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I.V. Paracetamol

БЕЗБЕДНА АНАЛГЕЗИЈА

менаџирање на болка кога сте загрижени за безбедноста

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

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

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

Резултат:

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

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

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

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

Табела3: *Споредба на ПОПГ помеѓу двете групи*

ПОГП	
I Група П	II Група НС
0	4

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

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

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I.V. Paracetamol е атрактивна компонента за мултиодално менаџирање на болка.

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- **Значително намалување на болка**
- **Редукција на дозата на опоидни лекови за - 40% во првите 24 часа**
- **Намалување на несаканите ефекти поврзани со монотерапија на NSAID и опоидни лекови**
- **Ублажување на акутна и хронична болка**

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CONTENT

FROM VALIDATION TO INTELLIGENT INTEGRATION: FAST AND eFAST ACROSS CONTEMPORARY EMERGENCY TRAUMA SYSTEMS

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What Was Known: A Diagnostic Revolution

Focused Assessment with Sonography for Trauma (FAST) emerged in the 1990s as a transformative bedside innovation that redefined the tempo of trauma evaluation. By replacing diagnostic peritoneal lavage with a rapid, non-invasive ultrasonographic assessment, FAST shifted early trauma imaging from invasive confirmation toward immediate physiologic decision support. Its early validation established high specificity for clinically significant hemoperitoneum and reproducibility in hemodynamically unstable patients.

The subsequent evolution into extended FAST (eFAST), incorporating thoracic assessment for pneumothorax and hemothorax, expanded ultrasound into a multi-compartment resuscitative tool (1–3). Rather than pursuing anatomical completeness, eFAST aligns imaging with survival physiology, focusing on the detection of air or fluid as markers of life-threatening pathology. Performed concurrently with resuscitation, it preserves the primacy of airway, breathing, and circulation while enabling real-time decision-making. Its repeatability supports dynamic reassessment during evolving shock states, and in selected populations such as pregnancy, it provides radiation-free evaluation without compromising diagnostic immediacy (2).

Extended FAST (eFAST) is structured as a rapid bedside examination performed by the treating clinician during active resuscitation. By focusing on the detection of air and free fluid, it translates ultrasonography into immediate physiologic decision-making, particularly in hemodynamically unstable patients, where a positive examination may directly prompt surgical intervention. In contrast, in stable patients, computed tomography remains the gold standard for detailed evaluation of solid organ and retroperitoneal injury, while eFAST may serve as a triage or follow-up modality (2,6).

During this foundational phase, the scientific discourse was primarily concerned with validation: sensitivity, specificity, predictive values, and interobserver reliability. The central question was clear — does FAST reliably detect life-threatening fluid collections?

Early validation studies established FAST as a highly specific tool for detecting clinically significant intraperitoneal free fluid, particularly in unstable trauma. Its sensitivity, however, remained context-dependent, shaped by injury pattern, timing, and operator expertise (3–6). From the outset, FAST functioned less as a screening instrument and more as a rule-in test guiding emergent operative decision-making. Several studies also examined interobserver agreement and

learning curves, demonstrating that structured training programs enabled non-radiologist clinicians — including emergency physicians and surgeons — to achieve reproducible diagnostic accuracy. This finding was pivotal, as it supported the decentralization of ultrasound from radiology departments into trauma bays and emergency settings (1,7-8). FAST marked a decisive departure from diagnostic peritoneal lavage (DPL), replacing invasive detection of bleeding with rapid, repeatable visualization that refined operative decision-making without interrupting resuscitation (9).

With the introduction of extended FAST (eFAST), further validation studies confirmed its high accuracy for pneumothorax detection, in several analyses demonstrating superior sensitivity compared with supine chest radiography in trauma patients. This expansion reinforced ultrasound's role as a multi-compartment bedside diagnostic modality rather than a purely abdominal tool (1,3,10). Contemporary systematic reviews continue to reaffirm these findings, consolidating decades of validation research and confirming the sustained diagnostic robustness of FAST/eFAST within trauma resuscitation protocols. What began as a question of diagnostic accuracy ultimately evolved into confirmation that FAST had secured its place within the trauma diagnostic armamentarium (3). The next phase of its evolution would no longer be defined by proof of accuracy, but by system-level integration.

The Present Moment: Algorithmic Integration and Systemic Deployment

By 2025–2026, the focus has shifted. FAST is no longer evaluated solely on whether it works, but on how it functions within structured trauma systems. Recent analyses examining integration within Advanced Trauma Life Support (ATLS) frameworks demonstrate that embedding FAST into predefined hemodynamic algorithms shortens time to operative intervention and refines triage pathways (1). FAST has matured from a binary diagnostic test into a decision-modifying component of trauma workflow architecture (3,11,12), effectively transitioning from an imaging modality to an operational doctrine within trauma resuscitation. Regional implementation data reinforce this paradigm. A prospective cohort study evaluating structured eFAST integration in polytrauma care demonstrated reduced diagnostic delay compared with CT-centric pathways while maintaining high concordance for thoracic and abdominal injury detection (4). Importantly, this study positioned FAST as a system-level intervention influencing workflow efficiency rather than merely diagnostic accuracy.

Yet integration demands governance. Variability in documentation, credentialing, and quality assurance remains a persistent challenge in contemporary POCUS practice (1,3,12). Thus, the modern debate surrounding FAST is no longer epistemic — it is structural.

Governance and the Low- and Middle-Income Countries (LMIC) Imperative

The maturation of FAST intersects profoundly with global health policy. The World Health Organization's Essential Diagnostics List and the Lancet Commission on Global Surgery underscore persistent inequities in access to advanced imaging modalities worldwide (13,14).

In many LMICs, CT imaging may be geographically limited, financially inaccessible, or operationally delayed. In such settings, FAST is not merely complementary; it frequently becomes the primary imaging modality guiding urgent decision-making. This reality elevates the ethical responsibility for structured implementation — encompassing formal training standards, credentialing frameworks, image archiving systems, and integration into national trauma protocols (1,3,14).

When governed effectively, FAST can mitigate diagnostic inequity and accelerate access to definitive care. Without governance, variability risks undermining its reliability. The evolution of FAST, therefore, reflects not only technological progress but also health system design, workforce development, and policy accountability.

The Emerging Horizon: Technological Augmentation

The evolution of FAST increasingly reflects technological refinement rather than structural reinvention. Contrast-enhanced ultrasound (CEUS) is under investigation as an extension of conventional FAST to improve the detection of solid organ injury and perfusion abnormalities (4,15). While computed tomography remains the diagnostic gold standard, CEUS may serve as radiation-sparing adjunct in selected hemodynamically stable trauma contexts. Beyond diagnostic enhancement, the contemporary trajectory of trauma ultrasound emphasizes functional integration. Serial FAST examinations enable dynamic assessment of evolving hemoperitoneum, particularly in borderline hemodynamic states, thereby extending its utility from screening to monitoring. Moreover, integration with focused cardiac and lung ultrasound facilitates hemodynamic phenotyping and resuscitation guidance, supporting more individualized damage-control decision-making.

Artificial intelligence (AI)–assisted ultrasound interpretation has entered early clinical evaluation, with emerging evidence suggesting improved detection of pathology and real-time acquisition guidance, potentially reducing operator variability (16). Parallel to algorithmic augmentation, robotic ultrasound systems represent a complementary technological frontier. Semi-autonomous robotic platforms enable controlled probe positioning, standardized acquisition, and force modulation, improving reproducibility and potentially supporting remote trauma assessment (17). The convergence of AI-driven interpretation and robotic-assisted acquisition may, in time, facilitate partially autonomous FAST protocols in prehospital and resource-limited environments. Importantly, the expanding role of ultrasound in trauma is not confined to diagnosis. It increasingly informs procedural interventions, risk stratification, and prognostic assessment, positioning FAST within the broader framework of precision resuscitation. However, technological expansion must be accompanied by governance addressing validation, regulatory oversight, algorithmic bias, and medico-legal accountability. The future of FAST will be defined not solely by enhanced imaging capability, but by responsible and system-integrated deployment.

Conclusion: Beyond Proof

FAST has undergone a substantial intellectual and clinical evolution. Initially validated as a rapid bedside tool characterized by high specificity and operational efficiency, it has matured into a structured component of trauma decision algorithms within integrated emergency systems. Its

contemporary trajectory extends beyond diagnostic validation toward technological augmentation through contrast-enhanced techniques, artificial intelligence–assisted interpretation, robotic standardization, and expanded telemedical integration. The central question is no longer whether FAST is diagnostically reliable. Rather, it is whether trauma systems are sufficiently prepared — in terms of training, governance, infrastructure, and ethical oversight — to integrate emerging technologies responsibly and equitably. This transition from validation to intelligent system-level integration defines the current and future paradigm of trauma ultrasonography.

Conflict of interest: The authors declare that they have no conflict of interest.

Use of Artificial Intelligence (AI) tools: The author declare that no artificial intelligence tools were used in the preparation of this manuscript.

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INCIDENTAL RENAL CYSTS ON CHEST CT: A RETROSPECTIVE ANALYSIS OF PREVALENCE AND IMAGING CHARACTERISTICS

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Abstract

Introduction: Chest computed tomography (CT) frequently includes portions of the upper abdomen, allowing incidental visualization of renal structures. Renal cysts are among the most common incidental abdominal findings.

Purpose: To determine the prevalence, imaging characteristics, and clinical significance of incidental renal cysts detected during routine chest CT examinations.

Material and Methods: This retrospective study reviewed 1,448 consecutive adult chest CT examinations performed over a seven month period from May-November 2025. Radiology reports were screened for renal findings, and images were re-evaluated when necessary. Renal cysts were categorized using the Bosniak classification. Demographic data and cyst characteristics were recorded. Descriptive and comparative statistical analyses were conducted, and interobserver agreement was evaluated using Cohen's kappa.

Results: Incidental renal cysts were identified in 370 patients (25.6%). The prevalence was higher in men than in women (30.6% vs 19.4%, $p < 0.001$). The highest number of cases were recorded in the 45–65-year age group (54.6%). Cysts were unilateral in 63.8% and bilateral in 36.2% of patients. Cortical cysts predominated (52.2%), while 11.6% were cortico-medullary. Mild hydronephrosis was found in 9.5% of patients. Most patients (55.4%) had a single cyst. Interobserver agreement was substantial ($\kappa = 0.66$). Only 2,5 % of patients had cysts requiring follow-up (Bosniak II-III).

Conclusion: Incidental renal cysts are common on chest CT and increase with age. Most are simple, unilateral, and benign. Routine reporting of incidental renal cysts is recommended to ensure appropriate follow-up when clinically warranted.

Keywords: *Bosniak classification; chest CT; incidental findings; renal cysts; prevalence.*

Introduction

Chest computed tomography (CT) frequently includes portions of the upper abdomen, allowing incidental visualization of renal structures. Renal cysts are among the most common incidental abdominal findings and generally represent benign simple cysts (1,2). However, complex cystic lesions with septations, calcifications, or enhancement are associated with a higher likelihood

of malignancy and may require imaging follow-up guided by the Bosniak classification (3,4).

Despite the widespread use of chest CT, the prevalence and clinical relevance of renal cysts incidentally detected on these examinations remain incompletely described. Quantifying the proportion of cysts that warrant further evaluation is important for radiologists and referring clinicians, as incidental findings influence diagnostic workflows, patient management, and imaging resource utilization (5,6). This study aims to determine the prevalence, imaging characteristics, and clinical significance of incidental renal cysts identified on routine chest CT examinations, with emphasis on Bosniak classification distribution and follow-up considerations.

Material and Methods

Study Design and Population

This retrospective study included 1,448 consecutive adult patients (≥18 years) who underwent chest CT at the University Clinic of Pulmonology and Allergology- Skopje, over a seven-month period, from May-November 2025. Of these, 370 patients were identified as having renal cysts and were included in a detailed analysis. Both contrast-enhanced and non-contrast scans were eligible. Exclusion criteria included known renal disease, prior renal surgery, or incomplete imaging.

Imaging Technique

Chest CT examinations were performed using a multidetector CT scanner, PHILIPS INCISIVE 128 slice, for optimized thoracic imaging protocols. Although the abdomen was not the primary target, the upper poles of both kidneys were visualized in all cases.

Data Collection

Radiology reports were electronically reviewed for renal findings. When necessary, images were re-evaluated by two radiologists with three and eight years of experience, respectively. Extracted data included the number of cysts (single vs multiple), laterality (unilateral vs bilateral), cyst location (cortical, cortico-medullary and medullary), Bosniak classification (I–IV) when applicable, presence of associated findings such as hydronephrosis, and the patient's age and sex. Patients were stratified into three age groups: 18–40 years, 45–65 years, and >65 years.

Interobserver Agreement

Cohen's kappa (κ) was calculated to assess interobserver agreement. The junior radiologist identified cysts in 352 patients; and the senior radiologist identified them in 361 patients. Agreement on cyst presence or absence was recorded for all cases. Interobserver reliability for Bosniak categorization and cyst detection has been previously shown to vary by reader experience and imaging modality (7).

Statistical Analysis

Descriptive statistics summarized demographic and cyst characteristics. Chi-square and t-tests were used for subgroup comparisons. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software.

Results

Study Population

Among 1,448 chest CT examinations, incidental renal cysts were identified in 370 patients (25.6%), including 245 men (30.6%) and 125 women (19.4%). The sex-related difference in prevalence was statistically significant ($\chi^2 = 23.74$, $p < 0.001$).

Prevalence by Age Group

Cyst prevalence increased with age:

- 18–40 years: 35 cases (9.5%)
- 45–65 years: 202 cases (54.6%)
- 65 years: 133 cases (35.9%)

More than half of all cysts occurred in patients aged 45–65 years.

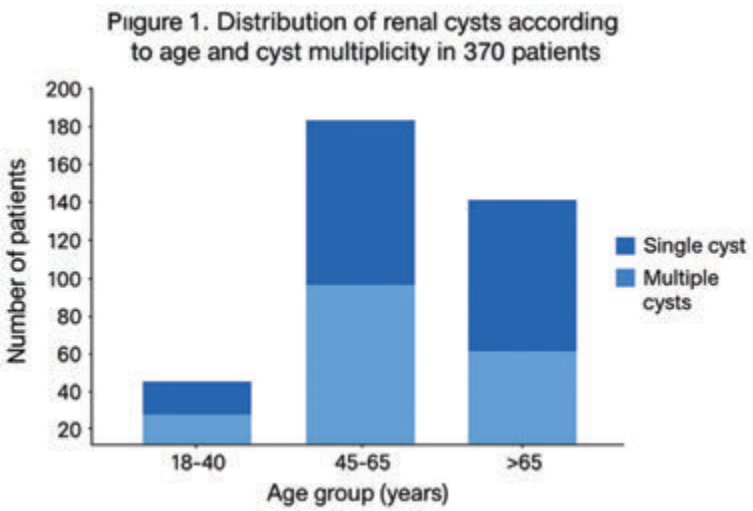

Figure 1.

Table 1. Renal Cyst Distribution by Age Group and Multiplicity

Age Group (years)	Total Patients	Patients with Renal Cysts, n (%)	Single Cyst, n (%)	Multiple Cysts, n (%)
18–40	37	35 (9.5%)	—	—
45–65	202	202 (54.6%)	—	—
>65	133	133 (35.9%)	—	—
Total	370	370 (100%)	205 (55.4%)	165 (44.6%)

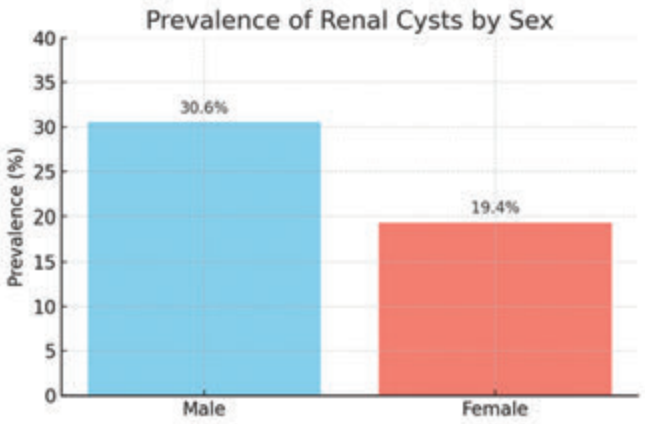

Figure 2.

Cyst Characteristics

- **Laterality:** Unilateral in 236 patients (63.8%); bilateral in 134 patients (36.2%).
- **Location:** Cortical in 193 patients (52.2%); Cortico-Medullary in 134 patients (36,2%), Medullary in 43 patients (11.6%).
- **Multiplicity:** Single cyst in 205 patients (55.4%); multiple cysts in 165 patients (44.6%).
- **Associated findings:** Mild hydronephrosis in 35 patients (9.5%). No severe hydronephrosis was observed.

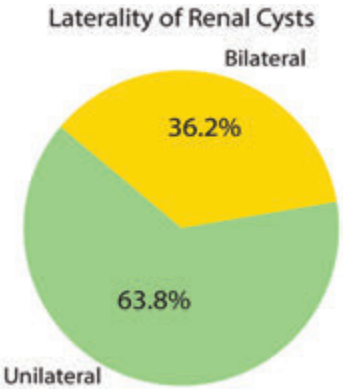

Figure 3.

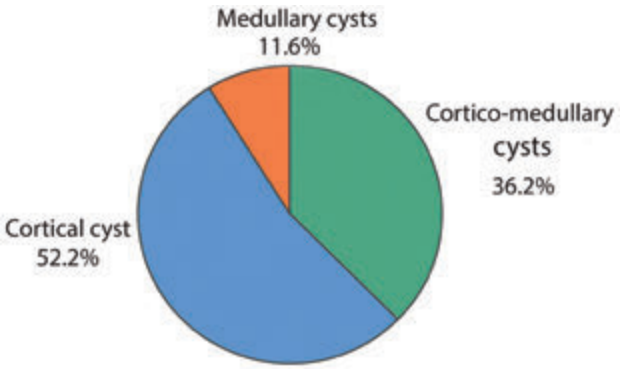

Figure 4.

Bosniak Classification

The majority of identified cysts were simple and benign:

Table 2. Bosniak Classification of Renal Cysts

Bosniak Type	Number of Patients (n)	Percentage (%)
I	361	97.6
II	8	2.2
III	1	0.3
IV	0	0

Only 9 patients (2.5%) had cysts requiring follow-up (Bosniak II–III), whereas the vast majority (97.6%) were simple, benign cysts not requiring additional imaging.

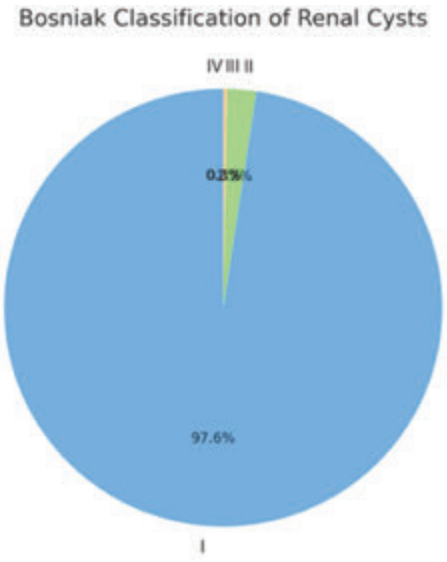

Figure 5.

Interobserver Agreement

The overall observed agreement was 97.6%. Cohen's kappa was $\kappa = 0.66$ (95% CI: 0.52–0.80), indicating substantial interobserver agreement.

Discussion

In this large retrospective cohort, incidental renal cysts were identified in 25.6% of chest CT examinations, consistent with previously reported prevalence rates of approximately 20–30% in adult populations (1,2,8). The significantly higher prevalence among men is consistent with prior epidemiological reports and may reflect sex-specific biological or environmental factors (5,11).

Cyst occurrence increased progressively with age: the majority of cases were observed in patients aged 45–65 years, with continued high prevalence in those >65 years. This pattern corroborates prior population-based studies linking aging to an increased burden of simple renal cysts, likely due to degenerative tubular changes (8,9,10). The low prevalence in younger adults supports the predominantly degenerative etiology of simple renal cysts (1).

Most cysts in our cohort were unilateral and cortically located - characteristics typical of benign simple cysts (3,4). Mild hydronephrosis was uncommon and only 2,5 % of cysts required follow-up; this finding underscores the predominantly benign nature of incidental renal cysts when limited upper pole coverage is obtained on chest CT (5,6). Nonetheless, accurate Bosniak categorization and reporting are essential to identify the small subset of complex cysts that warrant further evaluation or referral (3,4).

In our study, the interobserver agreement was substantial ($\kappa = 0.66$), and consistent with prior reports demonstrating moderate-to-substantial reliability for cyst detection and Bosniak classification, particularly when reader experience and dedicated abdominal imaging are available (7,11). The high observed agreement (97.6%) reflects reproducible detection of visually appreciable cysts on chest CT despite variable abdominal coverage.

These results support routine inspection and standardized reporting of renal findings on chest CT to ensure that clinically relevant incidental lesions are recognized and managed according to best-practice recommendations (12,13).

Conclusion

Incidental renal cysts are common on chest CT, affecting approximately one-quarter of patients. Prevalence increases markedly with age and is higher in men. Most cysts are unilateral, cortical, and benign; very few are associated with hydronephrosis, and only 2,5 % of the cysts in this cohort needed follow-up. Routine documentation of renal cysts during chest CT interpretation is recommended to support consistent reporting and appropriate follow-up when indicated.

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INFLUENCE OF DIFFERENT DOSES OF TRANEXAMIC ACID ON EARLY AND TOTAL POSTOPERATIVE BLEEDING IN NON - ANAEMIC PATIENTS UNDERGOING ON - PUMP CARDIAC SURGERY

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Abstract

Introduction: Postoperative bleeding is a frequent and clinically significant complication after cardiac surgery due to its invasive nature, cardiopulmonary bypass, and perioperative anticoagulation. Excessive bleeding is associated with re-exploration, prolonged intensive care unit stay, increased morbidity, and increased mortality. Antifibrinolytic therapy, particularly tranexamic acid (TXA), is strongly recommended to reduce bleeding and transfusion requirements, yet the optimal dosing strategy remains uncertain.

Aim: To assess the influence of three different doses of TXA on early and total postoperative bleeding in non-anaemic patients undergoing on-pump cardiac surgery.

Material and Methods: Prospective, randomized, single-center study of 180 non-anaemic patients, randomized in three TXA dosing groups: low-dose 20mg/kg, medium-dose 35mg/kg, and high-dose 50mg/kg. The following outcomes were monitored: postoperative bleeding at 4, 12, and 24 hours, total postoperative bleeding, and surgical revision due to bleeding or cardiac tamponade.

Results: Bleeding volumes did not differ significantly between TXA dosing groups at any predefined postoperative interval (0–4 hours, $p = 0.470$; 4–12 hours, $p = 0.853$; 12–24 hours, $p = 0.199$), nor did the cumulative bleeding volumes differ within 24 hours ($p = 0.647$) or the total postoperative bleeding volumes ($p = 0.758$). In multivariable models, the TXA dose was not an independent predictor of early postoperative bleeding, neither there are significant differences for low-dose ($B = 0.136$, $p = 0.214$) nor for medium-dose TXA ($B = 0.182$, $p = 0.087$) compared with the high-dose group. Similarly, the TXA dose was not associated with total postoperative bleeding (low-dose: $B = 0.019$, $p = 0.785$; medium-dose: $B = -0.011$, $p = 0.870$). Aortic valve surgery was associated with significantly lower total postoperative bleeding compared with combined procedures ($B = -0.393$, 95% CI −0.592 to −0.194; $p < 0.001$).

Conclusion: These findings do not support routine escalation of tranexamic acid dosing.

Key Words: *Cardiac surgery; Postoperative bleeding; Tranexamic acid.*

Introduction

Due to its invasive nature, the use of cardiopulmonary bypass (CPB) and perioperative anticoagulation, postoperative bleeding still remains a common and clinically relevant complication following cardiac surgery. Excessive bleeding is associated with higher rates of surgical re-exploration, prolonged intensive care unit (ICU) stay, increased morbidity, overall increase in healthcare utilization, and it is an independent risk factor associated with increased mortality (1). Antifibrinolytic therapy is recommended as a procoagulant intervention, to reduce bleeding, the need for transfusion of blood products, and reoperation for bleeding in cardiac surgery, Class 1, Level A recommendation (2). Tranexamic acid (TXA), synthesized for the first time in 1962 and added to the WHO essential medicines list since 2011, is a widely used antifibrinolytic agent. While its efficiency in reducing blood loss and transfusion requirements is well established, there is still uncertainty regarding the optimal dose and dosing strategies. There is evident heterogenicity in the literature regarding TXA doses, dosing regimens and the optimal dose that maximizes efficiency while avoiding unnecessary drug exposure. Furthermore, postoperative bleeding is the most common cause of postoperative anaemia. The decision for transfusion generally depends on institutional protocols (3), clinical judgement and patient-related factors, and may not accurately represent the true extent and dynamics of postoperative haemorrhage. Quantification of postoperative bleeding in non-anaemic patients, especially during the early postoperative period, can provide a more objective and physiologically relevant assessment of perioperative haemostasis when fibrinolytic activity is most pronounced. The aim of this study is to evaluate the influence of three different doses of tranexamic acid administered once prophylactically on early and total postoperative bleeding, to analyse the temporal pattern of postoperative bleeding across the different doses of TXA in non-anaemic patients undergoing on-pump cardiac surgery, and to compare the incidence of surgical revision for bleeding and tamponade across the different TXA dosing groups.

Material and Methods

This prospective, randomized, controlled, single-center study was conducted at Acibadem-Sistina Hospital Skopje, at the department of Cardiac Surgery, from May 2024 to May 2025. The study protocol was approved by the institutional ethics committee, and written consent was obtained from all participants prior to their enrolment. The study included adult non-anaemic patients older than 18 years, scheduled for elective or urgent aortocoronary bypass, aortic valve or combined on-pump cardiac surgery, and written consent was obtained. Non-anaemic patients were defined according to the World Health Organization (WHO) guidelines on haemoglobin cut-offs to define anaemia, i.e., men with Hgb ≥ 130g/L and women with Hgb ≥ 120g/L. Exclusion criteria were: patients with allergy to TXA; anaemic patients, men with Hgb < 130g/L and women with Hgb < 120g/L (4); patients for elective or urgent surgery on the aorta, mitral valve, off-pump and re-do cardiac surgery; pregnant patients; patients with chronic kidney disease stadium 4 and 5; patients with thrombocytopenia or other coagulation disorders; patients with hypercoagulability syndrome or prior thromboembolic event; patients with positive history of convulsive disorder or prior use of anticonvulsive therapy; patients on vitamin K antagonists ≤5 days prior to surgery or INR >1,5; patients on direct oral anticoagulants (DOAC) ≤2 days prior to surgery; patients on oral P2Y12 inhibitors without the recommended pause time before surgery, ticagrelor ≤2 days, clopidogrel ≤4 days and prasugrel ≤6 days. All included patients were analysed on an intention-to-treat basis.

Patients were randomly allocated on the day of hospitalisation using a computer-generated list of random numbers. Allocation concealment was ensured using a closed, opaque envelope in three equal study groups, depending on the dose of TXA administered once prophylactically. High-dose group: (n=60) TXA 50mg/kg was administered, medium-dose group (n=60) TXA 35mg/kg was administered, and low-dose group (n=60) TXA 20mg/kg was administered. The choice of the studied doses of TXA is within the safety margin doses, according to the International Society for Minimally Invasive Cardiothoracic Surgery (5), according to the guidelines for perioperative care in cardiac surgery of the Enhanced Recovery After Surgery Society (6) and according to the data of the meta-analysis on optimal dosing of TXA in cardiac surgery by Zufferey et al. (7). The assigned dose of tranexamic acid was administered intravenously 45 minutes prior to skin incision. All patients underwent standardized intraoperative management according to the institutional protocols. Postoperative care was standardized and provided under the supervision of a multidisciplinary heart team.

During the study, the following data was monitored: postoperative bleeding, thoracic drains output measured in millilitres at 4, 12 and 24 hours; total postoperative bleeding, total postoperative drainage measured in millilitres untill removal of thoracic drains; surgical revision for bleeding and surgical revision for tamponade. Continuous data with normal and non-normal distribution is presented as mean with standard deviation or median with interquartile range, respectively. Categorical data is presented as absolute or relative frequencies. Baseline comparability across the randomized groups is analysed with ANOVA or Kruskal-Wallis test as appropriate, and with Chi square or Fischer's exact test. The primary analysis of the influence of different TXA dosing groups on bleeding is presented as median with interquartile range, analysed with Kruskal-Wallis test for each bleeding point, whereas the dose dependent response trend is analysed with Jonckheere-Terpstra test for early bleeding at 4 hours, and total postoperative bleeding. A generalized linear model (gamma distribution with log link) is used to identify weather tranexamic acid is an independent predictor of early and total postoperative bleeding. To evaluate postoperative bleeding trajectories at 4, 12 and 24 hours across TXA groups, a linear mixed-effects model is applied. The incidence of revision for bleeding and tamponade is presented as absolute and relative frequency, while the comparison between the groups is analysed with Fisher's exact test. All monitored data was analysed using SPSS statistical software, version 26.0. Statistical significance was defined as p value < 0.05.

Results

A total of 180 non-anaemic patients undergoing on-pump cardiac surgery were enrolled to three TXA dosing groups. No statistically significant differences were observed between the randomized groups at baseline. Demographic data, medical history, and preoperative laboratory parameters are summarized in Table 1.

Table 1. Baseline data across low, medium and high-dose TXA groups

	low-dose TXA (20mg/kg)	medium-dose TXA (35mg/kg)	high-dose TXA (50mg/kg)	p value
Gender Male / Female	32 (53,3%) / 28 (46,7%)	38 (63,3%) / 22 (36,7%)	39 (65%) / 21 (35%)	0,368
Age (year)	66 (62-73)	69,5 (65-73,7)	66,5 (62,2-73,7)	0,295
BMI (kg/m?)	28,8 (25,8-31,2)	27,5 (24,9-31,5)	28,1 (25,5-32,4)	0,805

	low-dose TXA (20mg/kg)	medium-dose TXA (35mg/kg)	high-dose TXA (50mg/kg)	p value
ASA				0,947
2	10 (16,7%)	12 (20%)	11 (18,3%)	
3	49 (81,7%)	47 (78,3%)	47 (79,5%)	
4	1 (1,6%)	1 (1,7%)	2 (2,2%)	
Hypertension Yes / No	57 (95%) / 3 (5%)	57 (95%) / 3 (5%)	60 (100%) / 0 (0%)	0,212
COPD Yes / No	7 (11,7%) / 53 (88,3%)	11 (18,3%) / 49 (81,7%)	6 (10%) / 54 (90%)	0,364
Chronic kidney disease Yes / No	24 (40%) / 36 (60%)	16 (26,7%) / 44 (73,3%)	16 (26,7%) / 44 (73,3%)	0,190
Diabetes Melitus Yes / No	21 (35%) / 39 (65%)	23 (38,3%) / 37 (61,7%)	23 (38,3%) / 37 (61,7%)	0,909
Peripheral artery disease Yes / No	10 (16,7%) / 50 (83,3%)	17 (28,3%) / 43 (71,7%)	13 (21,7%) / 47 (78,3%)	0,304
Cerebrovascular incident Yes / No	7 (11,7%) / 53 (88,3%)	7 (11,7%) / 53 (88,3%)	2 (3,3%) / 58 (96,7%)	0,180
Myocardial infarction Yes / No	10 (16,7%) / 50 (83,3%)	9 (15%) / 51 (85%)	7 (11,7%) / 53 (88,3%)	0,730
Previous PCI Yes / No	7 (11,7%) / 53 (88,3%)	9 (15%) / 51 (85%)	10 (16,7%) / 50 (83,3%)	0,730
NYHA (1-4)				0,794
1	1 (1,7%)	2 (3,3%)	1 (1,7%)	
2	25 (41,6%)	21 (35%)	24 (40%)	
3	33 (55%)	35 (58,4%)	31 (51,6%)	
4	1 (1,7%)	2 (3,3%)	4 (6,7%)	
Euro SCORE II (%)	2,06 (1,15-2,74)	2 (1,16-3,88)	1,74 (1,04-3,2)	0,481
STS risk score (%)	1,11 (0,73-1,72)	1,26 (0,74-1,83)	1,06 (0,54-2)	0,400
Hemoglobin (g/L)	140 (133-149)	139,5 (131-149)	141 (133,3-153,8)	0,444
Platelet count x10^9/L	216,5 (188-268)	232 (191,5-275,5)	216,5 (193,3-250)	0,599
aPTT (s)	24,1 (22-26,1)	24,5 (22,5-25,7)	24,4 (23-25,6)	0,690
INR	1,06 (0,99-1,08)	1,02 (0,97-1,06)	1,03 (0,97-1,09)	0,146
Fibrinogen (g/L)	3,43 (2,83-3,77)	3,06 (2,62-3,89)	3,39 (2,92-3,85)	0,499

No statistically significant differences were observed between the study groups with respect to the urgency of the cardiac procedure (p = 0.639), with elective surgery predominating across all groups. The distribution of surgical procedure types did not differ significantly among groups (p = 0.437), with aortocoronary bypass surgery (CABG) being the most frequently performed procedure.

Table 2. Intra and Postoperative data across low, medium and high-dose TXA groups

	low-dose TXA (20mg/kg)	medium-dose TXA (35mg/kg)	high-dose TXA (50mg/kg)	p value
Operative urgency Elective / Urgent	53 (88,3%) / 7 (11,7%)	54 (90%) / 6 (10%)	56 (93,3%) / 4 (6,7%)	0,635
Procedure type				0,437
Aortocoronary bypass	37 (61,7%)	27 (45%)	31 (51,6%)	
Aortic valve surgery	17 (28,3%)	23 (38,3%)	19 (31,7%)	
Combined procedure	6 (10%)	10 (16,7%)	10 (16,7%)	
Aotric cross-clamp time (min)	46 (31-60,75)	49 (37,25-65,5)	50 (39,25-64,75)	0,295

	low-dose TXA (20mg/kg)	medium-dose TXA (35mg/kg)	high-dose TXA (50mg/kg)	p value
Cardiopulmonarybypass time (min)	70,5 (53,5-90,25)	72,5 (61,25-90,75)	74 (59-90,75)	0,549
Lowest temperature (°C)	34,8 (34,8-34,87)	34,8 (34,8-34,9)	34,8 (34,8-35,1)	0,919
Catecholamine support Yes / No	43 (71,7%) / 17 (28,3%)	46 (76,7%) / 14 (23,3%)	45 (75%) / 15 (25%)	0,815
Postoperative temperature (°C)	35,65 (35,32-36)	35,5 (35,1-35,8)	35,5 (35,12-35,8)	0,049
Postoperative ACT (s)	133,5 (125-141)	138 (125,25-144,5)	138 (131-149)	0,121
Postoperative Hemoglobin (g/L)	109,55±12,933	110,87±12,634	114,94±13,918	0,067
Postoperative Platelet count x10^9/L	179 (134-215,5)	186 (151-221)	180,5 (152,25-211,5)	0,800
Postoperative INR	1,21 (1,15-1,28)	1,19 (1,14-1,27)	1,19 (1,13-1,3)	0,780
Postoperative Fibrinogen (g/L)	2,675 (2,29-3,29)	2,51 (2,15-2,94)	2,68 (2,28-3,35)	0,208
Revision for bleeding Yes / No	0 (0%) / 60 (100%)	0 (0%) / 60 (100%)	1 (1,7%) / 59 (98,3%)	0,366
Revision for tamponade Yes / No	1 (1,7%) / 59 (98,3%)	3 (5%) / 57 (95%)	0 (0%) / 60 (100%)	0,167

The use of catecholamines following cardiopulmonary bypass was comparable across the TXA dosing groups. A statistically significant difference in postoperative body temperature was identified among the groups (p = 0.049), driven primarily by a difference between the medium and low dose TXA groups (p = 0.042). Intraoperative and postoperative data are summarized in Table 2.

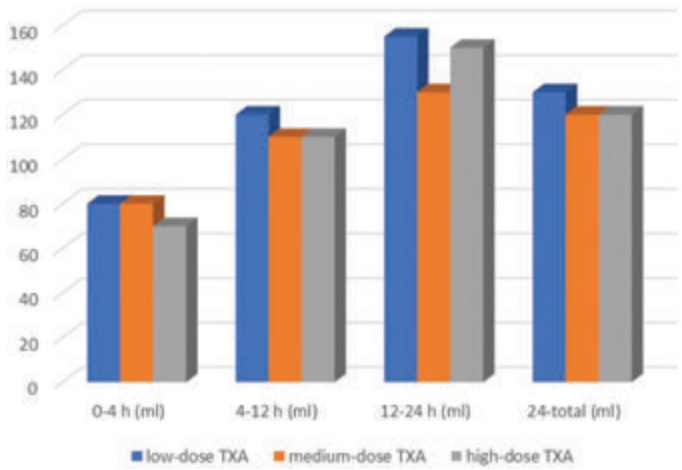

Figure 1. Graphical presentation of postoperative bleeding at predefined time intervals across different TXA dosing groups

Median bleeding volume for early postoperative bleeding, between 0-4 hours, was 80 (42.5–130) mL in the low-dose group, 80 (50–120) mL in the medium-dose group, and 70 (42.5–110) mL in the high-dose TXA group. No statistically significant difference was observed between TXA dosing groups (p = 0.470). Furthermore, no dose–response relationship was detected (p = 0.385). Bleeding volumes between 4-12 hours were comparable across the three TXA groups (p = 0.853), with median values of 120 (90–150) mL in the low-dose, 110 (62.5–170) mL in the medium-dose, and 110 (70–170) mL in the high-dose group. During the 12-24-hour interval, median bleeding volumes were 155 (92.5–210) mL in the low-dose group, 130 (90–170) mL in the medium-dose group and 150 (102.5–197.5) mL in the high-dose group (p = 0.199). Cumulative bleeding after 24 hours remained similar across groups (p = 0.647). Median bleeding volumes were 130 (80–200) mL in the low-dose, 120 (80–195) mL in the medium-dose, and 120

(70–190) mL in the high-dose group. Postoperative bleeding volumes at predefined time intervals are presented in Figure 1.

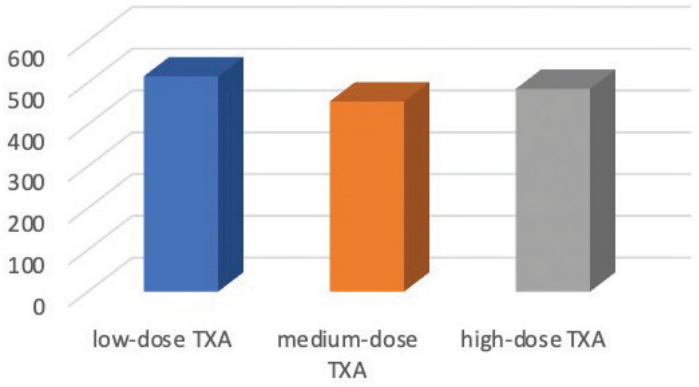

Figure 2. Graphical presentation of total postoperative bleeding across different TXA dosing groups

The total postoperative bleeding volume was 515 (370–675) mL in the low-dose, 455 (345–657.5) mL in the medium-dose, and 485 (360–620) mL in the high-dose TXA group (p = 0.758). In addition, no significant dose–response trend was identified (p = 0.510). Total postoperative bleeding volume is presented in Figure 2.

In the adjusted generalized linear model for early postoperative bleeding, compared with the high-dose TXA group, neither the low-dose (B = 0.136, p = 0.214) nor the medium-dose group (B = 0.182, p = 0.087) demonstrated significant difference in bleeding volume after adjustment for operative urgency, procedure type, cardiopulmonary bypass time, aortic cross-clamp time, lowest intraoperative temperature, and postoperative coagulation parameters. For total postoperative bleeding, compared with the high-dose TXA group, neither the low-dose (B = 0.019, p = 0.785) nor the medium-dose TXA group (B = −0.011, p = 0.870) demonstrated a significant difference after adjustment for operative characteristics and postoperative coagulation parameters.

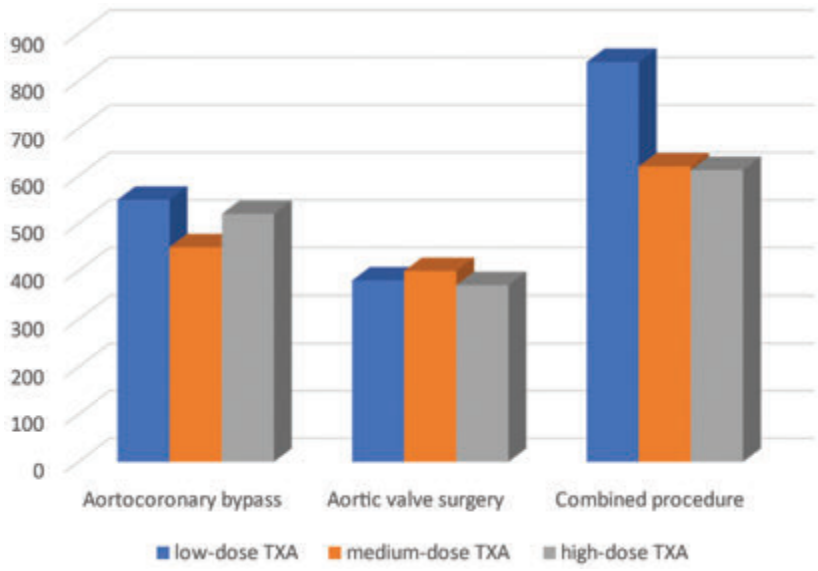

Figure 3. Graphical presentation of total postoperative bleeding across different TXA dosing groups vs procedure type

In addition, aortic valve surgery was associated with significantly lower total bleeding than combined procedures (B = −0.393; 95% CI −0.592 to −0.194; $p < 0.001$), as shown in Graph 3.

In a linear mixed-effects model used to evaluate postoperative bleeding trajectories at 4, 12, and 24 hours across tranexamic acid dosing groups, time was treated as a repeated measure, and a patient identifier was included as a random effect. Bleeding volume was log-transformed to account for non-normal distribution. Postoperative bleeding decreased significantly over time in all groups; however, the interaction between time and tranexamic acid dose indicated that bleeding trajectories did not differ between the dosing groups ($p = 0.397$). There was no significant difference in the incidence of revision for bleeding ($p = 0.366$) and tamponade ($p = 0.167$) across the TXA dosing groups, with only one revision for bleeding and no revision for tamponade in the high-dose TXA group versus one revision for tamponade in the low-dose and 3 revisions for tamponade in the medium-dose TXA group.

Discussion

In this prospective randomised study of non-anaemic patients undergoing on-pump cardiac surgery, analyses demonstrated no statistically significant differences in postoperative bleeding volumes across the low, medium, and high-dose TXA groups at any bleeding interval. These findings suggest that, in a non-anaemic cardiac surgical population, increasing the TXA dose may not confer additional reductions in objectively measured postoperative bleeding beyond a certain threshold. Importantly, the absence of a significant dose–response relationship for early bleeding ($p = 0.385$) and for total bleeding ($p = 0.510$) further supports the notion that higher TXA doses may not yield clinically meaningful haemostatic advantages over lower doses in terms of chest drain output alone. Our findings align with randomized and observational studies questioning the incremental benefit of high versus low-dose TXA in routine cardiac surgery. Meta-analyses by Zufferey et al. and Guo et al. demonstrate wide variability in TXA regimens, with both low and high-dose strategies reducing bleeding compared with no TXA, but without consistent superiority of higher doses for transfusion or major clinical outcomes, and with increased adverse effects, including seizures, at higher exposures (7, 8). Likewise, comparative studies by Sigaut et al. and Rangwala et al. report that although high-dose TXA may reduce bleeding in selected high-risk patients, overall benefits over lower doses are modest and frequently not statistically significant (9, 10). The OPTIMAL multicenter randomized trial by Shi et al. comparing high versus low-dose TXA infusions in cardiac surgery showed a modest reduction in red blood cell transfusion with high-dose TXA but no significant difference in postoperative chest tube output (11). This finding highlights the imperfect correlation between measured bleeding and transfusion, which is influenced by transfusion thresholds, haemodynamic management, and institutional practices. Other randomized studies assessing dose effects report heterogeneous results; in the coronary artery bypass surgery trial by Armellin et al., no significant differences were found in bleeding or transfusion between low and high-dose regimens, suggesting a plateau of antifibrinolytic efficacy beyond a certain dose (12). Meta-analytic data by Rangwala et al. similarly indicate that although high-dose TXA may reduce 24-hour blood loss or chest tube drainage in some cohorts, the effect size is small and must be weighed against potential dose-related risks (10).

Additionally, escalation of tranexamic acid (TXA) dosing was not independently associated with either early or total postoperative bleeding after adjustment for operative characteristics

and postoperative coagulation parameters. This finding aligns with the evidence from the AT-ACAS trial by Myles et al. and with the meta-analyses by Zufferey et al. and Guo et al. demonstrating that standard TXA dosing effectively attenuates fibrinolysis, while higher doses do not necessarily yield further reductions in bleeding and may increase the risk of adverse events (13, 7, 8). The absence of a dose–response relationship across both early and cumulative bleeding endpoints in the present analysis reinforces the concept of a therapeutic ceiling effect for TXA in adult cardiac surgery, which is confirmed by the meta-analyses by Zufferey et al. and Guo et al. (7, 8). Our results support the concept that, beyond a certain threshold, antifibrinolytic efficacy plateaus, and bleeding risk becomes predominantly driven by patient-specific and procedure-related haemostatic factors rather than antifibrinolytic dose alone. Early postoperative bleeding is largely driven by cardiopulmonary bypass–induced haemostatic derangements, including platelet dysfunction and consumption.

Our study's strength, according to the authors, is the assessment of clinically relevant bleeding time intervals combined with advanced statistical approaches that allow adjustment for confounders and comprehensive evaluation of dose–response relationships in this group of patients. Additionally, the investigated TXA dosing regimens are grounded on contemporary evidence, thus supporting clinical applicability. However, the single-center design and the exclusion of higher-risk populations limit extrapolation to broader surgical cohorts.

Conclusion

Escalation of tranexamic acid dosing was not associated with a reduction in either early or total postoperative bleeding after cardiac surgery, even after adjustment for operative characteristics and postoperative coagulation parameters. These findings support the use of lower tranexamic acid doses in non-anaemic patients undergoing on-pump cardiac surgery, potentially minimizing drug exposure without compromising haemostatic efficacy.

Ethical approval: The study was approved by the institutional ethics committee of Acibadem Sistina prior to patient enrolment, approval reference 02-15663/02.

Consent for publication: Written informed consent was obtained from all patients prior to inclusion in the study.

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COMPARISON OF DIAGNOSTIC VALUES OF SERUM PCR AND SERUM GALACTOMANNAN ANTIGEN ASSAY FOR DIAGNOSIS OF ASPERGILLOSIS

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Abstract

Introduction: Aspergillosis is a major threat to immunocompromised hosts, but also to immunocompetent patients. Early diagnosis remains a diagnostic challenge, and there is a need for rapid and sensitive diagnostic methods.

Aim: The aim of the study was to compare the diagnostic value of serum PCR assay with serum galactomannan antigen test, in the diagnosis of both invasive and non-invasive aspergillosis.

Material and methods: During a period of two years (2014 – 2016), sera from 125 patients divided into 4 groups (group I-immune deficiency, group II-prolonged stay in ICU, group III-chronic aspergillosis, group IV-cystic fibrosis), classified according to clinical diagnosis and EORTC/MSG criteria, were analysed at the Institute of Microbiology and Parasitology, Faculty of Medicine Skopje, with molecular (PCR) and serological methods (galactomannan.

Results: PCR in serum demonstrated the following sensitivity and specificity: 53.57% and 100% in group I, 36.36% and 100% in group II, 9.09% and 100% in group III, respectively. Serum PCR was not performed in the cystic fibrosis group. The sensitivity and specificity of galactomannan in serum were 64.29% and 57.14%, 40.91% and 62.5%, and 40.91% and 62.5% in groups I, II, and III, respectively.

Conclusion: Our results indicate that both PCR and galactomannan in serum could be useful adjunct tests for the diagnosis of both invasive and non-invasive aspergillosis, so an early antifungal treatment is initiated in order to achieve a more favorable clinical outcome.

Keywords: *Aspergillus; aspergillosis serum galactomannan; serum PCR.*

Introduction

Invasive fungal infections (IFIs) are severe systemic infections with high mortality rates, particularly in immunocompromised patients. Invasive pulmonary aspergillosis (IPA) is the most severe form of aspergillosis with the highest mortality rate. These infections are very common in patients with hematologic malignancies, chemotherapy-induced neutropenia, hematopoietic stem cell transplantation (HSCT), and solid organ transplantation (1,2). Many studies have recently demonstrated that IPA is more frequently registered in non-neutropenic, immunocompetent patients without classic risk factors, who have been treated in the intensive care unit

(ICU) (3). Most of these patients have chronic obstructive pulmonary disease (COPD), have received broad-spectrum antibiotic treatment or systemic corticosteroids, have impaired mucociliary clearance, diabetes, chronic renal disease, and liver failure; however, IPA can also be found in patients without underlying diseases (4). IPA is more frequently registered in critically ill patients treated in intensive care units (3). Chronic aspergillosis is a locally invasive form of aspergillosis and is seen mainly in patients with mild immunodeficiency or with chronic lung disease. Aspergilloma and allergic bronchopulmonary aspergillosis (ABPA) are noninvasive forms of aspergillosis (4).

Diagnosis of IPA remains a laboratory challenge, since clinical symptoms and signs are non-specific. The gold standard method for diagnosing IPA is the detection of fungi by histopathological examination of lung tissue. Standard mycological methods with culture on fungal media are time-consuming and insensitive. Diagnosis is also difficult because most of the diagnostic tools lack specificity or sensitivity in the early phase of the infection. Over the recent years, novel molecular and serological methods have been developed to improve diagnosis of IPA in patients at high risk. Rapid, noninvasive, culture-independent diagnostic methods have contributed towards faster and better detection of invasive IFI and are essential for timely antifungal treatment. Among these methods, serological diagnostic tests focus on detecting biomarkers such as galactomannan (GM) from *Aspergillus*, in serum or BAL, and detection of DNA from the fungus in primarily sterile specimens. These diagnostic approaches have gained importance in the mycology laboratory (5).

The aim of the study was to compare the diagnostic value of serum PCR assay with serum galactomannan antigen test, in the diagnosis of both invasive and non-invasive aspergillosis.

Material and Methods

Study design

The study was performed at the Laboratory for diagnosis of fungal infections at the Institute of Microbiology and Parasitology, Faculty of Medicine Skopje, Macedonia, during a 2-year period, as part of an ongoing PhD study during the 2014-2016 period.

Group of patients and mycological analyses

Sera from 125 patients divided into 4 groups (group I-immune deficiency, group II-prolonged stay in ICU, group III-chronic aspergillosis, group IV-cystic fibrosis), classified according to clinical diagnosis and EORTC/MSG criteria, were analysed at the Institute of Microbiology and Parasitology, Faculty of Medicine Skopje, with molecular and serological methods, during a period of two years (2014-2016). Samples were frozen and stored at –70°C for retrospective testing. These groups included patients with primary immune deficiency, critically ill patients treated in ICUs, patients with chronic aspergillosis and cystic fibrosis patients. IPA was defined according to the revised definitions by the EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study Group) consensus group (6).

Molecular Detection of *Aspergillus* DNA

Extraction of DNA from serum. A total of 3-5 ml of peripheral blood was mixed with 5 volumes of buffer for lysis of erythrocytes (0,155 M NH4Cl, 0,01 M NH4HCO3, 0,1 mM EDTA

(pH 7,4)), and this mixture was incubated for 10 minutes at 4°C. After lysis of erythrocytes, the specimen was centrifuged at 300×g for 10 minutes. The supernatant was discarded, and leucocytes were washed once in 1×PBS solution (1,4 M NaCl, 50 mM KCl, 90 mM Na2PO4 · 2H2O, 20 mM KH2PO4 (pH 7,4)) and centrifuged again. The leucocyte pellet was resuspended in 300 µl of 1×PBS solution, and the mixture was incubated with 100-125 U lyticase (lyticase-50.000 U; Sigma) for 30 minutes at 37°C. The residual material of human and fungal cells was treated with 500-1.000 µg proteinase K (Boehringer) and 0.5% SDS (Natrium dodecyl sulphate) (Sigma) at 55°C for 1 hour. The residual cell material was then lysed while incubated with an additional 100 µl *2×Aspergillus* buffer for extraction (400 mM Tris-Cl, 1 M NaCl, 20 mM EDTA, 2% Natrium dodecyl sulphate) for 30 minutes at 65°C. Purification of fungal and human DNA was performed with phenol-chloroform extraction. The precipitation of DNA was performed with the addition of 0.7 volume of isopropanol, further washed with 70% ethanol, and afterwards dried in air. The concentration of DNA was analyzed with a spectrophotometer at 260 and 280 nm. The DNA extracts were frozen at -20°C until the PCR procedure (7).

Controls for extraction. Negative controls were purified water without DNA. Positive controls were included for every extraction and verification, with inoculation of saline solution containing approximately 150 CFU of *A. fumigatus* conidial suspensions, in a volume of 500 µl. To determine the total number of injected CFU, 100 µl of the suspension containing around 30 CFU was inoculated on the surface of the Sabouraud dextrose agar, which was incubated for 72 hours at 30°C.

PCR for *Aspergillus*

The PCR reaction was performed in a 25 µL mixture containing approximately 50-150 nanograms of total DNA. This PCR mixture contained around 0.5 U Taq DNA polymerase, 6.25 nmol DNTP, 10 pmol primers (for the first PCR step – first set of primers: AFU 7S-AFU 7AS; for the second PCR step – another set of primers AFU 5S-AFU 5AS), which were derived from sequences of *A. fumigatus* 18S rRNA gene). The PCR was performed in an automated thermocycler. The PCR products were separated by 2.5% agarose gel electrophoresis, dyed with ethidium bromide, and visualized under UV light. The control included all components of the reaction mixture, except genomic DNA. As positive and negative controls for PCR, DNA of a human cell line, T47D, and a diluted solution of *A. fumigatus* were used as templates (7).

Detection of galactomannan

A commercially available sandwich ELISA test for the detection of GM antigen was performed according to the instructions of the manufacturer (8). Each sample was tested in duplicate, and the mean value was determined. The optical density of each well was read at 450 nm. The microtiter plates were read within 30 minutes after the addition of a stop solution. The optical density was determined spectrophotometrically using a microplate reader. The results were interpreted based on the index calculated from the measured OD at a wavelength of 450 nm. Although the threshold for a positive GM test result is still controversial, we used an optical density index cut-off of 0.5 for serum samples.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows. The results of our study are presented as numbers and percentages. The sensitivity,

specificity, positive predictive value, and negative predictive value were evaluated. Differences in the distribution of proven, probable, and possible fungal infections with *Aspergillus* were compared by the Pearson Chi square test. A p-value less than 0.05 was considered statistically significant.

Results

Sera from 125 patients were divided into 4 groups (patients with primary immune deficiencies, critically ill patients treated in intensive care units (ICUs), patients with chronic aspergillosis and cystic fibrosis (CF)) according to clinical diagnosis and EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study group) criteria (Fig. 1).

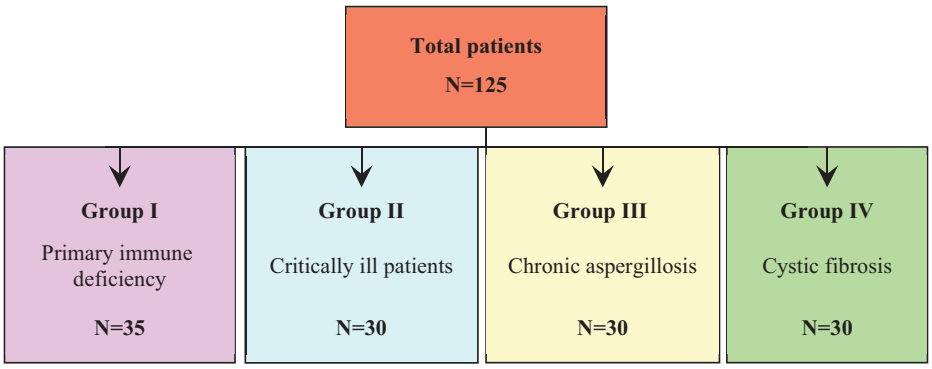

Figure 1. Classification of patient groups according to EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study group) criteria

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

Table 1. Characteristics of patients according to gender and age

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

[a]p(Chi-square test)

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

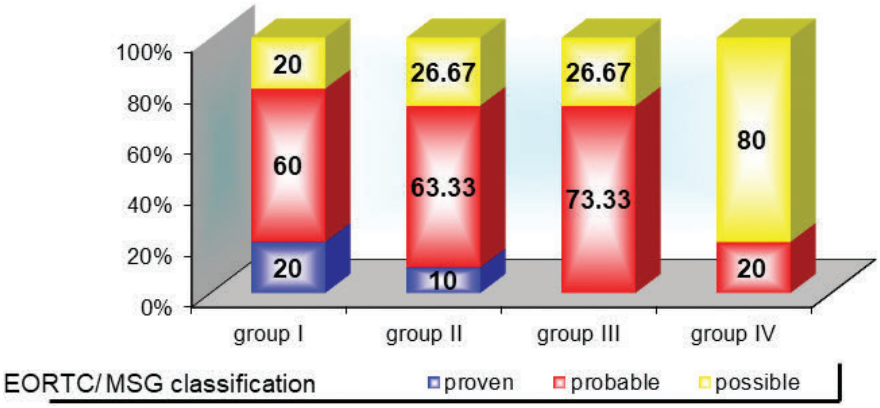

Figure 2. Distribution of fungal infections according to EORTC/MSG criteria in all groups

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

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

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

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

Regarding the application of PCR in serum, presence of *Aspergillus* DNA was confirmed in 42.86% patients with primary deficiency, 26.67% patients with prolonged ICU stay, and in 6.67% patients with chronic aspergillosis. Statistically significant differences were confirmed between group I versus group III (p=0.0014) and group IV (p<0.0001), and between group II versus group IV (p=0.0046) (Table 3).

Table 3. PCR in serum

Ggroup *Aspergillus*				
	Group I N=35	**Group II N=30**	**Group III N=30**	**Group IV N=30**
Serum PCR	**n (%)**	**n (%)**	**n (%)**	**n (%)**
No 100 (80%)	20 (57.14%)	22 (73.33%)	28 (93.33%)	30 (100%)
Yes 25 (20%)	15 (42.86%)	8 (26.67%)	2 (6.67%)	0
	Chi-square: 23.09 ap < 0.000039 I vs II ap=0.17 II vs III bp= 0.08 III vs IV bp= 0.5 I vs III bp= 0.0014** II vs IV bp= 0.0046** I vs IV bp<0.001			

ap(Chi-square test) b(Fisher exact test)

The results from comparative diagnostic performance of serum PCR test and serum galactomannan antigen test in the group of patients with immunodeficiency are shown in Table 4. The sensitivity, specificity, positive and negative predictive values of serum PCR test were: 53.57% / 100% / 100% / 35%. The sensitivity, specificity, positive and negative predictive values of serum galactomannan antigen test were: 64.29 % / 57.14% / 85.71% / 28.57%, in group I, respectively.

Table 4. Diagnostic performances of serum PCR test and serum galactomannan antigen test in the group of patients with primary immunodeficiency

Test	**Se(%)**	**Sp(%)**	**PPV(%)**	**NPV(%)**
Serum PCR	53.57	100	100	35
Galactomannan in serum	64.29	57.14	85.71	28.57

The results of the comparative diagnostic performance of the serum PCR test and the serum galactomannan antigen test in the group of critically ill patients and prolonged hospital stay in ICU are presented in Table 5. The sensitivity, specificity, positive and negative predictive values of the serum PCR test were: 36.36% / 100% / 100% / 36.36%. The sensitivity, specificity, positive and negative predictive values of the serum galactomannan antigen test were: 40.91% / 62.5% / 75% / 27.78%, in group II, respectively.

Table 5. Diagnostic performances of serum PCR test and serum galactomannan antigen test in the group of patients with prolonged hospital stay in the ICU

Test	**Se(%)**	**Sp(%)**	**PPV(%)**	**NPV(%)**
Serum PCR	36.36	100	100	36.36
Galactomannan in serum	40.91	62.5	75	27.78

The results of the comparative diagnostic performance of serum PCR test and serum galactomannan antigen test in the group of patients with chronic aspergillosis are presented in Table 6. The sensitivity, specificity, positive and negative predictive values of the serum PCR test were: 9.09% / 100% / 100% / 28.57%. The sensitivity, specificity, positive and negative predictive values of the serum galactomannan antigen test were: 40.91% / 62.5% / 75% / 27.78%, in group III, respectively.

Table 6. Diagnostic performances of serum PCR test and serum galactomannan antigen test in the group of patients with chronic aspergillosis

Test	Se(%)	Sp(%)	PPV(%)	NPV(%)
Serum PCR	9.09	100	100	28.57
Galactomannan in serum	40.91	62.5	75	27.78

In the group with cystic fibrosis, only galactomannan in serum was performed, therefore, the comparison of the two methods was not analyzed.

Discussion

Aspergillus is considered one of the leading common causes of death in immunocompromised patients, with mortality rates up to 40% to 50% in patients with acute leukemia and recipients of hematopoietic stem cell transplantation. Recently, immunocompetent patients without any risk factors for invasive fungal infections, have reportedly suffered from IPA as well. Early diagnosis of IPA can significantly improve patient prognosis and increase the chances of the patient's survival, provided the treatment is started earlier. This is still a significant challenge for both clinicians and laboratory workers (1).

Non-invasive and nonculture-based methods diagnostic strategies could offer a major benefit for early aspergillosis diagnosis. Screening for circulating *Aspergillus* DNA in the diagnosis of aspergillosis has been the subject of many studies for many years (8), and has demonstrated a potential in the definitive diagnosis of aspergillosis, especially when combined with other biomarkers. The detection of galactomannan (GM) can also contribute to early mycological diagnosis (10).

We compared the diagnostic value of the serum PCR assay with the serum galactomannan antigen test, in the diagnosis of both invasive and non-invasive aspergillosis. We have demonstrated the highest sensitivity of *Aspergillus* PCR in serum in the first group, with selected high-risk patients with immunodeficiencies. In our study, the sensitivity of the galactomannan antigen test was 64.29%, and compared with the molecular method, the serum PCR demonstrated slightly lower sensitivity (53.57%). The sensitivity of PCR, ranging from 72 to 88%, and the specificity ranging from 75 to 98.7%, were demonstrated by other studies. Some studies have reported sensitivity as low as 26% (11). A meta-analysis of 16 studies including 1618 patients, demonstrated an overall sensitivity of 88% and a specificity of 75%. If two consecutive tests are used to define positivity, the sensitivity and specificity would be 75% and 87%, respectively. The results of this study concluded that two positive tests are necessary to confirm the diagnosis, while one negative PCR result is sufficient to exclude it (12). As a screening tool, a negative PCR result can help rule out invasive aspergillosis. Most previous studies have focused on the sensitivity of serum PCR testing in high-risk patients, such as hematological malignancies or hematopoietic stem cell transplants (13). Raad has demonstrated a sensitivity of 100% for proven IPA infections, but only 57% for probable or possible invasive aspergillosis, in a study analyzing solid cancers (14). Studies that included patients with solid organ transplants or cancers have demonstrated lower sensitivity of serum PCR. In a meta-analysis of the diagnostic performance of *Aspergillus* PCR, the presence of at least two positive whole-blood PCR specimens in a high-risk patient should be considered very indicative, if not confirmatory, of IA (15). A similar sensitivity of 58% of

serum GM test was demonstrated in the study of Pfeiffer (16). Leeflang registered a sensitivity of 78% (17) and Arvanitis demonstrated a sensitivity of 92% with the serum GM test (11). It has been demonstrated that the detection of galactomannan levels in serum is inferior to BAL GM detection, which is considered to be a better way for distinguishing IPA from other infectious lung diseases.

The *Aspergillus* PCR in serum showed lower sensitivity (36.36%) in the group of critically ill patients with prolonged ICU stay. Bocci and coworkers also demonstrate that sensitivity is lower in serum samples than in respiratory specimens (1). According to the 2019 meta-analysis published by Cruciani, the pooled sensitivity and specificity of Aspergillus PCR from blood are reported to stand between 79% and 80% for a single positive result, and 60% and 94% for two consecutive positive test results in immunocompromised people (18). However, the performance of PCR in blood decreases during systemic mold-active prophylaxis or treatment, and in non-neutropenic patients (13). According to Boch and coworkers, serum PCR has a sensitivity as low as 11% in ICU patients, although it improved to 56% in BAL specimens (19). In a retrospective single-center comparative analysis of galactomannan, PCR, and mycologic analysis of pulmonary samples in both neutropenic and non-neutropenic patients, the PCR sensitivity tended to be better in neutropenic patients (82.1%) than in non-neutropenic patients (62.5%). Sensitivity of the serum GM test in our group of critically ill patients with prolonged stay in the ICU was 40.91%. According to Eigl, galactomannan is often absent in the serum of non-neutropenic patients, in whom airway-invasive growth is more typical (20). Thus, GM testing in BAL is preferred in this setting. Some studies reported results on the combined diagnostic capabilities of the GM and PCR assays in non-hematological patients, which is significantly improved compared with the use of either method alone. In the study by Lahmer and co-workers, serum GM levels have been elevated above the cutoff of >0.5, in 3 patients only (10%) (21). The sensitivity of the serum GM test was lower than in our study (30%). One of the problems with serum GM determination is the occurrence of false positive findings, which lowers its specificity, because critically ill patients are sometimes treated for bacteraemia, that could be an additional reason for false positive results.

Very low sensitivity of *Aspergillus* PCR in serum (9.09%) was demonstrated in the group with chronic aspergillosis. In the study by Imbert and coworkers, among 16 patients with noninvasive forms of aspergillosis, 10 were immunocompetent, 3 had metastatic malignancy, 2 had solid organ transplants and 1 had alcoholic liver cirrhosis. Clinical forms were simple aspergilloma ($n = 7$), colonization ($n = 4$), chronic cavitary aspergillosis ($n = 4$) and chronic bronchitis ($n = 1$). None of these patients had positive serum GM or PCR (22). Many studies have demonstrated low sensitivity for detecting *Aspergillus* DNA in patients with chronic aspergillosis. This has been explained by the hypothesis that *Aspergillus* DNA can be more easily detected in respiratory specimens from the site of infection than in blood or serum. A possible explanation for the lower sensitivity or a negative PCR in serum is that the specimen is not taken from the site of infection, and the transient DNAemia.

The utility of the serum GM antigen detection test for the diagnosis of pulmonary aspergillosis other than IPA is controversial. In our group of patients with chronic aspergillosis, the GM antigen test in serum demonstrated a sensitivity of 40.91%, similar to the findings in the study by Park and collaborators, who demonstrated a sensitivity of 38%. Hemoptysis has been suggested as a possible explanation for the high rate of serum GM positivity (9), probably due to bleeding from bronchial artery, allowing GM to reach the circulation. Patients with slowly progressive

pulmonary aspergillosis are likely to demonstrate serum GM positivity because of the release of fungal antigens into the bloodstream due to angioinvasive growth of *Aspergillus* (23). Kono and co-workers demonstrated sensitivity of serum GM levels as low as 14.3% for the diagnosis of chronic aspergillosis and ABPA (24). Park and co-workers found that the sensitivity was only 38% for serum GM (25). Kitasato and co-workers reported a sensitivity of serum GM of 21.4% at a cut-off ≥1.5 and 50% at a cut-off ≥0.5 for chronic aspergillosis (26). Fujiuchi et al. reported that at a cut-off level of ≥0.5, the sensitivity for CNPA was 63.4% (27). In contrast to these results, Sehgal and coworkers demonstrated poor sensitivity of serum GM for diagnosing chronic aspergillosis. According to Sehgal, the poor performance of the serum GM test is likely due to the less invasive nature of chronic aspergillosis (28). In a recent study, the sensitivity of serum GM was only 23%. Therefore, the serum GM antigen test cannot be used for the diagnosis of CPA (29).

Our study demonstrates that PCR is useful both in non-neutropenic patients and non-hematologic populations. As previously reported, our result indicates that performing both the GM antigen test and PCR on the same serum, increases the sensitivity of the diagnostic approach. Our study has few limitations, the major one being a single-center study. Additionally, we used only a single serum sample for investigation, which didn't allow assessment of reproducibility of the methods. Financial constraints prevented this analysis to be performed twice.

Conclusion

The results of this study indicate that a single method, either molecular or serological, cannot provide definite diagnosis of invasive or non-invasive aspergillosis. As these methods detect different biomarkers of the disease, combining them is likely more useful.

Implementation of different microbiological methods, as well as appropriate interpretation of results, in collaboration with clinicians, is the most important aspect for accurate and precise etiological diagnosis of aspergillosis and early initiation of antifungal treatment, leading to achieve a favorable clinical outcome.

Ethical approval: protocol number and date of approval: This study was approved by the Institutional Review Board of the Faculty of Medicine, University "Ss Cyril and Methodius", Skopje, Republic of North Macedonia (at the 10th regular session of the Institutional Review Board) (Decision No. dated 27 October 2011).

Consent for publication: Written informed consent was obtained from all patients prior to inclusion in the study.

Conflict of interest: The authors report no financial or personal conflicts of interest.

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Author Contributions: Gordana Mirchevska is the sole author of this work and was responsible for all aspects of the study, including conception, design, data acquisition, analysis, interpretation, manuscript drafting, and critical revision. The author approved the final version and takes full responsibility for the integrity and accuracy of this work.

Use of Artificial Intelligence (AI) tools: The authors declare that no artificial intelligence tools were used in the preparation of this manuscript.

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DIAGNOSTIC VALUE OF THE CA-125/CEA RATIO FOR DIFFERENTIATING PRIMARY OVARIAN CARCINOMA FROM GASTROINTESTINAL MALIGNANCIES IN A TERTIARY GYNECOLOGIC ONCOLOGY CENTER IN NORTH MACEDONIA

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Abstract

Background: Differentiating primary ovarian carcinoma from gastrointestinal (GI) malignancies is challenging. The CA-125/CEA ratio, with a cut-off around 25:1, may help distinguishing ovarian from non-ovarian cancers. We evaluated the performance of CA-125, CEA, and their ratio in women treated at a tertiary gynecologic oncology center in North Macedonia.

Methods: A prospective study of 72 women ≥18 years with adnexal masses, ascites, or elevated tumor markers suspicious for malignancy, treated surgically between 2019-2024. Preoperative serum CA-125, CEA, CA19-9, and CA72-4 were measured, and the definitive diagnosis was established histopathologically. Cases were classified as ovarian/gynecologic or GI malignancies. The primary endpoint was the ability of the CA-125/CEA ratio to differentiate ovarian from GI malignancy.

Results: The median age was 61 years, and 79.2% of patients were postmenopausal. Ovarian/gynecologic malignancy was diagnosed in 69/72 (95.8%), and 3/72 (4.2%) had GI malignancies. The CA-125/CEA ratio was significantly higher in ovarian malignancies (101.0 vs 11.4, p=0.033). A cut-off of ≤25 identified all 3 GI cancers (100% sensitivity), but misclassified 15 ovarian cancers (72.7% specificity). The ROC AUC was 0.86 for the CA-125/CEA ratio, compared to 0.61 for CA-125 alone.

Conclusions: A CA-125/CEA ratio ≤25 identified GI malignancies with high sensitivity but modest specificity. This approach may reduce unnecessary GI endoscopies in resource-limited settings like North Macedonia, though larger studies are needed.

Keywords: *CA-125; CEA; gastrointestinal metastasis; North Macedonia; ovarian cancer; tumor markers.*

Introduction

Most women with epithelial ovarian cancer present with advanced disease, and preoperative characterization of adnexal masses remains a major challenge despite advances in imaging and biomarker assessment. Differentiating primary ovarian carcinoma from ovarian metastases of gastrointestinal (GI) origin is crucial for optimal surgical planning, the need for combined gy-

necologic–colorectal teams, and the timing of endoscopic evaluation.

ESMO and ESGO guidelines recommend CA-125 as the standard serum marker in the diagnostic work-up of suspected ovarian cancer, often in combination with imaging and, where appropriate, HE4 and multivariate algorithms such as RMI or ROMA. However, they explicitly caution that CA-125 alone cannot reliably distinguish benign from malignant adnexal masses or identify the primary site.

Several older and more recent studies have proposed the CA-125/CEA ratio as a simple tool to help distinguish primary ovarian cancer from colorectal or other non-ovarian malignancies. Buamah et al. reported that all 47 women with ovarian cancer in their cohort had a CA-125/CEA ratio >25, whereas many colorectal and other GI cancers had a ratio below this threshold (3). Subsequent studies by Moro et al., Kurokawa et al., and others confirmed that combining CA-125 and CEA, often via a ratio, improves discrimination between primary adnexal masses and GI metastases (4,5). More recently, Zanon et al. suggested that CA-125/CEA may also be helpful in distinguishing advanced ovarian cancer from stage IV colorectal cancer (6).

In this context, Helweg-Larsen et al. (2023) demonstrated that combining CA-125 and CEA, including the use of the CA-125/CEA ratio, improved the diagnostic performance for ovarian cancer in a Danish population, supporting the historical cut-off of 25:1 for suggesting ovarian origin (7). Yu et al. (2024) further expanded this concept in a multicenter analysis focusing specifically on the discrimination between primary ovarian cancer and metastases from the GI tract (8).

In North Macedonia, access to advanced imaging and specialized multidisciplinary centers is improving but remains variable. A simple, inexpensive serum-based tool such as CA-125/CEA could help triage patients for GI endoscopy versus direct referral for gynecologic oncologic surgery, potentially reducing costs and delays in care.

Material and Methods

Study design and setting

We conducted a prospective observational study in a tertiary gynecologic oncology center in North Macedonia, including consecutive women referred with adnexal mass, ascites, or isolated elevation of tumor markers suspicious for malignancy during 2024 and 2025. The study design and core variables were pre-specified in a protocol and an abstract in Macedonian.

Patient population

Inclusion criteria:

- Female sex, age ≥18 years
- Presence of adnexal/pelvic mass, ascites, or isolated elevation of tumor markers interpreted as suspicious for malignancy
- Elevated CA-125 level (>35 U/mL) whenever available
- Planned surgical intervention and/or diagnostic biopsy
- Written informed consent

Exclusion criteria:

- Previously known primary GI carcinoma prior to the current adnexal presentation
- History of treated ovarian carcinoma
- Invalid or missing serum samples for tumor marker measurement

A total of 72 women fulfilled the criteria and were included in the final analysis.

Clinical and imaging assessment

Demographic and clinical data included year of birth (used to derive approximate age), menopausal status, family history of cancer, presenting symptoms, and imaging findings from ultrasound, CT, and/or MRI. Menopausal status was categorized as postmenopausal, premenopausal with regular menses, or perimenopausal/irregular cycle. Ascites was recorded qualitatively (present vs absent). Performance of colonoscopy and gastroscopy, and their findings were extracted from medical records

Biomarker assessment

Serum CA-125 (U/mL), CEA (ng/mL), CA19-9 (U/mL), and CA72-4 (U/mL) were measured pre-operatively in the institutional laboratory using standard immunoassays. Values recorded as "/" in the database were treated as missing. For the primary analysis, we required concomitant CA-125 and CEA measurements.

The CA-125/CEA ratio was calculated as:

$$\text{ratio} = \frac{\text{CA-125 (U/mL)}}{\text{CEA (ng/mL)}}$$

When CEA was reported as 0.0 ng/mL, the ratio was considered extremely high and classified as >25; such cases were included in the binary rule analysis but excluded from continuous ROC analysis to avoid infinite values.

Histopathologic classification

All patients underwent surgery and/or biopsy with definitive histopathologic diagnosis. Based on the final report, cases were categorized into two groups:

- **Primary ovarian/gynecologic malignancy:**
  - Epithelial ovarian carcinoma (high-grade serous, endometrioid, clear cell, mucinous, low-grade serous)
  - Carcinosarcoma and other Müllerian neoplasms
  - Synchronous ovarian–endometrial primaries
- **Gastrointestinal malignancy:**
  - Colorectal adenocarcinoma with ovarian and/or peritoneal involvement
  - Gastrointestinal stromal tumor (GIST) arising from the GI tract with peritoneal/ovarian spread

- In total, 69 cases were classified as primary ovarian/gynecologic malignancies and 3 as GI malignancies.

Outcomes and definitions

The primary outcome was the diagnostic performance of the CA-125/CEA ratio for differentiating primary ovarian/gynecologic malignancy from GI malignancy, using a cut-off ≤25 to suggest GI origin, in line with prior literature (1).

Results

Patient characteristics

Seventy-two women were included. The median age at diagnosis (approximated from year of birth) was 61 years (IQR 53–67; range 38–84). Most patients were postmenopausal (57/72, 79.2%), while 11/72 (15.3%) were premenopausal with regular cycles, and 4/72 (5.6%) had irregular menses. Ascites was documented in 32/72 (44.4%) patients.

Colonoscopy and gastroscopy were performed in 20 (27.8%) and 15 (20.8%) women, respectively. Among the three GI malignancies, one had a colonoscopic diagnosis of intramucosal adenocarcinoma in a villous polyp, while upper endoscopy was normal in two of the three cases.

Histopathologic diagnoses

Primary ovarian/gynecologic malignancies accounted for 69/72 (95.8%) cases, including high-grade serous carcinoma, mucinous cystadenocarcinoma, endometrioid and clear-cell histologies, carcinosarcomas, and synchronous ovarian–endometrial cancers. GI malignancies were identified in 3/72 (4.2%) patients: two colorectal adenocarcinomas with ovarian and peritoneal involvement and one GIST of intestinal origin with peritoneal dissemination.

Tumor markers in the overall cohort

Serum CA-125 values were available in 62/72 (86.1%) patients, CEA in 60/72 (83.3%), CA19-9 in 55/72 (76.4%), and CA72-4 in 39/72 (54.2%). Overall median values were:

- CA-125: 167.2 U/mL
- CEA: 1.60 ng/mL
- CA19-9: 12.6 U/mL
- CA72-4: 8.2 U/mL

As expected in a gynecologic oncology population, CA-125 levels were frequently and markedly elevated, whereas CEA was generally low.

Comparison between ovarian and GI malignancies

Table 1: Comparison of Tumor Markers Between Ovarian/Gynecologic and GI Malignancies

Marker	Ovarian/Gynecologic	GI Malignancies	p-value
CA-125 (U/mL)	170.4 (IQR: 66.51–476.75)	42.4 (IQR: 39.72–224.69)	0.49
CEA (ng/mL)	1.47 (IQR: 0.67–3.01)	3.73 (IQR: 2.96–63.87)	0.067
CA-125/CEA ratio	101.0 (IQR: 17.98–448.09)	11.4 (IQR: 7.32–14.14)	0.023

Diagnostic performance of the CA-125/CEA ratio

Concomitant CA-125 and CEA measurements were available in 58/72 (80.6%) patients, including all 3 GI malignancies and 55 ovarian/gynecologic cancers. Using the pre-specified rule:

- Test positive for GI origin: CA-125/CEA ≤25
- Test negative: CA-125/CEA >25

We observed the following 2×2 table:

True GI malignancies (n=3)	All 3 had CA-125/CEA ≤25 (true positives)
Ovarian/gynecologic malignancies (n=55)	10 had CA-125/CEA ≤25 (false positives)
	49 had CA-125/CEA >25 (true negatives)

From these data:

- **Sensitivity:** 100% (3/3; 95% CI 29.2–100)
- **Specificity:** 82.7% (40/55; 95% CI 59.0–83.9)
- **PPV:** 16.7% (3/18; 95% CI 3.6–41.4)
- **NPV:** 100% (40/40; 95% CI 91.2–100)

Thus, a CA-125/CEA ratio >25 essentially excluded GI origin in this cohort, while a ratio ≤25 strongly indicated that further GI work-up was warranted, albeit with a relatively low PPV due to the low prevalence of GI malignancies.

ROC analysis

Among patients with both markers available and CEA >0 (n=54), the ROC-AUCs for discriminating GI or ovarian/gynecologic origin were:

- CA-125 alone (higher in ovarian): AUC 0.61
- CEA alone (higher in GI): AUC 0.82
- CA-125/CEA ratio (lower in GI): AUC 0.86

These findings suggest that the CA-125/CEA ratio offers better discrimination than CA-125 alone and at least comparable, slightly improved performance to CEA alone in this dataset.

Discussion

In this prospective single-center study from North Macedonia, we found that:

- The CA-125/CEA ratio was significantly higher in primary ovarian/gynecologic malignancies compared with GI malignancies.
- Using a cut-off of ≤25 to indicate GI origin, the ratio achieved 100% sensitivity and 100% NPV for GI malignancy in our cohort, at the cost of modest specificity (72.7%) and low PPV (16.7%).
- ROC analysis showed that the CA-125/CEA ratio (AUC 0.86) outperformed CA-125 alone and slightly improved upon CEA alone for differentiating GI from ovarian origin.
- CA19-9 and CA72-4 did not show meaningful discriminatory value in this small series.

Buamah et al. originally proposed the CA-125/CEA ratio >25 as a marker strongly suggestive of ovarian origin, with all ovarian cancers in their series exceeding this threshold. Moro et al. later identified an optimal ratio of approximately 11.9 for distinguishing ovarian neoplasms from ovarian metastases in a large multicenter cohort, again demonstrating the ratio's superior performance over either marker alone. Kurokawa et al., and others further supported the notion that a combined CA-125/CEA assessment improves pre-operative discrimination between primary adnexal masses and GI metastases.

More recently, Zanon et al. reported that CA-125/CEA may help distinguish advanced ovarian cancer from stage IV colorectal cancer, especially in the context of peritoneal carcinomatosis where radiologic appearances overlap. In a Danish cohort, Helweg-Larsen et al. (2023) confirmed that the combination of CA-125 and CEA, including using the ratio, improves the identification of ovarian cancer among women with elevated CA-125.

Our findings align with these studies, reinforcing that a low CA-125/CEA ratio should trigger a careful search for GI origin, while a very high ratio strongly favors ovarian origin.

While the study highlights promising diagnostic performance, it is also important to acknowledge the economic impact of incorporating the CA-125/CEA ratio into preoperative work-ups. In settings with constrained resources, such as North Macedonia, the cost of procedures like colonoscopy (approximately €100 per procedure) could be reduced by using the CA-125/CEA ratio to help prioritize patients for GI evaluation. This could significantly reduce the number of unnecessary procedures, optimize resource allocation, and expedite diagnosis and treatment for patients. By effectively distinguishing GI from ovarian malignancies, unnecessary gastroscopies and colonoscopies can be minimized, leading to both cost savings and improved patient flow.

Limitation

The small number of **GI malignancies** (only 3 cases) limits the ability to draw definitive conclusions on the clinical performance of the CA-125/CEA ratio in larger, more diverse populations.

Despite this limitation, our study provides valuable insights into the utility of the CA-125/CEA ratio, particularly in resource-limited settings, and lays the groundwork for further multicenter validation studies to refine the approach.

Ethics approval: This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the University Clinic for Gynecology and Obstetrics, Mother Theresa Clinical Campus, Skopje, North Macedonia.

Consent for publication: Written informed consent was obtained from all patients prior to inclusion in the study.

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Author Contributions: : Asani P: study conception, data collection, manuscript drafting Aluloski I: methodology, supervision; Tanturovski M: statistical analysis; Joksimovikj M: clinical data interpretation; Abdija P: patient recruitment; Asani D: histopathology review

All authors approved the final manuscript.

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ARTHROSCOPIC ASSESSMENT OF DISTAL TIBIOFIBULAR SYNDESMOSIS IN ANKLE FRACTURES: PREVALENCE BY WEBER TYPE

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Abstract

Introduction: Ankle fractures are common injuries, but the true extent of damage to the distal tibiofibular syndesmosis is often underestimated when only radiographs and standard stress tests are used. Arthroscopy offers a direct and dynamic view of the syndesmosis and may uncover instability that would otherwise be missed in different Danis–Weber fracture types.

Material and methods: This retrospective-prospective, single-center study included 64 adults with unstable ankle fractures treated with routine ankle arthroscopy, followed by open reduction and internal fixation. Fractures were classified as Weber A, B, or C. During arthroscopy, the distal tibiofibular syndesmosis was probed under lateral stress and categorised as stable or unstable. The prevalence of arthroscopically confirmed syndesmotic instability was calculated for the whole cohort and for each Weber type, and the association between Weber type and instability was tested with the chi-square test.

Results: Our patient cohort consisted of 16 Weber A, 29 Weber B, and 19 Weber C fractures. Syndesmotic instability confirmed arthroscopically was found in 23 of 64 patients (35.9%). Instability was present in 1/16 Weber A (6.3%), 9/29 Weber B (31.0%), and 13/19 Weber C fractures (68.4%). The prevalence of instability increased from Weber A to Weber C, and the association between fracture type and arthroscopic instability was statistically significant (χ^2, $p < 0.001$).

Conclusions: In this series of unstable ankle fractures, roughly one in three patients had an unstable distal tibiofibular syndesmosis during arthroscopic testing, with the highest rates in Weber C and intermediate in Weber B fractures. Although uncommon, instability was also seen in one Weber A fracture, showing that fibular fracture level alone does not fully exclude syndesmotic involvement. Surgeons should consider selective or routine arthroscopic evaluation of the syndesmosis, especially in Weber B and C injuries.

Keywords: *ankle fracture; arthroscopy; syndesmosis; tibiofibular joint; Weber classification.*

Introduction

Ankle fractures are among the most frequent fractures treated in orthopaedic trauma practice and are usually managed with open reduction and internal fixation (1,2). Even when fixation is

technically adequate, some patients continue to complain of pain, and stiffness, thus giving way, and gradually develop post-traumatic ankle osteoarthritis (1-3). Unrecognised or insufficiently treated injury to the distal tibiofibular syndesmosis is considered one of the important reasons for such unsatisfactory outcomes (1-4).

In daily practice, the stability of the syndesmosis is commonly evaluated by standard radiographs and intraoperative stress tests (3,4). Several studies have shown that radiographic measurements such as tibiofibular overlap, tibiofibular clear space, and medial clear space have limited value, with reported sensitivities around 47–52% and only moderate agreement even among experienced observers (4-7). CT and MRI can improve detection of ligamentous injury, but conventional CT mainly reflects static diastasis and may miss milder forms of instability, while MRI, although highly accurate for identifying torn ligaments, is a non-weight-bearing, static modality that does not necessarily reflect functional tibiofibular instability (5,7–10). Intraoperative fluoroscopic stress views increase the detection rate compared with preoperative imaging, but still rely on indirect widening and side-to-side comparison and do not allow direct assessment of the tibiofibular recess (1,11,12). Arthroscopy, on the other hand, allows direct inspection of the distal tibiofibular recess and real-time observation of tibiofibular motion under stress, and is therefore often used as an intraoperative reference standard for diagnosing syndesmotic instability (1,11-13).

The Danis–Weber classification is simple and widely used, and in practice it is often considered a rough indicator of the risk of syndesmotic involvement (1,2,9). Weber C fractures are usually regarded as highly suspicious for syndesmotic injury, Weber B fractures as having an intermediate probability, and Weber A fractures as having a low probability of damaging the distal tibiofibular ligaments (1,2,9). However, the exact rate of arthroscopically confirmed syndesmotic instability in each Weber subgroup is still not well defined, particularly in consecutive series of unstable fractures treated with a uniform arthroscopy-assisted protocol (11-13,15,16).

The purpose of this study was to determine how often arthroscopic instability of the distal tibiofibular syndesmosis is present in unstable ankle fractures and how this prevalence changes across Weber A, B, and C fracture types. Our working hypothesis was that instability would be most frequent in Weber C fractures, less common in Weber B fractures, and rare, but not completely absent, in Weber A fractures.

Material and Method

Study Design

This observational study had a combined retrospective–prospective design and was conducted at a single tertiary orthopaedic trauma center between January 2021 and December 2024. Patients treated between 2021 and 2022 were identified retrospectively from institutional databases, while patients treated between 2023 and 2024 were prospectively enrolled according to predefined inclusion criteria. All procedures were performed by the same surgical team, following a uniform protocol consisting of diagnostic ankle arthroscopy immediately, followed by open reduction and internal fixation.

Inclusion and Exclusion Criteria

Patients were eligible if they met the following criteria: age 18 years or older; acute, unstable ankle fracture with an indication for operative treatment according to AO principles; and per-

formance of diagnostic ankle arthroscopy directly before open reduction and internal fixation. An ankle fracture was considered unstable when operative treatment was indicated according to AO principles, including bimalleolar or trimalleolar fractures, fractures associated with widening of the medial clear space suggestive of deltoid ligament incompetence, talar shift, or positive stress radiographs indicating mechanical instability.

Exclusion criteria were: heavily contaminated open fractures; previous surgery on the affected ankle; acute infection of the limb; severe soft-tissue compromise that made arthroscopy unsafe; and polytrauma that did not allow adherence to the standardised protocol.

Fracture Classification

All patients underwent standard ankle radiographs (anteroposterior, lateral and mortise views), and computed tomography was obtained in selected complex fracture patterns when considered necessary by the surgeon (1,2). Fractures were classified according to the Danis–Weber system as type A, B or C, depending on the level of the fibular fracture in relation to the syndesmosis (1,2,9).

Arthroscopic Technique and Assessment of Syndesmotic Stability

Ankle arthroscopy was performed with the patient in the supine position using standard anteromedial and anterolateral portals, without the use of distraction (11,12). After evacuation of the hematoma and minor synovectomy when needed, a systematic inspection of the joint was performed (11,17).

The distal tibiofibular syndesmosis was evaluated from the anterolateral portal. A probe was introduced into the syndesmotic region, and lateral stress was applied to the fibula while the relationship between the tibia and fibula was observed under direct arthroscopic vision (11-13,17).

For the purposes of this study, arthroscopic syndesmotic instability was defined as visible widening of the distal tibiofibular joint sufficient to allow free passage of the probe between the tibia and fibula under applied stress, and/or clear lateral translation of the fibula relative to the tibia during stress manoeuvres (11-13,17). Arthroscopic instability was assessed using a standardised probing technique. A 3-mm probe was introduced into the distal tibiofibular recess, and lateral stress was manually applied to the fibula. Instability was defined as visible widening allowing free passage of the probe between tibia and fibula under stress, and/or clear lateral translation of the fibula relative to the tibia. To ensure consistency, the assessment was performed by the senior operating surgeon in all cases.

Surgical Treatment of the Syndesmosis

Following arthroscopic evaluation, open reduction and internal fixation of the ankle fracture was performed according to AO principles, aiming to restore fibular length, rotation and alignment (1,2). When arthroscopy showed syndesmotic instability, tibiofibular fixation with one or more cortical screws was carried out at the discretion of the operating surgeon, in accordance with the department's standard practice and current recommendations (1,2,9,10).

Outcomes and Statistical Analysis

The main outcome measure was the proportion of patients with arthroscopically unstable distal tibiofibular syndesmosis in the entire cohort and within each Weber type. Descriptive statistics

were used to summarise the data as absolute numbers and percentages. The association between Weber type (A, B, C) and arthroscopic syndesmotic instability (stable vs unstable) was analysed using the chi-square test, with a significance level set at $p < 0.05$. All analyses were performed using SPSS for Windows, v. 29.0.

Results

Patient Characteristics and Fracture Distribution

A total of 64 patients met the inclusion criteria and had complete arthroscopic and radiographic data available for analysis. According to the Danis–Weber classification, 16 fractures (25.0%) were classified as type A, 29 (45.3%) as type B, and 19 (29.7%) as type C.

Overall Prevalence of Arthroscopic Syndesmotic Instability

Arthroscopic evaluation identified distal tibiofibular syndesmotic instability in 23 of 64 patients, corresponding to an overall prevalence of 35.9%.

Table 1. Arthroscopic syndesmotic instability by Weber fracture type

Weber type	*Total (n)*	*Instability n (%)*	*Stable n (%)*
A	16	1 (6.3%)	15 (93.7%)
B	29	9 (31.0%)	20 (69.0%)
C	19	13 (68.4%)	6 (31.6%)
Total	64	23 (35.9%)	41 (64.1%)

Prevalence According to Weber Type

When stratified by fracture type, the frequency of arthroscopically confirmed instability differed markedly between groups. Instability was observed in:

- 1 of 16 Weber A fractures (6.3%)
- 9 of 29 Weber B fractures (31.0%)
- 13 of 19 Weber C fractures (68.4%)

Thus, the absolute risk of instability increased progressively from Weber A to Weber C fractures (Table 1).

Association between Weber Type and Instability

Chi-square analysis demonstrated a statistically significant association between fracture type and arthroscopic syndesmotic instability (χ^2 test, $p < 0.001$).

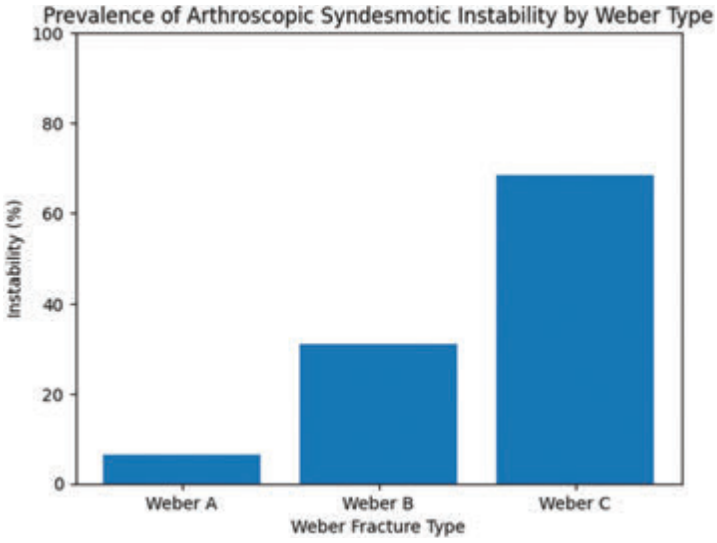

Figure 1. Arthroscopic syndesmotic instability by Weber fracture type

Effect Size (Odds Ratio Analysis)

Odds ratio analysis revealed a stepwise increase in the likelihood of instability across Weber categories.

Compared with Weber A fractures, Weber B fractures had approximately 6.8-fold higher odds of arthroscopic instability. Weber C fractures demonstrated more than 30-fold higher odds of instability. Furthermore, Weber C fractures had nearly 5-fold higher odds of instability compared with Weber B fractures.

Table 2. Odds ratios for arthroscopic syndesmotic instability

Comparison	*Odds Ratio (OR)*
Weber B vs A	6.75
Weber C vs A	32.5
Weber C vs B	4.8

Discussion

The principal finding of this study is that arthroscopic examination identified syndesmotic instability in more than one-third of surgically treated unstable ankle fractures. Importantly, the probability of instability increased progressively across Weber types, suggesting a biological gradient between fracture level and syndesmotic disruption.

These results support the widely held view that suprasyndesmotic fractures carry the highest risk of syndesmotic damage, but they also show that a substantial proportion of transsyndesmotic Weber B fractures harbour clinically relevant instability when assessed arthroscopically (1,11,13,14,17). Previous studies have reported that standard radiographs and intraoperative stress tests can underestimate syndesmotic injury, especially in Weber B patterns, and that ar-

throscopy may reveal additional cases of instability (11-16,17). Radiographic parameters such as tibiofibular overlap and clear space are strongly influenced by ankle rotation and projection, and correlate poorly with the true extent of syndesmotic damage on MRI, with reported sensitivities around 47–52% in some series (4-6). CT allows better visualization of bony detail and can detect diastasis more reliably than plain radiographs, however, conventional static CT and even weight-bearing CT have shown limited ability to distinguish between stable and unstable syndesmotic injuries (5,7–10). MRI is highly accurate for identifying torn ligaments, yet it provides a static, non-weight-bearing snapshot and does not capture dynamic instability under load (5,7-10). Intraoperative fluoroscopic stress views increase the detection rate compared with preoperative imaging, but still rely on indirect widening and side-to-side comparison and do not allow direct assessment of the tibiofibular recess. By contrast, arthroscopy directly visualises diastasis and translation during stress manoeuvres (4,8,12). Our series adds to this body of evidence by quantifying the prevalence of arthroscopically confirmed instability in a consecutive group of unstable fractures stratified by Weber type (1,11-13,15-17).

Although Weber A fractures are considered infrasyndesmotic and generally thought to spare the distal tibiofibular ligaments, arthroscopy identified instability in one patient in this subgroup (6.3%) (1,14,15). This low, but non-zero, rate suggests that syndesmotic involvement in Weber A fractures is possible, particularly in higher-energy injuries or in the presence of associated ligamentous damage (1-3). From a practical point of view, this means that a Weber A label alone should not lead to an automatic assumption of a completely normal syndesmosis.

The very high prevalence of instability in Weber C fractures (68.4%) observed in this study is consistent with earlier reports and underlines that such injuries should be approached with a strong suspicion of syndesmotic disruption (1,2,9). In this setting, arthroscopy can be helpful not only to confirm the indication for syndesmotic fixation, but also to assess reduction and stability after fixation (1,2,11-13,17).

From a clinical standpoint, these findings indicate that fracture level according to the Danis–Weber classification should be regarded as a risk indicator rather than a definitive determinant of syndesmotic integrity. Although Weber C fractures showed the highest prevalence of instability, nearly one third of Weber B fractures demonstrated arthroscopic instability, suggesting that reliance solely on fracture classification may lead to underdiagnosis in this subgroup. Therefore, additional intraoperative assessment beyond standard fluoroscopic stress testing may be warranted, particularly in Weber B injuries. Even in Weber A fractures, the presence of occasional instability underscores the importance of considering the overall injury pattern rather than fracture level alone when deciding on syndesmotic exploration and fixation.

This study has limitations. It is a single-center series with a relatively small sample size, which may limit the generalisability of the results. Only unstable fractures treated operatively with arthroscopy were included, so the findings cannot be directly extrapolated to all ankle fractures, including stable or non-operatively managed cases. Furthermore, the analysis focused on the binary outcome of stable versus unstable syndesmosis and did not address more detailed patterns of ligamentous injury, imaging correlations or long-term functional results.

Despite these limitations, the strengths of this study include the use of arthroscopy as an intraoperative reference for syndesmotic stability, and explicit stratification by Weber type in a consecutive cohort of unstable fractures.

Conclusion

In a retrospective - prospective series of 64 unstable rotational ankle fractures, arthroscopic examination showed distal tibiofibular syndesmotic instability in 35.9% of patients. The prevalence increased clearly from Weber A to Weber C fractures, with instability being rare in Weber A, present in approximately one third of Weber B, and common in more than two thirds of Weber C injuries. These findings indicate that fracture level according to the Danis–Weber classification is related to the risk of syndesmotic instability but does not fully replace direct intraoperative assessment. Selective or routine arthroscopic evaluation of the syndesmosis, particularly in Weber B and C fractures, may improve decision-making regarding syndesmotic stabilisation.

Ethical Approval: The research protocol was reviewed and approved by the Ethics Committee for Research Involving Human Subjects of the Faculty of Medicine - Skopje, Ss. Cyril and Methodius University, approval number 03-391/2, 09.02.2022.

Consent for publication: Written informed consent was obtained from all patients prior to inclusion in the study.

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INTEGRATED EVALUATION OF OVARIAN RESERVE MARKERS IN INFERTILE WOMEN: THE ROLE OF AGE, ANTI - MULLERIAN HORMONE, FOLLICLE-STIMULATING HORMONE, AND ANTRAL FOLLICLE COUNT

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Abstract

Introduction: Ovarian reserve is a pivotal indicator of reproductive potential, assessed through biochemical and ultrasonographic markers, with age playing a dominant role in its decline.

Objectives: The study aimed to evaluate the correlations between anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), and antral follicle count (AFC), and to assess the impact of age on these markers in infertile women.

Materials and methods: A cross-sectional study was conducted in 36 women aged 20–42 years. Serum AMH and FSH levels were measured, and AFC was assessed by transvaginal ultrasound. Data were analyzed using Spearman's correlation and linear regression.

Results: Age proved to be a negative predictor of AMH and AFC ($p < 0.05$) and positively associated with FSH. A strong positive correlation was found between AMH and AFC ($\rho = 0.866$; $p < 0.001$), while FSH showed significant negative correlations with both parameters. Regression analysis demonstrated that AMH decreases by approximately 14% per year ($B = -0.152$; $p = 0.020$).

Conclusion: AMH emerges as the most sensitive and stable marker of ovarian reserve, and combined assessment of AMH and AFC offers the most reliable detection of diminished ovarian function in infertile women.

Keywords: *anti-Müllerian hormone; antral follicle count; follicle-stimulating hormone; infertility; ovarian reserve.*

Introduction

Ovarian reserve (OR) is a complex clinical phenomenon primarily influenced by age, genetics, and environmental variables. (1) Although OR declines with age, considerable variability exists among women of similar age. (2) Diminished ovarian reserve (DOR) most commonly refers to the process of follicular depletion and a reduction in oocyte quality and describes women of reproductive age who menstruate and ovulate but whose fecundity and/or ovarian response to stimulation is reduced compared with women of similar age. (3,4) In recent years, with mod-

ern societal trends toward delayed childbearing, DOR has become one of the most frequent challenges in clinical reproductive medicine, particularly among women over 35 years of age. In large cohort and randomized studies, the prevalence of DOR ranges from 10% to 30% and largely depends on age, ethnicity, and the diagnostic criteria used for its definition.

The most commonly used markers for the assessment of ovarian reserve primarily serve as quantitative rather than qualitative indicators; that is, they have limited predictive value for oocyte quality. Age remains the main predictor of oocyte quality. (5)

An ideal ovarian reserve test should be affordable, non-invasive, and easy to interpret. It should also be easily reproducible, yield consistent results upon repetition, and demonstrate minimal variability throughout the menstrual cycle and/or between cycles. The test should detect a decline in ovarian reserve early enough to allow timely therapeutic intervention. Ultimately, it should possess good specificity and sensitivity for the detection of ovarian hypofunction. (6)

Today, the most commonly used markers of ovarian reserve include basal follicle-stimulating hormone (FSH) testing, cycle-independent measurement of anti-Müllerian hormone (AMH), and ultrasonographic determination of antral follicle count (AFC). These parameters currently represent fundamental tools for the assessment of ovarian reserve and are crucial in planning infertility treatment.

Modern reproductive medicine has reached a level of standardization through the use of AMH and AFC as more stable and predictable biomarkers. The most commonly used cut-off values for defining DOR—AMH < 1.2 ng/mL and AFC < 5—are derived from extensive studies and meta-analyses linking these marker values to a high predictive value for poor ovarian response and lower pregnancy rates in IVF treatment. (8)

FSH is primarily used to assess gonadal function. An increase in serum FSH indicates insufficient ovarian hormone production, follicular depletion, and consequently diminished ovarian reserve. Serum FSH levels exhibit daily, intra-cycle, and inter-cycle variability. Limitations of this test include daily and cycle-related variations, the absence of clearly defined cut-off values, and the use of different assays across laboratories. (9) Basal FSH measurement is performed between days 2 and 5 of the menstrual cycle, most commonly on day 3. Its values may be analyzed as a single parameter, but it is more often evaluated in combination and correlation with other hormones and ovarian reserve tests to improve diagnostic sensitivity and specificity for this condition and other reproductive disorders. For clinical and physiological assessment, immunoassay methods are used, which are sensitive, rapid, widely available, and cost-effective. FSH does not have a universally accepted cut-off value, while a normal serum concentration does not necessarily indicate adequate ovarian reserve. According to literature, the clinical usefulness of FSH measurement in the general subfertile population of regularly menstruating women remains unclear. (10)

AMH is a glycoprotein produced by granulosa cells of preantral and small antral follicles. Within the ovary, AMH expression increases in follicles up to 8 mm in diameter and is absent in follicles larger than 8 mm, showing a marked decline, as demonstrated in follicular fluid measurement. Therefore, it may be more appropriate to describe AMH as an indicator of functional ovarian reserve (FOR), representing the cohort of primordial follicles measuring 2–6 mm, from which one follicle is selected by FSH to grow and ovulate. AMH production in the ovary begins during fetal life, approximately around the 36th gestational week. Serum AMH levels increase

in young women with the onset of puberty, reaching a plateau around 25 years of age, when a positive correlation is observed due to the high number of primordial follicles. After this age, AMH levels decline to undetectable values before, during, and after menopause. (11) Because AMH is secreted during the early stages of folliculogenesis—by small growing follicles up to approximately 6 mm in diameter—its levels are relatively independent of circulating gonadotropin concentrations, allowing testing at any phase of the menstrual cycle. One of the main limitations in comparing results obtained by different methods is the lack of an international standard, despite 25 years of AMH testing. (12)

Measurement of antral follicle count (AFC) in the ovary using transvaginal ultrasound represents an acceptable surrogate marker and a valuable complement to biochemical markers in assessing ovarian reserve. AFC determination is a non-invasive and well-tolerated procedure. AFC is defined as the total number of ovarian follicles measuring 2–10 mm in diameter. The average AFC varies with age, and according to multiple studies, an antral follicle count ≤5 is considered low and indicative of diminished ovarian reserve. (13,14,15) In numerous studies, age-specific nomograms for AFC values have been established. According to these nomograms, at a mean age of 38 years, AFC is approximately 8, while at the average age of menopause onset (51 years), AFC is approximately 2, demonstrating a clear correlation between antral follicle count and age, with an average annual decline of 2.4%. (16)

Objectives

The aim of this study was to analyze the biochemical and ultrasonographic markers of ovarian reserve in infertile women of reproductive age. The study sought to examine the correlation between AMH, FSH, and AFC, as well as the impact of age on these parameters.

The specific objectives of the study were as follows: to determine the mean values of AMH, FSH, and AFC in infertile patients; to investigate the correlation between AMH and FSH, as well as between AMH and AFC across different age groups; to analyze the age dependency of these markers; and to evaluate the clinical value of AMH, FSH, and AFC as indicators of ovarian reserve.

Materials and Methods

This cross-sectional study was conducted at the Department of Infertility and Assisted Reproduction of the University Clinic of Gynecology and Obstetrics, Faculty of Medicine, Skopje. The study population consisted of 36 women of reproductive age, specifically aged 20 to 42 years, who were evaluated at the subspecialist outpatient clinic for infertility and assisted reproduction for infertility assessment and treatment over a three-month period.

All patients were evaluated using a standard infertility diagnostic protocol. For the purposes of this study, informed consent was obtained, and participants completed a brief questionnaire regarding demographic characteristics and menstrual history, as well as for the application of the exclusion criteria required for the study. All study participants were referred for laboratory evaluation of basal hormonal status and AMH levels. During the baseline gynecological ultrasound examination, antral follicle count was assessed in all participants.

Patients excluded from the study included those with existing ovarian pathology (benign or malignant ovarian lesions), endometriosis, previous ovarian surgery, prior oncological treatment (chemotherapy, radiotherapy, or surgery), use of hormonal contraceptive therapy within the three months preceding study inclusion, polycystic ovary syndrome (PCOS), and hyperprolactinemia.

Serum samples were obtained for assessment of basal hormonal status on the third day of the menstrual cycle, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin (PRL), and testosterone (T). Commercial chemiluminescence assay kits were used, with analysis performed on a Centaur analyzer (Siemens, Germany). Using the same serum samples, quantitative AMH levels were determined using Elecsys technology. Reference values for all parameters were applied according to the manufacturer's instructions.

Evaluation of the size and number of antral follicles was performed during the gynecological ultrasound examination in the follicular phase of the menstrual cycle. A Voluson Expert S6 ultrasound system (GE Medical Systems) equipped with a transvaginal probe (RIC-9-D) operating at 7.5 MHz was used. Both ovaries were scanned from the lateral to the medial margin, and all antral follicles measuring 2–10 mm in diameter were counted.

The data were digitized and processed using IBM SPSS Statistics, version 21 statistical software. Descriptive analysis was conducted for both categorical and continuous variables. Categorical data are presented as frequencies and percentages, while continuous variables are presented as medians and interquartile ranges (IQR), due to their asymmetric distribution. Associations between categorical variables were assessed using the chi-square test (χ^2), while correlations between biochemical and ultrasonographic markers (AMH, FSH, and AFC) were evaluated using Spearman's correlation coefficient (ρ). Correlations were analyzed separately across age groups.

The impact of age on each marker was assessed using linear regression analysis, with dependent variables log-transformed. A p-value < 0.05 was considered statistically significant.

Results

Age values were classified into three subgroups: 20–27 years, 28–35 years, and 35–42 years. The mean age of the participants was 36.6 ± 4.9 years (range 27–46 years). Ovarian reserve markers demonstrated substantial variability.

The mean AFC was 5.4 ± 3.2, with a median of 5 and an interquartile range (IQR) of 4 follicles (range 0–12). Serum AMH levels showed a markedly asymmetric distribution, with a median value of 0.29 ng/mL (IQR 0.71; range 0.01–2.18 ng/mL). FSH concentrations also demonstrated wide dispersion and positive skewness, with a median of 13.2 IU/L (IQR 24.05; range 4.2–125.0 IU/L). Age distribution was approximately symmetric, whereas all three analyzed parameters (AMH, AFC, and FSH) were non-normally distributed, indicating high individual variability characteristic of infertile women with varying degrees of ovarian reserve. According to the χ^2 analysis, differences between age categories were not statistically significant for AFC ($\chi^2 = 0.097$; $p = 0.953$), AMH ($\chi^2 = 1.144$; $p = 0.564$), or FSH ($\chi^2 = 1.672$; $p = 0.434$). This lack of significance may be explained by the fact that the sample consisted of a homogeneous group of infertile patients rather than the general population.

The majority of participants were 35 or older (52.8%), whereas 41.7% were aged 28–35 years, and only 5.6% were younger than 28 years. Across age groups, a trend toward an increasing prevalence of abnormal ovarian reserve marker values with advancing age was observed, although none of the differences reached statistical significance.

Among women older than 35, reduced AMH levels were most frequently observed (84.2%), followed by elevated FSH levels (73.7%) and reduced AFC (42.1%), whereas such abnormalities were less frequent in younger age groups. Correlations between ovarian reserve markers (AMH, AFC, and FSH) were analyzed separately for each age group. In the youngest group (20–27 years), statistical analysis was not conducted due to the small sample size (n = 2). In women aged 28–35 years, a strong and statistically significant positive correlation was found between AMH and AFC ($\rho = 0.866$; $p < 0.001$), indicating that higher AMH values were associated with a greater number of antral follicles. In contrast, a strong negative correlation was observed between AFC and FSH ($\rho = –0.679$; $p = 0.005$), as well as a moderately strong negative correlation between FSH and AMH ($\rho = –0.551$; $p = 0.033$). A similar pattern was observed in women older than 35. AMH and AFC remained strongly and positively correlated ($\rho = 0.748$; $p < 0.001$), while both markers demonstrated significant negative associations with FSH (AFC–FSH: $\rho = –0.660$; $p = 0.002$; AMH–FSH: $\rho = –0.646$; $p = 0.003$).

Table 1. Correlation between ovarian reserve markers (AMH, AFC, and FSH)

Age group (years)	Paired markers	Correlation coefficient (ρ)	p-value
28–35	AMH – AFC	ρ = +0.866	< 0.001
	FSH – AMH	ρ = –0.551	0.033
	FSH – AFC	ρ = –0.679	0.005
≥36	AMH – AFC	ρ = +0.748	< 0.001
	FSH – AMH	ρ = –0.646	0.003
	FSH – AFC	ρ = –0.660	0.002

Linear regression analysis of ovarian reserve markers revealed pronounced age-dependent trends. Age was identified as a statistically significant negative predictor of AMH levels ($B = –0.152$, $p = 0.020$). This finding suggests that with each additional year of life, AMH values decrease on average by approximately 14.1% ($EXP(–0.152) = 0.859$). A negative trend was observed for AFC ($B = –0.045$), although it did not reach statistical significance ($p = 0.055$). No significant association was found between age and FSH levels ($B = 0.046$, $p = 0.117$).

Overall, AMH was the only marker that demonstrated a statistically significant age-related decline and represents the most sensitive indicator of ovarian reserve reduction in this group of infertile patients.

Discussion

In this study, the majority of participants were older than 35 (52.8%), reflecting the predominance of women of advanced reproductive age within the sample, which is typical for infertile populations undergoing ovarian reserve assessment. Age-stratified analysis demonstrated a

clear pattern of decline in ovarian reserve markers. With increasing age, AMH and AFC values gradually decreased, while FSH levels showed a compensatory increase. Women aged 36–42 exhibited significantly lower AMH concentrations and fewer antral follicles compared with the 28–35-year age group, accompanied by a statistically significant increase in FSH levels ($p < 0.05$).

Correlation analysis confirmed these trends: age was negatively associated with AMH ($r < 0$, $p < 0.01$) and AFC ($r < 0$, $p < 0.01$), and positively associated with FSH ($r > 0$, $p < 0.01$). These findings reflect the physiological dynamics of ovarian aging, in which depletion of the follicular pool leads to reduced AMH secretion and increased gonadotropin production. Correlation analysis revealed significant relationships among ovarian reserve markers. Serum AMH levels showed a strong positive correlation with AFC, indicating that higher AMH concentrations are associated with a greater number of antral follicles. AMH demonstrated a significant negative correlation with FSH levels, consistent with the inverse relationship between diminished ovarian reserve and compensatory increases in gonadotropin secretion. FSH and AFC were negatively correlated, further confirming the physiological tendency toward increased FSH secretion with declining follicle numbers.

With advancing age, a gradual decline in AMH and AFC values was observed, while FSH exhibited an increasing trend, reflecting the age-dependent reduction of the follicular pool. These results are in line with previously published studies (17,18,20,21), which confirm the predictive and complementary value of AMH, FSH, and AFC as integrated markers of ovarian reserve in infertile women. This study demonstrated an age-dependent trend in the distribution of abnormal ovarian reserve marker values, although differences between age groups did not reach statistical significance. The absence of significant differences (AFC: $\chi^2 = 0.097$; $p = 0.953$; AMH: $\chi^2 = 1.144$; $p = 0.564$; FSH: $\chi^2 = 1.672$; $p = 0.434$) is most likely attributable to the homogenecity of the sample, which consisted exclusively of infertile patients rather than the general female population of reproductive age.

Nevertheless, the observed pattern is consistent with the well-established physiological decline in ovarian reserve with advancing age. AMH and AFC values gradually decreased, while FSH demonstrated an upward trend, similar to findings reported in previous studies (17,21). In another study, the authors emphasized that despite individual variability, AMH represents the most sensitive early indicator of ovarian aging, whereas FSH exhibits broader fluctuations and a later response. (22) The findings of the present study are consistent with these reports, suggesting that even within a relatively small and clinically homogeneous infertile sample, the physiological pattern of ovarian aging remains clearly evident.

Similar to findings reported by other authors, AFC in our analysis showed a comparable negative trend, while FSH varied and did not reach statistical significance, which may be explained by the homogeneous infertile population and biological variability in older women. (23,22) Overall, AMH remains the most stable and informative marker of ovarian aging, while AFC and FSH play supportive but less sensitive diagnostic roles.

In later reproductive years, particularly after the age of 35, AMH demonstrates an annual relative decline of approximately 8–10%, which further accelerates in the forties. Linear regression analysis in this study demonstrated that age is a statistically significant negative predictor of AMH levels ($B = –0.152$, $p = 0.020$), indicating that with each additional year of life, AMH decreases by an average of approximately 14.1%. A negative trend was observed for AFC ($B =$

–0.045; p = 0.055), and a mild positive trend for FSH (B = 0.046; p = 0.117), although neither reached statistical significance. Among all analyzed markers, AMH demonstrated the most pronounced and statistically significant age-related decline, confirming its sensitivity as an indicator of ovarian reserve.

Conclusions

The results of this study confirm that age has a significant impact on ovarian reserve in infertile women. With advancing age, AMH and AFC values gradually decline, while FSH demonstrates an increasing trend, reflecting the physiological compensation associated with diminished ovarian function. A strong positive correlation between AMH and AFC, as well as a significant negative association between FSH and both markers, was established in this study, confirming their complementary diagnostic potential. AMH emerged as the most sensitive indicator of ovarian aging, with an average annual decline of approximately 14%.

AMH stands out as the most stable and informative marker for the assessment of ovarian reserve and early detection of ovarian aging, while AFC represents a practical ultrasonographic indicator that complements its predictive value. Although useful in later stages of ovarian insufficiency, FSH exhibits greater biological variability and lower sensitivity.

The findings of this study support the need for combined use of AMH and AFC in the clinical assessment of ovarian capacity and in counseling infertile patients, particularly those of advanced reproductive age.

Ethical Approval: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee for Research Involving Humans, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje. Approval protocol number: 03-3567/11

Consent for publication: Written informed consent was obtained from all patients prior to inclusion in the study.

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SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS WITH NEWLY DIAGNOSED CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN PRIMARY HEALTH CARE

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Abstract

Introduction. Chronic obstructive pulmonary disease (COPD) is one of the most common respiratory diseases. However, it remains significantly unrecognized and undiagnosed in clinical practice. The aim of this study is to investigate the association between sociodemographic and clinical characteristics of patients with newly diagnosed chronic obstructive pulmonary disease in a population aged ≥ 40.

Materials and Methods. A one-year cross-sectional study was conducted in a family medicine practice in Skopje, including individuals aged 40 to 75 years without respiratory complaints. Sociodemographic questionnaires and six screening tests for COPD were evaluated. COPD diagnosis is established by spirometry, defined as a postbronchodilator FEV1/FVC ratio <0,70.

Results. The total number of participants was 175, of which 18 participants (9%) had newly diagnosed COPD. These participants were significantly older (p=0.003), male (p=0.03), with a low level of education (p=0.008), mainly workers (p=0.045), heavy smokers ≥30 pack/years (p=0.0007), or were exposed to biomass fuels (p=0.036). Tuberculosis (p=0.028), arterial hypertension (p=0.045), family history of respiratory disease (p=0.0135), chronic respiratory disease in childhood (p=0.001) and one lower respiratory tract infection in the last year (p=0.0447) were identified as significant risk factors for COPD.

Conclusion. A considerable proportion (9%) of asymptomatic adults aged ≥40 years had previously undiagnosed COPD. Older age, male sex, lower level of education, heavy smoking, biomass exposure, tuberculosis, hypertension, family history of respiratory disease, and recurrent childhood infections were significantly associated with newly diagnosed COPD.

Keywords: *Chronic obstructive pulmonary disease; primary health care; questionnaires; risk factors; sociodemographic characteristics.*

Introduction

Chronic obstructive pulmonary disease (COPD) is increasingly becoming one of the most common causes of morbidity, mortality, and disability worldwide. COPD is currently the third lead-

ing cause of death globally, and 90% of deaths occur in low- and middle-income countries (1). The global prevalence of COPD is estimated to be 10.3% and is projected to increase by 23% by 2050 (2). COPD is also the fifth leading cause of years of life lost due to disability DALYs (the Disability- Adjusted Life Years) (3). Despite this and the identification of the disease as a serious public health problem that requires an urgent solution, COPD often remains unrecognized and undiagnosed. COPD is a chronic, progressive disease, that progresses gradually over time. It is as a result of long-term, complex interactions between various endogenous and exogenous risk factors that damage the lungs and disrupt their normal development and aging process. While tobacco smoking is the leading risk factor for the disease, other factors also play a role in the development of COPD. Inhalation of toxic particles and gases from the environment (smoke from burning solid fuels, inorganic dust, chemical agents and/or vapors, and air pollution), delayed and impaired lung development in childhood, frequent respiratory infections in adult patients, family predisposition, presence of comorbidities, and low socioeconomic status additionally contribute to the development of the disease (1,4,5). The clinical and biological expression of these exposures differs substantially among individuals and is influenced by the age at exposure and the cumulative burden of interacting risk factors over time (6).

Macedonia has a relatively high reported prevalence of COPD (7.16%) (7), accompanied by a rising prevalence of smoking among people aged 15-64 (from 43% in 2002 to 46% in 2017) (8). A 2022 population-based study by Minov et al. in the Skopje region, reported a COPD prevalence of 4.6%, increasing with age, and identified active smoking and occupational exposure as key risk factors (9). Notably, nearly half of participants without a prior COPD diagnosis demonstrated persistent airflow obstruction. These findings strongly suggest that a substantial proportion of COPD cases in our setting remain unrecognized and undiagnosed (9). According to the 2019 World Health Organization (WHO) report, *Primary Health Care Organization, Performance and Quality in North Macedonia,* COPD ranks first in hospitalizations, second in referrals to secondary-level care and third among the most common reasons for visits to general practitioners (8). Together, these indicators reflect important gaps in early detection and optimal disease management, with many patients being diagnozed only at advanced stages. This unmet need for earlier recognition and intervention provided the rationale for conducting this present study.

The purpose of this paper is to investigate the association between sociodemographic and clinical characteristics of patients with newly diagnosed COPD in a population aged ≥ 40, in the primary health care setting.

Materials and Methods

A one-year cross-sectional study was conducted in a family medicine practice in Skopje, Republic of North Macedonia. Individuals aged 40 to 75, who presented for examination without respiratory symptoms were included. Individuals with previously diagnosed COPD or asthma, cognitive disorders, neurodegenerative diseases, inability to perform spirometry, contraindications to spirometry, acute lower respiratory tract infections, hypersensitivity to salbutamol and pregnant/breastfeeding individuals, were excluded from the study. The research was conducted by one family physician. Sociodemographic questionnaires and six COPD screening tests were administered. For spirometry tests, participants were referred to a reference outpatient clinic at secondary health care level. COPD was diagnosed based on post-bronchodilator

spirometry demonstrating a forced expiratory volume in one second to forced vital capacity ratio (FEV_1/FVC) <0,70. Spirometry was performed by a specialist who was not involved in the initial screening. The Ethics Committee for Research Involving Human Subjects, Faculty of Medicine, University of "Saints Cyril and Metodius" Skopje, Republic of North Macedonia gave approval for performing the study and publishing the results obtained (03-1208/5, 14.03.2023). All participants were informed about the study and provided written informed consent.

The sociodemographic questionnaire consisted of three sections. The first section included demographic characteristics: age, sex, body mass index (BMI), educational level, current occupation, socioeconomic status, place of residence, and exposure to passive smoking. The second section addressed smoking status and smoking intensity. Smoking status was defined as: current user of tobacco (smoking at least one cigarette per day for a minimum of six months), former user of tobacco (previously smoked at least one cigarette per day for at least six months, but does not currently smoke), non-smoker. Smoking intensity was calculated using the pack-years formula. This section also included questions regarding occupational or household exposure to harmful particles or chemicals, as well as exposure to fuels used for heating, cooking, and other household needs. The third section referred to the participants' health status. Information on family history of respiratory disease, chronic respiratory diseases in childhood, and frequency of common cold, bronchitis, or pneumonia during the previous year was collected. These variables were also incorporated within the COPD screening questionnaires (CDQ (10), CAPTURE (11), COPD SQ (12), SBQ(13,14)).

Statistical analysis of the data was performed using SPSS software (version 25.0; IBM SPSS, USA). The Kolmogorov-Smirnov test and Shapiro-Wilk test were used to assess the normality of data distribution. Categorical variables were presented as absolute numbers and percentages. Numerical variables were expressed as mean, standard deviation, minimum and maximum values, median, and interquartile range. For comparison between the COPD and non-COPD groups, Fisher's exact test and the chi-square test were used for categorical variables. For quantitative variables, depending on data distribution, Welch's test or the Mann-Whitney U test was applied.

Results

A total of 200 participants were included in the study, with a mean age of 53.5 ± 8.4 years. The sample consisted of 96 men (46%) and 104 women (52%). The study was completed by 175 participants, of whom 18 were diagnosed with COPD by spirometry. The frequency of COPD was 9%. Sex was significantly associated with COPD, with 72.78% of participants diagnosed with COPD being male, while only 27.78% were female (p=0.03). Participants with COPD were significantly older (59.2 ± 7.9 years) compared to those without COPD (52.6 ± 8.0 years) (p=0.003) (Table 1).

Table 1. Sociodemographic and other characteristics of the study's participants according to COPD status

Variables	Sample size n=175	COPD		p-value	difference test
		yes (n=18)	no (n=157)		
Sex n (%)					
Male	84 (48%)	13 (72.22%)	71 (45.22%)	X^2=4.72 *p=0.03	
Female	91 (52%)	5 (27.78%)	86 (54.78%)		

Variables	Sample size n=175	COPD		p-value	difference test
		yes (n=18)	no (n=157)		
Age (years) mean+SD)	53.2 ± 8.2	59.2 ± 7.9	52.6 ± 8.0	t=3.35 **p=0.003	
BMI (kg/m2) mean+SD	28.99 ± 5.3	28.56 ± 5.9	29.04 ± 5.2	t=0.36 p=0.72	
Ethnic groups n (%)					
Macedonian	66 (38.15%)	5 (27.78%)	61 (39.35%)	Fisher's exact p=0.554	
Albanian	105(60.69%)	13(72.22%)	92 (59.35%)		
Serbian	2 (1.16%)	0	2 (1.29%)		
Education n (%)					
No qualification	4 (2.29%)	3 (16.67%)	1 (0.64%)	Fisher's exact **p=0.008	p<0.0001
Primary school	75 (42.86%)	4 (22.22%)	71 (45.22%)		*p=0.046
High school	45 (25.71%)	6 (33.33%)	39 (24.84%)		p=0.435
Higher education	3 (1.71%)	0	3 (1.91%)		p=0.55
Bachelor's degree	36 (20.57%)	5 (27.78%)	31 (19.75%)		p=0.42
> higher than a Bachelor's degree	12 (6.86%)	0	12 (7.64%)		p=0.22
Profession n (%)					
Administrative workers	34 (19.43%)	5 (27.78%)	29 (18.47%)	Fisher's exact *p=0.045	p=0.344
Health care workers	38 (21.71%)	0	38 (24.2%)		*p=0.018
Housewives	42 (24%)	4 (22.22%)	38 (24.2%)		p=0.85
Manual workers	61 (34.86%)	9 (50%)	52 (33.12%)		p=0.15
Place of residence n (%)					
Urban	61 (34.86%)	5 (27.78%)	56 (35.67%)	X^2=0.68 p=0.411	
Rural	114(65.14%)	13(72.22%)	101(64.33%)		
Family history of respiratory disease n (%)					
Yes	38	8 (44.44%)	30 (19.11%)	X^2=6.1 *p=0.0135	
No	137	10(55.56%)	127(80.89%)		
Chronic respiratory diseases in childhood n (%)					
Yes	14	5 (27.78%)	9 (5.73%)	X^2=10.7 **p=0.001	
No	161	13(72.22%)	148(94.27%)		

X^2(Chi-square test); Welch's t-test *sig p<0.05, **sig p<0.01

There was a statistically significant association between educational level and COPD status (Fisher's exact test, p=0.008). This difference was primarily driven by the markedly higher proportion of participants without formal education in the COPD group (16.78%) compared to the non-COPD group (0.64%) (p<0.0001). Primary education was more frequent among

participants without COPD (45.22%) than among those with COPD (22.22%) (p=0.046). No statistically significant differences were observed across the remaining educational categories (Table 1). Profession was also significantly associated with COPD status (Fisher's exact test, p=0.045). However, this association appeared to be largely influenced by the absence of COPD among health care workers (0% vs 24.2%, p=0.018). Although manual workers constituted a higher proportion of the COPD group (50% vs 33.13%), this difference did not reach statistical significance (p=0.15). Similarly, no significant differences were observed among administrative workers (p=0.344) or housewives (p=0.85). No significant association was found between place of residence and COPD occurrence (p=0.411), although a higher proportion of participants lived in rural areas. This finding should be interpreted cautiously, as the overall study sample included approximately twice as many rural as urban residents (Table 1).

There was a statistically significant difference between the participants with and without COPD regarding family history of respiratory disease (p=0.0135), with 44.44% of participants with COPD reporting a positive family history compared to 19.11% of those without COPD. Similarly, chronic respiratory diseases in childhood were significantly (p=0.001) more common among participants with COPD (27.78%) than among those without COPD (5.73%) (Table 1).

Table 2. Smoking status, passive exposure to smoking in the household, and intensity of tobacco use according to COPD status

Variables	Sample size n=175	COPD		COPD
		yes (n=18)	no (n=157)	
Smoking n (%)				
0 Non-smoker	74 (42.53%)	5 (27.78%)	69 (44.23%)	Fisher's exact p=0.376
1 Former user of tobacco	20 (11.94%)	3 (16.67%)	17 (10.9%)	
2 Current user of tobacco	80 (45.98%)	10 (55.56%)	70 (44.87%)	
Passive exposure to smoking in the household n (%)				
Daily	86 (49.14%)	13 (72.22%)	73 (46.5%)	Fisher's exact p=0.079
Weekly	13 (7.43%)	1 (5.56%)	12 (7.64%)	
Monthly	7 (4%)	2 (11.11%)	5 (3.18%)	
Less than monthly	23 (13.14%)	1 (5.56%)	22 (14.01%)	
Never	44 (25.14%)	1 (5.56%)	43 (27.39%)	
Does not know	2 (1.14%)	0	2 (1.27%)	
Intensity of tobacco use (pack/years)				
0	75	5 (27.78%)	70 (44.59%)	Fisher's exact *p=0.017
1-14.9	26	1 (5.56%)	25 (15.92%)	
15-29.9	26	1 (5.56%)	25 (15.92%)	
≥30	48	11 (61.11%)	37 (23.57%)	

The smoking status of the participants (current, former, non-smoker) had no statistically significant association with COPD diagnosis (Fisher's exact test, p=0.376) (Table 2). Although current

smokers and former smokers were more prevalent in the COPD group, these differences did not reach statistical significance. Conversely, non-smokers were more common among participants without COPD (44.23%) than among those with COPD (27.78%), but again without statistical significance. Passive smoking exposure had no statistically significant association with COPD diagnosis (Fisher's exact test, p=0.079). However, daily exposure to passive smoking was more frequently reported among participants with COPD (72.22%) compared to those without COPD (46.5%). In contrast, smoking intensity demonstrated a statistically significant association with COPD (Fisher's exact test, p=0.079). Participants with a smoking history of ≥30 pack/years were overrepresented in the COPD group (61.11%) compared to the non-COPD group (23.57%) (p=0.0007) (Table 2).

Table 3. Exposure to air pollutants according to COPD status

Variables	Sample size n=175	COPD		p-value
		yes (n=18)	no (n=157)	
Cooking fumes n (%)				
No, never	126 (72%)	14 (77.78%)	112 (71.34%)	Fisher's exact p=0.91
Yes, currently	37 (21.14%)	3 (16.67%)	34 (21.66%)	
Yes, in the past	12 (6.86%)	1 (5.56%)	11 (7.01%)	
Biomass fuel n (%)				
No, never	66 (37.71%)	3 (16.67%)	63 (40.13%)	Fisher's exact *p=0.036
Yes, currently	77 (44%)	8 (44.44%)	69 (43.95%)	
Yes, in the past	32 (18.29%)	7 (38.89%)	25 (15.92%)	
Vapors from various substances n (%)				
No, never	161 (92%)	16 (88.89%)	145 (92.36%)	Fisher's exact p=0.3
Yes, currently	5 (2.86%)	0	5 (3.18%)	
Yes, in the past	9 (5.14%)	2 (11.11%)	7 (4.46%)	
Gases n (%)				
No, never	155 (88.57%)	14 (77.78%)	141 (89.81%)	Fisher's exact p=0.197
Yes, currently	6 (3.43%)	1 (5.56%)	5 (3.18%)	
Yes, in the past	14 (8%)	3 (16.67%)	11 (7.01%)	
Dust n (%)				
No, never	72 (41.14%)	6 (33.33%)	66 (42.04%)	Fisher's exact p=0.589
Yes, currently	84 (48%)	9 (50%)	75 (47.77%)	
Yes, in the past	19 (10.86%)	3 (16.67%)	16 (10.19%)	
Chimney/exhaust systems n (%)				
Yes	138 (86.25%)	17 (100%)	121 (84.62%)	Fisher's exact p=0.132
No	22 (13.75%)	0	22 (15.38%)	

Variables	Sample size n=175	COPD		p-value
		yes (n=18)	no (n=157)	
Years of exposure median (IQR)	30 (20 – 40)	33.5 (28.5 – 40)	30 (20 – 40)	Mann-Whitney U test Z=0.92 p=0.358

Exposure to biomass fuel was significantly associated with COPD (Fisher's exact test, p=0.036), with a higher proportion of participants with COPD reporting past exposure to biomass fuel compared to those without COPD (38.89% vs 15.92%, p=0.017) (Table 3). No statistically significant differences were observed between participants with and without COPD regarding exposure to cooking fumes (p=0.91), vapors from various substances (p=0.30), gases (p=0.197), dust (p=0.589), or chimney/exhaust systems (p=0.132). The duration of exposure did not differ significantly between groups (Mann-Whitney U test, p=0.358). The median duration of exposure was 33.5 years (IQR 28.5 – 40) in the COPD group and 30 years (IQR 20 – 40) in the non-COPD group (Table 3).

The overall proportions of participants with at least one comorbidity were similar in both groups, 77.78% in the COPD group and 76.43% in the non-COPD group, with no statistically significant difference (Fisher's exact test, p=1.0) (Table 4). Among individual comorbidities, arterial hypertension was significantly more prevalent in participants with COPD (77.78%) compared to those without COPD (51.59%) (p=0.045). Tuberculosis was also significantly more frequent in the COPD group (11.11% vs 0.64%, p=0.028). No statistically significant differences were observed between the groups with or without COPD for the other listed comorbidities (Table 4).

Table 4. Prevalence of comorbidities according to COPD status

Comorbidities	Sample size n=175	COPD		p-value
		yes (n=18)	no (n=157)	
Carcinoma	5 (2.86%)	1 (5.56%)	4 (2.55%)	p=0.423
Diabetes mellitus	27 (15.43%)	3 (16.67%)	24 (15.29%)	p=1.0
Arterial Hypertension	95 (54.29%)	14 (77.78%)	81 (51.59%)	*p=0.045
Angina pectoris, Myocardial infarct	4 (2.29%)	0	4 (2.55%)	p=1.0
Heart failure	0	0	0	0
Cerebrovascular accident	0	0	0	0
Nasal allergy	18 (10.29%)	1 (5.56%)	17 (10.83%)	p=1.0
Skin allergy	9 (5.14%)	0	9 (5.73%)	p=0.6
Food allergy	6 (3.43%)	0	6 (3.82%)	p=1.0
Insect sting allergy	5 (2.86%)	0	5 (3.18%)	p=1.0
Tuberculosis	3 (1.71%)	2 (11.11%)	1 (0.64%)	p=0.028
Osteoarthritis	10 (5.71%)	1 (5.56%)	9 (5.73%)	p=1.0
Rheumatoid arthritis	0	0	0	0

Comorbidities	Sample size n=175	COPD		p-value
		yes (n=18)	no (n=157)	
Osteoporosis	4 (2.29%)	1 (5.56%)	3 (1.91%)	p=0.355
Depression	19 (10.86%)	3 (16.67%)	16 (10.19%)	p=0.4199
Anxiety	18 (10.29%)	1 (5.56%)	17 (10.83%)	p=0.698
Eczema	5 (2.86%)	0	5 (3.18%)	p=1.0
Other allergies	6 (3.43%)	0	6 (3.82%)	p=1.0

Participants with COPD had a significantly higher number of common colds, bronchitis, or pneumonia in the 12 months preceding the study compared with participants without COPD (p=0.026) (Table 5).

Table 5. Frequency of respiratory infections in the past 12 months according to COPD status

Variables	Sample size n=175	COPD		p-value
		yes (n=18)	no (n=157)	
Common cold, Bronchitis or Pneumonia in the last 12 months n (%)				
0	80	3 (16.67 %)	77 (49.04%)	Fisher's exact *p=0.026
1	60	10 (55.56%)	50 (31.85%)	
2+	35	5 (27.78%)	30 (19.11%)	

Discussion

In this cross-sectional study, we investigated the association between sociodemographic and clinical characteristics, and newly diagnosed COPD in adults aged ≥40 years in primary health care. Our findings demonstrate that several sociodemographic and clinical factors were significantly associated with newly diagnosed COPD.

The study included 175 participants, of whom 52% were female and 48% male. Although both sexes were similarly represented in the overall sample, male sex was significantly more associated with COPD (77.22% vs. 27.7%, p=0.03). This finding is consistent with results from the Burden of Obstructive Lung Disease (BOLD) study, which reported a higher prevalence of stage II or higher COPD in men (11.8%) than in women (8.5%) (15). Similarly, the ELISABET study conducted in France showed higher COPD prevalence among men, despite comparable sex representation in the overall study (1,5,16). We have also identified age as a significant risk factor (p=0.003), confirming the well-established relationship between aging and COPD. The PLATINO study, conducted in five Latin American regions, demonstrated a strong positive association between age and COPD prevalence (17). Comparable findings were reported in a general adult population from the Skopje region, where COPD prevalence was four times higher in individuals older than 45, when compared with younger participants (6.7% vs. 1.6%, p=0.0000) (9).

Another important sociodemographic characteristic is educational level, which, in our study, was also significantly associated with COPD (p=0.008). A markedly higher proportion of pa-

tients with COPD had no formal education, which is widely recognized as an indicator of socioeconomic disadvantage. Lower socioeconomic status is associated with increased exposure to environmental pollutants, occupational hazards and limited access to preventive healthcare. Occupational exposure to dusts, fumes, and chemical agents has long been established as an independent contributor to chronic airflow limitation (18). Workers exposed to occupational hazards were reported to have a twofold higher COPD prevalence, emphasizing the role of occupational hazards in the Skopje region (19). Our findings therefore support the broader evidence linking socioeconomic vulnerability and lower educational levels with increased COPD risk (1,20,21). Importantly, approximately one-fifth of individuals with COPD worldwide have never smoked, underscoring the contribution of non-tobacco-related risk factors, including workplace exposures (22).

Exposure to biomass fuel was another significant factor in our study, particularly among participants with past exposure, suggesting that prolonged past exposure to these fuels has delayed health effects. A meta-analysis by Hu et al., including studies from several countries where biomass fuel is widely used, demonstrated a two- to threefold increased risk of COPD among individuals exposed to biomass smoke (23). Our findings are consistent with this global evidence and highlight the continued relevance of indoor air pollution as a preventable risk factor.

Smoking tobacco remains the most important and extensively studied risk factor for COPD in the past five decades, as evidence has been provided that COPD is much more common in smokers and former smokers compared to non-smokers (1). The disease occurs in 15-20% of current smokers, whereas 60-70% of individuals affected by COPD are current or former smokers (7). Nevertheless, it is also well documented that only a portion of smokers develop COPD, and that a substantial fraction of COPD cases can be attributed to additional environmental, occupational and early life factors (22,24).

Although we did not find a statistically significant association between smoking status and COPD in our cohort, smoking intensity showed a clear relationship (p=0.017). Participants with ≥30 pack/years were significantly more likely to have COPD, indicating that cumulative exposure may be more informative than smoking status alone. Similarly, in the Minov et al. study from the same region, smoking intensity of ≥20 pack/years was significantly associated with COPD (9). While many studies use ≥10 pack/years as an inclusion threshold, recent evidence suggests that even lower smoking intensity increases the 5-year risk for COPD development in middle-aged adults. Passive smoking is also recognized as a major global health risk. The Global Burden of Disease Study ranked it among the top ten leading risk factors for mortality worldwide (3). In terms of the DALYs, which measure the total burden of a disease, COPD was the fifth leading cause of years of life lost due to disability (25). Lifelong exposure to passive smoking doubles the risk of developing COPD, and the duration of exposure to passive smoking negatively affects lung development at the earlier stages of life, also leading to higher risks for developing COPD (26). Although we did not observe a statistically significant association (p=0.079), daily exposure to passive smoking was considerably more common among individuals with COPD (72.22% vs 46.5%), while participants who were never exposed to passive smoking in the household were more common in the group without COPD (27.3% vs. 5.5%). It is important to note that our assessment focused primarily on passive smoke exposure within the household. However, given the high prevalence of smoking in our country, passive exposure outside of the home environment is likely widespread. Such exposure may have reduced the variability between groups and potentially attenuated the observed association between passive smoking and COPD.

Genetic susceptibility and early-life influences also appear to play an important role. A positive family history of respiratory disease was significantly more common among smoking siblings with COPD, suggesting inherited or shared environmental vulnerability (27). In our study, family history of respiratory diseases and chronic respiratory diseases in childhood were significantly associated with COPD in adulthood. Impaired lung development due to asthma, allergies, infections, or other risk factors, during intrauterine development or childhood, can result in reduced peak lung function and increased COPD risk later in life (28–30).

COPD is often accompanied by other chronic diseases and conditions, sharing common risk factors and pathophysiological mechanisms. In our study, arterial hypertension was the most prevalent comorbidity and was significantly associated with COPD (p=0.045). Cross-sectional analysis of data from the U.S. National Health and Nutrition Examination Survey (1999-2018) also demonstrated a significant association between COPD and hypertension (OR=1.18, 95% CI 1.05–1.31), with a strong correlation observed in adults younger than 60 with high smoking intensity (31). Undiagnosed COPD is common among hypertensive individuals aged ≥40 in Brazil, further underscoring the need for targeted screening (32). Tuberculosis was also significantly more frequent among the participants in our study with COPD (p=0.028). Feng et al. confirmed a bidirectional association between tuberculosis and COPD, with increased risk of COPD among individuals with a history of tuberculosis (pooled OR=2.46, 95% CI: 1.95–3.10), and increased tuberculosis risk among individuals with COPD (pooled OR=2.21, 95% CI: 1.57–3.11) (33). These findings support integrated screening strategies, particularly in endemic regions. According to data from the Center for Public Health in Skopje (2023), the Skopje region remains among the four regions with the highest tuberculosis incidence (34), highlighting the local public health relevance of this association. Finally, frequent lower respiratory infections are an important clinical indicator associated with COPD development. This is consistent with the GOLD 2025 recommendations and the national guideline for COPD prevention, diagnosis, and management in primary care in North Macedonia, both of which emphasize early identification of high-risk individuals (1,5).

Limitations of the Study

Although this study provides important insight into the association between sociodemographic and clinical characteristics and newly diagnosed COPD, several limitations should be considered. The sample size was relatively small and restricted to a single geographic region, with data collected over a one-year period and limited to one family medicine practice. Therefore, the findings cannot be generalized to all adults aged ≥40 years in the Republic of North Macedonia.

Nevertheless, this study represents one of the first efforts to support the development of a structured COPD screening approach in primary care aimed at identifying individuals at increased risk who should be referred for spirometry. The research was conducted in accordance with current recommendations, using standardized spirometry based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) lung function criteria for defining and staging COPD. Importantly, spirometry confirmation of COPD was performed by a specialist who was not involved in the initial screening process and was unaware of participants' questionnaire responses, thereby reducing the risk of potential diagnostic bias. Although regionally conducted, the sample included participants from both urban and rural settings.

The results may contribute to strengthening preventive activities, promoting timely diagnosis and treatment, improving patients' quality of life, and reducing the overall burden of disease. We be-

lieve these findings may serve as a foundation for developing a national COPD screening strategy.

Conclusion

Nearly one in ten asymptomatic adults aged ≥40 had previously undiagnosed COPD, underscoring the substantial burden of unrecognized disease in primary care. Older age, sex, lower educational level, heavy smoking, biomass fuels exposure, tuberculosis, hypertension, family history of respiratory disease, and recurrent childhood infections were independently associated with newly diagnosed COPD. These findings highlight the need for systematic risk assessment and targeted spirometry screening of high-risk individuals in primary care. Early identification of COPD in apparently asymptomatic adults may enable timely intervention, reduce disease progression, and ultimately decrease the long-term clinical and socioeconomic burden of COPD.

Ethical approval: The Ethics Committee for Research Involving Human Subjects, Faculty of Medicine, University of "Saints Cyril and Metodius" Skopje, Republic of North Macedonia gave approval for performing the study and publishing the obtained results (03-1208/5).

Consent for publication: Written informed consent was obtained from all patients prior to inclusion in the study.

Conflict of interest: The authors report no conflicts of interest.

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Declaration of interest: All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

Author contribution statement: Kovachevikj Katerina conceived and designed the study, developed the research protocol, conducted data collection, performed statistical analysis, interpreted the findings, and drafted the manuscript. Janevska Sashka contributed to participant recruitment and data collection and provided technical and organizational support during the implementation of the study. Kovachevikj Miona contributed to the statistical analysis, data interpretation, and participated in the preparation, refinement and revision of the manuscript. Kondova Topuzovska Irena supervised the study, contributed to the study design and methodological framework, provided critical revisions, and approved the final version of the manuscript

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DEVELOPMENT OF DEMENTIA IN ELDERLY PATIENTS WITH POSTOPERATIVE DELIRIUM FOLLOWING HIP FRACTURE SURGERY

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Abstract

Introduction: Postoperative delirium (POD) is a prevalent and undesirable neurocognitive consequence that arises following surgery and anesthesia in geriatric adults. Patients experiencing postoperative delirium may be at increased risk of developing long-term postoperative cognitive dysfunction and dementia. However, it is still unclear how much postoperative delirium (POD) affects the likelihood of developing dementia in this patient population.

Objective: The aim of this study was to examine the association between the occurrence of postoperative delirium and the development of new-onset dementia in elderly patients within one year following hip fracture surgery.

Materials and Methods: The study included patients aged 65 and older who underwent surgical treatment for proximal femur fractures at the University Clinic for Traumatology and Orthopedics. Patients with pre-existing dementia or cognitive impairment were excluded. Preoperative cognitive status was evaluated using the Abbreviated Mental Test (AMT-10) and the Informant Questionnaire on Cognitive Decline in the Elderly – Short Form (IQCODE-SF). Postoperative delirium was assessed during hospitalization using the Confusion Assessment Method (CAM). Patients were followed for one year after surgery to identify newly diagnosed dementia through medical record reviews. Statistical analysis was performed with SPSS version 25.0.

Results: This pilot study involved 91 patients. Postoperative delirium occurred in 30 (32.97%) of them. At twelve-month follow-up, new-onset dementia was significantly more common in patients with postoperative delirium compared to those without POD (46.67% vs. 8.2%, p=0.000022). Multivariate logistic regression analysis showed that postoperative delirium was an independent predictor of dementia (OR = 9.765, 95% CI 2.939–22.452, $p < 0.0001$).

Conclusion: Postoperative delirium is a risk factor for subsequent dementia following hip fracture surgery. Elderly hip fracture patients who exhibit POD should be closely monitored for the development of dementia.

Keywords: *Delirium; dementia; elderly patients; hip fractures.*

Introduction

As life expectancy rises and the population ages, the incidence of elderly individuals requiring emergency and elective procedures is increasing (1). Postoperative delirium (POD) is common in this group, with incidence rates ranging from 20% to 55% after high-risk procedures such as vascular, orthopedic, and cardiac surgeries (2-5). Hip fractures are frequent in older adults and often require emergency surgery. A meta-analysis of 26 studies on postoperative delirium showed incidence rates ranging from 4.0% to 53.3% in patients with hip fractures and from 3.6% to 28.3% in elective patients (6). Delirium involves a sudden change in consciousness levels and quickly occurring attention disturbances. These fluctuations often vary throughout the day and can be linked to other cognitive issues, such as memory loss or disorientation (7,8). Postoperative delirium is associated with adverse outcomes, including increased morbidity and mortality, cognitive and functional decline leading to loss of independence and lower quality of life, longer hospital stays, institutionalization, and higher healthcare costs. Patients with postoperative delirium may also develop long-term postoperative cognitive dysfunction and dementia (9,10). Delirium has been identified as a risk factor for dementia (11). Dementia is a syndrome caused by various diseases that gradually destroy nerve cells and damage the brain, usually leading to a decline in cognitive functions—such as thinking—that goes beyond normal aging. While consciousness remains intact, the decline in thought processes is often accompanied by, or even precedes, changes in mood, lack of emotional control, behavior, or motivation. In 2021, 57 million people worldwide had dementia, and over 60% of them live in low- and middle-income countries. Nearly 10 million new cases are diagnosed each year (1). The role of postoperative delirium (POD) in developing dementia among patients with hip fractures remains uncertain. The aim of this study was to examine the association between the occurrence of postoperative delirium and the development of new-onset dementia in elderly patients within one year following hip fracture surgery.

Material and Methods

This pilot study included 91 patients aged ≥ 65 years without pre-existing cognitive impairment, classified as ASA I, II, or III, who were admitted to the University Clinic for Traumatology, Orthopedics, Anesthesia, Reanimation, Intensive Care, and Emergency department – Skopje for surgical treatment of proximal femur fractures during a two-year period. Written informed consent was obtained from all patients prior to their inclusion in the study. Patients with cognitive impairment, dementia or other neurodegenerative diseases, stroke with residual deficits, use of medications affecting cognitive functions, alcohol and drug abuse, blindness, deafness, contraindications to spinal anesthesia, and admission to the intensive care unit were excluded from the study. We assessed pre-existing cognitive impairment using two validated instruments: the Abbreviated Mental State Test (AMT 10) (12,13) and the Cognitive Decline Information Questionnaire - Short Form (IQCODE - SF) (14). Screening for POD began immediately after surgery and was monitored throughout the hospital stay with the Confusion Assessment Method (CAM) (15). Postoperatively, patients were divided into two groups: those with postoperative delirium and those without. They were monitored for the development of dementia through medical record review for one year after surgery. The diagnosis of dementia was confirmed by neurologists and psychiatrists in patients who had previously undergone psychological testing by psychologists. The Ethics Committee of the Faculty of Medicine in Skopje approved the study. Statistical analysis of the data was performed using SPSS (ver. 25.0; IBM, SPSS, USA).

The Shapiro-Wilk test was used to assess the normality of the data distribution. Categorical (attributive) variables are presented with absolute and relative numbers. Numerical (quantitative) variables are presented with mean, standard deviation, minimum, and maximum values. The Fisher's exact test and the chi-square test were used to compare categorical variables, and the Student t-test was used to compare quantitative variables. Logistic regression analysis was used to determine the predictive role of postoperative delirium in predicting dementia. Statistical significance was defined as $p<0.05$.

Results

This study presents the results of the analysis of samples and data from 91 patients admitted to the University Clinic for Traumatology, Orthopedics, Anesthesia, Reanimation, Intensive Care, and Emergency department – Skopje for surgical treatment of proximal femur fractures. The patients' age and gender distribution are shown in Table 1. Postoperative delirium occurred in 30 (32.97%) patients, and dementia within one year postoperatively was observed in 19 (20.88%). (Table 1)

Table 1. Patients' characteristics

Variable	
Gender n(%) female male	 77 (84.62) 14 (15.38)
Age (years) (mean ± SD) (min – max)	 (79.9 ± 6.4) (66 – 95)
POD n(%)	30 (32.97)
Dementia n(%)	19 (20.88)

Patient gender was not significantly associated with the occurrence of postoperative delirium and dementia (p=0.812 and p=1.0, respectively). (Table 2) The prevalence of postoperative delirium and dementia was similar in female and male patients (32.47% vs 35.71% and 20.78% vs 21.43%, respectively). (Table 2)

Table 2. Gender distribution - patients with/without POD and with/without dementia

variable		gender			p-level
		n	female n (%)	male n (%)	
POD	yes	30	25 (32.47)	5 (35.71)	X2=0.056 p=0.812
	no	61	52 (67.53)	9 (64.29)	
Dementia	yes	19	16 (20.78)	3 (21.43)	two-tailed p=1.0
	no	72	61 (79.22)	11 (78.57)	
total		91	77	14	

The age of patients with and without postoperative delirium did not differ significantly (81.1 ± 5.1 vs 79.2 ± 6.9 years, p=0.19). (Table 3) Patients with dementia were significantly older than those without dementia (82.6 ± 5.3 vs 79.2 ± 6.4 years, p=0.035). (Table 3, Figure 1)

Table 3. Age of patients with/without POD and with/without dementia

variable		statistical parameters - age			p-level
		n	mean ± SD	min – max	
POD	positive	30	81.1 ± 5.1	73 – 94	t=1.3 p=0.19
	negative	61	79.2 ± 6.9	66 – 95	
Dementia	yes	19	82.6 ± 5.4	73 – 94	t=2.14 p=0.0353
	no	72	79.1 ± 6.4	66 – 95	

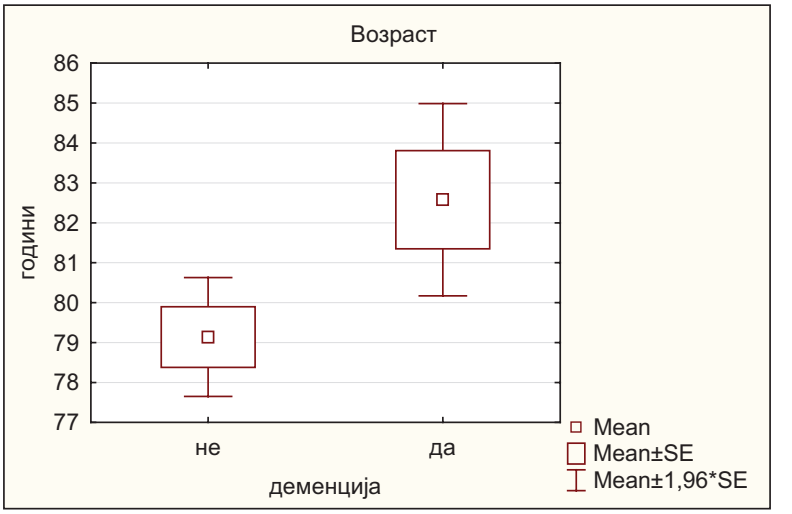

Figure 1. Average age – patients with/without dementia

Dementia was significantly more common in patients with postoperative delirium compared to patients who did not have postoperative delirium (46.67% vs 8.2%, p=0.000022). (Table 4, Figure 2)

Table 4. POD – patients with/without dementia

variable		dementia			p-level
		n	да n (%)	не n (%)	
POD	yes	30	14 (46.67)	16 (53.33)	X^2=18.02 ***p=0.000022
	no	61	5 (8.20)	56 (91.80)	
total		91	19	72	

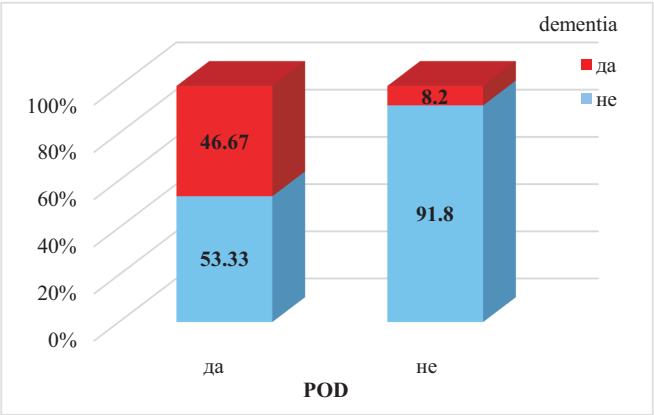

Figure 2. POD – individuals with or without dementia

Table 5 presents the results of univariate and multivariate logistic regression analysis evaluating the role of POD as an independent predictor of dementia. In the univariate analysis, both age and postoperative delirium were found to be factors significantly associated with dementia (p=0.04 and p<0.0001). The multivariate analysis confirmed only postoperative delirium as an independent significant predictor of dementia (p<0.0001). Patients with POD have a 9.765 times greater chance of developing dementia compared to patients without POD (OR = 9.765 (95% CI 2.939-22.452)).

Table 5. Binary logistic regression analysis evaluating the role of POD in the occurrence of dementia

variable	Univariate				Multivariate			
	p	**Exp (B)**	**95% CI for Exp (B)**		**p**	**Exp (B)**	**95% CI for Exp (B)**	
			Lower	**Upper**			**Lower**	**Upper**
age	0.04	1.092	1.004	1.188	0.069	1.101	0.993	1.220
POD	Ref.gr. n							
	0.000	9.8	3.065	21.339	0.000	9.765	2.939	22.452

Discussion

Our findings support the hypothesis that postoperative delirium is a risk factor for subsequent dementia following hip fracture surgery. Dementia was significantly more common in patients with postoperative delirium compared to patients who did not have postoperative delirium (46.67% vs 8.2%, p=0.000022). Patients with POD were 9.8 times more likely to develop dementia than patients without POD (OR = 9.765 (95% CI 2.939-22.452)). Recent systematic reviews also find that delirium in older hospitalized patients is strongly associated with long-term cognitive decline and new-onset dementia, particularly following hip fracture surgery. A 2020 JAMA Neurology meta-analysis (24 studies, ≈10,500 patients) found that delirium was associated with worse cognitive outcomes at ≥3 months (Hedges' g≈0.45, OR≈2.3) (16). A 2020 meta-analysis in Archives of Gerontology (6 cohort studies, 844 patients) found that postoperative delirium (POD) following hip surgery increased the risk of dementia approximately 9-fold (OR≈8.96, 95%CI 5.34–15.03) (17). A 2021 international meta-analysis in J. Geriatric Psychiatry (6 stud-

ies, older hospitalized patients) reported an almost 12-fold increased odds of new dementia (OR≈11.9, 95% CI 7.3–19.6) if delirium occurs (18). The largest and most recent review (Ageing 2025) included 253 studies (about 137,000 patients) and found that delirium increases the odds of dementia incidence by about 5.4 times (OR ≈ 5.37) and is associated with higher rates of objective cognitive decline (OR ≈ 1.58) (19).

It has been hypothesized that delirium can lead to uncovering or identifying pre-existing cognitive impairment that was unrecognized or undiagnosed. However, recent studies indicate that the relationship between delirium and cognitive impairment may be bidirectional, suggesting that dementia is a strong predictor of delirium, and delirium may also have an independent effect on the progression of cognitive decline (20).

Understanding whether delirium merely exposes pre-existing cognitive vulnerability or actively contributes to neurodegeneration remains a critical clinical and research question. Understanding this relationship is crucial as the world population ages and more individuals undergo surgery. If delirium increases the risk of dementia, then preventing and managing delirium becomes more than an immediate postoperative goal, as it may have long-term implications for patients' quality of life.

The role of anesthetic management in postoperative cognitive outcomes has also been explored. Comparative studies of inhalational anesthetics such as desflurane and sevoflurane have demonstrated differences in recovery characteristics and early cognitive function after general anesthesia, suggesting that perioperative factors may contribute to the development of postoperative neurocognitive disorders. In contrast to studies evaluating the effects of general anesthesia on postoperative cognitive function, the patients in our cohort were managed under spinal anesthesia. This may have minimized the potential impact of anesthetic agents on early postoperative neurocognitive changes and allowed a clearer assessment of the relationship between postoperative delirium and subsequent dementia (21).

This study has several limitations, including the relatively small sample size and the single-center design, which may limit the generalizability of the findings. In addition, dementia diagnosis during follow-up relied partly on medical record review, which may have underestimated the true incidence. Finally, the one-year follow-up period may not fully reflect long-term cognitive outcomes in elderly patients following hip fracture surgery.

Conclusion

Postoperative delirium following hip fracture surgery significantly increases the risk of dementia incidence within one year. Elderly hip fracture patients who present with delirium should be closely monitored for the development of dementia. More studies are needed to examine the long-term cognitive consequences of delirium.

Ethics Approval: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee for Research Involving Humans, Faculty of Medicine, "Ss. Cyril and Methodius" University in Skopje. Approval protocol number: 0905-1270/120

Consent for publication: Written informed consent was obtained from all patients prior to their inclusion in the study.

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Author contribution statement: BK drafted the first version of the manuscript. BK and GD collected data and revised the manuscript. BK and NJ revised the manuscript. BK revised the manuscript and approved the final version. BK, AGB and NJ designed and performed the study, acquired and analyzed the data, revised the manuscript and approved the final version.

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MANAGEMENT OF PEDIATRIC SPLENIC TRAUMA IN A RESOURCE - LIMITED TERTIARY CENTER: A FIVE - CASE SERIES

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Abstract

Objective: The aim of this report is to present a five-patient case series of pediatric splenic trauma managed in a resource-limited tertiary center, emphasizing diagnostic pathways, management strategies, and the role of hemoglobin and C-reactive protein (CRP) as practical monitoring biomarkers.

Case Report: Five children aged 3–12 years sustained splenic injury following blunt abdominal trauma caused by traffic accidents, falls, or bicycle-handlebar impact. Injury severity ranged from Grade II to Grade IV. Two patients presented with hemodynamic instability and underwent emergency splenectomy, both of whom developed massive hemoperitoneum and additional intra-abdominal injuries. The remaining three children were hemodynamically stable and were successfully managed non-operatively. All five patients required blood transfusion, with hemoglobin decline serving as the main clinical trigger. Serial CRP measurements demonstrated rapid elevation and faster decline in surgically managed patients, whereas conservatively treated patients showed slower normalization. Imaging relied on targeted abdominal ultrasonography and contrast-enhanced computed tomography, depending on stability. Hospital stays ranged from 5 to 18 days. There were no mortalities or major postoperative complications, and all patients recovered fully.

Conclusion: Non-operative management was safe and feasible in hemodynamically stable pediatric patients, while splenectomy remained necessary for unstable presentations and high-grade trauma. Hemoglobin and CRP trends proved practical, low-cost decision-support tools valuable in settings lacking interventional radiology or advanced trauma infrastructure.

Keywords: *non-operative management; pediatric trauma; resource-limited settings; splenic laceration; hemorrhage control.*

Introduction

Pediatric abdominal trauma represents a significant contributor to morbidity and mortality, with injury patterns shaped by the distinct anatomical and physiological characteristics of children. Blunt trauma predominates, most often caused by road traffic accidents, falls, and sports-related impacts, with the spleen and liver being the most frequently affected organs (1–4). Recent national data indicate that over 95% of pediatric splenic injuries are now managed non-operatively, while splenectomy rates remain stable at 6–7% (1). Optimal evaluation relies on rapid clinical assessment, selective imaging, and serial laboratory monitoring, particularly hemoglobin trends. (2,5).

Over recent decades, management strategies have shifted toward non-operative management (NOM) in hemodynamically stable children, reserving splenectomy and laparotomy for unstable cases or those with hollow-viscus injury (6,7). However, imaging utilization varies between pediatric and general trauma centers, influencing diagnostic accuracy and radiation exposure (8). When management aligns with evidence-based guidelines, outcomes are generally favorable, though they may be affected by patient age, institutional protocols, and available resources (9,10).

This case series presents five pediatric abdominal trauma cases, emphasizing splenic injury patterns, management strategies, and clinical outcomes within the context of current evidence.

Case Presentation

Five pediatric patients (ages 3–12 years) with abdominal trauma were retrospectively reviewed. All sustained splenic injury as a primary finding. Mechanisms included road traffic accidents, falls, and bicycle-handlebar trauma. Two patients required emergency splenectomy due to hemodynamic instability and complex intra-abdominal injury, while three were managed non-operatively. Blood transfusion was required in all cases, with hemoglobin decline serving as a key indicator for intervention. Table 1 summarizes the clinical characteristics, management approaches, and outcomes, while brief case narratives highlight key decision points.

Case 1

An 8-year-old girl sustained a Grade IV splenic laceration with polytrauma after a traffic accident. She was unstable and underwent emergency laparotomy with splenectomy, bowel resection, and ileal repair. Post-operative ileus was managed conservatively, and transfusion was required on day 2.

Case 2

A 5-year-old boy presented with **Grade II splenic laceration** and Grade III liver hematoma following a bicycle-handlebar injury. He remained hemodynamically stable and was treated conservatively. Hemoglobin decline on day 2 prompted a transfusion.

Case 3

A 3-year-old girl fell from a motorized toy vehicle, sustaining a Grade IV splenic laceration and hypovolemic shock. Urgent laparotomy revealed massive hemoperitoneum, requiring sple-

nectomy and intraoperative transfusion. She developed a low-grade postoperative fever that resolved with antibiotics.

Case 4

A 12-year-old girl sustained a Grade III splenic laceration and a Grade II renal laceration with associated pulmonary contusion following a high-speed traffic accident. She remained hemodynamically stable and was managed non-operatively. Hemoglobin declined on day 3, requiring transfusion, and a transient fever resolved with empirical antibiotics.

Case 5

An 11-year-old boy suffered a Grade II splenic laceration with subcapsular hematoma after a fall. Conservative management was pursued and complicated by transient paralytic ileus, which resolved with decompression. Hemoglobin decline on day 4 required transfusion.

Peak inflammatory and hematologic parameters across the five pediatric trauma cases are presented in Figure 1. Peak C-reactive protein (CRP) values varied among patients, while minimum hemoglobin levels ranged from 87 to 97 g/L.

Clinical characteristics, injury patterns, management strategies, and outcomes are summarized in Table 1. Two patients with high-grade splenic injuries required operative management, whereas three patients were successfully treated conservatively. All patients recovered without complications.

Representative contrast-enhanced abdominal CT images illustrating the spectrum of splenic injury patterns are shown in Figure 2.

Table 1. Clinical characteristics, management, and outcomes in five pediatric abdominal trauma patients

Case	Age (years)	Mechanism of injury	Major injury pattern	Management: Operative/non operative	Surgery	Transfusion	Hospital stay	Outcome
1	8	Traffic accident (polytrauma)	Grade IV splenic laceration, GI perforation, lung contusion	Operative	Splenectomy + bowel resection/ repair	Yes	17 days	Full recovery
2	5	Bicycle handlebar trauma	Grade II splenic laceration, Grade III liver hematoma, hemoperitoneum	Non-operative	No	Yes	5 days	Full recovery
3	3	Fall from motorized toy/bike	Grade IV splenic laceration, hypovolemic shock	Operative	Splenectomy + lavage	Yes	6 days	Full recovery

Case	Age (years)	Mechanism of injury	Major injury pattern	Management: Operative/non operative	Surgery	Transfusion	Hospital stay	Outcome
4	12	High-speed traffic accident	Grade III splenic laceration, Grade II renal laceration, lung contusion	Non-operative	No	Yes	18 days	Full recovery
5	11	Fall	Grade II splenic laceration, subcapsular hematoma	Non-operative	No	Yes	7 days	Full recovery

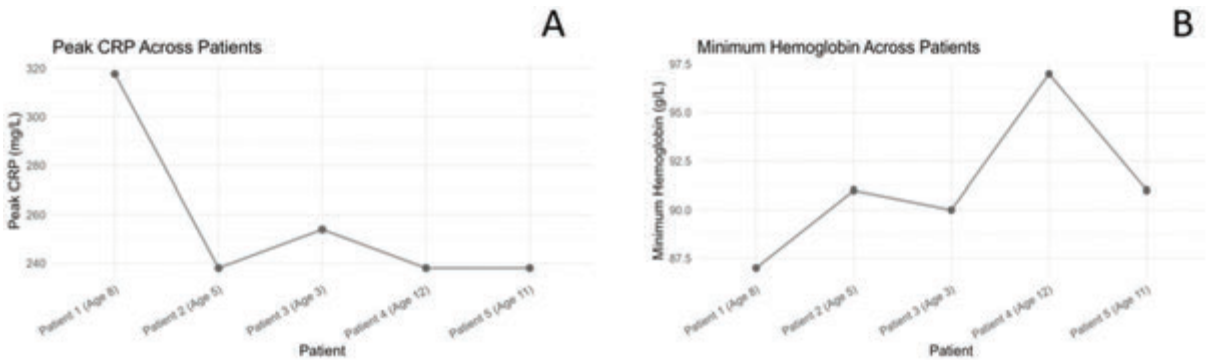

Figure 1. Peak C-reactive protein (CRP) levels (A) and minimum hemoglobin values (B) across five pediatric patients with splenic trauma.

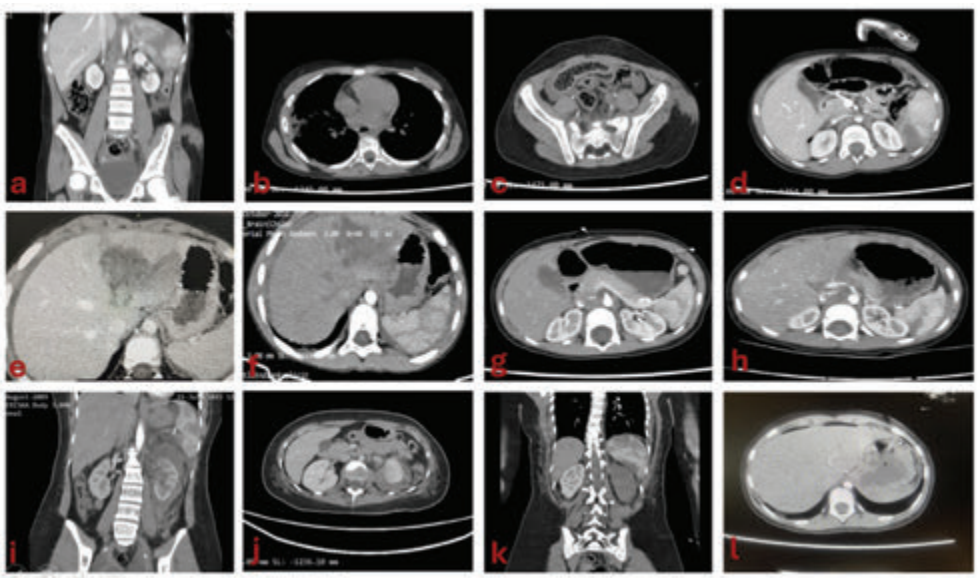

Figure 2. Contrast-enhanced abdominal CT demonstrating splenic injury patterns across five pediatric trauma cases.

Case 1 (a–d): *Grade IV splenic laceration* with large hemoperitoneum, associated gastrointestinal perforation and lung contusion. **Case 2 (e–f):** *Grade II splenic injury* presenting as a subcapsular hematoma with preserved perfusion; managed conservatively. **Case 3 (g–h):** *Grade IV splenic laceration* with perisplenic fluid. **Case 4 (i–k):** *Grade III splenic injury* with associated *Grade II renal laceration* and lung contusion; no contrast blush, treated non-operatively. **Case 5 (l):** *Grade II splenic laceration* with contained subcapsular hematoma and no evidence of active bleeding.

Discussion

In this five-patient series of pediatric abdominal trauma, splenic injury was the predominant finding, aligning with reports identifying the spleen as the most frequently affected organ in blunt trauma (1,4,9). Two patients required operative intervention, both splenectomies, due to hemodynamic instability and complex injury patterns, consistent with recommendations indicating surgery primarily for unstable patients or those with hollow-viscus perforation (6,7). Our operative rate (40%) exceeded large national datasets reporting splenectomy rates of 6.7% (1), likely reflecting the small sample size, high-grade injuries, limited interventional radiology, and constrained capacity for prolonged hemodynamic observation.

Our findings are consistent with previous institutional experiences in pediatric surgery, where timely intervention proved critical in cases of wandering spleen torsion (11) and complicated echinococcosis (12). Similar patterns are described in the literature where non-operative success rates remain high in stable splenic and hepatic injuries, with operative rates typically below 15–20% (6,9).

Mechanisms of injury ranged from high-energy trauma (road traffic accidents) to lower-energy, focused impacts such as bicycle-handlebar injuries, reflecting patterns described in comparable cohorts (3,4,9). In this series, younger patients with severe splenic injury required splenectomy, which aligns with evidence indicating that age alone does not determine splenic salvage potential when instability is present (4,9). However, some authors advocate prioritizing splenic preservation in younger children due to their greater immunologic vulnerability (7).

CRP values reflected inflammatory response variations and recovery trajectories; although non-specific, CRP may complement clinical assessment in settings lacking frequent imaging options. Similar findings are reported in pediatric polytrauma studies emphasizing biomarker-supported monitoring (5).

In this cohort, the length of stay ranged 5–18 days, slightly longer than the ranges reported for NOM (3–10 days) and operative cases (7–14 days) (4,6,9). Compared with the U.S. study by Eldredge et al. (1) and the Ethiopian series by Molla et al. (9), our splenectomy rate was intermediate. Universal transfusion in our cohort suggests a conservative transfusion threshold influenced by resource limitations rather than clinical deterioration alone.

Although pancreatic injury was not observed in this cohort, it remains a rare but clinically significant associated injury that may influence operative vs. non-operative decision pathways in pediatric abdominal trauma (13).

Overall, this case series reinforces the feasibility of safe non-operative management in stable patients, the necessity of timely surgery in unstable presentations, and the utility of laboratory

trends as decision-support tools in environments with limited subspecialty and imaging capacity.

This study has several limitations. First, the small sample size and the retrospective single-center design limit the generalizability of the findings. Second, the absence of interventional radiology and advanced trauma resources in our institution may have influenced management strategies, including operative decisions and transfusion practices. Finally, the observational nature of this case series does not allow for causal inference or comparison with standardized treatment protocols.

Conclusion

Splenic injury represented the predominant lesion in this series of pediatric abdominal trauma. NOM was safe and effective in stable patients, while splenectomy remained crucial for unstable cases. Serial hemoglobin and CRP monitoring supported clinical and imaging assessments. Favorable outcomes were achieved through timely diagnosis, appropriate intervention, and adherence to evidence-based guidelines. These findings may guide trauma protocols in centers with limited imaging, interventional radiology, and intensive monitoring resources.

Ethical Approval: Non-applicable.

Consent for publication: Written informed consent for publication of anonymized clinical information and imaging was obtained from the legal guardians of all patients.

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CASE REPORT *UDK: 618.14-073.756.8:*

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ARCUATE UTERUS IDENTIFIED ON PELVIC MRI: A NORMAL VARIANT MIMICKING SEPTATE UTERUS

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Abstract

Background: Accurate differentiation of Müllerian duct anomalies is a critical component of infertility assessment. A septate uterus is associated with adverse reproductive outcomes and often requires surgical correction, whereas an arcuate uterus is considered a benign anatomical variant with no proven clinical significance. Magnetic resonance imaging (MRI) offers superior characterization of uterine morphology, enabling precise diagnosis.

Case Presentation: A 35-year-old woman undergoing infertility evaluation was referred for pelvic MRI due to a suspected septate uterus. MRI demonstrated a normal external uterine fundal contour with a smooth, broad concave indentation of the endometrial fundus measuring less than 1 cm. No fibrous septum or cavity division was identified, findings consistent with an arcuate uterus. Both ovaries were normal, and a small amount of physiologic pelvic free fluid was present.

Conclusion: This case underscores the pivotal role of MRI in distinguishing an arcuate uterus from a septate uterus during infertility work-up. Accurate imaging diagnosis prevents unnecessary surgical intervention and allows appropriate reproductive counseling.

Keywords: *Arcuate uterus; Infertility; Müllerian duct anomalies; Pelvic MRI; Septate uterus*

Introduction

Müllerian duct anomalies (MDAs) comprise a heterogeneous group of congenital uterine malformations resulting from abnormal development, fusion, or resorption of the paramesonephric ducts during embryogenesis. These anomalies may alter uterine morphology and are clinically relevant in the context of infertility, recurrent pregnancy loss, dysmenorrhea, and adverse obstetric outcomes. Precise classification is essential, as management and prognosis vary substantially among different anomaly types. However, overlapping morphologic features often complicate diagnosis, particularly when imaging fails to adequately assess both the endometrial cavity and the external uterine contour (1).

The arcuate uterus represents a mild deviation within the spectrum of normal uterine anatomy rather than a true congenital malformation. It is characterized by a shallow, broad concavity of the endometrial fundal surface caused by minimal midline septal resorption failure. Unlike septate or bicornuate uteri, the arcuate uterus preserves a normal external fundal contour and has not been consistently associated with impaired fertility or adverse pregnancy outcomes. Never-

theless, its subtle appearance may mimic a partial septum, particularly on suboptimal imaging planes or limited modalities, leading to frequent misclassification and overtreatment (2,3).

Pelvic MRI is widely regarded as the reference standard for evaluation of MDAs owing to its excellent soft-tissue contrast, multiplanar capability, and reproducibility. Crucially, MRI allows simultaneous assessment of both the internal uterine cavity and the external serosal contour, a cornerstone of modern classification systems, including the ASRM 2021 and ESHRE/ESGE frameworks. In an arcuate uterus, MRI typically demonstrates a smooth fundal indentation measuring less than 1 cm with an otherwise normal convex or flat external contour—features that reliably differentiate it from a septate uterus, in which a fibrous or fibromuscular septum extends ≥1 cm toward the uterine cavity (4–6).

With the increasing use of MRI in infertility evaluation, recognition of the arcuate uterus as a benign variant is essential to avoid misdiagnosis and unnecessary surgical intervention. This case report illustrates the MRI appearance of an arcuate uterus initially suspected to be septate, highlighting key diagnostic features and emphasizing the importance of accurate morphologic interpretation.

Case Presentation

A 35-year-old woman was referred for pelvic MRI following ultrasound suspicion of a septate uterus during infertility evaluation. She reported no history of recurrent pregnancy loss, dysmenorrhea, or other gynecologic symptoms. MRI was performed using standard pelvic protocols, with high-resolution T2-weighted sequences in axial, sagittal, and coronal planes, without intravenous contrast.

Imaging Findings

MRI demonstrated a normal uterine size and configuration with a preserved external fundal contour. A smooth, broad concave indentation of the endometrial fundus measuring less than 1 cm in depth was identified. No fibrous septum, muscular ridge, or division of the uterine cavity was present. The uterine cavity appeared single and undistorted. Both ovaries were normal in size and morphology, containing multiple age-appropriate follicles. A small amount of physiologic free fluid was noted in the rectouterine pouch.

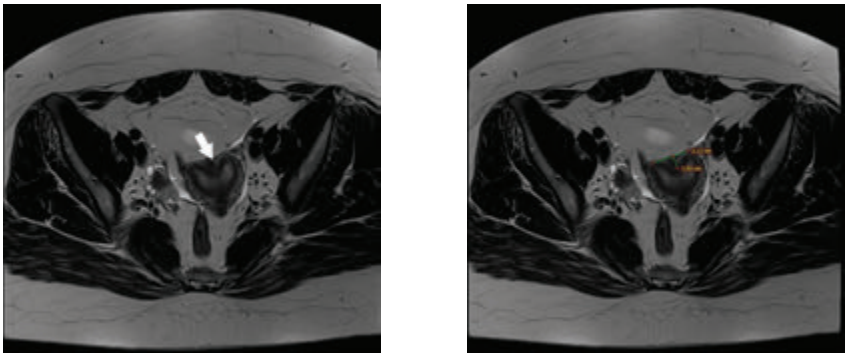

Figure 1 a) and b). Axial T2-weighted pelvic MRI images (a, b) demonstrate a smooth, broad concave indentation of the endometrial fundus measuring less than 1 cm in depth (white arrow), with preservation of the external uterine contour. No fibrous or muscular septum is identified, consistent with an arcuate uterus.

Discussion

Although the arcuate uterus is now widely accepted as a normal anatomical variant, it remains a frequent source of diagnostic ambiguity. Earlier classification systems, including the original 1988 ASRM framework, categorized an arcuate uterus as a mild resorption defect. Contemporary consensus, reflected in the ASRM 2021 update, recognizes it as a benign variant without demonstrable impact on fertility or pregnancy outcomes (1,5). Accurate differentiation from a septate uterus is critical, as the latter is associated with increased risk of miscarriage and may warrant hysteroscopic septum resection.

Diagnostic challenges arise particularly when imaging techniques inadequately visualize the uterine fundal contour. Two-dimensional ultrasound, although widely available, is limited by operator dependence and by its restricted evaluation of the external uterine surface. Three-dimensional ultrasound improves diagnostic accuracy but remains less accessible and susceptible to technical limitations. MRI, therefore, serves as a decisive problem-solving modality, offering reproducible, high-resolution assessment of both internal cavity morphology and serosal contour (3,6).

In an arcuate uterus, MRI consistently demonstrates a shallow, broad endometrial indentation measuring less than 1 cm in the absence of an external fundal cleft. In contrast, a septate uterus is defined by a fibrous or fibromuscular septum extending ≥1 cm into the uterine cavity, with preservation of the external contour. Applying these criteria helps prevent misclassification, as repeatedly highlighted in radiologic and gynecologic literature, and avoids unnecessary hysteroscopic intervention, thereby reducing avoidable anesthetic and perioperative risk (2,7).

The ESHRE/ESGE classification, while valuable for standardization, has been criticized for its increased sensitivity and potential overdiagnosis of a septate uterus when internal cavity measurements are emphasized without equal consideration of the external fundal contour. The ASRM 2021 classification addresses this limitation by reinstating indentation depth thresholds and explicitly defining arcuate uterus as a normal variant. MRI is uniquely suited to apply these criteria accurately, reinforcing its central role in equivocal cases.

The present case fulfills all ASRM 2021 criteria for arcuate uterus: a normal external uterine contour, an endometrial fundal indentation less than 1 cm, and absence of a true septum. Recognition of these features allowed confident exclusion of a septate uterus and avoidance of unnecessary intervention.

Conclusion

An arcuate uterus represents a benign anatomical variant without established reproductive significance. Accurate distinction from a septate uterus is essential, particularly in infertility evaluation. MRI provides a reliable assessment of uterine morphology and fundal contour, enabling precise classification and preventing unnecessary surgical treatment and related anesthetic risk. Awareness of this normal variant is crucial for both radiologists and clinicians to ensure appropriate patient counseling and management.

Ethics approval and consent to participate: A formal approval of the Ethics Committee was not required for this study.

Consent for publication: Written informed consent was obtained from the patient prior to inclusion.

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Authors' contributions: Conceptualization and study design: A.J.; Image acquisition and interpretation: S.N.; Literature review and analysis: A.J.; Manuscript drafting: A.J.; Critical revision of the manuscript for important intellectual content: S.N. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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APPLICATION OF ULTRASOUND - GUIDED FEMORAL NERVE BLOCK IN A PATIENT WITH SEVERELY IMPAIRED LEFT VENTRICULAR FUNCTION UNDERGOING FEMORO - POPLITEAL BYPASS RECONSTRUCTIVE SURGERY

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Abstract

Introduction: Patients with severe left ventricular dysfunction undergoing major vascular surgery represent a high-risk population for perioperative morbidity and mortality. Careful anesthetic management focused on maintaining hemodynamic stability while minimizing myocardial depression is essential in such patients.

Case report: We present the anesthetic management of an 84-year-old ASA IV patient with severely reduced left ventricular ejection fraction (35%), undergoing elective femoropopliteal bypass surgery due to critical peripheral arterial disease. The aim of this case report is to highlight the benefits of carefully titrated general anesthesia combined with an ultrasound-guided femoral nerve block and a low-dose dobutamine infusion to maintain stable hemodynamic conditions and reduce systemic opioid requirements, emphasizing an individualized anesthetic approach in a patient with complex cardiovascular and renal comorbidities. The block was performed using an in-plane ultrasound technique with bupivacaine and lidocaine. Throughout the entire procedure, the patient remained hemodynamically stable, without experiencing clinically significant episodes of hypotension, hypertension, arrhythmia, or tachycardia. The procedure lasted approximately 2 hours and 30 minutes and was completed without complications. The patient was extubated in the operating room, remained hemodynamically stable postoperatively, and was discharged from the hospital in stable condition.

Conclusion: The use of peripheral nerve blocks in combination with general anesthesia may provide excellent conditions for performing complex vascular procedures in patients with cardiac comorbidities. Ultrasound-guided femoral nerve block combined with carefully titrated general anesthesia may represent a useful opioid-sparing strategy for maintaining hemodynamic stability in high-risk vascular patients with severe left ventricular dysfunction.

Keywords: *Femoral nerve block; left ventricular dysfunction; opioid-sparing anesthesia; regional anesthesia; vascular surgery.*

Introduction

Elderly patients with advanced cardiovascular disease undergoing major vascular surgery represent one of the highest-risk populations in anesthetic practice. Surgical treatment is associated with significantly increased perioperative cardiovascular complications and mortality compared with patients without cardiac disease (1). Patients with coexistence of severe left ventricular systolic dysfunction, impaired diastolic filling, and extensive atherosclerotic disease have a significantly increased risk for perioperative morbidity and mortality. Therefore, all these well-known facts require carefully tailored anesthetic management focused on maintaining hemodynamic stability and preserving myocardial function while avoiding exacerbation of pre-existing organ dysfunction. The goals of anaesthetic management in these patients undergoing major surgery include optimization of preload, maximization of forward flow, maintenance of stable hemodynamics, and prevention of potentially dangerous complications such as arrhythmias and acute on chronic heart failure (2). Achieving these goals requires careful titration of anesthetic agents and continuous hemodynamic monitoring. In such patients, even minor alterations in preload, afterload, heart rate, or myocardial contractility may lead to profound and significant hemodynamic instability, leading to clinically relevant end-organ hypoperfusion. General anesthesia in patients with severe heart failure is frequently associated with adverse hemodynamic effects, including myocardial depression, vasodilatation, and impaired autonomic regulation. Excessive use of systemic anesthetic agents and opioids may further compromise cardiac output and tissue perfusion. Regarding the risk of occurrence of all these well-known side effects with significant hazardous potential, multimodal and opioid-sparing anesthetic techniques have gained increasing importance in guiding high-risk patients with cardiovascular comorbidities (3). Therefore, strategies aimed at minimizing the use of myocardial depressant drugs while ensuring adequate analgesia and optimal surgical conditions have become modalities of particular interest and importance. Such a technique is the combination of general anesthesia with regional anesthetic techniques, which provides effective analgesia with reduced opioid requirements and improves perioperative hemodynamic stability in high-risk patients. The anesthetic management of patients with severe left ventricular dysfunction undergoing major vascular surgery represents a significant clinical challenge. In the present case, carefully titrated general anesthesia was combined with ultrasound-guided femoral nerve block and continuous low-dose inotropic support in order to maintain hemodynamic stability, reduce myocardial depression, and limit opioid use. This case highlights the importance of an individualized hemodynamic approach in the anesthetic management of high-risk vascular patients.

Case Report

This case report describes the anaesthetic management of an 84-year-old ASA IV patient with severe left ventricular dysfunction undergoing femoropopliteal bypass surgery. The aim of this case report is to highlight the benefits of a carefully titrated general anesthesia combined with an ultrasound-guided femoral nerve block and a low-dose intraoperative inotropic support, emphasizing an individualized, opioid-sparing approach in a patient with complex cardiovascular and renal comorbidities. We present an 84-year-old female patient, 70 kg in weight and 160 cm in height, scheduled for elective lower limb revascularization surgery, where femoropopliteal bypass was the technique of choice due to critical peripheral arterial disease. According to the American Society of Anesthesiologists' physical status classification, our patient was classified as an ASA IV due to the presence of severe cardiovascular disease and multiple comorbidities.

The patient's medical history was significant for advanced ischemic heart disease. She underwent coronary artery bypass grafting 22 years prior and had suffered an anterolateral myocardial infarction 10 years prior to the current admission. Her echocardiography findings have revealed dilated left ventricular chambers with segmental wall motion abnormalities, combined systolic and diastolic dysfunction, and a severely reduced left ventricular ejection fraction of approximately 35%. Additional comorbidities included chronic renal impairment with unilateral renal agenesis with preoperatively elevated urea levels (17.5 mmol/L) and creatinine concentration of 122 μmol/L. The coagulation profile was within normal limits. Given the patient's advanced age, severe left ventricular dysfunction, renal impairment, and extensive cardiovascular history, a combined anesthetic approach was planned. The strategy consisted of carefully titrated general anesthesia combined with peripheral regional anesthesia to minimize myocardial depression, reduce opioid requirements, and preserve hemodynamic stability throughout the procedure. Prior to induction of general anaesthesia, invasive arterial blood pressure monitoring was established via radial arterial cannulation to allow continuous real-time assessment of hemodynamic parameters. Standard monitoring included electrocardiography, pulse oximetry, and capnography. A low-dose dobutamine infusion was initiated before induction and was titrated gradually depending on the patient's needs. Dobutamine infusion at 2 μg/kg/min was initiated prior to induction and maintained at doses ranging from approximately 2 to 2.5 μg/kg/min, providing inotropic support to maintain myocardial contractility. Induction of general anaesthesia was performed slowly and cautiously. The patient received midazolam 1 mg, fentanyl 50 μg, ketamine 50 mg, propofol 30 mg, and cisatracurium 7 mg. Drug doses used for induction and intraoperative management were calculated based on the patient's actual body weight. Cisatracurium was chosen due to its organ-independent metabolism, particularly suitable in the presence of renal impairment. Tracheal intubation was achieved smoothly without significant fluctuations in arterial blood pressure or heart rate. Following induction and stabilization, a central venous catheter was inserted to enable central venous pressure monitoring and facilitate fluid and vasoactive drug administration. General anesthesia was maintained with sevoflurane at low concentrations, targeting a minimum alveolar concentration (MAC) of approximately 0.3, in combination with controlled ventilation. An ultrasound-guided femoral nerve block was performed on the operative side using a total volume of 15 mL, consisting of 7.5 mL of 0.5% bupivacaine and 7.5 mL of 2% lidocaine. The block was performed using a high-frequency linear ultrasound probe with an in-plane needle approach, allowing continuous visualization of the needle tip and accurate deposition of local anesthetic adjacent to the femoral nerve. The block was administered to enhance intraoperative analgesia and to reduce the requirement for systemic anesthetic agents as part of an opioid-sparing strategy. During the surgical procedure, which lasted approximately 2 hours and 30 minutes, the patient received multimodal non-opioid analgesia, including metamizole and paracetamol. Additional medications administered as part of routine perioperative care included dexamethasone 8 mg, metoclopramide 10 mg, pantoprazole 40 mg, unfractionated heparin 5000 IU in line with surgical requirements, sodium bicarbonate 20 mL guided by arterial blood gas analysis, and furosemide 20 mg. Approximately 2500 mL of balanced crystalloid solution was administered intraoperatively in order to maintain adequate preload while avoiding fluid overload in a patient with reduced left ventricular function. Throughout the entire procedure, the patient remained hemodynamically stable, without experiencing clinically significant episodes of hypotension, hypertension, arrhythmia or tachycardia. Intraoperative mean arterial pressure ranged between approximately 80 and 100 mmHg, while heart rate ranged between 55 and 75 beats per minute. Arterial blood gas analysis demonstrated pH 7.32, pCO_2 35 mmHg, and pO_2 85.9 mmHg with lactate 2.62 mmol/L, without evidence of clinically significant tissue hypoperfusion. Intraoperatively, no additional opioids, or muscle

relaxants were required after induction of anesthesia. At the end of surgery, neuromuscular blockade was reversed, and the patient was successfully extubated in the operating theater. She was awake, hemodynamically stable, and pain-free, with no evidence of residual motor blockade. The patient was transferred to the surgical ward for postoperative monitoring. Hemodynamic parameters remained stable, and no signs of myocardial ischemia, arrhythmia, or cardiac decompensation were observed. The patient did not require admission to the intensive care unit. Postoperative analgesia remained adequate during the first postoperative day without the need for opioid administration. The postoperative course was uneventful, and the patient was discharged from the hospital in stable condition.

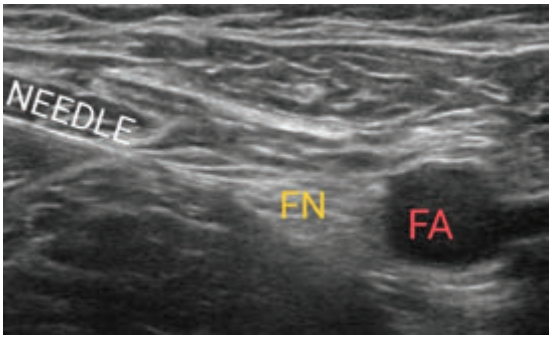

Figure 1. Ultrasound image demonstrating the femoral nerve (FN) adjacent to the femoral artery (FA) with in-plane needle visualization during ultrasound-guided femoral nerve block.

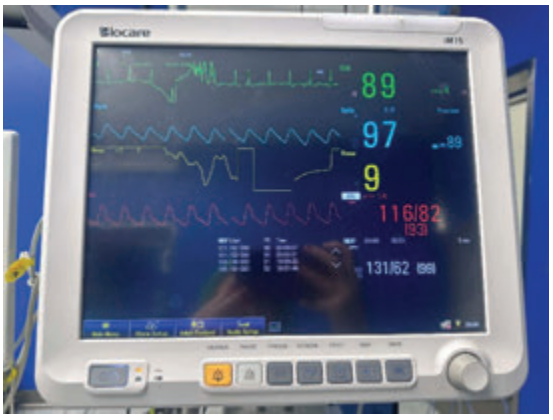

Figure 2. Representative intraoperative monitor display demonstrating stable hemodynamic parameters, including invasive arterial blood pressure and heart rate, during surgery under combined general and regional anesthesia.

Discussion

Vascular surgical techniques that involve open revascularization generally have a high risk of perioperative complications. Recent publications in the Macedonian Journal of Anesthesia have emphasized the importance of individualized perioperative management strategies in cardiac patients undergoing high-risk non-cardiac procedures, particularly in those with reduced left ventricular function (4). In this context, Garcia et al. identified the occurrence of perioperative complications in as many as 15.6% of patients with a 3.2% mortality rate (5). In another retrospective study, the occurrence of perioperative ischemic complications in patients undergoing

vascular surgery was 11.4%, while the same authors detected not only increased morbidity in patients with cardiovascular disease, but also increased perioperative mortality of 6.4%, emphasizing the presence of cardiovascular disease as a significant risk factor for the development of serious perioperative complications and mortality (6). Hence, the two previous studies emphasize the severity of cardiovascular comorbidity as a significant risk factor for an unfavorable outcome of vascular surgical procedures even when all measures of precaution are considered. The above case completely fits into the category of patients analyzed in the studies of Garcia and Thomas, which indicate that anesthetic management can play a significant role in the occurrence or prevention of perioperative cardiovascular complications and mortality. Namely, the study of Thomas and colleagues determined that epidural analgesia, as a regional technique complementary to general anesthesia, does not have a favorable effect on the incidence of cardiovascular complications and mortality (6). Therefore, epidural analgesia was not applied in the presented case; instead, a safer regional anesthetic technique, such as the peripheral femoral nerve block, was selected as an alternative to neuraxial anesthesia. The safety of peripheral nerve blocks and their impact on perioperative morbidity and mortality were not analyzed in the above studies, but they may represent a safer alternative to neuraxial anesthesia, as peripheral nerve blocks are not associated with significant reductions in peripheral vascular resistance or systemic vasodilation. According to Huttler et al., as many as 37% of patients undergoing major vascular surgery for peripheral arterial disease develop serious perioperative complications, while this percentage is significantly lower, at 19%, in patients with peripheral arterial disease undergoing minor vascular procedures (7). According to the aforementioned study, the surgical procedure performed on the patient presented in this paper is categorized as a major vascular surgery for peripheral arterial disease, with an exceptionally high risk of intra- and postoperative complications and mortality due to the presence of cardiovascular comorbidity. This fact justifies all the activities undertaken to reduce perioperative risk, including the use of invasive monitoring, continuous inotropic support from the very beginning of the procedure, and the application of peripheral nerve block as a regional technique aiming to reduce intraoperative consumption of opioids, hypnotics, and relaxants and thus ensuring hemodynamic stability. Echocardiographic findings that suggest the presence of elements of left ventricular failure as detected in the presented patient have been recognized and identified as a significant risk factor for postoperative complications in patients undergoing open vascular surgery (8).

The positive effects of regional anesthesia and peripheral nerve blocks have been recognized previously, with a reduced incidence of cardiovascular complications observed when peripheral nerve blocks are used compared with neuraxial anesthesia (9). Hence, their use before neuraxial anesthesia is clearly defined and included in European recommendations when guiding patients with cardiovascular comorbidities for non-cardiac surgery. In this regard, this paper presents the effect of the use of the peripheral femoral nerve block and its analgesic properties in cardiac-compromised patients, which is observed through the creation of ideal working conditions for the surgeon, with reduced systemic use of drugs. The hemodynamic stability of the patients and the reduced incidence of cardiovascular events in the perioperative period are most likely due to the lower stress response and the reduced or completely extinguished activation of the sympathetic nervous system during the application of peripheral nerve blocks in patients with cardiovascular comorbidities (9). This finding supports the use of ultrasound-guided femoral nerve blocks in routine clinical practice when performing vascular procedures on the peripheral arteries of the lower limb. The usefulness of peripheral nerve blocks in patients with existing cardiac pathology has also been seen in the meta-analysis of Memtsoudis and colleagues, where after analyzing 122 studies, a significantly lower incidence of cardiac complications in the pe-

rioperative period was observed, compared with patients where only general anesthesia was applied (10).

Knowledge regarding the effects of peripheral nerve blocks on the sympathetic nervous system compared with neuraxial anesthesia suggests that they may represent a safer option in patients with cardiovascular comorbidities, as peripheral nerve blocks do not cause a decrease in peripheral vascular resistance and systemic vasodilation. Peripheral nerve blocks may offer important advantages over neuraxial anesthesia in patients with significant cardiovascular comorbidities, as they are not associated with pronounced sympathetic blockade and sudden decreases in peripheral vascular resistance. This ability may be particularly beneficial in patients with severe left ventricular dysfunction, where maintaining stable hemodynamic conditions is essential. In such patients, even minor reductions in systemic vascular resistance or myocardial contractility may lead to significant hemodynamic instability and impaired end-organ perfusion, which highlights the importance of carefully titrated anesthetic techniques. Furthermore, the use of regional anesthesia contributed to an opioid-sparing anesthetic strategy, which may further support hemodynamic stability and reduce perioperative stress response in high-risk vascular patients. Hence, the choice of this technique, where general anesthesia is supplemented with regional anesthesia, was not only a personal choice of the attending anesthesiologists, but an approach supported by evidence-based medicine and recommendations from contemporary guidelines for the treatment of patients with cardiac pathology in non-cardiac surgery.

Conclusion

The use of peripheral nerve blocks in combination with general anesthesia can create excellent conditions for performing complex vascular procedures in patients with cardiac comorbidities. Namely, the absence of significant hemodynamic destabilization in an already cardiovascularly-compromised patient indicates the safety of the peripheral femoral nerve block, which can serve as a tool to reduce the systemic use of anesthetics. Ultrasound-guided femoral nerve block can and should be used in everyday anesthetic practice as a regional anesthetic technique complementary to general anesthesia during peripheral arterial reconstructive procedures of the lower limb. This case highlights the potential benefits of combining ultrasound-guided peripheral nerve blocks with carefully titrated general anesthesia in high-risk vascular patients with severe left ventricular dysfunction.

Ethical approval: This case report contains fully anonymized patient data and does not include any identifiable patient information. Ethical approval was not required for publication of a single case report according to institutional regulations.

Consent for publication: Written informed consent was obtained from the patients prior to inclusion in the study.

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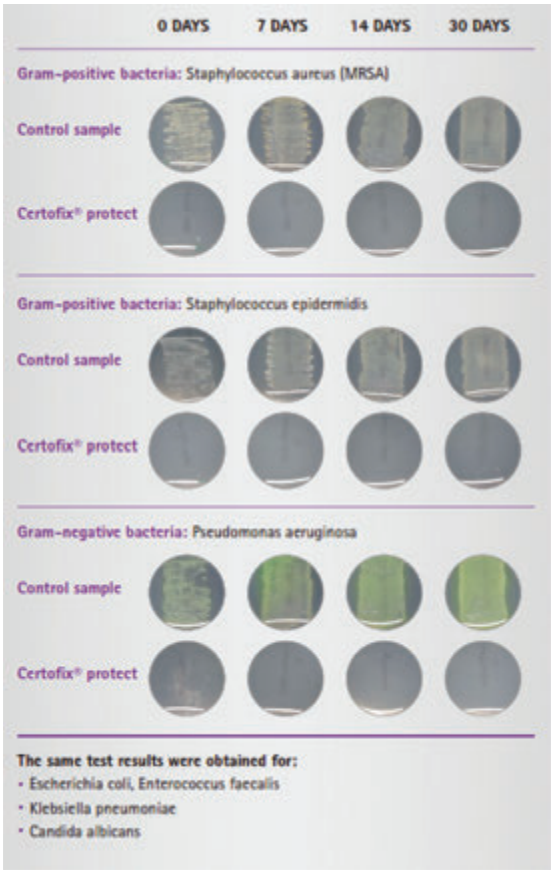

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