Subtype and Early Functional Outcomes" declare that they have no conflict of interest.

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Authors' contributions

Idea/Concept: MA, Desıgn: BAK, AMB, Control/Supervısıon: MA, DÇ, Data Collectıon And/Or Processıng: ÖLK, AA, EK, Analysıs And/Or Interpretatıon: MA, BAK, AMB, Lıterature Revıew: ÖLK, AA, EK, Wrıtıng The Artıcle: MA, Crıtıcal Revıew: MA, DÇ, References And Fundıngs: BAK, AA, Materıals: MA, AA, EK, Other: ÖLK, AA, EK.

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CASE REPORT

Cough-Induced Syncope: Unexpected Result of Malignant Pericardial Effusion

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Abstract

Background: Cough, shortness of breath, chest pain, and pleural and pericardial effusion are common symptoms in patients with lung cancer. We report a case of a 39-year-old male with a history of lung adenocarcinoma who initially presented with chest pain followed by recurrent episodes of cough-induced syncope. Echocardiographic assessment confirmed the presence and severity factor of pericardial effusion established. This case highlights the importance of suspecting pericardial effusion and potential cardiac tamponade in patients with known malignancies or rheumatological conditions presenting to the emergency department with cough or hypotensive episodes, particularly those reporting syncope. To minimize mortality risk, it is critical to implement a thorough diagnostic algorithm when such symptoms are observed.

Keywords: Cough-induced syncope, Pleural effusion, Pericardial effusion, Pericardiocentesis.

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INTRODUCTION

Pericardial effusion refers to the accumulation of fluid between the layers of the pericardium.

These effusions can have various origins, including extrapulmonary causes such as idiopathic factors, neoplasms, iatrogenic events, and autoimmune conditions. Notably, the occurrence of malignant pericardial effusion resulting from lung cancer is not uncommon (1, 2). Malignant pericardial involvement is observed in 20 % of cancer patients during post-mortem examinations, with up to 50% exhibiting a pericardial effusion (1,2, 3). One crucial determinant of the severity of pericardial effusion is the underlying cause. If it arises due to heart injuries, circulatory issues, or any other factors that can prompt rapid effusion development, prompt treatment is necessary to prevent potentially dangerous complications such as dyspnea, chest pain, palpitations, and syncope. Coughing causes a considerable increase in intrathoracic and intra-abdominal pressures, resulting in a decrease in cardiac output and a decrease in cerebral perfusion, which in turn causes a loss of consciousness; intrathoracic pressures could get as high as 300 mm Hg during cough spells (4). Syncope is more likely to occur during the acute hypotension that occurs after coughing spell, with peripheral blood flow recordings indicating vasoconstriction.

CASE REPORT

A 39-year-old male with a documented history of lung adenocarcinoma diagnosed in September 2023 following complaints of back pain, cough, and hemoptysis, presented with symptoms of weakness, dizziness, headache, and hypotension over the past two days. Our patient normally has a normal blood pressure range, which subsequently drops after the coughing spells. The patient's blood pressure was measured at 80/50 at home, accompanied by increased shortness of breath, chest pain, with severe non-productive coughing, and subsequent drops in blood pressure leading to syncope. Two brief episodes of these symptoms occurred prior to hospitalization, with complete recovery thereafter. No neurological deficit was observed. Notably, the patient's syncope did not coincide with any other precipitating factors or reflexes.

The patient's vital signs were as follows: blood pressure of 100/75 mmHg, pulse rate of 97, and oxygen saturation of 95 at emergency department admission. The patient's general appearance included occasional coughing, with no signs of cyanosis or worsening shortness of breath. Further examination revealed slightly diminished breath sounds at the lung bases. Given the patient's medical history and presenting symptoms, pericardial effusion was immediately considered as a potential diagnosis upon admission and later confirmed through imaging studies. The patient's hemogram revealed mild anemia (10.9 g/dL), while all other hemato-biochemical parameters were within normal range. An electrocardiogram showed sinus tachycardia (103 bpm) with low-amplitude QRS were observed (Figure 1).

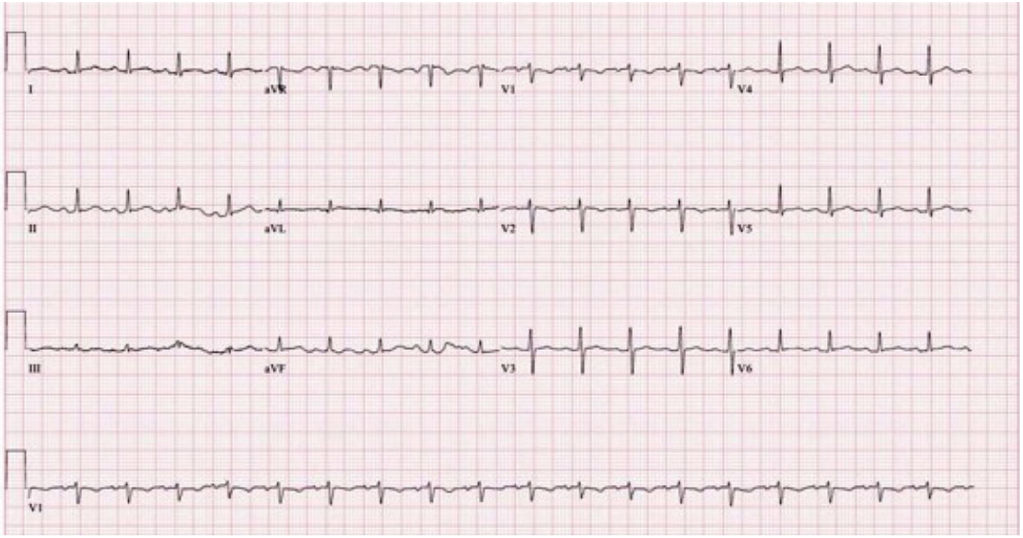

Figure 1: An electrocardiogram showed sinus tachycardia (103 bpm) with low-amplitude QRS

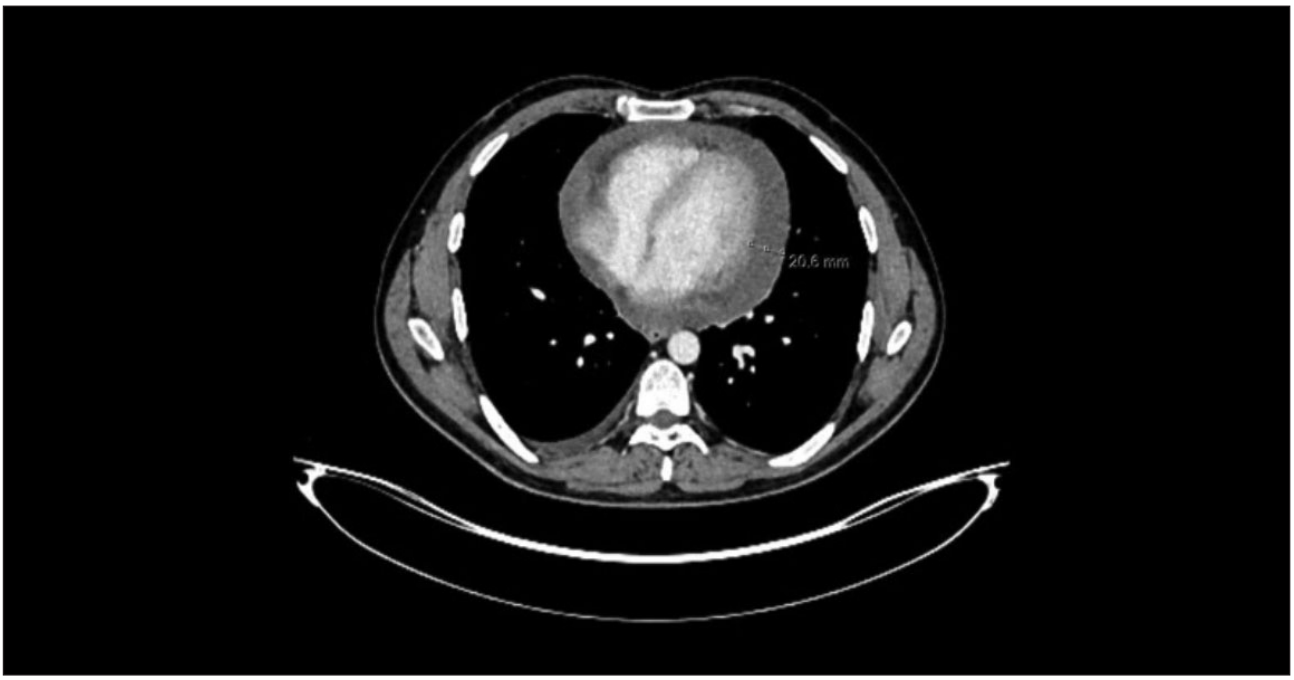

Figure 2: Computed tomography of the chest revealed a pericardial effusion with a maximal thickness of 20.6 mm.

Recent chest computed tomography confirmed worsening pericardial effusion (Figure 2), although no pulmonary embolism was detected. Transthoracic echocardiography revealed a large pericardial effusion. (https://osf.io/t5jsq/)

Based on these imaging results, pericardiocentesis was performed, resulting in the improvement of dyspnea and the eventual resolution of syncope. Analysis of the pericardial fluid confirmed the presence of metastatic adenocarcinoma, with findings consistent with ESA (epithelial-specific antigen) cells (BER-EP4) and Claudin-4 positivity. This intervention alleviated the patient's symptoms and provided critical diagnostic information to guide ongoing management. During follow-up, a pericardial biopsy was performed to exclude the possibility of a primary cardiac malignancy. The biopsy results further confirmed the diagnosis of metastatic adenocarcinoma, consistent with the patient's known history of lung cancer.

DISCUSSION

In our case, the patient was admitted to the emergency department with the uncommon combination of cough and syncope. Lung cancer patients may develop a pericardial effusion leading to cardiac tamponade. Malignant pericardial effusion should be considered as a potential differential diagnosis in lung cancer patients experiencing cough-induced syncope (2, 5). Although it may initially remain asymptomatic, upon reaching critical levels of intracardiac pressure, individuals present with symptoms such as elevated filling pressures, reduced cardiac output, and syncopal episodes. Thus, in any instance involving cough-induced syncope, it is imperative to rule out either cardiac tamponade or pericardial effusion. When reaching critical levels of intracardiac pressure, individuals present with symptoms such as elevated filling pressures, reduced cardiac output, and syncopal episodes. In any patient diagnosed with a malignancy or rheumatological medical conditions, presenting to the emergency department with cough or coughing spells, especially those describing hypotensive episodes or syncope, pericardial effusion and tamponade should be suspected. An appropriate examination algorithm must be applied (5).

Patients with malignancies or rheumatological medical conditions, presenting to the emergency department with cough or hypotensive episodes, particularly those

accompanied by syncope, should be evaluated for pericardial effusion and cardiac tamponade as high priority diagnoses, especially those describing hypotensive episodes or syncope, pericardial effusion and tamponade should be suspected. Implementing an appropriate diagnostic algorithm is essential to mitigate mortality risk.

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Abbreviations list

No abbreviations were used

Ethics approval and consent to participate

As this is a case report, no approval or consent to participate was required.

Consent for publication

The consent for publication has been attached to the submitted file.

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CASE REPORT

Laparoscopic Pelvic Ring Implant Removal From the Femoroacetabular Joint During Totally Extraperitoneal Herniorrhaphy: A Case Report and Surgical Technique

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Abstract

Minimally invasive surgeries have become more widespread in recently. Laparoscopy is actively used in many surgeries by general surgeons, urologiest, and gynaecologiest. Despite this widespread use of laparoscopy, its use in orthopaedic surgeries has not become widespread and as yet is only seen in literature as case reports and series. Fifty-five years old male patient admitted to orthopaedic outpatient clinic with complaints of right hip and inguinal C-shaped pain that had been ongoing for 3 months. Twelve years ago, the patient had undergone open anterior pelvic fixation (ilioinguinal incision) because of a simple type acetabular anterior wall fracture. An incisional hernia due to the previous pelvic surgery and a femoroacetabular screws was detected. There are two treatment options for this case; open implant removal followed by open hernia repair, or open implant removal than laparoscopic hernia repair in a different session. Insicional hernia treatment and femoraacetabular implant remove performed laparoscopically in the same session, and this is first case of literature. In light of this case, laparoscopy seems promising in the management of complications in orthopedic trauma surgery.

Key words: Implant removal, laparoscopy, pelvic trauma

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INTRODUCTION

Minimally invasive surgeries have become more widespread in recent decades (1). Operations that were performed with wide incisions in the past can now be performed mini open or percutaneously to increase patient comfort and reduce complications. With developments in arthroscopic implant technologies and production, tendon and ligament repairs, fracture fixations, removal of foreign bodies, and mass excisions can be performed arthroscopically (2,3). There is a great deal of literature about arthrosopic treatment techniques for the shoulder, knee, and hip joints and implant removal(4, 5) but although fixation methods with percutaneous techniques for pelvic ring injuries have become more widely used, arthroscopic, endoscopic, or laparoscopic techniques for the pelvic ring are limited (6,7).

Laparoscopy is actively used in many surgeries by general surgery, urology, and obstetrics and gynaecology departments. Surgeons can evaluate pelvic internal structures and intervene to abdominal organs during laparoscopy (8). Despite this widespread use of laparoscopy, its use in orthopaedic treatments has not become widespread and as yet is only seen in literature as case reports (9,10). There are 2 case reports in literature showing that laparoscopy can be used in orthopaedic surgery. Francia et al. presented a case where fixation could be made of a fracture in the ramus pubis rather than with anterior incisions, which proved that laparoscopy can be used for treatment purposes in orthopaedic surgery (9). Francia named this technique, "laparoscopic internal fixation" and stated that despite the longer surgical time, blood loss was reduced and hospital stay was shorter. This type of fracture fixation can be difficult because of if case have acute bleeding and acute injury. There may have not been more articles published on this subject as patient died postoperatively. In a case by Thati et al., They explained that laparoscopy can be used in the management of orthopaedic complications in a case report in which the K-wire migrated into the abdomen in the treatment of a femoral proximal fracture was removed laparoscopically (10).

The anterior incisions selected for conventional pelvis surgery can result in some complications such as abdominal organ injuries, major vascular injuries, and abdominal incisional hernia (7). In this techniqual report, the laparoscopic excision of screws extending to the femeroacetabular joint is described in a patient with abdominal incision hernia that developed after anterior pelvic incision.

CASE REPORT

Fifty-five years old male patient admitted to orthopaedic outpatient clinic with complaints of right hip and inguinal C-shaped pain that had been ongoing for 3 months. Twelve years ago, the patient had undergone open anterior pelvic fixation (ilioinguinal incision) because of a simple type anterior wall fracture according to the Judet-Letournel classification (11). In the physical examination, the hip internal and external rotation movements were limited and painful, and the AP pelvis x-ray showed femoroacetabular screws (Figure 1). An incisional hernia due to the previous pelvic surgery was also determined (Figure 2). There are two treatment options for this case; open implant removal followed by open hernia repair, or open implant removal than laparoscopic hernia repair in a different session.

It was planned to perform Totally Extraperitoneal Herniorrhaphy (TEP), which is frequently used for inguinal hernias because of the similarity of the hernia localisation to the point of direct inguinal hernia. As the orthopaedic incision for removal of the screws is not compatible with the TEP technique (12), it was planned to first remove the implant laparoscopically, then to apply preperitoneal mesh.

Surgical Technique

The surgery was performed with the patient positioned supine to provide appropriate fluoroscopy visualisation of the pelvic region. A bladder catheter was attached and it was ensured that the bladder was empty. With a 1cm incision inferior to the umbilicus, the subcutaneous adipose tissue was passed, then after passing through the Camper and Scarpa fascias, the musculus rectus abdominis fascia was reached. Passing carefully through the fascia, the preperitoneal area was reached. A 10 mm trochar with baloon was placed and inflated for perform dissection of peritoneum. The balloon was subsequently removed, and from this port, the preperitoneal area was insufflated with CO2 to be at 12mmHg pressure. Preperitoneal exploration was performed with camera that had been advanced. The symphis pubis was seen and the Retzius space was dissected. There was seen to be a hernia sac from a fascia defect, approximately 3cm in diameter, immediately right lateral of the symphis

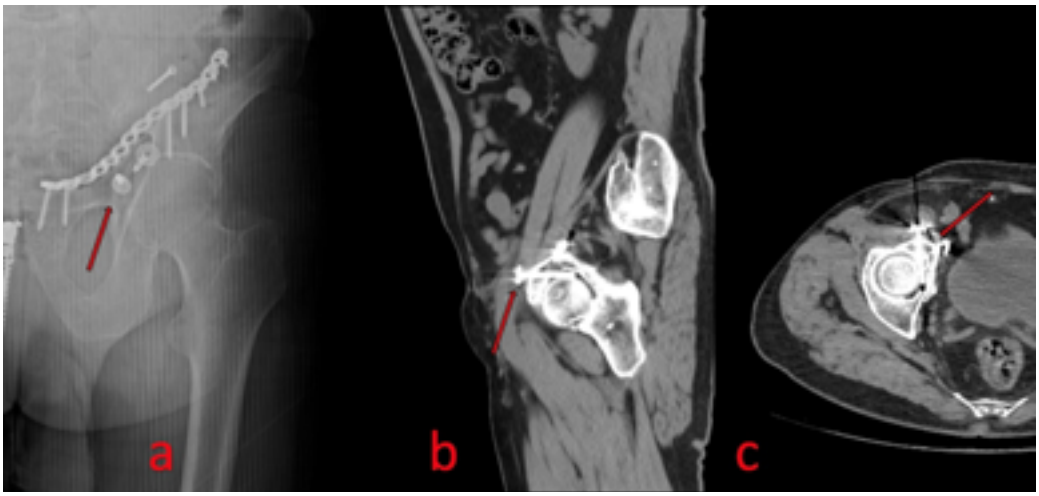

Figure 1: a) Preoperative pelvis anterior posterior (AP) X-ray shows the plate and free screws on the left ramus pubis and the screw that may extend into the femoroacetabular joint. b) Sagittal bone sequence computed tomography (CT) shows a screw in the joint and its location. c) Axial bone sequence CT shows the screws in the femoroacetabular joint.

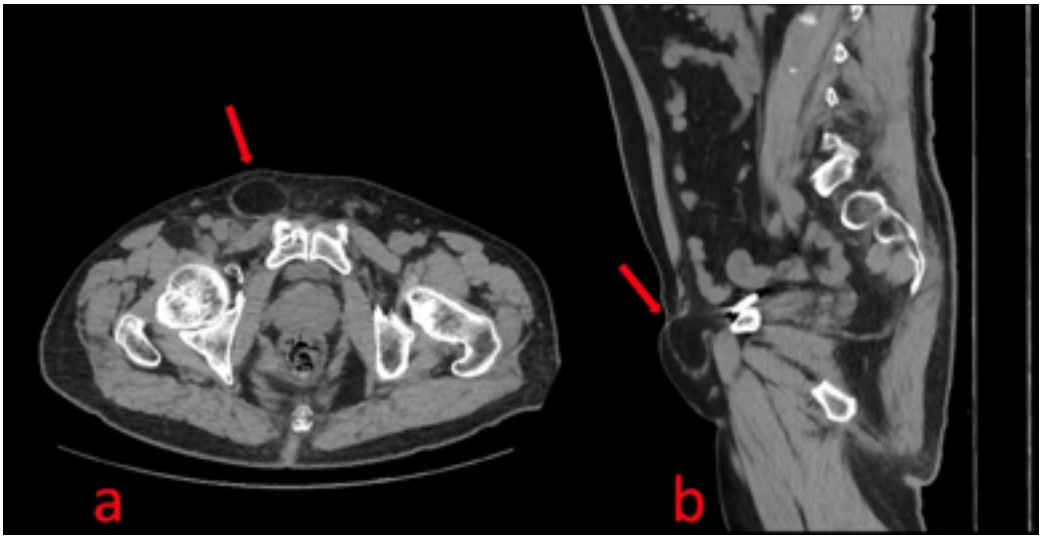

Figure 2: CT Image of non-incarcerated insicionel hernia sac due to previous surgery. No abdominal organ in sac because of spontaneus reduction by lay position during CT scan. a) Transvers view. b) Sagittal view.

pubis. Two 5mm laparoscopic ports were entered, each at 2cm below the existing port. Dissection was completed with sharp and blunt dissection as far as the Borgos space on the right lateral. The inguinal cord structures were seen. The hernia was medial of the cord structures and there was observed to be no relationship with these. The hernia sac was removed into to the abdomen after disecting from surrounding tissue with sharp and blunt dissection. At this time the plate placed in the previous operation was detected and was defined as a guide. Dissection was continued based on the number of holes in the plate . Perioperative fluoroscopy was performed to be able to determine the screws location (Figure 3). On visualisation of the proximity of the screws causing the problem, dissection was continued. The energy devices for cauterization were used at a minimal level to avoid injuries. On reaching the pin of the screws, a 5mm port was entered over this region to be a guide to the screwdriver, then the port was removed, and the screwdriver was entered via this route to the preperitoneal area, reaching the screws. The screws could not be excised with the magnetic screwdriver, the screws was removed by grasping the top of the screws with pincers. The scales remaining fixed were freed from surrounding tis-

sues with sharp and blunt dissection and were removed from the preperitoneal space. The camera was excised from a 10mm port and 15 x10cm mesh was advanced to the preperitoneal area. The mesh was spread on the anterior wall of the abdomen with one end reaching the symphis and the other reaching the spina iliaca anterior superior (SIAS), and this was fixed with absorbable tuckers. After obtaining hemostasis, the ports were removed under laparoscopic view (Figure 4).

Postoperatively, the patient did not require blood transfusion, no wound site problems developed. At the 16th hour postoperatively, the patient was mobilised and no mechanical symptoms were identified. At the 40th hour the patient was discharged from hospital.

DISCUSSION

This case is a techniqual note of a complication management after pelvic trauma surgery. Abdominal hernia treatment and intervention for pelvic ring can be performed laparoscopically in the same session. In the conventional surgical methods for pelvic fractures there are negative effects, such as bladder, vascular, nerve, and spermatic cord injuries, impaired hemodynamics because of the formation of incisional hernia and diminished patient comfort postoperatively. These complications have directed many surgeons to percutaneous procedures, but endoscopic, arthroscopic, and laparoscopic treatments are still limited (7).

In this report, the case is presented of a patient who underwent open surgery 12 years ago, with intra-articular implant and incisional hernia. The patient presented with the complaint of the incisional hernia, and also imaging examination, screws which could be causing cartilage damage within the joint were determined. Francia et al. noted that the laparoscopic internal fixation technique, but there is only their own case report in literature. The most likely reason that there are no published studies of this technique in large patient series is the postoperative death of patients or that surgeons wish to keep the operating time short in cases of pelvic injuries which already have hemodynamic problems. Our patient returned to work after 1 week postperatively, and currently at 3 months postoperatively has resumed an active life. Rather than complex cases that may require acute intervention for bleeding, laparoscopy can be considered for use in simple type fractures, conditions requiring re-operation such as implant removal, or for imaging purposes

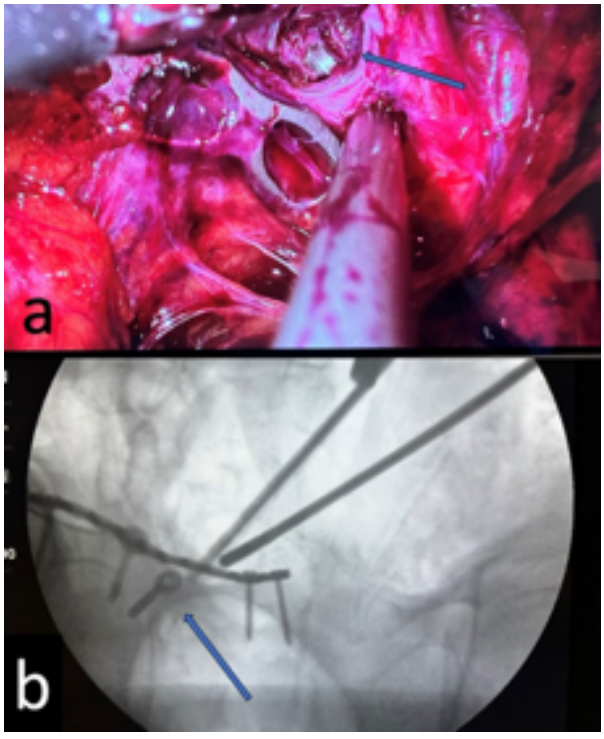

Figure 3: a) Laparoscopic image of plate and screw localization. b) Fluoroscopy evaluation to determine localization during surgery.

Figure 4. Peroperative floroscopic imagination after screws removal.

such as in percutaneous fixations. However, there is a need for further studes of large series on this subject.

In most of digestive and urogenital system operations, laparoscopic methods are better than open methods in respect of complications (13,14). In the current case, the implant was removed and incisional hernia repair was performed laparoscopically. In current case same incision was used, a single operation day was given, and the length of stay in hospital and number of operations were reduced. If the screw had been removed separately before the hernia surgery, there would have been an incision in the hernia area and wound healing would have been expected. If the hernia surgery had been performed before the procedure to remove the implant, the mesh in the hernia area could have been damaged while removing the implant, and the operation could have been difficult. It can be considered that a surgeon with laparoscopy and orthopaedic experience can comfortably perform lapaaroscopic surgeries. The aim of publishing these technical notes is to demonstrate that laparoscopy can be used in pelvic surgery, and although the technical learning curve is more difficult compared to open surgery, better results can be obtained.

In conclusion, we presented that unique teqnique that never explained in literature before. We believe that this previously undescribed surgery will shed light on future combined surgeries and will also bring a different approach to implant excisions. However, studies with more cases are needed to better evaluate the results.

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Abbreviations list

TEP: Totally Extraperitoneal Herniorrhaphy
AP: Anterior posterior
CT: Computed tomography
SIAS: Spina iliaca anterior superior

Ethics approval and consent to participate

Written informed consent was obtained from the patient's legal guardian for the publication of this report. All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki.

Availability of data and materials

Patient data are available to the corresponding author when requested with a reasonable justification.

Competing interests

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

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Authors' contributions

All authors contributed to the study conception and design. The operation was performed by Cem Ilgin Erol and Bilal Karabak. Data collection and literature research were carried out by doctors Yavuz Şahbat and Cem Ilgin Erol. The authors carried out the final revision of the article together. All authors read and approved the final manuscript.

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CASE REPORT

Valproic Acid As An Effective Treatment For Self-Injurious Behavior In A Patient With Wolf-Hirschhorn Syndrome: A Case Report

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Abstract

Wolf-Hirschhorn Syndrome (WHS) is a neurodevelopmental disorder (NDD) characterized by a microdeletion, often accompanied by maladaptive behaviors. First-line treatment typically includes antipsychotics; however, their efficacy varies, and alternative options remain limited. This case report aims to demonstrate the effectiveness of valproic acid monotherapy in managing maladaptive behaviors in a patient with WHS presenting with self-injurious behavior. A 10-year 4-month-old female patient with WHS exhibited intense self-injurious behaviors. When her demands were not met, she would bang her head against the wall with significant force, risking severe traumatic injury, and bite her hand. She had previously received sufficient dosage and durations of aripiprazole and risperidone treatments without benefit. Valproic acid was initiated at a dose of 400 mg/day in divided doses. After the first month of treatment, the patient ceased the behavior of banging her head. Additionally, the behavior of biting her hand significantly decreased. The Aberrant Behavior Checklist (ABC) score, initially assessed at 51 points, decreased to 28 points after the first month of treatment. The decrease in the ABC score was particularly marked in the subscales of irritability and social withdrawal. This outcome suggests that in patients diagnosed with neurodevelopmental disorders (NDD) where antipsychotics have failed, valproic acid as a mood stabilizer may be beneficial as monotherapy in reducing self-injurious behavior.

Key words: Neurodevelopmental Disorders, Self-Injurious Behavior, Valproic Acid, Wolf-Hirschhorn Syndrome, 4p Deletion

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INTRODUCTION

Wolf-Hirschhorn Syndrome (WHS) is a neurodevelopmental disorder (NDD) characterized by multiple congenital anomalies and intellectual disability. Its prevalence is estimated to range between 1 in 50,000 and 1 in 20,000 live births, with a higher occurrence in females, approximately at a 2:1 ratio. This condition results from a partial deletion in the distal segment of the short arm of chromosome 4 (4p16.3). The critical region for WHS includes the two key loci currently recognized as WHSCR1 and WHSCR2 (1). The syndrome is typically diagnosed in infancy or early childhood based on distinctive craniofacial features, growth retardation, intellectual disability, and confirmatory genetic testing. However, studies are being conducted on prenatal diagnostic methods. (2). Prognostic outcomes vary depending on the size of the deletion and associated complications. While many individuals experience significant developmental delays, early intervention and supportive therapies can improve quality of life (1).

The deletion of WHSCR2 region is essential for the manifestation of key characteristics associated with WHS, including "Greek warrior helmet" appearance, growth deficiency, global developmental delay, feeding difficulties, intellectual disability, seizures, and maladaptive behaviors such as self-injurious behavior (SIB). Seizures are a hallmark feature of WHS, occurring in approximately 50-100% of affected individuals (3). These seizures often emerge within the first two years of life and can be challenging to manage due to their refractory nature (1). When maladaptive behavior in NDD becomes challenging, behavioral therapies serve as the first-line treatment. However, when behavioral therapies fail, patients should be supported with pharmacotherapy. The evidence supporting pharmacological treatments for SIBs remains limited and primarily based on lower levels of evidence. There is a critical need for well-structured studies to guide clinical decision-making. The limited available evidence for the use of common pharmacologic agents, such as second-generation antipsychotics, and less common agents, such as clonidine, n-acetylcysteine, riluzole, naltrexone, and topical anesthetics, is reviewed. Most research has been conducted in autism spectrum disorder (ASD) populations, with findings often extrapolated to other NDDs. These limitations may influence treatment outcomes, though the potential risks of pharmacotherapy remain relevant. (4). Limited research exists on the efficacy of mood stabilizers in treating NDD-related maladaptive behavior (5). Herein, we present a case where mood stabilizers effectively mitigated SIB in a WHS patient after unsuccessful trials with two antipsychotics.

CASE REPORT

We present the case of a 10-year-old female with WHS, brought to our child and adolescent psychiatry outpatient clinic due to SIB. Born to a G4P3 mother following a consanguineous marriage, the patient exhibited developmental delays from the prenatal period. The birth occurred via cesarean section at 36 weeks due to recurrent indications. The patient had a history of incubator care for one month and was breastfed for four months. Hypotonia and microcephaly were noted at birth. She started walking at 2 with the help of physical therapy and produced her first word at 2 years old. Early interventions included physical therapy, occupational therapy, special education, and speech-language therapy. The patient had no clinical history of seizures. She has been undergoing neurology follow-ups every six months, and her most recent EEG, performed at the age of eight, revealed no deterioration or pathological findings. The patient, who is currently attending a special education school, receives shadow teacher support and is in the first grade despite being 10 years old. Nevertheless, she is still struggling with early literacy skills—reflecting her moderate intellectual disability and developmental delay. At presentation, the patient was 110 cm tall (z score = -4.30) and weighed 13 kg (z score = -5.19).

The patient's self-injurious behaviors began three years ago, including self-biting and head-hitting, which were triggered by familial comings and goings, unmet desires, and emotional distress. Prior to that, from the age of three, she exhibited delayed speech and, when unable to express herself, would cry and scream. Additionally, since that time, she has continued to suck her thumb as a self-regulation mechanism. While head-hitting behavior predominantly occurred at home, self-biting when frustrated was also observed in social settings outside the home. However, she generally attempted to establish adaptive social interactions unless confronted with an undesired situation.

The patient's first psychiatric consultation occurred two years ago, at the age of eight, due to concerns regarding

SIB. Initially, risperidone treatment was started at 0.25 mg/day and titrated up to 1.5 mg/day. However, after four months of treatment, the patient did not benefit from dose escalation and experienced daytime drowsiness as a side effect. As a result, risperidone was discontinued, and aripiprazole was initiated at 1 mL/day. The aripiprazole dose was gradually increased to 4 mL/day and maintained at this dose for six months. Although no significant side effects were observed, the treatment did not yield any clinical improvement.

The psychiatric evaluation was conducted through a comprehensive clinical interview with the patient's mother, as the patient had significant communication limitations. The assessment focused on developmental history, behavioral patterns, emotional regulation, and daily functioning. Direct observation of the patient was also performed, where her limited verbal skills, frustration tolerance, and self-injurious behaviors (such as head-banging and hand-biting) were noted. The patient's 16-year-old older sister and 14-year-old older brother were also invited to repeated interviews. During these assessments, both siblings were found to have normal mental capacity, and no psychopathology was detected in either of them. During examination, she could only use the words "mother, father, and sister" and expressed her needs by pointing. However, she actively sought social interaction and was receptive to social engagement. She had hair loss in the frontal area due to head-hitting (Figure 1).

She became frustrated quickly and started biting her right hand, which was swollen and injured. Given the failure of previous antipsychotic regimens, valproic acid was initiated at 400 mg/day in divided doses (as 200 mg/day in the morning and 200 mg/day in the evening) as monotherapy, along with behavioral suggestions to the mother. In addition to the clinical interview and observation, standardized measures were used, including the Aberrant Behavior Checklist (ABC) to quantify behavioral symptoms and assess treatment response. ABC score was 51 at baseline (Irritability: 22; Social withdrawal: 11; Stereotypic behavior: 0; Hyperactivity: 13; Inappropriate speech: 5). After one week, the valproic acid serum level was 82 mEq/L. After one month, head-hitting subsided markedly, and hand-biting frequency decreased. No adverse effects were reported and repeat ABC score was 28 (Irritability: 9; Social withdrawal: 4; Stereotypic behavior: 0; Hyperactivity: 11; Inappropriate speech: 4). The decrease in the ABC score was particularly marked in the subscales of irritability and social withdrawal.

DISCUSSION

SIB in NDDs presents a significant clinical challenge, often necessitating a multifaceted treatment approach. While behavioral interventions remain the first-line strategy for managing SIB, pharmacological treatment becomes crucial when behavioral therapies alone prove

Figure 1: Hair loss on the frontal area

insufficient. WHS, a rare neurodevelopmental disorder characterized by intellectual disability, behavioral challenges, and frequent comorbidities such as epilepsy, is among the conditions where SIB is commonly observed.

Psychiatric comorbidities frequently associated with WHS include developmental delays, intellectual disability, receptive and expressive language deficits, and stereotypic behaviors, often coexisting with seizures (1). Although maladaptive behaviors are less commonly emphasized in WHS, they can significantly impact the quality of life. Among these, SIB is particularly concerning, as demonstrated by a study by McGill et al., in which 48% of patients with WHS exhibited self-injurious behaviors, with teeth grinding (86%), self-biting (43%), and head-hitting (38%) being the most prevalent (6). Given the clinical burden of SIB in WHS, exploring pharmacological interventions beyond traditional behavioral strategies is essential. This report highlights the therapeutic potential of mood stabilizers in addressing SIB in WHS, particularly in cases where first-line pharmacological agents, such as antipsychotics, have been ineffective or poorly tolerated.

From a pharmacological perspective, treatment options for SIB in NDDs remain limited. Second-generation antipsychotics, such as risperidone and aripiprazole, are often considered first-line pharmacotherapeutic agents due to their ability to reduce irritability and aggression (4). However, in this case, both risperidone and aripiprazole failed to provide clinical benefit, with risperidone causing intolerable daytime drowsiness. This outcome aligns with existing literature suggesting that while antipsychotics can be effective for certain behavioral symptoms in NDDs, their efficacy in reducing SIB specifically remains inconsistent (4). Furthermore, their use is often associated with significant side effects, limiting long-term adherence.

In this case, valproic acid was introduced as monotherapy following the unsuccessful trials with antipsychotics. Valproic acid, a widely used mood stabilizer, functions by enhancing gamma-aminobutyric acid (GABA) neurotransmission, stabilizing neuronal excitability, and regulating mood, which may contribute to its observed efficacy in reducing self-injurious behaviors (4). Its use in this patient resulted in significant improvement in SIB, as evidenced by the marked reduction in self-biting and head-hitting behaviors within one month of treatment. Notably, the ABC scores demonstrated substantial improvement in irritability and social withdrawal subscales, further supporting its efficacy.

Despite limited research on valproic acid for SIB in NDDs, evidence from ASD studies suggests its potential in reducing irritability and maladaptive behaviors. A randomized double-blind placebo-controlled study demonstrated that divalproex treatment, with minimum valproate blood level 50 μg/ml in children with ASD, led to a significant reduction in Clinical Global Impression (CGI) and ABC scores, highlighting its effectiveness in decreasing irritability and maladaptive behaviors (5). These findings suggest that mood stabilizers, including valproic acid, may serve as alternative treatment options when conventional pharmacotherapies, such as antipsychotics, prove ineffective or are poorly tolerated. This case further contributes to the growing body of evidence supporting the role of mood stabilizers in managing SIB in NDD populations.

Nevertheless, the limited evidence base for pharmacological treatment of SIB highlights the urgent need for well-designed, controlled studies to guide clinical decision-making. Future research should aim to evaluate the efficacy and safety of mood stabilizers, including valproic acid, across a broader spectrum of NDDs and behavioral presentations.

In conclusion, this case demonstrates that valproic acid may serve as an effective alternative for managing SIB in NDDs when antipsychotics are ineffective or poorly tolerated. While the findings are promising, clinicians should adopt a personalized treatment approach, carefully considering the patient's unique clinical profile and monitoring for potential side effects.

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Abbreviations list

ABC: Aberrant Behavior Checklist
ASD: Autism spectrum disorder
CGI: Clinical Global Impression
EEG: Electroencephalogram
GABA: Gamma-aminobutyric acid
NDD: Neurodevelopmental disorder
SIB: Self-injurious behavior
WHS: Wolf-Hirschhorn Syndrome

Ethics approval and consent to participate

Written informed consent was obtained from the patient's legal guardian for the publication of this report. All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from the patient's legal guardian for the publication of this report.

Availability of data and materials

There is no data avaliable for this case report.

Competing interests

The data supporting this case report are stored both digitally and physically. Researchers interested in accessing the data may contact the corresponding author upon reasonable request.

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Authors' contributions

Idea/Concept: MU. Desıgn: MU. Control/Supervısıon MU, STH. Data Collectıon And/Or Processıng: MU. Analysıs And/Or Interpretatıon: MU. Lıterature Revıew: MU. Wrıtıng The Artıcle: MU. Crıtıcal Revıew: MU, STH, MFC. References And Fundıngs: MU. Materials: MU.

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