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CONTENTS

Original Articles

Review

Vaginal axis on MRI after laparoscopic pectopexy surgery: a controlled study

Fatih Şahin[1], Recep Yılmaz Bayraktarlı[2], Ozan Doğan[3]

[1]Department of Obstetrics and Gynecology, Prof. Dr. Cemil Taşçıoğlu City Hospital, İstanbul, Turkiye
[2]Department of Radiology, Prof. Dr. Cemil Taşçıoğlu City Hospital, İstanbul, Turkiye
[3]Department of Obstetrics and Gynecology, Private Practice Physician, İstanbul, Turkiye

ABSTRACT

Aims: Laparoscopic pectopexy has emerged as a feasible alternative to sacrocolpopexy (SCP) for treating female genital apical prolapse. Although several previous studies have reported changes in the vaginal axis in women who have undergone SCP, laparoscopic lateral mesh suspension, sacrospinous ligament fixation surgery for prolapse, there is a lack of data on changes in the vaginal axis after pectopexy. This study aimed to evaluate the degree of anatomical correction achieved by laparoscopic pectopexy in patients with apical genital prolapse using magnetic resonance imaging (MRI).

Methods: Individuals who experienced pectopexy and a nulliparous control group were enrolled in this prospective observational case-control investigation. MRI scans were conducted on both the control cohort and the study group before and after the procedure. The angles formed by the pubococcygeal line and the inferior vaginal segment, the levator plate and the pubococcygeal line, as well as the inferior and superior vaginal segments, were measured and compared.

Results: The change in angle between the lower vagina and upper vagina was statistically significant, with preoperative and postoperative values of 134.91°±6.25° and 166.82°±6.15°, respectively (p=0.0001). The angle between the lower vagina and pubococcygeal line showed a significant change, with preoperative and postoperative values of 44.64°±1.8° and 65.73°±10.19°, respectively (p=0.0001). Postoperative angles were not similar among nulliparous patients based on the MRI findings. The postoperative Urogenital Distress Inventory scores are significantly lower than the preoperative scores (p=0.0001).

Conclusion: The pectopexy procedure is not optimal for achieving a normal vaginal axis.

Keywords: Apical prolapse, pelvic organ prolapse, pectopexy, laparoscopic lateral mesh suspension, sacrospinous ligament fixation (SSLF)

INTRODUCTION

Pelvic organ prolapse (POP) poses a significant health issue that impacts the overall physical and psychological well-being of women. The likelihood of requiring surgery for POP throughout a woman's lifetime stands at 12.6.[1] Prolapse of the anterior vaginal wall, or cystocele, is the most common form of POP, detected twice as often as posterior vaginal prolapse and three times more common than apical prolapse.[2] The primary objective of surgical treatment for POP is to relieve symptoms and restore the anatomical integrity of pelvic support. Typically, the vaginal axis lies in a relatively horizontal position to the levator plate, forming an angle of approximately 130° between the middle and lower vagina.[3] Sacrocolpopexy (SCP), considered the gold standard approach for treating POP, involves altering the typical anatomical position of the vaginal axis toward the sacral promontory. However, this adjustment can lead to increased abdominal pressure on the anterior wall, which causes symptoms of

urgency or de novo anterior compartment prolapse. Although the long-term results of sacrospinous ligament fixation (SSLF), the primary vaginal surgery for correcting the apical anatomy in POP treatment, show promising outcomes,[4] it can increase the risk of anterior vaginal wall prolapse, similar to SCP, due to the deviation of the vaginal axis toward the posterior.[5]

The pectopexy procedure, initially described in 2007, utilizes iliopectineal ligaments on both sides for mesh attachment. In this procedure, the mesh is positioned along natural structures such as the round and broad ligaments, avoiding sensitive areas such as the ureter or bowel. A study has shown that the pectineal ligament (Cooper's ligament) exhibits stronger and more resilient tissue compared to the sacrospinous ligament and arcus tendineus of the fascia pelvis.[6] The iliopectineal ligament demonstrates strength and

provides a secure hold for sutures. Additionally, the lateral portion of the iliopectineal ligament offers ample material for suturing, making pelvic floor reconstruction easier. This specific segment of the ligament is located at the level of the second sacral vertebra (S2), which coincides with the optimal position for the physiological axis of the vagina. The S2 level serves as the anchor point for maintaining the natural axis of the vagina.[7] Subsequent studies have demonstrated comparable outcomes in terms of supporting the apical compartment during intermediate follow-up periods when compared to laparoscopic SCP. However, this is only one study, and these are medium-term results.

The objective of this study was to assess the degree of anatomical correction achieved through laparoscopic pectopexy and to compare the vaginal axis of patients with apical genital prolapse to that of nulliparous women using magnetic resonance imaging (MRI). The secondary aim of the study was to evaluate sexual and urinary system functions following reconstructive POP surgery.

METHODS

The study was carried out with the permission of Ethical Committe of İstanbul Prof. Dr. Cemil Taşçıoğlu City Hospital (Date: 28.06.2022, Decision No: 351) and registered with the National Clinical Trials Registry under NCT05876975. Every participant granted their informed approval. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A retrospective evaluation was conducted on patients who This observational prospective case-control study was conducted in a tertiary center between January and June 2023. The study group consisted of patients aged 18 and above diagnosed with apical POP and did not require an additional posterior colporrhaphy procedure. These patients had a specific preference for uterus-preserving surgery and were scheduled to undergo laparoscopic pectopexy. The assessment of POP was conducted using the POP-Q system. Exclusion criteria for the study included a uterine size exceeding 10 cm or the presence of a pelvic mass that could potentially interfere with accurate measurements. Patients with any congenital or acquired anatomical and reproductive anomalies, a diagnosed enterocele based on transperineal ultrasound before enrollment, an indication for hysterectomy, or the need for concomitant POP or anti-incontinence procedures were also excluded from the study. Patients who were scheduled to undergo laparoscopic pectopexy for apical prolapse were assigned to the study group. On the other hand, nulliparous women who visited the outpatient clinic with complaints unrelated to POP symptoms (e.g., menstrual irregularity) were randomly selected and assigned to the control group. The control group consisted of nulliparous individuals without POP symptoms, specifically those with asymptomatic grade 1 or lower POP, to minimize selection bias and enable comparison with a normal vaginal axis. Demographic information, including age, parity, and body mass index (BMI), was recorded for all participants. The pectopexy procedure was performed by a single surgeon.

The primary goal of the study was to assess the change in the vaginal axis by comparing preoperative and postoperative MRI measurements of the patients, as well as comparing them to the nulliparous control group. MRI scans were performed on the axial, coronal, and sagittal planes, and diffusion-weighted images using a standard body spiral technique. The scans had a section thickness of 5 mm and were obtained with the subjects in a supine position. The secondary goal involved evaluating the improvement of urinary symptoms related to prolapse in the study group. Validated scales were applied for this purpose, including the Urinary Distress Inventory, Short Form (UDI-6), which is a shortened version of a condition-specific quality of life instrument. The UDI-6 is frequently used due to its feasibility and is validated at level a according to the international continence society grading system.[8] The UDI-6 scale includes six items that assess various aspects of urinary symptoms and their impact on daily life: 1) frequent urination, 2) leakage related to the feeling of urgency, 3) leakage related to activity, 4) coughing or sneezing causing small amounts of leakage (drops), 5) difficulty emptying the bladder, and 6) pain or discomfort in the lower abdominal or genital area. Higher scores on the UDI-6 indicate a higher level of disability in these areas. For the assessment of sexual function, the Female Sexual Function Index (FSFI) was utilized. The FSFI consists of six domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. It comprises a total of 19 questions that relate to the participants' sexual life during the preceding 4 weeks. An overall FSFI score below 26.55 is indicative of female sexual dysfunction.[9] Scores higher than 26.55 indicate better sexual function.

Surgical Technique
There was no need for a special diet or bowel cleansing for the preoperative preparation of the patients. All patients were dressed with embolic compression stockings. Preoperatively 1.5 g Cefazolin was administered intravenously to the all patients for surgical prophylaxis. A 30-degree laparoscopic lens was guided into the abdomen with a 10-mm laparoscopic port from a 1 cm incision site on the lower edge of the umbilicus. Abdomen was inflated with carbon dioxide (CO_2) at 12 mm Hg pressure. Two 5-mm ports were placed to 2–4 cm inferomedial area of spina iliaca anterior superior bilaterally. One 15-mm port was placed on the left upper quadrant of abdomen. The round ligament part of 4 cm2 size which contains the lateral part of the ilopectineal ligament was used as the anatomical cue point. The peritoneum adjacent to the round ligament was superficially incised. The soft tissue in the pelvic wall was bluntly dissected until the iliopectineal ligament was seen, and the dissection was extended to the obturator nerve region. The same procedure was applied to the contralateral side. After the ilopectineal ligament was prepared, the peritoneal incision on the 2 sides was bluntly expanded along an imaginary line connecting the vaginal apex and pectineal line. Polypropylene monofilament mesh (3×15 cm) and 2-0 non-absorbable suture 10-mm sent from the port to the surgical area. The proximal end portions of mesh were fixed to the bilateral iliopectineal ligament with 2 sutures and the suture needle was taken out. Cervical bulge or vaginal apex were fixed to the middle of the mesh in the tension to prevent sagging. If the length of the mesh was long, the length of the

mesh was shortened before the second iliopectineal ligament was fixed. Laparoscopic tacker was used instead of suture while the mesh was fixed to the Karslı A.; Karslı O.; Kale A. 28) Prague Medical Report / Vol. 122 (2021) No. 1, p. 25–33 tissues in some patients (Jelovsek et al., 2007). The peritoneum was closed using 2-0 absorbable sutures. After the carbon dioxide was evacuated, the ports were removed.

Pelvic MRI Assessments

MRI images were acquired using a 1.5 Tesla MRI device (Solo, Siemens, Germany) with 16-channel phased array coils. The images were obtained while the patients were in supine position. The imaging protocol included T1A (TR/TE: 609/19 ms, slice thickness/gap: 5/1, matrix: 256 × 128, field of view: 30 cm, 1 excitation) and T2A axial STIR (TR/TE: 4000/46 ms, slice thickness/gap: 5/1, matrix: 256 × 256, field of view: 18-20 cm), as well as T2A axial (TR/TE: 7220/103) images. During the examination, no rectal or vaginal contrast material was used. However, defecation and urination were recommended before the MRI so that the bladder and rectum were not full. Subsequently, the imaging was performed with the bladder and rectum in their spontaneous state. Angle measurements were made based on the axial images passing through the midline of the sagittal plane. The evaluation included measurements of the symphysis pubis, vaginal axis, coccygeal bone structures, and levator plate planes. The line drawn from the lower contour of the symphysis pubis to the lower anterior edge of the second coccygeal bone formed the main reference line (also known as sacrococcygeal inferior pubis point line). The anterior vaginal wall between the introitus and the cervix was divided into two regions: the lower region, which refers to the distal half of the anterior vaginal wall, and the middle region, which refers to the proximal half of the anterior vaginal wall. The upper vaginal region was defined as the portion connecting the anterior and posterior fornixes, specifically the cervical portion. The line drawn from the symphysis pubis to the lower edge of the second coccygeal bone was considered the pubococcygeal line. The line parallel to the levator ani muscle from its origin to the posterior bend of the rectum was considered the levator plate. The patients were recalled for control examination at the 6th postoperative month for repeat MRI examination, and UDI-6 and FSFI forms were filled out once more. Reference points are illustrated in Figure 1.

To assess the change in the vaginal axis, a stable reference line was required. The pubococcygeal line was chosen as the reference point for this purpose. The position of the lower vaginal segment was evaluated by comparing it to both the pubococcygeal line and the upper segment. The levator plate's level may provide information about the relieved pressure following the operation. A longitudinal axis was drawn through the middle of the levator plate and the pubococcygeal line, extending between the inferior aspect of the symphysis pubis and the coccyx. This allowed for the measurement of angles to determine the change in the vaginal axis. Specifically, the angles measured were angle A (between the levator plate and the pubococcygeal line), angle B (between the lower and upper vaginal segments), and angle C (between the pubococcygeal line and the lower vaginal segment). These measurements were performed by a single specialized
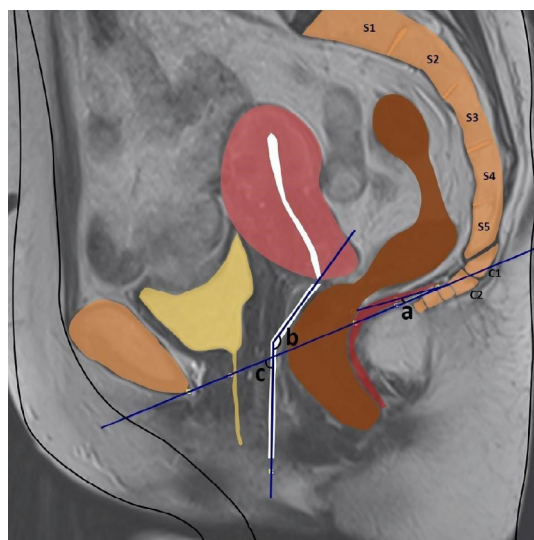
Figure 1. Reference points used in the study

radiologist who was blinded to both the participants and the study hypothesis. The angles are depicted in Figure 2.

Figure 2. Preoperative-postoperative MR, angles: A, B and C angle

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Statistical Analysis

In this study, statistical analyses were conducted using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software package program (Utah, USA).In the evaluation of the data, descriptive statistical methods such as mean and standard deviation were used, along with the Shapiro-Wilk normality test to examine the distribution of variables. A paired t-test was used for the comparison of preoperative and postoperative variables that exhibited a normal distribution, and an independent t-test was used for the comparison of paired groups. The reliability of the used UDI and FSFI scales was determined through the Cronbach alpha test. The outcomes were assessed at a significance threshold of p<0.05.

RESULTS

A total of 60 patients were included in the study, of which 30 underwent a laparoscopic pectopexy procedure. The other 30 patients comprised the control group, consisting of nulliparous women. The mean age of the operated group was 58.27±5.14, and the mean age of the nulliparous control group was 24.60±1.51 (p<0.01). The average BMI of the patients who underwent pectopexy was 26.64±1.91, whereas the control group had an average BMI of 24.00±1.49 (p=0.002). The median parity of the operated group was 3 (range 3-4). Demographic data are summarized in Table 1.

Table 1. Demographic data of the patients			
	Control group n:30	Study group n:30	p*
Age (mean±SD)	24.60±1.51	58.27±5.14	**p< 0.01**
BMI (mean±SD)	24.00±1.49	26.64±1.91	**0.002**
Parity (median)		3 (3-4)	
BMI: Body mass index, SD: Standart deviation			

There was a significant change in the POP-Q grades for the anterior and apical compartments (p=0.0001). In the group that underwent pectopexy, the POP-Q measurements showed significant improvement. The differences at postoperative points Ba, Bp, and C were 4.12±0.15, 3.38±0.18, and 8.40±0.38, respectively (p=0.0001). The angle between the preoperative and postoperative levator plate and pubococcygeal line (angle A) was 7.64°±0.92° and 11.00°±3.00°, respectively (p=0.005). The change in angle between the lower vagina and upper vagina (angle B) was statistically significant, with preoperative and postoperative values of 134.91°±6.25° and 166.82°±6.15°, respectively (p=0.0001). The angle between the lower vagina and pubococcygeal line (angle C) showed a significant change, with preoperative and postoperative values of 44.64°±1.8° and 65.73°±10.19°, respectively (p=0.0001). The findings are summarized in Table 2.

The angle between the levator plate and the pubococcygeal line (angle A) measured preoperatively for the study group and the control group was 7.64°±0.92° and 12.50°±3.1°, respectively (p=0.0001). The angle between the lower vagina and upper vagina (angle B) was significantly different between the preoperative study group (134.91°±6.25°) and the control group (150.3°±4.47°) (p=0.0001). The angle between the pubococcygeal line and the lower vagina (angle C) showed a statistically significant difference between the preoperative study group (44.64°±1.80°) and the control group (55.9°±5.04°) (p=0.0001). The angle between the levator plate and the pubococcygeal line (angle A) measured postoperatively for the study group and the control group was 11.00°±3.00° and 12.50°±3.1°, respectively (p=0.274). The angle between the lower vagina and upper vagina (angle B) was statistically significant for the study group and the control group, at 166.82°±6.15° and 150.3°±4.47°, respectively (p=0.0001). The angle between the pubococcygeal line and the lower vagina (angle C) showed a statistically significant difference between the postoperative study group (65.73°±10.19°) and the control group (55.9°±5.04°) (p=0.013). The findings are summarized in Table 3.

Figure 3 illustrates angle B in the study group and control group. The UDI-6 and FSFI questionnaires, which assess quality of life, are presented in Table 4.

The postoperative UDI scores (2.09±0.7) were significantly lower than the preoperative scores (12.27±0.91) (p=0.0001). The postoperative FSFI scores were significantly higher than the preoperative FSFI scores (p=0.0001).

DISCUSSION

In our study, we observed that the vaginal axis in women with POP after laparoscopic pectopexy was abnormal compared to that of the nulliparous women in the control group. Uterus-sparing pectopexy corrected visible POP but did not restore

Table 2. Preoperative and postoperative findings in the pectopexy group				
	Preoperative	Postoperative	Difference Mean±SD	p‡
Ba	1.65±0.18	-2.47±0.1	4.12±0.15	0.0001
Bp	0.69±1.74	-2.69 ± 0.44	3.38±0.18	0.0001
C	3.59±0.28	-4.81±0.29	8.40±0.38	0.0001
Angle A	7.64±0.92	11.00±3.00	-3.36±3.08	0.005
Angle B	134.91±6.25	166.82±6.15	-31.91±8.54	0.0001
Angle C	44.64±1.8	65.73±10.19	-21.09±10.53	0.0001
Angle A: between the levator plate and the pubococcygeal line, Angle B: between lower and upper vaginal segments, Angle C: between the pubococcygeal line and lower vaginal segment.				
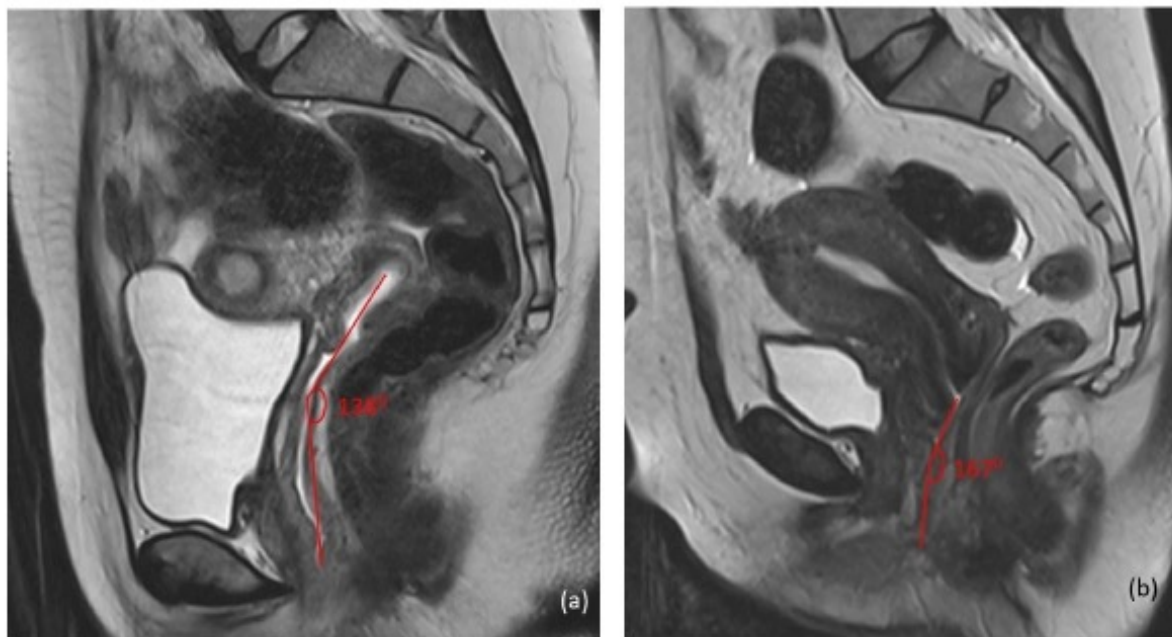
Figure 3. Reference points used in the study

Table 3. Comparison of angles on MRI scans			
	Nulliparous n:30	**Pectopexy n:30**	**p***
Preop Angle	12.50±3.1	7.64±0.92	0.0001
Postop Angle A		11.00±3.00	0.274
Preop Angle B	150.3±4.47	134.91±6.25	0.0001
Postop Angle B		166.82±6.15	0.0001
Preop Angle C	55.9±5.04	44.64±1.80	0.0001
Postop Angle C		65.73±10.19	0.013
Angle A: between the levator plate and the pubococcygeal line, Angle B: between lower and upper vaginal segments, Angle C: between the pubococcygeal line and lower vaginal segment.			

the vaginal axis to its previous state. Surgical management of apical prolapse includes SSLF, laparoscopic lateral mesh suspension (LLMS), and SCP. As a secondary objective to reconstructive apical prolapse surgeries, restoring the vaginal axis to its normal limits is also crucial for the physiological functioning of the pelvis and abdomen.[10] Besides significant deterioration of the vaginal axis after SCP, it can also cause complaints such as pelvic pain and dyspareunia. In the SCP technique, the normal vaginal axis displaces posteriorly,

causing de novo anterior prolapses by subjecting the anterior compartment to intra-abdominal pressure.[11] On the other hand, in recent years, the frequently performed LLMS has been shown to result in a vaginal axis close to normal after apical repair in MRI studies.[12] This has raised the question of whether LLMS surgery is the new gold standard in the treatment of apical prolapse in recent years.[13] In a different study, it was found that both SSLF and SCP resulted in deviation from the normal physiological axis in the vaginal axis assessment.[14]

In our MRI study, it was observed that the postoperative A, B, and C angles were not similar among nulliparous patients based on the MRI findings that we examined. This suggests that the pectopexy procedure may not be optimal for achieving a normal vaginal axis. The alignment of the vaginal axis has been recognized as a significant factor in pelvic organ support, and the restoration of vaginal depth and axis is regarded as a crucial objective in surgical management.[15] A study involving vaginograms on MRI after abdominal SCP and SSLF conducted on women in a supine position showed a 130° angle between the "upper and lower" vagina in a sample of 20 primarily nulliparous young women. In another study

Table 4.UDI-6, FSFI preoperative-postoperative					
		Preoperative	**Postoperative**	**Difference mean±SD**	**p‡**
UDI Score		12.27±0.91	2.09±0.7	10.18±1.08	**0.0001**
FSFI	**Desire**	2.56±0.47	4.91±0.45	-2.35±0.63	**0.0001**
	Sexual arousal	2.35±0.4	3.41±0.83	-1.06±1.06	**0.008**
	Lubrication	2.18±0.49	3.79±0.65	-1.61±0.51	**0.0001**
	Orgasm	2.36±0.28	3.75±1.03	-1.38±1.03	**0.001**
	Satisfaction	2.36±0.61	3.27±0.87	-0.91±1.29	**0.042**
	Pain/discomfort	1.6±0.74	0.58±0.49	1.02±0.85	**0.003**
	Total score	13.42±0.82	19.71±2.67	-6.29±2.51	**0.0001**
‡Paired t test, UDI-6:Urinary Distress Inventory Short Form,FSFI:Female Sexual Function Index					

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conducted with a larger sample, the angle between the upper and middle vagina was found to be 149°.[16] These quantitative findings can be valuable in the context of suspension surgeries, as they provide insight into the normal axis and angles of the vaginal region. Having established normal values through imaging of postoperative patients, future assessments can be compared against these reference values. However, it is important to acknowledge the significant variation observed within the normal range and not overlook this aspect.

Pectopexy surgery offers some advantages over SCP in obese patients. In SCP, surgical dissection involves several important structures, including the right ureter, hypogastric nerves, middle sacral vessels, and sacral promontory, which contains the left common iliac vein. Obese patients pose a challenge in bowel handling and retroperitoneal dissection for anterior longitudinal ligament preparation due to the difficulties in identifying major landmarks.[17] Obesity increases surgical difficulty due to limited surgical space for balancing abdominal pressure and ensuring adequate ventilation.[18] Unlike SCP, pectopexy restricts surgical areas in the anterior pelvic space and is less affected by obesity. In the past, repair methods for prolapse that did not eliminate the pouch of Douglas (such as those involving anterior fixation points) were linked to higher rates of recurrence of posterior compartment prolapse or enterocele.[19] However, none of the patients in this series experienced a recurrence of posterior prolapse after surgery.

Improvements in urinary function were observed as one of the secondary objectives of our study following pectopexy. The incidence of new-onset urinary incontinence, especially stress urinary incontinence (SUI), is relatively high after pelvic floor surgery. In a study, a total of 220 women with symptomatic apical prolapse who underwent laparoscopic sacrocolpopexy were prospectively evaluated; 100 women had previously undergone a hysterectomy. The incidence of SUI following apical prolapse repair was found to be 23.6%. Subsequent continence procedures were performed in 5.0% of patients, all of whom were women with a previous hysterectomy, resulting in an 11% risk in this group.[20] In our study there was no significant difference in stress incontinence scores before and after the operation, suggesting that this aspect could be a potential area of future research, particularly in relation to the emergence of de novo stress urinary incontinence following SCP Although urinary incontinence problems are more associated with ligament defects rather than the shifting of the vaginal axis, they are closely connected to defects in the anterior wall due to the distinct alignment of the upper and lower vagina. The position of the lower vagina plays a significant role in the restoration of the lower urinary tract and is less influenced by the upper vagina.[21]

Sexual dysfunction is one of the symptoms associated with POP that motivates women to seek medical help. Women with POP are likely to restrict sexual activity owing to a perceived of loss of attractiveness and fear of incontinence. Conservative (pelvic floor muscles training or pessary) or surgical management (transabdominally or transvaginally) can be offered to treat POP but questions remain regarding sexual outcome.[22] In our study, significant improvements were observed in the FSFI after achieving anatomical success. While the improvements in secondary outcomes may be associated with better anatomical correction, it's important to emphasize that this conclusion cannot be solely inferred from our findings. Similar improvements would likely be observed with SCP or SSLF procedures as well.

Limitations
The primary limitation of the current study was the small sample size and short follow-up time. Reaching a definitive decision and judgment regarding the study is challenging. However, the use of MRI findings helped mitigate potential bias. To the best of our knowledge, this is the first study to evaluate the vaginal axis using MRI following laparoscopic pectopexy. Within our study group, we observed no new risks associated with the pectopexy technique. The placement of the mesh did not interfere with any pelvic structures, thereby reducing the risk of bowel infection or disorders to zero.

CONCLUSION
Additionally, there may be a protective effect on the anterior compartment. It is important to note that the pectopexy procedure should only be performed by experienced surgeons, as it adds to their technical repertoire. In cases where anatomic variations pose challenges, laparoscopic pectopexy can be considered as an alternative to sacral colpopexy. Conducting multicenter investigations would be beneficial in validating the clinical utility of laparoscopic pectopexy in routine practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

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

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure

Author Contributions

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MEDICINE
PALLIATIVE CARE

Functional balance and quality of life in breast cancer survivors

Songül Keskin Kavak, Lale Aktekin

Department of Physical Medicine and Rehabilitation, Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, University of Health Sciences, Ankara, Turkiye

ABSTRACT

Aims: Breast cancer is an important health problem with the second mortality rate in cancer-related deaths in women. After mastectomy and radiotherapy, shoulder and upper extremity mobility may decrease, trunk and upper extremity muscles may weaken, and biomechanical and functional balance may be impaired in women who have survived breast cancer. In addition, increased limb volume due to breast cancer-related lymphedema (BCRL) may impair static and dynamic balance. To date, studies investigating the effect of lymphedema on balance in BCRL are limited. We aimed to examine the impact of lymphedema on balance and quality of life in breast cancer survivors.

Methods: In this prospective study, age, education, marital status, body mass index (BMI) (kg/m²), affected lymphedema limb (right-left), and extremity volume difference were evaluated. Fullerton Advanced Balance Scale (FAB-Scale) was applied to the patients to measure their level of balance. The Lymphedema Quality of Life Questionnaire (LYMQOL-Arm) was applied.

Results: The mean age of the 40 patients included in the study was 59.02±7.50 years. The proportion of patients with a Fab-scale ≤25 who were at risk of falls was 55%. There was no statistical difference between patients with Fab-scale ≤25 and patients with Fab-scale 25<in terms of quality of life score (LYMQOL-Arm) (p=0.344). There was a significant negative correlation between age and balance level (p=0.0138). There was no significant correlation between limb volume difference, BMI, quality of life, and balance level (p>0.05).

Conclusion: In our study, balance deteriorated and the risk of falls increased especially in elderly patients. Every woman with BCRL should be informed about balance and gait impairment and encouraged to receive lymphoedema treatment as soon as possible. We think that future studies examining functional stability, quality of life, and fall risk in the treatment of lymphedema and the development of special interventions related to balance will contribute to the oncological rehabilitation protocol.

Keywords: Breast cancer, lymphedema, quality of life, functional balance, fullerton advanced balance scale

INTRODUCTION

Despite new treatment technologies, breast cancer remains a major cause of mortality among women with the second highest number of deaths.[1] Radical mastectomy and modified radical mastectomy are the most commonly preferred surgical methods for the treatment of breast cancer.[2] Breast cancer treatment can cause tissue necrosis and scarring in the surgical site, reducing spine, chest, shoulder and upper limb mobility, weakening the trunk and upper limb muscles, and impairing biomechanical and functional balance.[3]

Breast cancer-related lymphedema (BCRL) is one of the major complications of radiotherapy after mastectomy. BCRL affects upper extremity functions with pain, swelling, increased diameter and stiffness in the affected arm. Impairment of upper body function affects exercise tolerance, neuromuscular function and functional balance.[4] This will increase the risk of falls and injuries in women who have had breast cancer.

In BCRL, an increase of at least 2 cm or 200 mL in volume around the arm compared to the unaffected arm is typical.[5]

Depending on the asymmetric limb volume, the body center of gravity will be displaced. This change may disturb the static and dynamic balance.[6] To date, the effect of lymphedema on balance in women who have survived breast cancer is not fully understood, and studies investigating this issue are limited. This study aimed to investigate the effects of lymphedema on balance and quality of life after mastectomy.

METHODS

Participants

In this cross-sectional and prospective study, patients aged 18-75 years, breast cancer survivors, with unilateral lymphedema, who were treated and followed up in the Physical Medicine and Rehabilitation outpatient clinic of Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital between July 2022 and December 2022 were included. All patients were informed about the study and informed consent forms were obtained. Our study was conducted following the

Corresponding Author: Songül Keskin Kavak, songuleren2005@gmail.com

CONSORT 2010 Flow Diagram
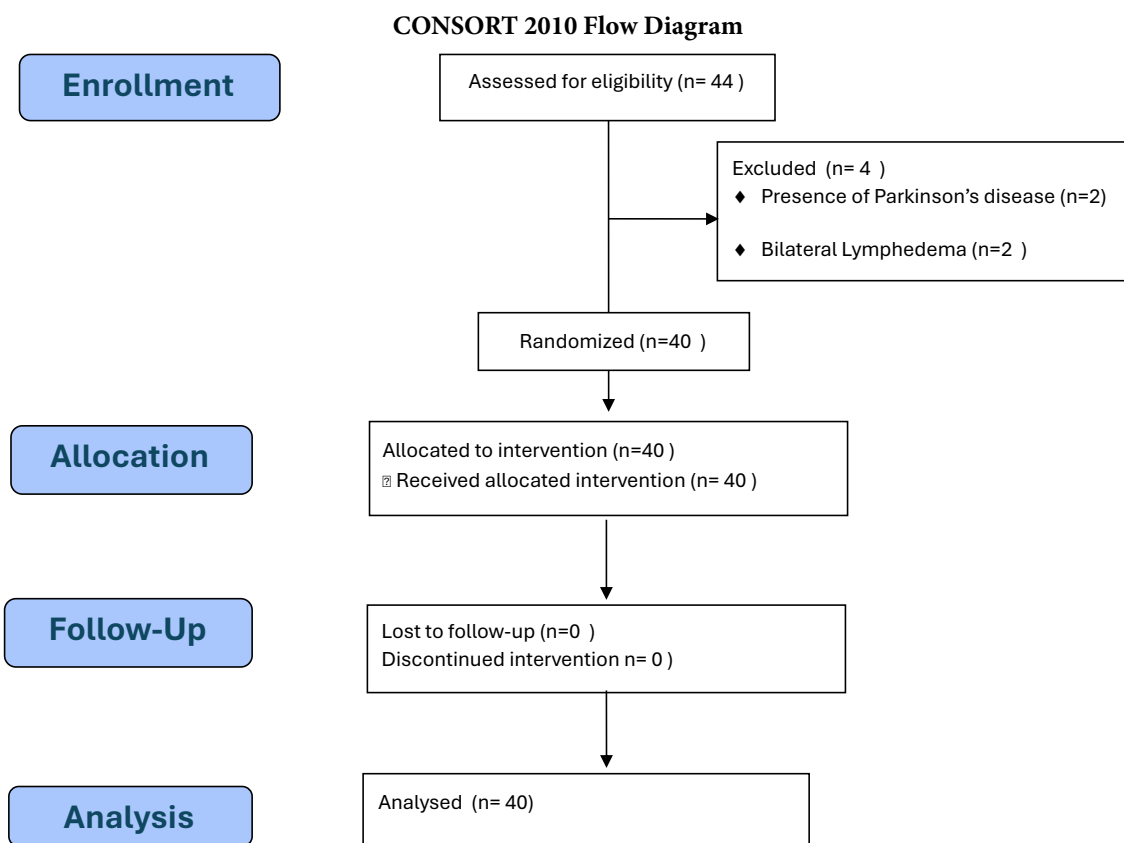
Figure 1. Study flow diagram

principles of Helsinki.The study protocol was approved by the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-interventonal Clinical Researches Ethics Committee (Date: 09.06.2022, Decision No: 2022-06/92).

Inclusion criteria: Patients aged 18-75 years, unilateral radical mastectomy (RM), with lymphoedema for at least 6 months after mastectomy. Exclusion criteria of the study: bilateral mastectomy, lumpectomy, traumatic musculoskeletal injury, patients with visual and vestibular impairment, diabetes, women with neurological deficits. Of the 44 patients included in the study, 2 patients had a diagnosis of Parkinson's disease and 2 patients had bilateral mastectomy and were not included in the study (Figure 1).

This study was guided by the Consolidated Standards for Reporting Trials (CONSORT) checklist.

Data Collection Tools
Demographic and clinical data such as age, educational status, marital status, body mass index (BMI) (kg/m²), affected lymphedema limb (right-left) were analysed. For the evaluation of limb volume difference, limb diameter measurements were made with a standard tape measure at 4 cm intervals starting from the metacarpophalangeal joint of the hand and then calculated for each segment using the frustrum formula. The difference between the affected limb and the unaffected limb was evaluated as limb volume difference.

The Fullerton Advanced Balance Scale (FAB-Scale):
Fullerton Advanced Balance Scale (FAB-Scale) was applied to the patients to measure the balance level. FAB-Scale is a performance-based test that evaluates functional balance (static and dynamic) status. Functional balance includes static and dynamic components such as general balance ability of the body, coordination of muscles, proprioception (awareness of body position), range of motion, muscle strength and flexibility. Turkish reliability and validity study of the scale has been conducted.[7] Each item of the 10-question questionnaire is scored using a 0-4 scale.The questions of the questionnaire are summarised below.

1. Standing with feet together, eyes closed,
2. Reaching forward to pick up an object,
3. Rotation in a circle,
4. Stepping on and over a bench,
5. Tandem walking,
6. Standing on one leg,
7. Standing on the foam with eyes closed,
8. Jumping for distance,
9. Dizzy walking,
10. Recovering from an unexpected loss of balance.[8,9]

The highest score that can be obtained from this multidimensional balance assessment is 40 and the lowest score is zero. FAB-Scale ≤25 indicates a fall risk.[10] Higher scores indicate better balance abilities. The FAB-SCALE is a questionnaire that is sensitive in detecting the effects of lymphoedema in women who have survived breast cancer.[11]

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The Lymphedema Quality of Life Questionnare (LYMQOL-Arm)

LYMQOL-Arm questions consist of 4 sub-units examining external appearance, upper extremity function, symptoms and mood, and the last unit, the "general quality of life" scale, is a lymphedema-specific quality of life questionnaire. In the 21-question questionnaire, the item scoring in each area is as follows: Not at all=1, somewhat=2, very=3, very=4. Higher scores indicate lower quality of life. The last question, general quality of life, is scored between 0 and 10. Higher scores indicate a better overall quality of life for the last question.[12]

Statistical Analysis

Statistical evaluation was performed with Blusky Statistics software. In the evaluation of the obtained data, continuous variables were presented as mean±standard deviation values and categorical variables were presented as frequency and related percentages. The relationships between continuous variables were evaluated using Spearman's correlation test. A P value <0.05 was considered statistically significant.

RESULTS

The mean age of the 40 patients included in the study was 59.02±7.50 years.27.5% (11) of the patients were overweight and 57.5% (23) were obese. The proportion of patients with a FAB-scale ≤25 and at risk of falls was 55% (22). The sociodemographic characteristics of the patients are summarised in Table 1.

The mean quality of life score of patients with FAB-scale ≤25 was 54.727±12.811, while the mean quality of life score of patients with FAB-scale 25< was 46.333±15.374. Although this difference was numerically different, it was not statistically significant (p=0.344). The mean FAB-Scale score was 22.04±8.93 in patients with right upper extremity lymphedema (23 patients, 57.25%) and 24.88±9.87 in patients with left upper extremity lymphedema (17 patients, 42.5%). There was no statistically significant difference between the affected lymphedema limb and balance level (p=0.563). There was a significant negative correlation between age and balance

level (p=0.0138). It was determined that balance impairment increased with increasing age. No significant correlation was observed between other parameters (p<0.05) (Table 2).

DISCUSSION

It is known that cancer survivors have decreased balance, increased risk of falls and this reduces the quality of life.[13] Many studies have been conducted on the physical, psychological and social complications caused by balance disorders and fall risk in women with breast cancer.[14-16] Patients who have had breast cancer may have similar static postural control in the 0-5 year postoperative period, but dynamic balance may change and functional balance may worsen.[17] However, our knowledge on

Table 1. Sociodemographic and clinical characteristics of the patients	
Age, Mean±SD (years)	**59.02±7.50**
Marital status Single Married	n (%) 28 (70) 12 (30)
Education Primary school Secondary school High school University	n (%) 29 (72.5) 1 (2.5) 5 (12.5) 5 (12.5)
BMI, Mean ±SD (kg/m²)	30.60±4.85
BMI (kg/m²) Normal (18.5-24.9) Overweight (25-29.9) Obese (30-34.9) Extremly obese (>35)	n (%) 5 (12.5) 11 (27.5) 23 (57.5) 1 (2.5)
Affected lymphedema limb Right Left	n (%) 23 (57.5) 17 (42.5)
Extremity volüme difference,Mean ±SD (ml)	655.35±356.48
FAB-scale, Mean ±SD	23.25±9.33
FAB-scale FAB-scale: ≤ 25 FAB-scale: 25 <	n (%) 22 (55) 18 (45.0)
LYMQOL-Arm, Mean ±SD	50.95±14.46
S.D.: Standart Deviation, BMI:Body Mass Index, FAB-Scale: The Fullerton Advanced Balance Scale, LYMQOL-Arm: Lymphedema Quality Of Life Questionnaire Arm	

Table2. The correlations of between age, BMI, FAB-Scale, LYMQOL-arm and extremity volume difference		Age	BMI	FAB-scale	LYMQOL-arm	Extremity volume difference
Age	r	1.0000	0.0730	-0.4886	0.1455	0.1460
	p		1.0000	**0.0138**	1.0000	1.0000
BMI	r	0.0730	1.0000	-0.3149	-0.0192	0.0755
	p	1.0000		0.4301	1.0000	1.0000
FAB-scale	r	-0.4886	-0.3149	1.0000	-0.2380	-0.2162
	p	**0.0138**	0.4301		1.0000	1.0000
LYMQOL-arm	r	0.1455	-0.0192	-0.2380	1.0000	0.2006
	p	1.0000	1.0000	1.0000		1.0000
Extremity volume difference	r	0.1460	0.0755	-0.2162	0.2006	1.0000
	p	1.0000	1.0000	1.0000	1.0000	
Spearman Correlation Test, BMI:Body mass index, FAB-Scale: The Fullerton Advanced Balance Scale, LYMQOL-Arm: Lymphedema Quality of Life Questionnaire Arm						

the effects of lymphedema, a common complication of breast cancer treatment, on balance is very limited. In this study, the relationship between functional balance and quality of life in patients with unilateral BCRL was investigated.

The FAB scale test is a sensitive screening tool to identify subtle changes in functional balance abilities [8]. In our study, 55% (22) of BCRL patients with a FAB-scale score ≤25 had a high fall risk. In a study conducted in the literature, 30 BCRL patients were treated with complete decongestive therapy for 2 weeks and improvement in FAB-Scale values of patients was determined after treatment.[11] Many more studies are needed to conclude that effective treatment of lymphedema can prevent the risk of balance and falls.

In this study, it was determined that the functional balance level of BCRL patients was not affected by the age difference. In a study by Başar et al.,[18] although asymmetric fluid distribution in the upper part of the body impaired stability more in pre-elderly (<60 years) women with unilateral BCRL, no difference was found in terms of fall risk with the healthy control group. There are a limited number of studies showing that the body centre of gravity is displaced towards the side with lymphedema in patients with BCRL, disrupting postural oscillation and increasing the risk of falls. In a study conducted by Angin et al,[19] patients with lymphedema were compared with a healthy control group. It was found that increased postural oscillation in patients with lymphedema led to low postural stability.

In a study by Balzarani et al.[20] it was shown that body sway decreased during walking tests and shoulder retro-position and abduction movements decreased according to the results of biomechanical analysis of patients with lymphedema. In this study, it was also shown that the shoulder was displaced towards the side with lymphedema, but this did not affect the general stability. In our study, no significant relationship was found between asymmetric limb volume difference and functional balance in the lymphedematous arm.

In studies examining the relationship between obesity and balance in the literature, it has been observed that obesity prolongs the oscillation phase of gait.[21] The results suggest that obesity may impair balance and may be a risk factor for falls, especially during prolonged physical activity.[22] It has been observed that women with breast cancer who had obesity (BMI≥25 kg/m²) before mastectomy are more likely to develop lymphedema within 6-18 months after surgery.[23]

In a meta-analysis of risk factors for the development of lymphedema, high body mass index and high weight gain were found to increase lymphedema.[24] In the case of lymphedema and obesity comorbidity, the increase in mass in different parts of the body may affect balance control and consequently activities of daily living. Although it was concluded that the quality of life of the patients in this study was not affected by the limb volume difference between both arms and body balance level, we think that a much larger number of patient studies are needed in this regard.

Limitations

Firstly, the wide age range (18-75 years) may have increased the variability and heterogeneity of the sample. In older patients (60-75 years), there may be age-related changes in the sensory and motor system, although not diagnosed. The lack of a control group and the single-arm exploratory study were important limitations of the study.

CONCLUSION

The results of this study showed that the majority of BCRL patients had poor balance, but there was no significant correlation between balance level and BMI, limb volume difference, quality of life, balance status worsened and the risk of falls increased in older patients. Every woman with breast cancer-related lymphedema should be informed about balance and gait impairment and encouraged to receive lymphedema treatment as soon as possible. In the future, we think that studies examining the relationships between functional stability, quality of life and fall risk in the treatment of lymphedema and the development of special interventions related to balance will contribute to the oncological rehabilitation protocol.

ETHICAL DECLARATIONS

Ethics Committee Approval
The study was carried out with the permission of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-interventonal Clinical Researches Ethics (Date: 09.06.2022, Decision No: 2022-06/92).

Informed Consent
All patients signed and free and informed consent form.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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A cross-sectional survey of eating behaviors and psychological factors among young people some psychological factors and eating behaviors

 Kerim Kaan Göküstün[1], Kübra Kayaoğlu[2]

[1]Department of Nutrition and Dietetics, Faculty of Health Sciences, Malatya Turgut Özal University, Malatya, Turkiye
[2]Department of Nursing, Faculty of Health Sciences, Malatya Turgut Özal University, Malatya, Turkiye

ABSTRACT

Aims: Understanding the cognitive, behavioral, and psychological issues associated with eating provides important insight into the development of diseases such as obesity and anorexia, and possibly ways to prevent or treat their occurrence. This study aims to examine the associations between cognitive, behavioral, and emotional aspects of eating habits and psychological factors such as depression, anxiety, and stress among young people.

Methods: The study was conducted with 390 university students, 43.3% male and 56.7% female. The data of the study were gathered via a survey form. The survey form includes a personal information form, the Three Factors Eating Questionnaire (TFEQ-R21) and the Depression, Anxiety and Stress Scale (DASS-21).

Results: It was determined that individuals with depression, anxiety and stress had higher uncontrolled eating, cognitive restraint and emotional eating scores than healthy individuals (p<0.05). Emotional eating scores of women were greater than those of men (r= 0.141; p=0.001). A 1-point increase in stress score was associated with 0.330 and 0.207 point increases in uncontrolled eating and cognitive restraint scores, respectively (p<0.001). A 1- point increase in depression score increases the emotional eating score by 0.261 points (p<0.001).

Conclusion: Depression, anxiety, and stress were significantly linked to disordered eating behaviors, highlighting the need for integrated mental health and nutritional interventions. In future studies, evaluating the effects of these psychological factors on food and nutrient intakes may contribute to the determination of the nutritional status of young adults.

Keywords: Anxiety, cognitive restraint, emotional eating, depression, uncontrolled eating, stress

INTRODUCTION

Eating behavior is a term used in relation to eating habits, food selection, food preparation and food consumption.[1] Gaining appropriate eating behavior is very crucial for maintaining a healthy life.[2] However, lifestyle transitions during young adulthood especially university students, such as leaving home to live independently, studying, social networks, first job, marriage, etc., can contribute to the disruption of eating behaviors.[3] Disruption of eating behaviors also leads to obesity, diabetes, cancer, cardiovascular diseases and numerous other health problems.[4,5] In terms of eating behaviors, 3 types of eating behaviors are generally emphasized.[2] These are cognitive restrained, emotional eating, and uncontrolled eating.[2] Uncontrolled eating behavior is the tendency to lose control over food when the individual feels hungry or when external factors (e.g. very tasty food) are present. It can occur even in the lack of physiological hunger. Cognitive restraint refers to the intentional restriction of food intake in order to control body shape and weight. Finally, emotional eating is overeating behavior that occurs in negative emotional states (anger, sadness, stress, etc.).[6]

Eating behavior is influenced by many factors such as genetics, environment, past experiences, cultural characteristics, media, body perception and psychiatric conditions.[4,7] Psychiatric conditions such as stress, depressive symptoms and anxiety can lead to alter eating behavior.[8] It is known that stress can alter food intake and eating behaviors in children, adolescents and adults.[9] The increase in glucocorticoids caused by acute stress may decrease hypothalamic-pituitary axis activity and nutrition, whereas in chronic stress high glucocorticoids may increase food intake through stimulatory effects.[8,10] Increased depressive and anxiety symptoms have been associated with increased food intake, excessive consumption of foods such as carbohydrates, sugar and fast food, negative emotional eating and impaired eating behaviors.[11,12] This study aimed to evaluate the relationship between depression, anxiety and stress and restrained eating, emotional eating, and external eating in university students.

Corresponding Author: Kerim Kaan Göküstün, kerimkaangokustun@ozal.edu.tr

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METHODS

Ethics

Before the study was conducted, written permission was obtained from Malatya Turgut Özal University Non-Interventional Research Ethics Committee (Decision No: 2022/112). After the participants were informed about the voluntary answers, the purpose of the study and how the results of the study would be used, their consent (informed consent principle) was obtained verbally and in writing. The students participating in the study were informed that information about themselves would not be disclosed to anyone else and the "principle of confidentiality" was complied with. The research was conducted following the principles of the Declaration of Helsinki.

Design

The current study is descriptive and cross-sectional.

Population and Sample of the Study

The data were gathered at a state university in Turkey between March 2024 and April 2024. The population of the study consisted of 3453 undergraduate students registered at Malatya Turgut Özal University between the dates of the study. The sample of the study was determined by power analysis. The sample size of the study was calculated using the mean, standard deviation, correlation (r) and coefficients of determination ($R2$) obtained from a pilot study with 30 participants. According to the calculation made by using the G*power 3.1 program, the sample size was determined to be at least 368 with an effect size of 0.40, a margin of error of 0.05, a confidence level of 0.95.

Inclusion or exclusion criteria:

Study inclusion criteria:

· Volunteering to participate in the study,
· 18 years of age or older,

Study exclusion criteria:

· Pregnant and lactating women,
· Individuals with any severe psychological disorder and who are taking medication for this reason,
· Individuals with eating disorders and chronic diseases that require special diets
· Individuals who did not fill out the questionnaire reliably by the researcher,
· Individuals who left the questionnaire form without completing it despite volunteering were excluded from the study.

Scales

The study data were collected using a personal information form, the three factor eating questionnaire (TFEQ-R21) and the depression, anxiety and stress scale (DASS-21).

1. Personal Information Form: The survey data were collected by the researchers through face-to-face interviews. In addition, the questionnaire was administered to the participants during class hours with permission. The data collection form was explained to the students by the researcher and the answers were recorded on the form. The personel information form includes descriptive information on age, gender, anthropometric measurements and financial status of the participants.

Anthropometric Measurements

Body weight and height: The body weight and height of individuals will be collected according to the participant's declaration.

Body mass index (BMI): It will be calculated in kg/m² with the formula body weight / height (m²).

2. Three Factors Eating Questionnaire (TFEQ-R21): It was first developed by Stunkard and Messick[13] in 1985 to measure behavioral and cognitive aspects of eating. The questionnaire originally included 51 items, however, it was reduced to 18 items by Karlsson et al.[14] (2000) due to its limited feasibility. The 21-item questionnaire form was revised and adapted to Turkish culture by Karakuş et al.[6] in 2016. All of the items in the scale are on a 4-point Likert scale and the response is scored as "absolutely wrong" 1, "mostly wrong" 2, "absolutely right" 3 and "mostly right" 4. The questionnaire shows a 3-factor structure among its components. Uncontrolled eating (UE) consist of 9 items (items 3, 6, 8, 9, 12, 13, 15, 19 and 20). The minimum score for sub-factor is 9 and the maximum score is 36 points. Cognitive restraint (CR) consist of 6 items (items 1, 5, 11, 17, 18 and 21). The minimum score for this sub-factor is 6 and the maximum score is 24 points. Emotional eating (EE) consist of 6 items (items 2, 4, 7, 10, 14 and 16). The minimum score for this sub-factor is 6 and the maximum score is 24 points. A higher score in any sub-factor in the questionnaire indicates that the eating behavior related to that factor is more predominant.

3. The Depression, Anxiety and Stress Scale (DASS-21): The Depression Anxiety Stress Scale (DASS) was first designed by Lovibond and Lovibond[15] (1995) consisting of 42 items. The adaptation of the 21-question DASS which was used in the scope of the study was made by Henry and Crawford[16] (2005) and it was revealed that the short form could be used. The scale was translated into Turkish by Yılmaz et al.[17] (2017). This scale (DASS-21) includes seven items each to evaluate the levels of depression, anxiety and stress. The first seven items in the scale are related to anxiety, seven items between eight-fourteen are related to depression and seven items between fifteen-twenty one are related to stress. In the scoring of the scale, the high scores are taken into consideration. Higher or lower scores for depression, anxiety and stress indicate that the participants experience these conditions at a higher or lower rate (Table 1). Participants who scored between zero-nine points, zero-seven points and zero-fourteen points on depression, anxiety and stress subscales, respectively, were defined as healthy.

Statistical Analysis

In the evaluation of the findings obtained in the study, IBM SPSS Statistics 25 (IBM SPSS, Turkey) program was used for statistical analysis. Descriptive statistics such as mean, standard deviation, minimum, maximum values, numbers and percentages were used to summarize the data.

In our study, it was determined whether the groups were normally distributed. Skewness and Kurtosis values were examined for the normality test. Skewness and Kurtosis[18]

values should be in the range of ±3 in order to understand that the data conform to normal distribution. Skewness and Kurtosis values were found to be between 0.817/-0.302 for the DASS-21 scale and 0.384/-1.863 for the three-factor eating questionnaire. It was determined that all scales and subscales showed normal distribution since the Skewness and Kurtosis values obtained from the scales and subscales were within the range of ±3. The difference between two independent groups was tested with the independent samples t-test. Multiple Linear Regression analysis with the backward selection method was performed for the effect of related variables on uncontrolled eating, cognitive restraint, and emotional eating scores, and standardized and unstandardized regression coefficients and VIF values for multicollinearity were obtained. P-value <0.05 was considered statistically significant.

RESULTS

The sociodemographic characteristics of the participants are given in Table 1. Initially, 428 university students were recruited between the specified dates. Since thirty-eight students did not participate in the study and did not fill out the questionnaire questions reliably, the study was completed with 390 students (91% completion rate). 43.3% of the participants were male and 56.7% were female. The mean age of the study participants was 20.58±2.22 years. The mean body weight, height and BMI of the participants were 65.08±13.21 kg, 170.53±9.15 cm and 22.23±3.25 kg/m², respectively. More than half of the participants (64.9%) were in the first grade. Those who answered "my income is less than my expenses" were found to be 59.5%. The mean depression, stress and anxiety scores of the participants were 13.08±5.06, 13.72±5.29 and 13.65±4.92 points, respectively. In the study, it was determined that the mean uncontrolled eating score of the participants was 17.51±6.29 points; the mean cognitive restraint score was 11.59±4.82 points and the mean emotional eating score was 10.74±4.65 points.

The distribution of uncontrolled eating, cognitive restraint and emotional eating scores of the participants in terms of depression, anxiety and stress are given in Table 3. According to DASS-21, 69.5% of the participants have depression, 86.9% have anxiety and 38.7% have stress. Uncontrolled eating, cognitive restraint and emotional eating scores of individuals with depression were higher than those of individuals without depression (p<0.001). Considering eating behaviors according to anxiety status, it was determined that all eating behavior scores of individuals with anxiety were higher and the difference was found to be statistically significant (p<0.05). Similar to depression and anxiety status, uncontrolled eating, cognitive restraint and emotional eating scores of stressed individuals were found to be higher than non-stressed individuals and the difference was statistically significant (p<0.001).

The correlations between the sociodemographic features and depression, anxiety and stress scores of the individuals who participated in the study and the scores of uncontrolled eating, cognitive restraint and emotional eating are also given in Table 3. Emotional eating scores of women were greater than those

Table 1. Sociodemographic characteristics of the participants		
Variables		**X±SD or n (%)**
Age (year)		20.58±2.22
Gender	Male	169 (43.3)
	Female	221 (56.7)
Body weight (kg)		65.08±13.21
Height (cm)		170.53±9.15
BMI (kg/m²)		22.23±3.25
Marital status	Single	380 (97.4)
	Married	10 (2.6)
Faculty/vocational school	Health science	133 (34.1)
	Medicine	10 (2.6)
	Vocational school of health	91 (23.3)
	Agriculture	21 (5.4)
	Engineering	133 (34.1)
	Other	2 (0.5)
Grade	1. grade	253 (64.9)
	2. grade	132 (33.8)
	3. grade	4 (1.0)
	4. grade	1 (0.3)
Income	My income is less than my expenses	232 (59.5)
	My income is equal to my expense	122 (31.3)
	My income is more than my expenses	36 (9.2)
DASS-21 scale subcategories		
Depression		13.08±5.06
Anxiety		13.72±5.29
Stress		13.65±4.92
TFEQ-21 scale subcategories		
Uncontrolled eating		17.51±6.29
Cognitive restraint		11.59±4.82
Emotional eating		10.74±4.65
Variables are expressed as number (%). mean±standard deviation. BMI: Body mass index DASS-21: Depression. Anxiety and Stress-21. TFEQ-21: Three Factor Eating Questionnaire-21.		

of men (r=0.165; p=0.001). Statistically significant correlations were found between body weight and uncontrolled eating (r=0.149), cognitive restraint (r=0.200) and emotional eating (r=0.112) (p<0.001). Statistically significant positive correlations were found between depression, anxiety and stress scores and uncontrolled eating, cognitive restraint and emotional eating scores (p<0.001).

The results of the regression analysis of the variables are given in Table 3. When the results were evaluated; BMI (B=0.696; t=4.195; p<0.001) and stress (B=0.330; t=2.919; p=0.004) scores were found to be effective on uncontrolled eating; 1 unit increase in BMI score increases the uncontrolled eating score by 0.696 points and 1 point increase in stress score

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Table 2. The correlations between the sociodemographic features, depression, anxiety and stress scores and uncontrolled eating, cognitive restraint and emotional eating.						
	Uncontrolled eating		Cognitive restraint		Emotional eating	
	r	p	r	p	r	p
Gender[*]	0.029	0.495	0.056	0.190	0.165	**0.001**
Age[*]	-0.043	0.396	-0.009	0.863	-0.073	0.152
Body weight[*]	0.149	**0.003**	0.200	**0.000**	0.112	**0.027**
BMI[*]	0.247	**0.000**	0.303	**0.000**	0.273	**0.000**
Income[**]	-0.040	0.329	-0.012	0.778	-0.039	0.360
Depression[*]	0.377	**0.000**	0.242	**0.000**	0.329	**0.000**
Anxiety[*]	0.381	**0.000**	0.205	**0.000**	0.310	**0.000**
Stress[*]	0.400	**0.000**	0.245	**0.000**	0.311	**0.000**
[*]The Pearson correlation coefficient, [**] Kendall's τ coefficient, BMI: Body mass index						

increases the uncontrolled eating score by 0.330 units. BMI is more effective than stress on uncontrolled eating. Gender (B=1.528; t=3.187; p=0.002), BMI (B=0.510; t=7.050; p<0.001) and stress (B=0.207; t=4.489; p<0.001) scores were found to be effective on cognitive restraint; cognitive restraint score of women was higher, 1 unit increase in BMI score increased cognitive restraint score by 0.510 points, 1 point increase in stress score increased cognitive restraint score by 0.207 points. BMI is more effective on cognitive restraint than stress and gender. BMI (B=0.709; t=4.725; p<0.001) and depression (B=0.261; t=6.233; p<0.001) scores were found to be effective on emotional eating; 1 unit increase in BMI score increases the emotional eating score by 0.709 points and 1 unit increase in depression score increases the emotional eating score by 0.261 points. BMI is more effective on emotional eating than depression.

DISCUSSION

In our study, uncontrolled eating, cognitive restraint and emotional eating scores of individuals with depression were found to be higher than those of individuals with no depression (Figure 1). Moreover, statistically significant correlations were found between depression and uncontrolled eating, cognitive restraint and emotional eating scores (Table 2). The findings of the studies carried out on this issue are similar to the findings of our study.[19,20] Depression is one of the important factors affecting eating behaviors. Individuals with symptoms of depression may increase or decrease their food intake.[21] High intensity negative emotions suppress food intake due to their association with physiological responses that reduce appetite.[22] However, negative emotions with less intensity can increase or decrease food intake according to individuals' characteristics and situations.[23] Individuals may engage in emotional eating to cope with stress and negatif emotions such as depression. It has been reported that individuals with emotional eating behavior increase their food intake and prefer unhealthy foods.[21]

In our study, cognitive restraint, uncontrolled eating and emotional eating scores were found to be higher in individuals with stress and anxiety compared to individuals without stress and anxiety (Figure 1). In addition, statistically significant

positive correlations were determined between anxiety and stress scores and cognitive restraint, uncontrolled eating and emotional eating scores (Table 2). Studies have found that there is a relationship between stress and anxiety and restrained, emotional, and external eating and disordered eating behaviors.[24,25] Induviduals may engage in eating behaviors such as emotional and external eating to cope with negative emotions including anxiety and stress.[26,27] In a study conducted by Groesz,[28] high stress levels were found to decrease eating control, induce hunger, and increase restrained and binge eating behaviors.

The relationship between gender and eating behaviors is widely known. In our study, emotional eating scores were found to be higher in women than in men (Table 2). Moreover, the cognitive restraint score of women was 1.528 points greater than that of men (Table 3). In a study conducted by Zakhour et al.[29] it was reported that restrictive eating scores were higher in women than in men. However, no significant difference was found in emotional eating scores compared to gender. In other studies, it was shown that emotional and restrictive eating scores were higher in women than in men.[30,31] In our study, it is thought that the reason for the difference in terms of emotional eating is that the way of coping with problems can vary according to gender. The reason why the cognitive restraint score is higher in women is that women tend to have a perfect body more than men. Moreover, women are more likely to engage in food-restricting behavior because they are more likely to consume foods with high energy content compared to men.[32]

Body weight has a critical importance on individuals' eating behaviors. In our study, statistically significant positive correlations were observed between uncontrolled eating, cognitive restraint and emotional eating scores and BMI and body weight (Table 2). Furthermore, a 1-unit increase in BMI was associated with 0.696, 0.510 and 0.709 unit increases in uncontrolled eating, cognitive restraint and emotional eating scores, respectively (Table 3). In a study conducted with adolescents, the cognitive restraint subscale scores of the three-factor eating scale were divided into quartiles from small to large. When the 1st quartile was compared with the 4th quartile, it was found that the participants in the 4th quartile

Table 3. The results of the regression analysis of the variables															
	Uncontrolled eating					**Cognitive restraint**					**Emotional eating**				
	B	**Beta**	**t**	**p**	**VIF**	**B**	**Beta**	**t**	**p**	**VIF**	**B**	**Beta**	**t**	**p**	**VIF**
Constant	-0.429		-0.202	0.840		-4.969		-2.475	**0.014**		-1.656		-0.595	0.552	
Age	-0.166	-0.059	-1.301	0.194	1.012	-0.038	-0.017	-0.369	0.712	1.026	-0.176	-0.084	-1.863	0.063	1.022
Gender	-0.286	-0.023	-0.314	0.754	2.564	1.528	0.157	3.187	**0.002**	1.130	1.204	0.128	1.795	0.073	2.561
Body weight	-0.068	-0.144	-1.672	0.095	3.678	0.030	0.081	0.611	0.542	8.210	-0.077	-0.220	-1.707	0.089	8.284
BMI	0.696	0.360	4.195	**<0.001**	3.671	0.510	0.344	7.050	**<0.001**	1.108	0.709	0.496	4.725	**<0.001**	5.511
Income	-0.127	-0.013	-0.295	0.768	1.018	0.083	0.011	0.242	0.809	1.019	0.044	0.006	0.137	0.891	1.019
Depression	0.040	0.032	0.302	0.763	5.717	0.087	0.091	0.959	0.338	4.203	0.261	0.284	6.233	**<0.001**	1.036
Anxiety	0.176	0.148	1.667	0.096	3.904	-0.093	-0.102	-0.954	0.341	5.302	0.083	0.094	1.000	0.318	4.438
Stress	0.330	0.258	2.919	**0.004**	3.895	0.207	0.211	4.489	**<0.001**	1.028	0.060	0.064	0.635	0.526	5.027
	R^2 =0.227; F(p) = 28.264 (**<0.001**)					R^2=0.169; F(p) = 26.204 (**<0.001**)					R^2=0.232; F(p) = 23.152 (**<0.001**)				
Multiple Linear Regression Analysis, BMI: Body-mass index															
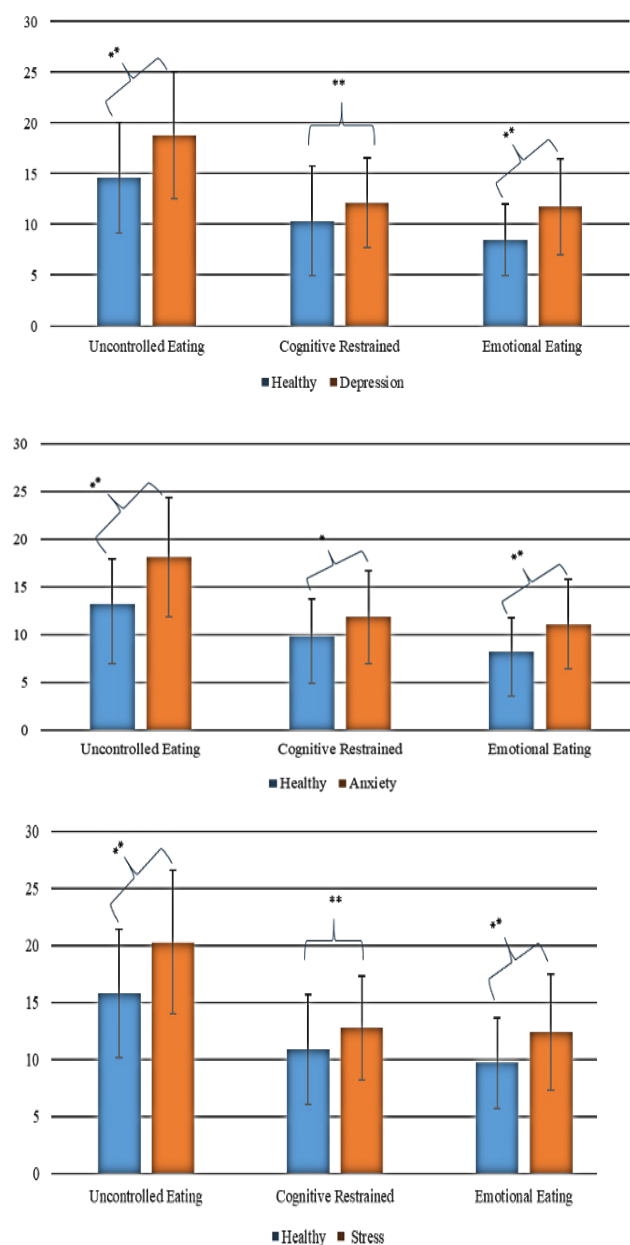
*p<0,005, **p<0,001
Figure 1. The distribution of uncontrolled eating, cognitive restraint and emotional eating scores of the participants in terms of depression, anxiety and stress

had higher BMI, waist circumference, fat mass and obesity degree than the participants in the 1st quartile.[33] In a study conducted with university students, positive correlations were observed between body weight and waist circumference and uncontrolled eating, cognitive restraint and emotional eating scores.[34] Moreover it was reported that as the uncontrolled eating score of individuals increased, their energy intake also elevated and dietary disinhibition and cognitive restraint behaviors increased the risk of being overweight/obese by 14.2% and 7.6%, respectively.[35]

Limitations

First, the results gathered from this study are limited to university students who received education in a single center over a specific period of time. Second since the data of the study were collected through a questionnaire form, there is a possibility of bias in participants' responses. Third, the cross-sectional nature of the study does not clearly demonstrate the reason for the relationship between depression, anxiety, stress and some sociodemographic features of participants and cognitive restraint, emotional eating and uncontrolled eating behaviors.

CONCLUSION

Psychological factors have an impact on food intake, nutritional status and eating behaviors.[36] University students are prone to impaired eating behaviors due to psychological alterations caused by lifestyle changes.[37] In our study, it was found that depression, anxiety and stress may have an effect on eating behaviors in university students. It was also found that body weight gain can be associated with cognitive restraint, emotional eating and uncontrolled eating behaviors. The acquisition of healthy eating habits instead of impaired eating behaviors can only be possible by improving the psychological factors underlying impaired eating behaviors. For this reason, dieticians and psychiatrists should collaborate to promote healthy eating habits.

In our study, only the effects of depression, anxiety and stress on uncontrolled eating, cognitive restraint and emotional eating were evaluated. In future studies, evaluating the effects

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of these psychological factors on food and nutrient intakes may contribute to the determination of the nutritional status of young adults. In addition, larger sample size studies can be more decisive in evaluating the effects of these psychological factors on uncontrolled eating, cognitive restraint, emotional eating and other eating behaviors.

ETHICAL DECLARATIONS

Ethics Committee Approval
The study was conducted, written permission was obtained from Malatya Turgut Özal University Non-interventional Researches Ethics Committee (Decision No: 2022/112).

Informed Consent
All patients signed and free and informed consent form.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
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Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Indicators of prolonged hospital stay and rehospitalizations in hyperemesis gravidarum

Büşra Demir Çendek[1,2], Zeynep Şeyhanlı[3,4], Arife Akay[1], Ayşe Ecenaz Yıldırım[2],
Nazan Vanlı Tonyalı[3,4], Salim Erkaya[1,5], Yaprak Engin Üstün[1]

[1]Department of Obstetrics and Gynecology, Etlik Zübeyde Hanım Maternity, Training and Research Hospital, Ankara, Turkiye
[2]Department of Obstetrics and Gynecology, Ankara Etlik City Hospital, Ankara, Turkiye
[3]Division of Perinatology, Department of Obstetrics and Gynecology, Etlik Zübeyde Hanım Maternity, Training and Research Hospital, Ankara, Turkiye
[4]Division of Perinatology, Department of Obstetrics and Gynecology, Ankara Etlik City Hospital, Ankara, Turkiye
[5]Division of Perinatology, Department of Obstetrics and Gynecology, Ankara Bilkent City Hospital, Ankara, Turkiye

ABSTRACT

Aims: Hyperemesis gravidarum (HG) can significantly impact the quality of life of pregnant women and is the primary factor leading to hospitalization during the first half of the pregnancy. The aim of this study is to determine the ability of basic laboratory indicators that determine the severity of HG and the indices that can be calculated from them to predict the total length of hospital stay and the number of recurrent hospitalizations.

Methods: A retrospective analysis was conducted on women diagnosed with HG at a tertiary hospital from 2018 to 2021. Following the application of the inclusion criteria, we included a total of 100 eligible patients with HG (study group) and 130 healthy pregnant women (control group). Subsequently, the groups were subjected to a comparative analysis.

Results: The study group had higher levels of hemoglobin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), red blood cell (RBC), white blood cells (WBC), neutrophil, mean platelet volüme (MPV), ketonuria, and lower levels of thyroid-stimulating hormone (TSH), eosinophil (p<0.005, for all). Additionally, neutrophil-to-lymphocyte ratio (NLR), systemic immune inflammation index (SII), systemic inflammatory response index (SIRI), and AST to platelet ratio index (APRI) (p<0.05, for all) were significantly higher in the study group than in the control group, but serum delta neutrophil index (DNI), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR) and pan-immune inflammation value (PIV) were statistically similar in both groups.

Conclusion: To the best of our knowledge, this is the first study to investigate the prediction of total hospital stay along with the number of recurrent hospitalizations with laboratory parameters in HG patients. The NLR, SII, SIRI, APRI, WBC, AST, neutrophil, and ketonuria have the potential to serve as valuable, economically viable, and readily available objective indicators for the diagnosis of HG and the prediction of recurrent hospitalization and duration of hospitalization.

Keywords: Hyperemesis gravidarum, complete blood count, ketonuria, hospitalization, predicting rehospitalization

INTRODUCTION

Nausea and vomiting in pregnancy (NVP) is a common and often recurring symptom that occurs frequently during pregnancy. The prevalence of NVP among pregnant women during the initial trimester ranges from approximately 50% to 80%.[1] Hyperemesis gravidarum (HG) is a term used in medicine used to describe severe nausea and vomiting that occurs during pregnancy. Most NVP cases resolve spontaneously during pregnancy. A small percentage develop HG, causing dehydration and ketonuria. These complications require hospitalization due to persistent symptoms, nutritional deficiencies, and electrolyte imbalance.[2]

Multiple potential mechanisms have been proposed to be implicated in the pathogenesis of HG. Numerous pathological conditions, including hormonal fluctuations, immunological mechanisms, *Helicobacter pylori* infection, aberrant gastric motility, genetic predisposition, and liver dysfunction, have been documented.[3] The precise cause of HG remains uncertain.[4] Multiple risk factors have been documented in relation to HG, encompassing nulliparity, low maternal age, multiple gestation, fetal anomalies, a prior pregnancy complicated by HG, female gender, psychiatric disorders, and both elevated and diminished maternal prepregnancy weight.[5–7]

NVP is the prevailing indication for hospital admission during the early stages of pregnancy. Indeed, it ranks as the second most prevalent reason for hospitalization during pregnancy,

following only premature birth.[8,9] HG frequently results in hospitalization during the early stages of pregnancy, thereby causing adverse outcomes such as unemployment, reduced social engagement, and diminished overall well-being. Clinical diagnosis is still the main method, so any indicator of disease severity may be useful. The relationship between hematological parameters and the presence and severity of HG is still not well understood. Few studies have examined HG women's re-hospitalization risk factors. In the present study, we aimed to investigate to what extent do laboratory indicators such as neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), serum delta neutrophil index (DNI), systemic immune inflammation index (SII), systemic inflammatory response index (SIRI), pan-immune inflammation value (PIV), the aspartate aminotransferase (AST) to platelet ratio index (APRI) from first trimester complete blood count (CBC) and ketonuria contribute to the prognostication of hospitalization in individuals diagnosed with HG.

METHODS

A retrospective analysis was conducted on clinical data from patients who were admitted to the hospital's early pregnancy department with a diagnosis of HG between 2018 and 2021. The control group comprised pregnant women who were in good health and fell within the same gestational age as the study group. These women consistently attended our prenatal clinic. This study received local ethics committee approval (Date: 28.02.2024, Decision No: 02/13) and was conducted in accordance with the guidelines specified in the Declaration of Helsinki.

The study included a cohort of 230 pregnant women, with 100 pregnant women diagnosed with HG during the gestational period of 6-14 weeks (study group), and 130 pregnant women serving as healthy controls during the same gestational period (control group). The determination of gestational age was achieved by utilizing the first day of the most recent menstrual period and subsequently confirming it through sonography. The hospital's electronic medical system was used to collect all patient demographic and clinical data. The age, gestational age, gravidity, and parity of each patient were recorded. The diagnostic criteria for HG included the following: a minimum of three instances of intense vomiting per day, a weight loss exceeding 5% before pregnancy, and the presence of at least one positive result for ketonuria in the dipstick urine test.

This study excluded first-trimester CBC data and women with missing data. In addition, the study excluded patients with gastrointestinal disorders, diseases that induce nausea and vomiting like diabetic ketoacidosis, thyroid disorders, neurological conditions that elevate intracranial pressure and lead to vomiting, and inflammatory diseases.

The randomization process for the control group consisted of selecting healthy pregnant women with gestational ages that matched those of the participants admitted to the outpatient clinic. The process was carried out in a sequential manner, directly after the admission of each woman who joined the HG group, following the application of the exclusion criteria.

During the hospitalization of all patients, blood and urine samples are routinely collected as a standard procedure. After being collected, all samples were tested on a daily basis using the same automated analyzer in the laboratory of the hospital. The CBC parameters, such as neutrophil count (NC), lymphocyte count (LC), white blood cells (WBC), monocyte count (MC), eosinophil count (EC), hemoglobin level, hematocrit (HCT), platelet count (PC), platelocrit (PCT), mean platelet volume (MPV), red blood cell (RBC), red cell distribution (RDW), DNI and biochemical parameters, such as alanine aminotransferase (ALT), AST, thyroid-stimulating hormone (TSH) values were documented. Ketonuria was classified into four grades: 1+, 2+, 3+, and 4+. Subsequently, the blood parameters and ratios of systemic inflammation, such as NLR, PLR, MLR, SII, SIRI, PIV, and APRI, were computed for each participant in the study. The calculations were based on the parameters obtained from the CBC using the specified formulas: "NL=NC/LC; PLR=PC/LC; MLR=MC/LC; SII=PCxNC/LC; SIRI=MCxNC/LC; PIV=PCxMC/LC; APRI=(AST/normal upper limit of AST/patient's PCx100".

The individual was granted release from the hospital subsequent to a notable enhancement in their oral food consumption capacity.

Statistical Analysis

The statistical analysis was conducted using the IBM® SPSS® Statistics v29.0 software, also known as the Statistical Package for the Social Sciences (SPSS), developed by IBM in Armonk, New York, USA. The suitability of numerical data for normal distribution was analyzed according to the Kolmogorov-Smirnov and Shapiro-Wilk tests. Numerical data were given as median (interquartile range (IQR) or min-max) or mean±SD. Categorical variables were presented as numbers (percentage) and the chi-square test was used. In this study consisting of two independent groups, Mann Whitney U test was used for non-parametric numerical variables and independent sample t test was used for parametric variables. In addition, by receiver operating characteristic (ROC) curve analysis, the cut-off values of immune markers with an area under the curve (AUC) greater than 0.5, along with their 95% confidence interval (CI) values, sensitivity and specificity values were reached. Correlation tests were used to evaluate the relationship between independent variables. Significant results were considered when p<0.05.

RESULTS

Among the 230 individuals included in the sample, it was noted that 100 participants (43.5%) were allocated to the HG group, also known as the study group, whereas 130 participants (56.5%) were assigned to the control group. Demographic, clinical, and laboratory characteristics and outcomes between the groups are shown in Table 1. Age, gravida, parity, and gestational age did not differ between study and control groups (p>0.05). According to Table 1, the study group had higher rates of hospitalization days, recurrent hospitalizations, extended hospital stays, and previous HG history (p<0.001, for all). The study group had higher levels of ALT (13.3 U/L vs. 12 U/L, p=0.029), AST (17 U/L vs. 16 U/L,

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Table 1. Demographic, clinical, and laboratory characteristics and outcomes between study and control groups			
Variable	**Study group**	**Control group**	**p-value**
Participant (n,%)	100 (43.5)	130 (56.5)	
Age (years, median, IQR)	27 (8)	27 (9)	0.177[a]
Gravida (n, median, IQR)	2 (2)	2 (1)	0.813[a]
Parity (n, median, IQR)	2 (1)	1 (2)	0.469[a]
Gestational age (day, Mean±SD)	69.95±16.77	73.10±29.06	0.304[b]
First hospitalization (n, %)			<0.001[c]
No	0 (0)	130 (100)	
1 day	39 (39)	0 (0)	
2 days	36 (36)	0 (0)	
≥3 days	25 (25)	0 (0)	
Re-Hospitalization (n,%)			<0.001[c]
No	0 (0)	130 (100)	
1	68 (68)	0 (0)	
2	22 (22)	0 (0)	
≥3	10 (10)	0 (0)	
Total length of hospital stay			<0.001[c]
No	0 (0)	130 (100)	
1 day	34 (34)	0 (0)	
2 days	26 (26)	0 (0)	
≥3 days	40 (40)	0 (0)	
Previous HG			<0.001[c]
No	51 (51)	128 (98.5)	
Yes	49 (49)	2 (1.5)	
RBC (10⁶/μL, mean±SD)	4.508±0.361	4.327±0.802	**0.024**[b]
Hemoglobin (g/dl, mean±SD)	12.94±0.97	12.62±1.14	**0.023**[b]
HCT (%, mean±SD)	38.32±2.79	38.04±3.99	0.540[b]
Platelets (10³/mm³, mean±SD)	263.820±70.06	263.592±57.95	0.970[b]
PCT (μg/L, mean±SD)	0.209±0.048	0.205±0.043	0.540[b]
WBC (10³/mm³, mean±SD)	8.620 (2.840)	7.870 (2.380)	0.001[a]
Neutrophil (10³/mm³, mean±SD)	6.610 (2.335)	5.580 (2.497)	<0.001[a]
Lymphocyte (10³/mm³, median, IQR)	1.590 (0.685)	1.610 (0.573)	0.077[a]
Monocyte (10³/mm³, median, IQR)	0.360 (0.170)	0.380 (0.157)	0.281[a]
Eosinophil (10³/μL, median, IQR)	0.050 (0.050)	0.700 (1.025)	<0.001[a]
RDW (%, median, IQR)	13.8 (1.0)	13.9 (1.4)	0.213[a]
DNI (median, IQR)	-3.0 (3.85)	-3.5 (4.13)	0.676[a]
MPV (fl, Median, IQR)	8 (1.1)	7.8 (0.8)	0.020[a]
TSH (mU/L, median, IQR)	0.72 (1.25)	1.15 (1.21)	<0.001[a]
Ketonuria (median, IQR)	4 (0)	0 (0)	<0.001[a]
AST (IU/L, median, IQR)	17 (6)	16 (5)	<0.001[a]
ALT (IU/L, median, IQR)	13.3 (9)	12 (6)	0.029[a]
NLR (median, IQR)	3.83 (2.66)	3.27 (1.32)	<0.001[a]
PLR (median, IQR)	169.23 (85.66)	159.07 (53.85)	0.117[a]
MLR (median, IQR)	0.24 (0.13)	0.24 (0.10)	0.248[a]
SII (median, IQR)	1094.42 (794.11)	899.72 (413.46)	<0.001[a]
SIRI (median, IQR)	1.76 (1.20)	1.31 (0.91)	0.002[a]
PIV (median, IQR)	64.40 (43.94)	60.10 (34.23)	0.39[a]
APRI (median, IQR)	0.20 (0.09)	0.17 (0.7)	<0.001[a]
[a]= Mann Whitney U Test, [b]= Indepented t test, [c]=Chi Square test, Bold p values are statistically significant (p<0.05)			

Abbreviations: HG; Hyperemesis gravidarum, RBC; Red blood cell, HCT; Hematocrit, PCT; Plateletcrit, WBC; White blood cell, RDW; Red cell distribution width, MPV; Mean platelet volüme, ALT; Alanine aminotransferase, AST;Aspartate aminotransferase, TSH; Thyroid stimulating hormone, DNI; Delta neutrophil index, PLR; Platelet to lymphocyte ratio, NLR; Neutrophil to lymphocyte ratio, MLR; Monocytes to lymphocyte ratio, SII; Systemic immune-inflammatory index, SIRI; Systemic inflammatory response index, PIV; Pan-immune inflammation value, APRI; Aspartate aminotransferase to platelet ratio index.

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Test result variables	Area under curve	Std. error	Asymptotic sig.	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
Ketonuria	0.942	0.022	<0.001	0.899	0.984
NLR	0.683	0.041	<0.001	0.603	0.763
SII	0.679	0.042	<0.001	0.596	0.762
Neutrophil (10³/mm³)	0.666	0.041	<0.001	0.586	0.746
AST (IU/L)	0.660	0.041	<0.001	0.581	0.740
WBC (10³/mm³)	0.630	0.042	0.003	0.546	0.713
SIRI	0.629	0.043	0.003	0.544	0.713
APRI	0.604	0.043	0.017	0.520	0.689
ALT (IU/L)	0.586	0.043	0.051	0.501	0.670
Hemoglobin (g/dl)	0.576	0.043	0.080	0.493	0.660
RBC (10⁶/μL)	0.560	0.043	0.171	0.476	0.644
MPV (fl)	0.559	0.045	0.176	0.472	0.647
TSH (mU/L)	0.353	0.039	<0.001	0.276	0.429
Eosinophil (10³/μL)	0.088	0.021	<0.001	0.047	0.130

Table 2. Evaluation of laboratory results that are statistically significant between the groups with receiver operating characteristic (ROC) curves analyses

Bold p values are statistically significant (p<0.05)
Abbreviations: RBC; Red blood cell, WBC; White blood cell, ALT; Alanine aminotransferase, AST; Aspartate aminotransferase, TSH; Thyroid stimulating hormone, MPV; Mean platelet volüme, NLR; Neutrophil to lymphocyte ratio, SII; Systemic immune-inflammatory index, SIRI; Systemic inflammatory response index, APRI; Aspartate aminotransferase to platelet ratio index

$p < 0.001$), hemoglobin (12.94 g/dl vs. 12.62 g/dl, p=0.023), RBC (4.508 10^6/μL vs. 4.327 10^6/μL, p=0.024), WBC (8.620 10^3/mm³ vs. 7.870 10^3/mm³, p=0.001), NC (6.610 10^3/mm³ vs. 5.580 10^3/mm³, p<0.001), MPV (8 fl vs. 7.8 fl, p=0.020), ketonuria (4 vs. 0, p<0.001), and lower levels of TSH (0.72 mU/L vs. 1.15 mU/L, p<0.001), EC (0.050 10^3/μL vs. 0.700 10^3/μL, p<0.001). Additionally, NLR, SII, SIRI and APRI (p<0.05 for all) were significantly higher in the HG group than in the control group, but DNI, PLR, MLR and PIV were statistically similar in both groups.

To evaluate laboratory results that are statistically significant between the groups, ROC curves were calculated and shown in Table 2. Ketonuria showed an AUC of 0.942 (95% CI: 0.899-0.984) and the optimal cut-off value was set at +2.75, resulting in a sensitivity of 80.5% and a specificity of 100% (p<0.001) (Figure 1). Also, the AUC for NLR was 0.683 (cut-off 3.47, 95% CI: 0.603-0.763, p<0.001, sensitivity 70.7%, specificity 54%), for SII it was 0.679 (cut-off 965.75, 95% CI: 0.596-0.762, p<0.001, sensitivity 69.6%, specificity 61.3%), for SIRI it was 0.629 (cut-off 1.468, 95% CI: 0.544-0.713, p=0.003, sensitivity 62%, specificity 61.3%), for AST it was 0.660 (cut-off 15.2 IU/L, 95% CI: 0.581-0.740, p<0.001, sensitivity 75%, specificity 49.2%), for NC it was 0.666 (cut-off 5.780 x10^3/mm³, 95% CI: 0.586-0.746, p<0.001, sensitivity 71.7%, specificity 56.6%), for WBC it was 0.630 (cut-off 7.975 x10^3/mm³, 95% CI: 0.546-0.713, p=0.003, sensitivity 68.5%, specificity 54%), for APRI it was 0.604 (cut-off 0.184, 95% CI: 0.520-0.689, p=0.017, sensitivity 60.9%, specificity 63.5%) (Figure 2).

In Table 3, correlation analysis was performed between the number of hospitilization days at the first hospitalization, the number of recurrent hospitalizations, the total length of hospital stay due to HG, and previous HG history and laboratory parameters in HG patients. It was revealed that there was a significant positive correlation between the
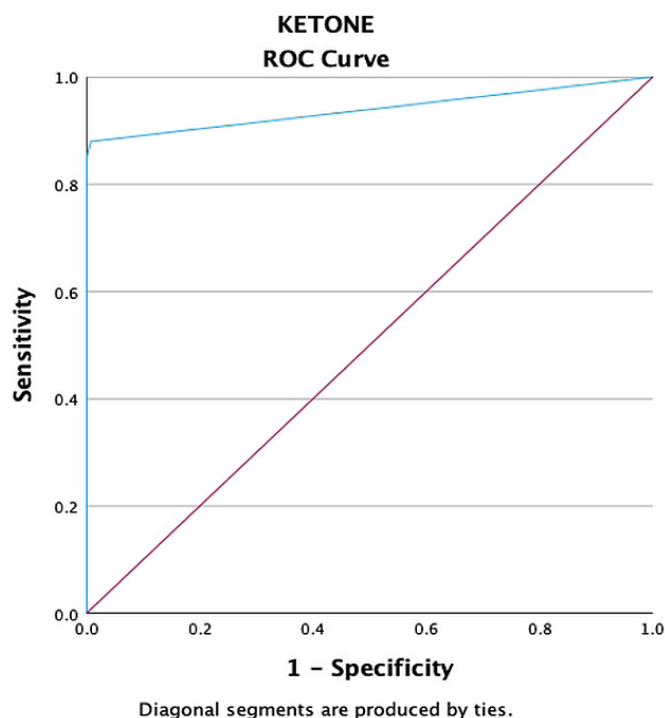
KETONE ROC Curve

Figure 1. Receiver operating characteristic (ROC) curves of ketone

number of days of hospitalization in the first hospitalization, the number of recurrent hospitalizations, the total hospital stay due to HG, and ketonuria, NLR, SII, NC, WBC, SIRI, APRI, AST, ALT and hemoglobin (p<0.05, for all). While ketonuria, NLR, SII, NC, WBC, SIRI, AST and hemoglobin showed a significant positive correlation with previous HG history, APRI and ALT did not show a significant correlation. RBC and MPV did not show a significant correlation with the number of recurrent hospitalizations, total hospital stay due to HG, previous HG history (p>0.05, for all). While MPV

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Table 3. Spearman correlation coefficients between hospitalization characteristics and previous HG with laboratory parameters in HG patients		First hospitalization	Re-Hospitalization	Total length of hospital stay	Previous HG
Ketonuria	Correlation coefficient	.833	.844	.831	.559
	Sig.	<.001	<.001	<.001	<.001
NLR	Correlation coefficient	.272	.291	.259	.232
	Sig.	<.001	<.001	<.001	<.001
SII	Correlation coefficient	.231	.280	.248	.262
	Sig.	<.001	<.001	<.001	<.001
Neutrophil (10³/mm³)	Correlation coefficient	.274	.252	.223	.163
	Sig.	<.001	<.001	<.001	.013
AST (IU/L)	Correlation coefficient	.268	.274	.266	.196
	Sig.	<.001	<.001	<.001	.003
WBC (10³/mm³)	Correlation coefficient	.215	.180	.162	.136
	Sig.	.001	.006	.014	.040
SIRI	Correlation coefficient	.191	.189	.162	.136
	Sig.	.004	.004	.014	.040
APRI	Correlation coefficient	.217	.198	.195	.080
	Sig.	<.001	.003	.003	.232
ALT (IU/L)	Correlation coefficient	.166	.169	.174	.119
	Sig.	.013	.012	.009	.077
Hemoglobin (g/dl)	Correlation coefficient	.161	.152	.158	.164
	Sig.	.015	.022	.017	.014
RBC (10⁶/µL)	Correlation coefficient	.110	.108	.105	.108
	Sig.	.096	.105	.114	.104
MPV (fl)	Correlation coefficient	.141	.124	.129	.020
	Sig.	.033	.061	.053	.767
TSH (mU/L)	Correlation coefficient	-.272	-.285	-.300	-.213
	Sig.	<.001	<.001	<.001	.002
Eosinophil (10³/µL)	Correlation coefficient	-.685	-.697	-.687	-.477
	Sig.	<.001	<.001	<.001	<.001

Bold p values are statistically significant (p<0.05)
Abbreviations: RBC; Red blood cell, WBC; White blood cell, ALT; Alanine aminotransferase, AST; Aspartate aminotransferase, TSH; Thyroid stimulating hormone, MPV; Mean platelet volüme, NLR; Neutrophil to lymphocyte ratio, SII; Systemic immune-inflammatory index, SIRI; Systemic inflammatory response index, APRI; Aspartate aminotransferase to platelet ratio index

showed a significant positive correlation with the number of days of hospitalization at the first hospitalization, RBC did not show a significant correlation. It was revealed that there was a significant negative correlation between the number of days of hospitalization during the first hospitalization, the number of recurrent hospitalizations, the total duration of hospital stay due to HG, previous HG history, and TSH and EC (p<0.05, for all). A cut-off value of 0.075 was determined for EC, with a sensitivity of 85.6% and specificity of 69.1% (AUC: 0.932, p<0.001, 95% CI: 0.870-0.953). Similarly, a cut-off value of 0.910 was established for TSH, with a sensitivity of 67.3% and specificity of 54.7% (AUC: 0.647, p<0.001, 95% CI: 0.571-0.724). These values were found to have diagnostic value for the control group, as depicted in Figure 3.

Table 4 displays the pregnancy outcomes of patients belonging to both the study and control groups. While all patients in the control group were included, only 66 patients in the study group were able to obtain pregnancy results. When assessing the pregnancy outcomes of the HG group, it was noted that 2 (3%) patients experienced an abortion during the first

trimester, 53 (80.3%) patients gave term birth, 9 (13.6%) patients gave preterm birth, and 2 (3%) patients gave postterm birth (p<0.001, for all).

DISCUSSION

The occurrence of NVP ranks as the second most prevalent diagnosis for antenatal hospitalization, accounting for 11.4% of all indications. The average duration of hospitalization for this condition is 2.7 days.[8] In the present study, it was observed that 40% of the HG group necessitated hospitalization for a cumulative duration of 3 days or longer, while 34% were hospitalized for a duration of less than 2 days. Additionally, a significant proportion of hospitalized women, ranging from 19% to 30%, experience subsequent hospitalizations within the same pregnancy.[3,10,11] A study conducted by Piwko et al.[12] examined the economic impact of NVP in the United States. The study determined that the cost of drug treatment for mild NVP (nausea and vomiting of pregnancy) was $40, while the cost for HG (hyperemesis gravidarum) was estimated
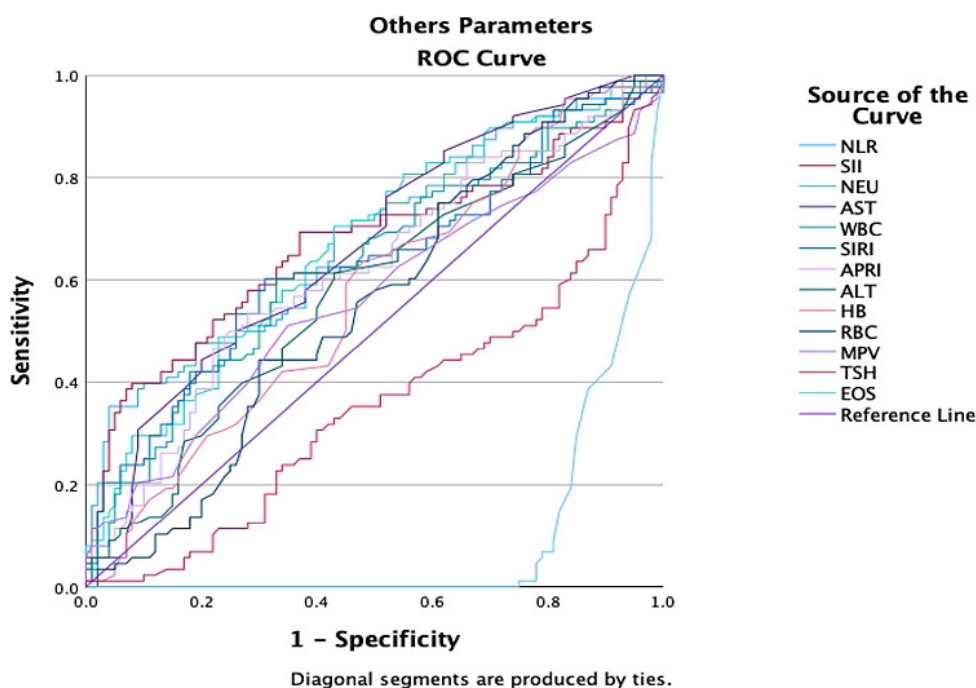
Figure 2. Receiver operating characteristic (ROC) curves of other parameters in the study group
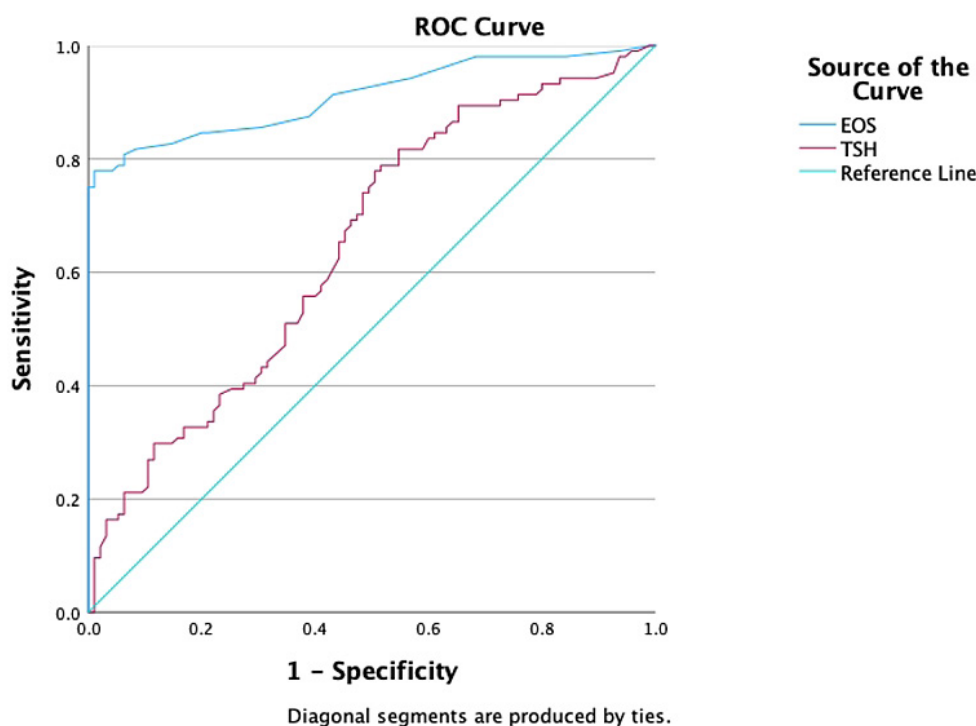
Figure 3. Receiver operating characteristic (ROC) curves of EOS and TSH in the control group

to be $267. The study documented that the mean hospital expenditure for each patient admission for HG was $12,453. The identification of patients with HG who are susceptible to an extended hospital stay offers several benefits. Firstly, it aids in the development of treatment strategies aimed at reducing the duration of hospitalization. Secondly, it aids in the identification of women who are at risk of re-hospitalization. Thirdly, it enhances the effectiveness of their treatment plan,

prevents the need for additional hospital admissions, and helps alleviate the economic burden on the nation.

Prior research has primarily examined the factors that increase the risk of HG, the outcomes for both the mother and the fetus, and the factors that contribute to hospitalization. There is a scarcity of research in the literature that investigates laboratory markers for extended hospitalization caused by HG. The study conducted by Tan et al.[13] found that there was

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Table 4. Outcome of pregnancy between study and control groups			
Variable	Study group	Control group	p-value
Outcome of pregnancy (n)	66	130	<0.001
First trimester abortion (n,%)	2 (3)	0 (0)	
Term birth (n,%)	53 (80.3)	128 (98.5)	
Preterm birth (n, %)	9 (13.6)	2 (1.5)	
Postterm birth (n,%)	2 (3)	0 (0)	

an independent association between hematocrit values of 41% or higher and an extended duration of hospitalization.The study conducted by Topçu et al.[14] aimed to identify risk factors associated with HG and investigate their potential correlation with both the duration of hospital stay and the severity of HG. Nevertheless, it was observed that factors such as age, body mass index, gestational week, need for combined antiemetic use, CBC parameters, liver and kidney function tests did not exhibit any significant association with the duration of hospital stay. However, it was found that serum maternal TSH levels below 0.1 μIU/mL and a frequency of 5 vomitings per day were significant predictors of longer hospital stays.

Research on NVP has focused on inflammatory indices and cell lines obtained from the CBC. The study conducted by Tayfur et al.[15] revealed significant differences in NC, LC, and PC, as well as NLR, PLR, and PCT, between the HG and control groups. This article was conducted in response to the increasing interest in inflammatory markers obtained from a single CBC. Furthermore, to our knowledge, this is the first study to investigate the prediction of total hospital stay along with the number of recurrent hospitalizations with hematological parameters and ketonuria values in HG patients. Nevertheless, due to the intricate nature of altered inflammation, it would be impractical, unreproducible, and devoid of significance to base decisions solely on a solitary cell line, such as NC, LC, or PC. In the present study, we examined the NLR, PLR, MLR, SII, SIRI, APRI and PIV assays, which collectively evaluate distinct inflammatory cell lines and have been previously examined for their potential in predicting and prognosticating various diseases involving inflammation in their pathogenesis.[16–19] Our study examined the correlation between hematological parameters, and ketonuria values, and the duration of initial hospitalization, total hospital stay, and recurrent hospitalizations in patients with HG. We found that as the values of ketonuria, NLR, SII, NC, WBC, SIRI, APRI, AST, ALT, and hemoglobin increased, there was a significant increase in both the number of hospitalizations and the duration of hospitalization. In addition, on the contrary to these laboratory parameters, it was observed that the decrease in TSH and EC values significantly increased the initial hospitalization time, total hospital stay and the number of recurrent hospitalizations. Hyperthyroid disorder, a potential risk factor for severe HG and an increased likelihood of hospitalization, should be evaluated and managed in all patients.[3] Consistent with the literature, in our study, it was observed that as the TSH value decreased, re-hospitalization and total hospitalization time increased. When all the results

are evaluated, patients with thyroid dysfunction should be evaluated and treated in order to reduce possible serious complications, prolonged and recurrent hospitalizations and costs in first trimester pregnancies.

Ketonuria serves as a diagnostic parameter for severe HG; however, the association between the severity of the disease and the extent of ketonuria remains uncertain. Multiple studies have investigated potential correlations between the disease severity and the extent of ketonuria.[20–22] The severity of the condition was assessed based on the readmission rate[20] and the duration of hospitalization exceeding 4 days.[21,22] There was no significant association found between ketonuria and an extended duration of hospitalization.[22] Further research has shown that there is no significant correlation between the presence of ketonuria and the severity of HG in relation to the need for admission again.[20,21] A comparative analysis between patients with and without hyperemesis gravidarum (HG) revealed that the HG group displayed elevated levels of ketonuria. Furthermore, it was discovered that a greater length of hospital stay was linked to elevated levels of ketonuria.[23] In our study, we observed that as the ketonuria value increased in the HG group, the initial hospitalization time, total hospital stay and the number of recurrent hospitalizations increased in a positive correlation (p<0.001).

A significant correlation was observed between a short gestational period during pregnancy and the likelihood of re-hospitalization.[24] Numerous studies consistently validate a heightened prevalence of HG during the initial weeks of gestation and the first trimester.[11,20,25] The participants in our study were patients in their first trimester.

Prior research on hospitalization resulting from HG indicates that women with a history of HG were more likely to be admitted to the hospital during their subsequent pregnancy.[3,10,26] The findings of our study validate these results, demonstrating a significant likelihood of HG in women who have previously been diagnosed with HG during subsequent pregnancies (p<0.001). Furthermore, our study revealed that the length of initial hospitalization in cases of HG did not have a statistically significant impact on the likelihood of re-hospitalization (p=0.276). Nevertheless, it was noted that a prior occurrence of HG resulted in a statistically significant rise in re-hospitalization. Upon dividing the HG group into subgroups based on the number of hospitalizations, it was observed that individuals with 2 or more hospitalizations had a significantly higher history of HG (96.9% vs 25%) (p<0.001). In addition, it was found that individuals with a prior history of HG had a 91.176-fold (95% CI: 11.552-719.641) increased risk of being hospitalized again due to HG in future pregnancies. The affects of HG on women's perspectives towards family planning, their desires to conceive again, and their levels of anxiety and trepidation regarding future pregnancies necessitate meticulous examination.[27] The attitudes and anxieties experienced by women who have previously experienced HG may have an impact on their likelihood of being readmitted to the hospital.

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Limitations

There are certain constraints in our study. Both groups have small populations. Our retrospective study could not use validated tools like the Pregnancy-Unique Quantification of Emesis and Nausea score because the hospital's database was inaccessible. This tool and supplementary variables like weight data in a prospective study can validate the index and improve medical care for women with HG.

CONCLUSION

NVP is a prevalent condition during pregnancy and seldom advances to severe HG necessitating hospitalization. Physicians can utilize the NLR, SII, SIRI, APRI, WBC, AST, NC, and ketonuria to assess the likelihood of a prolonged hospital stay and the frequency of recurrent hospitalizations. However, additional research is required in large-scale population studies. It is crucial to identify patients who are at a high risk of developing HG in order to prevent recurrent hospitalizations, prolonged hospital stays, potential complications, and to minimize economic expenses.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethical Committe of Etlik Zübeyde Hanım Women's Dıseases Training and Research Hospital (Date: 28.02.2024 Decision No: 02/13)

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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MEDICINE
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The role of clinical and radiological risk factors and triglyceride-glucose index in predicting recurrence of idiopathic granulomatous mastitis

©Semih Sağlık

Department of Radiology, Siirt Training and Research Hospital, Siirt, Turkiye

ABSTRACT

Aims: Idiopathic granulomatous mastitis (IGM) is a rare breast disease characterised by granulomatous inflammation that is clinically and radiologically similar to breast cancer. The main challenge in treating IGM is the development of treatment resistance and recurrence. Many studies have been carried out in the literature to identify markers of recurrence in this disease, but no satisfactory results have been obtained. The aim of this study was to determine the role of clinical, radiological and laboratory parameters in predicting recurrence in patients with IGM and to evaluate the relationship between the triglyceride-glucose (TyG) index and IGM recurrence.
Methods: In this study, the electronic medical records of 92 patients who were histopathologically diagnosed with IGM between January 2016 and February 2024 were retrospectively reviewed. Patients were divided into two groups according to recurrence status. Clinical, radiological and laboratory parameters were compared between groups.
Results: Recurrence was detected in 26.1% of the patients included in the study and the average follow-up period was 27.6±4.6 months. No statistically significant difference was found between the two groups with regard to age, follow-up time, menopausal status, breastfeeding, oral contraceptive use, smoking history, parity and pathological diagnosis (p>0.05 for all). In univariate analysis, axillary lymphadenopathy, long duration of breastfeeding, low serum albumin globulin ratio and high TyG index were identified as risk factors for IGM recurrence. In multivariate regression analysis, long duration of breastfeeding (p=0.042, OR: 4.12; 95% confidence interval (CI), 1.05-16.11) and high TyG index (p=0.005, OR: 5.75; 95% confidence interval (CI), 1.69-19.54) were found to be independent risk factors for recurrence.
Conclusion: Study results suggest that a high TyG index at initial presentation and long duration of breastfeeding increase the risk of recurrence in IGM patients. Therefore, questioning the breastfeeding history at the time of admission and determining and analyzing the TyG index can identify patients at high risk for recurrence.

Keywords: Idiopathic granulomatous mastitis, recurrence, ultrasonography, triglyceride-glucose index, axillary lymphadenopathy, breastfeeding duration

INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is a granulomatous inflammatory disease of the breast that is clinically and radiologically similar to breast cancer.[1] It is most common in premenopausal women and causes clinical symptoms such as pain, palpable mass, edema and ulceration.[2] As clinical and radiological findings can be confused with breast cancer, histopathological samples are required for differential diagnosis.[1,2] The main challenge in treating IGM patients is the development of treatment resistance and recurrence. There are studies suggesting that some factors such as smoking, pregnancy status, breastfeeding and secondary infections increase the likelihood of recurrence.[3-5] Anti-inflammatory agents, corticosteroids and surgical excision are included in the treatment of the disease and in preventing recurrences.[6,7]

Although surgical excision is the mainstay of treatment, recurrence rates of 5% to 50% have been reported despite wide surgical excision.[3,6] Therefore, identifying patients who are likely to develop a recurrence will help clinicians determine the type of treatment and follow-up period. Many studies have been conducted in the literature to determine the markers of recurrence in IGM patients, but no satisfactory results have been obtained.[2,3,7]

Insulin resistance (IR) is a pathological condition that plays an important role in the development of chronic metabolic disorders, often associated with diabetes. The gold standard for detecting IR is the euglycaemic hyperinsulinemic clamp test. However, as this method is time-consuming and expensive, the triglyceride-glucose (TyG) index, which is a good indicator of

Corresponding Author: Semih Sağlık, drsmhsglk@gmail.com

insulin resistance, has become a valuable indicator. The TyG index is closely related to systemic inflammation and has been shown to play an important role in determining the severity and prognosis of many diseases.[8-16] A few studies have examined the relationship between the TyG index and breast cancer and have shown that the TyG index is associated with breast cancer risk.[17-19] However, the relationship between the TyG index and IGM is not yet known.

The aim of this study was to determine the role of clinical, radiological and laboratory parameters in predicting recurrence in patients with idiopathic granulomatous mastitis and to evaluate the relationship between the TyG index and IGM recurrence.

METHODS

Study Participants
This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics Committee Approval was obtained from the Siirt University Non-İnvasive Ethics Committee (Date: 22.02.2024, Decision No: 101661).

In this single-centre retrospective study, the electronic medical records of patients with a histopathological diagnosis of idiopathic granulomatous mastitis between January 2016 and May 2024 were retrospectively reviewed. Patients diagnosed with granulomatous mastitis due to secondary causes (tuberculosis, granulomatous polyangiitis, sarcoidosis, etc.) or foreign bodies, patients with a history of malignancy, chronic liver or kidney disease, patients with missing fasting blood glucose or fasting triglyceride data, patients with conditions such as diabetes mellitus or pancreatitis, patients using lipid-lowering drugs, patients without adequate medical record data or follow-up information were excluded.

Study Data
Definitive diagnostic methods included fine needle aspiration biopsy (FNAB), tru-cut biopsy, or surgical excision. On microscopic examination, the presence of non-caseous granulomatous inflammation of the breast lobules was a pathological diagnostic criterion. Data on clinical and demographic characteristics of all patients, such as age, body mass index (BMI), parity, breastfeeding status, duration of breastfeeding, smoking history, menopausal status and history of oral contraceptive use were collected and recorded. When determining the breastfeeding duration of patients who had given birth more than once, after determining the breastfeeding duration for each child, the total breastfeeding duration was divided by the number of children and the average was taken. Triglyceride (TG), blood glucose, serum albumin, total protein, sedimentation (ESR), C-reactive protein (CRP), haematological parameters (Hg, neutrophil, lymphocyte, platelet and leukocyte levels), serum neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and albumin-to-globulin ratio (AGR) were recorded from the laboratory information system. AGR, NLR and PLR were obtained by dividing the relevant parameters by each other. Globulin values were obtained by subtracting albumin from total protein. TyG index was calculated as follows: TyG index=Ln [fasting TG (mg/dL)x fasting glucose (mg/dL)/2].[20]

Radiological Findings
Ultrasonography (USG) reports of all patients were accessed from the electronic medical record system and data on radiological imaging features of the disease were obtained. Patients without a USG report in the system were excluded from the study. In accordance with the information obtained from the USG reports, the findings were evaluated as follows; irregularly circumscribed, heterogeneous lesions and interrelated tubular collections, fluid collections compatible with abscess, irregularly circumscribed mass-like lesions, multiple millimetric hypoechoic lesions, heterogeneous thickened breast parenchyma, fistulisation to the skin and axillary lymphadenopathy. Axillary lymphadenopathy characteristics detected from USG reports were recorded in the registry. While lymph nodes with oval, thin cortex and wide fatty hilus were evaluated in favor of normal lymph nodes, cortical thickening, reduction or absence of fatty hilus, change in shape, disappearance of ovoid form and abnormal vascularization were evaluated in favor of lymphadenopathy.[21] (Figure 1).

Definition of Remission and Recurrence
Although there is no accepted definition for IGM remission in the literature, remission was defined as the complete disappearance of clinical complaints and inflammatory symptoms. In patients whose treatment was completed, the recurrence of clinical complaints and radiological imaging findings after at least 3 months of follow-up was considered as recurrence.[4] Patients who did not have sufficient follow-up information after treatment were questioned in terms of complete remission and recurrence in telephone interviews.

Statistical Analysis
Data analyzes of our study were determined using SPSS 20.0 software (Statistical Package for the Social Sciences, Chicago, IL). Variables regarding qualitative data are expressed as number (n) and percentage (%), and variables regarding quantitative data are expressed as mean±standard deviation (SD). In the evaluation of the study data, Student's t test was used for intergroup comparisons of normally distributed variables and Mann-Whitney U test was used for intergroup comparisons of parameters that did not show normal distribution. Chi-square test or Fisher's exact test was applied for the comparison of categorical variables depending on the sample size. Univariate and Multivariate Binary Logistic Regression analyses were used to determine the effective risk factors on IGM recurrence. ROC (Receiver Operating Characteristic) curve analysis was used to determine whether TyG index and breastfeeding duration were prognostic indicators in forecasting recurrence and to determine the optimal cut-off values. The significance level for statistical results was accepted as $p<0.05$.

RESULTS
This study included 92 female patients with histopathological diagnosis of IGM and complete follow-up data. The mean age at the time of diagnosis was 32.1±5.9 years and the mean follow-up period was 27.6±4.6 months. It was determined that 92.3% (n=85) of the patients had a history of at least one birth and 94.5% (n=87) were in the premenopausal period. The majority of the patients (86.5%, n=80) had a history of breastfeeding
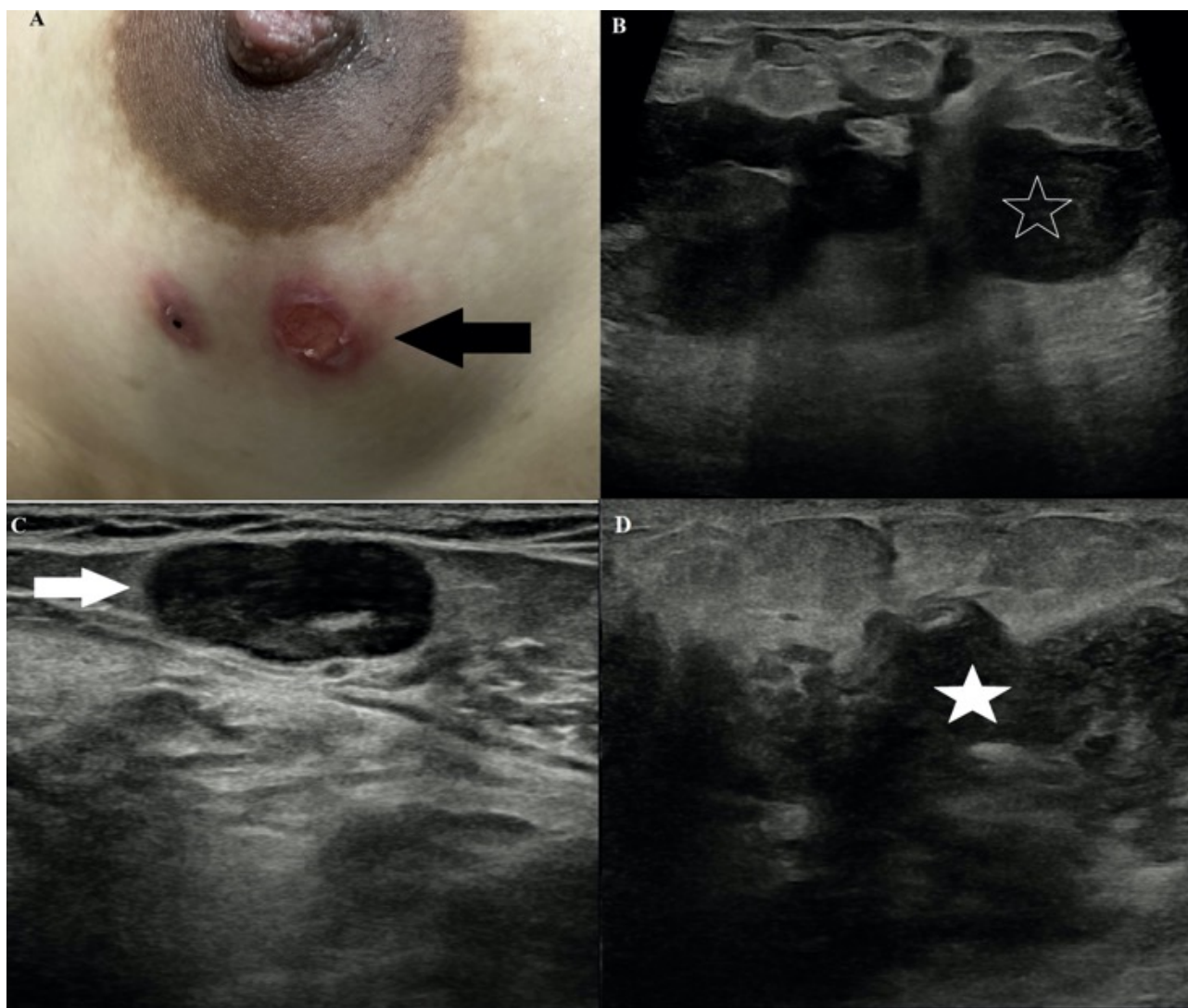
Figure 1. Ulcerative lesion on the skin in the lower quadrants of the left breast in a 36-year-old female patient with histopathological diagnosis of IGM (A, black arrow). USG examination of the same patient revealed heterogeneous lesions with irregular borders in the breast parenchyma (B, open star) and a lymph node with cortical thickening in the right axillary region (C, white arrow). The patient, who had complete remission after treatment, had a recurrence in the same breast 8 months later, and a simultaneous USG examination revealed that heterogeneous lesions reappeared in the breast parenchyma (D, closed star).

and the average duration of breastfeeding was 15.9±8.6 months. The mean body mass index was 30.3±5.5 kg/m2. In the study group, 26.1% (n=24) had a history of oral contraceptive use and 9.2% (n=9) had a history of smoking. The right breast was affected in 57.6% (n=53) of the patients and the left breast was affected in 42.4% (n=39). Histopathological diagnosis was made by fine needle biopsy in 4 patients (4.3%), tru-cut biopsy in 68 patients (73.9%) and excisional breast biopsy in 20 patients (21.8%) (Table 1).

Patients were divided into two groups according to recurrence status. There were 68 (73.9%) patients in the group without recurrence and 24 (26.1%) patients in the group with recurrence. No statistically significant difference was found between the two groups in terms of age, follow-up period, menopausal status, breastfeeding, oral contraceptive and smoking history, parity and pathological diagnosis (p>0.05 for all, Table 1). However, breastfeeding duration was found to be statistically higher in the recurrence group (p<0.001, Table 1, Figure 2A). When laboratory parameters were compared, serum albumin, total protein, globulin and AGR values were found to be statistically

higher in the recurrence group (p<0.05 for all, Table 1). TyG index was significantly higher in the recurrence group (p<0.001, Figure 2B). However, no statistically significant difference was detected between laboratory parameters such as serum sedimentation (ESR), C-reactive protein (CRP), fasting glucose and triglyceride, and hematological values (Hg, neutrophil, lymphocyte, platelet and leukocyte levels) between the two groups (all for p>0.05, Table 1).

Pain (n=83), palpable mass (n=68), erythema (n=43), induration (n=14) and dermal sinus (n=14) were among the most common clinical findings in the patients included in the study. USG reports revealed poorly circumscribed, irregular, heterogeneous lesions in 33.6% (n=31), multiloculated abscess collections in 28.2% (n=26), well-circumscribed hypoechoic mass in 16.3% (n=15), hypoechoic mass and heterogeneous lesions in 13.1% (n=12), and abscess collections and heterogeneous lesions in 15.2% (n=14). The results of the study indicated that there was no statistically significant difference between the clinical and ultrasonographic findings in both groups. Axillary lymphadenopathy was found in 34.7% (n=32) of all patients in

Table 1. Baseline characteristics and comparison of variables among IGM recurrence groups				
	IGM Recurrence			
Parameters	**No recurrence (n=68)**	**Recurrence (n=24)**	**Total (n=92)**	**p values**
Age (years)	31.5±6.2	33.7±4.6	32.1±5.9	0.125[a]
BMI (kg/m2)	29.9±5.7	31.4±4.8	30.3±5.5	0.259[a]
Follow-up (month)	27.2±4.5	29.1±4.7	27.6±4.6	0.091[a]
Breastfeeding n (%) No Yes	10 (14.7%) 58 (85.3%)	2 (8.4%) 22 (91.6%)	12 (13.1%) 80 (86.9%)	0.725[b]
Breastfeeding duration (month)	14±7.6	21.5±8.9	15.9±8.6	<0.001[a]
Oral contraceptive use n (%) No Yes	50 (73.5%) 18 (26.5%)	18 (75%) 6 (25%)	68 (73.9%) 24 (26.1%)	0.888[b]
Smoking n (%) No Yes	62 (91.2%) 6 (8.8%)	21 (87.5%) 3 (12.5%)	83 (90.2%) 9 (9.2%)	0.692[b]
Parity n (%) Nulliparous Parous	5 (7.3%) 63 (92.7%)	2 (8.3%) 22 (91.7%)	7 (7.6%) 85 (92.4%)	0.876[c]
Menopausal status, n (%) Premenopausal Postmenopausal	65 (95.6%) 3 (4.4%)	22 (91.6%) 2 (8.4%)	87 (94.5%) 5 (5.5%)	0.466[b]
Lesion side Right breast Left breast	40 (58.8%) 28 (41.2%)	13 (54.2%) 11 (45.8%)	53 (57.6%) 39 (42.4%)	0.691[c]
Pathological diagnosis, n (%) FNAC Core needle biopsy Surgical excision	3 (4.4%) 50 (73.5%) 15 (22.1%)	1 (4.1%) 18 (75%) 5 (20.9%)	4 (4.3%) 68 (73.9%) 20 (21.8%)	0.990[b]
HB (gr/dl)	12.4±1.2	12.2±1.11	12.3±1.2	0.577[d]
WBC (10⁹/L)	9.4±2.5	10.2±2.4	9.6±2.5	0.193[d]
CRP (mg/dl)	4.6±2.8	3.9±2.8	4.4±2.8	0.362[d]
Sedimentation (mm/h)	23.8±12.7	25.8±11.9	24.3±12.5	0.503[d]
Neutrophil (10⁹/L)	5.1±1.1	5.4±1.1	5.2±1	0.213[d]
Lymphocyte (10⁹/L)	2.7±0.8	2.9±0.9	2.7±0.8	0.423[d]
PLT (10⁹/L)	281±53	291±47	284±52	0.442[d]
ALB (g/L)	4.55±0.8	3.99±0.9	4.4±0.86	0.006[d]
Protein (g/L)	7.06±1.27	7.69±1.1	7.22±1.25	0.036[d]
Globulin (g/L)	3.1±0.6	3.3±0.4	3.2±0.6	0.009[d]
NLR	2.07±0.85	2.08±0.81	2.08±0.84	0.960[d]
PLR	112.7±40.4	108.8±33.8	111.7±38.6	0.682[d]
AGR	1.6±0.56	1.19±0.28	1.49±0.53	0.001[d]
Glucose (mg/dL)	97.4±13.7	102.8±12.1	98.8±13.5	0.087[d]
Triglyceride (mg/dL)	116.9±17.8	124.9±18.7	118.9±18.2	0.062[d]
TyG index	8.57±0.23	8.81±0.17	8.64±0.23	<0.001[d]

Notes: [a]Student's t-test with mean±standard deviation (SD). [b]Fisher's Exact test with n (%). [c]Chi-Square with n (%).[d]Mann Whitney U-test with median±interquartile range (IQR). Statistically significant results (p < 0.05).
Abbreviations: IGM, Idiopathic granulomatous mastitis; BMI, Body mass index; HB, Hemoglobin; WBC, White blood cell count; CRP, C-reactive protein; PLT, platelets; SM, Segmental mastectomy; FNAC, Fine needle aspiration cytology; TyG index, Triglyceride-glucose index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio

USG reports. Axillary lymphadenopathy was present in 26.5% (n=18) of patients with complete remission, while this rate was 58.3% (n=14) in recurrence patients. The chi-square test results indicated that the frequency of axillary lymphadenopathy was statistically significantly higher in patients who experienced recurrence (p=0.005, Table 2).

The AUC values of TyG index and breastfeeding duration in the receiver operating characteristics (ROC) curve analysis test were 0.805 (0.708-0.903) and 0.771 (0.644-0.899) with 95% confidence interval, respectively, and were therefore considered statistically significant (p<0.001 for all, Figure 3).Accordingly, when the TyG index cut-off was ≥8.68, its sensitivity and specificity were 75% and 70.6%, respectively, and when the
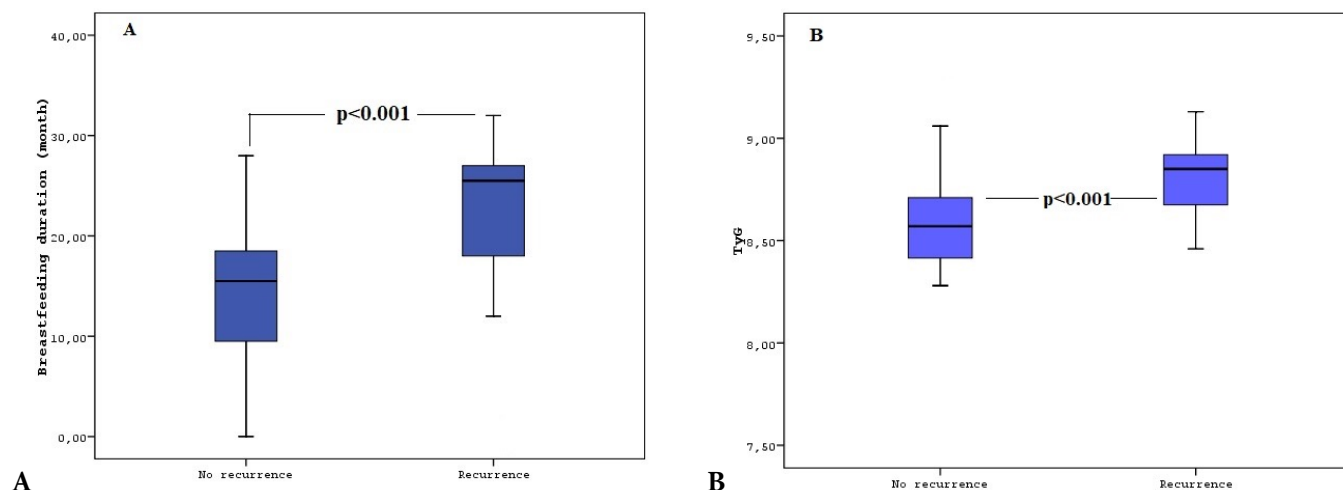
Figure 2. Boxplot of the distribution of (A) breastfeeding duration, (B) TyG index values among IGM recurrence groups. The horizontal lines inside each box represent the mean values and the lower and upper rows of each box represent the minimum and maximum values, respectively.

Table 2. Comparison of the clinical features and ultrasound findings of with non-recurrent and recurrent IGM				
	IGM Recurrence			
Parameters	No recurrence (n=68)	Recurrence (n=24)	Total (n=92)	p values
Clinical findigs				
Mass	49 (72.1%)	19 (79.1%)	68 (73.9%)	0.495[a]
Pain	63 (92.6%)	20 (83.3%)	83 (90.2%)	0.187[a]
Erythema	32 (47.1%)	11 (45.8%)	43 (46.7%)	0.918[b]
Induration	11 (16.2%)	3 (12.5%)	14 (15.2%)	0.666[a]
Sinus or ulcer	12 (17.6%)	2 (8.3%)	14 (15.2%)	0.275[b]
Ultrasound findings				
Ill-defined, irregular, heterogeneous lesions	24 (35.2%)	7 (29.1%)	31 (33.6%)	0.585[b]
Multiloculated abscess collections	17 (25%)	9 (37.5%)	26 (28.2%)	0.242[a]
Well-circumscribed hypoechoic mass	10 (14.7%)	5 (20.8%)	15 (16.3%)	0.485[a]
Hypoechoic mass and heterogeneous lesions	8 (11.7%)	4 (16.6%)	12 (13.1%)	0.540[a]
Abscess collections and heterogeneous lesions	12 (17.6%)	2 (8.3%)	14 (15.2%)	0.275[a]
Axillary lymphadenopathy				0.005[b]
Negative	50 (73.5%)	10 (41.6%)	60 (65.2%)	
Positive	18 (26.5%)	14 (58.3%)	32 (34.7%)	
Notes: [a]Fisher's Exact test with n (%). [b]Chi-Square with n (%). Statistically significant results (p < 0.05). Abbreviations: IGM, Idiopathic granulomatous mastitis				

breastfeeding duration cut-off was ≥24.5 months, its sensitivity and specificity were 79.2% and 61.8%, respectively, in predicting IGM recurrence.

Regression analysis was used to determine the effective parameters for IGM recurrence. In univariate regression analysis, axillary LAP (yes or no), long breastfeeding duration (≥24.5 months), low AGR values (≤1.183) and high TyG index (≥8.68) were identified as risk factors for IGM recurrence. In multivariate regression analysis, the cut-off value of breastfeeding duration greater than 24.5 months (p=0.042, OR: 4.12; 95% confidence interval (CI), 1.05-16.11) and the cut-off value of TyG index above 8.68 (p=0.005, OR: 5.75; 95% confidence interval (CI), 1.69-19.54) were found to be independent risk factors for IGM recurrence (Table 3).

DISCUSSION

IGM is a breast disease that can be confused clinically and radiologically with malignant and benign breast lesions and requires histopathological confirmation for definitive diagnosis.[1,22] Although IGM is considered a benign lesion of the breast, it still poses serious problems due to the development of permanent complications and recurrences.[4,22] Although many treatments and combinations have been used to treat IGM, including antibiotics, steroids, methotrexate and surgery, recurrence rates of up to 50% have been reported.[3,6] Therefore, knowing the risk of IGM recurrence and factors that can predict recurrence will influence patient-specific treatment and follow-up and increase the chance of success. In our study, we analysed the clinical, radiological and laboratory risk factors associated with IGM recurrence and found that the TyG index may be an effective biomarker in predicting recurrence and breastfeeding duration was an independent risk factor for recurrence.

ROC Curve

A

ROC Curve

B

Figure 3. The receiver operating characteristic (ROC) curve and the area under the ROC (AUC) of (A) TyG index and (B) breastfeeding duration in IGM recurrence prediction.

Table 3. Univariate and multivariate binary logistic regression analysis results to determine risk factors effective in IGM recurrence

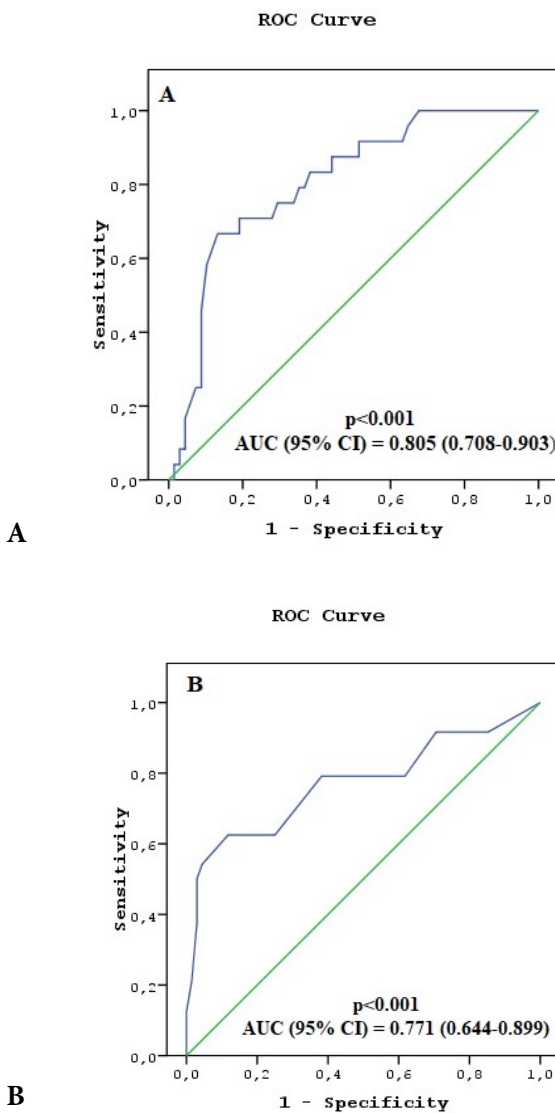|	Univariate		Multivariate	
	p values	OR (CI 95%)	p values	OR (CI 95%)
Axillary LAP Yes, against no	0.006	3.88 (1.46-10.03)	ns	
Breastfeeding duration (month) ≥24.5 against <24.5	0.002	6.33 (1.95-20.05)	0.042	4.12 (1.05-16.11)
AGR ≤1.183 against ≥1.183	0.001	0,18 (0.66-0.51)	ns	
TyG index ≥8.68 against <8,68	0.001	6.27 (2.18-18.01)	0.005	5.75 (1.69-19.54)

Note: Statistically significant results (p < 0.05).
Abbreviations: ns, not significant; OR, Odds ratio; CI, Confidence interval; TyG, Triglyceride-glucose index; AGR, Albumin-to-globulin ratio; LAP, Lymphadenopathy

Insulin resistance is defined as a reduced response to normal concentrations of insulin in the bloodstream. Metabolic disturbances caused by IR can induce oxidative stress, exacerbate inflammatory responses and impair endothelial function.[23,24] The TyG index, which is a good indicator of IR, has been associated with many diseases including cardiovascular, cerebrovascular and renal disease, subclinical atherosclerosis, non-alcoholic fatty liver disease and malignancy.[8,9,12-19] In addition, there are studies showing that the TyG index is associated with poor prognosis in infectious diseases such as COVID-19, chronic hepatitis B and C.[10,11] Although there are a few studies investigating the relationship between the TyG index and breast cancer, we did not find any studies investigating the relationship between IGM and the TyG index. To our knowledge, this is the first study to investigate the role of the TyG index in predicting recurrence in IGM patients. In our study, the TyG index was significantly higher in the recurrence group and the cut-off value in the ROC analysis was 8.68. A TyG index above this value emerged as an independent risk factor for recurrence in multivariate logistic regression analysis. Therefore, our findings suggest that the TyG index may be an effective and reliable biomarker for predicting recurrence in patients with IGM.

At this stage, it does not seem possible to point to a clear mechanism to explain the relationship between the TyG index and the recurrence of IGM. However, it is likely that the relationship between IR and chronic inflammation may be mediated by a number of different mechanisms. IR is known to cause an increase in pro-inflammatory cytokines, including tumour necrosis factor (TNF) and interleukin (IL).[25] In addition, IR can cause inflammation and tissue damage by activating cytokine producers in inflammatory cells that contribute to oxidative stress.[26] As a result, the altered immune response associated with IR may predispose patients with IGM to complications such as recurrence.

In our study, we did not detect a significant relationship between laboratory parameters such as WBC, CRP, ESR, lymphocyte and neutrophil between both groups. However, previous studies have found a significant association between the inflammatory biomarkers NLR and PLR and IGM recurrence.[27,28] However, our study did not find an association between these biomarkers and IGM recurrence. Ciftci et al.[4] found that low AGR was an independent risk factor for IGM recurrence in a study. In this study, the association of AGR with IGM recurrence was significant in univariate regression analysis but not in multivariate regression analysis. This may be because the concentrations of albumin and globulin are affected by a number of factors, such as the individual's diet and body fluid volume status.

In our study, the mean age at diagnosis of IGM patients was 32.1±5.9 years, with a follow-up of 27.6±4.6 months and a recurrence rate of 26%, which is consistent with previous literature studies.[3,5,22,27-31] However, similar to many studies in the literature, the majority of our patients were premenopausal (94.5%), had given birth at least once (92.4%) and most had a history of breastfeeding (86.9%).[3,5,30,31] In our study, we found that 73.9% of patients had a history of oral contraceptive use and 9.2% of them had a history of smoking. In the literature,

there is a significant association between history of pregnancy,[3] breastfeeding,[3,5] average number of births,[5] smoking,[3,5] BMI[5,32] and history of oral contraceptive us[33,34] and IGM recurrence. While there are studies reporting an association, there are also studies reporting the opposite.[22,31,35-37] In our study, no association was found between these findings and IGM recurrence.

Many studies suggest that breastfeeding is one of the most important risk factors for developing IGM.[5,38-40] During breastfeeding, the breast lobules secrete a protein-rich fluid and the milk ducts expand. After prolonged breastfeeding, the acini and ducts remain constantly active and dilated, facilitating rupture of these structures and causing local inflammation as a result of the spread of luminal secretions into the connective tissue. As a result, lymphocytes and macrophages migrating to this area initiate the granulomatous inflammatory response.[40] Yılmaz et al.[5] found that breastfeeding for more than 18 months may be a risk factor for IGM recurrence. In our study, prolonged breastfeeding was significantly higher in the recurrence group, and the cut-off in the ROC analysis was 24.5 months. In multivariable logistic regression analysis, breastfeeding duration above this level was an independent risk factor for recurrence. Therefore, our results indicate that IGM patients with a history of long-term breastfeeding should be informed and monitored more closely in case of recurrence.

The most common clinical finding in IGM is usually a painful or painless palpable mass in the unilateral breast.[41] The most common presenting complaint in this study was a palpable breast mass (68 patients, 73.9%), which is consistent with the literature. IGM are usually unilateral and bilateral involvement has rarely been reported.[6,42] While bilateral involvement was not observed in our study, 53 (57.6%) patients had right breast involvement and 39 (42.4%) patients had left breast involvement. Tasci et al.[33] reported in a study they performed that clinical data had no statistical effect on recurrence. Similarly, our study showed that patients' clinical findings did not have a significant impact on recurrence.

The definitive diagnosis of IGM is made by tru-cut biopsy, FNAC and surgical excision. In our study, tru-cut biopsy was the most commonly used diagnostic method, with a rate of 73.9%, because it is less invasive and provides a highly accurate diagnosis. FNAC is the least used diagnostic method because cytological diagnostic criteria have not been fully determined, its diagnostic power is low, and it can rarely be confused with carcinoma.[43] In our study, no statistical relationship was found between diagnostic methods and IGM recurrence.

Although there are no disease-specific imaging findings in the diagnosis of IGM, the most commonly used imaging modality is USG due to the young patient population.[44,45] Hypoechoic, heterogeneous, tubular-configured lesions, hypoechoic masses with lobulated contours, multiloculated abscess collections and skin fistulization can be visualized on USG.[46] Abscess formation is an important complication that determines the severity of IGM.[5] A few studies in the literature have reported that the presence of abscess detected by USG is a risk factor for recurrence.[5,47] In contrast, Abbi et al.[34] showed in their study that the absence of an abscess on histopathology was a

risk factor for recurrence. Tasci et al.[33] reported in their study that radiological findings in the breast parenchyma did not have a statistically significant effect on recurrence. In this study, we found that radiological findings detected in the breast parenchyma by USG did not have a significant effect on recurrence.

Axillary lymph node involvement may be seen in IGM patients and may be of concern. It has been reported in the literature that unilateral axillary lymphadenopathy, with cortical thickening and usually involving the hilar region, may develop in up to 70% of patients.[42,46,48,49] In this study, 34.7% of all IGM patients had axillary lymphadenopathy, compared to 58.3% of recurrent patients. We found that axillary lymphadenopathy was statistically significantly higher in patients with recurrence. The association of axillary lymphadenopathy with IGM recurrence was significant in univariate regression analysis. This study shows that axillary lymphadenopathy may be an effective factor in predicting IGM recurrence.

Limitations

The main limitation of this study is the relatively small number of patients who developed a recurrence. Secondly, the fact that the study was conducted in a single centre prevents us from making generalisations. For these reasons, future multicentre studies with a larger number of patients are needed to support our findings.

CONCLUSION

In conclusion, our results show that the risk of recurrence is higher in IGM patients with a TyG index greater than 8.68 at the time of initial presentation and a breastfeeding history of more than 24.5 months. Therefore, asking about breastfeeding history at admission and measuring and analysing the TyG index can identify patients at high risk of recurrence.

ETHICAL DECLARATIONS

Ethics Committee Approval
This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics Committee Approval was obtained from the Siirt University Non-invasive Ethics Committee (Date: 22.02.2024, Decision No: 101661).

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

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
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Management and reproductive outcomes following cesarean scar pregnancy: experiences of two tertiary centers in a cohort of 60 women

Zeynep Şeyhanlı[1], Burak Bayraktar[1], Gülsan Karabay[1], Mevlüt Bucak[1], Nazan Vanlı Tonyalı[1],
Gizem Aktemur[1], Betül Tokgöz Çakır[1], Büşra Demir Çendek[2], Şevki Çelen[1],
Ali Turhan Çağlar[1], Yaprak Üstün[3]

[1]Department of Perinatology, Ankara Etlik City Hospital, Ankara, Turkiye
[2]Department of Obstetrics and Gynecology, Ankara Etlik City Hospital, Ankara, Turkiye
[3]Department of Obstetrics and Gynecology, Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Ankara, Turkiye

ABSTRACT

Aims: This study aims to analyze the treatment approaches and reproductive outcomes of women diagnosed with cesarean scar pregnancy (CSP).

Methods: A retrospective analysis was conducted on sixty patients diagnosed with CSP between January 2020 and December 2023 at two tertiary centers with a combined total of 49,733 births during the study period. Demographic, clinical, and laboratory characteristics, complications, treatment methods, and reproductive outcomes were examined. Patients were categorized into two groups based on their treatment approach: isolated treatment (n=45, 75%) and combined treatment (n=15, 25%), and the outcomes of the two groups were compared.

Results: The mean age of all patients was 34 years (±5.5) (range: 21-46). The mean gestational age at admission was 6.86 weeks (±1.82), with 35% showing positive fetal heartbeats. Complications occurred in 28.3% of cases, with hematomas being the most common (26.7%). The combined treatment group had higher rates of blood transfusions and complications, including hematomas and bladder injuries (p=0.005 and p<0.001, respectively). Of the 16 patients (26.7%) who desired future pregnancy, 14 successfully conceived. Among these pregnancies, 7 resulted in early pregnancy loss, while 7 resulted in live births, all of which were delivered after 35 weeks of gestation.

Conclusion: Early diagnosis and evidence-based treatment of CSP are essential for preventing life-threatening obstetric complications. Larger, prospective studies are required to establish optimal diagnostic and treatment strategies.

Keywords: Cesarean scar pregnancy, treatment, treatment approaches, reproductive outcome

INTRODUCTION

Cesarean scar pregnancy (CSP) is defined as the implantation of a gestational sac within the scar of a previous cesarean delivery.[1] The prevalence of CSP has been increasing in recent years, with reported frequencies ranging from 1 in 1800 to 1 in 2000 pregnancies.[2] CSP poses a high risk of both short-term and long-term adverse outcomes, including severe hemorrhage, uterine rupture, hysterectomy, placenta accreta spectrum (PAS) disorders, compromised reproductive outcomes, and maternal death.[3,4] Early prenatal diagnosis of CSP is critical for informing prenatal counseling and treatment decisions.

The development of CSP is strongly associated with the presence of a cesarean scar defect, which may disrupt normal decidualization and increase the risk of abnormal implantation of the gestational sac.[5] Although the precise etiopathogenesis of CSP remains unclear, research suggests that scar defects create a vulnerability for improper placental attachment.[6,7] As first demonstrated by Timor-Tritsch et al.,[8] CSP shares histological features with pregnancies affected by PAS disorders, further indicating a possible link between cesarean scar abnormalities and abnormal placentation.

Ultrasound imaging plays a pivotal role in diagnosing cesarean scar pregnancies. Various classification systems have been developed to better categorize CSP. One of the most well-known systems is that studied by Kagen et al.,[9] which distinguishes between two types of CSP: Type 1, where the pregnancy is located "on the scar" (well-healed tissue), and Type 2, where the pregnancy is "in the niche" (imperfectly healed scar). Additionally, measurement of residual myometrial thickness between the bladder and the

gestational sac in scar pregnancies is one of the important ultrasonographic measurements that provide information about prognosis.[10]

Despite the growing number of case series in the literature, optimal treatment strategies and prognosis for subsequent pregnancies after CSP remain uncertain. Management options vary widely, ranging from expectant management, uterine suction curettage, local excision via laparotomy or laparoscopy, hysteroscopy, uterine artery embolization (UAE), methotrexate (MTX) therapy, to hysterectomy.[11] However, no standardized diagnostic or management guidelines currently exist. Therefore, every case of CSP that is managed and documented provides valuable insights and contributes to the broader understanding of this condition. Moreover, the long-term reproductive outcomes for women who wish to conceive following CSP have been the subject of longitudinal studies.[12,13] This study aims to investigate the etiology, risk factors, clinical presentation, efficacy of various treatment modalities, and reproductive outcomes in women diagnosed with cesarean scar pregnancies.

METHODS

This retrospective cohort study analyzed the data of 60 patients treated for CSP and subsequently followed over the long term at Ankara Etlik City Hospital and Etlik Zubeyde Hanım Women's Health Training and Research Hospital, between 2020 and 2023. These well-known reference centers reported a total of 49,733 births over the four-year study period in Turkey. The study was started with the approval of Ankara Etlik City Hospital Ethics Committee (Decision No: 2023-683). Since the study was designed retrospectively, written informed consent from patients was waived.

We examined demographic, clinical, and laboratory characteristics, complications, treatment methods, and reproductive outcomes of the patients. Variables analyzed included maternal age, body mass index (BMI), smoking status, gravidity, parity, history of —abortions, ectopic pregnancies, scar pregnancies, curettage, cesarean sections (CSs)- number of previous curettages and CSs, history of uterine surgery, and the interval between the last pregnancy and the current pregnancy. Presenting symptoms were categorized as asymptomatic, symptomatic (including abnormal vaginal bleeding, abdominal pain, or both). Ultrasonographic and laboratory data were collected, including gestational age, presence of fetal heartbeat, duration of hospitalization, β-human Chorionic Gonadotropin (β-hCG) levels at admission, β-hCG half-life, and hemoglobin levels at admission and discharge.

Transabdominal and transvaginal ultrasound examinations were conducted using Voluson (GE Healthcare, Milwaukee, Wisconsin) E6 and E8 machines. The diagnosis of CSP was based on the following criteria: (1) absence of a gestational sac in the uterine cavity or cervical canal; (2) gestational sac located in the anterior isthmus of the uterus, with or without fetal heart activity; (3) a defect or thinning of the myometrium between the bladder and the gestational sac; (4) presence of increased vascularity around the gestational sac by Doppler examination.[14-16] (Figure 1). Three-dimensional ultrasound was used infrequently but could aid in diagnosis when available.[17]

Although no algorithm was used to determine treatment modalities, treatment selection was largely based on patient-based assessments and clinical experience. In particular, factors such as the presence of a fetal heartbeat, β-hCG levels, and the clinical condition of the patient were important factors affecting the treatment decision. A range of treatment modalities was identified, including isolated treatments (e.g., dilation and curettage with or without a Foley catheter, methotrexate, wedge resection) and combined treatments (e.g., dilation and curettage with or without a Foley catheter+methotrexate, methotrexate+laparotomic wedge resection, and dilation and curettage+methotrexate+laparotomic wedge resection). Patients were categorized into two groups based on their treatment approach: isolated treatment (using a single method) and combined treatment (using multiple methods). These groups were then compared in terms of clinical outcomes.

Reproductive outcomes for women seeking future pregnancies after CSP treatment were documented through digital records and telephone interviews. Outcomes included early pregnancy loss (defined as loss before 13 weeks of gestation) and live birth.
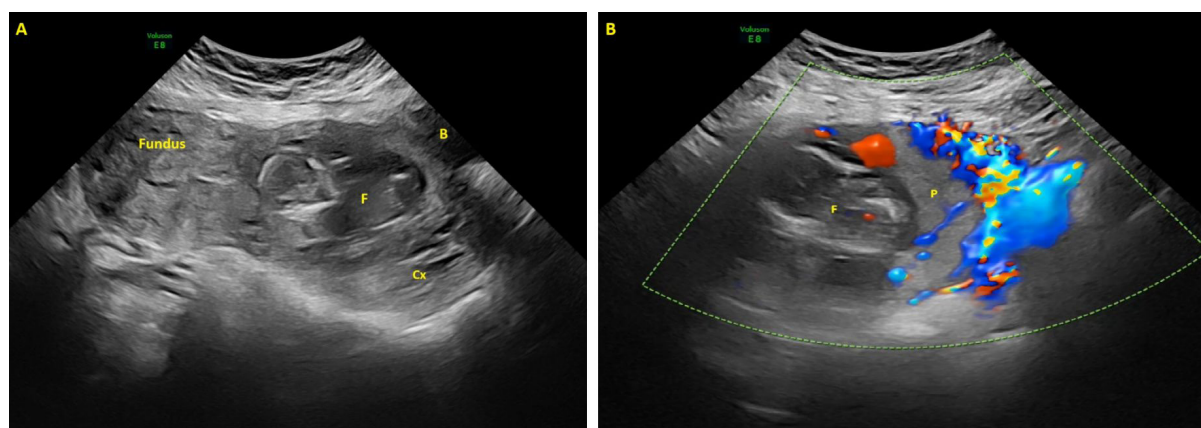

Figure 1. A) 12 weeks and 2 days cesarean scar pregnancy on grayscale imaging (F=Fetus, B=Bladder, Cx=Cervix) **B**) Color Doppler image showing increased vascularity surrounding the placental region (F=Fetus, P=Placenta)

Statistical Analysis

Stastical analysis was performed using IBM's Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corporation, Armonk, New York, US). Results are presented as mean±SD, median (min-max), and n (%). To check the normality of data distribution, the Shapiro-Wilk test was utilized. Group differences were evaluated using the Independent Samples T-test if normally distributed, and the Mann-Whitney U test if non-normally distributed, and the relationships between categorical variables were evaluated using the Chi-square test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

During the four-year study period, the incidence of CSP was approximately 1.2 per 1000 (60/49,733) pregnancies. Demographic, clinical, and laboratory characteristics of patients are shown in Table 1. The mean age of the patients was 34 years (±5.5), ranging from 21 to 46 years. No adolescent pregnancies (≤19 years) were identified, although 46.7% of the cohort were advanced maternal age pregnancies (≥35 years). The average BMI was 26.1 (±4.3), with a range of 17.7 to 37.4. Smoking was reported by 13.3% of patients. The mean gravidity was 4.15 (±1.93). A history of ectopic pregnancy was present in 1.6% of patients, and 3.3% had experienced a prior scar pregnancy. Curettage had been performed in

45% of cases, with 36.7% undergoing it once. All patients had a history of cesarean section, with varying numbers of previous procedures, and 5% had undergone other types of uterine surgery. The interval between the last pregnancy and the current CSP averaged 4.57 years (±3.79). At the time of admission, the mean gestational age was 6.86 weeks (±1.82), and 35% of cases had a positive fetal heartbeat. The average length of hospital stay was 5.46 days (±4.16). The mean serum β-hCG level at admission was 13,009.9 IU/L (±18,582.1), with 36.7% of patients presenting with levels ≥10,000 IU/L. The β-hCG half-life ranged from 12 to 240 hours, with a mean of 62.7 hours (±68.7). The mean hemoglobin level during hospitalization was 12.2 g/dL (±1.7), and the mean discharge hemoglobin was 11.4 g/dL (±1.7). Blood transfusions were required in 16.7% of cases. Underlying health conditions were present in 20% of patients, while 80% had no comorbidities. Hypertension, diabetes, hypothyroidism, hyperthyroidism, and epilepsy were observed in 6.6%, 5%, 3.4%, 3.4%, and 1.7% of patients, respectively. Complications occurred in 28.3% of cases, with hematomas being the most common (26.7%). Bladder injury occurred in 1.7% of cases. Complications occurred in 28.3% of cases, with hematomas being the most common (26.7%). Bladder injury occurred in 1.7% of cases. Treatment modalities included isolated approaches (75%) and combined methods (25%). The most frequent isolated treatment was dilation and curettage (40%), either with (28.3%) or without (40%) the use of a Foley catheter. The most

Table 1. Demographic, clinical, and laboratory characteristics of patients with scar pregnancy			
	Mean±SD	Median (min-max)	Number (n), Percent (%)
Maternal age (year)	34±5.5	33.5 (21-46)	-
Adolescent pregnancy ≤ 19 year	-	-	0
Advanced maternal age ≥ 35 year	-	-	28 (46.7%)
BMI (kg/m²)	26.1±4.3	25.9 (17.7-37.4)	-
Smoking	-	-	8 (13.3%)
Gravidity	4.15±1.93	4 (2-10)	-
Parity			
Nulliparous	-	-	0
Multiparous	-	-	60 (100%)
Living children	2.28±1.35	2 (1-8)	-
Abortus	0.78±1.12	0 (0-4)	-
History of ectopic pregnancy	-	-	1 (1.6%)
History of scar pregnancy	-	-	2 (3.3%)
History of curettage	-	-	27 (45%)
Previous curettage number			
0	-	-	33 (55%)
1	-	-	22 (36.7%)
2	-	-	3 (5%)
3	-	-	1 (1.7%)
≥4	-	-	1 (1.7%)
History cesarean section	-	-	60 (%100)
Previous cesarean section number			
1	-	-	21 (35%)
2	-	-	20 (33.3%)

Continued

Table 1. Demographic, clinical, and laboratory characteristics of patients with scar pregnancy			
	Mean±SD	**Median (min-max)**	**Number (n), Percent (%)**
3	-	-	12 (20%)
≥ 4	-	-	7 (11.6%)
Previous uterine surgery	-	-	3 (5%)
Time from last pregnancy to this pregnancy (year)	4.57±3.79	3 (1-17)	-
Pregnancy week (day)	6.86±1.82	6.3 (4-12)	-
Fetal heartbeat			
Positive	-	-	21 (35%)
None	-	-	39 (65%)
Hospitalization duration (day)	5.46±4.16	3 (2-17)	-
β-hCG at admission (IU/L)	13,009.9±18,582.1	5862 (429-85,297)	-
β-hCG ≥10,000 (IU/L)	-	-	22 (36.7%)
Half-life of β-hCG (hour)	62.7±68.7	24 (12-240)	-
Hemoglobin at admission (g/dL)	12.2±1.7	12.6 (6.2-16)	-
Hemoglobin at discharge (g/dL)	11.4±1.7	11.6 (7.6-14.5)	-
Blood transfusion	-	-	10 (16.7%)
Comorbidity			
None	-	-	48 (80%)
Yes			12 (20%)
Hypertension	-	-	4 (6.6%)
Diabetes	-	-	3 (5%)
Hypothyroidism	-	-	2 (3.4%)
Hyperthyroidism	-	-	2 (3.4%)
Epilepsy	-	-	1 (1.7%)
Complication			
None	-	-	43 (71.7%)
Yes			
Hematoma	-	-	16 (26.7%)
Bladder injury	-	-	1 (1.7%)
Treatment method			
Isolated	-	-	45 (75%)
Dilation curettage	-	-	41 (40%)
With Foley	-	-	17 (28.3%)
Without Foley	-	-	24 (40%)
Methotrexate	-	-	2 (3.3%)
Wedge resection	-	-	2 (3.3%)
Combined	-	-	15 (25%)
Dilation curettage+Methotrexate	-	-	6 (10%)
Dilation curettage+Foley+Methotrexate	-	-	6 (10%)
Methotrexate+Wedge resection	-	-	2 (3.3%)
Dilation curettage+ Methotrexate+Wedge resection	-	-	1 (1.7%)
Abbreviations: BMI: Body mass index, SD: Standart deviation, Min-Max: Minimum-Maksimum			

common combined treatments were dilation and curettage + methotrexate (10%) and dilation and curettage + a Foley catheter + methotrexate (10%) (Table 1).

Patient symptoms are listed in Table 2. In the cohort, 56.7% were symptomatic, while 43.3% were asymptomatic. The most common symptom was abnormal vaginal bleeding (35%), followed by abdominal pain (18.3%), and a small percentage (3.3%) experienced both (Table 2).

Table 2. Presenting symptoms of patients	
	n (%)
Symptoms	
Asymptomatic	26 (43.3%)
Symptomatic	34 (56.7%)
Abnormal vaginal bleeding	21 (35%)
Abdominal pain	11 (18.3%)
Abdominal pain+ Abnormal vaginal bleeding	2 (3.3%)

Table 3. Comparison of patient data based on isolated vs. combined treatment			
	Isolated treatment n=45	Combined treatment n=15	p
Maternal age (year) (mean±SD)	35±6	32±5	0.069
Adolescent pregnancy ≤ 19 year (n,%)	0	0	N/A
Advanced maternal age ≥ 35 year (n,%)	24 (53.3%)	4 (26.7%)	0.073
BMI (kg/m²) (mean±SD)	26.6±4.3	24.6±4.1	0.109
Smoking (n,%)	6 (13.3%)	2 (13.3%)	N/A
Gravidity median (min-max)	4 (2-10)	4 (2-8)	0.480
Parity (n,%)			N/A
Nulliparous	0	0	
Multiparous	45 (100%)	15 (100%)	
Living children median (min-max)	2 (1-8)	1 (1-5)	0.438
Abortus median (min-max)	0 (0-4)	1 (0-4)	0.140
History of ectopic pregnancy (n,%)	1 (2.2%)	0	0.560
History of scar pregnancy (n,%)	0	2 (13.3%)	0.012
History of curettage (n,%)	18 (40%)	9 (60%)	0.177
History cesarean section (n,%)	45 (100%)	15 (100%)	N/A
Previous uterin surgery (n,%)	2 (4.4%)	1 (6.6%)	0.732
Time from last pregnancy to this pregnancy (year) (mean±SD)	4.2±3.2	5.6±5.1	0.600
Pregnancy week (day) (mean±SD)	6.7±1.8	7.3±2	0.254
Fetal heartbeat (n,%)			0.019
Positive	12 (26.7%)	9 (60%)	
None	33 (73.3%)	6 (40%)	
Hospitalization duration (day)	3.6±2.1	10.9±4.1	<0.001
β-hCG at admission (IU/L) (mean±SD)	7798±8388	28645±29745	0.001
β-hCG ≥10,000 (IU/L)	13 (28.9%)	9 (60%)	0.030
Half-life of β-hCG (hour) (mean±SD)	30.8±27.8	158.4±66.5	<0.001
Hemoglobin at admission (g/dL) (mean±SD)	12.3±1.8	30.8±27.8	0.203
Hemoglobin at discharge (g/dL) (mean±SD)	11.6±1.7	10.8±1.8	0.147
Blood transfusion (n,%)	4 (8.9%)	6 (40%)	0.005
Comorbidity (n,%)			0.136
None	34 (75.5%)	14 (93.3%)	
Yes	11 (24.5%)	1 (6.3%)	
Diabetes	3 (6.6%)	0	
Hypertension	4 (8.8%)	0	
Hypothyroidism	1 (2.2%)	1 (6.6%)	
Hyperthyroidism	2 (4.4%)	0	
Epilepsy	1 (2.2%)	0	
Complication (n,%)			<0.001
None	40 (88.9%)	3 (20%)	
Yes	5 (11.1%)	12 (80%)	
Hematoma	5 (11.1%)	11 (73.3%)	
Bladder injury	0	1 (6.7%)	
Symptoms (n,%)			0.763
Asymptomatic	19 (42.2%)	7 (46.7%)	
Symptomatic	26 (57.8%)	8 (53.3%)	
Abnormal vaginal bleeding	16 (35.6%)	5 (33.3%)	
Abdominal pain	8 (17.8%)	3 (20%)	
Abdominal pain+Abnormal vaginal bleeding	2 (4.4%)	0	
Abbreviations: BMI: body mass index, SD: Standart Deviation, Min-Max: Minimum-Maksimum			

Table 3 presents a detailed comparison between patients treated with isolated and combined approaches. Both groups had similar mean and advanced maternal ages, BMIs, and obstetric histories, with no statistically significant differences. Notably, a history of scar pregnancy was found in 2 patients (13.3%) in the combined treatment group but in none of the isolated treatment group (p=0.012). The time between the last pregnancy and the current one, as well as the gestational age at admission, were similar between groups. However, the presence of a fetal heartbeat was significantly more frequent in the combined treatment group (60%) compared to the isolated group (26.7%) (p=0.019). The combined treatment group also had significantly longer hospital stays, higher β-hCG levels at admission, more cases with β-hCG ≥10,000 IU/L, and longer β-hCG half-lives (p<0.001, p=0.001, p=0.030, and p<0.001, respectively). Hemoglobin levels at admission and discharge did not differ significantly between the groups. Comorbidities were comparable between groups, though patients in the combined treatment group had a significantly higher rate of blood transfusions and complications, including hematomas and bladder injuries (p=0.005 and p<0.001, respectively). Symptom analysis revealed no statistically significant differences, with a substantial proportion of patients in both groups being asymptomatic (42.2% vs. 46.7%). (Table 3)

Pregnancy desires and pregnancy characteristics of the patients after scar pregnancy were examined in Figure 2. 16 (26.7%) patients desired pregnancy in the next period, 14 of them were able to become pregnant. Among these pregnancies, 7 resulted in early pregnancy loss, while 7 resulted in live births, all of which were delivered after 35 weeks of gestation (Figure 2).
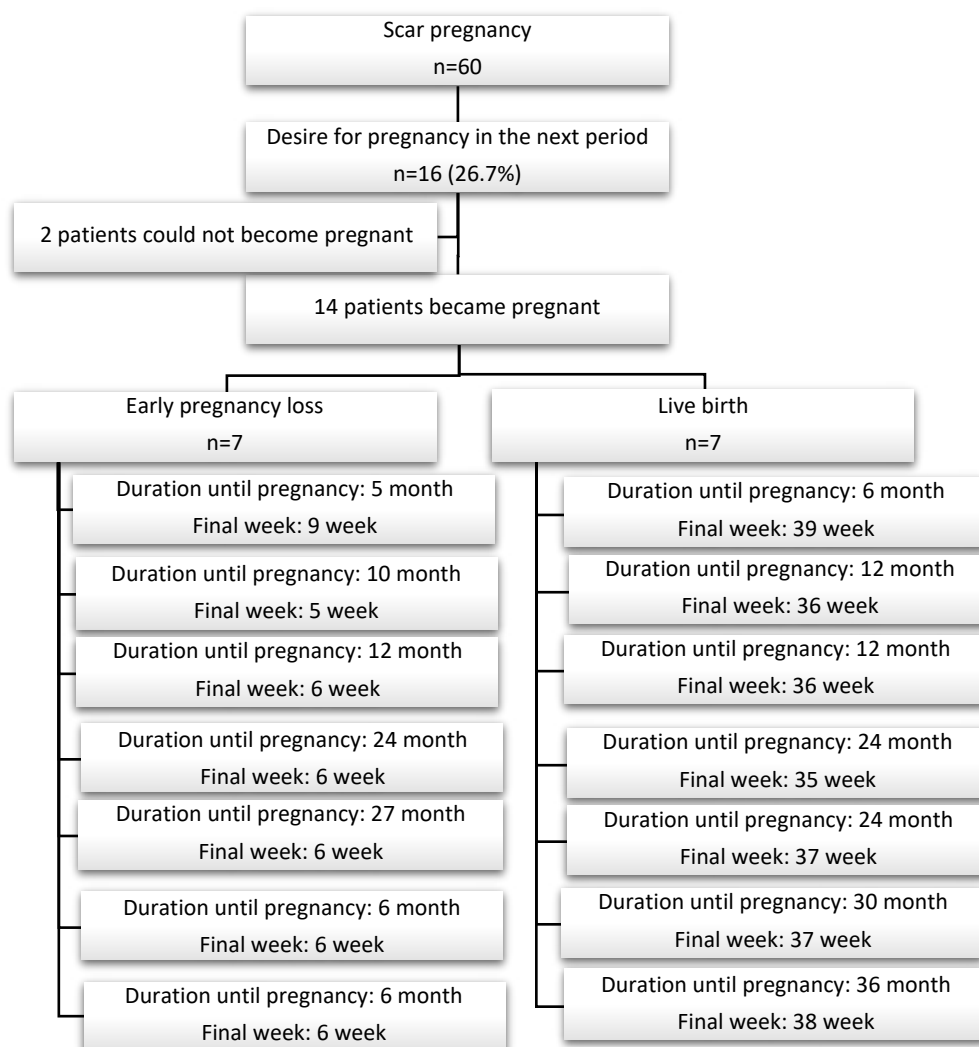

Figure 2. Pregnancy desires and pregnancy characteristics of the patients after scar pregnancy

DISCUSSION

This study provides an analysis of the demographic profiles, clinical characteristics, treatment approaches, and long-term reproductive outcomes in 60 patients diagnosed with CSP. All participants had undergone at least one cesarean section, with 35% having had only one, highlighting that CSP can occur even after minimal surgical birth history. A majority of patients (56.7%) were symptomatic upon admission, with abnormal vaginal bleeding being the most common symptom (35%). The clinical burden of CSP is evident in the significant hospitalization need, with an average stay of 5.46 days (±4.16), and a maximum stay of 17 days. The half-life of β-hCG averaged 62.7 hours (±68.7) and peaking at 240 hours. Hematomas were the most frequent complication, affecting 26.7% of patients. While 75% of cases were successfully managed with isolated treatment approaches, 25% required combination treatments. Notably, significant differences emerged between the isolated and combined treatment groups in key areas, including scar pregnancy history, fetal heartbeat presence, hospitalization duration, β-hCG levels at admission, half-life of β-hCG, blood transfusions, and complications.

The rising cesarean section rates globally have contributed to the increasing prevalence of CSP, which poses substantial risks for maternal morbidity and mortality. Due to limited demographic studies, the reported incidence of CSP varies across regions. In our study, the incidence was 1.2 per 1000 cesarean deliveries, consistent with prior research. Several risk factors for CSP have been proposed, although the exact mechanisms remain unclear. Known risk factors include second-stage cesarean sections, a retroflexed uterus, gestational diabetes, higher maternal BMI, perioperative infections, and previous myomectomy.[6,18,19] Our study found that 6.6% of CSP patients had hypertension, 5% had diabetes, and 6.8% had thyroid dysfunction. Research suggests that thyroid-stimulating hormone (TSH) and thyroid antibodies, such as those against thyroglobulin (TgAb), play a role in placental development by promoting extravillous trophoblast invasion and angiogenesis.[20,21] A recent study found that TSH and TgAb levels were significantly reduced in patients with PAS disorders, a condition closely related to CSP.[22] Given the similarities between CSP and PAS, maternal TSH levels may contribute to CSP development.

Early diagnosis of CSP is essential to prevent complications associated with terminating these pregnancies.[23] Previous studies have reported a mean gestational age at diagnosis of 7.5±2.5 weeks.[14] In our study, the mean gestational age at diagnosis was slightly earlier, at 6.86±1.82 weeks, likely due to our centers' experience and advanced equipment. However, while ultrasonography can identify markers for CSP, current prenatal imaging techniques cannot reliably predict the short- and long-term outcomes of CSP.[9,15,24,25] Since our study was retrospective and all patients requested abortion, we were unable to identify these ultrasonographic markers and determine their association with pregnancy outcomes.

A comprehensive study found that over 90% of CSP patients had only one cesarean section.[26] Some studies have linked the number of CSs to CSP risk. In our cohort, 35% of patients had only one previous cesarean section, while 64.9% had two or more, aligning with prior research linking multiple cesarean deliveries to increased CSP risk.

Symptomatology at diagnosis can distinguish CSP from early miscarriages. In a retrospective study, it was found that 86% of CSP patients had only vaginal bleeding, 9% had both and abdominal pain, and 4.5% had only abdominal pain.[27] In another study of diagnosis complaints, all patients had vaginal bleeding and half of them had abdominal pain.[4] In our study, 43.3% of patients were diagnosed during routine pregnancy follow-up without symptoms. Among symptomatic patients, 35% presented with vaginal bleeding, while 18.3% reported abdominal pain. This finding underscores the importance of early transvaginal ultrasonography for diagnosing asymptomatic patients.

Fetal heartbeat presence and elevated β-hCG levels at admission were more common in the combined treatment group, potentially indicating a poorer prognosis for these patients. The optimal treatment for cesarean scar pregnancies remains uncertain, as various treatment methods have been explored in the literature, each with varying results. In our study, patients underwent different treatment approaches, including dilation and curettage (with or without a Foley catheter), systemic or local methotrexate (administered via the transcervical route), and wedge resection.

Limitations

There is limited data regarding the impact of CSP management on future reproductive outcomes. A recent systematic review and meta-analysis found that 17.6% of CSP cases recurred, while 82.6% of patients achieved intrauterine pregnancy, and 70.6% had successful pregnancies.[12] In our study, 26.7% of patients expressed a desire for future pregnancy, and of those, 50% achieved live births after 35 weeks of gestation, while the remaining 50% experienced early pregnancy loss. Although we observed no recurrent CSP cases in our cohort, the risk of recurrence remains a concern, as reflected in the 17.6% recurrence rate noted in the meta-analysis of 3,598 patients.[12]

One of the strengths of this study is the inclusion of data from two large tertiary referral centers with extensive experience in diagnosing and managing CSP. Additionally, our study comprehensively examines a wide range of demographic, clinical, laboratory, and reproductive outcome data. However, the study is limited by its retrospective design. Furthermore, we could not classify CSP cases based on ultrasonographic markers such as "on the scar", "in the niche", "cross-over sign", and "residual myometrial thickness" due to the lack of prospective follow-up for patients who opted to continue their pregnancies. Future studies should address these limitations through prospective designs and larger sample sizes.

CONCLUSION

Prenatal diagnosis of CSP is critical and requires a detailed assessment of the relationship between the gestational sac and the cesarean scar during the first trimester. Delaying the decision to terminate CSP increases the likelihood of complications. Due to the limited scientific data available, counseling patients who choose to continue their pregnancy is challenging. Our study

provides insights into predicting which patients may require combined treatment approaches, which can guide follow-up and treatment planning. The reproductive outcomes observed in our cohort may also aid in counseling patients about future fertility. Further research with larger sample sizes is needed to reach more definitive conclusions.

ETHICAL DECLARATIONS

Ethics Committee Approval
The study was started with the approval of Ankara Etlik City Hospital Ethics Committee (Decision No: 2023-683).

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

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Trends in pediatric kidney stone research between 2004-2023: a bibliometric study

Hülya Gözde Önal

Department of Pediatric Nephrology, Samsun Training and Research Hospital, Samsun, Turkiye

ABSTRACT

Aims: The purpose of this current investigation is twofold: first, to review the available literature published in the last twenty years on pediatric nephrolithiasis; and second, to evaluate the progression of research on this topic during the indicated period. In this respect, through bibliometric analysis the present study aims to reveal trends, crucial authors, important institutions and outstanding journals of this line of research. It also takes an attempt to compare the increasing trend of publication productivity and citation frequency and the distribution of the research outputs across the countries/regions of the world to map the progress and potential prospects of pediatric kidney stone research.

Methods: The present study aimed to perform a bibliometric analysis of knowledge production. In pediatric kidney stone from 2004 to 2023 using WoS Core Collection. Articles were searched using the term "Kidney Stones in Children" including all articles, reviews and papers indexed, reviews and conference papers. The examination focused on the overall publication output, number of citations received, and journal citation; with methods including keyword frequency, bibliographic coupling, co-citation analysis, and co-authorship networks. Element positions, co-occurrence frequencies, and clusters were developed from the data source by using VOSviewer software. The study covered publication distribution, citation behaviour, keyword frequencies, and collaboration map.

Results: According to the presented research, the level of academic interest in this topic has risen dramatically over the years, and its popularity peaked in 2020. This result is expected because leading academic centres and name-referenced universities like University of Pennsylvania and Children's Hospital of Philadelphia contributed significantly to the current literature. Ten most preferred journals are Journal of Urology, Journal of Pediatric Urology and many more. The findings reveal the overall international cooperation with especial emphasis on relations between institutions in the US and European countries. Carrying out the keyword analysis, authors have determined that "urolithiasis", "nephrolithiasis", and "kidney stones" are the most topical concerns. Aside from general surgery, much of the most frequently cited research is relevant to surgical practices and dietary recommendations. The purpose of this review is to enhance the understanding of the tendencies of the studies the most active contributors and cooperation patterns in the pediatric kidney stones.

Conclusion: This bibliometric analysis reveals a significant rise in pediatric kidney stones research, peaking in 2020. Key contributors include the University of Pennsylvania and the Children's Hospital of Philadelphia, with strong international collaborations. Original research articles and top journals, like the Journal of Urology, remain central. The U.S. leads in contributions, with notable input from Turkish institutions.

Keywords: Pediatric urolithiasis, kidney stones in children, pediatric nephrolithiasis, bibliometric study

INTRODUCTION

Kidney stones, abbreviated as NL, are one of the major non-communicable diseases that have a life time prevalence of 11.0% in males and 5.6 %in females by aged 70 years.[1] Formerly a disease seen as influencing mainly older men, NL incidence has been on the rise among children, especially female children.[2] This demographic change calls for efforts to understand more about NL incidence trends and their predisposing factors as well as endeavours towards finding ways of reversing the observed increase in prevalence of NL in the young population.[3]

NL is not equally distributed throughout the world, and prevalence is higher in areas that are characterized by arid climate.[4,5] Some environmental factors like temperature has been reported to increase the incidence of NL hence the belief that global warming can help to explain the rising incidence of NL across the world.[6] For example, the southeastern region of the United States often called the "stone belt" has twice more frequency of NL than the north western region; this frequency is believed to increase as the climate improvements persist.[7] Likewise, the Afro-Asian stone belt extending from Sudan

Corresponding Author: Hülya Gözde Önal, drhulyagozde@hotmail.com

through the Philippines[4] has a high rate of NL attributable to both environmental and dietary influences.[8]

Another risk factor that has been identified is the genetic make-up because it has been clearly seen to have a bearing on NL occurrence. First-degree relatives of patients with kidney stones have 2-16 times higher incidence of NL than other individuals with no such history.[4] A recent study pointed to monogenic causal mutation for NL or nephrocalcinosis (NC) in 106 children without prior known aetiologies in 21%.[9] More than 30 genes have been reported to be associated with NL or NC with features of AD, AR, and X-linked inheritance. Such genetic factors, together with the environments, prove that NL is not easy to explain and has multiple causative factors.[10]

Over the last few decades developed countries have observed a very steep rise in the pediatric NL incidence and this is not associated with either geographical or genetic factors.[4,5] For instance, the incidence rate of this disease in South Carolina increased from 7.9 per one hundred thousand in 1996 to 18.5 per one hundred thousand in 2007, as per the sexually transmitted diseases fact sheet and women were found to have higher rates than men.[5] Similar trend is observed in other cold climate countries such as Iceland where the incidence rose from 3.7 per 100,000 in 1995-1999 to 11.0 per 100,000 in 1999-2004, especially among girls aged between 13-17 years.[11] The causes of increased rate of incidence in females within childhood and adolescence are however not well understood.

Several factors have also been associated with the rising trend of NL and these are; diet, obesity and the environment.[11,12] The cooler temperatures of an office environment may increase the risk of stone formation because these states mean dehydrated bodies leading to concentrated urine. Other non-modifiable risk factors for NL include high sodium and fructose intake as well.[6] Also, metabolic risk factors for stone development have been reported to be associated with increased obesity among children and the adolescents. Knowledge of these risk factors is important to enable the formulation of an appropriate prevention and management model of pediatric NL.[6]

There are metabolic risk factors of pediatric urolithiasis which in turn plays a role in the formation of the kid kidney stones. These metabolic derangements skew urine chemistry and hence encourages formation of stone precipitating compounds. The important risk factors includes hypercalciuria, hypocitraturia, hyperuricosuria, hyperoxaluria and hypomagnesuria. Hypercalciuria that refers to high levels of calcium in urine is one of the most common metabolic derangements associated with stone formation in children. High levels of calcium in the urine can combine with oxalate or phosphate and create stones known as calcium-based stones.[13,14] Moreover, hypocitraturia, which is abnormally low urinary citrate, causes the inability to appropriate calcium binding, and thus enhances the possibility of calcium crystallization and can affect stone formation.[15]

Other metabolic abnormalities include hyperuricosuria, this is elevated levels of uric acid in urine and promotes uric acid as well as calcium oxalate stones formation. There is evidence that calcium oxalate can crystallize on the surface of uric acid crystals; therefore, this is an important factor for paediatric population.[4] First, hyperoxaluria or increased urinary oxalate

excretion enhances calcium oxalate crystallization and it is established that stone formation in children is dominated by this constituent.[16] Finally, hypomagnesuria lowers the body's ability to suppress calcium crystal formation because magnesium usually hinders the process of crystallization.[15] The metabolic risks are usually managed through dietary changes and medications to prevent recurrence of the formations in children and youth.[15]

The purpose of the study titled "Trends in pediatric kidney stone research between 2004-2023: a bibliometric study" is to provide an exhaustive synthesis of the development of research in pediatric nephrolithiasis for the last two decades. To achieve these objectives, the present paper employs bibliometric analysis and seeks to uncover trends, authors, institution, and journals with the most impact in this subject area. The study will also look at the increase in publication rate, citation rate and distribution of the research among various countries and regions.

The current research work offers a strategic investigation seeking to address major research voids in the existing literature on pediatric kidney stone. Not only does bibliometric analysis demonstrate the literature's productivity and the involvement of key institutions, but it also describes the development of research topics and indicates what issues future investigations should focus on. This approach can be valuable when assessing international partnerships and the exchange of ideas across borders and provides a global view of scientific progress. Considering the rising occurrence of pediatric kidney stones and the extant literature on surgical options, metabolic disturbances, and dietary management, this review synthesizes fragmented works to lay a substantial groundwork for future studies. The information obtained through the bibliometric analysis, especially when it comes to the identification of the studies in the comparatively understudied fields like minimally invasive methods and genetic profiles, allows to recognize which topics should be paid more attention to by the researchers and other practitioners in the field of medicine. In conclusion, it is not just an atlas of the scientific knowledge distribution but also a helpful guide for any further development of the international cooperation in the field of pediatric kidney stones treatment and prevention.

METHODS

Since this research is a bibliometric study, it did not require ethics committee approval. It is conducted with the institution's permission. All procedures were carried out in accordance with the ethical rules and the principles.

In this study, a bibliometric analysis of research on kidney stones in children conducted between 2004 and 2023 was carried out. Bibliographic data were extracted from the Web of Science (WoS) Core Collection database. In the search section of the website, the term "kidney stone in children" was entered, and a total of 1303 results were obtained. A search was conducted by selecting categories from the Web of Science Categories section such as urology, nephrology, pediatrics, medicine general integral, and clinical nephrology. The

WoS Core Collection is a widely used and reliable database for bibliometric analyses, encompassing over 20,000 peer-reviewed, high-quality journals published globally across various fields.

Articles from 2004 to 2023 were collected using the search term "Kidney Stones in Children" Inclusion criteria for the study encompassed all articles, reviews, editorial materials, books, book chapters, conference papers, and all research indexed on WoS. The research was limited to articles published in English within the specified time frame.

Documents retrieved from the Web of Science database were analyzed based on trends related to the years of publication, citation counts, journals in which they were published, and the most cited authors and citation counts. The analysis included keyword co-occurrence networks, bibliographic coupling of publications, co-citation networks for references, journals, and authors, and co-authorship networks examining collaborations between countries and institutions. Keyword co-occurrence networks measure the most frequently used keywords in documents, bibliographic coupling occurs when two documents cite the same third document, co-citation networks analyze when two documents cite the same third source, and co-authorship networks analyze the volume of publications and how they are connected to each other.[17] For bibliometric analysis, data on article titles, abstracts, publication years, journal names and impact factors, authors, institutions, countries, WoS subject categories, keywords, and citation counts were collected. The annual publication growth, the relative research interest (RRI) in kidney stone research in children, and its percentage within the medical literature were determined.

Distribution of publications by institutions, authors, WoS subject categories, and journals was also analyzed. Network visualization maps were created, and the most-cited articles in research on kidney stones in children were identified using VOSviewer software (Leiden University, Leiden, Netherlands; version 1.6.11). The software uses circles that form a cluster

to specify the position of an element, and the size of a circle reflects the total number of co-occurrences, indicating the elements within a clustering technique. Colors reflect the cluster to which an element belongs.[18] The more important an element is, the larger its effect and circle become, and color assignment for elements is determined based on their associated cluster.[18] The total distance between elements provides information about their relationships based on their co-occurrence in documents.[19] Proximity between elements reveals the strength of their relationship, while a larger distance indicates insufficient relationship and similarity. Additionally, a lack of connection strength indicates no relationship between elements. Based on the above, the research questions addressed are as follows:

What is the distribution of articles by year?

What is the distribution of articles by the journals in which they are published?

What are the most cited articles and their citation counts in the study?

What is the most commonly used keyword in the keyword network?

What are the prominent elements in the reference, journal, and author co-citation networks?

What is the similarity status of articles according to bibliographic coupling analysis?

What is the status of collaboration among universities and countries according to co-authorship analysis?

RESULTS

1-Distribution of Articles Published in WoS by Year

The distribution of articles published in the WoS over the years has been analyzed, and the results of this analysis are presented in Graph 1 below.
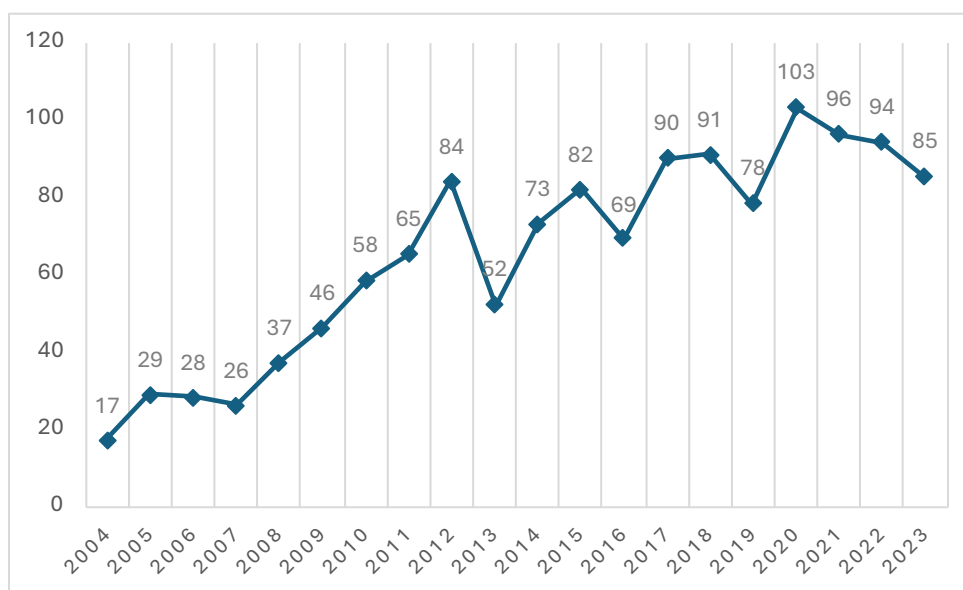
Graph 1. Distribution of articles published in WoS by year

When examining the distribution of articles related to kidney stones in children published in the WoS over the years, it is evident that academic interest in this topic has significantly increased over time. Starting with 17 articles in 2004, interest grew steadily. Notably, there was a significant rise in the number of publications starting in 2010, with 58 articles published that year, increasing to 84 articles in 2012. The year 2015 also saw a high number of publications, with 82 articles. However, the highest production of articles in 2020 contributing to the body of knowledge in the management of kidney stones in children was observed. The number remains high in 2021 and 2022 with the publication of 96 and 94 articles. Even in 2023 there was a slight drop with 85 articles but this also shows that there is much academic engagement on the subject.

These data show the increasing trend in the number of academic publications regarding the problem of kidney stones in children with the maximum interest in 2020. This trend might be associated with development in the medical and healthcare fields, higher research and clinical value and the public health relevance of this problem.

Table 1. Distribution of authors with the most publications	
Researcher	**Number of publications**
A1	33
A2	20
A3	16
A4	16
A5	16
A6	14
A7	14
A8	14
A9	11
A10	11
A11	11

2- Distribution of Publications by the Most Prolific Researchers in WoS

The distribution of publications by the most prolific authors in journals indexed in the WoS database has been examined, and the results of this distribution are presented in Table 1 below.

3-Journals with the Most Frequent Publications and Their Impact Factors in WoS

Analyzing the data presented in Graph 2, we can find out the journals most often selected by the researchers studying the problem of childhood kidney stones, according to the WoS database. Furthermore, the journal impact factors are also analysed and discussed in the following section.

Graph 2 shows the distribution of the selected research articles over the preferred journals among the researchers focusing on pediatric kidney stones and the impact factor of these selected journals. According to the data, the Journal of Urology is the most preferred journal, with 94 publications (WoS Impact Factor: 5.90). Following this, the Journal of Pediatric Urology has 90 publications (WoS Impact Factor: 2.0), Pediatric Nephrology has 76 publications (WoS Impact Factor: 2.6), Urology has 50 publications (WoS Impact Factor: 2.1), Journal of Endourology has 47 publications (WoS Impact Factor: 2.9), Urolithiasis has 45 publications (WoS Impact Factor: 2.0), Frontiers in Pediatrics has 24 publications (WoS Impact Factor: 2.1), World Journal of Urology has 18 publications (WoS Impact Factor: 2.8), International Urology and Nephrology has 18 publications (WoS Impact Factor: 1.8), and the Saudi Journal of Kidney Diseases and Transplantation has 17 publications (WoS Impact Factor: 0.5). These journals are among the most preferred outlets for research on pediatric kidney stones, emphasizing their importance in the field through their impact factors and publication counts.

4- Institutions with the Most Affiliations and Connection Counts in WoS

Graph 3 presents an analysis of the institutions most affiliated with researchers studying pediatric kidney stones as indexed
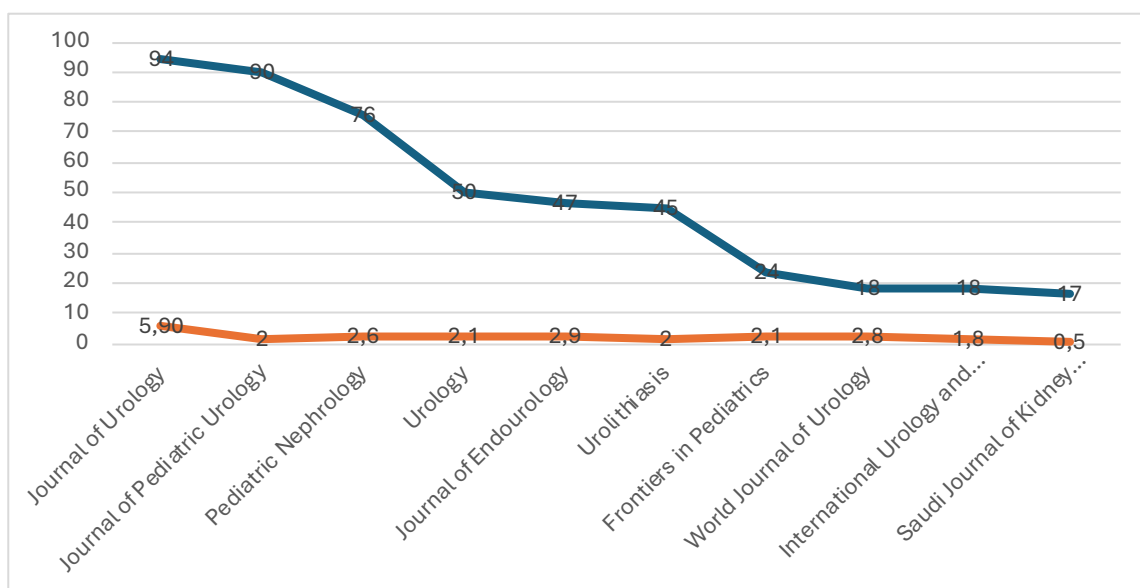
Graph 2. Most frequent journals for publications and their impact factors
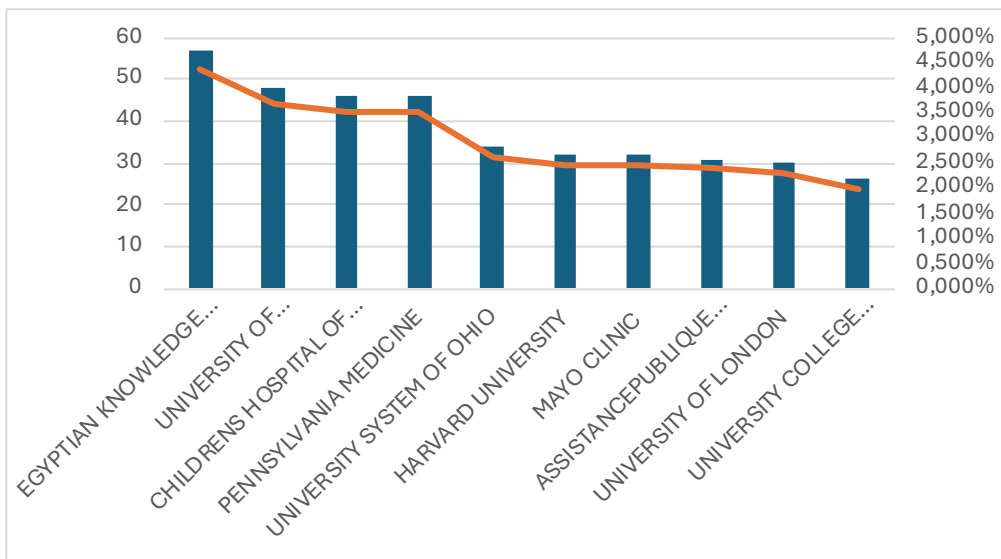
Graph 3. Institutions providing the most support, connection counts, and percentages

in WoS, including the number of connections and their percentages.

Upon examining Graph 3, it is evident that the institution with the most connections in pediatric kidney stone research is the Egyptian Knowledge Bank (EKB), with 57 connections, accounting for 4.375% of the total. The University of Pennsylvania ranks second with 48 connections, representing 3.684%, followed by the Children's Hospital of Philadelphia and Pennsylvania Medicine, both of which have 46 connections, contributing 3.530% each. The University System of Ohio has provided 34 connections, representing 2.609% of the total. Harvard University and Mayo Clinic each have 32 connections, corresponding to 2.456% of the total. Other significant contributing institutions include Assistance Publique Hôpitaux de Paris (APHP), the University of London, and University College London. These data underscore the importance of international collaborations in pediatric kidney stone research and highlight the leading institutions in this field.

Table 2. Institutions with the most publications in WoS		
Institution Name	**Number of publications (F)**	**Number of citations**
University of Pennsylvania	41	1622
Childrens Hospital of Philadelphia	37	1088
Mayo Clinic	31	1486
Dicle Üniversitesi	20	308
Hacettepe Üniversitesi	17	247
Guangzhou Medical University	15	333
Mansoura University	15	266
Capital Medical University	14	156
Duke University	13	350
Nationwide Children's Hospital	13	319
Cairo University	13	169

5-Author Institutions

Table 2 presents an analysis of the institutions affiliated with the authors of the publications indexed in WoS, along with the collaboration among these institutions.

According to the data presented in Table 2, certain institutions stand out in terms of their collaboration and the number of publications by their affiliated authors in WoS. The University of Pennsylvania leads with 41 publications and 1622 citations, highlighting its significance as a major research center in the field of pediatric kidney stones. Children's Hospital of Philadelphia follows closely with 37 publications and 1088 citations, demonstrating its influence in this area.

Among Turkish universities, Dicle University is noteworthy with 20 publications and 308 citations, followed by Hacettepe University with 17 publications and 247 citations. International institutions like Guangzhou Medical University (15 publications, 333 citations) and Mansoura University (15 publications, 266 citations) have also made significant contributions. These findings indicate that certain institutions have a more substantial impact on pediatric kidney stone research, contributing important scientific knowledge to the field.

Figure 1 illustrates the collaboration network among international institutions involved in pediatric kidney stone research. Each node (dot) represents an institution, while the lines between nodes indicate collaborations between these institutions. The size of the nodes reflects the centrality and intensity of collaboration within the network. The University of Pennsylvania, depicted as a large green node, is at the center of the network, demonstrating strong collaborations with many other institutions and highlighting its central role in pediatric kidney stone research. Mayo Clinic, represented as another prominent blue node, also exhibits a broad network of collaborations. Dicle University, shown as a red node, stands out among Turkish universities, signifying its significant contribution to research on pediatric kidney stones in Turkey.

Colors typically represent different geographical regions or collaboration groups. For instance, the green group includes

Figure 1. Bibliometric network visualization of institutions (Node size represents the institution with the most publications, colors indicate clusters, and lines show collaborations)

Figure 2. Author collaboration bibliometric network visualization (Node size represents key authors, and lines between nodes indicate collaboration)

North American-based universities, while the red group is composed of Turkish universities. This visualization clearly demonstrates the extent of the international collaboration network and the central roles played by certain institutions within this network.

6- Author Collaboration Network

The network of collaborations among authors of publications indexed in WoS is analyzed and presented in Figure 2.

Figure 2 visualizes the collaboration network among authors involved in pediatric kidney stone research. Each node represents an author, and the lines between nodes indicate

collaborations between these authors. The size of the nodes reflects the centrality and intensity of collaboration of the authors within the network. Gregory E. Tasian is at the center of the network and appears to have collaborated with many different authors, indicating his significant role and extensive collaboration in the field. John C. Lieske and Bernd Hoppe are also notable authors with dense collaboration networks. Kemal Sarica and Hasan Serkan Doğan are significant researchers among Turkish authors, highlighted in green and blue clusters, respectively, showing their prominent role in Turkish research on pediatric kidney stones.

Table 3. Most cited source types in WoS		
Source type	**Number of sources**	**Percentage**
Article	1,033	79.27%
Review article	210	16.11%
Editorial material	28	2.15%
Others	32	2.47%

Colors typically represent specific research groups or geographical regions. This visualization clearly demonstrates the extent of international collaboration in pediatric kidney stone research and the central roles played by certain authors within this network.

7- Distribution of Source Types Cited

The distribution of source types cited in articles published in journals indexed in WoS has been analyzed, and the data is presented in Table 3.

As shown in Table 3, the most cited source type in WoS-indexed journals is "Article," which constitutes 79.27% of the citations with a total of 1,033 citations. The second most cited source type is "Review Article," accounting for 16.11% of the citations with 210 citations. "Editorial Material," with 28 citations and 2.15%, ranks third, while "Others" has 32 citations, representing 2.47% of the total citations. These data indicate that researchers predominantly prefer to cite original articles and review articles.

8- Most Cited Papers

The most cited publications among those listed in WoS journals have been examined, and the data is presented in Table 4.

As indicated in Table 4, some of the most cited articles on kidney stones in children published in journals indexed in WoS have been reviewed. The article title, author name, and citation count are presented in Table 4. These data demonstrate the impact that certain studies have had in the academic community and the influence of their contributions in specific scientific fields.

For example, the article titled "Surgical Management of Stones: American Urological Association/Endourological Society Guideline" by Assimos Dean et al., with 682 citations, highlights its significance as a key reference in the surgical management of stone diseases. Similarly, the article "Lumasiran an RNAi therapeutic for primary hyperoxaluria type 1" by Garrelfs Sander et al., with 261 citations, provides a critical contribution to the treatment of primary hyperoxaluria type 1.

The study by VanDervoort Kristy et al., titled "Urolithiasis in Pediatric Patients: Urinary stone disease in children: a single center study of the incidence, clinical presentation, and outcome has 239 citations and provides a valuable presentation of different clinical features and outcome of urinary stone diseases in children. Meanwhile, the article by Dwyer Moira E. et al., titled "Temporal Trends in Incidence of Kidney Stones Among Children: among them, 'A 25-Year Population-Based Study' got 228 percent with increasing trends in the incidence of kidney stones in children years.

The most cited article, the article: Uric Acid and the Kidney by Fathallah-Shaykh S. A. and Cramer M. T., cited with 177 times, comprehensively present this issue of nephrolithiasis and uric acid. Also, the article "Increasing Incidence of Kidney Stones in Children Evaluated in the Emergency Department" by Sas David J. et al [174 citations] addresses the same issue.

Each of them is crucial to develop both theoretical and practical knowledge contributing to the fields and all of them have become well-represented in the academic literature.

9- Keyword Analysis

A further distribution of the keywords used in articles cited in the WoS database is shown in Figure 3. The above analysis uses Figure 3 to illustrate the most concerning keywords observed in the articles identified by the Web of Science (WoS) database. The keywords in the bibliometric network shown above several keywords that appear too many of times and those that have been more emphasized in the literature.

From these keywords some of the most commonly used terms identified include: urolithiasis, nephrolithiasis, and kidney

Table 4. Most cited papers		
Paper Title	**Authors**	**Number of Citations**
Surgical management of stones: American urological association/endourological society guideline	Assimos, Dean et al.	682
Lumasiran, an Rnai therapeutic for primary hyperoxaluria type 1	Garrelfs, Sander F. et al.	261
Urolithiasis in pediatric patients: a single center study of incidence, clinical presentation and outcome	VanDervoort, Kristy et al.	239
Temporal trends in incidence of kidney stones among children: a 25-year population based study	Dwyer, Moira E. et al.	228
Uric acid and the kidney	Fathallah-Shaykh, S. A and Cramer, M. T.	177
Increasing incidence of kidney stones in children evaluated in the emergency department	Sas, David J. et al.	175
Rare inherited kidney diseases: challenges, opportunities, and perspectives	Devuyst, O. et al.	164
Hereditary causes of kidney stones and chronic kidney disease	Edvardsson, V.O. et. al.	163
Annual incidence of nephrolithiasis among children and adults in south carolina from 1997 to 2012	Tasian, G. E. et. al.	160
Percutaneous nephrolithotomy for complex pediatric renal calculus disease	Desai, M. R. et. al.	158
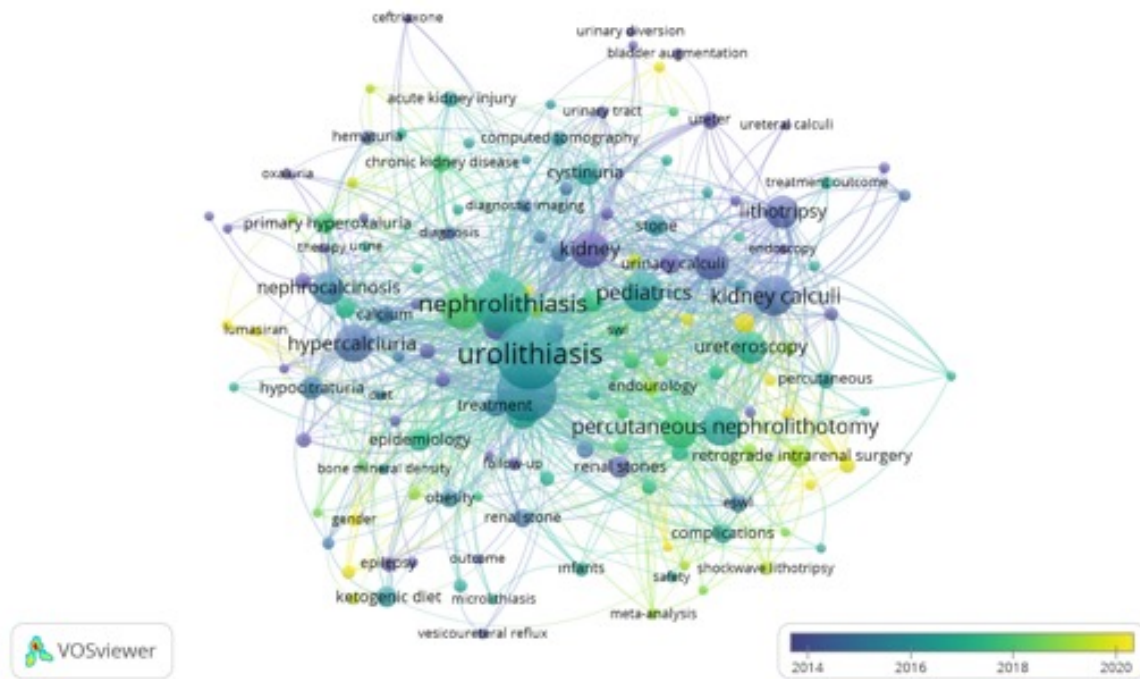
Figure 3. Bibliometric network visualization of keywords (Node size represents the most frequently addressed topics, with yellow areas indicating current topics)

calculi. These terms denote the focal areas of investigation in the field and show how often these topics are discussed in the literature. Keywords in use are a representative of research agendas and topics of interest in the subject area, indicating which areas are positioned as priorities within the academic activity. This analysis is really helpful for the current trends for the researchers while identifying the possible research gaps. It can be stated that distribution of keywords can be viewed as one of the strategic instruments of defining further focuses of an academic study.

10- Distribution of Cited Sources in Publications
In the present paper, we investigated the distribution of citations to sources in articles published in the journals included in the WoS and the results are shown in Figure 4. Figure 4 depicts proportions of articles citing sources in the journals from the database of WoS. This analysis helps to identified which studies and source are influential in the academic literature and which sources are cited most often.

Figure 4 can be seen as the citation source map where the citation density is encoded by the blue-yellow color scale with blue color representing works cited less frequently and yellow color representing works cited more frequently. This
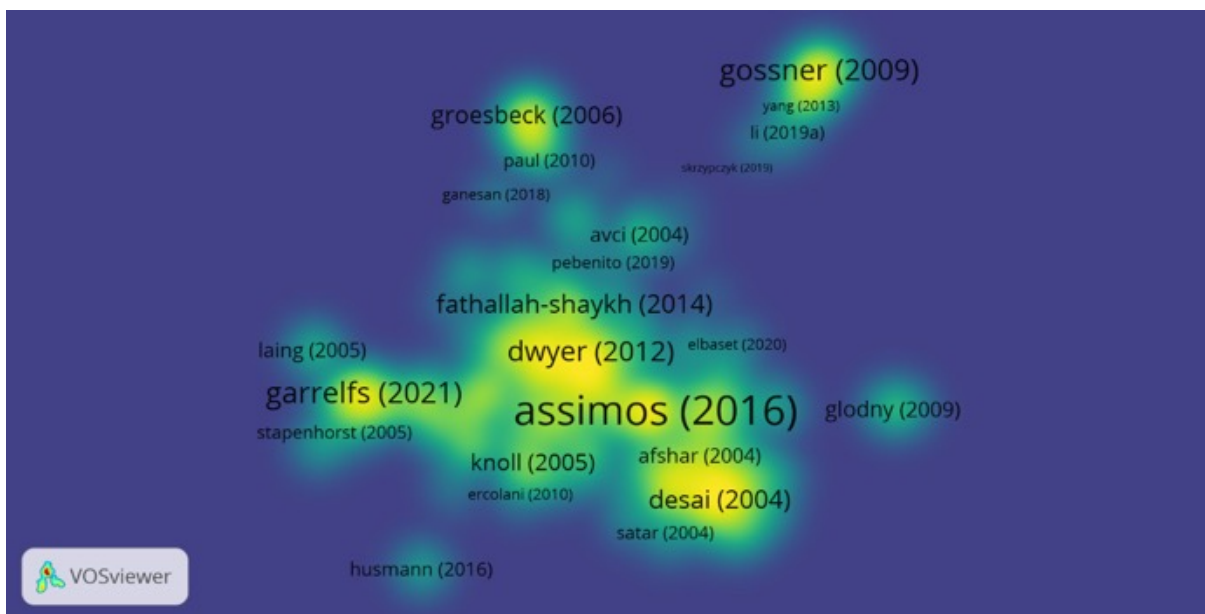
Figure 4. Citation source map (Citation density is represented by a gradient from blue to yellow)

visualization is useful to identify which research contributes more in terms of citations and on the other hand, what research sources are more connected to other studies.

Labels on the map indicate to which extent specific studies are cited in the literature. For instance, the works of "Assimos, 2016" and "Dwyer, 2012" are written in the largest font and bright colors, which mean the sources are frequently cited and occupy the most important position in the reference literature. Other related benchmarks, including "Garrelfs, 2021" is also highlighted in the other areas of the document also they are presented as essential and seminal works within the subject area.

It is very helpful of this kind of analysis to know which sources and studies are treated as the most basic and important in the field. It also has an important function for the researcher in being able to identify essential studies and trends in the literature. All of these pointed out studies identified on this map are well regarded by the scientific community and pieces together as the history of many subsequent works.

11-Distribution of Citations by Country
The distribution has been made according to the citation made by country for articles in the journal indexed in WoS reflected in the Figure 5 below.

Figure 5 analyzes the distribution of citations by country of the articles included in the journals that are presented in the WoS database. This picture depicts the pattern of citations and also depicts the interactions between countries concerning their academic production.

In the figure, circles mean the importance of the countries in the academic databases and the number of citations. For example, the United States and Turkey are shown by larger circles as they are authors involved in scientific production and as recipients of many citations. In this case the lines between circles denote the research cooperation between countries. The nature of dense lines depicts intensity and frequencies of this kind of relationships. For example, one can observe that the relative density of these lines is higher where the cooperation between the United States on the one hand and the European countries on the other hand is stronger.

Above mentioned kind of analysis is quite important in terms of understanding the structural position of the countries in the global academic network and their roles in this network. Moreover, by using this map, evaluation of Turkey situation, as well as Turkish's partnerships in the literature can be made.

DISCUSSION
The present bibliometric analysis of the pediatric kidney stone related research presents some intriguing findings that are consistent with the general trends in three major research areas, namely pediatric nephrology, pediatric urology and related fields. In the last 20 years, research activity in this domain has observed a significant growth, with the highest level of output most recently in 2020. In line with this, the development of the present work reflects the expanding focus on pediatric health care needs as Chen et al.[20] revealed the escalating number of publications on pediatric stone disease indicating its status as a promising line of research. Similarly, Ghidini et al.[21] and Matta et al.[22] observed an expanding focus on pediatric nephrology and pediatric urology, particularly concerning congenital anomalies, metabolic risk factors and surgical techniques, which have been central to the field. Like many researchers, Pedroza et al.[23] also stress on the unexplored association of cardiovascular risk with urolithiasis, although
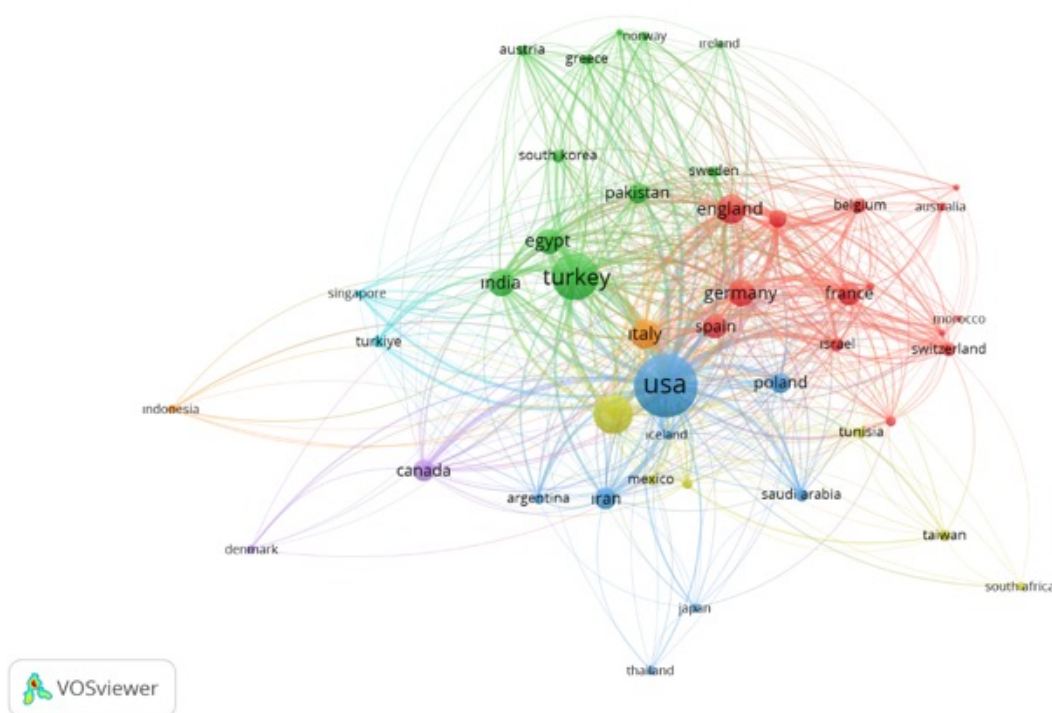

Figure 5. Distribution of citations by country (Circle size represents focal countries; lines between circles represent collaboration)

they have recommended that exploring the underlying system effects of kidney stones, especially in children, may further be explored in research studies in the future. This shows the complexity of the effects of kidney stones which may not be confined to the urinary system only but manifested in several areas of the body; this concept reemphasizes the concept of disease orientation.

The increased publication output in this field reflects the growing recognition of the importance and urgency of the topic. This trend is consistent with the prioritization of pediatric healthcare, which has gained more attention over time. However, the surge in publication numbers does not necessarily reflect uniform quality across studies. Some research has pointed out that while output is increasing, the variability in the depth of analysis and clinical applicability could present challenges for future research to effectively build upon existing studies. These metabolic abnormalities lead to imbalances in the urinary composition, promoting the crystallization and aggregation of stone-forming substances. Recent studies have also emphasized the role of nutrition in pediatric kidney stone formation, suggesting that dietary factors such as increased intake of animal proteins and sodium are contributing to rising cases of urolithiasis in children.[24] This is further supported by Siener and Metzner,[25] who found that dietary interventions focusing on weight management and the reduction of oxalate and sodium intake can significantly reduce the risk of stone formation, underscoring the role of dietary strategies in prevention. As studies increasingly focus on addressing these metabolic risk factors through preventive strategies like dietary modifications and medication, the field has made significant progress in understanding and managing pediatric kidney stone disease.[15] The growth also signifies advancements in medical practices, an increase in clinical research, and the broader public health significance of pediatric kidney stones. Leading researchers and institutions, such as the University of Pennsylvania and the Children's Hospital of Philadelphia, have made substantial contributions to this field, often in collaboration with international partners, particularly between the U.S. and European institutions. Institutional support is crucial in guiding research and ensuring a broad impact, which in turn fosters international collaboration.[26,27] Tan et al.[28] also highlighted the significant rise in urolithiasis cases in China, further emphasizing the global impact of lifestyle changes on pediatric kidney stone formation. Their study points to the need for global collaborations to address this rising trend.[28] Likewise, Nedbal et al.[29] also reported the growing incorporation of modern technologies such as artificial intelligence, machine learning, and virtual reality in the field of urolithiasis suggesting that there is a growing shift towards new diagnostic and interventional technologies that could well revolutionize pediatric care if continued in the next few years.

The analysis further highlights that original research articles are the most frequently cited source type, emphasizing the importance of new findings in the field. This rise, while promising, may also reflect the increasing availability of specialized technologies and diagnostic tools, which could skew the apparent urgency toward certain clinical approaches

while underrepresenting others, such as long-term prevention and follow-up care. Leading journals such as the Journal of Urology and the Journal of Pediatric Urology continue to play a central role in disseminating knowledge on pediatric kidney stones. The prestigious status of these journals makes them the preferred platforms for researchers aiming to share their findings with a wider academic audience. This is corroborated by Ghidini et al.[21] who identified the Journal of Urology as the most productive journal for top-cited articles in pediatric urology. Similarly, Fernandez et al.[30] noted that journals like the Journal of Pediatric Urology significantly influence citation counts in the field of pediatric stone disease.[30,31]

However, the citation impact varies across different studies. For example, Matta et al.[22] reported a lower median citation rate per article in pediatric urology compared to other urologic sub-specialties. This is a crucial consideration, as it may indicate that while there is a focus on pediatric urology, the depth of research and its translational impact into clinical practice are still in developmental stages, particularly in comparison to adult urology. This suggests that while the research output in pediatric kidney stones is growing, its academic impact may still be developing in certain areas. This could be due to the relatively nascent focus on pediatric urology in comparison to adult urology, where research on urolithiasis has been more robustly established over the years.[32]

Keyword analysis reveals that terms such as "urolithiasis", "nephrolithiasis" and "kidney calculi" are central to the literature, indicating that these are primary research focuses. The most cited papers provide critical insights into surgical management and dietary guidelines, demonstrating their influence on clinical practices. Keywords define the boundaries of the research area and indicate areas where future studies should focus. The field of pediatric kidney stones has primarily concentrated on risk factors, therapeutic approaches, and emerging techniques like mini-percutaneous nephrolithotomy and retrograde intrarenal surgery.[27] Yuvanc et al.[33] has also emphasized the demand for increased treatment options of urinary tract stone disease since medical and complementary therapies have gained popularity over the proceeding years more especially in pediatric patients with recurring conditions. The scope of the research includes both medical and nutritional approaches, such as pharmacotherapy, nutrition therapy, and medical expulsive therapy, presenting a variety of options for the treatment and prevention of kidney stones.[33] Juliebø-Jones et al.[34] also supported this view by stressing the importance of advanced surgical techniques, including minimally invasive methods, which they identified as crucial in improving outcomes for pediatric patients suffering from recurrent kidney stones. The developed scoring system provides an easily completed questionnaire to estimate the risk of recurrence in urinary stone disease. This approach is beneficial in guiding patients toward metabolic testing or suggesting preventive measures, making it both a health-advantageous and cost-effective solution.[35] However, less attention has been given to the psychosocial effects of pediatric kidney stones, an area that could benefit from more focused research as the condition can have long-term impacts on the well-being and quality of life of affected children. These

findings align with those of Ghidini et al.,[21] who identified "congenital anomalies" and robotic-assisted laparoscopic surgery as key areas of interest in pediatric urology. Matta et al.[22] also observed a shift from surgical techniques to exploring disease mechanisms, indicating an evolving focus within the broader field of pediatric urology.

Furthermore, an analysis of pediatric UTI research by Kumar et al.[36] highlighted "vesicoureteric reflux", "management" and "diagnosis" as critical themes, reflecting a similar emphasis on understanding disease mechanisms and improving clinical outcomes. This consistency across different subfields of pediatric nephrology and pediatric urology suggests a broader trend toward addressing specific clinical challenges through focused research efforts.

The distribution of citations by country reveals that the United States is a leading contributor to the field, with strong academic collaborations with European countries, reflecting the global nature of research in pediatric kidney stones. Moreover, recent analyses have shown that China is emerging as a significant contributor to pediatric kidney stone research, with increasing output in both clinical and basic science studies.[31] The rise in China's contribution could be attributed to increasing governmental support for research and development, particularly in the fields of medical technology and pediatric healthcare. Turkish institutions, such as Dicle University and Hacettepe University, also make significant contributions, indicating an active research environment in Turkey. This is consistent with Ramakrishnan et al.[37] findings, which also noted that the United States is the leading contributor to pediatric kidney stones research. Both studies emphasize the role of prominent institutions and countries in advancing the field, highlighting the importance of international collaboration. As more countries continue to invest in pediatric kidney stones research, the global landscape is expected to diversify further, enhancing cross-national collaborations and enriching the field.[27] However, it remains important to ensure that future collaborations also focus on under-researched areas and prioritize not only treatment but also prevention strategies to mitigate the global burden of pediatric kidney stones.

Limitations
This study has several limitations. First, the analysis is based solely on data from the WoS Core Collection, which excludes articles from other major databases such as Scopus, PubMed, and Google Scholar. Second, the study only considers articles published in English, potentially excluding significant research published in other languages, thereby limiting the scope of the analysis. Third, the time frame of the study is restricted to articles published between 2004 and 2023, meaning that earlier or more recent developments in pediatric kidney stone research are not captured in this review.

CONCLUSION
Overall, this analysis underscores the growing importance of pediatric kidney stones as a vital research area, with increasing contributions from a diverse range of researchers and institutions worldwide. This surge in academic interest reflects a broader trend within pediatric nephrology and pediatric urology, where specific clinical challenges, such as rising rates of nephrolithiasis among children, are being addressed through focused, evidence-based research. Key themes emerging from the data include advancements in surgical techniques, risk factor identification, and innovative treatment approaches, all of which are central to improving patient outcomes. The ongoing growth in research output, particularly the identification of new research hotspots like minimally invasive procedures and genetic predispositions, further highlights the dynamic and evolving nature of this field. As research continues to expand, it will be crucial for scholars and institutions to foster international collaboration and maintain a forward-thinking approach to advance pediatric healthcare and enhance the quality of care for children affected by kidney stones.

ETHICAL DECLARATIONS

Ethics Committee Approval
Since this research is a bibliometric study, it did not require ethics committee approval. It is conducted with the institution's permission.

Informed Consent
Since this research is a bibliometric study, it did not require informed consents.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study received no financial support.

Author Contributions
All authors declare that they participated in the design, execution, and analysis of the study and have approved the final version.

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Effects of hematological parameters on long term mortality in acute ischemic stroke patients

Fatih Nazmi Yaman[1], Kamil Doğan[2], Özlem Güler[1], Cemile Buket Tugan Yıldız[3]

[1]Department of Emergency Medicine, Faculty of Medicine, Kahramanmaraş Sütçü İmam Universtiy, Kahramanmaraş, Turkiye
[2]Department of Radiology, Faculty of Medicine, Kahramanmaraş Sütçü İmam Universtiy, Kahramanmaraş, Turkiye
[3]Department of Neurology, Faculty of Medicine, Kahramanmaraş Sütçü İmam Universtiy, Kahramanmaraş, Turkiye

ABSTRACT

Aims: Mortality can be seen in acute ischemic stroke (AIS) in the early or late period. We investigated the role of mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and stroke volume in late-term mortality.

Methods: This retrospective cross-sectional study included 132 AIS patients who applied to the emergency department of a university hospital over a consecutive 12-month period. Some patients were excluded from the study according to the exclusion criteria. Patients were divided into groups as survivors and deceased. MPV, NLR, PLR levels in each group were evaluated according to the National Institutes of Health Stroke Scale (NIHSS) scores. Diffusion-weighted MR images (DWIMRs) were evaluated and the infarct volumes of the patients were calculated.

Results: The data of a total of 83 AIS patients who remained after exclusion were analyzed. The mean age, NIHSS score and infarct volume of the deceased were statistically significantly higher than the survivors (p<0.01, p=0.026, p=0.021, respectively). According to Spearman's analysis, NLR, MPV and PLR were negatively correlated with Glasgow Coma Scale (GCS) at presentation, while they were positively correlated with NIHSS and infarct volume. In ROC curve analysis, the optimal cut-off values of NLR, MPV and PLR as predictors of long-term mortality were determined as 4.68, 7.20 and 167.66, respectively. At this level, their sensitivities were 54.84, 48.39, 61.29, respectively, their specificities were 75, 73.08, 73.8, respectively, their positive predictive values were 56.7, 51.7, 57.6, respectively, and their negative predictive values were 73.6, 70.4, 76, respectively, (AUC: 0.64[0.52-0.74 95% CI], 0.64[0.52-0.74 95% CI], 0.66[0.55-0.76 95% CI]).

Conclusion: The results showed that MPV, PLR, infarct volume and mean age were independent predictors of 3-year all-cause mortality in AIS patients.

Keywords: Ischemic stroke, mean platelet volume, neutrophil/ lymphocyte ratio, platelet lymphocyte ratio, mortality

INTRODUCTION

Acute ischemic stroke (AIS) is sudden onset loss of focal cerebral functions that is clinically longer than 24 hours. AIS is the second leading cause of deaths and dementia worldwide, third long-term disability. 80-85% are of ischemic origin, resulting in complete or partial occlusion of one or more cerebral vessels in the atherothrombotic zone.[1]

Diffusion-weighted MR (DWI MRs) images are a highly sensitive imaging tool for early ischemic changes in the acute phase and demonstrate cerebral ischemic changes within five minutes of onset of symptoms. The lesion volume at DWI MRs is associated with clinical significance scores. It has been accepted that infarct volume in DWI MRs can predict clinical outcome and may be a potential parameter in AIS patients.[2]

Leukocytes that play a major role in the active inflammatory process also have a critical role in atherosclerosis. It has been

suggested that hematologic parameters, such as white blood cells (WBC) and neutrophils, can predict infarct size, prognosis, and mortality in acute ischemic events. Neutrophils are the earliest subtype of leukocytes that leak from the ischemic brain area.[3] Platelets have a major effect on the formation of atherosclerotic plaques and are thus known to play an important role in the pathogenesis of atherothrombosis. Mean platelet volume (MPV) is an indicator of platelet function and increased platelet reactivity. MPV levels are known to be significantly higher in hospitalized patients with AIS.[4]

The aim of this study was to investigate the relationship between useful, reliable and cheap hematologic parameters and infarct volume with all-cause 3-year mortality in AIS patients.

Corresponding Author: Kamil Doğan, dr.kamil.dogan@gmail.com

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METHODS

Ethical Approval

The study followed the tenets of the Declaration of Helsinki and was approved by the Kahramanmaraş Sütçü İmam University Ethics Committee (Date: 29.08.2018, Desicion No: 2018/15/30).

Study Population and Protocol

This study is descriptive and retrospectively reviews the AIS diagnosed patients with the diagnostic codes in ICD-10 (G46, G46.8, I67, I67.8, I67.9, I68, I68.8, I69, I69.8) over a consecutive 12-month period. Their demographic and clinical characteristics, laboratory results, comorbities, subtype of acute stroke, inital symptoms, Glasgow Coma Scale (GCS), National Institutes of Health Stroke Scale (NIHSS), hospital stay, 3-year mortality rates after stroke and also the infarct volumes in DWI MRs were recorded in the standard data format that wascreated.

Computerized Tomography (CT) and DWI MRs were reviewed by the Radiologist. Patients with intracranial hemorrhage (epidural, subdural, subarachnoid, intracerebral, intracerebellar, etc.) in the CT were not included in the study. Thus, while the study started with 132 patients, 49 patients were excluded from the study with this exclusion. Finally, 83 patients diagnosed with AIS who fulfilled inclusion criteria and were admitted to the Emergency Department within the first 48 hours after the onset of symptoms were included (Figure 1).

Inclusing Criteria

Gender: Males/Females.
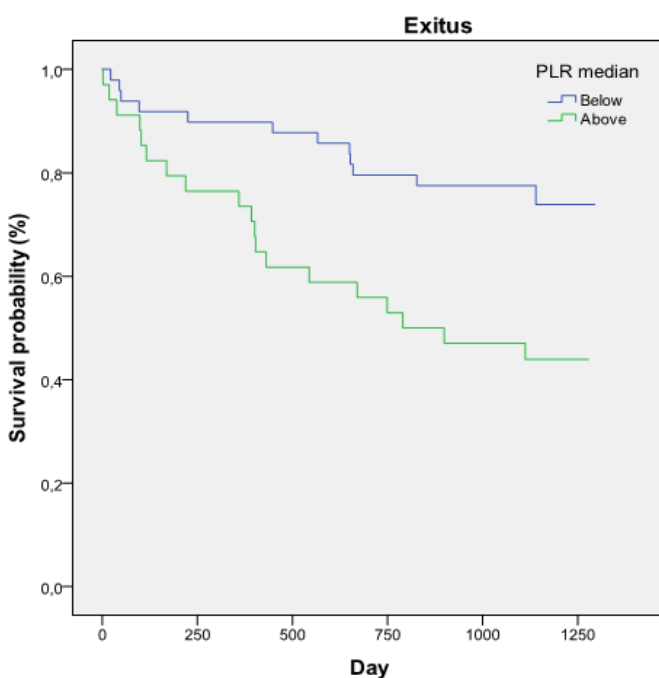
Age Range: 18 years and above. Ischemic stroke

Figure 1. Kaplan-Meier survival curve according to the PLR (platelet/lymphocyte ratio) medianvalue.

Exluding Criteria

Those who applied more than 48 hours after the onset of symptoms, cerebral venous sinus thrombosis, thrombocytopenia, hereditary platelet disease,

Drug use that can affect the number of platelets (antiplatelet agents, antineoplastic agents,hydroxyurea),

Hemorrhagic stroke in CT,

Unknown onset of symptoms (common neurological disorder and dementia, noncommunicable patients, relatives who do not have adequate knowledge, or patients who cannot be relatives),

Hematologic disorder, Immunosuppressive drug use (steroids),

Have an infection history within 2 weeks before stroke,Patients with high fever and infection,

Stroke stories in the last 6 months,

Patients with missing data (laboratory results, medical history),

Outcome measures were assessed by the NIHSS score and GCS on admission. Finaldiagnosis of AIS was performed by a senior neurologist (C.B.T.Y.) and radiologist (K.D.).

According to DWI MRs images, patients were divided into 2 groups as infratentorial infarct and supratentorial infarct. The supratentorial infarct group was divided into 2 groups as lacunar (≤1.5cm) and non-lacunar (> 1.5cm) infarcts.[3] Later, the non-lacunar infarct group wasalso divided into 2 groups as (1) cardioembolic stroke (AF rhythm ECG, valvular heart disease,ECO or TEE thrombus formation)[2] and atherosclerotic stroke (Aortic calcific plaque without documented carotid artery disease or evident hearth disease).[3]

Patients underwent DWI MRs imaging using the Philips Ingenia 1.5 Tesla magnetic resonance device (Philips Healthcare Nederland). For DWI MRs, echo-planar imaging was made in the transverse plane over the spinecho sequence, and imaging parameters were used as TR/TE:3100/100; matrix:192x192; NEX:3; section thickness:5 mm; inter-section gap:1.5 mm; examination time:4-5 minutes and FOV:230x230 mm. Diffusion gradients were taken in three planes perpendicular to one another and ADC maps were attained by using 2 different b values (500 and 1.000 sec/mm²). Lesions that met both hyperintense features on DWI images and hypointense features on ADC images were accepted as acute ischemia. In the measurement of ischemia volume (AxBxC)/2 formula was used. The largest dimension in the axial plane was the longest dimension, the other dimension perpendicular to it was A and B values, and the C value was taken into account when considering the vertical axial section thickness. Infarct volumes of the patients were also calculated by the defined formula.[2]

The in-hospital mortality of patients was determined according to the epicrisis reports. The 3- year mortality of out-of-hospital mortality was found out by using Turkiye Republic Ministry of Health, General Directorate of Public Health, Death Notification System using the ID numbers of the patients. The time of stroke-till-death in all patients was

calculated as days. The patients were divided into 2 groups as alives and deaths.

Laboratory Data

Laboratory data at the time of admission (within 48 hours after onset of symptoms), consisted of the platelet count (PLT, 10^9/L), mean platelet volume (MPV, fL), platelet distribution width (PDW, fL), WBC, 10^9/L, neutrophyl count/L), lymphocyte count (10^9/L), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), liver, renal function tests and glucose (mg / dL).

Hemogram and routine biochemical panel were assessed using peripheral venous blood samples taken when the patients applied to emergency department. Hemogram samples were collected in calsium ethylenediaminetetra-acetic acid tubes. Laboratory data were automatically analyzed using XN-3000 Hematology Analyzer (SYSMEX Corporation, Korea, Japan) and Advia 1800 Chemistry Instrument (SIEMENS, Erlangen, Germany).

Statistical Analysis

SPSS 17.0 program was used in the analysis of the data. The normal distribution relevance of the data was tested by the Shapiro-Wilk test and by the Levene test of variance homogeneity. The independent sample t test was used for normally distributed data and Mann- Whitney U test was used not normally distributed data to compare two independent groups. Pearson correlation analysis was used to examine the correlations of the normally distributed variables and Spearman's rho for not normally distributed variables. The quantitative data in tables are expressed with mean±std (standard deviation) or median [interquartile range (IQR)]. Cox regression analysis was used to determine 3-year mortality determinants. Age, gender, hypertension, diabetes mellitus, glucose levels, creatinin, infarct volume, NIHSS, GCS, NLR, MPV and PLR were included as independent variables in this regression model. Optimal cut-off points of all clinical variables (NLR, MPV, PLR, age, NIHSS and others) of patients who alive and deaths were assessed by receiver operating characteristic (ROC) analysis. Maximum value of sensitivity specificity were determined by calculating the area under the curve (AUC) of the relevant tests. Sensitivity, specificity and positive and negative predictive values were also assessed at the best cut-off value for each clinical variable. Categorical data are expressed as n (number) and percent (%). The data were analyzed at 95% confidence level and those with a p- value less than 0.05 were considered significant.

RESULTS

The mean age of 83 consecutive patients with AIS diagnosis was 67.49±15.30. Forty-three (51.8%) were male and 40 (48.2%) were female. Seventy (84.3%) of the cases were atherosclerotic, 13 (15.7%) were cardio embolic. Median ischemic volume was 5.50 (IQR: 1- 40). Median NLR, MPV and PLR levels of all patients were 3.69 (IQR: 2.15-5.99), 6.40 (IQR: 5.80- 8.20) and 154.11 (IQR: 109.05-221.64), respectively. Median NIHSS and GCS values at the time of admission were 4 (IQR: 2-8) and 15 (IQR: 13-15), respectively. The three-year mortality rate was calculated as 37.3% (n = 31).

The mean age, NIHSS and infarct volume of non survivors were statistically higher than survivors (p<0.01, p=0.026, p=0.021, respectively). The mean GCS in the non survivors group was statistically significantly lower than the surviving group (p=0.009). There was a statistically significant difference between the surviving and non surviving patients in terms of median NLR, MPV and PLR levels (p=0.033, p=0.034, p=0.011, respectively). The demographic and clinical characteristics of all patients are summarized in Table 1.

The location and characteristics of the lesions in the radiological evaluation are shown in a table (Table 2).

According to correlation analysis, NLR, MPV, and PLR were negatively correlated with the GCS at admission and were positively correlated with NIHSS and infarct volume (Table 3).

When 3 years of survival of patients are examined according to median NLR, PLR and infarct volume, Kaplan-Meier survival curves were significantly different between the two groups. (p=0.017, p=0.004, p=0.001, respectively; Figure 1 and Figure 2).

Cox regression analysis revealed that MPV, PLR and infarct volume variables were significant independent risk factors for death (p=0.016, p=0.024, p=0.008, respectively).

Optimal cut-off values of NLR, MPV and PLR were determined as 4.68, 7.20 and 167.66 as long-term mortality predictors in ROC curve analysis, respectively. At this level sensitivities were 54.84, 48.39, 61.29; specificities were 75.0, 73.08, 73.8; positive predictive values were 56.7, 51.7, 57.6 and negative predictive values were 73.6, 70.4, 76.0, respectively. (AUC: 0.64 [0.52-0.74% 95 CI], 0.64 [0.52-0.74% 95 CI], 0.66 [0.55-0.76% 95 CI])

DISCUSSION

In this study, in the group that died of acute ischemic stroke, the mean age, NIHSS score and we found that the infarct volume was statistically significantly higher than the surviving group.

We also found and share the cut-off values for NLR, MPV and PLR levels in objectively assessing the probability of survival and death in cases of acute ischemic stroke.

Despite the results at the probability level in different studies, this study shows that mortality can be predicted with statistically significant data. This is a very significant contribution to the literature and clinical practice.

It has been reported that the inflammatory process plays an important role in the development of ischemic injury and develops within 6-24 hours.[3] Leukocyte-endothelial cell activation which is the rate-determining step in inflammation is almost absent in normal healthy cerebral microcirculation, however it occurs mainly after the onset of brain ischemia. The rapid increase of leukocytes and other blood cells (e.g. platelets) can be attributed to the increased release of adhesion molecules in both cerebral endothelial cells and circulating blood cells. These adhesion molecules allow the release of different inflammatory cell populations (initially neutrophils, then mononuclear leukocytes) and also platelets in a coordinated sequence to the cerebral microvascular structure

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Table 1. Demographics and laboratory findings of survived and non survived patients

Demographic and laboratory	Survived (n=52)	Nonsurvived (n=31)	p
Age, year, median (IQR)	65.5 (28-84)	80 (46-93)	0.000
Gender, F/M	23/29	17/14	0.349
Hypertension, %	35 (67.3%)	24 (77.4%)	0.326
Diabetes mellitus, %	17 (32.7%)	9 (29%)	0.681
AF, %	9 (17.3%)	5 (16.1%)	0.890
CAD, %	12 (23.1%)	8 (25.8%)	0.779
Dislipidemia, %	38 (73.1%)	14 (45.2%)	0.011
Smoking, %	10 (19.2%)	7 (22.6%)	0.715
Systolic BP, mmHg, median (IQR)	140 (107-250)	145 (85-220)	0.695
Diastolic BP, mmHg, median (IQR)	85 (54-150)	90 (50-100)	0.765
HR, /min, median (IQR)	85 (51-114)	88 (68-117)	0.042
GCS, median (IQR)	15 (8-15)	14 (7-15)	0.009
NIHSS, median (IQR)	3 (0-17)	5 (1-18)	0.026
Infarct volume, mmt, median (IQR)	3.5 (0.1–202.5)	12 (0.1–262.5)	0.021
WBC,10^3/μL, median (IQR)	8.9 (4.2-25)	8.7 (4.2 – 24.8)	0.770
Neutrophil, 10^3/μL, median (IQR)	6.28 (2.17-22)	5.83 (2.21-20.90)	0.519
Lymphocyte, 10t/μL, median (IQR)	1.7 (0.8–5.8)	1.3 (0.3 – 3.5)	0.033
Platelet, 10^9/L, median (IQR)	258.5 (103-587)	249 (94-561)	0.713
RDW, fL, median (IQR)	14 (12.3–22.7)	15.2 (12.7-18.4)	0.000
NLR, median (IQR)	3.2 (1.1 – 12.6)	4.9 (0.9-36)	0.033
MPV, median (IQR)	6.3 (5.2 – 12.5)	7 (5.5-13)	0.034
PLR, median (IQR)	129.2 (34.5-460.8)	190.2 (27-652.3)	0.011
Glucose, mg/dL, median (IQR)	115.5 (76-518)	127 (50-293)	0.713
Creatinin, mg/dL, median (IQR)	0.8 (0.3–12.7)	0.8 (0.2–1.7)	0.865
ALT, U/L, median (IQR)	26 (16-90)	25 (13-89)	0.436
AST, U/L, median (IQR)	21 (8-84)	15 (5-67)	0.007
Hospitalization time, median (IQR)	7 (1-46)	8 (1-97)	0.038

Abbreviations: F/M, females/males; AF, atrial fibrillation; CAD, coronary artery disease; BP,blood pressure; HR, heart rate; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; WBC, white blood cell count; RDW, red cell distribution width; NLR, neutrophil/lymphocyte ratio; MPV, mean platelet volume; PLR, platelet/lymphocyte ratio; ALT,alanin aminotransferaz; AST, aspartat aminotransferaz; IQR, interquartile range.

Table 2. Location and characteristics of lesions between two groups in radiological evaluation

Location and characteristics of lesions	Survived	Nonsurvived
Supratentorial, n, %	47 (62.7%)	28 (37.3%)
Infratentorial, n, %	2 (50%)	2 (50%)
Supra-infratentorial, n, %	3 (75%)	1 (25%)
Lacunar, n, %	20 (69%)	9 (31%)
Nonlacunar,n, %	32 (59.3%)	42 (40.7%)

after ischemia-reperfusion. These increased inflammatory blood cells make cerebral microvascular perfusion even more dangerous and contribute to the development of ischemic infarction.[5] Leukocytes are thought to contribute to brain ischemia and tissue damage associated with reperfusion, and neutropenic animals have been advocated for studies that have improved infarcts and neurological outcomes. It has been reported that neutrophils may accumulate in ischemic and reperfused areas in initial response to injury in inflammatory diseases of the central nervous system such as stroke.[3]

Neutrophils have a mixed effect in animal models of stroke, with some studies correlating the presence of neutrophils with injury, while other studies have shown that pre-stroke neutrophil infiltration reduces disease severity. In ischemic stroke, most published studies on the induction and increase of leukocytes have focused on the early injury response and have emphasized the importance of neutrophils.[6] However, most animal studies have focused on the role of cerebral microvascular dysfunction and lymphocytes in tissue injury that occurs several days after ischemic stroke injury.[3] Our study supported these studies and found that neutrophil counts were high and lymphocyte counts were low in the non-surviving group.

It is emphasized that increased NLR is independently associated with coronary artery disease (CAD) severity and may lead to poor prognosis in patients during the 3-year follow-up period.[7] It has been argued that in patients with peripheral arterial disease, high neutrophil counts may add prognostic information to traditional atherothrombotic risk factors and other inflammatory parameters, which may indicate a greatly increased risk for atherosclerotic cardiovascular events.[8] It was also emphasized that high NLR increases the risk of long-term mortality in patients undergoing percutaneous coronary intervention (PCI).[9] Despite the fact that the total

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Table 3. A linear relationship among NLR, MPV, PLR, infarct volume and the othercontinuous variables

Variables	NLR		MPV		PLR		Infarct volume	
	r	p	r	p	r	p	r	p
Age	.087	.432	.112	.313	.218	.048	.097	.385
NIHSS	.342	.002	.026	.819	.232	.035	.429	.001
Infarct volume	.204	.065	.167	.131	.122	.270	-	-
GCS	-.352	.001	-.069	.536	-.137	.218	-.426	.001
Glukoz	.311	.004	.028	.803	.015	.896	.161	.145
Creatinin	.066	.553	-.103	.353	-.005	.964	-.030	.786
Sistolic BP	.106	.340	-.115	.301	.034	.763	.003	.977
Diastolic BP	.007	.949	-.006	.956	.031	.778	-.052	.641
Hospitalization time	.184	.096	.135	.225	.148	.182	.454	.001

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale;BP, blood pressure; NLR, neutrophil/lymphocyte ratio; MPV, mean platelet volume; PLR, platelet/lymphocyte ratio; p, level of statistical significance; r, sperman correlation coefficient.
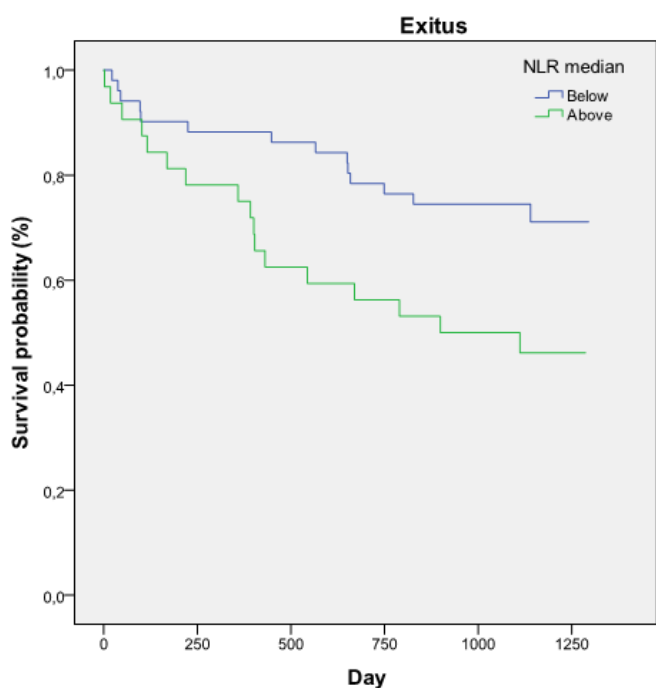

Figure 2. Kaplan-Meier survival curve according to the NLR (Neutrophil/lymphocyte ratio)median value.

number of WBCs was reported to be an independent decisive factor about mortality in patients with high risk CAD, NLR was more predictive about long-term mortality and it was reported to have significant effects on CAD risk assessment.[9,10] Similarly, it has been suggested that NLR is an independent effect of mortality and morbidity in AIS patients.[7,11] It has also been reported that NLR at the time of admission may be a predictor of short-term mortality independently of infarct volume in AIS patients.[3] In our study, NLR was found to be statistically significantly higher in the non survived group, but in regression analysis it was reported that NLR was not a predictor of long term mortality.

There are also some publications in rat stroke models demonstrate that antineutrophil treatment is useless despite the fact that many molecules altering leukocyte infiltration in ischemic regions have been shown to reduce infarct size.[12] Acute inflammation, which can be followed by peripheral inflammatory parameters in AIS patients, may affect the magnitude of the infarct and is positively correlated with infarct volume and NLR.[3] It has been reported that increased NLR can predict infarct size independently of ethology.[3] The positive correlation of NLR with infarct volume and NIHSS and negative correlation of NLR with GCS in our study are compatible with other studies. In addition, the infarct volume was found to be statistically significantly higher in the non survived group that it could be a predictor of long term mortality. Löuvbld et al.[2] also reported that the DWI MRs imaging infarct volume is correlated with the clinical severity and outcome of the disease in the AIS patients and indicated that it could be a predictor of long term mortality.

MPV is considered to be a marker of platelet activation and associated with systemic inflammatory responses. Although it is generally accepted that increased platelet activation is associated with ischemic stroke and coronary heart disease, some studies suggest that there is noassociation between MPV and ischemic stroke.[13-15] Similar to the findings of Mohammed et al,[16] the association between NIHSS score and elevated MPV in AIS patients, resulted in an increase in morbidity and cardiovascular mortality in patients with high MPV after ischemic stroke. Ray et al.[17] reported that MPV increases and platelet count reduces in both of acute and nonacute phases of cerebral ischemia. Domaç et al.[14] reported that MPV levels, that reflect platelet reactivity, increased just before stroke in patients with severe stroke. Löuvbld et al.[2] reported that in the AIS patients, the DWI MRs imaging infarct volume correlated with the clinical severity and outcome of the disease and indicated that it could be a predictor. There was a similarity with literature and MPV value was found statistically higher in the non survived group in our study. MPV may be a predictor of long-term mortality in AIS patients. In addition, positive correlation was found among MPV, ischemia volume and NIHSS and negative correlation with GCS.

PLR is an easily obtained biomarker that combines the prognostic value of platelet and lymphocyte counts with systemic inflammatory burden in cardiovascular diseases. Platelets play an important role in the development, destabilization, and rupture of atherosclerotic plaques. It is thought that increased PLR may accelerate restenosis and plaque instability, thus contributing to the progression of atherosclerosis. This is associated with poor prognosis in

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ischemic events. Stable CAD patients undergoing elective stent implantation with high PLR have been reported to have a higher mortality rate. PLR has also been suggested to be a predictor of long-term mortality in CAD.[18] Temiz et al. [19] reported that increased PLR is an independent predictor of in-hospital cardiovascular mortality in patients with ST-elevation AMI, and the threshold value of PLR is 144. The relationship between increased platelet count and cardiovascular mortality has been shown in many studies.[20-22] It has been suggested that increased PLR ratios in stroke patients may indirectly predict infarct volume. The possible pathophysiological mechanism of this relationship is the migration of inflammatory mediators to the penumbra and an increase in the infarct area.[23] Altintas et al.[1] reported that AIS patients had better functional outcomes with low PLR values than with high PLR values. It was also found that mortality rates increased four to five times when PLR was higher than 145 (PLR>145). Similarly, in our study, PLR was statistically significantly higher in the non-survivor group. It was determined that PLR could be a predictor of long-term mortality. In addition, PLR was found to be positively correlated with infarct volume and NIHSS and negatively correlated with GCS.

Limitations

This current study has many limitations. First, the study was retrospective in nature. Since the density of data in the electronic medical record system is always high, the number of lost data is high. This can also lead to prejudice. Second, we could not obtain blood samples to compare prognostic significance of early and late hematologic parameters. In addition, these parameters were compared only with the survival and non survival group, and no comparison with the healthy control group was made. Third, in-hospital mortality, short-term and long-term mortality were not comparable to hematologic parameters because the number of cases was not sufficient.

CONCLUSION

MPV and PLR values were found as an independent predictor for 3 year mortality of AIS patients. Additionally infarct volume and average age were an independent predictor for 3 year mortality of AIS patients, too.

ETHICAL DECLARATIONS

Ethics Committee Approval
The study followed the tenets of the Declaration of Helsinki and was approved by the Kahramanmaraş Sütçü İmam University Ethics Committee (Date: 29.08.2018, Decision No: 2018/15/30).

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

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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MEDICINE
PALLIATIVE CARE

Effects of two different grafts on radiological and functional outcomes in the surgical treatment of calcaneus fractures

İbrahim Bozkurt[1], Mehmet Musa Emir[2]

[1]Department of Orthopaedics and Traumatology, Ankara Bilkent City Hospital, Ankara, Turkiye
[2]Department of Orthopaedics and Traumatology, Batman İluh State Hospital, Batman, Turkiye

ABSTRACT

Aims: There are no standards regarding the use and selection of grafts for calcaneal fractures in the literature. This study aims to contribute to the literature by evaluating the effects of allografts and synthetic grafts on union and functional outcomes in the treatment of calcaneal fractures.

Methods: Intraarticular calcaneal fractures treated surgically between 2011 and 2018 with a minimum follow-up of 2 years were included in the study. Patients were divided into two groups based on the type of graft used: synthetic grafts (G45S5 bioactive glass, Noraker®) or allografts. The Böhler angle and Gissane angle were measured radiologically. Functional outcomes were assessed using the American Orthopaedic Foot & Ankle Society (AOFAS) Score and Maryland Foot Score at the final follow-up.

Results: The average age in the synthetic graft group was 37.5±12.4 years, while that of the allograft group was 37.8±8.6 years. Radiographic evaluations of both groups showed some degree of collapse in the posterior facet of the talocalcaneal joint in both postoperative and 2-year follow-up images. No significant differences were found between the groups in terms of the AOFAS Score or Maryland Foot Score at the 2-year postoperative evaluation.

Conclusion: There was no significant difference in functional and radiological outcomes between synthetic and allografts in the surgical treatment of calcaneal fractures.

Keywords: Calcaneus fracture, allograft, synthetic graft

INTRODUCTION

Calcaneus fractures are typically seen as a result of high-energy traumas such as falls from a height or motor vehicle accidents.[1] Between 60% and 75% of these fractures are intraarticular, with particular treatment challenges arising from the collapse and depression of the posterior facet of the talocalcaneal joint.[2,3]

Treatment goals for calcaneus fractures include the accurate anatomical restoration of displaced joints and the correction of the height, width, and length of the calcaneus for stable osteosynthesis. Surgical treatment of calcaneus fractures should also ensure the anatomical reconstruction of the foot's subtalar and calcaneocuboid joints.[4] In some cases, graft augmentation is used to support the facet in fractures with joint depression.[5]

In calcaneus fractures, when the underlying bone is crushed and the subtalar joint is depressed, reconstruction involving the elevation of the bone fragments leaves a gap that needs to be filled with a bone substitute, such as an autograft, allograft, xenograft, or synthetic prosthesis.[6] Autografts are obtained from the patients themselves and integrate better than allografts or xenografts. They aid in healing with their osteoinductive and osteogenic properties but also come with complications such as additional surgical procedures and donor-site comorbidities.[6]

Demineralized allografts are commonly used to fill voids. Allografts enhance bone healing in areas where healing is difficult, providing osteoinductive properties and mechanical support when necessary.[6]

The primary advantages of xenografts are their lower cost and easier availability,[7] although they have greater antigenicity compared to allografts. Data on bone xenografts in humans is limited. Bovine-based xenografts are considered to offer structural integrity and ease of use in reconstructive foot surgeries.[6] β-Tricalcium phosphate (β-TCP) ceramics, on the other hand, have been reported to exhibit rapid in vivo biological degradation.[8]

In this study, we aimed to contribute to the literature regarding graft selection in the treatment of calcaneus fractures, as there are no standards for graft usage in these cases. We also aimed

Corresponding Author: İbrahim Bozkurt, dr.bozkurtibrahim@gmail.com

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to evaluate the effects of allografts and synthetic grafts on union and functional outcomes in calcaneus fractures.

METHODS

The study was carried out with the permission of Ethical Committe of Ankara Bilkent City Hospital (Date: 28.04.2021, Decision No: 21-1704). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Between 2011 and 2018, 67 patients with intra-articular calcaneus fractures were operated on. Among these 67 patients, 5 had fractures in the contralateral extremity, and 3 developed wound infections during postoperative follow-up. Therefore, a total of 59 patients were included in the study. These 59 patients were retrospectively analyzed. The inclusion criteria were being over 18 years of age, having undergone surgery for closed fractures, patients who received grafts and being followed up for at least two years. Patients with open fractures, those who did not receive grafts, and those with other fractures in the same or contralateral lower extremity were excluded from the study. In the surgical treatment, synthetic G45S5 bioactive glass (Noraker®, Lyon, France) or an allograft was used. Patients were divided into two groups based on the type of graft used: synthetic grafts or allografts. Preoperative, early postoperative, and final follow-up radiographs, including ankle, anteroposterior, lateral, and axial views, were obtained for all patients. The Bohler and Gissane angles were measured radiologically. The Sanders classification was applied based on preoperative computed tomography scans and only patients with Sanders type 3-4 fractures were included in the analysis. Posterior facet collapse was evaluated by interpreting the Bohler and Gissane angles on the X-ray. The American Orthopaedic Foot & Ankle Society (AOFAS) Score and Maryland Foot Score at the final follow-up were used to evaluate functional outcomes.

Surgical Technique

Patients were positioned laterally on a radiolucent table with a tourniquet applied to the upper thigh. A lateral L-shaped extended incision was made. A subperiosteal flap was created, preserving the surrounding soft tissue and the sural nerve. After clearly visualizing the fracture line, the lateral wall fragments were lifted from the calcaneus like a shell, exposing the depressed posterior facet. By placing an osteotome or using periosteal stripping as leverage, the depressed fragment was elevated to its normal superior position. Temporary fixation of the posterior facet was achieved by passing Kirschner wires from the talar portion to the sustentaculum. Reduction of the posterior facet, calcaneocuboid joint, anterior process, and sustentaculum as well as varus/valgus alignment were checked using fluoroscopy with lateral, Harris axial, and serial Broden views. At this stage, bone defects were observed in the area where the posterior facet was elevated, and based on the surgeon's preference, a synthetic graft or allograft was tightly placed into the calcaneus. In both groups, after reduction, permanent fixation was performed using an anatomical calcaneal plate with low-profile, locking, and headless screws. A final fluoroscopic control was conducted and all Kirschner wires were removed. The wound was closed using subcutaneous absorbable 2-0 sutures and a subcutaneous drain was placed. The skin was closed with non-absorbable 3-0 sutures. A dressing was applied, followed by thick cotton wool padding and a short leg splint.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 22.0 for Windows. Descriptive statistics were expressed as frequency, percentage, mean, standard deviation, median, and minimum-maximum values. Since the Shapiro–Wilk test indicated non-normal distribution for the quantitative variables, non-parametric tests were used. The Mann-Whitney U test and Wilcoxon test were employed to determine the relationships between parameters. The chi-square test was used for categorical data analysis. Results were evaluated with a 95% confidence interval and $p<0.05$ was considered significant.

RESULTS

The mean age was 37.5±12.4 years in the synthetic graft group and 37.8±8.6 years in the allograft group (Table 1). There was no significant difference between the two groups in terms of preoperative Bohler and Gissane angles. Comparing the postoperative and 2-year Bohler and Gissane angles, no significant difference was found between the groups. Posterior facet collapse of the talocalcaneal joint was observed in both groups when comparing postoperative to 2-year radiographs. In the allograft group, posterior facet collapse was detected in 13 patients, while in the synthetic graft group, it was found in 10 patients. Functional outcomes as evaluated at the 2-year follow-up with the AOFAS Score and Maryland Foot Score also revealed no significant difference between the groups. Early wound infections were observed in one patient in the synthetic graft group and two patients in the allograft group (Table 2).

Table 1. Demographic characteristics

Characteristic	Synthetic graft (n=27)	Allograft (n=32)	P
Sex, female/male	8/19	10/22	
Age, years, mean	37.5±12.4	37.8±8.6	0.653

Table 2. Clinical and radiological characteristics

Measurement	Gissane angle (°)			Böhler angle (°)		
	Synthetic graft (n=27)	Allograft (n=32)	P	Synthetic graft (n=27)	Allograft (n=32)	P
Preoperatively, mean±standard deviation	145.6±20.5	138.9±21.3	0.080	12.7±10.3	12±15.8	0.749
Postoperatively, mean±standard deviation	130.6±12.4	127.1±12.7	0.273	29.3±5.8	27.7±8.6	0.189
Two-year follow-up, mean ± standard deviation	132±13	128.3±13.3	0.266	28.1±6.1	26.2±9.8	0.111
	AOFAS Score			Maryland Foot Score		
	Synthetic graft (n=27)	Allograft (n=32)		Synthetic graft (n=27)	Allograft (n=32)	
	82.3±4.7	82.5±5.6	0.963	52.3±3.6	52.5±4.4	0.837

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DISCUSSION

This study compared the effects of synthetic grafts and allografts on radiological and functional outcomes in the surgical treatment of calcaneus fractures. The results showed that both types of grafts significantly improved the patients' postoperative Bohler and Gissane angles. However, posterior facet collapse of the talocalcaneal joint was observed in both groups during the 2-year follow-up, consistent with previous studies on calcaneus fractures. The literature reports that posterior facet collapse is a common problem following surgery for calcaneus fractures.[4]

Analyses of functional outcomes using the AOFAS Score and Maryland Foot Score revealed no significant differences between the synthetic and allograft groups. These findings suggest that both graft types provide successful outcomes in the surgical treatment of calcaneus fractures without functional superiority of one over the other. The significant advantages of synthetic grafts include their cost-effectiveness and availability.[6] These advantages, in addition to the rapid biological degradation and supportive bone-healing properties of synthetic grafts, may make them preferable.[9]

Other studies in the literature have generally examined the effects of a single graft type, with limited studies comparing different grafts. This study provides information to guide clinical practice by directly comparing both graft types. Recent systematic reviews and meta-analyses have also shown that synthetic grafts yield long-term results similar to those of allografts. Autografts in particular are thought to accelerate the healing process due to their osteoinductive and osteogenic properties. However, the extent to which these advantages are reflected in clinical outcomes remains unclear. In some previous studies, patients who received autografts showed slightly faster union compared to synthetic grafts, but this did not create a significant difference in long-term follow-up.[9,10] These findings align with those obtained in the present study and suggest that synthetic grafts can serve as a viable alternative to autografts. β-TCP-based synthetic materials have been particularly widely discussed in the literature due to their rapid biological degradation and supportive bone-healing effects.[8]

Some researchers have suggested that the use of synthetic grafts accelerates bone healing but does not achieve the same long-term level of osteointegration as allografts.[7] However, in this study, synthetic grafts and allografts provided similar functional results over a 2-year follow-up period. While allografts are generally considered superior due to their osteoinductive and osteogenic properties,[6] our study found that those advantages did not result in a clinically significant difference.

The infection findings of this study are also notable. Early wound infections were observed in one patient in the synthetic graft group and two patients in the allograft group. The lack of a significant difference in infection rates between the two graft types suggests that graft selection is not a decisive factor in infection risk. Although the literature suggests that allografts may offer some advantages in terms of infection risk,[7] our findings do not support that theory. Other studies in the literature have similarly reported that infection rates do not vary significantly based on graft type.[12] Further studies with larger patient populations are needed to achieve more meaningful results regarding wound infection rates.

We believe that improving the biocompatibility of synthetic grafts and minimizing infection risk may be essential points of focus for future research. The impact of graft usage on bone union is also an important finding. No significant difference was observed between the groups in terms of union times after surgeries. Although the literature suggests that the osteoinductive properties of allografts may accelerate union,[6] synthetic grafts have been shown to support bone healing successfully.[8] This finding suggests that synthetic grafts may be a suitable treatment option, especially when cost and accessibility are prioritized.

This study offers clinicians different options in terms of cost-effectiveness and accessibility regarding graft selection and suggests that synthetic grafts can be considered as an alternative according to other studies in the literature.

Limitations
Due to this study's single-centre and retrospective nature, it is not possible to rule out potential factors that may have influenced our findings. Other limiting factors of the study include the lack of long-term results for a control group without grafts.

CONCLUSION

No significant differences were found between synthetic grafts and allografts regarding functional and radiological outcomes in the surgical treatment of calcaneus fractures. This suggests that synthetic grafts can serve as viable alternatives to allografts, particularly in terms of cost-effectiveness. However, the occurrence of posterior facet collapse with both graft types underscores the importance of closely monitoring long-term outcomes in the treatment of these fractures. Furthermore, future studies with longer follow-up periods and larger patient populations are needed to compare different graft materials. Such studies will provide clearer insight into the impact of graft selection on fracture healing.

ETHICAL DECLARATIONS

Ethics Committee Approval
The study was carried out with the permission of Ethical Committe of Ankara Bilkent City Hospital (Date: 28.04.2021, Decision No: 21-1704).

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

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Neurosarcoidosis

Tuba Akıncı[1], Berna Akıncı Özyürek[2]

[1]Department of Neurology, Haydarpaşa Numune Training and Research Hospital, İstanbul, Turkiye
[2]Department of Chest Diseases, Ankara Atatürk Sanatorium Training and Research Hospital, University of Health Sciences, Ankara, Turkiye

ABSTRACT

Sarcoidosis is an autoimmune multisystemic inflammatory disease characterized by non-caseating granulomatous infection, most commonly involving the lung and lymph nodes. About 5–15% of cases involve the central nervous system (CNS), neurologic involvement in sarcoidosis is in the form of peripheral or central nervous system involvement. Recent years have seen substantial advancements in our understanding of neurosarcoidosis, including updated diagnostic standards and improved methods for treatment. We provide an overview of current developments in the identification and management of neurosarcoidosis in this review.

Keywords: Sarcoidosis, central nervous system, tumor necrosis factor

INTRODUCTION

Sarcoidosis is an autoimmune multisystemic inflammatory disease characterized by non-caseating granulomatous inflammation, most commonly involving the lung and lymph nodes. Its etiology is not known exactly. The prevalence and incidence of the disease may vary geographically and environmentally; it is 1.5 times more common in women than in men. It is especially common between 20-60 years of age. Organ involvement may vary according to age and race. Neurologic involvement in sarcoidosis is in the form of peripheral or central nervous system involvement, its incidence is between 5-10% and its morbidity and mortality are high.[1,2] Neurologic symptoms constitute the initial symptoms in 50-70% of patients with NS.[3] Approximately 10-20% of patients with NS (so-called isolated NS) do not have identifiable systemic sarcoidosis.[4-6] NS usually develops within 2 years after diagnosis (75%).[7]

CLINICAL FEATURES

Central Nervous System

Cranial neuropathy: It develops as a result of granulomatous inflammation of cranial nerve nuclei, fascicles or nerves. It is the most common clinical manifestation of NS. Multiple, consecutive cranial neuropathic involvements should bring neurosarcoidosis to mind. It shows a subacute, progressive course. The most commonly affected nerves are the optic, facial and vestibulocochlear nerves.[5]

The facial nerve is the most commonly affected cranial nerve in sarcoidosis and may be the first finding.[8] Sarcoidosis may cause facial paralysis by many mechanisms including meningeal inflammation, parotitis, spinal involvement, stroke/vasculitis or compression from intraparenchymal lesions. Although unilateral involvement is common, simultaneous or sequential bilateral involvement may also occur.[8] MRI is usually normal, but when abnormal, the most common findings are facial nerve contrast enhancement or leptomeningeal contrast enhancement.[8] Lyme disease should be excluded when bilateral facial paralysis is seen. Parotitis should be considered when facial paralysis occurs with unilateral throat or neck pain and swelling. Heerfordt Waldenström syndrome causing parotitis, facial paralysis, fever and ocular inflammation is pathognomonic for sarcoidosis.[9] NS may cause optic neuritis or peri neuritis, which may involve the optic chiasm.

Vestibulocochlear nerve involvement with vestibular dysfunction and/or hearing loss is typically associated with possible leptomeninges's at the base of the brain. Other cranial neuropathies related to NS are less common.[10]

Hypothalamic/pituitary involvement: Hypothalamic/pituitary involvement and associated neuroendocrine dysfunction is seen in 10%-25% of cases. Endocrine dysfunction most commonly includes anterior hypopituitarism (LH/FSH 89%; TSH 67%; GH 50% and ACTH 49%), hyperprolactinemia (49%) and diabetes insipidus (65%) and may be the presenting symptom of NS in approximately half of patients with sellar disease.[11] MRI findings include thickening and contrast enhancement of the pituitary gland or stalk, sometimes extending to the hypothalamus and often multifocal findings.[12]

Corresponding Author: Tuba Akıncı, tubaags@yahoo.com

Spinal involvement: Spinal cord involvement may occur by different mechanisms including spinal cord parenchymal lesion, leptomeningeal involvement, extradural space infiltration, and extraspinal tissue involvement compressing the cord. Recent studies have reported that myelopathy can be observed in 19% to 26% of patients with NS.[11,13] On imaging, it may be seen as intraparenchymal T2 hyperintensities and nodular/linear contrast enhancement in the surrounding leptomeninges.[14,15] Longitudinally extensive myelitis (LETM≥3 vertebral segments) is common[14] and should be differentiated from other causes of LETM. Other MRI findings supporting the diagnosis of neurosarcoidosis include dorsal cord subpial gadolinium enhancement pattern in ≥2 spinal segments and contrast enhancement lasting >2 months despite treatment.[16] Central canal and dorsal subpial contrast enhancement creates a trident-like image on axial images, suggesting neurosarcoidosis in patients with subacute myelitis.[17] In a 2020 series, 4 main sarcoidosis myelitis patterns were defined; LETM (45%), short tumefactive myelitis (23%), meningitis/ meningoradiculitis (23%), anterior myelitis adjacent to degenerative disc (10%).[18] As in the brain, mass-like spinal dural, contrasting lesions can be seen. Although cervical and thoracic involvement is more likely, involvement of the conus medullaris and cauda equina can also be seen.

Meningeal involvement: Neurosarcoidosis most commonly affects the leptomeninges (pia and arachnoid mater). If the pia or leptomeninges are involved, subacute meningitis syndrome may occur and this condition may become chronic over time. It has a preference for the skull base (basilar meningitis) and may extend to the spinal cord meninges.[5] Headache is common in patients with radiographic leptomeningeal involvement, but the presence of fever and nuchal rigidity suggestive of clinical meningitis is rarely observed.[19] Compression of the ascending nerve roots in the brain stem may cause cranial neuropathies. On MRI, leptomeningeal involvement which may also have a nodular component may be observed.

Parenchymal involvement: Parenchymal involvement of neurosarcoidosis causes symptoms specific to the involved area. Multifocal lesions are more common than solitary lesions.[20,21] It may occur as a result of meningeal dissemination or vascular involvement. Intraparenchymal mass-like lesions may occur in roughly 15% of cases and may cause seizures/focal deficits. Contrast enhancing, T2 hyperintense, T1 isointense lesions are among the characteristic MRI findings. NS-associated cerebrovascular disease may present with involvement of small, medium and large veins/venules. Venous sinus thrombosis due to vascular compression may also be seen[22], but there may be many potential causes of typical ischemic or hemorrhagic stroke in patients with known sarcoidosis and may not be directly attributable to NS.

Encephalopathy: Subcortical encephalopathy, including dementia, can be seen in neurosarcoidosis. Non-contrasting, nonspecific white matter lesions may be detected. Since they do not correlate with clinical findings in NS and do not decrease with immunosuppressive treatment, their relationship with NS is unclear and often suggests comorbid small vessel disease.[10]

Neuropsychiatric Illness: Depression and other neuropsychiatric symptoms are nonspecific and may not be directly related to NS. It has been reported that 60-66% of patients with NS develop depression and up to 20% develop other neuropsychiatric symptoms including psychosis.[7]

Peripheral Nervous System (PSS)

The PSS sarcoidosis spectrum includes polyneuropathies or polyradiculoneuropathy, which can involve both large and small fibers with pure motor, sensory or sensorimotor features, including a Guillain-Barre-like syndrome. Peripheral neuropathy is reported in approximately 15-20% of patients. Peripheral nerve vasculitis can produce mononeuritis multiplex-like involvement with axonal features. Symmetric chronic sensorimotor axonal type of peripheral neuropathy is most commonly detected by EMG. The relationship between neuropathy and sarcoidosis can be more clearly supported by biopsy. Both nerve and muscle should be examined together in biopsy. Subclinical muscle involvement is also found in 90% of nerve biopsies.[23]

Small fiber neuropathy: Small fiber neuropathy is common in systemic sarcoidosis, but its pathogenesis is unclear.[24] Therefore, it is considered as a sign of paraneurosarcoidosis in the current consensus diagnostic criteria and does not always suggest granulomatous inflammation.[25] A large 2017 study found that in approximately 25% of sarcoidosis patients with confirmed small fiber neuropathy, the neuropathy had an additional possible etiology.[24]

Myopathy: A 2018 study of 48 patients with symptomatic muscle sarcoidosis identified 4 patterns based on clinical presentation, EMG and pathology. These include nodular (27%); smoldering (29%); acute, subacute or progressive myopathic (35%); and combined myopathic and neurogenic pattern (10%). The clinical course varies depending on the phenotype.[26]

DIAGNOSIS

Diagnostic Criteria for Neurosarcoidosis

The updated consensus criteria were published in 2018 and classify cases as "definite, probable, possible" NS according to pathologic and clinical findings.[25]

Definite; 1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes.

2. The nervous system pathology is consistent with neurosarcoidosis. Type a; extraneural sarcoidosis is evident. Type b; non-extraneural sarcoidosis is evident (isolated CNS sarcoidosis).

Probable; 1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes. 2.There is pathologic confirmation of systemic granulomatous disease consistent with sarcoidosis.

Possible; 1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/orEMG/NCS findings typical of granulomatous inflammation of the nervous system, and after rigorous exclusion of other causes.

2. There is no pathologic confirmation of granulomatous disease.

Serum Tests
These tests are mostly used to elucidate possible organ involvement or other possible etiology of sarcoidosis, as there is no specific or sensitive test. Acute phase reactants may be elevated but are not specific. Vitamin D hypervitaminosis and hypercalcemia may occasionally be detected and should be investigated in terms of hyperparathyroidism.[10] Serum ACE levels are found to be increased in 60% of pulmonary sarcoidosis cases.[27] A study in 2019 showed that serum dissolved IL-2 receptor levels were 88% sensitive and 85% specific in sarcoidosis, while ACE levels were 62% sensitive and 76% specific.[28]

CSF Analysis
Lumbar puncture is recommended in patients with CNS neurosarcoidosis to investigate the presence of intrathecal inflammation and to exclude other possible etiologies, especially if leptomeningeal involvement is present. Most CNS NS have abnormal results on CSF analysis, but no test is specific. Typically, increased CSF protein and mild or moderate pleocytosis (<100 cells) with lymphocyte predominance may be detected. Neutrophils may be detected, eosinophils are rare. Isolated increased CSF protein may suggest inflammation but is not specific.[10] It is one of the rare diseases that may cause hypoglycorrhachia without being infectious, but <20 mg/dl should suggest fungal, mycobacterial and malignant etiologies.[29]

Oligoclonal band (OBC) and elevated IgG index can be observed in 20-40% of neurosarcoidosis cases but are nonspecific.[30] CSF ACE level has low sensitivity and low specificity.[31] Hypoglycorrhagia and high CSF ACE levels have been found to be associated with NS in patients with LETM.[21] In a study comparing NS, MS and other inflammatory diseases, an increase in CSF CD4/CD8 and IL-6 was found in favor of neurosarcoidosis.[32] CSF IL-6 >50 pg/ml was found to be associated with NS progression or relapse.[32]

Neuroimaging
When examining suspected cases of neurosarcoidosis, MRI with or without contrast is the most appropriate imaging modality. Typical MRI may show pachy/leptomeningeal involvement, perivascular infiltration, MS-like lesions, mass-like lesions, cranial nerve infiltration, pituitary involvement.

Contrast uptake is not specific but is valuable in terms of MS neurosarcoidosis. Deep medullary vein congestion and radial perivenular involvement may be significant for NS.[33] MRI has a role in response to treatment and clinical decision making.

Systemic Evaluation
Early diagnostic goals in neurosarcoidosis include looking for findings in favor of systemic sarcoidosis to support the diagnosis. A detailed physical examination is essential in systemic evaluation. Eye and fundus examination is necessary for ocular involvement. In roughly half of patients with CNS neurosarcoidosis, abnormalities are found on chest radiography (PAAG).[34,35] When clinical suspicion for sarcoidosis is high and PAAG is normal, thoracic, abdominal and pelvic CT may be valuable in determining sarcoidosis.

When structural imaging does not reveal target tissue for biopsy, combined fluorodeoxyglucose PET (FDG-PET)/CT may reveal metabolically active lymph nodes or other occult lesions that may appear normal on CT.[36] FDG-PET can also show metabolically active lesions in the brain or spinal cord, but these are almost always better seen on MRI.

Biopsy
Meningeal, brain or spinal cord biopsy is sometimes indicated if the diagnosis remains suspicious. Extra neural tissue biopsy from other clinically affected organs is generally preferred when possible as it is less risky; skin, lymph node, and lung (transbronchial) biopsies may provide high yield.[34,35] Muscle and peripheral nerve biopsy, including quantitative nerve terminal analysis to document small fiber sensory neuropathy[37] and epidermal biopsy including sweat gland innervation, can all be easily performed for the appropriate syndrome. In the absence of a defined systemic disease, a central or peripheral nervous system biopsy should be considered instead of empiric therapy to establish the diagnosis. Biopsy to reveal an alternative neurologic diagnosis should also be considered for patients with known systemic sarcoidosis and neurologic disease who progressively deteriorate despite treatment.[38] Sarcoid granulomas are not histologically different from other granulomas and related granulomas require exclusion of acid-fast bacilli and fungi with special stains and infectious processes with cultures.

TREATMENT

The aim of disease-modifying therapy is to prevent or minimize damage to organs from granulomatous inflammation. Immunosuppressive therapy may not be required in mild disease. However, in cases with CNS neurosarcoidosis and peripheral thick nerve fiber involvement, early immunosuppressive therapy is recommended to reduce neurological damage and disability. A multidisciplinary approach is required in multisystem involvement. No randomized trials are yet available to guide NS treatment; therefore, treatment is based on expert opinion and observations from case series and single reports.[10]

Glucocorticoids
Glucocorticoids are the first-line agents in the treatment of neurosarcoidosis and the dose and duration of treatment should be determined according to the severity of the disease and response to treatment; they act rapidly in most patients.[7,35]

Patients with severe symptoms may be treated with a dose of 1 g IV methylprednisolone daily for 3-5 days followed by a tapered course of oral glucocorticoids. In milder cases, bioequivalent doses of 0.5-1 mg/kg/day prednisone or other glucocorticoid formulations may be effective. For patients with mild or moderate symptoms, monotherapy with prednisone

may be adequate and prednisone can be gradually tapered over several months when clinical and imaging response is adequate. When tapering glucocorticoids in NS, care should be taken to consider and evaluate relapse or worsening. Early switch to steroid-sparing therapy may be considered in cases of safety and toxicity concerns with glucocorticoids. Given the frequent recurrence of disease activity when steroids are discontinued, close clinical and radiologic follow-up is important during glucocorticoid taper.

Steroid Sparing Agents
Patients whose condition worsens despite aggressive glucocorticoid therapy, who cannot tolerate glucocorticoids, or who have a primary contraindication to glucocorticoid therapy may benefit from alternative therapies.[4,39,40] Expert opinion suggests that alternative therapies should be considered early in treatment for patients receiving high-dose glucocorticoid therapy and in whom symptoms such as parenchymal inflammation, hydrocephalus or optic neuropathy are likely to require long-term treatment.

There are no prospective studies comparing various alternative therapies in patients with neurosarcoidosis. The decision on the specific agent should be based on ease of use, cost and avoidance of complications of a particular drug. A number of steroid sparing agents have been used in the treatment of NS, including azathioprine, methotrexate, mycophenolate mofetil, hydroxychloroquine, cyclophosphamide and TNF inhibitors.[10] In a small case series, mycophenolate mofetil was effective in the treatment of diseases affecting the central nervous system (CNS) but not in sarcoid myopathy.[41] A retrospective multicenter study showed that relapse in patients with neurosarcoidosis methotrexate and mycophenolate mofetil in prevention.[42] Methotrexate treatment was associated with 0.2 relapses per year, while mycophenolate mofetil was associated with 0.6 relapses per year, and adverse effects were found to be more common with methotrexate than with mycophenolate mofetil. It may take several months for agents such as azathioprine, methotrexate and mycophenolate mofetil to achieve full clinical immunosuppressive effect, during which time it may be beneficial to continue oral glucocorticoids. The patient's response to any specific drug cannot be predicted and two or three agents should be tried before concluding that the patient's disease is resistant.[10]

TNF Inhibitors
The best-studied TNF-alpha antagonist in NS is infliximab, a chimeric monoclonal antibody against TNF-alpha that appears to be able to inhibit granuloma formation and induce complement- and cell-mediated apoptosis in sarcoidosis. Observational studies suggest that infliximab may be useful in selected patients with pulmonary and extrapulmonary sarcoidosis refractory to glucocorticoid therapy.[43-49] In a series of seven patients with glucocorticoid-resistant neurosarcoidosis, infliximab treatment was associated with symptom relief, regression of neurologic deficits and reduction in disease activity on MRI.[50] The use of infliximab requires an initial intravenous infusion (5 mg/kg ideal body weight) and is then administered periodically as the clinical course progresses.

Adalimumab is an injectable TNF-alpha antagonist that may be effective in the treatment of small fiber neuropathy.[51,52]

B Cell Targeted Therapy
Rituximab is thought to be effective in systemic sarcoidosis and possible neurosarcoidosis.[53]

For patients with refractory disease, treatment with other novel agents may be considered. In these patients, tocilizumab (interleukin 6 IL_6 receptor antagonist) and tofacitinib (a JAK inhibitor) have been used.[54,55] Tofacitinib has been favorable for treatment-resistant cutaneous sarcoidosis. Clinical improvement has also been observed with tocilizumab in treatment-resistant sarcoidosis with lung, sinus and cutaneous involvement. Since small fiber neuropathy typically does not respond to conventional immunosuppressive drug therapy, adalimumab or intravenous immune globulin (IVIG) therapies are frequently used in the treatment of small fiber sensory or autonomic neuropathy.[24,56] Cranial or spinal radiotherapy has been used for refractory disease and should be considered when patients have failed glucocorticoid therapy and at least two trials of alternative agents.[57] It is also occasionally needed for patients with acute, life-threatening disease. Immunosuppression usually persists during radiation therapy, albeit at less intense levels.

PROGNOSIS

The goal of immunosuppression in NS is to minimize the risk of neurological damage from granulomatous inflammation. In many patients, the goal is complete elimination of the neuroinflammatory response. In others, suppression of the inflammatory response, even without complete remission, is the appropriate balance of therapeutic risk. Treatment response is assessed by anamnesis, examination and neuroimaging studies.

In a patient who is clinically well and has abnormal MRI findings attributable to NS, a reasonable approach is to repeat imaging 2-4 months after initiation of treatment. The frequency of MRI monitoring can then be gradually spaced over time depending on treatment response.

When there are no abnormal findings on MRI, MRI changes of unknown etiology, or discordance between clinical symptoms and MRI findings, it may be clinically useful to repeat CSF examination to monitor disease activity and confirm remission. The clinical response may lag behind the MRI response; if there is damage from the underlying inflammatory process, the neurological impairment may not necessarily improve, but should not worsen. Although the disease may regress and some patients may discontinue treatment, there is a risk of recurrence with discontinuation.

CONCLUSION

Recent advances in the diagnosis and treatment of neurosarcoidosis suggest updated diagnostic criteria and an important role for TNF-alpha inhibitors in aggressive and/or refractory cases. Optimal treatment strategies need randomised clinical trials.

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Referee Evaluation Process
Externally peer-reviewed.

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The authors have no conflicts of interest to declare.

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All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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