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Editor-in-Chief

Dear Readers,

We recently marked the 104th anniversary of the August 30 Victory, a turning point in Türkiye's struggle for independence. May the spirit of independence embodied by this historic victory continue to inspire lasting peace, solidarity, and hope for all humanity.

We will continue to share the knowledge and experience gained through our efforts to improve human life and health.

With this spirit, we are pleased to present the third issue of Gülhane Medical Journal this year. This issue includes noteworthy research articles and case reports from various fields of medicine.

I want to express my sincere gratitude to all our editors who contributed to preparing this issue, to the authors who shared their work with the scientific community, and to our valued readers for their continued interest.

Sincerely,

M. Ali Gülçelik, M.D., Prof.
Editor-in-Chief

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Evaluation of clinical features, diagnosis, treatment, and surgical outcomes in cases of hydatid cysts with atypical localization: a retrospective study

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ABSTRACT

Aims: This single-center case series aimed to evaluate the clinical features, diagnostic challenges, and surgical outcomes of hydatid cysts in atypical locations.

Methods: This retrospective study included patients who underwent surgery between 2014 and 2024 for pathologically confirmed hydatid cysts located outside the liver, spleen, and pancreas. Postoperative recurrence, intraoperative and postoperative complications, and the need for reoperation were evaluated. All patients were assessed by ultrasonography, computed tomography, or both according to standard diagnostic protocols for hydatid disease, and received albendazole as adjuvant therapy regardless of cyst localization.

Results: Ten patients (mean age 44.5±17.7 years; 8 females, 2 males) were included. Cysts were localized to the musculoskeletal tissues (n=5, 50%), the retroperitoneum (n=3, 30%), the adrenal gland (n=1, 10%), and the adnexal region (n=1, 10%). Total cyst excision was performed in eight patients (80%), while cystotomy and drainage were required in two patients (20%). Postoperative recurrence was observed in two patients (20%): one following excision of a gluteal cyst and the other after drainage of a retroperitoneal cyst; both underwent reoperation. No intraoperative or postoperative complications or mortality were observed during the follow-up period.

Conclusions: This case series demonstrates that hydatid cysts with atypical localization present with diverse anatomical involvement and may be associated with an increased risk of postoperative recurrence, particularly after non-radical surgical procedures. Careful preoperative evaluation and complete surgical excision, when feasible, may reduce the need for reoperation in these patients.

Introduction

Hydatid cyst disease is an ancient zoonotic infection caused by *Echinococcus granulosus*. This disease is prevalent worldwide, particularly in the Middle East, including Iran, Iraq, and Türkiye. Dogs and other canids act as definitive hosts for the parasite, while sheep, cattle, goats, and camels serve as intermediate hosts. Humans become accidentally infected by ingesting water or food contaminated with the parasite eggs excreted in the feces of dogs. Once ingested, the larvae penetrate the intestinal wall, enter the bloodstream, and migrate to various regions of the body, where they grow and form hydatid cysts (1,2).

The majority of hydatid cyst cases occur in the liver (60-70%) and in the lungs (20%). While the liver and lungs are the most frequently involved organs, atypical localizations present unique diagnostic and therapeutic difficulties. In endemic areas, these unusual presentations may be easily overlooked, leading to delays in diagnosis and treatment (1,2).

Although the epidemiology and management of hepatic and pulmonary hydatid cysts are well documented, there is limited comprehensive data on hydatid cysts arising in non-solid organs or soft tissue structures (1,2). Most available evidence consists of isolated case reports and small series, which do not provide a clear understanding of their clinical spectrum, surgical challenges, or outcomes. Consequently, it remains arguable whether established principles derived from hepatic and pulmonary diseases can be directly applied to these atypical sites. In the current literature, the term “atypical localization” is commonly used to describe hydatid cyst involvement outside the liver and lungs, including musculoskeletal, retroperitoneal, pelvic, adrenal, and other extrahepatic sites (3,4).

This knowledge gap is significant because hydatid cysts at uncommon sites, such as the spleen, retroperitoneum, musculoskeletal system, and adnexal and adrenal regions, have been reported only sporadically, with incidence rates ranging from 0.2% to 10%, depending on the site (3,4). Rare localizations include the spleen (0.9-8%), skeleton (0.2-3%), kidneys (0.4-3.7%), brain (0.4-1%), myocardium (0.02-1.1%), peritoneum (2-5.2%), retroperitoneum (6-10%), and subcutaneous tissue (1.6%) (3,4).

These unusual cysts can mimic other pathologies, complicate operative management due to anatomical constraints, and increase the risk of recurrence (4). The lack of specific radiological findings and the rarity of the condition often make it difficult to consider in the differential diagnosis.Therefore, in any endemic region, even when hydatid cysts are located in atypical sites, a high index of suspicion should be maintained to overcome diagnostic challenges (4).

The aim of the present study is to report a 10-year single-center retrospective case series of hydatid cysts with atypical localization, focusing on their anatomical distribution, clinical features, diagnostic challenges, and surgical outcomes.

Methods

Study design and setting

The hospital records of patients who underwent surgery for hydatid cysts in the general surgery clinic were retrospectively reviewed for 10 years, from 2014 to 2024. Cases were considered hydatid cysts when pathological examination of surgically resected specimens confirmed the diagnosis postoperatively. The patients’ demographic information, clinical findings, diagnostic methods, surgical treatments, postoperative complications, hospital stay, and follow-up data were retrospectively reviewed and analyzed.

Ethical Approval

This study received approval from the Süleyman Demirel University Health Sciences Ethics Committee (approval number: 7, date: 06.01.2025). This study was conducted in accordance with the principles of the Declaration of Helsinki. Patients were not required to give their informed consent for inclusion in this retrospective study because we used anonymous clinical data and individuals cannot be identified from the presented data.

Case identification and study cohort

During the 10-year study period, all surgically treated hydatid cyst cases were reviewed, and patients with atypical localization were identified based on predefined inclusion criteria. During the study period, a total of 85 surgically treated hydatid cyst cases were reviewed. Seventy-five cases with hepatic, splenic, or pancreatic involvement were excluded; 10 cases with atypical localization constituted the final study cohort.

Inclusion criteria and definitions

Patients with pathologically confirmed hydatid cysts located outside the liver, spleen, and pancreas were included to focus on atypical localizations, as defined in the current literature.

Typical and atypical case situations were defined for this study. Typical hydatid cysts were defined as cysts involving the liver, spleen, or pancreas, whereas atypical hydatid cysts were defined as those located outside these organs.

Outcomes

The main outcomes assessed were postoperative recurrence, intraoperative and postoperative complications, and the need for reoperation.

Statistical Analysis

Descriptive statistics, including means, standard deviations, ranges, and percentages, were calculated using Microsoft Excel, and no comparative statistical analyses were performed.

Results

Patient characteristics

A total of 10 patients with atypical hydatid cyst localizations were included in the study. The mean age was 44.5±17.7 years (range: 18-74), with 8 females (80%) and 2 males (20%). The cysts were localized to musculoskeletal tissues, including the right gluteus muscle, right rectus muscle, medial thigh, left psoas muscle, and subcutaneous tissue of the anterior abdominal wall (n=5, 50%). Retroperitoneal localization was observed in three patients (n=3, 30%), including lesions at the T12-L1 vertebral level and posterior to the bladder, with or without concurrent liver involvement. Isolated involvement of the right adnexal region and right adrenal gland were identified in one patient each (n=1, 10% each). Table 1 summarizes the demographic and clinical characteristics of the patients, and Figure 1 illustrates the anatomical distribution of the cysts. Percentages are calculated based on the total number of patients with atypically localized hydatid cysts (n=10).

Clinical presentation

The clinical manifestations of atypically localized hydatid cysts were heterogeneous and primarily related to the anatomical site of involvement. The most frequent symptom was localized pain, reported in six patients (inguinal region, right upper quadrant, left upper quadrant, and epigastric region). Two patients presented with swelling and palpable masses, one in the right gluteus muscle and the other in the medial thigh. In addition, one patient presented with abdominal wall swelling and another presented with pelvic pain mimicking gynecological pathology. None of the patients had systemic symptoms such as fever or weight loss at the time of admission (Table 1).

Diagnostic imaging and surgical treatment

All patients underwent preoperative imaging via ultrasonography (USG) and/or computed tomography (CT) to evaluate cyst characteristics. The dimensions of the cysts were as follows: length: mean 6.8±3.3 cm (range: 4-15 cm), width: mean 5.05±2.1 cm (range: 2-9 cm). Cystectomy was performed on 8 patients. In 2 cases, cystotomy and drainage were performed because of anatomical complexity. Serology was positive in 9 patients and negative in 1.

Diagnostic imaging findings, cyst dimensions, radiological characteristics, retrospective World Health Organization-Informal Working Group on Echinococcosis (WHO-IWGE) classification, and recurrence patterns are summarized in Table 2. Imaging revealed heterogeneous and often indeterminate cystic appearances that depended on anatomical location, and definitive WHO-IWGE classification was possible in only a limited number of cases. In most patients, imaging findings alone were insufficient to make a confident preoperative diagnosis; the final diagnosis of hydatid disease was established intraoperatively and subsequently confirmed by histopathology.

Preoperative imaging findings were heterogeneous and varied by anatomical location. Based on a retrospective evaluation using the WHO-IWGE classification, definitive classification was possible in only 3 of 10 cases (30%): two cystic echinococcosis stage 3 lesions and one CE2 lesion. In the remaining 7 cases (70%), the imaging findings were non-specific and could not be confidently classified according to the WHO-IWGE criteria.

Several lesions demonstrated imaging characteristics overlapping with simple cysts or cystic neoplasms, including well-defined or septated cystic appearances that lacked pathognomonic features of hydatid disease. Consequently, the indication for surgery was not based on imaging findings alone. Surgical decision-making relied on a combination of clinical symptoms, endemic background, anatomical localization, serological results, and intraoperative findings. The final diagnosis of hydatid disease in these cases was established intraoperatively and confirmed by histopathological examination.

Medical treatment and follow-up

All patients received postoperative albendazole therapy at a dose of 10 mg/kg/day. Preoperative albendazole was administered in three cases. Postoperative medical treatment was prescribed according to institutional protocol for a minimum duration of three months, with treatment duration extended in selected patients based on intraoperative findings and clinical judgment. Due to the retrospective nature of the study and incomplete outpatient treatment records, the precise mean treatment duration and its range could not be reliably calculated.

The minimum follow-up was at least 24 months. Follow-up beyond this period was variable and not uniformly documented for all patients, particularly in cases treated earlier in the study period. During follow-up, two patients (20%) developed recurrence, and both required reoperation.

The first recurrence occurred in a patient who had initially undergone cystectomy for a right gluteal intramuscular hydatid cyst. Routine follow-up imaging detected recurrence 4 months after the primary surgery, revealing multiple hydatid cysts in the retroperitoneal region adjacent to the rectum and bladder. The patient underwent reoperation, and no further recurrence was observed during follow-up.

The second recurrence was observed in a patient who had previously undergone drainage and curettage for a retroperitoneal hydatid cyst located at the T12-L1 level. Two years after the initial operation, follow-up imaging identified a recurrent cyst in the same retroperitoneal region. The patient underwent reoperation with drainage and curettage; no recurrence was detected thereafter.

No mortality or serious postoperative complications were recorded during the follow-up period.

Table 1. Demographic, clinical, and surgical characteristics of patients with atypically localized hydatid cysts

Case number	Age	Gender	Presenting complaint	Surgical method	Serology	Location	Preop anthelmintic	Postop anthelmintic	Recurrent
Case 1	29	Male	Swelling over the right gluteus	Cystectomy	Positive	Right gluteus	Albendazole (10 mg/kg/day)	Albendazole (10 mg/kg/day)	Present (rectum-bladder neighborhood hydatid cyst reop)
Case 2	50	Female	Epigastric pain	Cystectomy	Negative	Right rectus muscle	None	Albendazole (10 mg/kg/day)	None
Case 3	47	Female	Pain in the Inguinal area	Cystectomy	Positive	Pelvis (left ureter-bladder)	None	Albendazole (10 mg/kg/day)	None
Case 4	50	Female	Right quadrant pain	Drainage + curettage	Positive	T12-L1 Retroperitoneum	Albendazole (10 mg/kg/day)	Albendazole (10mg/kg/day)	Present (retroperitoneum)
Case 5	74	Female	Pain in the right inguinal region	Cystectomy	Positive	Right adnexal region	None	Albendazole (10 mg/kg/day)	None
Case 6	51	Female	Pain in the right upper quadrant	Cystectomy	Positive	Liver+right adrenal	None	Albendazole (10 mg/kg/day)	None
Case 7	20	Male	Lower quadrant pain	Cystectomy	Positive	Liver+bladder posterior	None	Albendazole (10 mg/kg/day)	None
Case 8	18	Female	Swelling in the medial right thigh	Cystectomy	Positive	Right medial thigh	Albendazole (10 mg/kg/day)	Albendazole (10 mg/kg/day)	None
Case 9	62	Female	Pain in the left upper quadrant	Cystotomy + drainage + curettage	Positive	Left upper abdominal anterior wall	None	Albendazole (10 mg/kg/day)	None
Case 10	44	Female	Pain in the right upper quadrant	Cystectomy	Positive	Left psoas muscle	None	Albendazole (10 mg/kg/day)	None

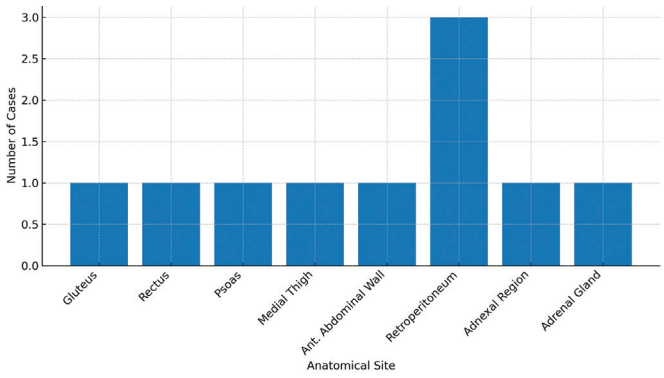

Figure 1. Anatomical distribution of atypically localized hydatid cysts

Discussion

Hydatid cyst disease most frequently involves the liver and lungs; however, atypical localizations also occur and represent significant diagnostic and therapeutic challenges. Our series supports the existing knowledge that musculoskeletal and retroperitoneal sites are among the most common atypical localizations, consistent with prior reports (4). These unusual presentations often manifest with non-specific symptoms, leading to delays in diagnosis and treatment.

Atypical localizations of hydatid cysts are rarely reported in the literature and are most often presented as case reports or small retrospective series. Although novel intraoperative diagnostic methods, such as the lipid test evaluated in the Lili-Hics trial for liver hydatid cysts (5), have been proposed, imaging modalities remain the essential and irreplaceable tools for preoperative evaluation and surgical planning in atypical localizations.

In the literature, hydatid cysts with atypical localizations are well known to present significant diagnostic challenges due to non-specific imaging findings and frequent radiological overlap with simple cysts, abscesses, or cystic neoplasms, particularly in retroperitoneal, muscular, and soft tissue locations (6,7). Several authors have emphasized that characteristic imaging features, such as daughter cysts or calcified membranes, are inconsistently observed outside the liver; definitive preoperative diagnosis is often not possible, even in endemic regions.

Consistent with these reports, imaging findings in our series were heterogeneous; retrospective WHO-IWGE classification was feasible in only 30% of cases, with the majority demonstrating non-specific cystic appearances. In line with previous case series and reviews, USG proved useful for superficial and soft tissue lesions, whereas CT and magnetic resonance imaging were essential for assessing deep-seated lesions and their relationship to adjacent anatomical structures (6,7). Our findings support existing literature demonstrating that imaging alone is frequently insufficient for definitive diagnosis of atypically localized hydatid cysts, and that surgical decision-making often relies on a combination of clinical suspicion, endemic exposure, serology, and intraoperative findings.

Due to the heterogeneity of atypical localizations and the predominance of case reports and small series in the literature, comparable quantitative data on the proportion of lesions that meet WHO-IWGE imaging criteria are not clearly defined, limiting direct numerical comparison with previously published studies.

In our study, 5 out of 10 cases [gluteus, rectus, psoas, anterior abdominal wall (subcutaneous), and medial thigh, each accounting for 1.17%] were localized in musculoskeletal soft tissue. Primary soft-tissue involvement by hydatid cysts is rare, even in endemic regions, with an incidence of approximately 0.5-4.7%. Primary muscular hydatid disease is even rarer. All 5 cases in our study were primary, with no associated liver disease. One case involved a hydatid cyst in the skin and subcutaneous tissue. Subcutaneous tissue involvement has been described in 1.5% of hydatidosis cases, with a reported range of 0.6-2.6%. In the differential diagnosis of slowly growing masses in soft tissues, solitary subcutaneous hydatid cysts should always be considered (8-10).

In our study, three cases demonstrated retroperitoneal location, including lesions that were adjacent to the ureter and bladder, posterior to the bladder, or at the T12-L1 vertebral level. In the literature, retroperitoneal hydatid cysts are reported to constitute approximately 6-16% of cases, while pelvic hydatid cysts are considerably rarer, with an incidence of around 2.25% (6,8). Bone involvement, most commonly affecting the spine, accounts for 0.5-2.5% of hydatid cyst cases (11,12). The coexistence of retroperitoneal and spinal hydatid cysts, observed in one of our patients, is consistent with these rare but recognized patterns of dissemination described in previous studies.

Notably, only two patients in our series had concomitant hepatic hydatid cysts, whereas the remaining cases represented primary extrahepatic disease. This finding contrasts with most published series, in which secondary involvement following hepatic disease predominates, and suggests a relatively higher proportion of primary atypical localizations in our cohort (3,8). Such variation may reflect the small size and selective nature of retrospective series focusing specifically on atypical presentations.

In addition, our series included hydatid cysts located in exceptionally rare sites, such as the adrenal gland and adnexal organs. These localizations are considered extraordinary and have been documented almost exclusively through isolated case reports in the literature (13,14). The presence of such rare localizations further supports the hypothesis that alternative dissemination mechanisms, including hematogenous or lymphatic spread, may play a role in the pathogenesis of primary extrahepatic hydatid disease (15,16).

Table 2. Diagnostic imaging characteristics, surgical indications, and recurrence patterns of atypically localized hydatid cysts

Case no	Imaging modality	Dimension (cm)	Imaging appearance	WHO-IWGE	Features suggestive of HC	Indication for surgery	Recurrence
Case 1	USG	5.5x3	Cystic lesion located between the gluteal muscle groups with imaging features compatible with a type 3 hydatid cyst	CE3	Positive serology, endemic area, intramuscular localization, typical hydatid fluid and germinative membrane intraoperatively	Symptomatic mass and imaging findings suspicious for hydatid cyst	Present-MRI, rectum-bladder region, CE3
Case 2	CT	5x6	Multiloculated cystic lesion within the right rectus muscle	None	Deep muscular localization, endemic area, intraoperative findings compatible with hydatid cyst, histopathology consistent with hydatid disease	Symptomatic lesion with imaging suspicion for hydatid cyst despite negative serology	None
Case 3	CT	10x9	Well-defined, septated cystic lesion in the left pelvic region (ovarian fossa), adjacent to the ureter-bladder	None	Positive serology, endemic area, pelvic localization, intraoperative findings compatible with hydatid cyst, histopathology consistent with hydatid disease	Symptomatic pelvic mass with indeterminate imaging findings, including possible cystic neoplastic pathology in the differential diagnosis	None
Case 4	CT	6x5	Well-defined mass-like cystic lesion in the right retroperitoneal paravertebral region, posterior to the kidney, with adjacent rib destruction	None	Positive serology, endemic area, retroperitoneal localization, intraoperative findings of vesicular hydatid cyst content	Symptomatic retroperitoneal lesion with indeterminate imaging findings and concern for invasive pathology	Present-CT, retroperitoneum
Case 5	CT	5x6	Septated hypodense cystic lesion in the right adnexal region, located between the bladder and uterus	None	Positive serology, endemic area, adnexal localization, imaging suspicion for hydatid cyst, intact cyst removal intraoperatively, histopathology consistent with hydatid disease	Symptomatic adnexal cystic mass with imaging findings suspicious for hydatid cyst	None
Case 6	USG	4x3	Hypoechoic lesions in the posterior segment of the right hepatic lobe with indeterminate internal structure, with concomitant cystic lesions in the right adrenal gland	None	Positive serology, endemic area, intraoperative findings of vesicular hydatid cyst content in the liver, two hydatid cysts in the right adrenal gland confirmed intraoperatively, histopathology consistent with hydatid disease	Symptomatic upper quadrant pain with indeterminate imaging findings and intraoperative confirmation of hydatid disease involving the liver and adrenal gland	None
Case 7	USG	7x5.5	Cystic lesion located posterior to the bladder with concomitant hepatic cystic lesion, with imaging features compatible with type 3 hydatid cyst	CE3	Positive serology, endemic area, pelvic localization, imaging features compatible with type 3 hydatid cyst, intraoperative findings consistent with hydatid disease, histopathology confirming hydatid cyst	Symptomatic lower quadrant pain with imaging findings compatible with hydatid cyst and involvement of both hepatic and posterior bladder regions	None

Table 2. Continued

Case no	Imaging modality	Dimension (cm)	Imaging appearance	WHO-IWGE	Features suggestive of HC	Indication for surgery	Recurrence
Case 8	USG	6x4	Hypoechoic cystic lesion located between the subcutaneous fat and muscle tissue in the medial thigh, with a small adjacent nodular cystic component	None	Positive serology, endemic area, soft tissue localization, imaging suspicion for hydatid cyst, intraoperative findings consistent with infected hydatid cyst	Symptomatic soft tissue mass with indeterminate imaging findings and suspicion of hydatid cyst	None
Case 9	USG	4.5x2	Subcutaneous cystic lesion in the left upper abdominal anterior wall with multivesicular anechoic components and a heterogeneous thick wall	CE2	Positive serology, endemic area, subcutaneous abdominal wall localization, imaging features of multivesicular cyst, intraoperative findings compatible with hydatid cyst	Symptomatic anterior abdominal wall cystic lesion with imaging findings highly suggestive of hydatid cyst	None
Case 10	CT	15x7	Large cystic lesion surrounding the left psoas muscle	None	Positive serology, endemic area, deep muscular (psoas) localization, imaging suspicion for hydatid cyst, intraoperative findings compatible with hydatid cyst	Symptomatic retroperitoneal muscular mass with indeterminate imaging findings suspicious for hydatid cyst	None

WHO-IWGE: World Health Organization-Informal Working Group on Echinococcosis, HC: Hydatid cyst, USG: Ultrasonography, CT: Computed tomography, MRI: Magnetic resonance imaging

In our study, total cyst excision was performed in 8 cases, while cystotomy and drainage were conducted in 2 cases. The gold-standard treatment for hydatid cysts is complete excision; preventing rupture and spillage during the procedure is critical. The greatest associated risk is anaphylactic shock. No surgical complications were reported in the selected cases. In one of the two cases in which total excision was not feasible, the cyst was retroperitoneal and associated with the vertebrae. In the other case, the cyst was subcutaneous. In both cases, cystotomy and drainage were performed.

In the present series, recurrence patterns differed between the two affected patients. One recurrence occurred four months after complete excision (cystectomy) of a right gluteal intramuscular hydatid cyst, manifesting as a new lesion in a different anatomical region (retroperitoneal). The second recurrence, which developed in the same anatomical location, was detected two years after an initial non-radical procedure (drainage and curettage) performed for a retroperitoneal hydatid cyst with vertebral involvement. These findings suggest that recurrence in hydatid disease may occur both as an early manifestation at a different site, despite complete excision, and as a late local recurrence following non-radical surgical approaches, particularly in anatomically complex regions. However, due to the limited number of cases and the retrospective design of the study, no definitive conclusions regarding the relationship between surgical technique and recurrence risk can be drawn.

The gold-standard drug for adjuvant therapy is albendazole, administered at a dose of 10-15 mg/kg/day for 1-6 months. In our study, 3 cases received preoperative albendazole, and all cases were treated with postoperative albendazole for a minimum of 3 months (3).

Recurrence was observed in 2 cases (20%). In one case, a hydatid cyst was identified in the retroperitoneum two years after excision of a right gluteal cyst. This was considered a recurrence because of the patient's prior history and was managed surgically. The other recurrence occurred in a case of a retroperitoneal cyst associated with the vertebrae that was initially treated with cystotomy. Notably, both cases of recurrence had received albendazole therapy preoperatively and postoperatively. In the literature, recurrence rates for hydatid disease vary widely depending on the localization of the cysts, ranging from 0% to 50% (11,17). In ruptured hepatic cysts specifically, recurrence and serious complications such as bile leakage and anaphylaxis have also been reported, supporting the need for long-term follow-up and adjuvant therapy (18).

Study Limitations

The retrospective design and the limited number of cases represent important limitations of this study. However,

these limitations are largely attributable to the inherent rarity of hydatid cysts in atypical locations. To maintain a focused and clinically meaningful cohort, splenic and pancreatic hydatid cysts, which are relatively more frequently reported after hepatic and pulmonary involvement, were deliberately excluded to emphasize truly uncommon sites.

Despite the small sample size, many of the cases included in this series represent exceptionally rare localizations, each of which could be considered noteworthy even as an individual case in the literature. The principal strength of this study lies in the systematic aggregation and comparative analysis of these rare presentations within a single cohort, providing a concise and clinically relevant overview of diagnostic challenges, surgical strategies, and outcomes in atypically localized hydatid disease.

Our findings underscore the considerable diagnostic difficulties associated with hydatid cysts in unusual anatomical locations, which are consistent with previous reports. A high index of suspicion remains essential for preoperative diagnosis, and in endemic regions, hydatid disease should be included in the differential diagnosis of cystic masses with atypical localization or indeterminate imaging features. In our practice, albendazole therapy was administered both preoperatively and postoperatively according to institutional protocol, and long-term follow-up proved critical, as recurrence may occur months to years after initial surgery. These observations highlight the importance of combined surgical and medical management and prolonged surveillance in patients with atypically localized hydatid cysts.

In the future, digital health tools and IoT-based follow-up systems may contribute to long-term surveillance and early detection of recurrence, particularly in patients with atypically localized hydatid cysts requiring prolonged monitoring (19).

Conclusion

This retrospective case series demonstrates that hydatid cysts in atypical locations have a wide anatomical distribution and may be associated with a considerable risk of postoperative recurrence, particularly when complete cyst excision cannot be achieved. Musculoskeletal and retroperitoneal localizations were the most frequently observed atypical sites. Careful preoperative evaluation and radical surgical excision, when feasible, appear to be critical in reducing recurrence and the need for reoperation. Surgeons should maintain a high index of suspicion for atypically localized hydatid cysts, especially in endemic regions, to ensure timely diagnosis and appropriate surgical management.

Ethics

Ethics Committee Approval: This study received approval from the Süleyman Demirel University Health Sciences Ethics Committee (approval number: 7, date: 06.01.2025).

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.Z.S., İ.S., Concept: B.T., Design: İ.S., B.T., S.A., Data Collection or Processing: İ.S., B.T., A.B.E., Analysis or Interpretation: B.T., İ.K., A.B.E., Literature Search: M.Z.S., S.A., İ.K., Writing: M.Z.S., İ.S., B.T., S.A., İ.K., A.B.E.

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Evaluation of multifocal intraocular lens suitability in cataract patients in a public hospital: in terms of ocular comorbidities

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ABSTRACT

Aims: No data exist in the literature regarding suitability screening for multifocal intraocular lenses (MFIOLs), which are generally not covered by health insurance in public hospitals in Türkiye. This study aims to determine the proportion of patients unsuitable for MFIOL and to identify restrictive ocular comorbidities among patients undergoing cataract surgery at a tertiary public hospital.

Methods: This retrospective observational study included patients aged 40 years and older who underwent cataract surgery at a tertiary teaching hospital during an approximately 10-month period. Patients with a monofocal intraocular lens in one eye or those without indications for bilateral cataract surgery were excluded from the study. Before surgery, patients underwent comprehensive ophthalmological examinations, optical biometry measurements, and other necessary tests. Based on these assessments, ocular comorbidities were identified. The primary endpoint was to determine and analyze the proportions and characteristics of patients who were or were not suitable for MFIOL implantation, according to indications and contraindications defined in the current literature.

Results: Of the 1476 patients evaluated in the study, 721 (48.8%, mean age 71.5±8.7 years; 55.6% female) had undergone bilateral cataract surgery. Of these, 289 patients (40.1%) were found ineligible for MFIOL implantation based on predefined contraindications. The remaining 432 patients (59.9%) were found to be eligible for MFIOL. Of the 289 patients who met ineligibility criteria for MFIOL in one or both eyes, 6 (2.1%) had ocular surface and corneal disease, 13 (4.5%) had pupil abnormalities, 80 (27.7%) had retinal disease, 25 (8.7%) had glaucoma or optic neuropathy, and 118 (40.8%) had combined causes.

Conclusions: Ocular comorbidities were identified as restrictive factors for MFIOL in 40% of patients. It appears that if MFIOLs were covered by health insurance in public hospitals, approximately two-thirds of patients could benefit from MFIOLs.

Introduction

The most common practice in cataract surgery worldwide is phacoemulsification with implantation of monofocal intraocular lenses (IOLs) (1). The main reasons for this situation are the reliability of these lenses' long-term results and their cost-effectiveness in public hospitals, in line with state health policies (1). After monofocal IOL implantation, some patients may require glasses, most commonly for reading. Multifocal IOLs (MFIOL) reduce the patient's dependence on glasses after surgery (2,3). However, unlike monofocal lenses, not every cataract patient is a suitable candidate for an MFIOL because MFIOLs have certain disadvantages. The quality of vision and distance visual acuity may not be as good as with monofocal IOLs; this may decrease contrast sensitivity and cause photic phenomena such as glare, starbursts, and halos (4,5). These may affect the patient's daily activities and professional skills after surgery. Therefore, a healthy ocular surface and absence of optic nerve and macular pathology are important before surgery. In addition, the patient's personality characteristics, daily activities, professional work life, and expectations from the surgery must be taken into consideration. These features will provide an estimate of the extent to which the patient can tolerate potential adverse effects.

If preoperative diagnostic evaluations and patient selection criteria are not taken into consideration, additional surgical interventions such as replacement of an MFIOL with a monofocal IOL may be required. Although patients are suitable for MFIOL based on examinations and tests, they may not consent to MFIOL if informed about potential risks. In public hospitals with high patient populations, MFIOLs are not routinely used due to insufficient time for these detailed evaluations and associated additional costs. If these limitations are eliminated, the widespread use of MFIOL in public hospitals will provide better results for both patients and physicians. No data regarding MFIOL suitability screening in a public hospital in Türkiye were found in the literature. This study aims to determine the proportion of patients who are suitable or unsuitable for MFIOL implantation in a public hospital and to identify ocular comorbidities that render patients unsuitable.

Methods

Study design and participants

This retrospective observational study evaluated data from patients aged 40 and over who underwent cataract surgery at a tertiary teaching hospital between May 2024 and February 2025. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the University of Health Sciences Türkiye, Gülhane Scientific Research Ethics Committee (approval no: 2025-194, date: 08.04.2025). This study included all patients aged 40 and over who underwent cataract surgery between the specified dates and had comprehensive ophthalmological examinations and tests as part of preoperative preparation. Patients with incomplete examination data, those with a monofocal IOL in one eye, or those without an indication for bilateral cataract surgery were excluded from the study.

Data collection

The data analyzed in this study were obtained from patient files and the electronic medical record system. Patients' systemic and ocular medical histories were evaluated. Each patient underwent a comprehensive eye examination, including visual acuity (uncorrected and best- corrected), slit-lamp biomicroscopy, dilated fundus examination, and applanation tonometry. These comprehensive examinations were performed by three experienced physicians (ACY, BAÇİ, and OA). The reliability of the data was ensured by all three physicians, who confirmed the examinations and diagnoses. Spectralis optical coherence tomography (OCT, Heidelberg Engineering, Heidelberg, Germany) of the macula and optic nerve was used to examine the patients, primarily for macular disease, vitreomacular interface diseases, and glaucoma. Visual field examination was performed with the Humphrey Field Analyzer (Humphrey Field Analyzer; Carl Zeiss Meditec, Inc., Dublin, CA, USA) in patients who required evaluation for glaucoma and optic neuropathies. Corneal topography with the Pentacam high resolution (Oculus Optikgeräte GmbH, Wetzlar, Germany) was performed on patients with a history of refractive surgery or suspected ectatic disease. The IOL Master 500 (Carl Zeiss Meditec AG, Germany) was used to obtain biometric measurements (keratometric values, corneal astigmatism, anterior chamber depth, and axial length) and to calculate IOL power. The following criteria were defined for severe dry eye: tear break-up time <10 seconds, tear meniscus height <0.1 mm, and Schirmer test score <5 mm. Keratometric measurements from corneal topography and corneal thickness measurements were evaluated for evidence of corneal ectasia and prior refractive surgery. Under normal lighting conditions, pupils with a diameter less than 2.5 mm were defined as small. Thinning of the nerve fiber layer and visual field defects consistent with pathology were used to diagnose optic nerve diseases. Corneal opacity, zonular weakness, diabetic retinopathy, strabismus, and other pathologies considered unsuitable for MFIOL were diagnosed based on clinical observation. A guideline study has been published that provides a comprehensive overview of best clinical practices for the selection and use of MFIOLs and sets out patient eligibility criteria for MFIOL (6). In accordance with this guideline, the contraindications for MFIOL implantation used to identify suitable and unsuitable groups in this study are summarized in Table 1.

Table 1. Established contraindications for MFIOL implantation
Ocular surface disease (severe dry eye), corneal disease (opacity, ectasia, dystrophy, etc.)
History of refractive surgery, irregular astigmatism
Pupil issues (small pupil, ectopic pupil, iris coloboma, etc.)
Zonular issues (zonular weakness, pseudoexfoliation, trauma, etc.)
Impaired fundus visualization (due to advanced cataract, vitreous degeneration, or hemorrhage)
Retinal disease (diabetic retinopathy, retinal vascular occlusion, AMD, vitreomacular interface diseases, retinal dystrophies, etc.)
Optic nerve disease (glaucoma, optic neuropathies)
Strabismus/amblyopia
Combined
Other (uncertain biometric measurements, etc.)
MFIOL: Multifocal intraocular lens, AMD: Age-related macular degeneration

Statistical Analysis

IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY) was used for data analysis. Quantitative variables were defined as mean ± standard deviation, and qualitative variables as numbers and percentages (%). Normality of the continuous variables was assessed using the Kolmogorov-Smirnov test and Skewness and Kurtosis values. Based on these results, the data were considered normally distributed. To compare the characteristics of suitable and unsuitable candidates for MFIOL implantation, the chi-square test was applied to qualitative variables, and the t-test was applied to quantitative variables. A p-value of 0.05 or less was considered statistically significant.

Results

Demographic and clinical characteristics

The study evaluated 1476 patients who underwent cataract surgery during the study period. Seven hundred and fifty-five patients (51.2%) were excluded from the study because they had a monofocal IOL in one eye or lacked an indication for bilateral cataract surgery.

Data from 721 patients (48.8%) who underwent bilateral cataract surgery were analyzed. The mean age of these patients was 71.5±8.7 years (range 40-93 years, 55.6% female). Four hundred and thirty-two patients (59.9%) were evaluated as suitable candidates for bilateral implantation of MFIOLs. It was observed that patients who were suitable candidates for MFIOL were younger than those who were not suitable candidates (70.2±8.1 years vs. 72.1±8.9 years, p<0.001). Five hundred eighty-eight patients were ≥65 years of age. Only 277 (47.1%) of the patients in this age group were considered suitable candidates for MFIOL implantation. In contrast, 52 of 133 patients (39.0%) who were <65 years of age were considered good candidates for MFIOL implantation. No significant difference was observed between the suitable and unsuitable groups in terms of gender. Table 2 shows the demographic and clinical characteristics of candidates who were suitable for MFIOL and those who were not.

Main outcomes

Two hundred and eighty-nine patients (40.1%) had contraindications to MFIOL implantation, as shown in Table 1. The flowchart showing the study population is presented in Figure 1. Of the 289 patients with ineligibility criteria for MFIOL in one or both eyes, 6 (2.1%) had ocular surface and corneal disease, 13 (4.5%) had pupil abnormalities, 80 (27.7%) had retinal disease, 25 (8.7%) had glaucoma or optic neuropathy, and 118 (40.8%) had combined causes. Of the six corneal diseases, two were due to corneal opacity, and one each was due to severe dry eye, keratoconus, and map-dot fingerprint dystrophy; the remaining one occurred in a corneal transplant patient. Of the 80 patients with retinal disease, 33 (41.2%) had age-related macular degeneration (AMD), 22 (27.5%) had diabetic retinopathy, 17 (21.2%) had vitreomacular interface disease, 4 (5.0%) had degenerative myopia, 3 (3.7%) had retinal vascular occlusion, and 1 had retinitis pigmentosa. The distribution of reasons for unsuitability for MFIOL implantation is shown in Table 3.

Discussion

This study showed that 40.1% of patients who underwent bilateral cataract surgery at a tertiary state hospital over a period of approximately ten months had ocular comorbidities that prevented MFIOL implantation. Among ocular comorbidities, retinal diseases were the most frequent, accounting for 27.7%.

Of the patients who underwent bilateral cataract surgery, 59.9% were considered suitable for MFIOL implantation with respect to ocular comorbidities. While Halkiadakis et al. (7) reported this rate as 60.7% in their study evaluating 1200 patients, Deshpande et al. (8), who included 1691 patients, found this rate as 54.4%. The results showed that more than half of the patients were suitable for MFIOL. However, these ratios need to be interpreted carefully. This is because Halkiadakis et

Table 2. Demographic and clinical characteristics of suitable and unsuitable candidates for MFIOL implantation

	Suitable candidates (n=432)	Unsuitable candidates (n=289)	p
Age (years)			
Mean	70.2±8.1	72.1±8.9	**<0.001**
Range of ages	45 to 88	40 to 93	
Male, n (%)	110 (25.5)	210 (72.7)	0.015
Corneal astigmatism (D)			
Mean corneal astigmatism	0.57±0.24	1.20±0.86	**<0.001**
Range of corneal astigmatism	0.09 to 1.00	0.09 to 8.75	
Mean K1	43.44±1.61	43.35±1.77	0.36
Mean K2	44.01±1.64	44.54±1.87	**<0.001**
Anterior chamber depth (mm)	3.11±0.38	3.04±0.41	0.25
Axial length (mm)	23.47±0.94	23.41±1.12	0.34
IOL power (D)	21.08±2.21	20.98±2.82	0.46
Intraocular pressure (mmHg)	15.1±1.9	15.4±2.6	0.24

Data are presented as numbers and percentages, means, and standard deviations
Significant p-values are shown in bold
K1: Flat keratometry, K2: Steep keratometry, D: Diopter, IOL: Intraocular lens, MFIOL: Multifocal intraocular lens

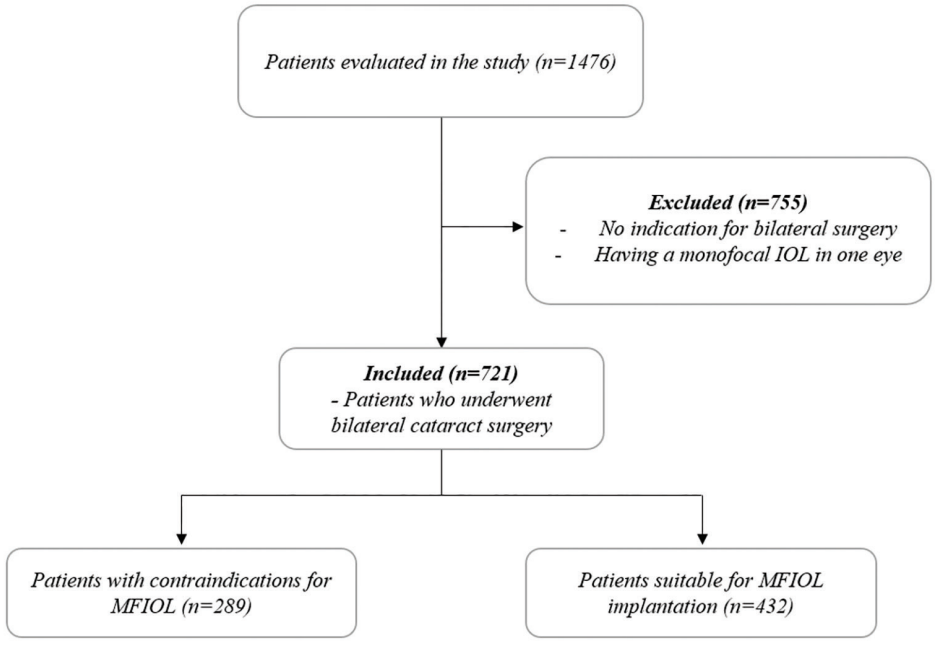

Figure 1. Flowchart showing the distribution of the study population
MFIOL: Multifocal intraocular lens, IOL: Intraocular lens

al. (7) used the same inclusion and exclusion criteria as in the present study. In addition, the mean age, which is closely related to ocular comorbidities, was quite similar to that of the present study (73.4±8). However, Deshpande et al. (8), when evaluating ineligibility for MFIOL, considered parameters such as angle kappa and personality traits, unlike the present study.

Ocular comorbidity is one of the main conditions that limit MFIOL implantation. According to the results of this study, 40% of the patients had an ocular disease in addition to cataract in one or both eyes. Pham et al. (9) reported an ocular comorbidity rate of 40% in 653 eyes that underwent cataract surgery, similar to this study. In the Auckland Cataract Study, this rate was found to be 26% in patients who underwent cataract surgery (10).

In the present study, the most common contraindication for MFIOL implantation was retinal pathology, which constituted the sole contraindication in 80 of 721 patients (11.1%). A comprehensive review of data collected by the Swedish National Cataract Registry, which includes data on more than 2.4 million cataract surgeries between 1992 and 2021, showed that more than 20% of patients had macular disease or diabetic retinopathy (11).

Table 3. Distribution of reasons for not being suitable for MFIOL implantation

	n (%)
Ocular surface disease (severe dry eye), corneal disease (opacity, ectasia, dystrophy, etc.)	6 (2.1)
History of refractive surgery, irregular astigmatism	3 (1)
Pupil issues (small pupil, ectopic pupil, iris coloboma, etc.)	13 (4.5)
Zonular issues (zonular weakness, pseudoexfoliation, trauma etc.)	3 (1)
Impaired fundus visualization (due to advanced cataract, vitreous degeneration, or hemorrhage)	30 (10.3)
Retinal disease (diabetic retinopathy, retinal vascular occlusion, AMD, vitreomacular interface diseases, retinal dystrophies etc.)	80 (27.7)
Optic nerve disease (glaucoma, optic neuropathies)	25 (8.7)
Strabismus/amblyopia	1 (0.03)
Combined	118 (40.8)
Other (uncertain biometric measurements, etc.)	10 (3.4)
Total	**289**

MFIOL: Multifocal intraocular lens, AMD: Age-related macular degeneration

In the current study, 41.2% of patients had AMD, 27.5% had diabetic retinopathy, and 21.2% had vitreomacular interface disease. Retinal pathology affects contrast sensitivity in these patients and makes fundus imaging difficult during vitreoretinal surgery (12,13). This situation can pose significant challenges for the surgeon due to the multiple images that may emerge.

Thirteen patients were not considered suitable candidates for MFIOL because of small pupils or an iris coloboma. Pupil size and shape are important in terms of potential dysphotopsia complaints (14). Pathologies such as iris colobomas and eccentric pupils may cause dysfunction of MFIOLs and therefore should be considered absolute contraindications (6).

In this study, one patient was not considered a suitable candidate for MFIOL because of a history of penetrating keratoplasty; two patients had corneal opacity, one had severe dry eye, one had keratoconus, one had map-dot-fingerprint dystrophy, and three patients had a history of refractive surgery. Keratoconus and forme fruste keratoconus are considered contraindications for MFIOL implantation because they are associated with coma (15,16).

Three patients were excluded as MFIOL candidates due to zonular weakness. The success of MFIOLs depends on proper implantation and centration. When the MFIOL is decentered or tilted, decreased contrast sensitivity, aberrations, and decreased visual acuity may occur (17). There are also different views that argue that mild zonular weakness is not a definite contraindication, regardless of etiology (6,18).

8.7% of patients were considered unsuitable candidates due to glaucoma or other optic neuropathies. Any optic nerve pathology that restricts visual acuity, contrast sensitivity, color perception, or field of view should be considered a contraindication to MFIOLs (6). Therefore, preoperative optic nerve evaluation with OCT and, if necessary, automated perimetry visual-field testing, may also identify patients with undiagnosed glaucoma. A significant proportion of patients in this study were unaware they had glaucoma. In some studies, the prevalence of undiagnosed glaucoma has been reported as high as 50% (19).

In this study, patients who did not have an indication for bilateral cataract surgery or who had previously undergone cataract surgery in one eye with implantation of a monofocal IOL were excluded. Some reduction in contrast sensitivity is expected with MFIOLs, and binocular implantation is advocated for improved visual quality and satisfaction (6). There are studies that argue that bilateral MFIOL implantation has a significant benefit in terms of improving binocular visual acuity, and that this effect is evident at all distances (20).

A key finding of the current study is that age is the main factor differentiating suitable from unsuitable candidates for MFIOL. This was, in fact, predictable as the frequency of comorbidities increases with age. These findings support the idea that younger patients achieve better visual gains after cataract surgery compared to older patients (21).

Study Limitations

This study has some limitations. The study, being single-center and including patients with specific demographic and socioeconomic characteristics, may limit the generalizability of the results. We had no data on how many of the technically suitable candidates for MFIOL would consent to undergo implantation when the potential risks were explained. Due to its retrospective design, some parameters not routinely evaluated before cataract surgery but important for MFIOL suitability (such as corneal aberrations, pupil size, and angle kappa) were not analyzed. This situation may have led to an overestimation of the proportion of suitable candidates for MFIOL implantation. In a public hospital setting with a high patient volume, factors that may

make a patient an unsuitable candidate for MFIOL (personality traits, daily activities, expectations from surgery, etc.) were not evaluated. The strength of this study lies in reporting results from a large series of patients at a public hospital in Türkiye that performs a high volume of cataract surgeries.

Conclusion

This study demonstrated the frequency of contraindications to MFIOL implantation due to ocular comorbidities in the Turkish population at a tertiary public hospital. This study also provides insight into the proportion of patients who could benefit from the inclusion of MFIOLs in health insurance coverage at public hospitals.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the University of Health Sciences Türkiye, Gülhane Scientific Research Ethics Committee (approval no: 2025-194, date: 08.04.2025).

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

Author Contributions

Surgical and Medical Practices: A.C.Y., B.A.Ç.İ., O.A., F.M.M., Concept: A.C.Y., O.A., F.M.M., Design: A.C.Y., O.A., Data Collection or Processing: A.C.Y., B.A.Ç.İ., Analysis or Interpretation: A.C.Y., O.A., F.M.M., Literature Search: A.C.Y., B.A.Ç.İ., Writing: A.C.Y.

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Impact of diabetes-related knowledge, attitudes, and practices and other factors on glycemic control in type 2 diabetes patients in Southern Iraq

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ABSTRACT

Aims: The prevalence of type 2 diabetes (T2D) has increased significantly in Iraq, making it critical to understand knowledge, attitudes, and practices (KAP) to improve diabetes management and health outcomes. This study explores the impact of KAP and other factors on glycemic control among T2D patients in Southern Iraq.

Methods: A cross-sectional study was conducted among patients with T2D, aged 18-64 years, excluding those with type 1 diabetes, gestational diabetes, or severe conditions such as cancer or kidney failure. Their KAP was assessed using a validated and reliable questionnaire.

Results: A total of 390 patients (163 males and 227 females), with a mean age of 48.5±13.0 years, were included in the study. The findings revealed moderate levels of knowledge (63.4%) and practices (58.2%), while attitudes towards diabetes management were notably negative (40.7%). Key predictors of glycated hemoglobin (HbA1c) included body mass index, diabetes knowledge, gender, marital status, family history, duration of diabetes, blood pressure, employment status, education level, and comorbidities, which collectively explained 37% of the variance in HbA1c levels [adjusted R^2=0.37, $F(11, 389)$=17.645, $p<0.001$].

Conclusions: This study found that T2D patients in Southern Iraq have moderate knowledge and practices, but poor attitudes toward diabetes management. Sociodemographic and clinical factors significantly affect glycemic control, indicating a need for targeted education and improved diabetes care programs to enhance patient outcomes.

Introduction

Type 2 diabetes (T2D) has become a critical global health worry, affecting millions and contributing to a significant burden of morbidity and mortality (1). The prevalence of T2D in the Middle East and North Africa in 2021 and 2045 was 16.2% and 19.3%, respectively (2). Iraq is experiencing a diabetes mellitus epidemic, with a prevalence of around 20% (3). This figure has increased approximately fourfold over the past four decades and is expected to keep rising (4). Poor glycemic control (86.2%) was indicated in studies among T2D patients in Basrah, Iraq (5-7).

Healthcare providers provide medical care, but patients with diabetes are responsible for day-to-day diabetes management (8). Non-adherence to self-management practices is a significant cause of poor glycemic control among T2D patients

(9). Most non-adherent individuals have inadequate knowledge, attitudes, and practices (KAP) regarding diabetes management (10). It is considered a significant obstacle in diabetes management (11). The outcomes of diabetes are influenced by patients' KAP and the effectiveness of their self-management (11). Most studies have used blood glucose levels and KAP measurements to evaluate diabetes management (12,13). Understanding KAP regarding glycemic control and diabetes management can provide valuable insights for developing effective preventive and treatment strategies for patients (13).

So far, only one study has examined KAP concerning hospital care and self-management among patients with T2D in Baghdad with a small sample size (14), and none has been conducted in Basrah. Only one tool was developed in Basrah, Iraq (15), and implemented in only one educational program in the same region (7). These studies lacked a valid and reliable questionnaire, which is crucial for a country of such size. Therefore, developing a valid and reliable questionnaire to explore KAP related to hospital care and self-management, and to assess their relationship to glycemic control, could help identify underlying barriers to poor glycemic control. This study investigates the impact of diabetes-related KAP and other factors, including anthropometric, sociodemographic, and medical factors, on glycemic control among T2D patients in Southern Iraq.

Methods

Study design, setting and participants

This descriptive-analytical cross-sectional study was conducted between February and August 2024 among patients with T2D at the Faiha Specialized Diabetes, Endocrine, and Metabolism Center (FDEMC) in Basrah, Southern Iraq. FDEMC receives patients with T2D from across the governorate on weekdays (Sunday-Thursday). FDEMC is recognized as the first major diabetes center in Basrah. It is a well-known medical center, distinguished by its primary laboratories and advanced equipment for essential investigations. These specifications made it suitable for this study. Patients aged 18 to 64 years with a confirmed diagnosis of T2D who attended FDEMC during the study period were eligible for inclusion. Patients were excluded if they had type 1 diabetes; had gestational diabetes or were pregnant; exhibited thyroid dysfunction; were receiving cortisol treatment; had severe conditions, such as cancer or renal failure; or were unable to provide informed consent.

Sample size and sampling procedure

The sample size was calculated using a formula from a cross-sectional study by Daniel (16), based on the prevalence of T2D in Basrah, reported at 19.7% among patients with T2D (17), as follows:

$$n = (Z1 - a/2)\, 2\, p\, (1 - p)/d^2$$

With a 95% confidence level and a 20% dropout rate (16), at least 390 patients were to be recruited for the study. Patients were selected from the hospital registry using systematic random sampling. Based on an average of 100 daily visits to the FDEMC, we recruited 10 patients per day during routine visits. To ensure randomness, we established a random starting point using SPSS version 25 and then selected every seventh patient from the daily visit list. This period was calculated by dividing the average daily patient count (100) by the required daily sample size.

Data collection

Data were collected using an adapted questionnaire to assess KAP related to diabetes management. Information was gathered from all patients attending routine visits at FDEMC. Data collection involved one-on-one interviews lasting approximately 10 minutes in a private room. The most recent anthropometric and biochemical data were obtained from the patient's medical records. Illiterate patients received assistance through verbal administration of the questionnaire, and their responses were recorded.

Study instrument and measurements

This study used a questionnaire that contained five sections: socio-demographic characteristics, medical characteristics, anthropometry, glycemic and biochemical data, and the KAP study scale. The socio-demographic data, encompassing age, gender, marital status, educational attainment, employment status, and monthly household income, were collected using a standardized questionnaire. Information on the duration of T2D, familial history, and comorbidities was extracted from medical records.

Patients' body weight and height were measured using a standardized method. Weight was measured using a calibrated digital scale (SECA, British Indicators, London, U.K.) and recorded to the nearest 0.1 kg. Patients were instructed to wear light clothing and to remove shoes, watches, wallets, jewelry, and other accessories that might affect measurement accuracy. Height was measured without footwear using a height scale (SECA; British Indicators Ltd., London, U.K.) and recorded to the nearest 0.1 cm. The patients positioned themselves upright on the audiometer's floorboard, aligning their backs with the vertical backboard. Body weight and height were used to compute body mass index (BMI). The patient's blood pressure readings and the most recent blood test results for glycated hemoglobin (HbA1c), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, and triglycerides were collected from the patient's medical records. The guidelines provided by the American Diabetes Association (1) establish the ideal ranges.

The KAP study questionnaire is a key component of the study tool and was adapted from previous research (13,14).

The researcher implemented modifications in collaboration with endocrinologists at FDEMC. Permission to use the questionnaire was obtained from the corresponding author via email. Four dietitians and six endocrinologists reviewed the draft questionnaire for content validity. To address language barriers, a qualified bilingual translator translated the questionnaire from English into Arabic, and the Arabic version was used for data collection. The questionnaire was pilot-tested for face validity among fifteen diabetic patients who were not part of the study population. Three endocrinology consultants confirmed its validity.

The KAP study questionnaire has three main parts, as shown in Table 1.

Validity and reliability

The content validity ratio (CVR) is calculated as CVR=(n_e-N/2)/(N/2), where n_e is the number of experts who consider an item essential, and N is the total number of experts. This method entails subtracting half the number of experts from the total number of "essential" ratings for each item, then dividing the result by half the number of experts (18). The CVR is a suitable statistical method for assessing the validity of individual items in the instrument, using evaluations provided by a panel of content experts. The content validity index (CVI) quantifies the mean CVR across all items in the instrument. CVR and CVI provide researchers and consumers with a quantitative assessment of the validity of a simulation evaluation instrument (18).

In this study, the CVR values had a minimum of 0.92, indicating that more than half of the experts agreed on the essentiality of each item. Four dietitians and six endocrinologists assessed the questionnaire items for necessity, relevance, clarity, and simplicity and measured the CVR, R-CVI, C-CVI, and S-CVI. According to Lawshe's table, a significance level of 0.75 was used (19). All items exhibited CVR or CVI values equal to or exceeding 0.75. All items exhibited CVR and CVI values of at least 0.75.

Ethical considerations

The study was conducted in accordance with the Medical Research Ethics guidelines outlined in the Helsinki Declaration. The ethics committee for this study was approved by the Falha Specialized Diabetes Endocrine and Metabolism Center (approval no: FDEMC/56/35/22, date: 02.11.2023). Informed consent was obtained from the patients.

Statistical analysis

The data analyses were conducted using IBM SPSS Statistics (version 25), developed by IBM Corporation, based in Armonk, New York, USA. The significance level is established at $p<0.05$. Continuous variables are presented as means and standard deviations, whereas categorical variables are presented as percentages and frequencies. Data normality was assessed using the Kolmogorov-Smirnov test. Patients were categorized by sex, and mean differences for continuous variables were analyzed using one-way analysis of variance (ANOVA). Pearson's chi-square test or Fisher's exact test was used for categorical data, and Phi and Cramer's V were applied to nominal data. Tukey's post-hoc test was used to examine differences among several groups. The Pearson correlation coefficient was employed to evaluate the relationship between continuous variables. Categorical variables were converted to dichotomous (0.1) values and subsequently used to compute Pearson correlation coefficients.

The relationship between diabetes knowledge, as measured by KAP scores, and glycemic control was analyzed using a stepwise multiple linear regression. Variables were included in the models if their p-values were <0.20 in the bivariate analysis. In the multiple linear regression analyses, variables were categorized to ensure that all relevant categories were included in the predictive models. Categorical variables with two categories were coded using dummy coding; for example, sex was coded as 1 for males and 0 for females. For variables with more than two levels, such as marital status, we created a dichotomous variable: 1 for married (the reference category) and 0 for all other statuses. A 95% confidence interval was established.

Results

Three hundred and ninety patients with T2D, with a mean age of 48.5±13.0 years, were evaluated (163 males and 227 females). More than 80% of them were married and lived in urban areas. Homemakers constituted the majority (53.6%), and 27.7% had a primary school education. About 55% of patients have both a family history of diabetes and comorbidities. The duration of T2D was 5-9 years in 41.3% of cases. Of the patients, 128 (32.8%) were classified as class 1 obese (BMI 30.0-34.9 kg/m^2), representing the largest subgroup. Regarding glycemic control, 312 patients (80.0%) had poor control (HbA1c >7.0%).

Table 1. Structure and scoring of the KAP questionnaire

Section	Number of items	Question format	Scoring range	Score calculation	Categorization (%)
Knowledge	10	Multiple choice, yes/no	0-20	(Score/20)×100%	Low: <50, moderate: 50-75, high: 76-100
Attitudes	10	Likert-like (-1, 0, +1)	-10 to +10	[(Score+10)/20]×100%	Negative: <50, neutral: 50-75, positive: 76-100
Practices	10	Multiple choice, yes/no	0-20	(Score/20)×100%	Poor: <50, moderate: 50-75, good: 76-100

KAP: Knowledge, attitudes, practices

Lipid profiles that include serum cholesterol, LDL, high-density lipoprotein, and triglycerides were 177.3±44.5, 119.5±73.7, 40.6±14.7, and 198.7±138.9 mg/dL, respectively. Systolic and diastolic pressures were within the normal range. All factors differed significantly between males and females ($p<0.05$), except comorbidities, body mass index, serum cholesterol, LDL, and systolic blood pressure (Table 2).

Table 3 shows highly significant differences in glycemic control by sex and by family history of T2D ($p<0.001$) ($t=-3.8$ and -5.7, respectively). The variance ratio between socio-demographic factors and HbA1c% was highly significant ($p<0.001$); the socio-demographic factors included marital status, education, and occupation ($F=10.0$, 4.4, and 5.7, respectively). Significant negative correlations were observed between HbA1c% and age, BMI, and systolic blood pressure ($r=-0.144$, -0.330, and -0.087, respectively; $p<0.05$). At the same time, LDL and triglycerides were positively and significantly correlated with HbA1c% ($r>0.152$ and $r>0.113$, respectively; $p<0.05$).

Table 4 shows that the mean scores for KAP were 63.4±8.9, 40.7±18.9, and 58.2±18.9, respectively, indicating that patients had moderate knowledge, negative attitudes, and moderate practices. A positive correlation between knowledge scores and HbA1c levels was observed ($r=0.214$, $p=0.032$), indicating that higher diabetes knowledge was associated with poorer glycemic control, which is counterintuitive. The attitude score was significantly negatively correlated with HbA1c ($r=-0.159$, $p=0.032$). In a one-way ANOVA, the F ratio shows significant differences between HbA1c and KAP scores ($p<0.001$).

Table 5 displays the factors (predictors) that significantly predicted the HbA1c levels, including BMI, knowledge, female, married, no family history of diabetes, long duration of diabetes (≥10 years), diastolic blood pressure, employed, university or above, preparatory school, and comorbidities (adjusted $R^2=0.37$, $F(11, 389)=17.645$, $p<0.001$). These variables accounted for 37% of the variability in HbA1c in this study. In the model, BMI was positively associated with HbA1c levels. For every 1-unit increase in BMI, HbA1c increased by 0.25% ($\beta=0.25$, 95% confidence interval: 0.18-0.32, $p<0.001$), indicating that higher BMI is associated with poorer glycemic control.

Discussion

The finding that the average knowledge of diabetes management among Iraqi patients is 63.4% suggests that this population has a relatively good understanding of diabetes compared with many other countries. This level is significantly higher than those reported in studies in Jordan (53.3%) (20) and Saudi Arabia (37.6%) (21). Differences in diabetes knowledge may stem from factors such as healthcare quality, access to education, and cultural attitudes. In Iraq, higher educational attainment may result from improved healthcare services, better educational resources, and public health initiatives focused on diabetes awareness.

The comparability of Iraqi patients' knowledge to that of populations in Saudi Arabia (57%) (22) suggests a regional trend in which certain Middle Eastern and North African countries may be more proactive in diabetes education and management. It could reflect national health policies that prioritize non-communicable diseases, including diabetes, and invest in health promotion activities that empower patients with knowledge. A 2021 study (7) showed that patients in Iraq improved their diabetes knowledge from an average score of 50.3% before an educational program to 71.4% afterwards.

The results indicate a significant positive correlation between knowledge scores and HbA1c levels in this study, aligning with Saudi Arabia's findings (23). Although this may seem counterintuitive, it can be explained by several factors not covered by our model. First, patients with poor glycemic control may actively seek more information about diabetes, resulting in reverse causality. Second, factors such as health awareness (the ability to apply knowledge), depression, medication adherence, and access to healthcare resources, none of which were measured in this study, may mediate or confound the relationship between knowledge and glycemic control. Third, knowledge alone may not be sufficient to effect behavioral change without corresponding improvements in attitudes, self-efficacy, and practical skills. Future studies should incorporate these psychosocial and healthcare access variables to better understand the pathways linking knowledge to glycemic outcomes.

The results of this study indicate that 40.7% of patients exhibit negative attitudes toward diabetes management. This percentage is notably higher than that observed in studies from Saudi Arabia (30.9%) (21). One potential reason for this discrepancy could be differences in study settings. Attitudes toward diabetes as an incurable or inevitable condition can contribute to feelings of hopelessness regarding treatment. Furthermore, the burden of daily self-management tasks, including dietary restrictions, medication adherence, and blood sugar monitoring, can cause frustration and exhaustion, especially given the limited educational and support services available to people with diabetes in Iraq.

The overall diabetes management practices among patients in this study were 58.2%, indicating good practice. The 58.2% rate in Iraq is comparable to that of nearby countries, such as Iran (52.2%) (24). To understand diabetes management in a region, the following key points should be considered. Similar cultural and healthcare factors influence management. Improved access to diabetes education and healthcare can lead to more effective diabetes management. Programs that raise awareness and improve facilities help patients manage their condition.

Table 2. Socio-demographic, anthropometric, and medical characteristics of patients (n=390)				
Variables	**Males (n=163)**	**Females (n=227)**	**Total (n=390)**	**p-value**
Age (years), mean ± SD	52.3±11.609	45.6±13.2	48.5±13.0	**<0.001**[a]
Body mass index (kg/m²), mean ± SD	31.4±7.2	32.8±6.7	32.2±6.9	0.834[a]
HbA1c, %, (Mmol/mol), mean ± SD	8.7±2.0 (72.2±22.3)	9.6±2.2 (81.3±23.7)	9.2±2.2 (77.5±23.5)	**0.018**[a]
Cholesterol (mg/dL), mean ± SD	181.0±38.8	174.6±48.1	177.3±44.5	0.081[a]
LDL (mg/dL), mean ± SD	110.2±41.9	126.2±89.3	119.5±73.7	0.398[a]
HDL (mg/dL), mean ± SD	37.5±12.8	42.8±15.6	40.6±14.7	**<0.001**[a]
Triglyceride (mg/dL), mean ± SD	210.5±174.2	190.2±106.3	198.7±138.9	0.058[a]
Systolic blood pressure (mg/dL), mean ± SD	133.7±26.3	135.7±17.8	134.8±21.8	0.441[a]
Diastolic blood pressure (mg/dL), mean ± SD	81.8±11.1	79.3±9.5	80.3±10.3	**0.002**[a]
Monthly income (USD), mean ± SD	418.9±184.0	540.4±184.1	489.6±193.4	**<0.001**[a]
Residence, n (%)				
Urban	158 (40.5)	188 (48.2)	346 (88.7)	**<0.001**[b]
Rural	5 (1.3)	39 (10.0)	44 (11.3)	
Marital status, n (%)				
Single	20 (5.1)	30 (7.7)	50 (12.8)	
Married	128 (32.8)	187 (47.9)	315 (80.8)	**<0.001**[b]
Divorced	15 (3.8)	0 (0.0)	15 (3.8)	
Widowed (widower)	0 (0.0)	10 (100.0)	10 (100.0)	
Education, n (%)				
Illiterate	10 (2.6)	60 (15.4)	70 (17.9)	
Read and write	50 (12.8)	27 (6.9)	77 (19.7)	
Primary	44 (11.3)	64 (16.4)	108 (27.7)	**<0.001**[b]
Intermediate	30 (7.7)	52 (13.3)	82 (21.0)	
Preparatory	10 (2.6)	19 (4.9)	29 (7.4)	
University or above	19 (4.9)	5 (1.3)	24 (6.2)	
Occupation, n (%)				
Employed	35 (9.0)	9 (2.3)	44 (11.3)	
Retired	25 (6.4)	5 (1.3)	30 (7.7)	**<0.001**[b]
Free job	93(23.8)	14 (3.6)	107 (27.4)	
House wife	10 (2.6)	199 (51.0)	209 (53.6)	
Family history of diabetes, n (%)				
Yes	78 (20.0)	139 (35.6)	217 (55.6)	**0.001**[b]
No	80 (20.5)	88 (22.6)	168 (43.1)	
Time since diagnosis in years, n (%)				
0-4	54 (13.8)	49 (12.6)	103 (26.4)	
5-9	59 (15.1)	102 (26.2)	161 (41.3)	**0.033**[b]
10 and above	50 (12.8)	76 (19.5)	126 (32.3)	
Comorbidities, n (%)				
Yes	95 (24.4)	123 (31.5)	218 (55.9)	0.469[b]
No	68 (17.4)	104 (26.7)	172 (44.1)	

[a]: Independent samples test, [b]: Pearson chi-square, N (%): Data are presented as number and percentage, the bold p-values is significant at the 0.05 level
SD: Standard deviation, HbA1c: Glycated hemoglobin, mmol/mol: millimoles per mole, LDL: Low-density lipoprotein, USD: United States dollar, HDL: High-density lipoprotein

Table 3. Socio-demographic and medical characteristics associated with HbA1c (n=390)

Variables	HbA1c, mean ± SD%, (mmol/mol)	t-test	p-value
Sex		-3.8	**<0.001**
Males	8.7±2.0 (72.2±22.3)		
Females	9.6±2.2 (81.3±23.7)		
Residence		0.682	0.496
Urban	9.2±2.3 (77.7±24.5)		
Rural	9.0±1.2 (75.4±13.7)		
Family history of DM		-5.7	**<0.001**
Yes	8.7±2.0 (71.7±22.7)		
No	9.9±2.2 (85.1±22.8)		
Comorbidities		-1.4	0.142
Yes	9.1±2.0 (76.1±22.1)		
No	9.4±2.4 (79.2±25.2)		
Variables	**HbA1c, mean ± SD %, (mmol/mol)**	**F-ratio**	**p-value**
Marital status		10.0	**<0.001**
Single	10.6±1.8 (92.7±20.1)		
Married	8.9±2.2 (74.5±23.2)		
Divorced	9.2±2.2 (77.7±24.1)		
Widowed (widower)	10.8±1.2 (94.5±13.8)		
Education		4.4	**<0.001**
İlliterate	9.6±2.2 (80.4±20.0)		
Read and write	9.0±2.1 (75.7±23.2)		
Primary	8.6±2.1 (71.4±22.1)		
İntermediate	10.0±1.6 (86.3±25.9)		
Preparatory	9.2±2.2 (77.8±17.7)		
University or above	8.6±2.6 (71.4±29.4)		
Occupation		5.7	**<0.001**
Employed	9.0±1.7 (74.9±19.4)		
Retired	8.8±2.3 (73.2±25.8)		
Free job	8.6±2.0 (71.2±22.9)		
Housewife	9.6±2.0 (81.8±23.6)		
Time since diagnosis		1.6	0.196
0-4 years	9.0±2.5 (75.1±27.9)		
5-9 years	9.2±2.1 (76.4±20.7)		
10 years and above	9.5±2.1 (80.8±22.9)		
Variables	**Mean ± SD**	**r**	**p-value**
Age (years)	48.5±13.0	-0.144	**0.004**
Monthly income (USD)	489.6±193.4	-0.086	0.090
Body mass index (kg/m^2)	32.2±6.9	-0.330	**<0.001**
Low-density lipoprotein (mg/dL)	119.5±73.7	0.152	**0.003**
Triglyceride (mg/dL)	198.7±138.9	0.113	**0.025**
Systolic blood pressure (mmHg)	134.8±21.8	-0.121	**0.017**
Diastolic blood pressure (mmHg)	80.3±10.3	0.087	0.086

f: statistics of ANOVA (variance ratio test), r: Pearson correlation coefficients with HbA1c, All biochemistry tests were measured in mg/dL. The bold p-values is significant at the 0.05 level
HbA1c: Glycated hemoglobin, SD: Standard deviation, USD: United States dollar

This study examines key predictors identified, which explain 37% of the variability in HbA1c. This finding contrasts with a study conducted by Kowsar and Mansouri (25) in Iraq, which identified a positive correlation between elevated BMI and increased HbA1c levels. The discrepancies between these studies highlight the complexity of the relationship between BMI and glycemic control and suggest that factors such as lifestyle, diet, and genetic predispositions may significantly influence these readings.

Gender disparities in diabetes outcomes are significant, with studies revealing that female patients in Iraq face unique challenges in diabetes management. A study by Ahmed et al. (26), conducted in Sudan found that women had higher HbA1c levels than men. In contrast, another recent study in Libya (27) reported different results. Elevated HbA1c levels in female patients result from biological, socioeconomic, psychosocial, and healthcare factors. Marital status has been recognized as a predictor of glycemic control, particularly given its role in social support. A study by Ford and Robitaille (28) supports this finding, showing that married individuals tend to have lower HbA1c levels than their unmarried counterparts.

A study by Lee et al. (29) found that individuals without a family history of diabetes tend to be less proactive in managing their health, which results in higher HbA1c levels. It proposes

Table 4. Patients' knowledge, attitudes, practices, and correlation with HbA1c (n=390)

Variables	Total score (mean ± SD)	Total score, n (%)	r	p-value[a]
Total knowledge score	63.4±8.9		0.214	**0.032**
Poor knowledge		25 (6.4)		
Good knowledge		306 (78.5)		
Excellent knowledge		59 (15.1)		
Total attitude score	40.7±18.9		-0.159	0.045
Negative attitude		303 (77.7)		
Neutral attitude		73 (18.7)		
Positive attitude		14 (3.6)		
Total practice score	58.2±18.9		0.163	0.089
Poor practice		146 (37.4)		
Good practice		160 (41.0)		
Excellent practice		84 (21.5)		

[a]: Independent samples test, the p-value is significant at the 0.05 level, r: Pearson correlation coefficient, the p-value is significant at the 0.05 level, all KAP scores are out of 100
SD: Standard deviation, HbA1c: Glycated hemoglobin

Table 5. Predictive factors for HbA1c percentages (n=390)

Variables	B (95% CI)	β	R^2	Adjusted R^2	t	p-value
Constant	7.391	-	-	-	6.999	**<0.001**
Body mass index	0.082	0.256	0.081	0.079	5.259	**<0.001**
Knowledge	0.062	0.250	0.156	0.151	5.312	**<0.001**
Female	1.302	0.288	0.220	0.214	6.383	**<0.001**
Married	-1.383	-0.244	0.259	0.251	-5.592	**<0.001**
No family history of DM	0.885	0.196	0.280	0.270	4.039	**<0.001**
Long duration of DM	0.992	0.208	0.294	0.283	4.653	**<0.001**
Diastolic blood pressure	0.043	0.197	0.309	0.297	3.898	**<0.001**
Employed	1.809	0.257	0.320	0.306	5.204	**<0.001**
University or above	-1.489	-0.160	0.375	0.355	-3.590	**<0.001**
Preparatory school	-1.021	-0.120	0.388	0.367	-2.864	**0.004**
Comorbidities	0.483	0.108	0.397	0.375	2.359	**0.019**

Reference categories =1. Variables: sex: 1 if male, zero if female; marital status: 1 if married, while 0 for others; family history: 1 if yes, zero if no; duration of DM; 1 if 0-4 years, 0 for others; employment: 1 if employed, 0 for others; education: 1 for illiterate, 0 for others; and comorbidities: 1 if yes, zero if no. The p-value is significant at the ≤0.05 level
B: Unstandardized coefficients, β: Standardized coefficients, CI: Confidence interval, -: Standardized coefficients, R^2: The proportion of variance in the criterion, t: t-statistic, DM: Diabetes mellitus, HbA1c: Glycated hemoglobin

that the absence of a family history of diabetes can affect an individual's perception of risk and management practices. The duration of diabetes is closely linked to glycemic control, as Sheleme et al. (30), noted in Ethiopia, where longer diabetes duration correlated with higher HbA1c levels. Comorbidities such as hypertension complicate diabetes management and often lead to poorer glycemic control.

A 2018 study by Bijlsma-Rutte et al. (31) found that employed individuals had lower HbA1c levels than the unemployed, whereas the current study showed the opposite. These discrepancies highlight the complexity of diabetes management and the various factors influencing blood sugar control. Lower levels of education are associated with poor glycemic control. A study by Liao et al. (32) found that individuals who had completed university or preparatory school had significantly lower HbA1c levels than those with less education. Higher educational attainment likely improves glycemic control by enhancing health literacy, improving comprehension of self-management instructions, enabling better navigation of the healthcare system, and increasing the capacity to process and apply complex diabetes information.

Study Limitations

This study has several limitations that should be considered when interpreting the results. First, the cross-sectional design prevents establishing causal relationships among KAP, and glycemic control. Second, the study was conducted at a single tertiary healthcare center in Basra, which may limit the generalizability of the findings to primary healthcare centers or other areas in Iraq. Third, KAP were assessed using a questionnaire administered during a single interview, and responses may be subject to recall and social desirability bias. Fourth, several potentially important confounding factors were not measured, including medication adherence, diet, physical activity levels, depression, social support, and access to healthcare, which may have influenced the observed associations. The study sample was limited to patients aged 18-64 years, excluding older adults, who may experience different challenges and outcomes in diabetes management.

Clinical implications

These findings have several implications for clinical practice in Iraq and similar contexts. First, the average level of knowledge and negative attitudes suggest that diabetes education programs should go beyond simply providing information and should address beliefs, feelings, and self-confidence. Cognitive-behavioral techniques and motivational interviewing may be more effective than theoretical instruction alone. Second, identifying high-risk groups, including women, unmarried individuals, those with limited education, and the unemployed, can help guide awareness efforts and resource allocation. Third, given that 37% of the variance in HbA1c levels is attributable to modifiable factors, structured diabetes self-management education programs should be implemented and evaluated. Fourth, healthcare providers should periodically assess patients' KAP using concise screening tools to identify those who require additional support. Policymakers should consider investing in community-based diabetes support programs, particularly for the most vulnerable groups, and should ensure that diabetes education is available to patients with limited literacy.

Conclusion

The majority of patients have good knowledge of and practices in diabetes management but hold negative attitudes. Several predictors influence glycemic control, including BMI, diabetes management knowledge, female sex, marital status, family history of diabetes, duration of diabetes, blood pressure, employment status, level of education, and comorbidities. These factors account for 37% of the variation in HbA1c levels. The relationship between BMI and glycemic control is complex and may be influenced by lifestyle factors. Improving diabetes-related knowledge and practices is essential for reducing negative attitudes and enhancing health outcomes, especially among women who face unique challenges. A comprehensive approach is needed to improve diabetes care in Iraq, and further research is required to better understand this condition.

Ethics

Ethics Committee Approval: The ethics committee for this study was approved by the Falha Specialized Diabetes Endocrine and Metabolism Center (approval no: FDEMC/56/35/22, date: 02.11.2023).

Informed Consent: Informed consent was obtained from the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A.H., F.F.G., H.A.A., Concept: S.A.H., Design: S.A.H., F.F.G., Data Collection or Processing: S.A.H., F.F.G., Analysis or Interpretation: S.A.H., H.A.A., Literature Search: F.F.G., Writing: S.A.H.

Conflict of Interest: The authors declared no conflict of interest.

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Association between depression, anxiety, stress levels, and pre-pregnancy fear of childbirth among undergraduate midwifery students

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ABSTRACT

Aims: This study examined the relationship between depression, anxiety, and stress levels and pre-pregnancy fear of childbirth (FOC) among undergraduate midwifery students.

Methods: This descriptive correlational study was conducted among undergraduate midwifery students enrolled at one state university and one private university in Istanbul during the 2023 academic year. Data were collected online using a personal information form, the Depression Anxiety Stress Scale (DASS), and the Pre-Pregnancy FOC Scale (PPFCS).

Results: A total of 378 undergraduate midwifery students were included in the study. The mean age was 21.18±1.85 years, and all of the participants were female (100%). Severe depression, moderate anxiety, and severe stress were identified in 37.8%, 34.9%, and 41.8% of participants, respectively. Depression, anxiety, and stress scores differed significantly by academic year and socioeconomic status ($p<0.05$), with fourth-year students reporting lower levels of psychological symptoms. Students with lower income levels had significantly higher psychological distress scores and greater pre-pregnancy FOC (both $p<0.05$). In multivariable analysis, stress was identified as a significant predictor of FOC ($\beta=0.220$, $p=0.014$), whereas depression and anxiety were not significant predictors. Correlation analysis revealed a weak but statistically significant positive association between total scores on the DASS and the PPFCS ($r=0.337$; $p<0.05$).

Conclusions: This study demonstrated that depression, anxiety, and stress are prevalent among undergraduate midwifery students and are associated with pre-pregnancy FOC.

Introduction

Students enrolled in applied health sciences are often exposed to persistent stress and anxiety, particularly during clinical education. Midwifery students constitute one of the student groups experiencing high levels of psychological burden due to the emotionally demanding nature of their training and their early exposure to childbirth and women's health care (1). Stress represents the body's response to challenging situations, whereas anxiety may emerge as a prolonged reaction to stress and may adversely affect social, academic, and professional

functioning. Depression, characterized by persistent low mood and reduced self-worth, together with stress and anxiety, can impair learning processes, reduce academic performance, and negatively influence future professional functioning (2). Moreover, elevated psychological distress during education may compromise the quality of care provided by students during clinical practice and later as professional midwives.

In Türkiye, midwifery students are predominantly female and generally in late adolescence or early adulthood. These developmental periods are associated with increased psychological vulnerability, and female students are reported to experience higher levels of depression and anxiety compared with males (3). Such demographic characteristics may further increase the risk of psychological distress among midwifery students, making this group particularly vulnerable to stress-related mental health problems.

Midwifery education presents unique academic and clinical challenges that may contribute to increased stress and anxiety. High stress levels during training have been associated with depression, sleep disturbances, irritability, learning difficulties, and reduced professional competence (4,5). Many students enter midwifery programs with limited prior exposure to hospital environments and encounter clinical practice for the first time during their education (6). Unfamiliar clinical settings, fear of making mistakes or harming patients, insufficient practical skills, and negative feedback from healthcare professionals or academic staff may reduce self-confidence and increase psychological distress (6-8).

Fear of childbirth (FOC) is an important psychological factor that may influence both personal birth-related attitudes and professional identity development among midwifery students. FOC is considered a multifactorial phenomenon shaped by cognitive, emotional, and experiential processes (9,10). Among midwifery students, exposure to childbirth through clinical observation may contribute to the development of fear via vicarious traumatic experiences, particularly when students witness severe labor pain, obstetric complications, or negative maternal outcomes (11,12). Qualitative studies with midwifery students have also shown that witnessing difficult or traumatic births may lead to secondary trauma, emotional exhaustion, and defensive clinical practices, which in turn can disrupt perceptions of safety and increase threat appraisal (13). Such experiences may influence cognitive appraisal processes, leading to heightened threat perception, anticipatory anxiety, and negative expectations regarding childbirth (14). Psychological symptoms such as anxiety, depression, and stress may further intensify FOC through different mechanisms (15). Anxiety is associated with increased sensitivity to perceived threats and catastrophic thinking patterns, whereas depressive symptoms may contribute to pessimistic interpretations and reduced coping capacity; the broader psychopathology literature indicates that widely used trait anxiety scales strongly reflect general negative affect and depressive emotionality, and that anxiety and depressive symptoms are closely intertwined (16). Chronic stress may impair emotional regulation and resilience, thereby increasing vulnerability to fear responses; moreover, persistent stress and inadequate social support during pregnancy and the postpartum period have been shown to be associated with the continuation of depressive, anxiety, and trauma-related symptoms and with reduced psychological well-being (17,18).

Although midwifery education aims to enhance self-efficacy and promote positive perceptions of childbirth, delivery rooms are demanding learning environments that may intensify stress and anxiety (19). In Türkiye, clinical education constitutes approximately half of the undergraduate midwifery curriculum and involves close and repeated exposure to childbirth. Witnessing labor pain, concerns about causing harm, complex clinical responsibilities, and limited support in clinical settings may further increase psychological distress (20). Despite these challenges, evidence regarding the combined effects of depression, anxiety, and stress on FOC among midwifery students remains limited (21).

Midwives play a critical role in maternal and child health services in Türkiye and are expected to provide sexual and reproductive health education, counseling, and care throughout the lifespan. Maintaining good mental health during undergraduate education is therefore essential for both professional competence and long-term workforce sustainability (22). Although previous studies in Türkiye have examined stress and anxiety during clinical practice among midwifery students (7), the relationship between depression, anxiety, and stress levels and pre-pregnancy FOC has not been adequately investigated. Moreover, only a limited number of studies have examined FOC in relation to overall psychological distress conceptualized as a unified construct, particularly among midwifery students. In Türkiye, the structure of midwifery education involves early and intensive clinical exposure, which may uniquely influence students' psychological experiences and perceptions of childbirth. Addressing this gap is important, as persistent psychological symptoms during education may have long-term consequences for professional development and well-being. Therefore, this study aimed to examine the relationship between levels of depression, anxiety, and stress and pre-pregnancy FOC among undergraduate midwifery students.

Methods

Study design, setting, and participants

This study employed a descriptive, cross-sectional, correlational design and was conducted between February 20 and April 30, 2023, in the midwifery departments of Marmara University and Üsküdar University in İstanbul, Türkiye, as well as

in the hospitals affiliated with these institutions where midwifery students received clinical training. Marmara University is a public university, whereas Üsküdar University is a private university. These institutions were selected to represent the two main types of higher education systems in Türkiye. Since public and private universities generally follow similar curricula and clinical training standards in midwifery education, the inclusion of both types of universities and their affiliated clinical training settings was considered appropriate to reflect institutional diversity while maintaining feasibility. The study population consisted exclusively of undergraduate midwifery students who were predominantly female and enrolled in a four-year educational program combining theoretical courses with progressive clinical training.

During the planning phase, efforts were made to include institutions with students in all four academic years to ensure representation of different educational levels. Accordingly, one public university and one private university that met this criterion were selected.

Participants were included if they were enrolled in an undergraduate midwifery program and voluntarily agreed to participate in the study. Students who did not provide informed consent or who submitted incomplete questionnaires were excluded from the analysis.

Although this approach aimed to enhance representativeness within the selected institutions, the sample was limited to two universities. Therefore, the findings may not be fully representative of all undergraduate midwifery students in Istanbul or Türkiye; this limitation should be considered when interpreting the results.

The minimum required sample size was calculated to be 316 participants using the formula for a known population at a 99% confidence level. All eligible students from the selected institutions were invited to participate, and 378 volunteer students completed the study.

Data collection procedure

Data were collected using an online survey platform. Senior student representatives at each university were contacted, and the survey link was distributed through official student WhatsApp groups. Completion of the questionnaire required approximately 10-15 minutes. The survey consisted of a sociodemographic information form and two standardized assessment instruments.

Data collection instruments

Sociodemographic form

The sociodemographic form was developed by the researchers based on previous literature examining psychological distress and related factors among university and midwifery students (2,7,23). The questionnaire included questions related to age, academic year, marital status, income level, family structure, employment status, place of longest residence, history of psychiatric diagnosis, and use of psychiatric medication.

Depression Anxiety Stress Scale (DASS)

Psychological distress was assessed using the DASS developed by Lovibond and Lovibond (24). The Turkish validity and reliability study was conducted by Akın and Çetin (25). The scale consists of 42 items across three subscales (depression, anxiety, and stress), each comprising 14 items. Responses are rated on a four-point Likert scale, with higher scores indicating greater symptom severity. In the Turkish validation study, the Cronbach's alpha coefficients ranged between 0.90 and 0.92 for the subscales. In the current study, the internal consistency coefficient (Cronbach's alpha) for the total scale was 0.96.

Participants were categorized into severity levels (normal, mild, moderate, severe, and extremely severe) according to the standard cut-off scores provided in the original DASS manual by Lovibond and Lovibond (24), as these classifications are not specified in the Turkish validation study. The cut-off values were 0-9, 10-13, 14-20, 21-27, and ≥28 for depression; 0-7, 8-9, 10-14, 15-19, and ≥20 for anxiety; and 0-14, 15-18, 19-25, 26-33, and ≥34 for stress.

Pre-Pregnancy FOC Scale (PPFCS)

FOC was measured using the PPFCS, developed by Stoll et al. (26) and adapted into Turkish by Uçar and Taşhan (27). The scale includes 10 items rated on a six-point Likert scale, yielding total scores ranging from 10 to 60, with higher scores indicating greater fear. The Cronbach's alpha coefficient in this study was 0.89.

Study outcomes

The primary outcome was the independent association of depression, anxiety, and stress scores with pre-pregnancy FOC, as measured using the PPFCS.

Secondary outcomes were differences in depression, anxiety, stress, and PPFCS scores according to academic year and socioeconomic status, as well as the distribution of psychological symptom severity levels within the sample.

Ethical considerations

Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Marmara University Faculty of Health Sciences (approval no: 162, date: 29.12.2022). All procedures were conducted in accordance with the principles of the Declaration of Helsinki. Participants were informed about the purpose and procedures of the study, and electronic informed consent was obtained prior to participation.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were calculated, with continuous variables presented as mean ± standard deviation and median values, and categorical variables expressed as frequencies and percentages. The normality of the data distribution was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Group comparisons were conducted using independent samples t-tests and one-way analysis of variance. Associations between categorical variables were examined using the chi-square test. Pearson correlation analysis was applied to evaluate the relationship between psychological distress scores and pre-pregnancy FOC scores. Statistical significance was set at $p<0.05$.

A post-hoc power analysis was conducted using G*Power software (version 3.1) to evaluate whether the sample size was sufficient to detect the observed correlation between psychological distress and FOC. Based on the detected effect size (r=0.337), an alpha level of 0.05, and a sample size of 378 participants, the statistical power was calculated to be greater than 0.99, indicating adequate power.

Results

Participant characteristics

A total of 378 undergraduate midwifery students were included in the study. The mean age was 21.18±1.85 years with 82.5% aged between 18 and 22 years, and all of the participants were female (100%). The majority of students (98.7%) were single. No participants were excluded due to incomplete data, as all submitted questionnaires were complete and eligible for analysis.

Of the participants, 65.6% were enrolled at a public university, and 33.1% were fourth-year students. Regarding socioeconomic status, 68.3% reported that their income was equal to their expenses. Most students reported no history of psychiatric diagnosis (91.8%) and no use of psychiatric medication (89.4%). The majority had a nuclear family structure (82.8%), were not employed (91.0%), and reported predominantly living in a provincial center (66.6%). Detailed sociodemographic characteristics are presented in Table 1.

Table 1. Participants socio-demographic characteristics (n=378)

University	n	%
State	248	65.6
Foundation	130	34.4
School year		
1	74	19.6
2	84	22.2
3	95	25.1
4	125	33.1
Age		
18-22	312	82.5
≥23	66	17.5
Marital status		
Married	5	1.3
Single	373	98.7
Socioeconomic level		
Income<expenses	87	23.0
Income=expenses	258	68.3
Income>expenses	33	8.7
Presence of a psychiatric disorder		
Yes	31	8.2
No	347	91.8
Use of psychiatric medication		
Yes	40	10.6
No	338	89.4
Family type		
Nuclear	313	82.8
Extended	65	17.2
Employment		
Yes	34	9.0
No	344	91.0
Place of the longest residence		
Village	40	10.6
District	86	22.8
Province	252	66.6

Distribution of depression, anxiety, and stress levels

Based on the DASS, 37.8% of the students were classified as having severe depression, 34.9% as having moderate anxiety, and 41.8% were classified as having severe stress. The distribution of symptom severity levels across the three subscales is shown in Table 2.

FOC according to sociodemographic characteristics

Mean scores on the PPFCS did not differ significantly across university types, academic year (first year vs. other years), age group, marital status, psychiatric medication use, presence of psychiatric diagnosis, family structure, employment status, or place of longest residence ($p>0.05$). Similarly, no statistically significant differences by socioeconomic status were observed, although students reporting lower income levels had higher fear scores ($p>0.05$) (Table 3).

Depression, anxiety, and stress scores according to sociodemographic characteristics

Depression, anxiety, and stress scores differed significantly by academic year and socioeconomic status ($p<0.05$). Fourth-year students reported significantly lower psychological symptom

Table 2. Depression, anxiety and stress levels of the participants according to their depression anxiety stress scale scores

Levels	Depression		Anxiety		Stress	
	n	%	n	%	n	%
Normal	11	2.9	15	4.0	1	0.3
Mild	38	10.1	57	15.1	24	6.3
Moderate	93	24.6	132	34.9	50	13.2
Severe	143	37.8	130	34.4	158	41.8
Extremely severe	93	24.6	44	11.6	145	38.4

Table 3. Comparison of the mean fear of childbirth scale scores by socio-demographic characteristics

Characteristics	Fear of childbirth scale score (mean ± SD)	Test statistic	p-value
University			
State	35.83±9.82	t=0.168	0.867
Foundation	35.65±10.74		
School year			
1	36.70±10.74		
2	36.80±10.09	F=1.815	0.144
3	36.38±9.45		
4	34.06±9.45		
Age			
18-22	35.58±10.16	t=-0.767	0.444
≥23	36.64±10.03		
Marital status			
Married	40.20±13.68	t=0.985	0.325
Single	35.71±10.90		
Socioeconomic level			
Income<expenses	36.95±9.76	F=1.759	0.174
Income=expenses	35.71±9.71		
Income>expenses	33.09±13.63		
Presence of a psychiatric disorder		t=0.886	0.886
Yes	35.51±9.52		
No	35.78±10.19		
Use of psychiatric medication		t=-0.572	0.568
Yes	34.90±9.55		
No	35.86±10.20		
Family type			
Nuclear	36.08±10.09	t=1.318	0.188
Extended	34.26±10.27		
Employment			
Yes	35.76±10.91	t=-0.001	0.999
No	35.76±10.07		
Place of the longest residence			
Village	38.85±9.44	F=2,345	0.097
District	36.08±11.04		
Province	35.17±9.86		

t: Independent samples t-test, F: One-way ANOVA, SD: Standard deviation

scores compared with students in earlier years. Additionally, students with lower income levels had higher depression, anxiety, and stress scores. Students using psychiatric medication also demonstrated significantly higher psychological distress across all subscales ($p<0.05$). Detailed comparisons are presented in Table 4.

Primary outcome: predictors of FOC

A multiple linear regression analysis was conducted to examine whether depression, anxiety, and stress predict FOC (PPFCS). The overall model was statistically significant [$F(3.374)=17.418$, $p<0.001$] and explained 12.3% of the variance in PPFCS scores ($R^2=0.123$; adjusted $R^2=0.116$; n=378).

When the predictors were entered simultaneously, stress emerged as a significant positive predictor of FOC [B=0.271; standard error (SE)=0.110; β=0.220; t=2.472; p=0.014], indicating that higher stress levels were associated with higher FOC scores. In contrast, depression (B=0.132; SE=0.096; β=0.114; p=0.170) and anxiety (B=0.057; SE=0.117; β=0.039; p=0.626) were not significant predictors after controlling for the other variables. Regression results are presented in Table 5.

Secondary outcome: association between psychological distress and FOC

Correlation analysis revealed a weak but statistically significant positive association between total scores on the DASS and the PPFCS ($r=0.337$; $p<0.05$), indicating that higher psychological distress was associated with greater FOC.

Discussion

The present study demonstrated an association between pre-pregnancy FOC and depression, anxiety, and stress levels among undergraduate midwifery students. The findings indicate that psychological distress is common in this population and is significantly influenced by academic year and socioeconomic status. Although the relationship between psychological distress and FOC was weak, it was statistically significant, suggesting an interaction between emotional well-being and perceptions related to childbirth.

In addition to relational findings, the distribution of symptom severity indicated that a substantial proportion of students experienced severe depression and stress. These high

Table 4. Comparison of participants' socio-demographic characteristics and their Depression Anxiety Stress Scale scores

Characteristics	Depression, median (IQR)	Test statistic	p-value	Anxiety, median (IQR)	Test statistic	p-value	Stress, median (IQR)	Test statistic	p-value	Post-hoc comparisons
University										
State	28 (23-34)	z=-1.210	0.226	25 (21-30)	z=-0.443	0.658	32 (27-37)	z=0.232	0.816	
Foundation	27 (22-32)			25 (19-29)			31 (27-39)			
School year										
1	28 (23-36)			26 (21-31)			33 (27-39)			
2	28 (22-34)	χ^2=17.194	**<0.001**	26 (21-31)	χ^2=11.531	**0.009**	33 (29-41)	χ^2=15.733	**0.001**	Dunn-Bonferroni 4 vs 1, 2, 3 (all adjusted p<0.05)
3	29 (26-35)			25 (22-29)			32 (28-37)			
4	25 (19-31)			23 (22-29)			30 (24-34)			
Age		z=-1.569			z=-1.183					
18-22	28 (23-34)		0.117	25 (20-30)		0.237	32 (27-38)	z=-1.611	0.107	
≥23	27 (20-31)			24 (19-28)			31 (26-34)			
Marital status								z=-1.093		
Married	22 (19-26)	z=-1.823	0.068	22 (19-28)	z=-0.792	0.428	27 (25-33)		0.274	
Single	28 (22-34)			25 (20-30)			31 (27-37)			
Socioeconomic level										Dunn-Bonferroni depression: 1-2, 1-3; anxiety: 1-2; stress: 1-2 (all adjusted p<0.05)
Income<expenses	29 (24-37)	χ^2=7.672	**0.022**	26 (23-31)	χ^2=6.914	**0.032**	33 (29-39)	χ^2=7.139	**0.028**	
Income=expense	27 (22-33)			24 (20-29)			31 (27-36)			
Income>expenses	26 (21-32)			26 (19-31)			29 (24-42)			
Presence of a psychiatric disorder		z=-1.819	0.069		**z=-3.309**	**<0.001**		z=-1.580	0.114	
Yes	30 (26-36)			29 (26-32)			34 (28-39)			
No	27 (22-33)			25 (20-29)			31 (27-37)			
Use of psychiatric medication		**z=-2.185**	**0.029**		**z=-3.008**	**0.003**		**z=-2.220**	**0.026**	
Yes	30 (25-37)			28 (23-32)			35 (28-41)			
No	27 (22-33)			25 (20-29)			31 (27-36)			
Family type										
Nuclear	28 (22-34)	z=-0.377	0.706	25 (21-30)	z=-0.425	0.671	32 (27-38)	z=-1.713	0.087	
Extended	27 (23-33)			25 (19-30)			30 (27-34)			
Employment					z=-1.338					
Yes	28 (25-36)	z=-0.701	0.483	26 (23-33)		0.181	34 (30-41)	z=-1.644	0.100	
No	28 (22-33)			25 (20-29)			31 (27-37)			
Place of the longest residence										
Village	28 (22-34)	χ^2=1.106	0.575	25 (21-28)	χ^2=1.369	0.504	32 (28-35)	χ^2=0.369	0.832	
District	29 (22-34)			26 (20-31)			32 (27-39)			
District	27 (22-33)			25 (20-29)			31 (27-37)			

χ^2: Kruskal-Wallis H test, z: standardized test statistic for Mann-Whitney U test
IQR: Interquartile range

Table 5. Multiple linear regression predicting fear of childbirth (PPFCS) from depression, anxiety, and stress

Dependent variable	Predictors	B	β	SE	t	p-value
PPFCS	Depression	0.132	0.114	0.096	1.374	0.170
	Anxiety	0.057	0.039	0.117	0.488	0.626
	Stress	0.271	0.220	0.110	2.472	**0.014**

R^2=0.123; Adjusted R^2=0.116; F(3, 374)=17.418; p<0.001; n=378
PPFCS: Pre-Pregnancy Fear of Childbirth Scale, B: Unstandardized coefficient, β: Standardized coefficient, SE: Standard error

prevalence rates suggest that midwifery students may face a considerable psychological burden during their education and highlight the need for early screening and preventive mental health strategies.

Consistent with previous studies, fourth-year students reported significantly lower levels of depression, anxiety, and stress than students in earlier academic years. Early phases of university education are often characterized by adjustment difficulties, including adaptation to academic demands, separation from family, financial challenges, and exposure to unfamiliar clinical environments (6,7). Initial clinical experiences, particularly first encounters with childbirth and hospital settings, may further intensify stress and anxiety (6,28). International evidence similarly reports high stress prevalence among midwifery students, with approximately 40-56% experiencing elevated stress during training, especially following early clinical exposure (5,28,29). These findings suggest that increased experience, professional confidence, and familiarity with clinical settings in later years may have a protective effect on students' mental health.

Socioeconomic status emerged as a key determinant of both psychological distress and FOC. Students whose incomes were lower than their expenses reported significantly higher levels of depression, anxiety, and stress. This finding is consistent with studies from different countries indicating that financial hardship constitutes a major stressor for midwifery students and is associated with reduced psychological well-being and increased risk of academic difficulties (30,31). In Türkiye, ongoing economic challenges may exacerbate these stressors, underscoring the importance of institutional support mechanisms, scholarships, and social assistance programs to reduce financial strain among students.

The weak but significant correlation between depression, anxiety, stress, and pre-pregnancy FOC suggests that psychological distress may contribute to negative perceptions of childbirth. However, the relatively low strength of this association may indicate a buffering role of midwifery education. Educational content related to childbirth, repeated clinical exposure, and increasing professional competence may help reduce fear over time (19,27). Since FOC was not examined in relation to the intensity or duration of clinical exposure, future longitudinal studies are warranted to clarify these relationships.

Bivariate evidence consistently shows that stress, anxiety, and depression are positively associated with FOC, reflecting their shared negative affect component (10). In multivariable models, however, predictors often "drop out" because much of their association with FOC is shared variance rather than unique effects-sometimes a broader construct such as negative affectivity accounts for the relationship, while in other samples stress retains the strongest independent contribution (15). Findings also vary across populations, with some studies showing anxiety and/or depression remaining significant after adjustment, suggesting contextual and measurement influences (9,32). Importantly, many individuals with high FOC do not have clinically significant anxiety or depression, pointing to additional mechanisms (e.g., personality, prior birth trauma, pain catastrophizing, low self-efficacy, attachment factors, and care-related context) that likely contribute to FOC beyond general distress (33,34).

In line with these findings, the regression analysis in the present study demonstrated that stress, rather than depression or anxiety, independently predicted FOC. This suggests that stress-related mechanisms, such as emotional overload, perceived lack of control, and reduced coping capacity, may play a more central role in shaping childbirth-related fears among midwifery students.

Study Limitations

This study has several strengths, including students from both public and private universities, validated psychometric instruments, and adequate statistical power supported by post-hoc analysis. However, several methodological limitations should be considered. First, the study employed a voluntary, non-probability sampling approach, which may introduce selection bias and limit the representativeness of the findings. In addition, the sampling frame was limited to two universities, which may not fully reflect the broader population of midwifery students in İstanbul or in Türkiye.

Second, data were collected through self-report measures, which may be subject to reporting bias and social desirability effects. Third, potential confounding variables—such as personality traits, prior traumatic experiences, coping styles, and levels of clinical exposure—were not controlled for in the analyses. Finally, the cross-sectional design and lack of

longitudinal follow-up preclude causal inferences and limit the ability to examine changes over time. Future studies using longitudinal designs and probabilistic sampling strategies are recommended to address these limitations and enhance the generalizability of findings.

Conclusion

This study demonstrated that stress, anxiety, and depression are common among midwifery students and are influenced by academic year and socioeconomic status. The findings highlight the need for early monitoring of mental health problems and structured support throughout both academic and clinical education.

Integrating content that promotes mental health and enhances coping skills into midwifery curricula may strengthen students' psychological well-being and professional resilience. In addition, addressing socioeconomic challenges through comprehensive approaches may play a key role in supporting students' mental health.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Marmara University Faculty of Health Sciences (approval no: 162, date: 29.12.2022).

Informed Consent: Participants were informed about the purpose and procedures of the study, and electronic informed consent was obtained prior to participation.

Footnotes

Authorship Contributions

Concept: N.K., F.B.B., A.B., E.B., H.K.D., Design: N.K., F.B.B., A.B., E.B., H.K.D., Data Collection or Processing: N.K., F.B.B., E.B., H.K.D., Analysis or Interpretation: N.K., F.B.B., A.B., Literature Search: N.K., F.B.B., E.B., H.K.D., A.A., Writing: N.K., A.B., E.B., H.K.D., A.A.

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Persistent median artery in carpal tunnel release: prevalence and surgical implications

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Keywords: Persistent median artery, carpal tunnel syndrome, anatomical variation, median nerve

ABSTRACT

Aims: This study evaluates intraoperative anatomical variations encountered during open carpal tunnel release (CTR) and aims to determine the prevalence of the persistent median artery (PMA) encountered during open CTR and to evaluate its anatomical features, clinical significance, and surgical outcomes.

Methods: This retrospective observational study reviewed the operative reports of patients who underwent open CTR at our institution between January 2015 and April 2024. Adults diagnosed with carpal tunnel syndrome based on clinical and electrophysiological findings who were treated with isolated open CTR were included. Patients undergoing additional wrist procedures or revision CTR were excluded. The primary endpoint was the intraoperative identification of PMA, defined as an artery persisting within the carpal tunnel. Operative notes were examined to record their anatomical course and management.

Results: A total of 1,032 patients underwent CTR [mean age 53.4±11.6 years; 678 females (65.7%)]. PMA was identified in 9 cases (0.9%), with a mean age of 51.2±8.7 years and predominance in females (66.7%). The PMA coursed superficial to the median nerve in 6 patients (66.7%) and deep to the median nerve in 3 patients (33.3%). All arteries were preserved, and no intraoperative vascular or neural injuries occurred. The mean postoperative follow-up duration was 6.2±2.4 months. No hematoma, wound complications, or symptom recurrence were reported during the follow-up period.

Conclusions: PMA is a rare anatomic variant encountered in less than 1% of open CTR procedures. Its close relationship with the median nerve, although rare, emphasizes the importance of careful dissection. Recognition of this structure intraoperatively may help minimize complications and ensure safe surgical outcomes.

Introduction

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy of the upper extremity, resulting from compression of the median nerve as it passes through the carpal tunnel at the wrist (1).This syndrome usually presents with symptoms such as numbness, tingling, and pain in the distribution of the median nerve and, in advanced cases, motor weakness and thenar muscle atrophy (2). Surgical decompression of the carpal tunnel is widely accepted as an effective treatment for patients with moderate to severe symptoms (3). Although carpal tunnel anatomy is generally predictable, surgeons must be alert to anatomic variations that may affect the surgical approach and outcome (4). One of these variations is the persistent median artery (PMA), a developmental vascular structure that does not regress during embryogenesis. While it usually regresses by the eighth week of intrauterine life, the median artery may persist in a small percentage of individuals (5). Its presence may be incidental or may contribute to median nerve compression through direct mass effect or associated thrombosis or aneurysm formation (6).

The prevalence of PMA in the general population is variable, ranging from 1% to 27%, largely due to methodological differences among cadaveric, radiological, and intraoperative studies, as well as population-specific anatomical variation (7,8). The artery may course superficial to or deep to the median nerve and, in some cases, make a significant contribution to the palmar arch, making its preservation important. Inadvertent damage to the PMA during carpal tunnel release (CTR) can result in bleeding, a hematoma, or more serious complications if the PMA is dominant.

In this study, we describe the intraoperative findings of PMA encountered during routine open CTR. We hypothesized that the PMA is a rare but clinically significant anatomic variant that can be encountered during open CTR and that its recognition and preservation contribute to safe surgical outcomes.

Methods

Study design and ethical approval

This retrospective study was conducted after obtaining internal ethical approval from the Selçuk University Rectorate Local Ethics Committee and in accordance with the principles outlined in the Declaration of Helsinki (approval no: 2025/329, date: 03.06.2025). The medical records of patients who underwent CTR surgery at our institution between January 2015 and April 2024 were reviewed.

Patient selection

Preoperative diagnosis of CTS was based on clinical symptoms and supported by NCS. Patients who received CTR under regional anesthesia, local anesthesia, or wide-awake local anesthesia without a tourniquet (WALANT) were included in the study.

Inclusion criteria:

• Adults diagnosed with CTS by clinical and nerve conduction studies (NCS) findings.

• Treated with isolated open CTR.

Exclusion criteria:

• Revision CTR.

• Concomitant wrist procedures (e.g., tendon transfers, mass excisions).

• Incomplete records or inadequate follow-up.

Surgical technique

All procedures were performed by fellowship-trained hand surgeons or orthopedists using a standard open technique via a longitudinal palmar incision. When the PMA coursed deep to the median nerve, careful blunt dissection was performed to expose the artery, and the artery was preserved in all cases without ligation. No attempt was made to mobilize or transpose the artery if it was asymptomatic.

Data collection and intraoperative assessment

Demographic data, including age, sex, laterality, and anesthesia type, were recorded. Operative notes were carefully reviewed to identify cases in which a PMA was noted intraoperatively (Figure 1). The presence, size, location (relative to the median nerve), and management of the PMA (e.g., preserved or ligated) were documented when available.

Intraoperative complications, including vascular injury, excessive bleeding, or nerve damage, were also noted.

Postoperative follow-up

Postoperative follow-up data, including early complications and recurrence, were reviewed when available.

Statistical analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The study cohort included over 1,000 consecutive cases of CTR, ensuring adequate power for descriptive analysis of anatomical variations. Descriptive statistics were used to summarize demographic data and the frequency of PMA. Continuous variables were presented as means and standard deviations, and categorical variables were reported as frequencies and percentages.

Results

A total of 1,032 patients underwent open CTR at our institution between January 2015 and April 2024. Of these, 678 (65.7%) were female, 354 (34.3%) were male, and their mean age was 53.4±11.6 years (range: 27-81). Surgery was

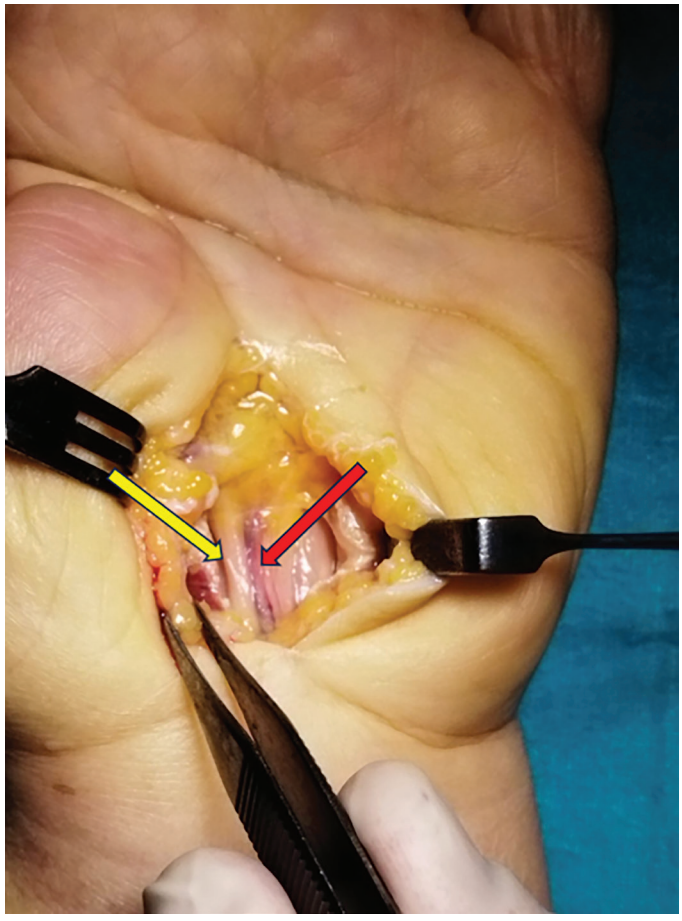

Figure 1. Persistent median artery (red arrow) and median nerve (yellow arrow)

performed on the right wrist in 562 cases (54.4%) and on the left wrist in 470 cases (45.6%).

Procedures were performed under local anesthesia in 612 patients (59.3%), under regional anesthesia in 298 patients (28.9%), and with the WALANT technique in 122 patients (11.8%) (Table 1).

PMA was encountered in 9 patients (0.9%) during surgery. 6 of them were female, and 3 were male, and the mean age was 51.2±8.7 years. PMA was located superficial to the median nerve in 6 patients (66.7%) and deep to the median nerve in 3 patients (33.3%) (Table 2). In 5 cases (55.6%), the artery showed significant pulsatility and appeared to contribute to distal perfusion, necessitating careful dissection and preservation. In all cases, the artery was unilateral; bilateral PMA was not observed.

All PMAs were successfully preserved without ligation (Figure 2). No vascular injuries, intraoperative bleeding, or thrombotic events were reported in PMA-positive cases. Surgeons reported that the presence of the artery necessitates a more meticulous dissection, especially when it courses superficial to the nerve.

Table 1. Patient characteristics and anesthesia types (n=1,032)

Variable	Mean ± SD
Mean age (years)	53.4±11.6
	n (%)
Gender	
Female	678 (65.7)
Male	354 (34.3)
Laterality	
Right	562 (54.4)
Left	470 (45.6)
Local anesthesia	612 (59.3)
Regional anesthesia	298 (28.9)
WALANT	122 (11.8)

SD: Standard deviation, WALANT: Wide-awake local anesthesia no tourniquet

Postoperative follow-up time was 6.2±2.4 months. During the follow-up period, all 9 PMA-positive patients experienced relief of their preoperative symptoms, and no complications such as hematoma, wound dehiscence, delayed healing, or symptom recurrence were observed.

Discussion

The presence of PMA within the carpal tunnel is a rare but surgically important anatomical variation. Although often overlooked, PMA may influence both the pathophysiology of CTS and the safety of surgical intervention. In our cohort of 1,032 patients undergoing open CTR over nine years, we identified PMA in 9 patients, corresponding to a prevalence of 0.9%. This finding is consistent with previously reported intraoperative prevalence rates ranging from 0.6% to 8.3% (9-11).

The prevalence reported in our study is significantly lower than that reported in many anatomical and radiological studies. This discrepancy can be explained by methodological differences: cadaveric studies generally report rates between 4% and 27% depending on population, dissection technique, and definition criteria (12-15), while imaging studies, such as high-resolution ultrasonography, reveal rates around 6-15% (16). In contrast, clinical surgical series that rely on intraoperative identification, such as Osiak et al. (17), report lower prevalence values (2.8%), which are more consistent with our findings. Our relatively low rate of 0.9% may therefore be attributable to the limitations of intraoperative detection in the absence of preoperative imaging or detailed dissection protocols. Unlike imaging-based studies, we did not employ Doppler ultrasonography or magnetic resonance imaging, and thus our data reflect only arteries that were macroscopically evident at the time of surgical exploration.

The clinical importance of the PMA during CTR extends beyond its anatomic curiosity. Several case reports have highlighted examples of intraoperative bleeding, nerve

compression, and ischemic complications associated with PMA injury or thrombosis (18-20). In our series, the PMA was most commonly located superficial to, or anteromedial to, the median nerve, and in no case required ligation. No postoperative vascular or neurologic complications were observed, which is consistent with the literature suggesting that, with adequate surgical awareness, the PMA can be safely preserved without adverse outcomes.

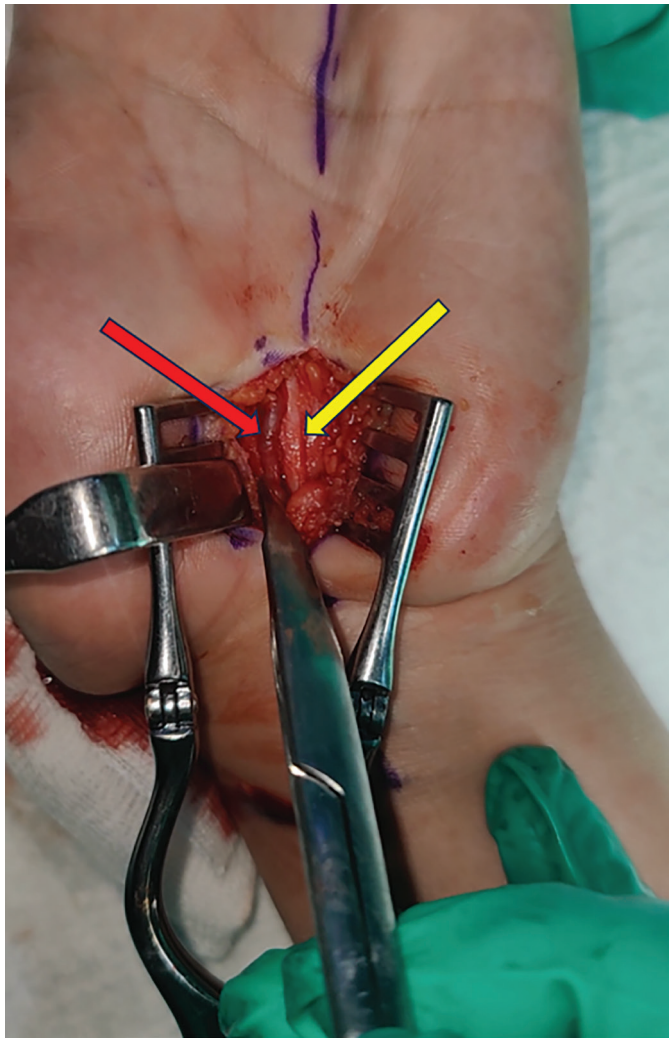

Figure 2. Persistent median artery (red arrow) and median nerve (yellow arrow)

In recent years, preoperative ultrasonography has been emphasized as a useful tool in detecting vascular variants in patients scheduled for CTR, especially in those with atypical symptoms or revision cases (21,22). High-frequency ultrasound can detect PMA and bifid median nerve preoperatively, potentially reducing intraoperative surprises and complications. Although routine imaging is not cost-effective for all patients, its selective use in complex or high-risk cases has been recommended in recent guidelines (23).

Another important aspect is the evolving trend toward ultrasound-guided and endoscopic CTR techniques. While these approaches offer benefits, including reduced morbidity and faster recovery, they also limit direct visualization of the structures within the carpal tunnel. Some authors have expressed concern that unrecognized PMA may increase the risk of iatrogenic vascular injury in such situations (24,25). Therefore, attention to anatomy is essential regardless of the technique chosen. Future research should aim to establish standardized protocols for both preoperative evaluation and intraoperative management of PMA, encompassing both traditional open and novel minimally invasive techniques.

Study Limitations

We acknowledge that our study has several limitations, including its retrospective design and reliance on surgeon-reported intraoperative findings, which may introduce observational bias. The lack of preoperative vascular imaging limits our ability to estimate the “true” anatomic prevalence of PMA in this population. Another limitation is the absence of inter-surgeon reliability assessment. Although procedures were performed by fellowship-trained hand surgeons and orthopedists, no evaluation of interobserver variability was performed. Furthermore, although data collection and analysis

Table 2. Characteristics of patients with persistent median artery (n=9)

Patient no	Sex	Age	Side	PMA location	Management	Intraoperative complications	Postoperative complications
1	F	47	R	Superficial	Preserved	None	None
2	M	55	L	Deep	Preserved	None	None
3	F	49	R	Superficial	Preserved	None	None
4	F	61	L	Superficial	Preserved	None	None
5	M	50	L	Deep	Preserved	None	None
6	F	52	R	Superficial	Preserved	None	None
7	M	58	R	Deep	Preserved	None	None
8	F	44	L	Superficial	Preserved	None	None
9	F	53	R	Superficial	Preserved	None	None

PMA: Persistent median artery

were carried out by two independent raters, no statistical measure of interrater reliability (e.g., Cohen's kappa) was calculated, thereby weakening the claim that bias was minimized. However, the large cohort size and consistent surgical technique used across multiple anesthesia modalities by experienced surgeons increase the generalizability of our results. Our study also provides valuable epidemiological data from the Middle Eastern population, contributing to the geographic diversity of the PMA prevalence literature.

Conclusion

This study shows that PMA is a rare anatomic variant encountered during open CTR and has a prevalence of 0.9% in our series. This relatively low rate likely reflects the limitations of intraoperative detection in the absence of imaging support. Although rare, the PMA remains a surgically important structure due to its close relationship with the median nerve and its potential contribution to hand vascularization. Recognizing this variation and adapting surgical technique accordingly may help minimize complications and ensure safe surgical outcomes.

Ethics

Ethics Committee Approval: This retrospective study was conducted after obtaining internal ethical approval from the Selçuk University Rectorate Local Ethics Committee and in accordance with the principles outlined in the Declaration of Helsinki (approval no: 2025/329, date: 03.06.2025).

Informed Consent: This retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.S.E., M.E., A.Ö., Concept: E.S.E., M.E., A.Ö., Design: E.S.E., A.Ö., Data Collection or Processing: E.S.E., Analysis or Interpretation: E.S.E., M.E., A.Ö., Literature Search: E.S.E., Writing: E.S.E., M.E., A.Ö.

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Ten years of experience in hypospadias management at a tertiary pediatric center in North Macedonia

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ABSTRACT

Aims: Hypospadias is one of the most common congenital anomalies of the male urogenital tract, yet regional outcome data from Southeastern Europe remain limited. This study aimed to evaluate epidemiological patterns, surgical management strategies, and postoperative outcomes over 10 years in North Macedonia.

Methods: A retrospective cohort study was conducted in North Macedonia including patients managed for hypospadias and related postoperative sequelae between January 2011 and December 2020. Demographic, clinical, operative, and outcome data were extracted from institutional records. Primary hypospadias cases were analyzed by anatomical subtype, while surgically treated patients were evaluated for surgical techniques and postoperative complications.

Results: A total of 647 patient records were identified, including 507 patients with primary hypospadias, of whom 469 were surgically treated. Mean age at treatment was 4.9±3.6 years, and mean hospitalization duration was 7.1±3.4 days. Anterior hypospadias was the most common subtype (78.5%), followed by glandular hypospadias (10.3%). Tubularized incised plate (TIP) urethroplasty was the predominant reconstructive technique (73.6%). Proximal variants were associated with longer hospitalization. Urethrocutaneous fistula (7.9%) and urethral stenosis (2.6%) were the most frequent postoperative complications. Most patients were from major urban municipalities.

Conclusions: In this 10-year cohort, hypospadias management included the predominant use of TIP urethroplasty, a substantial proportion of cases requiring reoperation, and longer hospitalization for proximal defects. Most patients originated from major urban municipalities.

Introduction

Hypospadias is among the most common congenital anomalies of the male urogenital tract and is characterized by ectopic ventral placement of the urethral meatus, frequently accompanied by ventral curvature and preputial malformation (1-3). Reported incidence varies across geographic regions, likely reflecting differences in genetic background, environmental exposures, endocrine influences, and case ascertainment practices (2-4). Embryologically, the condition results from incomplete fusion of the urethral folds during fetal development, mediated in part by androgen-dependent signaling pathways (3).

Clinical severity is primarily determined by meatal location, with distal forms generally more common and proximal variants associated with greater reconstructive complexity, higher complication risk, and increased likelihood of staged repair (1,4,5). Over recent decades, multiple operative strategies have been developed, including tubularized incised plate (TIP/Snodgrass) urethroplasty, Mathieu repair, meatal advancement

and glanuloplasty incorporated (MAGPI), flap-based procedures, and staged reconstructions for severe cases (5-8). Among these, TIP urethroplasty has become the dominant approach for distal and selected midshaft defects because of its reproducibility and favorable functional outcomes (2,7-10).

Despite technical advances, postoperative morbidity remains clinically relevant. Urethrocutaneous fistula, meatal or urethral stenosis, cosmetic dissatisfaction, and need for reoperation continue to be reported, particularly in proximal and reoperative cases (9-16). In addition, disparities in referral pathways, access to subspecialized care, and heterogeneity in outcome reporting may substantially influence treatment timing and measured results (11,14,17-20).

Although the global literature on hypospadias repair is extensive, contemporary data from Southeastern Europe remain limited. Regional institutional analyses may clarify referral patterns, operative practices, complication burden, and health-system factors influencing care delivery. This study presents a 10-year experience at a tertiary pediatric surgical center, focusing on epidemiology, surgical management, and postoperative outcomes (19,21-24).

Methods

Study design and setting

This retrospective cohort study was conducted in North Macedonia at a tertiary referral center for congenital urogenital anomalies. The study evaluated pediatric and adolescent male patients who were managed for hypospadias and related urogenital conditions between January 2011 and December 2020.

Study population

Eligible patients were identified through institutional electronic medical records and operative databases. The study population comprised patients aged 0-23 years who underwent evaluation and received surgical or conservative management for primary hypospadias, postoperative complications after prior repair, or associated urogenital anomalies requiring institutional care. Older adolescents and young adults represented delayed referrals or secondary or reoperative presentations of congenital hypospadias that were initially diagnosed in childhood.

Patients with incomplete medical documentation precluding extraction of essential study variables, with uncertain diagnoses, or who received treatment performed exclusively outside the study center without adequate follow-up records were excluded. The final analytic cohort consisted of 647 eligible records.

Data collection

Clinical and operative data were extracted using a standardized data collection framework. Variables included: age at admission, geographic origin, anatomical subtype, number and type of procedures, length of hospital stay, associated comorbidities, and documented postoperative complications or reinterventions.

Classification of hypospadias

Hypospadias was classified by urethral meatal location as anterior (distal), middle (penile shaft) or proximal. Classification was based on available diagnostic and operative records.

Surgical management

Operative procedures were categorized according to the documented reconstructive techniques, including TIP (Snodgrass) urethroplasty, Modified Byars flap reconstruction, Mathieu urethroplasty, Perović repair, MAGPI, Hodgson repair, and other reconstructive approaches. Surgical complexity was defined as the requirement for two or more procedures, including staged repairs or secondary interventions. Correction of chordee, when present, was performed intraoperatively according to standard surgical principles and the surgeon's preference.

Outcomes and definitions

Patients were stratified into predefined age categories (0-2, 3-5, 6-10, and ≥11 years), representing early referral, the recommended age window for primary repair, later childhood, and delayed presentation. Primary outcomes were the distribution of anatomical subtypes, the utilization of operative techniques, hospitalization burden, and postoperative complications and reinterventions. Postoperative complications and reinterventions were defined as documented urethrocutaneous fistula; urethral stenosis; urinary retention; wound-related complications (e.g., hematoma); cosmetic abnormalities (e.g., buried penis); or any postoperative presentation requiring further evaluation, follow-up, or secondary surgical intervention. Secondary outcomes included the municipality of origin and associated anomalies.

Follow-up information was obtained from the institutional archive's available inpatient records, outpatient documentation, and reintervention records. Because follow-up was retrospective and non-standardized, both the duration and the completeness varied among patients. Therefore, the reported complication rates reflect documented institutional outcomes rather than standardized long-term follow-up data. Given the retrospective design, long-term standardized functional, cosmetic, urinary, and psychosocial outcomes were not uniformly available. Outcome assessment was therefore limited to postoperative complications and reinterventions recorded in institutional documentation.

Ethical considerations

Ethical approval for this retrospective review of archived medical records from the 2011-2020 study period was

obtained from the local Human Research Ethics Committee of the "St. Cyril and Methodius" University in Skopje Faculty of Medicine (approval no: 03-5522/1, date: 23.09.2025) before data extraction and formal statistical analysis. Because of the retrospective design, the use of previously recorded data, and the anonymization of all patient information, the ethics committee waived the requirement for individual informed consent. No patient contact or intervention occurred. The study was conducted in accordance with the Declaration of Helsinki and applicable Good Clinical Practice principles.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are expressed as frequencies and percentages. Group comparisons for continuous variables were performed using one-way analysis of variance, while categorical associations were assessed using the chi-square test or Fisher's exact test, as appropriate. Additionally, multivariable logistic regression analysis was performed to explore independent predictors of postoperative complications and reinterventions in the cohort. Variables included in the multivariable model were selected based on clinical relevance and were supported by preliminary univariate analyses. One patient was excluded from multivariable regression analysis due to missing covariate data. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A two-sided p-value <0.05 was considered statistically significant.

Statistical analyses were performed using RStudio (RStudio Team, Boston, MA, USA), running R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Cohort characteristics

A total of 647 patient records related to hypospadias and its postoperative sequelae were identified during the 2011-2020 study period (Figure 1). Of these, 507 patients with primary hypospadias were eligible for anatomical subtype analysis, whereas 469 surgically managed patients were included in analyses of operative technique and postoperative outcomes. The mean age at treatment in the overall cohort was 4.9±3.6 years, and the mean hospitalization duration was 7.1±3.4 days. Most corrective procedures were performed during early childhood, with progressively fewer interventions observed in adolescence and young adulthood. Patients were more frequently referred to by major urban municipalities, particularly Skopje and other larger regional centers.

Anatomical subtype distribution

Among patients with primary hypospadias, anterior hypospadias was the predominant anatomical subtype, accounting for nearly four-fifths of classified presentations. Glandular hypospadias was the second most frequent subtype, whereas proximal variants such as penoscrotal and scrotal hypospadias were comparatively uncommon. The length of

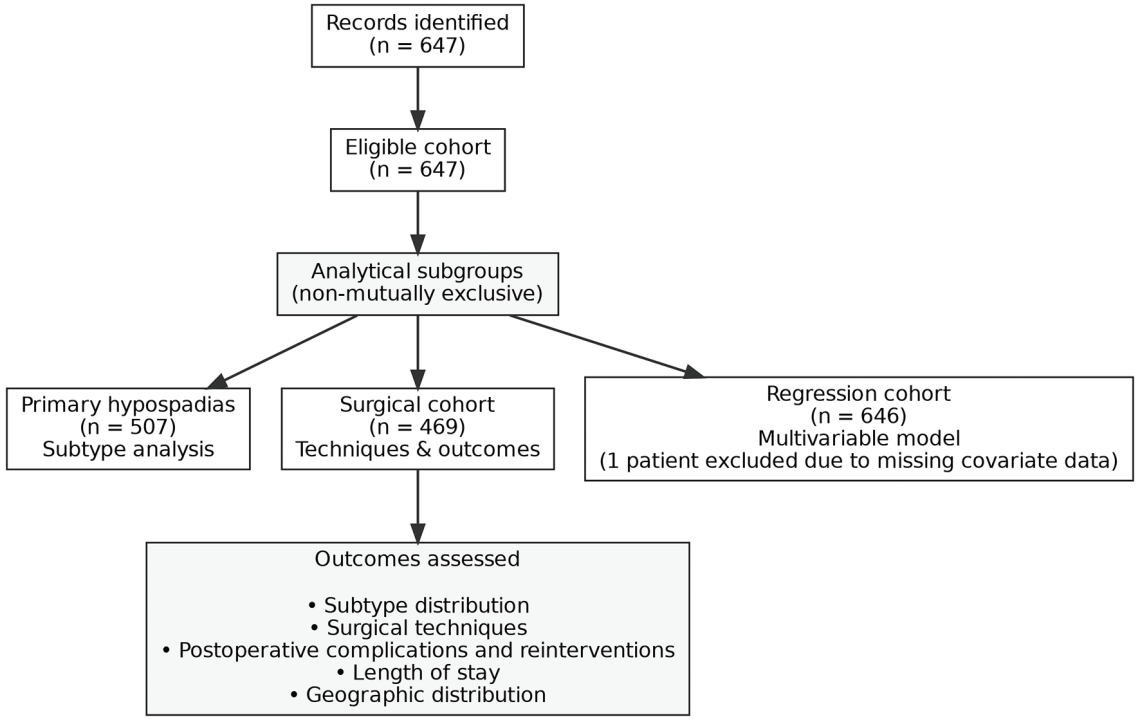

Figure 1. STROBE flow diagram illustrating patient selection, cohort stratification, and analytical subgroups included in the study

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

hospitalization differed significantly by anatomical subtype: more proximal and surgically complex forms were associated with longer inpatient stays, whereas age at treatment did not differ significantly between groups (Table 1).

Surgical burden and operative techniques

Most patients (83.9%) underwent a single operative intervention; 15.0% required two procedures, and only a small minority underwent three or more procedures. Neither patient age nor hospitalization duration differed significantly according to procedural burden (Table 2).

TIP urethroplasty was the predominant reconstructive method and accounted for nearly three-quarters of definitive repairs. Modified Byars-flap reconstruction was the second most frequently used technique, whereas the Mathieu, Perović, MAGPI, and Hodgson procedures were applied selectively based on anatomical complexity and surgeon preference (Table 3).

Postoperative outcomes

Reoperative presentation following repair was documented in 29.9% of surgically managed patients. Among specific postoperative complications, urethrocutaneous fistula was the most frequent (7.9%), followed by urethral stenosis (2.6%). Less common complications included urinary retention, hematoma, and cosmetic abnormalities such as buried penis. A substantial proportion of patients (59.3%) had no documented postoperative complications (Table 4).

Table 1. Anatomical subtype distribution and patient characteristics among primary hypospadias cases (n=507)

Anatomical subtype	n	%	Age (years)	LOS (days)
Anterior hypospadias	398	78.5	4.6±3.4	7.4±3.1
Glandular hypospadias	52	10.3	4.9±3.3	6.7±2.9
Penoscrotal hypospadias	24	4.7	5.0±3.6	8.5±4.4
Midshaft (corporalis/penile) hypospadias	20	3.9	4.5±3.2	9.0±3.9
Scrotal hypospadias	13	2.6	4.4±3.0	8.3±3.2
Total	**507**	**100**	**4.7±3.4**	**7.5±3.2**

Overall comparison (ANOVA): Age p=0.842; LOS: p=0.031
LOS: Length of hospital stay

Table 2. Surgical burden and hospitalization according to number of procedures in the total cohort (n=647)

Number of procedures	n	%	Age (years)	LOS (days)
1 procedure	543	83.9	5.0±3.8	7.1±3.3
2 procedures	97	15.0	4.6±3.0	7.1±4.0
≥3 procedures	7	1.1	7.1±3.4	7.7±5.7
Total	**647**	**100**	**4.9±3.6**	**7.1±3.4**

Overall comparison (ANOVA): Age p=0.181; LOS: p=0.900
LOS: Length of hospital stay

Predictors of postoperative complications and reinterventions

Multivariable logistic regression analysis demonstrated that increasing age was independently associated with higher odds of postoperative complications and reinterventions (adjusted OR: 1.10, 95% CI: 1.04-1.15; p<0.001). In contrast, the use of TIP urethroplasty was independently associated with lower odds of adverse outcomes (adjusted OR: 0.22, 95% CI: 0.13-0.38; p<0.001). Proximal hypospadias showed borderline statistical significance as a predictor of adverse presentations, whereas multiple procedures were not independently associated with adverse presentations (Table 5).

Discussion

This 10-year institutional cohort provides a contemporary overview of hypospadias management at a tertiary referral center and yields four principal observations: interventions occurred later than internationally recommended age windows; TIP urethroplasty was the dominant reconstructive strategy; proximal and reoperative cases were associated with greater treatment burden; and urban clustering most likely reflected referral centralization and proximity to tertiary care services.

The mean age at treatment in our cohort was approximately 5 years, substantially exceeding the commonly recommended repair window of 6 to 18 months (2,3). Early correction is generally

Table 3. Reconstructive techniques used for hypospadias repair among surgically managed patients (n=469)

Surgical technique	n	%
Tubularized incised plate (TIP/Snodgrass) urethroplasty	345	73.6
Modified Byars flap	80	17.1
Mathieu urethroplasty	18	3.8
Perović technique	18	3.8
MAGPI	6	1.3
Hodgson urethroplasty	2	0.4
Total	**469**	**100**

TIP: Tubularized incised plate, MAGPI: Mathieu repair, meatal advancement and glanuloplasty incorporated

Table 4. Detailed postoperative complications and reinterventions among surgically managed patients (n=469)

Variable	n	%
Reoperative/follow-up after prior repair	140	29.9
Urethrocutaneous fistula	37	7.9
Urethral stenosis	12	2.6
Urinary retention	1	0.2
Hematoma/wound-related complication	1	0.2
Buried penis/cosmetic complication	1	0.2
No documented complication	278	59.3

Table 5. Multivariable logistic regression analysis for predictors of postoperative adverse presentations in the cohort (n=646)

Variable	Adjusted OR	95% CI	p-value
Age (per 1-year increase)	1.10	1.04-1.15	<0.001
Proximal hypospadias	0.24	0.06-1.07	0.061
TIP urethroplasty	0.22	0.13-0.38	<0.001
Multiple procedures	1.04	0.63-1.72	0.887

Model likelihood ratio p<0.001
TIP: Tubularized incised plate, CI: Confidence interval, OR: Odds ratio

favored because it may reduce treatment-related psychological stress, facilitate perioperative care, and allow reconstruction before increasing genital awareness in later childhood (2,3). The delayed timing observed in our series likely reflects broader health-system factors rather than isolated surgical preference. Possible contributors include delayed recognition in primary care, late referral pathways, waiting-list constraints, socioeconomic barriers, and unequal availability of pediatric urologic expertise outside metropolitan centers (11,17,19,24). Similar delays have been reported in lower-resource settings where centralized expertise influences access and timing of intervention (11,17). Delayed presentation may also increase reconstructive complexity and intensify psychosocial stress for patients and families.

TIP urethroplasty was the most frequently utilized reconstructive technique, accounting for nearly three-quarters of definitive repairs. This pattern is consistent with contemporary international practice, where TIP remains a preferred technique for distal and selected midshaft hypospadias because of its technical reproducibility, broad applicability, and favorable cosmetic and functional outcomes (5,7-10). Meta-analytic evidence has shown acceptable complication rates in non-proximal repairs, although outcomes remain influenced by tissue quality, surgeon experience, case selection, and duration of follow-up (9,20). More recent series continue to support the central role of TIP while confirming that fistula formation and urethral stenosis remain clinically relevant postoperative concerns (12,15,22). The operative distribution observed in our cohort reflects the predominant use of TIP urethroplasty, with selective use of flap-based and alternative techniques according to anatomical severity and reconstructive requirements.

Anterior hypospadias was the predominant anatomical subtype, whereas proximal variants were less frequent. This distribution is consistent with established epidemiologic data demonstrating predominance of distal forms worldwide (1-4). The high frequency of anterior lesions has practical implications, as distal defects are generally amenable to single-stage reconstruction with favorable outcomes, whereas proximal forms more often require individualized or staged strategies.

Hospitalization duration was significantly longer for proximal forms; this clinically coherent finding likely reflects greater operative complexity, increased use of flaps or staged reconstruction, and more intensive postoperative monitoring. Previous multicenter studies similarly identify proximal meatal location as a major determinant of complication risk and need for secondary intervention (15,16). Penoscrotal and scrotal defects are frequently associated with marked chordee, deficient ventral tissues, or hypoplastic urethral plates, each of which may complicate one-stage repair and prolong recovery (4,15). In addition, the relatively prolonged hospital stay in our cohort may reflect institutional postoperative protocols (including catheter management strategies and inpatient monitoring practices) and potential socioeconomic factors influencing discharge timing. These findings reinforce the importance of early referral of complex cases to experienced reconstructive centers.

The postoperative burden in our study was substantial. Nearly one-third of surgically managed patients were reoperative or follow-up cases, while urethrocutaneous fistula and urethral stenosis were the leading complications. The broader categorization of postoperative complications in our study highlights the spectrum of major and minor adverse events and reinforces the importance of comprehensive reporting beyond fistula and stenosis. These remain the most consistently reported adverse outcomes after hypospadias repair across contemporary literature (9,13,16,22). Although such complications may not always prolong the index hospitalization, they frequently necessitate repeated monitoring, secondary surgery, re-exposure to anesthesia, and additional burden on families. Their clinical significance, therefore, extends beyond immediate inpatient metrics.

Multivariable analysis demonstrated that increasing age was independently associated with adverse postoperative outcomes, whereas TIP urethroplasty was associated with lower odds of such outcomes. Although these findings should be interpreted cautiously given the retrospective observational nature of the data, they support the potential importance of timely referral and standardized selection of techniques for appropriately selected patients.

A higher proportion of cases originated in Skopje and other larger municipalities, which may reflect the centralization of referrals. Similar patterns are observed in healthcare systems where specialized pediatric reconstructive services are concentrated within tertiary institutions (19,24). Although centralization may improve technical expertise and outcomes,

it may also create travel burdens, delayed presentations, and unequal access for families from remote areas. Structured referral pathways and broader regional access to specialist assessment may help reduce these disparities.

Recent advances may further improve outcomes in pediatric hypospadias surgery. Enhanced perioperative pathways, including ultrasound-guided penile or caudal regional anesthesia, have demonstrated benefits in postoperative analgesia and recovery quality (21). Technical refinements in tissue handling, multilayer coverage, and suture selection may also influence fistula prevention (20). In parallel, emerging artificial intelligence-based tools may eventually assist with preoperative assessment, risk prediction, and standardized outcome evaluation, although these applications remain investigational at present (23).

Study Limitations

Several limitations should be acknowledged. The retrospective single-center design limits causal inference and generalizability. Standardized long-term follow-up data regarding urinary function, cosmetic appearance, sexual development, patient satisfaction, and psychosocial outcomes were not consistently available across the full cohort, precluding comprehensive assessment using validated instruments such as Hypospadias Objective Scoring Evaluation and Hypospadias Objective Penile Evaluation. The lack of a standardized follow-up duration may have contributed to underestimating late postoperative complications. Consequently, the present findings primarily reflect documented surgical and early clinical outcomes rather than long-term patient-centered results. Inclusion of a broad age range reflects the real-world referral pattern of delayed primary presentations and reoperative cases in adolescents or young adults encountered at a tertiary center. In addition, minor complications managed in outpatient settings, delayed presentations treated elsewhere, or events incompletely documented in historical records may have underestimated the true postoperative complication burden. The broader categorization of postoperative complications in our study highlights the spectrum of both major and minor adverse events, reinforcing the importance of comprehensive reporting beyond fistula and stenosis alone. Evolving surgical preferences over the 10-year study period may also have influenced technique selection and outcomes.

Despite these limitations, this study represents one of the larger contemporary regional series from Southeastern Europe and, to the best of our knowledge, the first dedicated cohort analysis of hypospadias management from North Macedonia. It provides clinically relevant insight into treatment timing, operative practice, and postoperative burden. From a clinical perspective, these findings highlight the need for earlier diagnosis, timely referral to specialized centers, and structured postoperative surveillance to minimize complications and improve long-term outcomes. These findings underscore the importance of early referrals, centralized surgical expertise, structured long-term follow-up, and standardized reporting to optimize outcomes in hypospadias management.

Conclusion

In this 10-year cohort study, hypospadias management in North Macedonia was characterized by delayed interventions, predominant use of TIP urethroplasty, and a substantial reoperative burden. Proximal defects were associated with longer hospitalizations and greater treatment complexity, while most patients originated from major urban municipalities.

Ethics

Ethics Committee Approval: Ethical approval for this retrospective review of Human Research Ethics Committee of the “St. Cyril and Methodius” University in Skopje Faculty of Medicine (approval no: 03-5522/1, date: 23.09.2025) prior to data extraction and formal statistical analysis.

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.M., H.S., M.K., Concept: S.M., H.S., Design: S.M., H.S., Data Collection or Processing: S.M., H.S., M.K., Analysis or Interpretation: S.M., H.S., M.K., Literature Search: S.M., H.S., M.K., Writing: S.M., H.S., M.K.

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

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Serum fractalkine levels and their association with cardiovascular parameters in patients with overt hyperthyroidism

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ABSTRACT

Aims: Hyperthyroidism is a common endocrine disorder with significant cardiovascular (CV) implications. Emerging evidence links fractalkine to both heart failure (HF) and atherosclerosis. We aimed to compare serum fractalkine levels between patients with hyperthyroidism and healthy controls and to investigate its potential association with CV risk markers.

Methods: This case-control study included treatment-naive adults with overt hyperthyroidism and age- and sex-matched healthy controls with normal thyroid function tests. Participants with cardiovascular disease or major systemic disorders were excluded. All participants underwent physical examination, hormonal profiling, serum fractalkine measurement, electrocardiography, and echocardiographic assessment using both conventional and tissue Doppler techniques to evaluate left and right ventricular function.

Results: The study included 41 treatment-naive patients with overt hyperthyroidism (mean age: 45±12.9 years) and 41 age-matched healthy controls (mean age: 45±8.2 years). Patients with hyperthyroidism had significantly higher serum fractalkine levels than healthy controls (p=0.01). Within the hyperthyroid group, fractalkine levels positively correlated with carotid intima-media thickness (CIMT), a marker of subclinical atherosclerosis (r=0.317, p=0.043), and negatively correlated with mitral annular velocity in late diastole (a'), a diastolic parameter indicative of HF with preserved ejection fraction (HFpEF) (r =-0.344, p=0.028). Linear regression analysis identified fractalkine as an independent predictor of increased CIMT and of reduced a'.

Conclusions: This study demonstrated that fractalkine levels are elevated in patients with hyperthyroidism and are associated with early markers of CV dysfunction, including subclinical atherosclerosis and HFpEF.

Introduction

Hyperthyroidism is a common endocrine disorder with significant implications for the cardiovascular (CV) system. In particular, individuals aged 60 years and older, as well as those with pre-existing cardiac conditions, have been documented to confront an elevated risk of atrial fibrillation (AF), coronary events, and heart failure (HF) in the presence of hyperthyroidism (1). It is noteworthy that studies have underscored the enduring impact of hyperthyroidism on CV morbidity and mortality, persisting up to 35 years post-treatment (2). Despite our current understanding of the CV morbidity and mortality associated with hyperthyroidism, the specific characteristics and outcomes of individual cardiac complications have not been comprehensively studied.

Fractalkine (CX3CL1) belongs to the small-molecule chemokine family known for its ability to induce chemotaxis of myeloid cells (3). It is expressed in various tissues, including the brain, gastrointestinal tract, skin, endothelium, kidney, and lungs. Fractalkine is also expressed on activated platelet surfaces, contributing to macrophage adhesion within atherosclerotic plaques. Emerging evidence underscores its pivotal role in the pathogenesis of specific diseases, such as atherosclerosis and CV conditions, where inflammatory factors play a crucial role (4). Studies have shown that individuals with polymorphisms in CX3CR1, the receptor for fractalkine, exhibit varying degrees of protection against coronary artery disease (5). Thyroid hormone receptors are localized to the plasma membrane of endothelial cells, including integrin αvβ3. Fractalkine binds to integrin αvβ3, inducing changes in the physical state of the integrin and activating it (6). The proximity of the binding site to thyroid hormones suggests that thyroid hormones may modulate the effects of fractalkine. Moreover, fractalkine has been shown to have proliferative, anti-apoptotic, and pro-angiogenic effects on the vascular system through its interaction with integrin αvβ3 (7).

Despite evidence demonstrating a sustained elevated risk of CV disease (CVD) in patients with hyperthyroidism, even after undergoing treatment, the current literature lacks a specific marker indicating the risk of developing CVD attributable to elevated T4 levels in these individuals. Building upon these considerations, our hypothesis suggests that increased T4 levels may affect fractalkine levels and its signaling pathway, thereby contributing to elevated CVD risk. The main objective of the study was to compare serum fractalkine levels between individuals with treatment-naive hyperthyroidism and a control group, emphasizing the exclusion of participants with pre-existing CVD or related risk factors to eliminate confounding. Moreover, our second objective was to investigate potential correlations between serum fractalkine levels and markers of CV abnormalities, assessed by electrocardiography, conventional echocardiography, tissue Doppler echocardiography, and carotid intima-media thickness (CIMT) measurement.

Methods

Study design and setting

The present study was designed as a case-control study and was conducted between March 2021 and March 2022, involving 41 healthy subjects and 41 patients with overt hyperthyroidism. The inclusion criteria for the patient group were treatment-naive, newly diagnosed overt hyperthyroidism and age over 18 years. The control group consisted of age- and sex-matched euthyroid, healthy individuals who met the same exclusion criteria as the patient group. Exclusion criteria included a history of CAD, dysrhythmia, diabetes mellitus, hypertension, structural heart disease, valvular heart disease, anemia, renal and hepatic failure, lung disease, connective tissue disease, and malignancy. None of the participants had used antithyroid medication before enrollment in the study. Additionally, no medications known to affect CV parameters were permitted.

The study involved a comprehensive assessment, including physical examination, hormonal analyses, measurement of serum fractalkine levels, and electrocardiographic (ECG) evaluation. Electrocardiography (standard 12-lead ECG) was carried out for the participants at a paper velocity of 25 mm/s. Changes in left and right ventricular (RV) hemodynamics and performance were assessed by conventional and tissue Doppler echocardiography (TDI). All ECG and echocardiographic analyses were performed by a single observer who was blinded to the study groups. This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of Gülhane Training and Research Hospital (approval no: 2021/6, date: 24.03.2021). Written informed consent was obtained from all participants prior to their enrollment in the study.

Laboratory tests

Serum levels of thyrotropin (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) were measured using automated immunochemiluminescent assay (ICMA) kits (Roche GmbH, Mannheim, Germany). The coefficients of variation for these thyroid profile assays were below 10%. The reference ranges for TSH, FT4, and FT3 were 0.38 to 5.33 mIU/L, 0.58 to 1.38 ng/dL, and 2.0 to 4.4 pg/mL, respectively. Hyperthyroidism was clinically diagnosed and confirmed by elevated FT4 and/or FT3 levels along with suppressed serum TSH levels. The serum fractalkine levels were assessed using the Human Fractalkine/CX3CL1 ELISA Kit (PicoKine, EK0356) obtained from BOSTER Biological Technology (Wuhan, China). Due to the non-normal distribution of serum fractalkine levels, logarithmic transformations were applied before analysis.

Echocardiographic examination

Echocardiographic measurements in the patients enrolled in the study were obtained using M-mode, two-dimensional, and

color-flow Doppler imaging with a Vivid S60N echocardiography device equipped with a 2.5-MHz transducer. These measurements were conducted by a cardiologist who was blinded to the clinical details of each patient and of the control group, as well as to the results of other examinations. Additionally, tissue Doppler imaging was performed using transducer frequencies of 3.5-4.0 MHz. The spectral pulsed-Doppler signal filters were adjusted until a Nyquist limit of 15-20 cm/sec was achieved, and the minimal optimal gain was applied. Patients were imaged in the left lateral decubitus position at rest. Echocardiographic examinations were performed according to the American Society of Echocardiography guidelines (8).

Left ventricular (LV) systolic function was evaluated using the ejection fraction (EF) calculated according to the Teichholz formula (8). LV diastolic function was assessed by mitral inflow velocities, specifically peak E (early diastolic), peak A (late diastolic), and the E/A ratio. Mitral annular velocities in early diastole (e') and late diastole (a') and the E/e' ratio were also evaluated. All measurements were recorded as the mean of three cardiac cycles. Left atrial (LA) dimension, LV end-systolic and end-diastolic dimensions, diastolic ventricular septal thickness, and diastolic LV PWT were measured in the parasternal long-axis view. LV mass (LVM) was calculated using Devereux's formula (9) and indexed to body surface area (BSA). LV hypertrophy was defined as LVM index (LVMI) >120 g/m^2 for men and >116 g/m^2 for women (10). LA volume was measured using the method of discs in the apical four-chamber view and indexed to the BSA.

RV size was analyzed in the apical four-chamber view by measuring the basal diameter and in the parasternal longitudinal view. RV systolic function was assessed by measuring tricuspid annular plane systolic excursion (TAPSE) and peak systolic velocity (S'). TAPSE, a simple method of estimating RV function, was measured as the difference in the distance between the tricuspid annulus and the RV apex at end-diastole and end-systole of the same cardiac cycle. Tricuspid S' was evaluated by tissue Doppler and measured at the free-wall side of the tricuspid annulus.

Carotid artery intima-media thickness

CIMT was assessed by B-mode ultrasonography using an 18-MHz linear transducer with an Esaote ultrasound device. Measurements were performed with the patients in the supine position and with their necks turned to the opposite side. The standard measurement of CIMT was carried out at a distance of 1 cm from the bifurcation points of the right and left common carotid arteries. During this measurement, the mean right and left CIMT values were calculated and recorded using the available software (Syngo Arterial Health Package). In this study, right and left CIMT measurements were taken 3 times independently, and the results were recorded as averages.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows version 26.0. Normality was assessed using the Kolmogorov-Smirnov test. Continuous variables with normal distributions were expressed as mean ± standard deviation, while categorical variables were presented as frequencies (%). Student's t-test was used to compare means of parametric variables, and the Mann-Whitney test was used for variables with non-parametric distributions. Chi-square tests were used to compare categorical variables. Pearson's test was used for parametric correlations, and Spearman's test for non-parametric correlations. Multiple linear regression analysis was used to assess significant associations of serum log-fractalkine with CIMT and with echocardiographic parameters. A priori power analysis was performed using G*Power 3.1, with an alpha level *(α) of 0.05 and statistical power (1-β) β of 0.80. The sample size calculation was based on the study's primary endpoints, namely CV parameters [including echocardiographic indices of diastolic function relevant to HF with preserved EF (HFpEF)] and vascular markers such as CIMT, and assumed a moderate-to-large effect size informed by previous studies. Serum fractalkine levels were considered secondary endpoints, and the estimated sample size was deemed sufficient to detect effect sizes comparable to those reported in prior studies on inflammatory biomarkers. Accordingly, a minimum of 40 patients per group was required. A significance level of $p \leq 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics

This case-control study included 41 consecutive patients with overt hyperthyroidism (34 female; 45±12.9 years) and 41 healthy controls (27 female; 45±8.2 years) who met the inclusion criteria. The etiology of hyperthyroidism was Graves' disease (GD) in 90.2% of cases and toxic multinodular goiter in 9.8% of cases. Clinical characteristics such as age, sex, systolic blood pressure, and diastolic blood pressure did not differ significantly between the patient and control groups. Clinical and biochemical parameters differed between the groups, with patients with hyperthyroidism showing lower body mass index (BMI) and levels of serum creatinine, low-density lipoprotein cholesterol, and total cholesterol, as well as higher heart rate, CIMT, and fasting blood glucose compared with controls (Table 1). Additionally, fractalkine was significantly higher in patients with hyperthyroidism (p=0.01) (Figure 1). All the subjects were in sinus rhythm without any significant ST-segment deviation.

Echocardiographic characteristics

All measured echocardiographic parameters were within the reference ranges in all subjects (Table 2). There were no differences between the two groups in LVM, LVMI,

interventricular septal thickness, posterior wall thickness (PWT), LV end-diastolic diameter, and LVEF. The RV systolic function, TAPSE, and Tricuspid S' were significantly higher in the patient group compared with controls (Table 2).

Regarding diastolic function, the patient group exhibited significantly higher values of LA volume index (LAVI), E, and e' (Table 2). Mean E/e' in hyperthyroid patients was 6.53±1.73, which was in the normal range.

Relationship of fractalkine with clinical, metabolic, and echocardiographic parameters

Correlation analyses between fractalkine and clinical, metabolic, and echocardiographic parameters were performed. In the whole group, Fractalkine was positively correlated with CIMT (r=0.301, p=0.006) and FT4 (r=0.251, p=0.023), and negatively correlated with gender (r=-0.270, p=0.014), TSH (r=-0.250, p=0.024), and a' (r=-0.255, p=0.021). In the patient group, fractalkine correlated positively with CIMT (r=0.317, p=0.043) (Figure 2) and negatively with a' (r=-0.344, p=0.028).

We developed a model using linear regression analysis that included age, gender, BMI, and fractalkine to assess CV parameters in the hyperthyroidism group. The model identified fractalkine as a risk factor for increased CIMT and for decreased a' (Table 3).

Table 1. Comparison of characteristics between the hyperthyroid and control subjects

Variables	Hyperthyroidism (n=41)	Control (n=41)	p-value
Age (years)	45±12.9	45±8.2	0.968*
Female, n (%)	34 (82.9%)	27 (65.9%)	0.077*
BMI (kg/m²)	24.54±4.65	27.36±2.75	**<0.001***
BSA (m²)	1.68±0.18	1.82±0.19	**<0.001***
SBP (mmHg)	116.0±12.4	115.3±17.1	0.922*
DBP (mmHg)	81.8±9.6	78.6±7.9	0.240*
Heart rate (beats/min)	86.3±14.9	78.5±9.5	**0.006***
PR (ms)	121.9±23.6	137.02±18.6	**0.002***
CIMT (mm)	0.41±0.05	0.37±0.04	**<0.001***
TSH (mIU/L)	0.005 (0.003-0.007)	1.52 (0.5-4.8)	**<0.001#**
FT4 (ng/dL)	2.25 (0.84-5.31)	0.80 (0.6-1.1)	**<0.001#**
FT3 (pg/mL)	7.61 (2.87-25.27)	3.7 (2.8-4.5)	**<0.001#**
FBG (mg/dL)	90.3 (71-112)	82.7 (65-108)	**0.003#**
Scr (mg/dL)	0.70 (0.5-1.03)	0.90 (0.6-1.1)	**<0.001#**
Total cholesterol (mg/dL)	170.34±33.16	213.83±37.22	**<0.001***
LDL (mg/dL)	95.24± 23.53	135.46±35.43	**<0.001***
Triglyceride (mg/dL)	118.78±57.74	137.90±73.64	0.195*
Log-fractalkine	1.77±0.76	1.39±0.56	**0.010***

*: Student's t-test; #: Mann-Whitney U test
BMI: Body mass index, BSA: Body surface area, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CIMT: Carotid intima-media thickness, TSH: Thyroid stimulating hormone, FT4: Free thyroxine, FT3: Free triiodothyronine, FBG: Fasting blood glucose, Scr: Serum creatinine, LDL: Low-density lipoprotein

Table 2. Comparison of echocardiographic parameters between the hyperthyroid and control subjects

Variables	Hyperthyroidism (n=41)	Control (n=41)	p-value
LVM (g)	128.99±24.98	138.51±25.12	0.089*
LVMI (g/m²)	76.71±12.93	76.21±12.83	0.860*
IVST (mm)	8.61±0.95	8.87±0.81	0.172*
PWT (mm)	8.56±0.77	8.75±0.62	0.213*
LVEDD (mm)	44.95±3.13	46.02±2.84	0.109*
LVEF (%)	64.39±2.08	63.53±2.30	0.082*
E (cm/sec)	78.52±22.04	66.48±14.37	**0.005***
A (cm/sec)	74.51±19.45	71.17±14.19	0.377*
E/A ratio	1.12±0.43	0.96±0.28	0.058*
LAD (mm)	31.95±4.26	34.39±3.74	**0.007***
LAVI (mL/m²)	22.00±7.61	18.07±3.93	**0.005***
e' (cm/sec)	12.23±2.59	10.52±2.70	**0.005***

Table 2. Continued

Variables	Hyperthyroidism (n=41)	Control (n=41)	p-value
a' (cm/sec)	10.29±1.83	10.27±1.78	0.282*
E/e'	6.53±1.73	6.58±1.64	0.889*
RVTAPSE (mm)	23.05±2.20	21.75±1.74	**0.004***
Tricuspid S'	12.82±1.37	11.75±1.46	**<0.001***
RV1	29.95±3.83	31.73±5.81	0.106*
RV2	27.0±4.09	26.60±2.91	0.620*
RV3	61.36±6.27	61.92±6.58	0.695*

*: Student's t-test
LVM: Left ventricular mass, LVMI: Left ventricular mass index, IVST: Interventricular septum thickness, PWT: Posterior wall thickness, LVEDD: Left ventricular end-diastolic diameter, LVEF: Left ventricular ejection fraction, E: Early diastolic mitral inflow velocities, e': Early diastolic mitral annular velocity, A: Late diastolic mitral inflow velocities, a': Late diastolic mitral annular velocity, RVTAPSE: Right ventricular tricuspid annular plane systolic excursion, Tricuspid S': Tricuspid lateral annulus systolic velocity, RV1: Right ventricular basal dimension, RV2: Right ventricular mid dimension, RV3: Right ventricular longitudinal dimension, LAD: Left atrial diameter, LAVI: Left atrial volume index

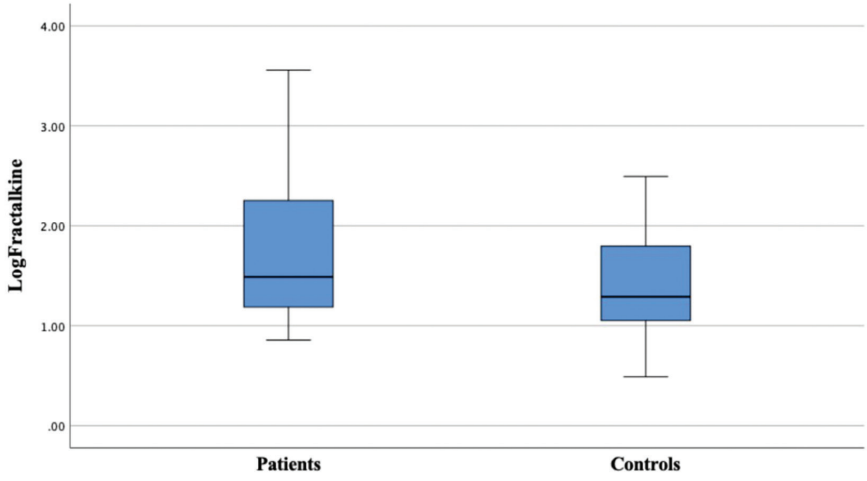

Figure 1. The distribution of fractalkine values in patient and control groups

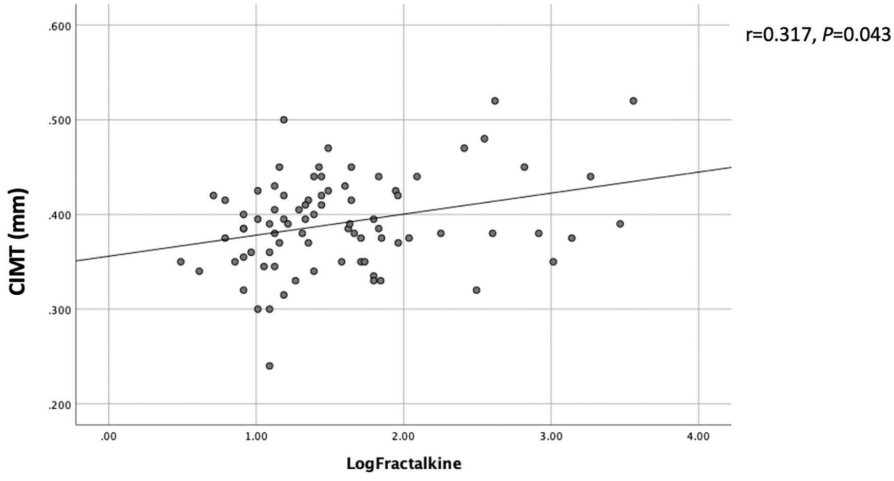

Figure 2. Correlation of serum fractalkine levels with CIMT in hyperthyroidism group
CIMT: Carotid intima-media thickness

Table 3. Relation of fractalkine with cardiovascular parameters in regression analysis

Variables	B	p-value	95% CI
HR	-2.397	0.473	-9.101 to 4.308
CIMT	0.018	0.042	0.001 to 0.038
LVM	1.903	0.682	-7.428 to 11.234
LVMI	0.852	0.765	-4.889 to 6.593
LVEF	-0.685	0.137	-1.598 to 0.228
LAD	0.915	0.291	-0.815 to 2.644
LAVI	-0.152	0.929	-3.592 to 3.289
E	-3.910	0.398	-13.176 to 5.357
A	-3.666	0.374	-11.925 to 4.593
E/A	0.034	0.704	-0.145 to 0.213
e'	-0.525	0.353	-1.655 to 0.606
a'	-0.929	0.019	-1.699 to -0.159
E/e'	0.002	0.996	-0.743 to 0.746
RVTAPSE	-0.537	0.253	-1.474 to 0.400
Tricuspid S'	-0.162	0.600	-0.781 to 0.457

Model including age, gender, BMI, and fractalkine
HR: Heart rate, LVM: Left ventricular mass, LVMI: Left ventricular mass index, LVEF: Left ventricular ejection fraction, E: Early diastolic mitral inflow velocities, e': Early diastolic mitral annular velocity, A: Late diastolic mitral inflow velocities, a': Late diastolic mitral annular velocity, RVTAPSE: Right ventricular tricuspid annular plane systolic excursion, Tricuspid S': Tricuspid lateral annulus systolic velocity, LAD: Left atrial diameter, LAVI: Left atrial volume index, BMI: Body mass index

Discussion

In the present study, serum fractalkine levels were higher in patients with hyperthyroidism compared to controls and were associated with increased CIMT. All echocardiographic parameters were within normal reference ranges; however, certain indices, including TAPSE, Tricuspid S', LAVI, E, and e', were significantly higher in the hyperthyroid group. In this context, our study aimed to assess serum fractalkine levels in patients with hyperthyroidism and to investigate their association with CV parameters in treatment-naive individuals. We observed that higher fractalkine levels were associated with the diastolic parameter a', which has been related to HFpEF. These results suggest that fractalkine may be associated with early CV alterations in hyperthyroidism.

The chemokine fractalkine, also known as CX3CL1, is expressed in a variety of cells, including inflammatory cells, cardiomyocytes, endothelial cells, and smooth muscle cells (11). Possessing leukocyte-chemotactic and vasoconstrictive properties, fractalkine plays a pivotal role in CVD. In 2014, Fujita et al. (6) discovered that the chemokine domain of fractalkine also binds directly to integrin $\alpha v\beta 3$ independently of CX3CR1 and thereby activates the integrin. This binding site is near the Arg-Gly-Asp recognition site of integrin $\alpha v\beta 3$, proximal to the thyroid hormone-tetrac receptor on that integrin. Consequently, fractalkine may exert integrin-dependent functions in cells lacking CX3CR1 expression. The presence of this chemokine binding site on integrin $\alpha v\beta 3$ raises the possibility of interactions between hormone binding and fractalkine binding sites on integrin that may be influenced by high levels of T4 (7). Davis et al. (7,12) have indicated that the regulation of the thyroid hormone receptor on integrin $\alpha v\beta 3$ is subject to the expression of fractalkine, a chemotactic cytokine, and its receptor genes. In our study, we found that serum fractalkine levels were higher in treatment-naive hyperthyroid patients without known CVD than in an age- and gender-matched control group. Consequently, it may be hypothesized that elevated endogenous T4 levels contribute to the development of CVD by enhancing activation of the fractalkine-integrin $\alpha v\beta 3$-T4 signaling pathway. However, as fractalkine is not yet an established biomarker in routine clinical practice, these findings should be considered hypothesis-generating and should be validated in larger, prospective studies.

Numerous pieces of evidence support the involvement of fractalkine in CVD (13,14). Husberg et al. (14) were the first to discover an increase in fractalkine protein within the heart tissue of HF patients using western blot analysis. They also noted elevated levels of serum fractalkine in HF patients. In 2019, Ji et al. (15) demonstrated a significant rise in serum fractalkine levels in HF patients compared to healthy individuals, with levels escalating in tandem with the severity of HF. Additionally, they observed heightened fractalkine levels in HF patients who faced readmission within a year. Furthermore, Richter et al. (16) reported fractalkine as an independent predictor of mortality in advanced HF patients. In a cohort of AF patients recruited prospectively, Guo et al. (17) established that serum fractalkine independently predicted the risk of major adverse CV and cerebrovascular events. They concluded that lower plasma fractalkine levels were associated with a

reduced risk of such events in AF patients. Moreover, Gu et al. (13) employed two models of HF resulting from myocardial infarction and demonstrated that fractalkine neutralizing antibody therapy significantly improved the survival rate of mice. They also discussed the preventive effects of this therapy on cardiac hypertrophy and remodeling post-myocardial infarction. Fractalkine-associated pathways contribute to the development and severity of CVDs, suggesting potential for developing treatment strategies that target these pathways. In our treatment-naive hyperthyroid patients, elevated serum fractalkine levels were observed even in the absence of overt CVDs. This finding may suggest an association between fractalkine and early CV alterations; however, its clinical significance remains to be clarified.

It has been demonstrated that approximately 6% of patients with overt hyperthyroidism develop HF (18). Patients with HF are clinically categorized into two groups based on LVEF: those with reduced LVEF (HFrEF) and those with preserved LVEF (HFpEF); 50% of patients fall into the latter category. A recent clinical trial revealed that patients with HFpEF exhibit a prognosis similar to that of those with HFrEF, emphasizing the clinical significance of both categories (19). Oike et al. (20) proposed that a decreased a' during sinus rhythm, serving as an indicator of atrial pump dysfunction, could be a valuable risk marker in HFpEF patients. They demonstrated a higher prevalence of CV and HF-related events in HFpEF patients with low a' levels during sinus rhythm. In our study, LVEF was within the normal range and comparable between the control and hyperthyroid groups. Furthermore, there was no notable difference in the parameter a' between the two groups. However, a statistically significant negative correlation was observed between fractalkine levels and a' in our hyperthyroid patient group, indicating that increased serum fractalkine levels corresponded to lower a' levels.

Since LVEF remains unimpaired in half of individuals with hyperthyroidism-related HF, diastolic dysfunction may also contribute to the development of this condition. However, the studies found controversial results on diastolic function (21-26). Yue et al. (25), who included young hyperthyroid patients in their study similar to ours, found increased diastolic function, as determined by e'. However, they also demonstrated an escalation in diastolic dysfunction associated with advancing age, reaching approximately 100% in individuals aged over 60 years (25), along with a higher BMI (26). No evidence of diastolic dysfunction was observed in either group; however, the parameter e', indicative of LV myocardial relaxation, was notably higher in the hyperthyroidism group. This finding may be explained by the youthfulness of our patient cohort and their lower BMI, which is consistent with existing literature. The increase in diastolic function may be attributed to a compensatory mechanism, which could lead to diastolic dysfunction. However, further studies are needed to validate this hypothesis. No association between fractalkine levels and e' was observed in our study.

There is limited information available regarding the impact of hyperthyroidism on RV systolic function. A simplified measure of RV systolic function, based on RVTAPSE and tricuspid S' may suffice to characterize RV performance. Controversial results were reported on RVTAPSE and Tricuspid S' in hyperthyroid patients (27,28). Some studies reported comparable TAPSE between control and hyperthyroid groups (27), while others reported decreased values (21) or increased values (28). In our study, RVTAPSE and Tricuspid S' were higher in the hyperthyroid group. Similarly, Arinc et al. (28) reported an increase in RV systolic function measured by tissue Doppler imaging. Our findings may once again be explained by a potential compensatory mechanism, observed in young, lean patients without CVD or any discernible risk factors, that may or may not culminate in RV systolic dysfunction. No association was observed between fractalkine levels and RVTAPSE and Tricuspid S' in our study.

Furthermore, we observed increased LAVI in hyperthyroid patients, although values remained within normal reference ranges. Aroditis et al. (21) also noted higher LAVI in Graves' patients compared to controls. However, Shojaeifard et al. (29) reported no significant differences in LAVI between groups. The elevated LAVI values in our patient group, coupled with a prolonged duration of hyperthyroidism, suggest an increased risk of AF. Additionally, our patients exhibited a significantly shorter PR interval, indicating susceptibility to supraventricular arrhythmias. However, our study did not establish a correlation between serum fractalkine levels and either LAVI or PR interval, suggesting no association between fractalkine levels and the risk of arrhythmias.

CIMT, which assesses structural changes in the vascular wall, is a useful noninvasive marker of subclinical atherosclerosis (30). Vascular changes predict CV events independently of CV risk factors such as hypertension or dyslipidemia. In our study, the hyperthyroid group exhibited a statistically significant increase in CIMT compared with healthy controls. The underlying mechanisms of increased CIMT in our patient group, which mainly consists of GD patients, may involve inflammatory and autoimmune processes. The excessive secretion of thyroid hormones and chemokines, such as fractalkine, may contribute to vascular atherosclerosis. Recently, Pettersson-Pablo et al. (31) reported a significant correlation between fractalkine and CIMT in a multivariable model among young healthy adults. Notably, this study is the first to establish a significant relationship between serum fractalkine levels and CIMT in hyperthyroid patients.

Study Limitations

The primary limitations of this study include its cross-sectional, single-center design, relatively small sample size, and lack of prospective follow-up for arrhythmic outcomes. In addition, the absence of quantitative TSH receptor antibody measurements limits our ability to determine whether the observed association between fractalkine and hyperthyroidism is primarily related to elevated thyroid hormone levels or to underlying autoimmune inflammatory processes. Furthermore, the inclusion of both patients with GD and those with toxic nodular goiter may have introduced heterogeneity, as these conditions have distinct pathophysiological mechanisms that could differentially influence the results. Finally, the predominantly female study population may limit the generalizability of the findings.

Conclusion

Our study demonstrated that fractalkine levels were higher in individuals with hyperthyroidism than in controls. In addition, fractalkine levels were associated with CIMT and a diastolic parameter related to HFpEF. These findings suggest a potential association between fractalkine and CV alterations in hyperthyroid patients. Overall, our results indicate that fractalkine may be associated with CV parameters in individuals with hyperthyroidism.

Ethics

Ethics Committee Approval: Ethical approval was granted by the Ethics Committee of Gülhane Training and Research Hospital (approval no: 2021/6, date: 24.03.2021).

Informed Consent: Written informed consent was obtained from all participants prior to their enrollment in the study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: N.E.G., Concept: N.E.G., Design: Ş.A., N.E.G., Data Collection or Processing: M.A., Ş.A., S.A., Analysis or Interpretation: Ş.A., N.E.G., Literature Search: Ş.A., N.E.G., Writing: M.A., Ş.A., N.E.G.

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CD20-positive multiple myeloma complicated by cold agglutinin disease

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ABSTRACT

Cluster of differentiation 20 (CD20) expression is rarely observed in multiple myeloma (MM) and is typically associated with immature plasma cell morphology and aggressive clinical behavior. Cold agglutinin disease (CAD) is also uncommon in MM and usually suggests other hematologic malignancies. We present a rare case of CD20-positive MM complicated by CAD in a 77-year-old woman who initially had pancytopenia, bone pain, and renal failure. Diagnostic work-up revealed light chain MM with kappa restriction, cast nephropathy, and diffuse CD20 expression in plasma cells. She was treated with bortezomib, cyclophosphamide, and dexamethasone (VCD), achieving hematologic improvement and partial renal recovery. During the third cycle, she developed severe anemia and hemolysis due to cold agglutinins, which were managed successfully with corticosteroids and supportive care. Retrospective immunohistochemistry confirmed CD20 positivity. This case underscores the diagnostic and therapeutic complexity of atypical MM presentations and highlights the importance of re-evaluating immunophenotypic features when the clinical course deviates from expectations. While CD20-targeted therapies are not routinely used in MM, their relevance in selected subtypes warrants further exploration. Our case illustrates the potential for paraneoplastic hemolysis and phenotypic diversity in MM, emphasizing the need for a multidisciplinary approach to diagnosis and management.

Introduction

Cluster of differentiation 20 (CD20) is typically absent in terminally differentiated plasma cells and is not routinely expressed in plasma cell dyscrasias. Its expression is often associated with immature or plasmablastic morphology and has been linked to more aggressive clinical behavior (1). Cold agglutinin antibodies are also rarely reported in the context of multiple myeloma (MM), and their presence typically prompts investigation for alternative underlying hematologic malignancies such as lymphoma (2). Herein, we describe an unusual case of MM with both CD20 positivity and cold agglutinin hemolytic anemia, highlighting the diagnostic complexity and potential therapeutic implications.

Case Report

A 77-year-old woman was admitted with pancytopenia and subacute renal failure. She had a recent history of analgesic use, and the initial evaluation suggested acute tubulointerstitial nephritis, which prompted treatment with methylprednisolone (0.5 mg/kg/day). Laboratory workup revealed the following values: hemoglobin 6.9 g/dL; neutrophils 660/mm^3; platelets 81.000/mm^3; serum creatinine 2.99 mg/dL; and urea 105 mg/dL. Hematology consultation was requested after progressive cytopenias were noted. Peripheral smear revealed teardrop cells and a leukoerythroblastic picture; there was no organomegaly, but the patient reported widespread bone pain. The reticulocyte count was low, consistent with hypoproliferative anemia. Steroids were discontinued. Bone marrow aspiration was attempted but resulted in a dry tap. Imprint smears showed an increased number of plasma cells, but the findings were initially non-diagnostic. Due to a dry tap during bone marrow aspiration, fluorescence *in situ* hybridization analysis could not be performed; therefore, the status of t(4;14) and t(11;14) translocations remains unknown.

Renal biopsy demonstrated tubular cast formation and associated inflammation. The presence of kappa light chain-positive casts was consistent with cast nephropathy, with no evidence of neoplastic plasma cells (Figure 1). Serum protein electrophoresis showed immunoparesis without an M spike. Serum free light- chain levels were low. Bone marrow biopsy showed infiltration by CD138+, CD38+, MUM1+, kappa+ atypical plasma cells (Figure 2). Expression of Cyclin D1 and c-*MYC* was observed, and reticulin fibrosis ranged from moderate to severe. Congo red staining was negative.

Serum and urine immunofixation revealed kappa monoclonality. The free kappa and lambda light chains were 136 mg/L and 3.84 mg/L, respectively. Positron emission tomography-computed tomography showed diffuse axial marrow fluorodeoxyglucose (FDG) uptake and mild splenic FDG uptake (maximum standardized uptake value 4.6), suggesting extramedullary involvement. Based on these findings, a diagnosis of light-chain MM was made, and treatment with a bortezomib, cyclophosphamide, and dexamethasone (VCD) regimen was initiated. The patient showed improvement in cytopenias with complete resolution of neutropenia and thrombocytopenia. Renal function partially recovered, and a partial hematologic response was achieved.

During the third cycle of therapy, the patient presented with severe anemia (hemoglobin: 4.9 g/dL), jaundice, and fatigue. Despite negative direct and indirect Coombs tests, cold agglutinin antibodies were detected qualitatively, and the titer was not assessed. Serum lactate dehydrogenase level was 335 U/L, serum C3 was 1 g/L, and serum C4 was 0.35 g/L. High-dose methylprednisolone (1 mg/kg/day) was administered. Citrate-treated, crossmatched blood transfusions were administered without reaction, and the hemoglobin concentration improved to 11.6 g/dL. The patient died of coronavirus disease-19 (COVID-19) infection shortly after cold agglutinin disease (CAD) resolved.

Retrospective immunohistochemical analysis of the initial bone marrow biopsy performed after the onset of CAD revealed diffuse CD20 expression in plasma cells (Figure 2). While this did not alter the initial therapeutic strategy, the co-occurrence of CD20 expression and CAD raises important considerations regarding the potential for alternative or adjunctive therapeutic approaches in similar future cases.

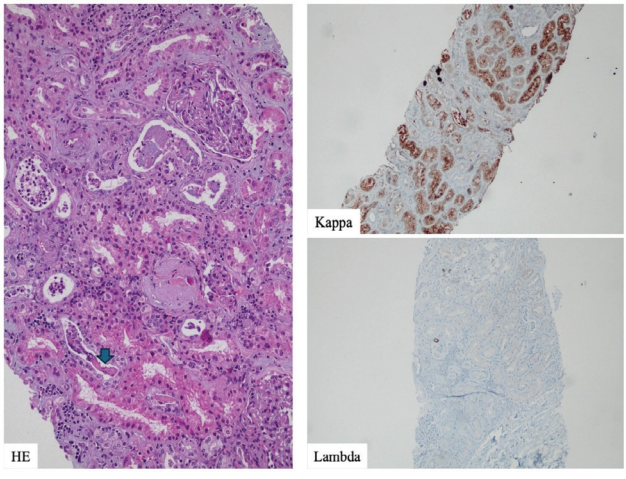

Figure 1. The pathological findings of the renal biopsy specimen. Renal biopsy specimen showing no infiltration of neoplastic plasma cells. The arrow indicates eosinophilic amorphous material within the tubular lumen in a focal area, consistent with kappa-positive cast nephropathy (H&E stain, magnification ×30)

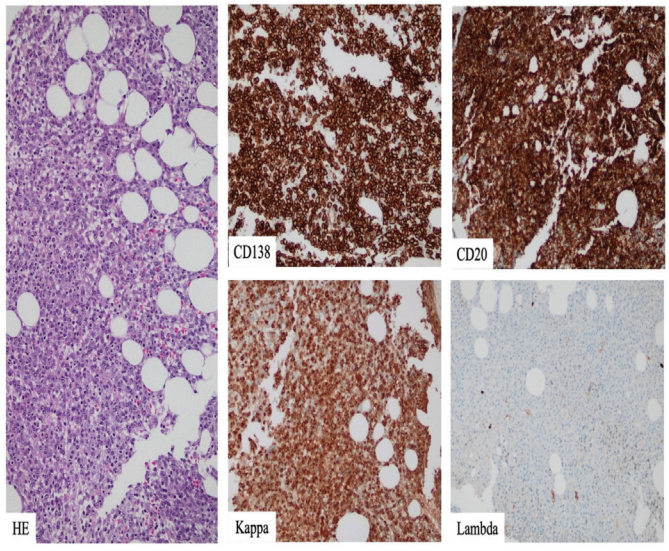

Figure 2. The bone marrow biopsy findings. Bone marrow biopsy showing sheets of neoplastic plasma cells on H&E staining (magnification ×30). Immunohistochemical analysis demonstrated diffuse CD20 positivity in nearly all plasma cells

CD: Cluster of differentiation

Discussion

CD20 is a transmembrane phosphoprotein functioning as a calcium ion channel on the B-cell membrane, involved in activation and differentiation. Its biological significance in plasma cells remains uncertain (3). CD20 expression is rare in MM, representing deviation from the conventional plasma cell immunophenotype and suggesting clonal heterogeneity or an alternative differentiation pathway (4). In a study by Yavasoglu et al. (3) including 61 MM cases, CD20 positivity (>10%) was observed in 48.9% of patients. Similarly, Li et al. (5) analyzed 62 CD20-positive MM cases and found that this phenotype was often associated with t(11;14) translocation, lower CD56 expression, and reduced extramedullary disease, suggesting a distinct biological subset.

Khatun et al. (6) reported a psoriatic patient with cold agglutinin disease secondary to non-immunoglobulin M (IgM) MM, manifesting hepatomegaly rather than splenomegaly, and a lymphoma-like disease course. CD20 expression was not evaluated in that case.

Cold agglutinins are IgM antibodies that bind erythrocytes at low temperatures, leading to complement-mediated hemolysis. They are most often seen in lymphoproliferative disorders or secondary to infections and autoimmune diseases (7). No secondary cause was identified in our patient, suggesting a paraneoplastic mechanism directly related to MM (8). The coexistence of cold agglutinin hemolytic anemia and mildly FDG-avid spleen prompted re-evaluation for B-cell markers, revealing CD20 expression on plasma cells-an unexpected feature in typical MM. This observation underscores that, in MM patients presenting with immune cytopenias and subtle splenic findings, CD20-positive plasma cell disease should be considered in the differential diagnosis.

Similarly, cold-induced cutaneous manifestations initially attributed to cold agglutinin disease have been linked to underlying MM, highlighting the need to investigate hematologic malignancies in such presentations. While the previously reported case lacked organomegaly or lymphadenopathy (9), our patient exhibited non-palpable splenomegaly and increased FDG uptake in the spleen, compatible with a lymphoplasmacytic pattern or CD20-positive MM. Differential diagnosis such as Waldenström macroglobulinemia were considered; however, the absence of lymphoplasmacytic infiltration and IgM monoclonal protein supported the diagnosis of CD20-positive multiple myeloma. Kidney pathological findings and the patient's clinical presentation were compatible with multiple myeloma instead of Waldenström macroglobulinemia.

Our patient demonstrated kappa light chain restriction, CD20 expression, suspected splenic involvement, and cold agglutinin-mediated hemolysis, reflecting the biological diversity of MM. Although anti-CD20 therapy is not standard in MM, its potential role in CD20-positive subtypes warrants further study (10-12). Notably, recent data suggest that CD20 expression in MM may define a subgroup with small mature plasma cell morphology and t(11;14) translocation, which may exhibit indolent clinical behavior but distinct treatment response profiles (1,13). Our patient responded favorably to corticosteroids and VCD without rituximab, but the retrospective identification of CD20 expression highlights its possible prognostic and therapeutic implications in atypical or refractory cases. Although CD20 expression in MM is rare, anti-CD20 monoclonal antibody therapy (rituximab) has been used in isolated cases. However, evidence regarding clinical benefit or prognostic impact remains limited. Unfortunately, our patient developed a COVID-19 infection shortly after starting steroid treatment; the anemia improved during that treatment. Therefore, rituximab was not used.

According to the study by Khaled et al. (14), CD20 expression may emerge at relapse as a secondary genetic event linked to disease aggressiveness, proposing its role as a prognostic and therapeutic marker. Early CD20 expression, as observed in our patient, may therefore represent an immunophenotypic shift along the B-cell to plasma-cell continuum.

Mohamed et al. (15) described a 69-year-old woman with primary CAD and a small clonal plasma cell population who achieved transfusion independence with daratumumab after rituximab failure. This highlights daratumumab as a potential option for refractory CAD associated with clonal B-cell disorders and suggests that it may have implications for CD20-positive MM with immune cytopenias.

IgA-type plasma cell neoplasia presenting with cold agglutinin-mediated hemolytic anemia, as exemplified by our patient, has also been documented in the literature, underscoring the necessity of comprehensive clinicopathological correlation to ensure accurate diagnosis of such atypical presentations (16).

This case illustrates a rare MM phenotype characterized by CD20 expression, CAD, and kappa light chain-associated cast nephropathy. It emphasizes the importance of re-evaluating the immunophenotype in MM patients with immune-mediated cytopenias or organ involvement, and supports multidisciplinary correlation for accurate classification and optimized management.

Ethics

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.C.Ö., A.Y., M.A., Concept: D.K., Ö.C., Design: D.K., H.C.Ö., Ö.C., A.Y., Data Collection or

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Fatal hypercalcaemic crisis and acute kidney injury revealing undiagnosed multiple myeloma in an elderly woman: a case report

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ABSTRACT

Hypercalcaemic crisis is an uncommon initial presentation of multiple myeloma and may rapidly become life-threatening if not recognized promptly. An 83-year-old woman presented with severe hypercalcaemia and acute kidney injury, accompanied by progressive confusion and reduced consciousness. Serum protein electrophoresis revealed a monoclonal immunoglobulin G -lambda spike. The electrocardiography showed a shortened QT interval and Osborn waves. Despite hydration, corticosteroids, and supportive therapy, the patient deteriorated and died within 31 hours. This case underscores the importance of early biochemical evaluation in elderly patients with unexplained hypercalcaemia, as delayed recognition significantly worsens the prognosis.

Introduction

Hypercalcaemia represents a clinically significant metabolic abnormality most frequently encountered in association with primary hyperparathyroidism and malignant disease, which together account for the majority of cases (1). Although relatively uncommon in the general population, its incidence increases substantially with advancing age (2). In the oncological setting, hypercalcaemia often reflects advanced disease burden and carries important prognostic implications.

Multiple myeloma is a plasma cell dyscrasia predominantly affecting older adults and constitutes a leading haematological cause of malignancy-associated hypercalcaemia (3-6). Excessive osteoclastic bone resorption, driven by tumour-related cytokine signaling, results in calcium release and progressive skeletal destruction (7-9). Severe hypercalcaemia may culminate in a hypercalcaemic crisis, a medical emergency characterized by neurological impairment, cardiovascular instability, and renal dysfunction, with mortality rates reported to exceed 50% in the absence of timely treatment (10,11).

Recognition of hypercalcaemia in older adults is frequently delayed because presenting symptoms are non-specific and may be misattributed to ageing or comorbid conditions. Consequently, early biochemical investigation plays a crucial role in identifying reversible causes and preventing catastrophic outcomes.

We report a fatal hypercalcaemic crisis with acute kidney injury as the initial manifestation of previously undiagnosed multiple myeloma in an elderly woman, highlighting the diagnostic challenges and the narrow therapeutic window associated with this presentation.

Case Report

An 83-year-old woman was admitted to the nephrology department with acute kidney injury and progressive deterioration in mental status. According to family members, she had experienced increasing weakness, constipation, back pain, and gait instability over one week, followed by a marked reduction in alertness. For approximately three days before admission, she remained in a stuporous state and was unable to communicate or follow commands. There was no known history of malignancy, and she was not receiving medications known to influence calcium metabolism. Her medical history included arterial hypertension, an ischaemic stroke involving the right middle cerebral artery territory two decades earlier, and a surgically treated lumbar disc herniation.

The patient's regular medications included valsartan/amlodipine 160/80 mg, atenolol 100 mg, corneline 20 mg, atorvastatin 20 mg, pentoxifylline, pantoprazole, and intermittent diazepam. She was not receiving calcium supplements, vitamin D, thiazide diuretics, lithium, or any other medications known to affect calcium metabolism.

On examination, the patient responded only to painful stimuli. Blood pressure, heart rate, and oxygen saturation were within normal limits, and urine output was preserved. Clinical signs of intravascular dehydration were evident, including dry mucous membranes and reduced skin turgor; mild bilateral lower-limb oedema was attributed to hypoalbuminaemia and reduced mobility. Residual neurological deficits from prior cerebrovascular disease included left facial paresis and left-sided hemiparesis. Cardiopulmonary and abdominal examinations revealed no additional abnormalities.

Albumin-corrected calcium, calculated using the standard formula [corrected calcium = measured total calcium+0.02×(40-serum albumin)], was approximately 4.2 mmol/L (16.9 mg/dL), confirming a hypercalcaemic crisis. Laboratory findings were also consistent with acute kidney injury, reflected by elevated urea [31.7 mmol/L (190 mg/dL)] and creatinine [229 µmol/L (2.59 mg/dL)]. The estimated glomerular filtration rate [estimated glomerular filtration rate (eGFR), chronic kidney disease epidemiology collaboration] was 18 mL/min/1.73 m^2, consistent with severe renal impairment. Additional abnormalities included leukocytosis, normocytic anaemia, marked hyperproteinaemia with hypoalbuminaemia, and elevated globulin levels. Immunological testing revealed a marked increase in immunoglobulin G with lambda free light-chain predominance and a suppressed kappa-to-lambda ratio, findings indicative of monoclonal gammopathy. Alkaline phosphatase levels were within the normal range, and urinalysis was negative for Bence-Jones protein. A summary of biochemical and immunological findings is provided in Table 1.

Electrocardiography demonstrated left bundle branch block, significant QT interval shortening, and prominent Osborne (J) waves, consistent with severe hypercalcaemia. Non-contrast computed tomography of the brain showed diffuse cortical atrophy and chronic small-vessel ischaemic changes, without evidence of acute intracranial pathology (Figure 1).

Management included aggressive intravenous administration of isotonic saline and enteral fluid replacement via a nasogastric tube to correct dehydration and enhance renal calcium

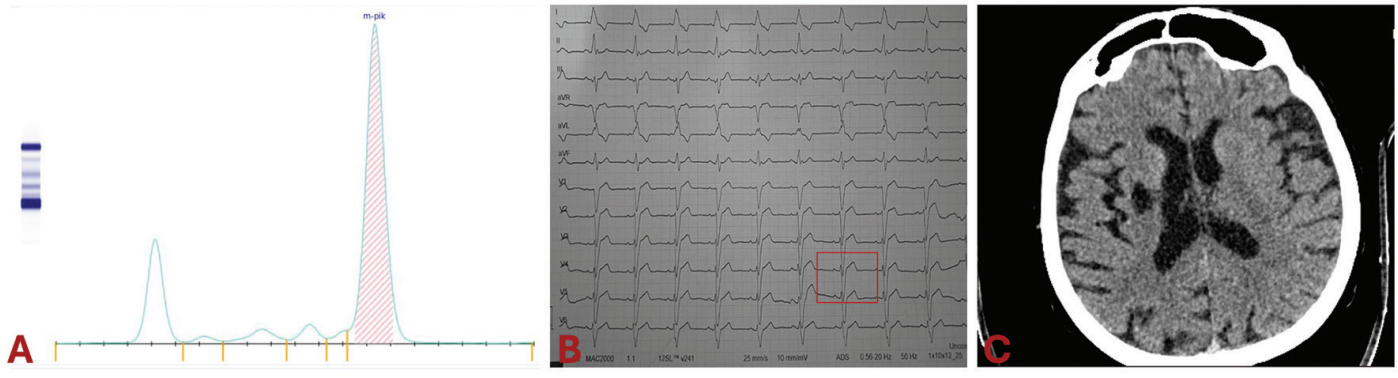

Figure 1. Electrocardiographic, laboratory, and neuroimaging findings in severe hypercalcaemia. (A) Serum protein electrophoresis demonstrating a dominant monoclonal M-spike in the gamma region, consistent with monoclonal gammopathy. (B) Twelve-lead electrocardiogram showing left bundle branch block, marked QT-interval shortening, and prominent Osborne (J) waves (highlighted), characteristic of severe hypercalcaemia. (C) Non-contrast axial brain computed tomography scan demonstrating global cortical atrophy and chronic small-vessel ischemic changes, without evidence of acute intracranial pathology

Table 1. Biochemical and immunological findings in hypercalcaemic crisis at presentation

Parameter	Patient value	Reference range	Clinical interpretation
Inflammatory markers			
C-reactive protein	7.4 mg/L	<5	Mild inflammatory response
Procalcitonin	0.21 ng/mL	<0.5	No evidence of bacterial sepsis
Haematology			
White blood cells	25.5×10^9/L	4-9	Leucocytosis with left shift
Haemoglobin	102 g/L	120-180	Anaemia (CRAB criterion)
Platelets	237×10^9/L	150-450	Normal
Renal and metabolic parameters			
Urea	31.7 mmol/L (190 mg/dL)	2.7-7.8	Acute kidney injury
Creatinine	229 µmol/L (2.59 mg/dL)	45-109	Reduced eGFR
eGFR	18 mL/min/1.73 m^2	>60	Severe renal impairment
Uric acid	787 µmol/L	150-450	Hyperuricemia
Sodium	132 mmol/L	136-145	Mild hyponatremia
Potassium	3.7 mmol/L	3.8-5.5	Slightly decreased
Calcium-phosphate metabolism			
Total calcium	3.9 mmol/L	2.1-2.6	Severe hypercalcemia
Corrected calcium	4.2 mmol/L (16.9 mg/dL)	—	Hypercalcaemic crisis
Parathyroid hormone	92.6 pg/mL	12-88	Inappropriately normal/slightly elevated (secondary to renal dysfunction)
Vitamin D (25-OH)	<20 nmol/L	50-125	Deficiency
Alkaline phosphatase	67 U/L	36-126	Normal (osteolytic pattern)
Protein profile and immunology			
Total protein	127 g/L	63-83	Marked hyperproteinemia
Albumin	23 g/L	35-50	Hypoalbuminemia
Globulins	104 g/L	28-33	Markedly elevated
IgG	96.6 g/L	7.8-16.2	Monoclonal IgG excess
Free light chains (λ)	11.8 g/L	0.9-2.1	Markedly increased
Free light chains (κ)	0.08 g/L	1.7-3.7	Suppressed
κ/λ ratio	0.007	1.35-2.65	Lambda-restricted clonality
Serum protein electrophoresis			
Gamma globulin fraction	81.1 g/L (68.2%)	4.8-11.9 g/L (6.2-15.4%)	Dominant monoclonal component
Albumin fraction	23.1 g/L (19.4%)	46-56 g/L (60.3-72.8%)	Reduced
M-component	M1: 76.7 g/L (64.5%)	—	Paraproteinemia
A/G ratio	0.24	—	Markedly reduced
Urine analysis			
Bence-Jones protein	Negative	Negative	Absent
Coagulation marker			
D-dimer	2100 ng/mL	<500	Elevated (stress/inflammation related)

eGFR: Estimated glomerular filtration rate, IgG: Immunoglobulin G, CRAB: HyperCalcaemia, renal impairment, anaemia, and bone lesions, A/G: Albumin-to-globulin ratio

excretion. Empirical cephalosporin therapy was initiated due to mildly elevated inflammatory markers. Following a haematology consultation, multiple myeloma was strongly suspected, and a bone marrow biopsy was planned. Corticosteroid therapy was commenced; however, bisphosphonate treatment with zoledronic acid was contraindicated due to a severely reduced eGFR (18 mL/min).

Despite supportive measures, the patient's neurological and cardiovascular status deteriorated rapidly. Thirty-one hours after admission, she progressed to a deep coma and developed

refractory bradycardia, followed by asystole. Cardiopulmonary resuscitation was unsuccessful. Post-mortem evaluation, including review of skeletal imaging and skull radiographs, revealed multiple lytic bone lesions and a monoclonal spike on serum protein electrophoresis, confirming previously unrecognized multiple myeloma as the underlying cause of the hypercalcaemic crisis and acute kidney injury.

The patient described in this report is deceased, and written informed consent could not be obtained; however, all identifying information has been removed to ensure complete anonymity.

Discussion

Multiple myeloma may remain clinically silent for prolonged periods, with diagnosis frequently established only after the development of end-organ damage. Although hypercalcaemia is a recognized feature of symptomatic disease, presentation as a hypercalcaemic crisis is uncommon and is associated with substantial mortality (3,7-9,12). In the present case, the severity of metabolic derangement and neurological impairment at admission suggests that the underlying plasma cell disorder had progressed significantly before clinical recognition.

The pathogenesis of hypercalcaemia in multiple myeloma is predominantly related to excessive osteoclastic bone resorption driven by tumour-derived cytokines, including receptor activator of nuclear factor-κB ligand and interleukin-6, with concomitant suppression of osteoblast activity (3,7,14). This mechanism accounts for the presence of extensive osteolytic lesions and explains the normal alkaline phosphatase levels observed in this patient, a finding that helps distinguish osteolytic malignancy from primary hyperparathyroidism or osteoblastic metastatic disease (3,7,14).

Neurological deterioration, progressing from confusion to stupor and coma, represents a hallmark of severe hypercalcaemia and reflects direct neurotoxicity, cerebral dehydration, and impaired neuronal excitability (10,11). In this case, electrocardiographic abnormalities, including QT interval shortening, left bundle branch block, and Osborn (J) waves, indicated profound electrolyte imbalance. Although Osborne waves are classically associated with hypothermia, they have been rarely described in severe hypercalcaemia and may signal advanced metabolic instability with increased risk of fatal arrhythmias (15). Their presence may therefore serve as an important, albeit under-recognized, diagnostic clue in hypercalcaemic emergencies.

Renal dysfunction in this patient was likely multifactorial, resulting from hypercalcaemia-induced renal vasoconstriction, intravascular volume depletion, and light-chain-mediated nephrotoxicity (4,12). The combination of acute kidney injury and markedly reduced eGFR significantly limited therapeutic options, precluding early administration of bisphosphonates and delaying consideration of renal replacement therapy. This narrow therapeutic window highlights the critical importance of early detection and intervention before irreversible organ damage occurs. In patients with malignancy-associated acute kidney injury, severe renal impairment substantially restricts therapeutic options, and the use of potentially nephrotoxic agents such as intravenous bisphosphonates should be avoided or postponed because of the risk of further deterioration in kidney function (4).

The absence of detectable Bence-Jones protein in the urine does not exclude multiple myeloma, as urinary testing may be negative in cases with predominant intact immunoglobulin secretion or low free light-chain excretion. Serum protein electrophoresis and free light-chain assays were more sensitive in detecting monoclonal gammopathies and were diagnostic in this patient.

In this case, the acute kidney injury was considered predominantly prerenal, resulting from severe dehydration and hypercalcaemia-induced renal vasoconstriction, with a possible contributory role of light-chain-related nephrotoxicity.

Although intravenous bisphosphonates represent standard therapy for malignancy-associated hypercalcaemia, their use was deferred in this patient due to severely reduced renal function (eGFR 18 mL/min/1.73 m^2) and the associated risk of worsening acute kidney injury, particularly given the limited time window for therapeutic benefit.

Given the extremely rapid progression to cardiopulmonary arrest within 31 hours, the window for initiating renal replacement therapy was critically limited. Despite initially stable hemodynamics, the progression to deep coma and refractory bradyarrhythmia occurred before dialysis could be safely initiated, reflecting the fulminant nature of the hypercalcaemic crisis in this elderly patient.

The rapid and fatal course observed in this case underscores the diagnostic challenge posed by non-specific symptoms in elderly patients, in whom early manifestations of hypercalcaemia may be misattributed to ageing or comorbid disease. Clinicians should maintain a high index of suspicion for multiple myeloma in older individuals presenting with unexplained hypercalcaemia, renal impairment, anaemia, or neurological changes. Prompt biochemical evaluation and timely initiation of disease-directed therapy remain essential to preventing catastrophic outcomes in this high-risk population.

Conclusion

This case highlights hypercalcaemic crisis as a rare but severe initial presentation of multiple myeloma, particularly in elderly patients with non-specific symptoms. The combination of marked hypercalcaemia, acute kidney injury, and delayed diagnosis resulted in a rapid and fatal course. Early recognition of the clinical triad of hypercalcaemia, renal dysfunction, and

anaemia is essential, as prompt treatment and timely myeloma-directed therapy may significantly improve outcomes.

Ethics

Informed Consent: Written informed consent could not be obtained due to the patient's death; publication was approved in accordance with institutional policy and ethical standards.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.S., S.P.K., B.G., Concept: H.S., S.P.K., A.C.T., B.G., Design: H.S., S.P.K., Data Collection or Processing: H.S., S.P.K., A.C.T., Z.P., B.G.; Analysis or Interpretation: H.S., S.P.K.; Literature Search: H.S., S.P.K., A.C.T., Z.P., B.G.; Writing: H.S., S.P.K., B.G.

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Concomitant Lennert-type peripheral T-cell lymphoma with presumed smear-negative pulmonary tuberculosis based on clinical and radiological findings: a case report

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ABSTRACT

Lennert lymphoma (LL), a rare lymphoepithelioid variant of peripheral T-cell lymphoma (PTCL), is characterized by an indolent clinical course compared to other PTCL subtypes. The coexistence of LL and pulmonary tuberculosis (TB), particularly smear-negative TB, is extremely rare and presents unique diagnostic and therapeutic challenges. We report a case of a 76-year-old man with underlying type 2 diabetes mellitus who presented with progressive left inguinal swelling, night sweats, weight loss, and loss of appetite over four months. Examination revealed multiple bilateral cervical and inguinal lymphadenopathy. Laboratory tests showed anaemia, leukocytosis, and raised inflammatory markers. Histopathological examination of the inguinal lymph node demonstrated total effacement of the lymphoid architecture by malignant lymphoid cells, admixed with epithelioid histiocytes and Reed-Sternberg-like cells. Immunohistochemistry confirmed LL with a $CD3^+/CD4^+/CD8^-$ immunophenotype. Initial staging computed tomography (CT) revealed multi-organ lymphadenopathy and tree-in-bud nodules in the right upper lobe, suggestive of pulmonary TB. Repeated sputum examinations for acid-fast bacilli were negative. The patient was empirically treated for presumptive smear-negative pulmonary TB and LL. He was treated with cyclophosphamide, epirubicin, vincristine, etoposide, and prednisone chemotherapy and HRZE anti-tuberculous therapy. Empirical anti-tuberculous therapy showed clinical response radiologically; however, despite initial clinical improvement, diagnostic complexities and treatment interactions between lymphoma and TB.

Introduction

Peripheral T-cell Lymphoma (PTCL) is an uncommon type of aggressive non-Hodgkin lymphoma. Lennert lymphoma (LL), a rare variant of PTCL, offers a better prognosis than other PTCL variants. Pulmonary tuberculosis (TB) is associated with immunodeficiency and B-cell lymphoma, which can cause T-cell immunodeficiency (1), and $CD4^+$ T-cells are vital for defense against pulmonary TB (2). Previous studies suggest TB increases the risk of lymphoma, particularly B-cell non-Hodgkin lymphoma; however, a definite causal relationship cannot be established between T-cell lymphoma and TB (3). Reactivation of pulmonary TB has also been reported mainly in Hodgkin lymphoma, rarely in T-cell lymphoma (4). To the best of our knowledge, concurrent LL and pulmonary TB have never been reported in the literature. We report a case of concurrent LL, a rare subtype of nodal PTCL, and smear-negative pulmonary TB in a 76-year-old man with known type 2 diabetes.

Case Report

A 76-year-old male with underlying type 2 diabetes mellitus, under regular follow-up at a health clinic, presented with a large left inguinal swelling of four months' duration, associated with night sweats, loss of appetite, and weight loss. There was no history of vomiting, jaundice, or fever. Other than that, there were no significant comorbidities or prior surgical procedures. He was a social drinker and did not smoke cigarettes or take any recreational drugs in the past. Informed consent was obtained from the patient's spouse for the anonymous use and publication of clinical and imaging data.

On examination, he was alert, pale, afebrile, and without jaundice. The abdomen was soft and non-tender; the liver and spleen were not palpable. His vital signs were unremarkable: blood pressure 100/60 mmHg; pulse rate 80 beats per minute, regular and of good volume; respiratory rate 18 breaths per minute; and he was afebrile with a temperature of 37 °C. Multiple cervical lymph nodes were present, the largest at left level Va. There was enlargement of multiple inguinal lymph nodes, the largest in the left inguinal region measuring approximately 4×3 cm.

Initial complete blood count showed bicytopenia and leukocytosis with haemoglobin 9.4 g/dL, total white blood cell $14.74\times10^3/\mu L$, neutrophil $13.12\times10^3/\mu L$, lymphocyte $4.7\times10^3/\mu L$, monocytes $0.86\times10^3/\mu L$, and platelets $137\times10^3/\mu L$. Subsequently, the peripheral blood film showed moderate anaemia with RBC features of iron deficiency anaemia, leukocytosis with neutrophilia, likely secondary to infection, and thrombocytopenia. Iron studies favour iron deficiency anaemia, with a low serum iron level of 6.9 μmol/L, unsaturated iron-binding capacity of 24.9 μmol/L, total iron-binding capacity of 31.8 μmol/L, and transferrin saturation of 21.7%. Liver function tests were within normal limits, with total protein 81 g/L, albumin 41 g/L, globulin 40 g/L, total bilirubin 6.3 μmol/L, alkaline phosphatase 127 U/L, alanine transaminase (ALT) 14 U/L, and aspartate transaminase (AST) 19 U/L. Lactate dehydrogenase was slightly elevated at 297 U/L, and C-reactive protein (CRP) was markedly elevated at 267 mg/L. Screening tests for hepatitis B (hepatitis B surface antigen), anti-hepatitis, and anti-human immunodeficiency virus were non-reactive.

An ultrasound-guided biopsy of the left inguinal lymph node was performed. Histopathological examination (HPE) of the lymph node showed total effacement of lymphoid architecture by malignant lymphoid cells that were closely intermixed with epithelioid histiocytes (Figure 1a) and scattered large Reed-Sternberg-like cells (Figure 1b). The malignant lymphoid cells display small-to-medium size, hyperchromatic nuclei with moderate nuclear pleomorphism, inconspicuous nucleoli, and scanty to clear cytoplasm. These malignant lymphoid cells were positive for CD3 (Figure 1c), CD5, and CD4 (Figure 1d), with downregulation of CD2 and CD7 (Figure 1e). They were negative for CD20, BCL6, CD79a, PAX5, CD8 (Figure 1f), CD23, CD10, PD1, CD56, CD30, ALK-1, CD15, TIA, perforin, and EBER ISH. The Ki-67 proliferative index was approximately 50%. Scattered large EBER-ISH-positive B-cells were present. The epithelioid histiocytes were highlighted by CD68 staining. The Ziehl-Neelsen stain was negative for acid-fast bacilli.

Initial computed tomography (CT) of the thorax, abdomen, and pelvis for staging (Figure 2) showed a left parotid mass, a pancreatic tail mass, and a large left thigh mass, accompanied by multiple abdominal and inguinal lymphadenopathy, likely representing multiorgan lymphoma involvement. In addition, the lung showed tree-in-bud nodules in the right upper lobe, suspicious for pulmonary tuberculosis. Conventional sputum acid-fast bacilli and auramine-stained smears were repeatedly performed and were negative for acid-fast bacilli; the mycobacterial culture was negative. CRP was elevated at 33 mg/L; however, erythrocyte sedimentation rate was not performed due to unavailability of the reagent at the time. Additional tests to confirm TB, such as polymerase chain reaction for TB, interferon-gamma release assay, and GeneXpert, were not available at our center at the time of the patient's presentation. Moreover, because of a low platelet count and severe anaemia throughout his illness, a biopsy of his lung lesion was not performed, as the procedure would likely cause more harm.

He was treated for advanced nodal PTCL, empirically treated for smear-negative pulmonary TB with lymph node involvement based on CT and HPE findings, and was started on cyclophosphamide, epirubicin, vincristine, etoposide, and prednisone (CHOEP) chemotherapy (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisolone) for three cycles. Based on the imaging, microbiological tests, and the high incidence of pulmonary TB in this area, he was also empirically treated for smear-negative pulmonary TB with a two-month

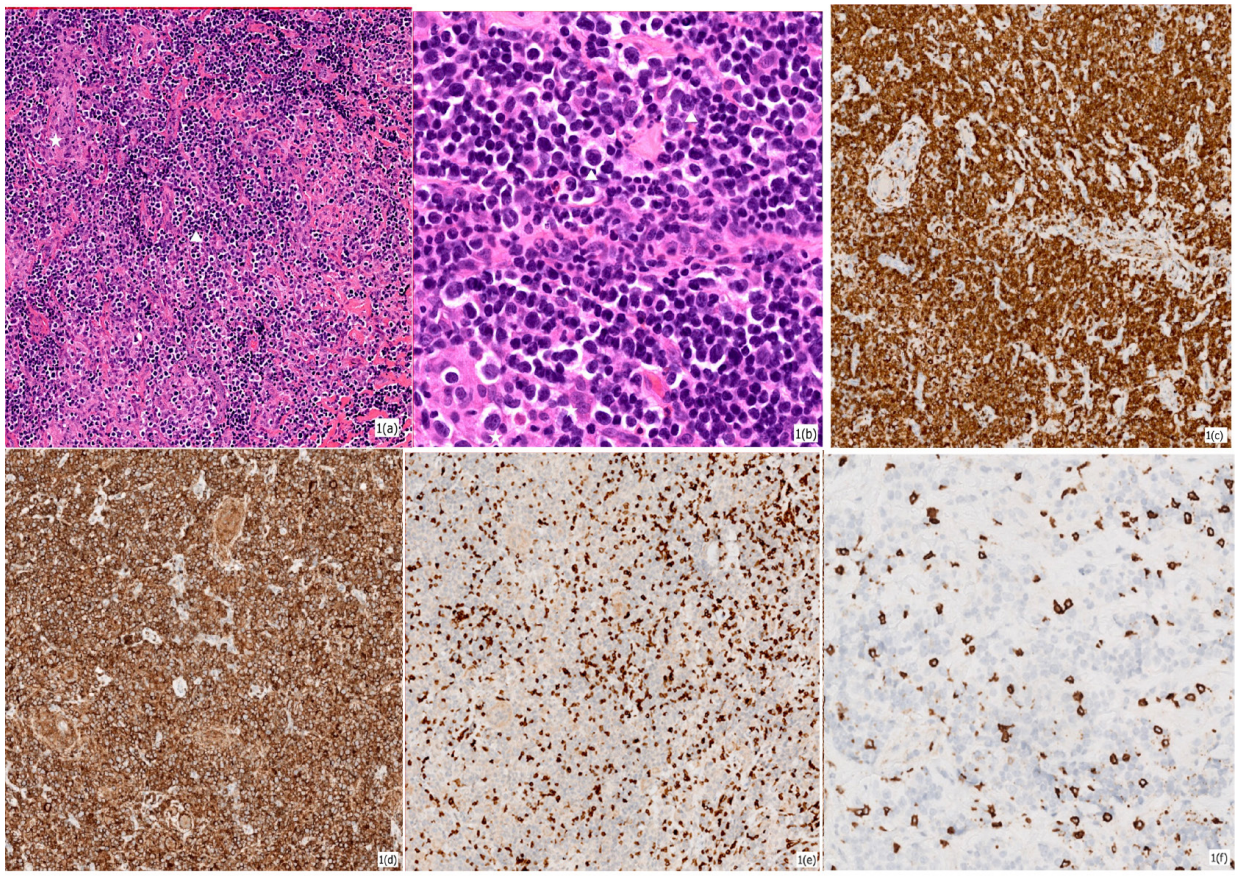

Figure 1. Histopathological examination of the left inguinal lymph node (a) showed malignant lymphoid cells (arrowhead) with epithelioid histiocytes in the background (star) [H&E staining (x100 magnification)]. (b) The malignant lymphoid cells display small to medium size, hyperchromatic nuclei with moderate nuclear pleomorphism, inconspicuous nucleoli, and scanty to clear cytoplasm (arrowhead) admixed with scattered large Reed-Sternberg-like cells (star) [H&E staining (x400 magnification)]. The malignant cells were diffusely positive for CD3 [(c) CD3 immunohistochemistry (x100 magnification)] and CD4 [(d) CD4 immunohistochemistry (x100 magnification)] with down-regulation of CD7 [(e) CD7 immunohistochemistry (x100 magnification)] but negative for CD8 [(f) CD8 immunohistochemistry (x200 magnification)]

H&E: Hematoxylin and eosin

course of anti-tuberculous treatment consisting of isoniazid, rifampicin, ethambutol, and pyrazinamide (EHRZ). He was then planned for a four-month maintenance phase of isoniazid and rifampicin (HR). As he was afebrile and had no other significant signs of infection, no antibiotic treatment was given before anti-tuberculous treatment.

However, after two months of isoniazid and rifampicin, the platelet count decreased to $82\times10^3/\mu L$. Therefore, rifampicin was discontinued, and the combination of isoniazid, EHRZ was introduced. After nine days of treatment, the patient felt lethargic and unwell; his liver function tests showed elevated ALT and AST levels of 120 U/L and 84 U/L, respectively. As a result, pyrazinamide was withheld, and a combination treatment of isoniazid and ethambutol (HE) was given for a month due to transaminitis; the patient showed some improvement in symptoms. After consultation with a respiratory physician and an infectious disease consultant, the intensive combination treatment of isoniazid, rifampicin, EHRZ was reintroduced following five months of isoniazid and ethambutol treatment, which brought the total duration of anti-tuberculous treatment for his smear-negative TB to nine months.

During his follow-up, his diabetic control was not optimal, as the HbA1c readings were 7.5-7.7%. Repeated CT of the thorax, abdomen, and pelvis for disease monitoring (Figure 3) showed PTCL progression, including a new intraparotid node and enlarging pancreatic and left-thigh masses, although lung findings of smear-negative PTB had improved with disappearance of tree-in-buds on CT of the thorax. Salvage chemotherapy, gemcitabine, carboplatin, dexamethasone, was administered for two cycles, followed by 20 fractions of radiotherapy. However, disease progression continued with new bilateral inguinal lymphadenopathy. He was transitioned to palliative chemotherapy with etoposide and procarbazine. 16 months after initial diagnosis and treatment, he succumbed to the disease.

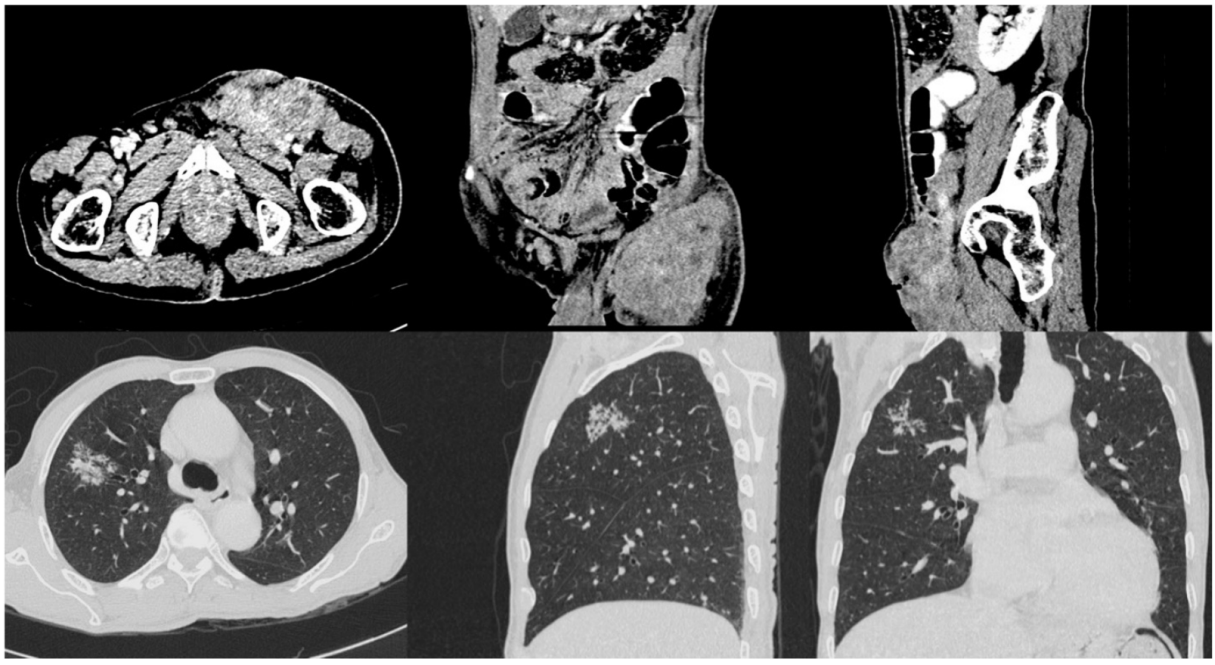

Figure 2. Initial CT scan of the thorax, abdomen and pelvis showed a left inguinal heterogeneously enhancing mass measuring 5.8 cm x11.2 cm x9.4 cm (AP x W x CC), with a central non-enhancing region likely due to necrosis. Anteriorly, there is superficial ulcerating extension of this mass, with poor fat plane with the adjacent vessel and muscles. Part of the left superficial femoral vein was compressed with partial encasement by this mass; however, no obvious filling defect seen. There were focal tree-in-buds densities in the right upper lobe however, no enlarged intrathoracic lymph nodes
CT: Computed tomography

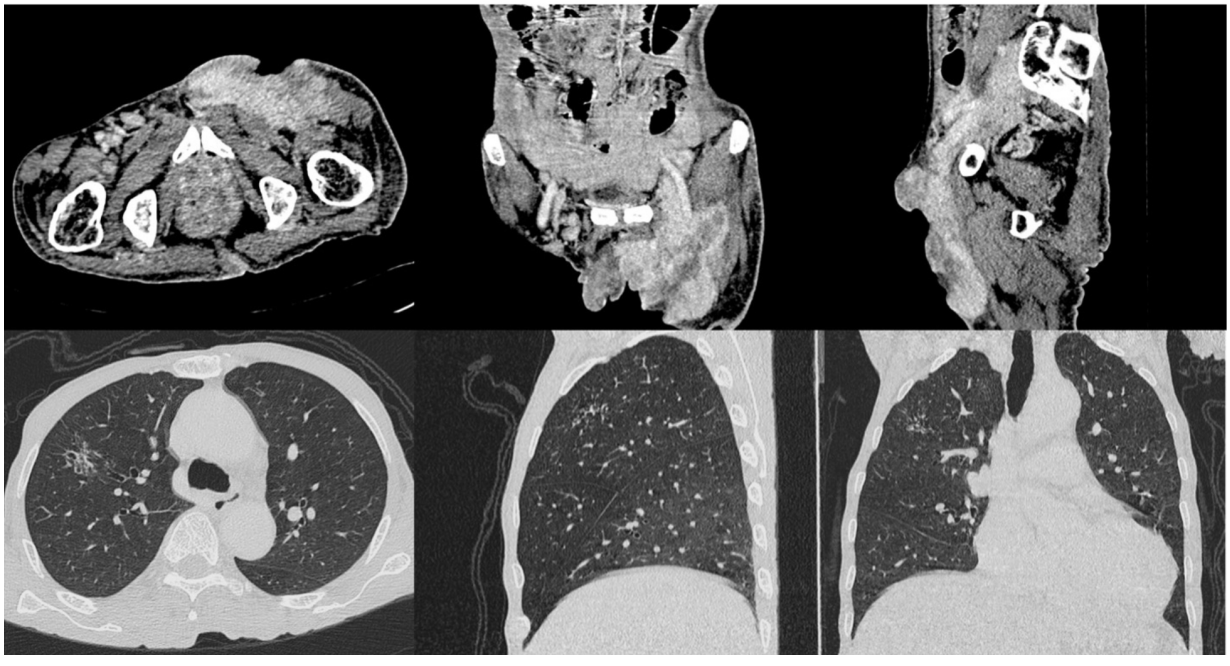

Figure 3. Repeated CT scan of thorax, abdomen and pelvis post chemotherapy showed the left inguinal heterogeneously enhancing mass was larger, measuring 6.1 cm x 14.5 cm x 16.7 cm (AP x W x CC), extending into the left pelvic region. This mass encases part of the left external iliac vein and part of the left common and superficial femoral veins, with no opacification of these vessels seen in the region of the mass. Resolving right upper lobe tree in bud densities also noted
CT: Computed tomography

Discussion

LL was first described by Lennert and Feller (5) in 1968 (6). Then, in 1988, Patsouris et al. (7) confirmed LL had a T-cell origin via immunohistochemical studies. However, only in 1992 was LL officially recognized as a lymphoma of T-cell origin, low-grade in the Kiel classification (5). Ultimately, the World Health Organisation classifies LL as a "lymphoepithelioid cell variant of the PTCL, not otherwise specified (PTCL/NOS)" (8,9).

Diabetes mellitus is a significant metabolic disorder that causes immunodeficiency, which leads to an increased risk of pulmonary TB. Macrophages are an important immunological defense against TB. The hyperglycemic state in diabetes mellitus leads to an increase in ROS and the proinflammatory cytokines interleukin-1 (IL-1) and IL-6, which, at high enough concentrations, can inhibit the function of macrophages (10). The proportion of patients with TB infection was higher among those with lymphoma. In a large study of 1,057 patients with lymphoma, it was found that TB infection exists in 11.9% of patients with T/NK-cell lymphoma, and among these patients, the PTCL variant was the second most common (3). The immunodeficiency caused by diabetes and LL likely contributed to TB infection in our patient.

Concurrent PTB and lymphoma are rarely encountered, and these two entities are difficult to distinguish on imaging alone. Patients with both diseases often present with lymph node enlargement on imaging. However, a study by Yang et al. (11) suggested that although there is little difference in the distribution patterns of the involved lymph nodes, their enhancement patterns differ. Peripheral enhancement of lymph nodes is seen in TB, and homogeneous lymph node enhancement points more towards untreated lymphoma (11). This imaging appearance of lymph nodes is also supported in a different study done by Tang et al. (12), in which they added that in cases of pulmonary TB, the location of the lymph nodes is often peri-hilar, whereas in lymphoma it often involves para-aortic lymph nodes. In a different study by Yang et al. (13) focusing on CT findings and survival of patients with PTCL, few imaging features may suggest PTCL, such as ill-defined margins, invasion of the surrounding structures, lesion heterogeneity, and presence of tumour necrosis, with poor survival seen in patients with the first two imaging features. According to Hare et al. (14), the most common imaging features of pulmonary lymphoma are multiple nodules or masses, usually with air bronchograms. However, it is not the mainstay for diagnosis, and hence multidisciplinary team involvement is needed to get an accurate diagnosis (14).

The diagnosis of nodal LL is typically made via histopathological evaluation of lymph nodes, which reveals effacement of lymphoid architecture by tumour cells composed of atypical lymphocytes and epithelioid histiocytes, sometimes admixed with plasma cells, eosinophils, as well as large Reed-Sternberg-like cells (8,9). Most LL cases showed an immunophenotype of $CD3^+/CD4^-/CD8^+$ (8,9,15); however, a small percentage of patients may present as $CD3^+/CD4^+/CD8^-$ or $CD3^+/CD4^-/CD8^-$ (16). Among the $CD3^+$ LL phenotype, $CD4^-/CD8^+$ is more common (about 38% of all PTCL) and $CD4^+CD8^+$ is rare (about 8% of all PTCL). LL with $CD4^-/CD8^8$ had better survival than other $CD8^+$ lymphomas (15). It is also noted that among LL cases, 31% of patients exhibited EBER-positive non-neoplastic B-cells (17). A large multi-center study revealed that PTCL/LL with EBER-positive non-neoplastic B-cells was linked to worse overall survival, particularly in patients younger than 60 years, and was consistent with an aggressive form of lymphoma (18). In our case, similar morphological features were seen, with total effacement of lymphoid architecture by tumour cells composed of atypical lymphocytes and epithelioid histiocytes, admixed with plasma cells, eosinophils, and large Reed-Sternberg-like cells. The immunophenotype, however, follows the latter, which is a $CD3^+/CD4^+/CD8^-$ immunophenotype with the presence of EBER-positive non-neoplastic B-cells, which carry a worse prognosis.

Although tree-in-buds appearance is classically described for endobronchial spread of *Mycobacterium* TB, it is also recognized as a CT manifestation of various entities such as infection (bacterial, fungal, viral, parasitic), congenital disorders (cystic fibrosis, Kartagener syndrome), idiopathic disorders (obliterative bronchiolitis, panbronchiolitis), aspiration or inhalation of foreign substances, immunologic abnormalities or connective tissue disorders (19). In addition, it may also appear in metastatic diseases such as renal cell carcinoma (most common), liver, prostate, breast, ovarian, stomach cancers, and Ewing's sarcoma (20). It is also possible in intravascular and Mantle cell lymphoma, as reported by Manglani et al. (21) and Albacar Ingla et al. (22). In our case, because PTB is endemic in our setting and the patient presented with a tree-in-bud appearance, we empirically treated our patient for smear-negative PTB, and upon completion of treatment, the disappearance of the tree-in-bud appearance may indicate a response to treatment.

The principle of management for cases of concomitant lymphoma and TB infection is challenging and requires multidisciplinary effort (23). Most of the cases of LL were treated with a combination of CHOEP regimen chemotherapy (24,25). However, this regimen can have significant interactions with anti-tuberculous treatment, particularly with rifampicin, as it affects the metabolism of several chemotherapy drugs, including vincristine, via CYP3A4 (26). Although LL was considered more favourable than other variants of PTCL (9), unfortunately, despite intensive treatment, comorbid diabetes and TB infection were difficult to treat and led to the demise of our patient. We report this case in the hope of providing additional references for clinicians and pathologists to guide future work on the management of this rare variant of PTCL and the concomitant smear-negative pulmonary TB. However, as this is a single-case report, the generalizability

of the findings and the response to treatment might be limited; the management of similar concurrent disease entities should be individualized, with involvement of a multidisciplinary team.

Conclusion

This case highlights the rare coexistence of LL and smear-negative pulmonary TB in a patient with type 2 diabetes mellitus. The overlapping clinical and radiological features of these two conditions posed significant diagnostic and therapeutic challenges. Early recognition of such concomitant presentations is crucial, as both diseases require timely and carefully coordinated management to minimize complications and drug interactions. Multidisciplinary collaboration remains essential in optimizing outcomes for patients with dual diagnoses of lymphoma and TB, particularly in those with underlying immunocompromised states.

Ethics

Informed Consent: Informed consent was obtained from the patient's spouse for the anonymous use and publication of clinical and imaging data.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.F.A., M.S.A.S., V.S.S., S.L.L., Concept: M.F.A., A.N.M.Y., Design: M.F.A., A.N.M.Y., Data Collection or Processing: M.F.A., M.S.A.S., V.S.S., S.L.L., Analysis or Interpretation: M.F.A., M.S.A.S., V.S.S., S.L.L., Literature Search: M.F.A., A.N.M.Y., M.S.A.S., Writing: M.F.A., A.N.M.Y., M.S.A.S.

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A rectovaginal epidermoid cyst mimicking an adnexal mass: a rare case report

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Keywords: Epidermoid cyst, rectovaginal space, laparoscopy, adnexal mass, pelvic mass

ABSTRACT

Epidermoid cysts are benign lesions arising from ectodermal epithelium and are most commonly located in the skin or subcutaneous tissue. Pelvic localization is rare. This article presents the case of a 41-year-old woman who presented with pelvic pain and was found to have an adnexal cystic mass on preoperative ultrasound and magnetic resonance imaging. During laparoscopic excision, a massive 15-cm cyst originating from the rectovaginal space was identified. Histopathological examination confirmed an epidermoid cyst. This case highlights that rectovaginal epidermoid cysts should be considered in the differential diagnosis of apparent adnexal masses when both ovaries appear normal, and that complete laparoscopic excision can provide both definitive diagnosis and treatment.

Introduction

Epidermoid cysts are benign lesions originating from ectodermal epithelium and are typically found in the skin and subcutaneous tissues. Pelvic localization is extremely rare and has been reported in only a few cases in the literature (1). When these cysts originate from deep pelvic compartments such as the rectovaginal, presacral, or retrorectal regions, they can pose diagnostic challenges both clinically and radiologically (2).

The rectovaginal space is a complex anatomical region bounded anteriorly by the posterior wall of the vagina and posteriorly by the rectum. Lesions in this region may cause pelvic pain, dyspareunia, or constipation. However, they are difficult to diagnose due to the absence of specific clinical findings and their radiological similarity to adnexal pathologies (3). We present a giant rectovaginal epidermoid cyst mimicking an adnexal mass and discuss the diagnostic approach and surgical treatment.

Case Report

A 41-year-old parous woman presented with progressive pelvic pain of approximately six months' duration. The pain,

which was initially mild, became constant over time and worsened particularly with prolonged sitting. Dyspareunia developed within the last two months. The patient had no history of surgery or comorbidities.

On pelvic examination, a mass with a smooth surface and limited mobility was detected in the posterior fornix; no adnexal tenderness was noted. Abdominal examination revealed no rebound tenderness or guarding; however, tenderness was elicited on deep palpation.

Transvaginal ultrasound revealed a complex cystic lesion approximately 15 cm, characterized by thick septations and heterogeneous echogenicity, and was interpreted as a right adnexal mass. Pelvic magnetic resonance imaging (MRI) was performed to determine the origin of the lesion.

On MRI, a lobulated cystic mass measuring approximately 15×8 cm was identified between the uterus and rectum (Figure 1). This mass demonstrated low signal intensity on T1-weighted sequences and heterogeneously high signal intensity on T2-weighted sequences. Diffusion-weighted imaging revealed marked diffusion restriction. No fat component was seen on fat-suppressed sequences, and only minimal enhancement was observed in the cyst wall after contrast administration. These findings were consistent with a benign but nonspecific cystic lesion.

Serum tumor markers were within normal limits [cancer antigen (CA)-125: 18.5 U/mL; CA 15-3: 32 U/mL; CA 19-9: 13 U/mL].

Since the patient's symptoms persisted despite medical treatment, laparoscopic surgery was scheduled for definitive diagnosis and treatment. Informed consent forms were obtained from the patient prior to surgery. During the procedure, both ovaries and fallopian tubes appeared normal; however, a cystic lesion extending from the rectovaginal space to the Douglas pouch was observed. The cyst extended laterally toward the obturator fossa and inferiorly toward the vaginal wall, causing the uterus to deviate anteriorly (Figure 2).

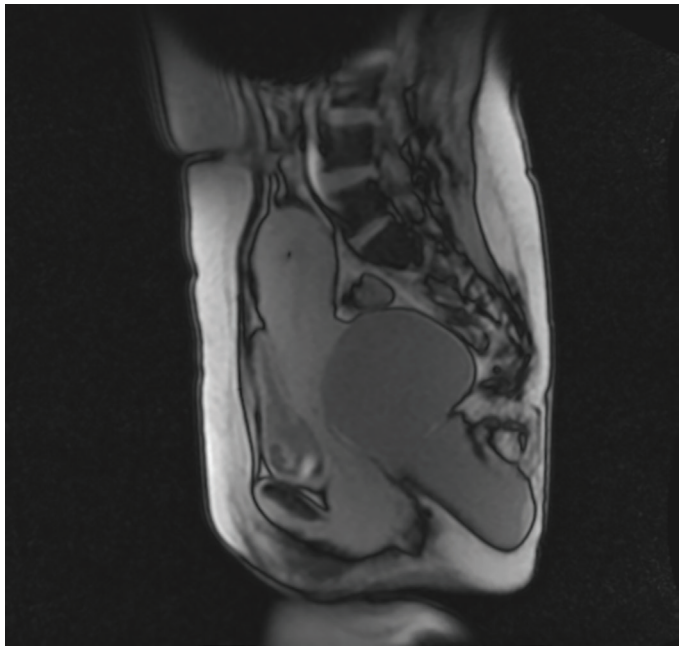

Figure 1. Sagittal pelvic MRI showing a well-defined cystic mass in the rectovaginal space with anterior displacement of the uterus
MRI: Magnetic resonance imaging

The posterior walls of the rectum and vagina were carefully dissected; the bilateral ureters were visualised. The rectal wall was preserved throughout the procedure. The cyst was removed intact. It was confirmed that the cyst wall was completely separated from the rectovaginal space. The cyst was removed from the abdomen using an endobag, and the Douglas pouch mucosa was sutured. No bleeding or organ damage occurred (Figure 3).

Histopathological examination revealed a cyst lined with stratified squamous epithelium, containing lamellar keratin and lacking dermal extensions, confirming the diagnosis of an epidermoid cyst. No dysplasia or malignancy was detected.

The postoperative period proceeded without complications. The patient was discharged on the second day after surgery. At the three-month follow-up, pelvic pain and dyspareunia had completely resolved, and no recurrence was detected. At the two-year follow-up, no recurrence was detected either on clinical examination or on ultrasound.

Discussion

This case highlights the diagnostic challenges and surgical options of a large rectovaginal epidermoid cyst that mimics an adnexal mass on imaging. Although pelvic epidermoid cysts typically occur in the skin and subcutaneous tissues, they can rarely be found in deep pelvic locations; a limited number of cases have been reported in the presacral, retrorectal, retroperitoneal, or paravaginal regions (4-6). These cysts may

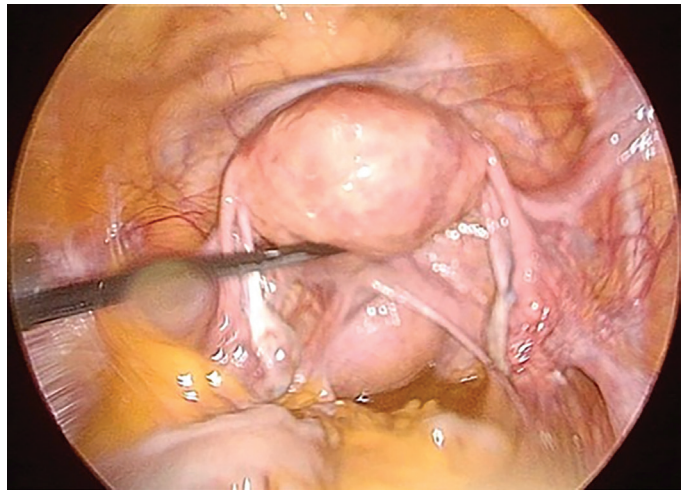

Figure 2. Laparoscopic view of a large cystic lesion occupying the rectovaginal space and displacing the uterus and bladder anteriorly

arise congenitally due to ectodermal inclusion during embryonic development or may develop following traumatic implantation of epidermal tissue into deeper structures (7-9).

Clinical symptoms largely depend on the size and location of the cyst and sometimes there may be non-specific symptoms (1,2,4,6). Presacral epidermoid cysts have been reported as a rare cause of chronic constipation, while giant retrorectal or retroperitoneal cysts may present with progressive pelvic pain (4-6). In this case, the patient's symptoms were consistent with the mass effect of a progressively enlarging cyst in the rectovaginal space.

Radiological imaging plays an important role in the evaluation of pelvic masses; however, findings in epidermoid cysts are generally non-specific (1,7). MRI can help determine the anatomical location; however, as reported by Sasaki et al. (5) and Fdili Alaoui et al. (6), the signal characteristics may overlap with those of dermoid cysts, Müllerian cysts, or other retroperitoneal developmental lesions. Although the ovaries appeared normal on both ultrasound and MRI, the lesion was still interpreted as an adnexal lesion; this underscores the necessity of considering cystic lesions in the deep midline or posterior pelvis. Histopathological examination remains the gold standard for diagnosis, as rare cases of malignant transformation arising from benign cysts have been reported in the literature (10,11). Recently, Yonghan et al. (12) reported a case of a retroperitoneal epidermoid cyst diagnosed by ultrasound, which exhibited imaging findings similar to those in our case. However, unlike the retroperitoneal location in their case, we reported a case originating from the rectovaginal area, which represents an anatomically even rarer location (12).

Although transsacral or open abdominal approaches have traditionally been used, minimally invasive techniques are increasingly favoured (3,13). Laparoscopic excision allows definitive diagnosis and effective treatment, with advantages such as reduced morbidity, shorter hospital stays, and faster recovery. It also minimises the risk of complications such as infection, rupture, recurrence, and rare malignant transformation (6). In the case reported by Yonghan et al. (12), laparoscopic surgery was chosen as the first-line treatment approach, and successful clinical outcomes were achieved in the patient using this minimally invasive method. Previous studies have shown that laparoscopic treatment is safe and feasible even for large or recurrent retrorectal cysts (3,13). In our case, laparoscopic surgery enabled complete excision of the cyst in the rectovaginal space.

This case adds to the limited literature on rectovaginal epidermoid cysts. The large size of the lesion and its radiological resemblance to an adnexal mass highlight the diagnostic challenges. When imaging findings are inconclusive, rare non-adnexal pathologies should be considered in the differential diagnosis. Given the anatomical relationships of the rectovaginal space, laparoscopic excision can be safely performed by experienced surgeons and can yield favorable outcomes.

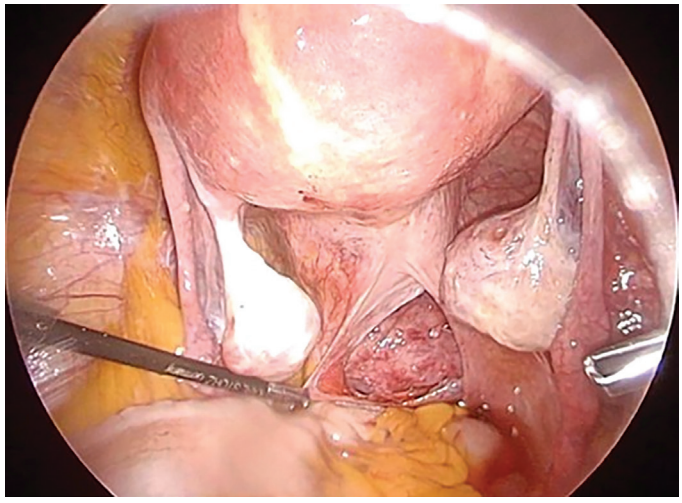

Figure 3. Intraoperative view demonstrating retroperitoneal dissection of the rectovaginal epidermoid cyst from the surrounding pelvic structures

Ethics

Informed Consent: Informed consent forms were obtained from the patient prior to surgery.

Footnotes

Authorship Contributions

Surgical Medical Practices: Ö.Ö., Consept: Ö.Ö., Ş.C.Y., Design: Ö.Ö., Ş.C.Y., Data Collection or Processing: Ö.Ö., Ş.C.Y., Analysis or Interpretation: Ö.Ö., Literature Search: Ö.Ö., Ş.C.Y., Writing: Ö.Ö., Ş.C.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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