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Comparison of the efficacy of dexmedetomidine and dexmedetomidine-magnesium combination in sedation management in intensive care

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MAIN POINTS

- This study has shown that magnesium can be used safely with other sedative agents for sedation.
- Although magnesium added to dexmedetomidine is not significantly different, it is clear that it provides sufficient sedation.
- It has been concluded that magnesium can be used safely in intensive care patients both in adaptation to mechanical ventilation and in the prevention of delirium.

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ABSTRACT

Aim: The aim of this study was to evaluate the correlation of sedation with subjective clinical sedation scores and compare plasma cortisol levels as an objective marker between two groups: patients sedated with dexmedetomidine alone and patients sedated with a combination of dexmedetomidine and magnesium via mechanical ventilation.

Materials and Methods: A total of 50 patients were enrolled and divided into two groups. Group 1 (dexmedetomidine group) received a loading dose 1µg/kg, followed by a continuous infusion 0.2-1.4 µg/kg/hour for 24 hours. Group 2 (dexmedetomidine+magnesium group) received a loading dose 1 µg/kg of dexmedetomidine, followed by a continuous infusion 0.2-1.4 µg/kg/hour for 24 hours, along with two bolus doses of 2 grams of magnesium and a continuous infusion of 16mg/24 hours. Sedation scale scores, Glasgow coma scores, heart rate, and plasma cortisol levels at baseline and at 24 hours were recorded throughout the 24-hour study period.

Results: On the 24th hour, cortisol levels were significantly lower in Group 2 ($p<0.05$). Heart rate was significantly lower in Group 2, except at baseline ($p<0.05$). No significant differences between the groups regarding sedation scale scores or Glasgow coma scores ($p>0.05$) were found.

Conclusion: Although adding magnesium to dexmedetomidine provided sufficient sedation and may have enhanced compliance with mechanical ventilation, no significant difference was found in achieving the target sedation levels in a clinical setting.

Keywords: Intensive care, Sedation, Dexmedetomidine, Magnesium, Cortisol
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INTRODUCTION

Intensive care units (ICU) are primarily characterized by advanced organ support systems. Mechanical ventilation support, especially in respiratory failure, is life-saving but comes with several challenges. Regardless of the cause, sedation in patients receiving treatment in ICU units constitutes a significant portion of treatment protocols [1]. Sedation in the ICU can benefit both patients and healthcare providers, as it helps reduce anxiety and agitation, improve patient outcomes, and facilitate necessary medical procedures [2].

Patients in ICU often experience severe pain and discomfort due to the nature of their illnesses or injuries, and sedation is used to alleviate these symptoms. In addition, sedation can facilitate invasive procedures such as intubation, mechanical ventilation, catheterization, tracheostomy, and surgical interventions [3].

However, while sedation can be beneficial for critically ill patients, there are potential risks associated with its use. One of the main risks is excessive sedation, which can lead to respiratory depression and other complications. Furthermore, sedation can increase the risk of delirium, a common complication associated with prolonged ICU stays. Despite the potential benefits of sedation and analgesia in ICU treatment protocols, clinicians face multiple challenges in administering effective and adequate sedation without causing overdose.

Studies comparing sedative drugs have shown that no single sedative stands out significantly above others [4]. The best results are achieved when the depth of sedation, pain, and the presence of delirium can be monitored as standard, and pain is treated quickly and precisely. the minimum effective dose for patient comfort and safety is used, and early mobilization is facilitated whenever possible [5].

Magnesium, as a sedative, analgesic, and antihypertensive agent, can be used alone or as an adjuvant to enhance the effects of other medications. In ICUs, magnesium can prevent nociception related to central sensitization by blocking the NMDA receptor's calcium ionophore, as well as reduce the consumption of other sedatives used for sedation. This can result in faster recovery, earlier extubation, and shorter mechanical ventilation durations [6].

Although the doses of sedative drugs needed to provide comfort and reduce patient anxiety in ICUs are well-determined based on scientific data, the response to sedative agents is often unpredictable, and individual metabolism rates of these agents can vary. Over time, different evaluation scales, classified as objective and subjective methods, have been introduced for clinicians. Among objective methods, the most commonly known is electroencephalography (EEG), which demonstrates the central effects of sedation. Other objective methods include plasma drug concentrations, lower esophageal contractility, bispectral index (BIS) monitoring, and frontolectomyogram. In contrast, subjective methods, which are considered easier and more practical, have gained more traction in clinical practice and include scales such as the Riker Sedation-Agitation Scale (SAS), Motor Activity Scale (MAAS), Ramsay Sedation Scale (RSS), and Richmond Agitation-Sedation Scale.

In this study, it was aimed to evaluate the correlation between dexmedetomidine and dexmedetomidine-added magnesium sedation applications in patients who had to receive primary mechanical ventilation support, using subjective clinical sedation scores. The secondary objective is to compare plasma cortisol levels as an objective finding between the two groups.

MATERIALS AND METHODS

The study was approved by the local ethics committee (Atatürk University Faculty of Medicine Clinical Research Ethics Committee, Decision no: 09) and was conducted at the Atatürk University Faculty of Medicine, Department of Anesthesia and Reanimation, Intensive Care Unit, between May 1, 2022 and May 1, 2023.

Written consent of the patients was obtained. This was a randomized and double-blind study involving a total of 50 patients aged 18-85, who required mechanical ventilation support, with sedation levels sufficient to increase compliance with mechanical ventilation but without requiring deep sedation, and that allowed for rapid awakening upon request.

Patients with cerebral ischemia during ICU admission, those requiring deep sedation, those who had previously undergone cranial surgery, those with a Glasgow Coma Scale (GCS) score of 3 at ICU admission, those with known neurological diseases, or those requiring significant opioid and muscle relaxant infusions at ICU admission, were excluded from the study. Additionally, patients with severe fluid-electrolyte imbalances or those with issues in hemodynamic stabilization and those with serious cardiovascular diseases were also excluded.

Power analysis

Since no similar studies were in the literature, a pilot study was conducted with 20 patients to calculate the sample size. The minimum sample size required for each group was calculated using the G Power 3.1.9.2 program, with a significance level (α) of 0.05, a 95% confidence interval, and a critical t value of 1.6802300. Based on this calculation, the minimum required number of patients per group was determined to be 22. The study was planned with a total of 50 patients, considering potential data losses.

Methods

All patients in the study received standard ICU monitoring, and a standard sedation protocol was applied after randomization. patients were divided into two groups.

- Group 1 (Dexmedetomidine Group): A loading dose 1 μg/kg of dexmedetomidine was given over 10 minutes, followed by a continuous infusion at a dose range 0.2-1.4 μg/kg/hour for 24 hours. As a placebo, an isotonic solution providing a double-blind randomization was infused with a 2 ml bolus over 30 minutes, followed by a 16 ml/24 hours infusion.
- Group 2 (Dexmedetomidine+Magnesium Group): After a 2 g magnesium bolus administered over 30 minutes, a 16 mg/24 hours magnesium infusion was applied in conjunction with a continuous dexmedetomidine infusion at a dose range of 0.2-1.4 μg/kg/hour for 24 hours.

The total amount of dexmedetomidine used by patients in both groups was recorded. Paracetamol was administered if the patients required analgesia, and the doses and times were recorded. Patients were monitored for 24 hours, and if any additional sedative or muscle relaxant agents were administered during this time, the patient was excluded from the study. The individuals administering the medication and the evaluators of the patients' scores were unaware of the group allocation.

The sedation levels of the patients were recorded during ICU admission using the SAS, RSS, MAAS, and concurrent GCS scores. All evaluations and patient inclusion followed a criterion to ensure that patients were normothermic.

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Additionally, during the study period, the patients' SpO_2, heart rate, and non-invasive arterial pressures (systolic, diastolic, and mean pressure) were monitored and recorded. Before the initiation and after the completion of the sedative infusion, laboratory tests were performed to measure biochemical parameters, including urea, creatinine, serum Na^+(Sodium ion), serum K^+(Potassium ion), serum AST (Aspartate Aminotransferase), and serum ALT (Alanine Aminotransferase). Analgesic use was recorded throughout the 24-hour period. Magnesium levels at ICU admission and after sedation cessation were also recorded. Blood samples for plasma cortisol levels were taken immediately before starting sedation and immediately before discontinuation of sedation.

Statistical analysis

Descriptive statistics were used to present continuous data as mean and standard deviation, while categorical data were presented as frequency and percentage. The distribution of numerical data was assessed using the skewness test. For normally distributed numerical data, the Student t-test was used comparison between two independent groups. When the data were not normally distributed, the Mann-Whitney U test was applied. Categorical variables were performed with the chi- square test. P<0.05 was considered significant. IBM SPSS version 23.0 (Armonk, NY: IBM Corp.) was used for statistical analysis.

RESULTS

The average age of the patients was calculated as 53.26 ± 13.48 (Min: 30; Max: 77). There was no significant difference in age between the groups (p>0.05). Additionally, no significant difference was observed between the groups in terms of Body Mass Index (p>0.05) (Table 1).

Of the patients, 62% (n=31) were male, 38% (n=19) were female. No significant difference in gender was found between the groups (p>0.05).

Regarding magnesium (Mg) and cortisol values at hour 0,

Table 1. Demographic characteristics and analgesia amounts of the groups

	Group I (n=25)	Group II (n=25)	P value
Age (year)	56.16±13.31	50.36±13.27	0.130
Height (cm)	167.72±9.08	169.28±9.68	0.560
Weight (kg)	76.32±6.44	74.84±6.47	0.422
BMI (kg/m^2)	27.38±3.97	26.39±4.04	0.387
Analgesia	1350.00±595.81	2062.50±590.72	0.339

All data are given as mean ± standard deviation. BMI: Body Mass Index.

Table 2. Basal and 24th hour Mg and Cortisol levels of the groups

	Group I (n=25)	Group II (n=25)	P value
Basal Mg Levels	2.31±0.46	2.00±0.76$^\alpha$	**0.002**
Basal Cortisol levels	35.33±19.59	21.43±9.89$^\alpha$	**0.007**
24th hour Mg levels	2.00±0.44	2.77±0.98$^\beta$	**<0.001**
24th hour Cortisol levels	32.72±17.80	14.77±5.45$^\alpha$	**<0.001**

All data are given as mean ± standard deviation. $^\alpha$ p < 0.05 significant decrease in favor of group 2, $^\beta$ p < 0,05 significant decrease in favor of group 1.

Table 3. Comparison of changes in heart rate between groups

	Group I (n=25)	Group II (n=25)	P value
Baseline Value	95.64±14.52	96.48±17.99	0.857
2nd hour	94.12±21.66	80.72±18.23$^\alpha$	**0.022**
4th hour	98.76±20.57	82.08±19.66$^\alpha$	**0.005**
6th hour	95.92±18.51	77.88±18.88$^\alpha$	**0.001**
8th hour	96.04±18.49	77.28±22.14$^\alpha$	**0.002**
10th hour	93.76±17.63	75.40±17.83$^\alpha$	**0.001**
12th hour	95.32±19.89	75.12±15.54$^\alpha$	**0.000**
14th hour	95.00±23.29	73.76±17.25$^\alpha$	**0.001**
16th hour	93.80±23.20	74.24±18.54$^\alpha$	**0.002**
18th hour	92.44±24.22	73.32±19.54$^\alpha$	**0.004**
20th hour	90.76±22.42	72.96±19.96$^\alpha$	**0.005**
22nd hour	89.08±20.79	75.96±18.01$^\alpha$	**0.021**
24th hour	89.60±20.02	75.52±17.81$^\alpha$	**0.012**

All data are given as mean ± standard deviation. $^\alpha$ p < 0.05 significant decrease in favor of group 2.

Table 4. Changes in Glasgow Coma Scale (GCS) according to groups.

	Group I (n=25)	Group II (n=25)	P value
Baseline Value	6.72±2.92	6.32±2.35	0.597
2nd hour	5.00±2.46	5.00±1.84	0.708
4th hour	4.88±2.35	4.72±1.74	0.902
6th hour	4.96±2.35	4.68±1.79	0.919
8th hour	4.96±2.76	4.92±1.93	0.424
10th hour	4.92±2.70	4.68±1.93	0.644
12th hour	4.96±2.42	4.56±1.75	0.855
14th hour	4.72±2.49	4.52±2.22	0.910
16th hour	4.64±2.27	4.28±1.99	0.875
18th hour	4.68±2.37	4.16±2.03	0.502
20th hour	5.12±2.72	4.16±2.01	0.324
22nd hour	5.16±2.56	4.16±2.01	0.128
24th hour	4.96±2.35	4.16±2.03	0.129

All data are given as mean ± standard deviation.

Table 5. Changes in Sedation Agitation Scale (SAS) according to groups

	Group I (n=25)	Group II (n=25)	P value
Baseline Value	2.96±1.767	2.2±1.555	0.101
2nd hour	1.68±1.03	1.56±0.768	0.877
4th hour	1.56±0.712	1.48±0.653	0.715
6th hour	1.60±0.764	1.48±0.653	0.636
8th hour	1.64±0.952	1.8±1.041	0.559
10th hour	1.64±0.952	1.60±0.816	0.921
12th hour	1.68±0.900	1.52±0.823	0.448
14th hour	1.96±1.428	1.76±1.20	0.679
16th hour	1.76±1.052	1.60±1.155	0.433
18th hour	2.00±1.472	1.56±1.158	0.243
20th hour	2.00±1.291	1.60±1.155	0.229
22nd hour	1.92±1.115	1.56±1.044	0.241
24th hour	1.76±1.20	1.60±1.08	0.729

All data are given as mean ± standard deviation.

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Table 6. Changes in Ramsey Sedation Scale (RSS) according to groups

	Group I (n=25)	Group II (n=25)	P value
Baseline Value	4.36±1.524	4.68±1.406	0.444
2nd hour	5.04±1.06	5.20±0.816	0.553
4th hour	4.96±1.020	5.20±0.913	0.385
6th hour	4.88±1.054	5.12±0.927	0.397
8th hour	4.92±1.222	5.04±0.978	0.703
10th hour	4.88±1.054	5.04±0.978	0.614
12th hour	4.80±1.190	5.12±1.054	0.319
14th hour	4.68±1.406	4.84±1.106	0.657
16th hour	4.96±1.136	4.92±1.187	0.904
18th hour	4.72±1.646	4.92±1.187	0.624
20th hour	4.80±1.155	4.84±1.143	0.903
22nd hour	4.80±1.190	5.00±1.155	0.549
24th hour	5.20±0.866	4.96±1.136	0.405

All data are given as mean ± standard deviation.

group 1 had significantly higher levels ($p<0.05$). At hour 24, the magnesium level was significantly lower in group 1, while the cortisol level at hour 24 was significantly higher in group 1 ($p<0.05$) (Table 2).

Heart rate was significantly lower in group 2 at all time points except for hour 0 ($p<0.05$) (Table 2).

Looking at the Glasgow Coma Scale (GCS) scores, no significant differences were observed between the groups at any time point ($p>0.05$) (Table 3).

When analyzing the Motor Activity Assessment Scale (MAAS) scores, group 1 had significantly higher scores at hour 0 ($p<0.05$), but no significant differences were seen at other time points ($p> 0.05$) (Table 4).

Regarding the Riker Sedation-Agitation Scale (SAS) scores, there were no statistically significant differences between groups at any time point ($p>0.05$) (Table 5).

Similarly, when evaluating the Ramsay Sedation Scale (RSS) scores, there were no statistically significant differences between groups at any time point ($p>0.05$) (Table 6).

DISCUSSION

Patients treated in intensive care units (ICUs) undergo numerous invasive procedures, such as endotracheal intubation and mechanical ventilation. Pain and discomfort are among the most frequent concerns reported by these patients during their ICU stay [7]. Agitation may lead to dangerous situations, such as the accidental removal of endotracheal tubes or intravenous catheters, which can have life-threatening consequences [3]. As a result, sedatives and analgesics are commonly used in the ICU.

In our study, at hour 24, cortisol levels in Group II (dexmedetomidine + magnesium) were significantly lower compared to Group I (dexmedetomidine only), suggesting that the addition of magnesium to dexmedetomidine sedation better suppressed sympathetic stimulation, preventing cortisol release from the adrenal cortex, and ultimately controlling the stress response more effectively. In another study comparing two groups of mechanically ventilated patients sedated with either midazolam or dexmedetomidine, no significant differences in biomarker levels (cortisol, ACTH, adrenaline, and noradrenaline) were observed after 5 days of follow-up. However, our study observed a significant difference in cortisol levels, which we believe is due to the addition of magnesium, an adjunct with direct sedative effects [8].

In a recent randomized controlled study published by Kurni et al., propofol and midazolam sedation were administered separately to 60 patients with traumatic brain injury, and serum cortisol levels were compared at the end of 48 hours. The change in cortisol levels in both groups was found to be similar and no statistical difference was observed. In our study, we think that the addition of adjuvant magnesium in addition to the sedative medication in the second group made a significant difference in the comparison of cortisol levels at the end of 24 hours [9].

When examining heart rate differences, we found decrease in heart rate of dexmedetomidine + magnesium group compared to the dexmedetomidine-only group at all time points. This bradycardia is attributed to dexmedetomidine's effect on alpha-2 adrenergic receptors. The addition of magnesium potentiated the effects of dexmedetomidine, resulting in a more pronounced decrease in heart rate. Sivriköz et al., unlike our study, did not find a statistical difference in the patient groups whom they sedated with a combination of magnesium and dexmedetomidine in terms of heart rate in the groups to which magnesium was added [10] (The preceding in order sentence should be rewritten to clarify the meaning). Again, Havrylov and colleagues found an increase in heart rates in their patients whom they sedated by adding magnesium to dexmedetomidine, unlike our study, although it was not statistically significant [11].

Regarding sedation depth, as assessed by the GCS, SAS, MAAS, and RSS scales, no significant differences were seen between the two groups. This indicates that adequate and comparable sedation depths were achieved in both groups. Altun et al., in their study, showed that, contrary to our results, the depth of sedation in the group in which magnesium was added to midazolam was less than the group in which only midazolam was used [12]. Memiş et al., in their study by adding magnesium to sufentanil, did not find any difference in sedation levels between the groups in which only sufentanil and magnesium were added to sufentanil, which is consistent with our study [13].

Limitations

The limitations of our study include the small sample size, not having an age limit even though all patients were adults, and evaluating cortisol values only as a stress factor and not studying other parameters.

CONCLUSION

In conclusion, although the combination of dexmedetomidine and magnesium achieved sufficient sedation and in-

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creased patient comfort, it did not result in statistically significant differences in sedation depth or other clinical outcomes. While magnesium has proven beneficial as an adjunct in hypertension treatment, analgesia, and muscle recovery, its role as an adjunct in sedation did not significantly impact our study.

Ethics Committee Approval: Ethical approval was obtained for this study from the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (Date: 31.03.2023, Decision no: 09).

Informed Consent: Written consent of the patients was obtained.

Peer-review: Externally peer-reviewed.

Conflict of Interest: There is no conflict of interest between the authors.

Author Contributions: Concept: FK; Design: FK; Supervision: FK; Fundings: FK; Materials: FK; Data Collection and/or Processing: ÖÖ; Analysis and/or Interpretation: ÖÖ; Literature Review: ÖÖ; Writing: FK, ÖÖ, ND, HK; Critical Review: ND, HK.

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Factors associated with complications of parathyroidectomy in the elderly: A single-center experience

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MAIN POINTS

- This study evaluates risk factors for postoperative complications in elderly patients undergoing parathyroidectomy.
- Permanent hypocalcemia was the most frequent complication, significantly associated with multiple adenomas and hyperplasia.
- Elevated preoperative ALP, PTH, and reduced free T3 levels were linked to higher complication rates.
- Histopathological subtype (hyperplasia vs. adenoma) had a significant impact on both complication and mortality rates.
- Comprehensive preoperative evaluation and individualized surgical planning are critical to improving outcomes in geriatric parathyroid surgery.

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ABSTRACT

Aim: The expanding older adult population has led to a corresponding increase in parathyroidectomy procedures among geriatric patients. Due to the prevalence of comorbidities and reduced physiological reserves, elderly patients may experience a greater incidence of postoperative complications. This study aims to evaluate the relationship between clinical parameters and complications associated with parathyroidectomy in individuals aged 65 years and above.

Materials and Methods: This is an observational study included patients aged 65 years and older who underwent parathyroid surgery at a tertiary care center between January 2009 and February 2022. Demographic, clinical, surgical, and laboratory data were analyzed. Patients were divided into two groups according to the presence or absence of postoperative complications. A subgroup analysis was conducted for patients who developed permanent hypocalcemia. Statistical comparisons were made between groups. DEXA T scores were obtained from the lumbar spine and hip regions.

Results: Elderly patients accounted for 5.9% (23/388) of all parathyroidectomy cases. The overall postoperative complication rate was 21.7%, and the rate of permanent hypocalcemia was 17.4%. Statistically significant differences were found between the patients with and without complications in terms of free T3, preoperative ALP, PTH, and postoperative calcium levels. Histopathological findings (adenoma vs. hyperplasia) and the number of excised adenomas were significantly associated with complications and permanent hypocalcemia. Mortality was significantly higher in the complication group ($p=0.017$). No cases of persistent hyperparathyroidism were observed during follow-up. A significant association was found between preoperative phosphorus levels and DEXA T-scores.

Conclusion: Parathyroidectomy in elderly patients carries a notable risk of postoperative complications. Identifying high-risk patients based on clinical and biochemical parameters may help guide preoperative planning and postoperative monitoring.

Keywords: Elderly, Parathyroidectomy, Postoperative complications

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INTRODUCTION

The increasing elderly population worldwide has led to a significant rise in the number of surgical procedures performed for geriatric patients [1]. Among these, parathyroidectomy remains a crucial intervention, particularly for primary hyperparathyroidism and other parathyroid disorders. While generally considered safe and effective, elderly patients often present with multiple comorbidities, reduced physiological reserve, and age-related metabolic changes, potentially increasing their risk of perioperative and postoperative complications.

A 2009 guideline published by the World Health Organization (WHO) identified surgical complications as a major cause of global mortality and morbidity, with a significant proportion deemed preventable [2]. Common postoperative complications in elderly patients undergoing parathyroidectomy include permanent hypocalcemia, bleeding, vocal cord paralysis, recurrent laryngeal nerve injury, airway trauma, sepsis, and mortality [3]. Studies indicate that factors such as age, sex, the presence of comorbidities, and preoperative biochemical markers may influence the risk of these complications [4, 5].

Moreover, the presence of multiple comorbidities in elderly patients has been shown to adversely affect surgical outcomes and prolong recovery times, often leading to higher complication rates [6]. While some reports suggest that age alone should not contraindicate parathyroidectomy, elderly patients remain a vulnerable population requiring careful evaluation and risk stratification [7–9]. Notably, comparative studies have demonstrated that certain complications, such as hypocalcemia and infection, may be more prevalent in elderly individuals compared to younger patients [10, 11].

This study aims to investigate the relationship between clinical parameters and complications occurring during and after parathyroidectomy in patients aged 65 and older. Furthermore, it seeks to identify relevant risk factors to enhance the safety and outcomes of parathyroid surgery in the geriatric population.

MATERIALS AND METHODS

This retrospective observational study was conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. We reviewed the medical records of patients aged 65 years and older who underwent parathyroid surgery at the Department of General Surgery, Turgut Özal Medical Center, İnönü University, between January 2009 and February 2022. Patients under 65 years old were excluded from this analysis.

The study was approved by the Health Sciences Non-Interventional Clinical Research Ethics Committee of İnönü University Faculty of Medicine (Decision No: 2022-3220) and adhered to the principles of the Declaration of Helsinki.

Study population and data collection

We recorded demographic characteristics, comorbidities, surgical indications, type of anesthesia, surgical procedures (unilateral or bilateral exploration), intraoperative frozen section results, use of neuromonitoring, and histopathological findings. Pre- and postoperative laboratory values, including calcium, phosphorus, PTH, ALP, and other relevant parameters, were also documented. DEXA T-scores were obtained from the lumbar spine and hip regions. Postoperative complications, such as bleeding, seroma, recurrent laryngeal nerve paralysis, transient and permanent hypocalcemia, reoperation, tracheal injury, and postoperative infection/sepsis, were evaluated. Patients were categorized into two groups based on the presence or absence of postoperative complications, and those who developed permanent hypocalcemia were also analyzed separately.

Sample size and sampling method

All eligible patients aged 65 years and older who underwent parathyroid surgery during the study period were included using a non-probability consecutive sampling method. A power analysis using G*Power Version 3.1.9.7, with 95% confidence and 80% power, indicated a minimum requirement of 4 patients per group to detect an effect size of 2.

Statistical analysis

Numerical data were expressed as medians with minimum and maximum values. The Mann-Whitney U test was used to compare continuous variables between groups, and Fisher's exact test was used for categorical data. Correlations between numerical variables were evaluated using Spearman's rank correlation coefficient. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM Statsitical Software Package for Social Sciences for 22 (SPSS Statistics for Windows, Version 22.0) (IBM,Armonk, NY: IBM Corp.).

RESULTS

A total of 23 patients aged 65 years and older were included in this study, representing 5.9% of the 388 patients aged 18 years and older who underwent parathyroid surgery. Among the older patient group, 3 (13.0%) were male and 20 (87.0%) were female. No perioperative complications were recorded.

Patients were categorized into those who did not develop postoperative complications (n=18, 78.3%) and those who did (n=5, 21.7%). In the complication group, four patients developed permanent hypocalcemia, and one experienced a postoperative hematoma. The median ages of the non-complication and complication groups were 67 (range: 65–79) and 68 (range: 65–75) years, respectively, with no statistically significant difference between the groups (p=0.638). Similarly, there was no significant difference in sex distribution between the groups (p=0.539).

No significant differences were observed between the two groups regarding parathyroid tissue weight, maximum diameter, or the number of excised adenomas. Preoperative and postoperative laboratory parameters, including TSH, free T4, WBC, Hgb, Hct, Plt, lymphocyte count, PLR, RDW, preoperative Ca, P, CRP, vitamin D, postoperative P, PTH, and ALP, did not differ significantly between the complication and non-complication groups.

However, statistically significant differences were found in free T3 (p=0.042), preoperative ALP (p=0.015), preoperative PTH (p=0.046), and postoperative calcium levels (p=0.012) between the two groups.

Complication rates did not differ significantly between groups based on thyroidectomy, use of intraoperative frozen section, or neuromonitorization. Similarly, comorbidities such as diabetes mellitus and hypertension did not significantly impact complication development. However, histopathological findings (adenoma vs. hyperplasia) were significantly associated with complication risk (p=0.048). Survival status also differed significantly, with four patients in the complication group dying during follow-up compared to one

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Table 1. Summary of Demographic, Clinical and Laboratory Parameters

	No Postoperative Complication		Postoperative Complication Present		
	n	Median (min.-maks.)	n	Median (min.-maks.)	p-value
Age	18	67 (65-79)	5	68 (65-75)	0.638
Weight (g)	16	1.05 (0.1-2.5)	4	1.65 (0.4-3)	0.335
Largest Diameter (cm)	18	1.9 (0.7-3)	5	2 (0.8-3)	0.914
Number of Adenomas	18	1 (1-2)	5	2 (1-4)	0.055
Hospital Stay (Days)	18	2 (1-6)	5	3 (2-5)	0.111
DEXA T Score	16	-2.55 (-4.5 - -0.2)	2	-2.65 (-3.7 - -1.6)	0.837
Asa Score	17	2 (2-4)	5	3 (2-3)	0.14
TSH	18	1.24 (0.02-6.32)	5	1.76 (0.25-3.84)	0.538
Free T4	18	1.04 (0.55-1.57)	5	1.03 (0.84-1.29)	0.587
Free T3	15	3.18 (1.88-4.91)	5	2.61 (2.48-3.04)	**0.042**
WBC	18	8.45 (4.53-15.16)	5	8 (6.95-11.2)	0.691
Hgb	18	13.5 (0-17.5)	5	13.4 (9.4-14)	0.363
Hct	18	40.5 (34.1-57.2)	5	38.8 (27.1-43.2)	0.257
Plt	18	240.5 (193-592)	5	246 (169-539)	0.857
Lymphocyte	18	2.28 (1.18-4.44)	5	1.7 (1.2-2.86)	0.199
PLR	18	111.05 (52.14-201.69)	5	184.71 (86.01-283.68)	0.199
RDW	18	14.3 (13-17.6)	5	14.5 (13.2-16.2)	0.914
Preoperative Ca	18	11.25 (10.2-12.5)	5	11 (8.4-11.9)	0.363
Preoperative P	18	2.35 (1.7-3.4)	5	2.7 (1.4-6)	0.587
Preoperative ALP	18	79.5 (56-244)	5	174 (95-925)	**0.015**
Preoperative CRP	6	0.33 (0.3-0.46)	3	0.84 (0.43-4.5)	0.095
Preoperative PTH	18	198.7 (78.4-506)	5	489 (116-2260)	**0.046**
Vitamin D	16	28.79 (3.35-48.56)	4	18.02 (8-34.78)	0.682
Peroperative PTH	9	11.8 (4.58-89.4)	4	8.25 (0.2-55.6)	0.414
Postoperative Ca	18	9.1 (8.2-10.2)	5	8.3 (6.5-9.3)	**0.012**
Postoperative P	15	3.4 (1.5-5)	5	2.5 (1.6-3.7)	0.119
Postoperative PTH	18	41.55 (3.06-121)	5	24.3 (0.7-70.2)	0.29
Postoperative ALP	14	88 (49-231)	5	157 (90-1252)	0.056

		Postoperative Complication n(%)		
		Present	Absent	p-value
Gender	Male Female	2 (11.1) 16 (88.9)	1 (20.0) 4 (80.0)	0.539
Thyroidectomy	Not Performed Performed	6 (33.3) 12 (66.7)	0 (0) 5 (100)	0.272
Intraoperative Frozen	Absent Present	6 (33.3) 12 (66.7)	2 (40) 3 (60)	1.000
Neuromonitoring	Absent Present	13 (72.2) 5 (27.8)	4 (80.0) 1 (20.0)	1.000
Histopathological Result	Adenoma Hyperplasia	16 (88.9) 2 (11.1)	2 (40) 3 (60)	**0.048**
Diabetes Mellitus	Absent Present	13 (72.2) 5 (27.8)	3 (60) 2 (40)	0.621
Hypertension	Absent Present	2 (11.1) 16 (88.9)	0 (0) 5 (100)	1.000
Survival Status	Alive Deceased	15 (83.3) 3 (16.7)	1 (20) 4 (80)	**0.017**

Abbreviations: ALP, Alkaline Phosphatase; ASA, American Society of Anesthesiologists; Ca, Calcium; CRP, C-Reactive Protein; DEXA, Dual-Energy X-ray Absorptiometry; Hct, Hematocrit; Hgb, Hemoglobin; P, Phosphorus; PLR, Platelet-to-Lymphocyte Ratio; PTH, Parathyroid Hormone; RDW, Red Cell Distribution Width; TSH, Thyroid-Stimulating Hormone; WBC, White Blood Cell.

patient in the non-complication group (due to postoperative respiratory failure) (p=0.017). These outcomes are summarized in Table 1.

Further analysis based on the development of permanent hypocalcemia revealed that four patients (17.4%) developed this complication, while 19 (82.6%) did not. The median number of excised adenomas was significantly higher in the permanent hypocalcemia group (2.5) compared to the non-hypocalcemia group (1) (p=0.021). The median length of hospital stay was also significantly longer in the hypocal-

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Table 2. Analysis Results of Factors Affecting Permanent Hypocalcemia Complication

	Permanent Hypocalcemia Absent		Permanent Hypocalcemia Present		
	n	Median (min.-maks.)	n	Median (min.-maks.)	p-value
Age	19	67 (64-79)	4	71 (64-75)	0.667
Weight (g)	17	1.1 (0.1-2.5)	3	1.3 (0.4-3)	0.689
Largest Diameter (cm)	19	2 (0.7-3)	4	1.5 (0.8-3)	0.785
Number of Adenomas	19	1 (1-2)	4	2.5 (1-4)	**0.021**
Hospital Stay (Days)	19	2 (1-6)	4	3.5 (3-5)	**0.027**
DEXA T Score	17	-2.5 (-4.5--0.2)	1	-3.7 (-3.7--3.7)	0.444
Asa Score	18	2 (2-4)	4	3 (2-3)	0.262
TSH	19	1.41 (0.02-6.32)	4	1.73 (0.25-3.84)	0.725
Free T4	19	1.04 (0.55-1.57)	4	0.94 (0.84-1.11)	0.218
Free T3	16	3.17 (1.88-4.91)	4	2.72 (2.48-3.04)	0.148
WBC	19	8.4 (4.53-15.16)	4	8.95 (6.95-11.2)	0.557
Hgb	19	13.3 (0-17.5)	4	13.4 (9.4-14)	0.785
Htc	19	40.2 (32.6-57.2)	4	40.65 (27.1-43.2)	0.667
Plt	19	240 (193-592)	4	280 (169-539)	0.557
Lymphocyte	19	2.26 (1.18-4.44)	4	1.8 (1.4-2.86)	0.557
PLR	19	112.11 (52.14-201.69)	4	152.71 (86.01-283.68)	0.409
RDW	19	14.4 (13-17.6)	4	13.95 (13.2-16.2)	0.907
Preoperative Ca	19	11.3 (10.2-12.5)	4	10.35 (8.4-11.9)	0.162
Preoperative P	19	2.3 (1.4-3.4)	4	2.8 (2.5-6)	0.138
Preoperative ALP	19	80 (56-244)	4	234 (119-925)	**0.012**
Preoperative CRP	6	0.33 (0.3-0.46)	3	0.84 (0.43-4.5)	0.095
Preoperative PTH	19	199.4 (78.4-506)	4	911 (116-2260)	0.116
Vitamin D	17	28.69 (3.35-48.56)	3	26.13 (8-34.78)	1.000
Perioperative PTH	9	11.8 (4.58-89.4)	4	8.25 (0.2-55.6)	0.414
Postoperative Ca	19	9.1 (8.2-10.2)	4	8.1 (6.5-8.3)	**0.001**
Postoperative P	16	3.35 (1.5-5)	4	2.45 (1.6-3.7)	0.211
Postoperative PTH	19	41.3 (3.06-121)	4	28.85 (0.7-70.2)	0.409
Postoperative ALP	15	90 (49-231)	4	252 (143-1252)	**0.020**

		Permanent Hypocalcemia n(%)		
		Absent	Present	p-value
Gender	Male	3 (15.8)	0 (0)	1.000
	Female	16 (84.2)	4 (100)	
Thyroidectomy	Not Performed	6 (31.6)	0 (0)	0.539
	Performed	13 (68.4)	4 (100)	
Intraoperative Frozen	Absent	6 (31.6)	2 (50)	0.589
	Present	13 (68.4)	2 (50)	
Neuromonitoring	Absent	14 (73.7)	3 (75)	1.000
	Present	5 (26.3)	1 (25)	
Histopathological Result	Adenoma	17 (89.5)	1 (25)	**0.021**
	Hyperplasia	2 (10.5)	3 (75)	
Diabetes Mellitus	Absent	14 (73.7)	2 (50)	0.557
	Present	5 (26.3)	2 (50)	
Hypertension	Absent	2 (10.5)	0 (0)	1.000
	Present	17 (89.5)	4 (100)	
Survival Status	Alive	15 (78.9)	1 (25)	0.067
	Deceased	4 (21.1)	3 (75)	

Abbreviations: ALP, Alkaline Phosphatase; ASA, American Society of Anesthesiologists; Ca, Calcium; CRP, C-Reactive Protein; DEXA, Dual-Energy X-ray Absorptiometry; Hct, Hematocrit; Hgb, Hemoglobin; P, Phosphorus; PLR, Platelet-to-Lymphocyte Ratio; PTH, Parathyroid Hormone; RDW, Red Cell Distribution Width; TSH, Thyroid-Stimulating Hormone; WBC, White Blood Cell.

cemia group (3.5 days vs. 2 days, p=0.027). Preoperative and postoperative ALP levels and postoperative calcium values were significantly higher in the permanent hypocalcemia group (p=0.012, p=0.020, and p=0.001, respectively). Histopathological diagnosis (hyperplasia vs. adenoma) significantly affected the development of permanent hypocalcemia (p=0.021). These findings are summarized in Table 2.

When comparing patients with preoperative nephrolithiasis (n=3) to those without (n=17), no statistically significant differences were found in preoperative Ca, P, ALP, CRP, or

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Table 3. Comparison of Factors Affecting the Formation of Nephrolithiasis

	No Nephrolithiasis		Nephrolithiasis		
	n	Median (min.-maks.)	n	Median (min.-maks.)	p-value
Preoperative Ca	17	11.2 (8.4-12.5)	3	11 (11-11.9)	0.921
Preoperative P	17	2.3 (1.4-6)	3	2.5 (2.1-3.4)	0.616
Preoperative ALP	17	93 (56-925)	3	80 (65-174)	0.616
Preoperative CRP	5	0.45 (0.31-0.84)	3	0,33 (0.3-0.43)	0.393
Preoperative PTH	17	259 (78.4-2260)	3	184.2 (116-245)	0.258
Perioperative PTH	9	14.6 (5-89.4)	3	4.58 (0.2-6.2)	**0.036**

Abbreviations: Ca, Calcium; P, Phosphorus; ALP, Alkaline Phosphatase; CRP, C-Reactive Protein; PTH, Parathyroid Hormone.

Table 4. Analysis Results of Parameters Affecting Dexa T Score

	Dexa T Score		
	r_s	p-value	n
Preoperative Ca	0.201	0.424	18
Preoperative P	-0.549	**0.018**	18
Preoperative ALP	-0.028	0.912	18
Preoperative CRP	-0.357	0.432	7
Preoperative PTH	-0.268	0.282	18
Peroperative PTH	0.329	0.353	10

Abbreviations: Ca, Calcium; P, Phosphorus; ALP, Alkaline Phosphatase; CRP, C-Reactive Protein; PTH, Parathyroid Hormone.

PTH levels. However, perioperative PTH levels were significantly associated with nephrolithiasis (p=0.036). These results are summarized in Table 3.

Regarding DEXA T-scores from the lumbar spine and hip, no significant correlations were found with preoperative Ca, ALP, CRP, or PTH values. However, a significant inverse correlation was observed between preoperative phosphorus levels and DEXA T-scores (p=0.018). These parameters are presented in Table 4.

DISCUSSION

This study investigates the relationship between clinical parameters and postoperative complications following parathyroidectomy in patients aged 65 years and older. As the global elderly population grows, surgical procedures among geriatric patients are becoming increasingly common, necessitating improved perioperative management. In our study, the postoperative complication rate was 21.7%, and permanent hypocalcemia occurred in 17.4% of patients. These rates are higher than those reported in many previous studies [7–9].

In the literature, complication rates vary significantly. Thomas et al. reported approximately 6.5% in elderly patients undergoing parathyroidectomy [7], while Kebebew et al. reported rates as low as 4% [8]. Our higher rate may be attributed to patient comorbidities, lower surgical volume, and inconsistent definitions of minor versus major complications in prior studies [10].

Data in Table 1 showed no significant differences in demographic factors such as age, tissue weight, and maximum diameter between the groups. However, the free T3 level was significantly lower in the complication group (p=0.042). This finding supports previous studies suggesting that low triiodothyronine levels may adversely affect postoperative recovery in elderly patients by impairing metabolic processes [11, 12].

Higher preoperative ALP and PTH levels were also significantly associated with the development of complications (p=0.015 and p=0.046, respectively). These findings are consistent with those of Nasiri et al., who demonstrated that elevated preoperative biochemical markers such as calcium, PTH, and ALP could predict postoperative calcium decline and hypocalcemia [13]. Therefore, careful biochemical assessment may serve as a useful tool for preoperative risk stratification.

The incidence of permanent hypocalcemia in our study was 17.4%. This subgroup also exhibited longer hospital stays and a higher number of adenomas compared to those without hypocalcemia (p=0.027 and p=0.021, respectively). Similar findings have been reported by Zamboni et al. and Ghemigian et al., who noted that multiple adenomas and their total weight significantly influence surgical outcomes [14, 15].

Histopathologically, patients with hyperplasia had a significantly higher risk of both general complications and permanent hypocalcemia compared to those with adenomas (p=0.048 and p=0.021, respectively). Kaya et al. also emphasized that hypocalcemia is more prevalent in patients with parathyroid hyperplasia [16]. These findings underscore the importance of distinguishing between histological subtypes for predicting surgical outcomes.

Minimally invasive parathyroidectomy techniques, including focused parathyroidectomy, intraoperative PTH monitoring, and radioguided approaches, have shown favorable outcomes in elderly patients and can significantly reduce complication rates [17–20]. Although surgical risks are generally higher in older patients, several studies advocate for parathyroidectomy over conservative management even in asymptomatic cases, citing better long-term outcomes [21, 22].

In our study, operative reports showed no recorded intraoperative complications. Some authors suggest that complications which are easily resolved may go unreported due to concerns about the perception of surgical quality [23].

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Another factor influencing complication rates is surgical volume and surgeon experience. Studies by Saunders et al. and Stavrakis et al. have demonstrated that procedures performed at high-volume centers or by experienced endocrine surgeons are associated with better outcomes [24, 25]. Our relatively high complication rate may reflect the lower surgical volume, which is typical of single-center experiences.

Regarding survival, the mortality rate was significantly higher in patients who developed complications (p=0.017). Four of the five patients in the complication group died during follow-up, while only one patient died in the non-complication group. These findings highlight the importance of rigorous postoperative monitoring and a multidisciplinary approach to care for elderly patients [26]. Optimizing post-surgical care and rehabilitation may also enhance quality of life [27, 28].

Although age alone should not contraindicate surgery, the presence of comorbidities, such as diabetes and hypertension—common in geriatric patients—requires a thorough preoperative evaluation [7, 29]. Multidimensional assessments and risk stratification tools may be particularly helpful in surgical planning.

Limitations

This study has several limitations. First, it was a single-center, retrospective analysis with a limited sample size, which may have affected the generalizability of the results. Second, this study does not include a comparison with younger patients under 65 years of age. Third, 24-hour urinary calcium data were not available for most patients, as such testing was not routinely performed in elderly individuals due to its complexity and lack of direct impact on surgical decision-making. Lastly, randomization, blinding, and sampling methods were not applicable due to the retrospective nature of the study.

CONCLUSION

This study highlights the importance of evaluating complication risks in elderly patients undergoing parathyroidectomy. Complication and mortality rates were found to be higher in this age group, particularly in the presence of multiple adenomas, elevated preoperative biochemical markers, and histopathological diagnosis of hyperplasia. Permanent hypocalcemia was one of the most significant complications, associated with longer hospital stays and poorer outcomes.

The findings emphasize the need for comprehensive preoperative evaluation, including biochemical and radiological assessments, as well as careful surgical planning to minimize risks. Early identification of high-risk patients and the use of minimally invasive techniques may contribute to improved outcomes.

As the global elderly population continues to rise, more older adults are expected to undergo parathyroid surgery. Future multicenter prospective studies with larger sample sizes and comparisons with younger cohorts are warranted to confirm these findings and enhance the quality and safety of care in this growing patient population.

Ethics Committee Approval: Ethics committee approval for the study was obtained from the Inonu University Faculty of Medicine Health Sciences Non-Interventional Clinical Research Ethics Committee, with the decision numbered 2022-3220.

Informed Consent: This retrospective study was approved by the institutional ethics committee, and the requirement for informed consent was waived.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: ZÖ, YD, BI; Design: ZÖ, YD, HGB, BI; Supervision: ZÖ, YD, HGB, BI; Fundings: ZÖ, YD, HGB, BI; Materials: ZÖ, YD, HGB, BI; Data Collection and/or Processing: ZÖ, YD, HGB; Analysis and/or Interpretation: ZÖ, YD, HGB, BI; Literature Review: ZÖ, YD, BI; Writing: ZÖ, YD; Critical Review: ZÖ, YD, BI.

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Long-term complications in kidney transplantation -- 14 years of experience

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MAIN POINTS

- Cholelithiasis is one of the most frequent gastroenterological problems in society. Post-transplant cholelithiasis was encountered in 34% of the patients in our study.
- The post-transplant CMV rate was the highest in the first year, while that of BKV was significant in the first two years. Post-transplant opportunistic fungal infections, mucor, less frequently encountered in the literature, developed in 2 patients.
- NODAT incidence, particularly after renal transplantation, was determined to be between 7 and 30%. However, during long-term renal transplantation follow-up, the incidence of NODAT was 4–25%.

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ABSTRACT

Aim: The increase in the number of kidney transplants and prolonged survival following kidney transplantation has increased the risk of posttransplant complications. The present study aims to investigate complications in kidney transplant recipients (eg, cardiac, hepatobiliary, opportunistic infections, avascular necrosis, NODAT) in our institution.

Materials and Methods: A total of 300 patients who underwent renal transplantation in our institution have been evaluated in this retrospective analysis. The sociodemographic properties of age, sex, graft type, need for pre-transplant dialysis, and KFRT etiologies were obtained from hospital records. Avascular necrosis, malignancy, heart failure, or development of coronary arterial disorder, NODAT, opportunistic infections, and hepatobiliary complications have been evaluated.

Results: The NODAT incidence in renal transplant patients was 17.5% in the case of living donor renal transplants versus 28.6% in cadaveric renal transplants ($p=0.07$). Again, 34% of the patients had hepatobiliary disorders such as cholelithiasis in the follow-ups, which was significantly higher in patients who received cadaveric transplants ($p=0.009$). Cytomegalovirus infection was observed in 50 patients, and BK virus infection in 36 patients. The rate of CMV infection was significantly higher in the first year after kidney transplantation. BK virus infections were found to be considerably higher in the first two years ($p<0.05$).

Conclusion: This study evaluated the risk factors and incidence of complications in renal transplant recipients. Our results regarding the incidence and or cholelithiasis and risk factors related to this condition are novel. We also emphasized the importance of hepatobiliary complications in this patient group.

Keywords: Renal transplant, Cholelithiasis, Opportunistic infection, New-onset diabetes after transplantation

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INTRODUCTION

Renal transplantation is the gold standard treatment option for chronic renal failure. Kidney failure replacement therapy (KFRT) has found worldwide acceptance since 1954 [1, 2]. In time, the public awareness of the topic increased, and the donor acceptance criteria were extended [3]. Currently, immunosuppressive treatments have been considered [4]. These developments caused a gradual increase in the number of renal transplants [2, 5]. Chronic rejection represents the most significant factor contributing to long-term graft function loss [6, 7]. However, rejection rates vary from center to center. The best strategy to diagnose and treat complications such as rejections is to form a follow-up strategy [5].

Previous studies on complications of transplantation showed that avascular necrosis, malignancy, cardiac pathologies, diabetes (NODAT – new-onset diabetes after transplantation), and opportunistic infections were the most common ones following renal transplants [8 – 11]. Hepatobiliary complications are uncommon following renal transplantation. Notably, Turkey experienced one of the highest increases in annual renal transplant numbers worldwide from 2003 to 2013, ranking among the top 10 countries [12]. The increase in the annual number of renal transplantations and the prolonged graft and patient survival following renal transplants resulted in a higher incidence of complications that are observed.

The present study aims to investigate the incidence and risk factors related to complications following renal transplantation, including cardiac, hepatobiliary, opportunistic infections, avascular necrosis, NODAT in our institution.

MATERIALS AND METHODS

Study design

A total of 300 patients who underwent renal transplantation in Nephrology Clinics of Turgut Özal Medical Medical Center were analyzed retrospectively for the present study. In total, 632 patients were admitted to Turgut Özal Medical Centre Nephrology outpatient clinic for evaluation. Nonprobability selection was used for patient allocation to the study. Those who did not meet the inclusion criteria were excluded from the study. Patients ≥18 years of age who received renal transplants and who were followed for at least three months with functional grafts between January 2007 and January 2021 were included in the analysis. Pregnant patients, patients aged <18 years, and patients who were followed up for less than 3 months were excluded from the study. In addition, patients who had insufficient data were also excluded from our study.

A total of 300 patients were enrolled in this study. All procedures were conducted in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), aligning with the Helsinki Declaration of 1975, as revised in 2008. The study received approval from the institutional review board for ethical and scientific conduct (Date: May 4, 2021; Approval No: 2021/2055).

Study parameters

Sociodemographic and clinical data, including age, sex, graft type, pre-transplant dialysis status, and kidney failure with renal replacement therapy (KFRT) etiologies, were obtained from hospital records. The study evaluated the incidence of avascular necrosis, malignancy, cardiac deficiency, coronary artery disorder, new-onset diabetes after transplant (NODAT), opportunistic infections, and hepatobiliary complications.

The primary outcome was the frequency of hepatobiliary complications. Secondary outcomes included rates of opportunistic infections, cardiac complications, diabetes, avascular necrosis, and malignancies.

Statistical analysis

All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) for Windows 26.0 (SPSS Inc., Chicago, IL, USA). Number (n) and percentage (%) were given for descriptive data. Mean, median, standard deviation, and min-max values were given for continuous variables. Statistical tests and assumptions for hypothesis testing are the Pearson Chi-Square Test and the Fisher Exact test for categorical data. The distribution between the functional graft and KFRT periods was evaluated using the Kolmogorov–Smirnov test. Any p-value less than 0.05 was considered as statistically significant.

RESULTS

All renal transplant patients included in this study were evaluated for complications. The NODAT incidence was 17.5% after living donor renal transplants, whereas it was 28.6% following cadaveric transplants (p=0.07) (Table 1). Thirty-four percent of the patients had biliary or liver disorders such as cholelithiasis.

The incidence of hepatobiliary complications was significantly higher in the transplants from cadavers type (p=0.009) (Table 1). The ages of patients who developed cholelithiasis were assessed. Remarkably, the association between the age at the time of transplantation and cholelithiasis development was observed. Younger patients developed cholelithiasis more frequently; however, this difference was not statistically significant (p=0.034) (Table 2).

The incidence of cardiovascular disease was reported to be high in the post-transplant surveys [10]. In our study, we determined the incidence of cardiovascular disease in our cohort to be 7.3%. The incidence of cardiovascular diseases in living and deceased donor transplants was 7.5% and 6.1% in the cadaveric transplants (p=0.50) (Table 1).

The incidence of avascular necrosis in our patient cohort was 7.2%, and there was no significant difference according to the graft type (p=0.54) (Table 1).

Our long-term follow-up showed that hematologic and solid organ malignancies developed in 4% of our patients who received living donor renal transplants. No significant difference was observed according to the graft type (p=0.65) (Table 1).

Cytomegalovirus (CMV) infection was the most common opportunistic infection, affecting 50 patients. BK virus was the second most common cause of opportunistic infection in 36 patients. We found that CMV infection was significantly more prevalent in the first year after renal transplantation, while BK virus infection was considerably more common in the first two years (p=0.001) (Table 3). In addition, two patients developed Mucor mycosis, an opportunistic fungal infection sometimes seen after transplantation.

Our surveys after renal transplants showed that urological disorders, such as ureteral obstruction or pyelonephritis, occurred in 38.2% of patients. Interestingly, there was no statistically significant difference in these urological problems based on the type of graft received (p=0.57) (Table 2).

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Table 1. Comparison of non-urological complications developing after transplantation in kidney transplant patients by graft type.

	Total N(%)	Alive Donor* N(%)	Cadaver N(%)	p
Diabetes				
Yes	51(19.5)	37(17.5)	14(28.6)	0.07***
No	210(80.5	175 (82.5)	35(71.4)	
Malignity				
Yes	11(4.2)	9(4.3)	2(4.1)	0.65**
No	249(95.8)	202 (95.7)	47(95.9)	
Cholelithiasis				
Yes	34(13.2)	22(10.5)	12(24.5)	0.009**
No	224(86.8)	187(89.5)	37(75.5)	
Avascular Necrosis				
Yes	18(7.2)	16(7.5)	2(4.1)	0.54**
No	243(92.8)	196(92.5)	47(95.9)	
Coronary Artery / Cardiac Disorder				
Yes	19(7.3)	16(7.5)	3(6.1)	0.50**
No	242(92.7)	196(92.5)	46(93.9)	

*Related and non-related **Fisher Exact Test ***Pearson Chi Square*

Table 2. The relation between cholelithiasis development and transplantation age in the patients receiving renal transplants.

	Patients With Developing Cholelithiasis N	%	p
Sex			
Female	14	14.9	0.598*
Male	21	12.6	
Age Group			
18-30	15	18.5	0.175*
31-44	8	9.9	
>45	8	10.7	
Graft			
Cadever	12	24.5	0.027*
Alive non relative	21	11.0	
Alive relative	1	5.6	
Survey Period			
0-1 year	1	3.7	0.005**
0-2 years	2	5.7	
0-3 years	6	25.0	
0-5years	4	8.7	
5-10years	16	26.2	
10-20years	6	11.8	
HbsAg			
Negative	28	11.4	0.003**
Positive	7	41.2	

*Fisher Exact Test **Pearson Chi Square*

DISCUSSION

Renal transplantation commenced globally in 1954 [1]. Following transplantation, acute rejection Renal transplantation commenced globally in 1954 [1]. Following transplantation, acute rejections posed a considerable challenge; however, advancements in immunosuppressive agents significantly elevated first-year patient survival rates [8]. Concomitant with improved survival, the adverse effects of these new immunosuppressants became more frequently observed, with patient mortality often attributable to malignancy, cardiac pathologies, and opportunistic infections [13]. Despite numerous publications in the existing literature addressing various post-transplant complications, there is a notable paucity of data concerning the development, incidence, or risk factors associated with cholelithiasis.s caused a considerable challenge; however, advancements in immunosuppressive agents significantly elevated first-year patient survival rates [8]. The prolonged survival of the patients resulted in observation of adverse effects of these new immunosuppressants, with patient mortality often attributable to de novo malignancies in the post-transplant period, cardiac pathologies, and opportunistic infections [13]. Despite numerous publications in the existing literature addressing various post-transplant complications, there is a notable paucity of data concerning the development, incidence, or risk factors associated with cholelithiasis.

Cholelithiasis represents a prevalent gastroenterological issue within the general population, with an estimated incidence between 10% and 15%. Prophylactic cholecystectomy is a consideration for patients with solid organ transplants, thalassemia, or diabetes [14]. Despite its frequency, research specifically addressing the development of post-transplant cholelithiasis is notably absent from published literature. Furthermore, studies on cholelithiasis, particularly prior to renal transplantation, are quite limited, with one report indicating an incidence of 18.69% [15]. Within our cohort, post-transplant cholelithiasis occurred in 34% of patients. Of

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Table 3. Comparison of several variables with regard to survey period in the renal transplant patients.

	CMV				BK				Posttransplant urological complication status			
Survey Period	Yes		No		Yes		No		Yes		No	
	N	%	N	%	N	%	N	%	N	%	N	%
0-1 year	14	56.0	11	44	5	20.0	20	80.0	12	44.4	15	55.6
0-2 years	11	31.4	24	68.6	11	31.4	24	68.6	14	40.0	21	60.0
0-3 years	7	29.2	17	70.8	3	12.5	21	87.5	8	33.3	16	66.7
0-5years	8	18.2	36	81.8	5	11.4	39	88.6	17	37.0	29	63.0
5-10years	4	6.6	57	93.4	7	11.5	54	88.5	23	37.7	38	62.3
10-20years	5	9.8	46	90.2	4	7.8	47	92.2	17	32.7	35	67.3
Irregular follow-up	1	5.9	16	94.1	1	14.0	16	86.0	11	50.0	11	50.0
Total N(%)**	**257 (100)**				**257 (100)**				**267 (100)**			
p	**0.001***				**0.08***				**0.84***			

**Pearson Chi-Square Test, CMV: Sitomegalo Virus, BK:Human Poliomma Virus.*

these, 40% were female, and 20% had co-morbid diabetes. Although not statistically significant, a trend towards higher transplantation age was observed in younger individuals. Further investigations are warranted to elucidate the mechanisms contributing to these hepatobiliary disorders, with potential factors including diabetes, gallbladder dysmotility, or ciclosporin.

NODAT represents a frequent and significant complication following renal transplantation, associated with increased morbidity and mortality [16]. The reported first-year incidence of NODAT post-transplant ranges from 7% to 30% [11], whereas long-term renal transplantation follow-up studies indicate an incidence between 4% and 25% [17]. In our investigation, which included follow-up periods of up to 20 years, the NODAT development rate was 17.5% in living donor recipients and 28.6% in deceased donor recipients, consistent with existing literature. Established risk factors for NODAT encompass male sex, advanced age, deceased donor renal transplant, a history of acute rejection, polycystic kidney disease, the use of certain immunosuppressive agents, hepatitis C, and cytomegalovirus (CMV) infection [18]. Similarly, in our study, NODAT was encountered more frequently among individuals with polycystic kidney disease or a history of acute rejection. Conversely, no significant difference in NODAT development was observed according to gender. After a kidney transplant, heart-related problems are the top cause of death [10]. Interestingly, if heart issues are controlled when a patient is on renal replacement treatment for kidney failure, their survival improves [19]. Studies have shown that about 15% of transplant patients develop coronary artery disease and heart failure, with new cases appearing at a rate of 7% over four years [19, 20]. Our study's findings are right in line with this, showing a 7.3% rate of these heart conditions. Another concern is avascular necrosis, a bone complication after transplant, largely caused by corticosteroids. Before today's advanced immunosuppressants, this problem affected as many as a third of patients. Now, thanks to current treatments, that number has dropped significantly to just 4–7% [9, 21].

Considering risk factors for avascular necrosis in both the general population and renal transplant recipients, alcohol consumption, steroid use, dyslipidemia, and secondary hyperparathyroidism are significant contributors. Specifically, corticosteroids used in post-transplant immunosuppressive treatment and those administered for acute rejection are known risk factors for necrosis development [9, 21]. In our hospital, we use anti-thymocyte globulin (ATG) for induction therapy, followed by a maintenance regimen of oral prednisone, mycophenolate mofetil, and tacrolimus. Our data shows that avascular necrosis developed in 7.2% of patients, with a higher incidence observed in recipients of living donor transplants. Although not statistically significant, 15.8% of patients in the necrosis group experienced rejection after transplantation.

Opportunistic infections are also crucial for patient survival after transplantation. Both CMV (Cytomegalovirus) and BK viruses can replicate in kidney tissue, potentially leading to acute allograft rejection [22]. While the incidence of post-transplant CMV infection ranges from 8% to 32%, BK virus rates are reported between 1% and 10% [23, 24]. In our study, post-transplant CMV infection was most frequent in the first year, whereas BK virus infection was particularly significant within the first two years. Mucor mycosis, an opportunistic fungal infection less commonly reported in literature, developed in two of our patients.

Our study evaluates complications and their risk factors in renal transplantation patients during long-term follow-up. We reviewed various complications that may arise post-transplant. Notably, data on hepatobiliary complications in the literature are very limited, making our study unique in its detailed analysis of cholelithiasis. Furthermore, we assessed NODAT and opportunistic infections, examining their associated risk factors. This study thus provides valuable regional data on these aspects.

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CONCLUSION

Comprehensive studies on long-term renal transplant complications in Turkey are scarce. Our study addresses this gap by detailing complication rates and comprehensively compiling their risk factors. It is particularly original in providing data on post-transplant cholelithiasis development and incidence, in addition to highlighting other hepatobiliary complications.

Abbreviations

ATG : Antithymoctye globulin

BKV : Human polyomavirus 1

CMV : Cytomegalovirus

KFRT : Kidney failure replacement therapy

NODAT : New onset diabetes after transplantation

RRT : Renal replacement treatment

SPSS : Statistical Package for the Social Sciences

Ethics Committee Approval: This study was conducted in accordance with the ethical standards of our local and national committees on human experimentation and the 2008 revision of the Helsinki Declaration of 1975. Ethics committee approval was secured from our institution prior to commencing the research (Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee, Date: May 4, 2021; Approval No: 2021/2055).

Informed Consent: Given the retrospective nature of the study, informed consent was not required from individual participants.

Peer-review: Externally peer-reviewed.

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Impact of COVID-19-related prolonged catheterization on bipolar TURP outcomes

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MAIN POINTS

- The COVID-19 pandemic led to prolonged catheterization in BPH patients awaiting B-TURP due to surgical delays.
- Prolonged catheterization was found to be an independent risk factor for impaired long-term voiding function after B-TURP.
- Despite similar total IPSS scores, catheterized patients showed increased voiding symptoms and higher IPSS voiding/storage ratios postoperatively.
- Structured catheter care protocols may reduce infection risk but do not mitigate functional deterioration caused by extended catheter use.

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ABSTRACT

Aim: To evaluate the early and long-term clinical outcomes of bipolar transurethral resection of the prostate (B-TURP) surgery in patients with prolonged preoperative urethral catheterization due to their operations being postponed during the COVID-19 pandemic.

Materials and Methods: Patients with benign prostatic hyperplasia (BPH) whose B-TURP procedures were delayed due to the COVID-19 pandemic were analyzed. The patients were divided into two groups: Patients awaiting surgery without a catheter were defined as Group A, while those who developed acute urinary retention (AUR) and were catheterized were defined as Group B. Preoperative and postoperative International Prostate Symptom Score (IPSS) values, IPSS subscores (voiding and storage), early and long-term clinical outcomes, and complications were compared.

Results: Group A included 53 patients who were operated on without a catheter, and Group B included 68 patients who waited for surgery with a catheter in place for an average of 89.6 days. No statistically significant differences were found between Group A and Group B in terms of age, body mass index, IPSS, American Society of Anesthesiologists score, length of hospital stay, or total follow-up duration (p>0.05). However, Group B had significantly higher prostate-specific antigen levels, prostate volume, operative time, specimen weight, and perioperative catheterization time compared to Group A (p<0.01). While total IPSS scores were similar between the groups, Group B exhibited significantly higher IPSS voiding scores, but significantly lower IPSS storage scores compared to Group A (p<0.001). When assessing the IPSS voiding-to-storage (V/S) ratio, both the 12-month and long-term values were significantly higher in Group B than in Group A (p<0.001).

Conclusion: Postponing the elective surgeries and the necessity of prolonged catheterization during the COVID-19 pandemic resulted in functional voiding impairments following B-TURP in patients who developed AUR due to BPH.

Keywords: Benign prostatic hyperplasia, Bipolar transurethral resection of the prostate, COVID-19, Lower urinary tract symptoms, Voiding symptoms, Storage symptoms

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a histological diagnosis characterized by the overgrowth of epithelial and stromal cells located in the transition zone of the prostate gland. BPH is the most common cause of benign prostatic enlargement, benign prostatic obstruction, and bladder outlet obstruction in older men [1]. The global outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China, in late 2019. It was shortly thereafter declared a pandemic by the World Health Organization. Following the spread of the epidemic, national and international urology societies, as well as health authorities in various countries, issued recommendations to guide the prioritization of clinical and surgical activities during the pandemic. They advised deferring elective surgeries for BPH or BPH-related complications during the COVID-19 pandemic to reduce overcrowding in healthcare systems and minimize the risk of in-hospital cross-infection [2]. Postponing these procedures during the COVID-19 pandemic led to challenges such as a high disease prevalence in the community, a backlog of elective surgeries, significant treatment delays, and a marked decline in the quality of life (QoL) for patients [3,4].

Patients who developed acute urinary retention (AUR) due to acute obstruction from BPH were required to remain catheterized for prolonged periods as a result of the pandemic [5]. Overcrowding in the healthcare system during the COVID-19 crisis further delayed surgeries, resulting in extended waiting periods for catheterized patients before surgical intervention [6,7].

In this study, we evaluated the clinical outcomes, complications, and functional results of bipolar transurethral resection of the prostate (B-TURP) in patients with BPH whose surgeries were delayed due to the COVID-19 pandemic. Our objective was to assess the surgical outcomes in patients subjected to prolonged catheterization and to determine whether extended catheter use affects postoperative voiding function and contributes to early or long-term complications.

MATERIALS AND METHODS

The clinical trials at Adıyaman University were approved by the local ethics committee (decision number 2022/1-7, dated January 18, 2022) and sanctioned by the Turkish Ministry of Health.

Medical records of patients indicated for benign prostatic hyperplasia (BPH) surgery, but whose procedures were postponed due to the COVID-19 pandemic, were retrospectively reviewed from March 2020 to December 2021. Exclusion criteria included prostate cancer, prior prostate or urethral surgery, and a diagnosis of neurogenic bladder disorder preceding the acute urinary retention (AUR) episode. Our BPH management algorithm during the pandemic was established in accordance with directives from the Turkish Ministry of Health and hospital administration. An overview of this algorithm is provided in Figure 1.

Catheter-free patients with an International Prostate Symptom Score (IPSS) of >24, who did not benefit from medical treatment and were indicated for B-TURP, were categorized into Group A. Group B included patients who experienced AUR, underwent catheterization, and were subsequently offered a B-TURP following a failed catheter-free trial. Preoperative prophylactic measures for catheterized patients awaiting surgery included catheter care training, regular intermittent catheter replacement, and the use of a silicone catheter along with methenamine hippurate for a recommended duration of 10 days. All patients underwent preoperative reverse transcription-polymerase chain reaction (PCR) testing via oropharyngeal and nasopharyngeal swabs. Surgeries for PCR-positive patients were postponed. Patients with positive urine cultures received appropriate antibiotic therapy for seven days, followed by repeat urine cultures.

All patients were administered prophylactic antibiotic therapy with ceftriaxone 1g during anesthesia. All surgeries were performed using a bipolar plasma kinetic system and a 26-Fr continuous flow resectoscope. We used the Gyrus plasma kinetic unit for the procedures, setting the cutting power at 120 W and coagulation power at 80 W. Saline solution was employed for bladder irrigation throughout. Each operation concluded with the placement of a 22-Fr Couvelaire catheter. Operative time was defined as the duration from insertion of the resectoscope to placement of the catheter. Continuous bladder irrigation was started with saline, and catheter removal was based on hematuria status. Patients who voided successfully twice after catheter removal were discharged the same day. Patients unable to void were recatheterized and discharged with instructions to attempt decatheterization one week later.

The following parameters were evaluated for both groups: age, body mass index (BMI), IPSS, American Society of Anesthesiologists (ASA) score, prostate volume, prostate-specific antigen (PSA), perioperative COVID-19 infection, operative time, hospital stay, resection rate (calculated as weight of resected specimen/prostate volume on urinary system ultrasound), presence of urinary system tract infection, hematuria and clot formation, catheterization time, need for recatheterization after postoperative catheter removal, and early postoperative secondary surgery rates, as well as IPSS voiding score/storage (V/S) ratio, maximum flow rate (Qmax), post-void residual (PVR), QoL index, urethral stricture, urinary incontinence, bladder neck contracture, and reoperation requirements at 12-month and long-term follow-ups.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 25 (IBM Corporation, Armonk, NY, US). The normality of the distribution of continuous variables was examined using the Kolmogorov-Smirnov test, and homogeneity of variances was tested with the Levene test. Descriptive statistics for categorical variables were expressed as frequency (n) and percentage (%), while continuous variables were presented as mean ± standard deviation, median (minimum–maximum), or median (25^{th}–75^{th}) percentile values, as appropriate. Based on the results of normality testing, Student's t-test was used to compare continuous variables that met parametric test assumptions. For those that did not meet these assumptions, the Mann-Whitney U test was employed. Categorical data were analyzed using the Fisher-Freeman-Halton test unless otherwise stated. In all 2x2 contingency tables, the continuity-corrected $\chi 2$ test was used when one or more cells had expected frequencies of 5 to 25. When one or more of the cells had expected frequencies of 5 or less, Fisher's exact test was applied. At the 12-month follow-up and in the long term, factors distinguishing patients with an IPSS V/S ratio of ≤ 1 from those with a ratio of >1 were examined using multivariate logistic regression analysis. Odds ratios (ORs) and

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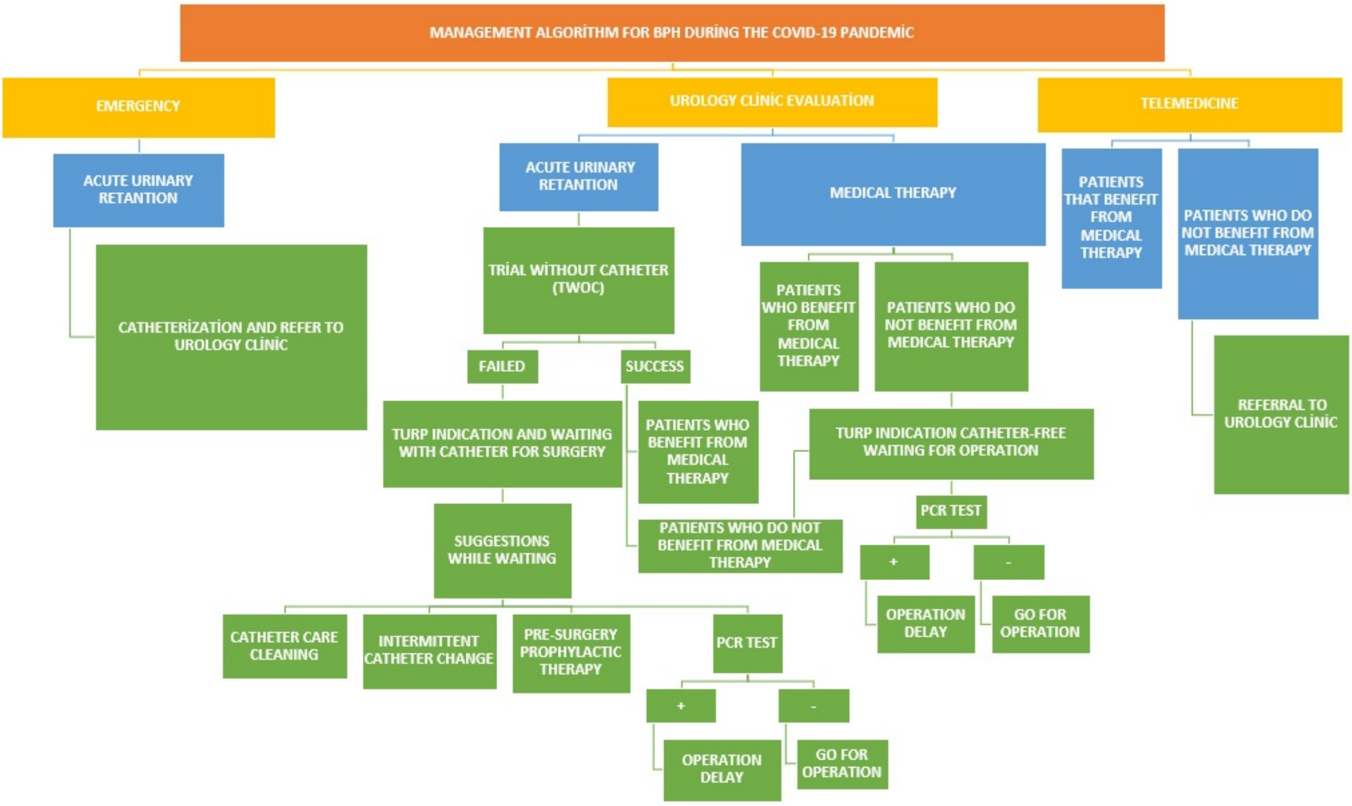

Figure 1. Benign prostatic hyperplasia algorithm used during the COVID-19 pandemic.

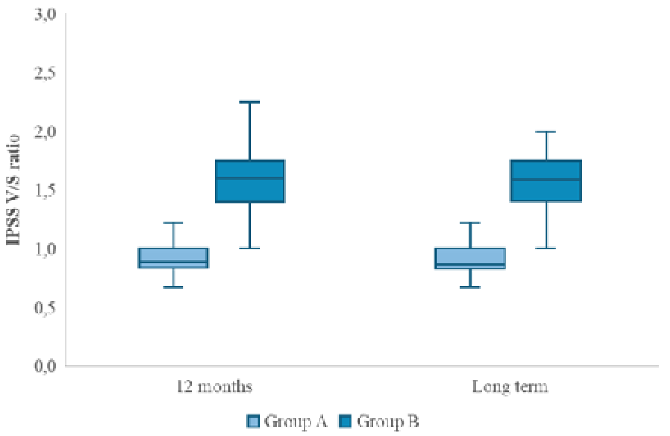

Figure 2. Box-plot graph of the International Prostate Symptom Score voiding/storage (IPSS V/S) ratio in Group A and Group B at 12-month and long-term follow-ups. The lines in the center of each box represent the median IPSS values, while the lower and upper edges of the boxes correspond to the 25th and 75th percentile values, respectively. The vertical lines extending from the edges of the boxes represent the minimum and maximum values, respectively.

95% confidence intervals (CIs) were calculated for each independent variable. A p-value of less than 0.05 was considered statistically significant.

RESULTS

During the pandemic, B-TURP was performed on a total of 162 patients, of whom 42 were excluded based on the exclusion criteria and 121 were included in the final analysis. No statistically significant differences were found between Group A and Group B in terms of age, BMI, IPSS, ASA classification, length of hospital stay, or total follow-up duration ($p > 0.05$). However, Group B had significantly higher PSA levels, prostate volume, operative time, specimen weight, and perioperative catheterization time compared to Group A ($p<0.01$). Additionally, the resection ratio was significantly lower in Group A ($p < 0.001$) (Table 1).

The comparison of perioperative complications between the two groups is shown in Table 2. Accordingly, only the rate of immediate AUR recatheterization statistically significantly differed between the groups ($p = 0.035$). The incidence of all other complications was similar in both groups.

Table 3 presents the comparisons of 12-month and long-term outcomes. While total IPSS scores were similar between the groups, Group B exhibited significantly higher IPSS voiding scores but significantly lower IPSS storage scores compared to Group A ($p<0.001$). Furthermore, when assessing the IPSS V/S ratio, both the 12-month and long-term values were significantly higher in Group B than in Group A ($p<0.001$) (Figure 2). The frequency of having an IPSS V/S ratio greater than 1 was also significantly higher in Group B at both 12 months and in the long term ($p<0.001$). Although Qmax levels were similar between the groups ($p>0.05$), Group B showed significantly higher PVR values ($p = 0.021$). No statistically significant difference was observed between the groups regarding

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Table 1. Baseline characteristics.

	Group A (n = 53)	Group B (n = 68)	p
Age (years)*	70.4 ± 9.3	73.6 ± 9.0	0.066[a]
BMI (kg/m^2)**	28.0 (25.5--32.0)	28.0 (26.0--33.0)	0.607[b]
Perioperative catheterization time (day)***	--	88.0 (40--136)	--
IPSS	25.8 ± 1.62	26.3 ± 1.78	0.134[a]
PSA	1.90 (0.98--3.57)	3.97 (1.89--7.54)	**<0.001[b]**
ASA classification			0.329[c]
1	18 (34.0%)	20 (29.4%)	
2	20 (37.7%)	18 (26.5%)	
3	14 (26.4%)	27 (39.7%)	
4	1 (1.9%)	3 (4.4%)	
Prostate volume (cm^3)**	50.0 (40.0--58.5)	95.0 (75.0--119.2)	**<0.001[b]**
Operation time (min)***	50.0 (30.0--150.0)	55.0 (40--160)	**0.004[b]**
Specimen weight (cm^3)**	26.0 (20.0--31.5)	40.0 (35.0--50.7)	**<0.001[b]**
Resection rate**	0.54 (0.46--0.62)	0.42 (0.37--0.51)	**<0.001[b]**
Perioperative catheterization time (day)***	2.0 (2.0--3.0)	3.0 (2.0--5.0)	**<0.001[b]**
Length of hospital stay (day)***	4.0 (1.0--12.0)	4.0 (2.0--16.0)	0.122[b]
Follow-up time (month)***	16.0 (12.0--24.0)	17.0 (12.0--25.0)	0.339[b]

Descriptive statistics for continuous variables are shown as *mean ± standard deviation, **median (25th–75th) percentiles, or ***median (minimum–maximum), where appropriate. [a]Student's t-test, [b]Mann-Whitney U test, [c]Fisher-Freeman-Halton test. Group A: patients awaiting surgery without a catheter, Group B: patients with prolonged catheterization, BMI: body mass index, IPSS: international prostate symptom score, PSA: prostate-specific antigen, ASA: American Society of Anesthesiologists.

Table 2. Perioperative complications.

	Group A (n = 53)	Group B (n = 68)	p
Perioperative COVID-19 infection	4 (7.5%)	3 (4.4%)	0.698[a]
Death from COVID-19	1 (1.9%)	1 (1.5%)	>0.999[a]
Urinary tract infection	21 (40.4%)	27 (40.3%)	>0.999[b]
Hematuria	10 (19.2%)	12 (17.9%)	>0.999[b]
Clot retention	9 (17.3%)	12 (17.9%)	>0.999[b]
Immediate AUR/recatheterization	-	6 (9.0%)	**0.035[a]**
Immediate reoperation rate	-	3 (4.5%)	0.256[a]

[a]Fisher's exact test, [b]Continuity-corrected χ^2 test. Group A: patients awaiting surgery without a catheter, Group B: patients with prolonged catheterization.

QoL scores (p>0.05).

The number of complications at the 12th postoperative month and during long-term follow-up was similar between the groups (Table 4).

Finally, Table 5 reports both univariate and multivariate analyses comparing patients with an IPSS V/S ratio of 1 or below to those with a ratio above 1 at 12 months and in the long term.

At the 12-month evaluation, although mean age did not differ significantly between the two groups (p = 0.101), patients with an IPSS V/S ratio above 1 had significantly more frequent perioperative catheterizations, longer operative times, and a lower resection ratio (p<0.001, p = 0.009, and p<0.001, respectively). Multivariate logistic regression analysis demonstrated that perioperative catheterization was an independent risk factor for predicting an IPSS V/S ratio above 1. After adjusting for all potential confounding factors, perioperative catheterization significantly increased the likelihood of having an IPSS V/S ratio exceeding 1 (OR = 97.135, 95% CI: 22.713–415.416, p<0.001).

Our long-term findings showed that although mean age did not differ significantly between the two groups (p = 0.140), patients with an IPSS V/S ratio above 1 continued to exhibit significantly higher rate of perioperative catheterizations, longer operative times, and a lower resection ratio (p<0.001, p = 0.002, and p<0.001, respectively). Multivariate logistic regression analysis again demonstrated that perioperative catheterization was an independent risk factor for predicting an IPSS V/S ratio above 1. After adjusting for all potential confounding factors, perioperative catheterization significantly increased the likelihood of an IPSS V/S ratio exceeding 1 (OR = 77.048, 95% CI: 19.305–307.514, p<0.001).

DISCUSSION

While it was initially believed that SARS-CoV-2 primarily targeted the lungs in the early stages of the pandemic, the overwhelming burden it placed on the healthcare system had long-term negative effects on patients and various medical conditions [7,8]. Due to the heightened health burden and the feared risk of cross-infection during the COVID-19 pandemic, significant changes occurred in urology practice. Hos-

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Table 3. Results of 12-month and long-term follow-up visits.

	Group A (n = 53)	Group B (n = 68)	p
IPSS			
12 months	12.0 (11.0--13.0)	11.0 (10.0--13.0)	0.380[a]
Long term	12.0 (10.0--13.0)	11.0 (10.0--13.0)	0.684[a]
IPSS voiding score			
12 months	6.0 (5.0--6.0)	7.0 (6.0--8.0)	**<0.001[a]**
Long term	6.0 (5.0--6.0)	7.0 (6.0--8.0)	**<0.001[a]**
IPSS storage score			
12 months	6.0 (6.0--7.0)	4.0 (4.0--5.0)	**<0.001[a]**
Long term	6.0 (5.3--7.0)	4.0 (4.0--5.0)	**<0.001[a]**
IPSS V/S			
12 months	0.88 (0.84--1.00)	1.60 (1.40--1.75)	**<0.001[a]**
Long term	0.87 (0.83--1.00)	1.59 (1.41--1.75)	**<0.001[a]**
IPSS voiding/storage > 1.0			
12 months	7 (13.5%)	63 (94.0%)	**<0.001[b]**
Long term	7 (13.5%)	62 (92.5%)	**<0.001[b]**
Q_{max}			
12 months	15.0 (12.0--16.8)	15.0 (13.0--16.0)	0.623[a]
Long term	15.0 (12.0--16.8)	14.0 (13.0--16.0)	0.535[a]
PVR			
12 months	50.0 (35.0--65.0)	56.0 (45.0--70.0)	**0.021[a]**
Long term	50.0 (35.0--65.0)	56.0 (45.0--70.0)	**0.021[a]**
QoL index			
12 months	1.0 (0.0--1.0)	1.0 (0.0--1.0)	0.938[a]
Long term	1.0 (0.0--1.0)	1.0 (0.0--2.0)	0.866[a]

Descriptive statistics are shown as median (25^{th}–75^{th}) percentiles. [a]Mann-Whitney U test, [b]Continuity-corrected χ^2 test. Group A: patients awaiting surgery without a catheter, Group B: patients with prolonged catheterization. IPSS: international prostate symptom score, Q_{max}: maximum flow rate, PVR: post-void residual, QoL: quality of life

Table 4. Complications at 12-month and long-term follow-up visits.

Parameter	Group A, n (%)	Group B, n (%)
Urethral strictures		
12 months	2 (3.8)	3 (4.4)
Long term	2 (3.8)	1 (1.4)
Incontinence		
12 months	1 (1.9)	2 (2.9)
Long term	1 (1.9)	2 (2.9)
Reoperation		
12 months	2 (3.8)	3 (4.4)
Long term	3 (5.7)	2 (2.9)
Bladder neck contracture		
12 months	0	0
Long term	2 (3.8)	0

Group A: patients awaiting surgery without a catheter, Group B: patients with prolonged catheterization.

pitals were compelled to implement extensive measures to address a potential increase in COVID-19 cases [9]. Despite patients' requests to postpone elective surgeries due to the fear of contracting COVID-19 during their hospital stay, individuals experienced a consistent and progressive deterioration not only in their QoL but also in the progression of their underlying diseases, as elective medical and surgical treatments became unattainable [10].

During the COVID-19 pandemic, many patients with urinary symptoms sought telemedicine consultations. While these virtual appointments provided a non-contact solution for medical consultation and continuity of care, they did not resolve the issue of postponed surgical interventions [4,11,12]. Various triage systems were implemented to manage the challenges posed by the COVID-19 pandemic in urology services [13,14]. Recommendations were made to defer elective surgeries for benign pathologies until the burden of COVID-19 on the hospital system was alleviated [15,16]. It has been reported that there was a decrease of more than 90% in surgical procedures and outpatient clinic attendance, while the rate of AUR visits to emergency departments remained unchanged [17].

A hierarchy for canceled surgeries was established to mitigate healthcare delays and facilitate the orderly resumption of postponed activities with proper planning [18,3]. Plans were devised to postpone elective surgeries and resume endourological procedures as soon as the local prevalence of COVID-19 subsided [7]. Patients with symptomatic obstruction underwent surgery with knowledge of their COVID-19 status, determined by PCR testing of oropharyngeal and nasopharyngeal swabs, following an elective preoperative protocol [15]. If a patient tested positive for COVID-19 via PCR, surgery was postponed until full recovery due to the increased

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Table 5. Results of univariate and multivariate analyses for IPSS V/S.

	IPSS V/S ≤ 1.0	IPSS V/S > 1.0	p	OR (%95 CI)	p
12 months	n = 49	n = 70			
Age (years) *	70.5 ± 8.6	73.3 ± 9.6	0.101[a]	0.999 (0.932--1.072)	0.982
Perioperative catheterization	4 (8.2%)	63 (90.0%)	**<0.001[b]**	97.135 (22.713--415.416)	**<0.001**
Operative time (min)**	50.0 (30.0--150.0)	55.0 (30.0--160.0)	**0.009[c]**	1.007 (0.980--1.034)	0.620
Resection rate***	0.53 (0.45--0.62)	0.45 (0.37--0.53)	**<0.001[c]**	1.215 (0.006--248.607)	0.943
Long term	n = 50	n = 69			
Age (years) *	70.7 ± 8.7	73.2 ± 9.6	0.140[a]	0.992 (0.926--1.062)	0.810
Perioperative catheterization time	5 (10.0%)	62 (89.9%)	**<0.001[b]**	77.048 (19.305--307.514)	**<0.001**
Operative time (min)**	50.0 (30.0--150.0)	55.0 (40.0--160.0)	**0.002[c]**	1.015 (0.989--1.041)	0.259
Resection rate ***	0.53 (0.43--0.62)	0.44 (0.37--0.53)	**<0.001[c]**	1.255 (0.008--208.566)	0.931

Descriptive statistics for continuous variables are shown as *mean ± standard deviation, **median (minimum–maximum), or ***median (25^{th}–75^{th}) percentiles, where appropriate. [a]Student's t-test, [b]Continuity-corrected χ^2 test, [c]Mann-Whitney U test. IPSS V/S: International Prostate Symptom Score voiding/storage ratio.

risk of complications and potential impact on mortality [19]. Operations were conducted under spinal anesthesia whenever possible as a measure to conserve ventilators [20,21].

Acknowledging that the COVID-19 pandemic disproportionately affects older and male patients, the elderly male population with lower urinary tract symptoms (LUTS) was significantly impacted by this public health crisis [22]. Literature has demonstrated a strong correlation between COVID-19 and LUTS [10]; thus, some publications recommended investigating COVID-19 infection in any patient presenting with LUTS during the pandemic, while others suggested that COVID-19 might be associated with poorer prognosis in patients with BPH [23,24]. Studies have also reported an increased risk factor of urinary retention in patients with LUTS due to BPH during the COVID-19 outbreak [25]. We were already aware of the evidence indicating that emergency surgery following AUR is associated with high morbidity. In clinical practice, it was established that the initiation of alpha-blockers and a catheter-free trial reduced the need for BPH surgery [26,27]. However, few studies have concurrently investigated both the objective and subjective voiding outcomes of B-TURP in catheterized patients. Long-term preoperative Foley catheterization outcomes have been reported in patients with AUR in developing countries, where pre-pandemic urological care was limited and financially inadequate, and hospitals had restricted surgery quotas [28]. Despite the emergence of new modalities aimed at reducing hospital stays as alternatives to open prostatectomy during the pandemic, we had to perform B-TURP in large prostates due to availability and cost constraints.

In our study, mean prostate volume and PSA levels were higher in the catheterized group. The increased prostate volume and potential inflammation caused by catheterization may have contributed to elevated PSA levels. Additionally, a cohort study in the literature attributed PSA elevation to SARS-CoV-2, suggesting that the virus itself may increase PSA levels [29].

The higher postoperative long-term IPSS values observed in our study compared to previous studies may be attributed to delayed treatment access during the pandemic. While Qmax was similar between the two groups, the lower postoperative IPSS in the catheterized group indicated higher subjective satisfaction. On the other hand, the post hoc power analysis conducted for both the 12-month and long-term IPSS V/S > 1 ratios demonstrated an overall power of approximately 99.999%, suggesting that the observed group differences were supported by robust statistical power. Eliminating urethral catheters may have also contributed to a better QoL in preoperatively catheterized patients. Moreover, the high IPSS V/S ratio in the catheterized group, despite a low overall IPSS, may indicate detrusor insufficiency. As stated in previous studies, in prostate surgery, the IPSS V/S ratio has shown more effective results in younger patients, with higher resection rates and lower preoperative PVR [30], which is also supported by our study. Huang et al. reported better voiding function in patients with BPH-related AUR who underwent immediate transurethral surgery [31]. This may explain the impaired voiding symptoms in the catheterized group in our study.

According to the literature, patients with BPH experiencing AUR face a higher risk of complications, longer hospital stays, and greater comorbidities after B-TURP compared to those without AUR [32]. Although other studies have reported higher infection rates in patients with urinary retention, our study did not show a significant difference in infection rates between patients waiting for surgery with and without a catheter. This discrepancy may be attributed to our implementation of catheter care training, regular intermittent catheter replacement, the use of silicone catheters, and the administration of 10-day course of methenamine hippurate as prophylactic treatment before surgery in the catheterized group [33].

Postoperative recatheterization was not required for any patient in the group awaiting surgery without preoperative catheterization. Conversely, 9% of patients in the catheter-

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ized group necessitated postoperative recatheterization, a rate commensurate with prior research. Early reoperation was attributed to causes such as bladder clot formation, uncontrolled hemorrhage, or insufficient resection. Our study's long-term complication profile, characterized by a limited patient cohort and complication incidence, aligns with published rates: urethral stricture (2.2%–9.8%), bladder neck contracture (0.3%–9.2%), and urinary incontinence (0.3%–5.2%) [34].

Limitations

The retrospective and single-center design inherently limits the generalizability of these findings. A significant limitation was the uneven matching of the two groups, with Group B containing more severe BPH cases. This group exhibited higher PSA levels, larger prostate sizes, elevated recatheterization rates, greater resection volumes, and extended postoperative hospital stays. The observed increase in voiding symptoms after B-TURP in the catheterized Group B presents a confounding factor, as it is unclear whether this was due to their initial prostate size or the prolonged catheterization. Therefore, a matched subset analysis would be more appropriate for meaningful comparisons. Moreover, the study merely points to the existence of symptom subscores without explaining their underlying rationale. Finally, preoperative scoring for patients with a Foley catheter who cannot spontaneously urinate introduces a potential for bias or skew.

CONCLUSION

Due to the pandemic, disruptions in routine urology practice, especially delays in surgical treatment, were observed. Elective surgeries were performed with necessary precautions as soon as local COVID-19 prevalence declined. In patients who developed AUR due to BPH during the COVID-19 pandemic, the postponement of elective surgeries and prolonged preoperative catheterization led to functional impairments in voiding symptoms following B-TURP.

Ethics Committee Approval: The study was approved by the Ethics Committee for Non-Interventional Procedures of Adıyaman University (2022/1-7) on January 18, 2022.

Informed Consent: Written informed consent was obtained from the legal guardians of all participating patients.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare no competing interests.

Author Contributions: Concept: B.K.; Design: B.K., M.K.K., A.Ç.; Supervision: B.K., M.Ö.Y; Materials: B.K., C.B.; Data Collection and/or Processing: B.K., M.K.K.; Analysis and/or Interpretation: B.K., Literature Review: B.K., Writing: B.K., Critical Review: B.K.

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Assessing the effect of semen parameters on pregnancy outcome in couples undergoing intrauterine insemination for unexplained infertility and male infertility

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MAIN POINTS

- This study compares semen parameters and pregnancy outcomes between unexplained infertility and male infertility cases IUI.
- In unexplained infertility, no significant association was found between semen parameters and pregnancy rates.
- We observed that in male infertility, pre-wash TPMS density is more predictive of pregnancy outcomes than total TPMS count. And the TPMSC value after washing was also observed to be important in pregnancy prediction, since the TPMSC after washing is also concentrated semen.

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ABSTRACT

Aim: The aim is to investigate the effect of semen parameters in predicting pregnancy outcomes in the unexplained infertility and male infertility groups among couples who received insemination within the scope of infertility treatment.

Materials and Methods: In our study, spermiogram data were retrospectively obtained from 57 couples diagnosed with male infertility and 251 couples diagnosed with unexplained infertility who applied to Gaziantep Cengiz Gökçek Obstetrics and Gynecology Hospital ART Clinic and underwent IUI between July 2021 and July 2023, and the demographic data of the patients were analyzed. Before IUI, ovulation induction with an aromatase inhibitor and recombinant FSH was performed in female patients. Semen was collected from the male patient on the day of the procedure, and semen analysis was performed. Semen prepared by applying the semen preparation protocol was injected into the uterus with an insemination catheter. Pregnancy in the patients was assessed by serum beta-hCG on day 14 after the procedure.

Results: The positive pregnancy rate for male infertility was 10.5%, and the positive pregnancy rate for unexplained infertility was 13.5%. There was no association between unexplained infertility and spermiogram parameters. In male infertility, there was a relation between Total Progressive Motile Sperm (TPMS) density and post-wash TPMS Count (TPMSC) and positivity of pregnancy (p=0.035, p=0.017, respectively).

Conclusion: Semen parameters generally don't predict pregnancy outcomes in couples with unexplained infertility. However, for couples seeking help for male infertility, calculating Total Progressive Motile Sperm (TPMS) density and post-wash TPMS Count (TPMSC) during the initial semen evaluation is a crucial step in predicting pregnancy outcomes.

Keywords: Male infertility, Unexplained infertility, Spermiogram, Intrauterine insemination

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INTRODUCTION

Infertility is defined as the inability to achieve pregnancy within 12 months despite regular unprotected intercourse in couples of reproductive age. The male plays a role in 20-30% of cases, the female factor in 20-35%, and both factors in 25-40%, while the cause of infertility is unknown in 15-30% of cases [1]. Unexplained infertility is defined as a situation in which the basic tests used to diagnose infertility are normal, but the factors affecting fertility cannot be identified [2]. Although no male or female factor can be identified, it accounts for 30% of infertile couples [3]. Male infertility is the inability of a man to have children due to various unknown or known reasons, such as hormonal disorders, infections, varicocele, and cryptorchidism in the couple. In these couples, the woman has no barriers to pregnancy [4-6]. With the development of assisted reproductive techniques (ART), success rates in infertility treatment have begun to increase. Among these, intrauterine insemination (IUI), also known as insemination, is used as a first-line treatment because it is cheaper, easier to use and less invasive than other ART. By crossing the cervical mucus barrier, IUI aims to increase the number of motile sperm in the fertilized region. Pregnancy rates following intrauterine insemination (IUI) typically range from 10-20% [7], though they vary based on factors like the couple's age, the causes of infertility, and the clinic. Sperm analysis is a primary diagnostic tool for infertility, offering crucial insights for selecting appropriate assisted reproductive techniques [8].Current semen analysis parameters, as recommended by the World Health Organization in 2010, include volume, viscosity, liquefaction time, total sperm count, total motility, progressive motile sperm count, pH, sperm concentration, morphology (defined by Kruger [9]), and leukocyte count.Despite their apparent importance, the clinical value of these sperm parameters in predicting fertility, especially for IUI success, is not yet clearly established. While some studies find no significant relationship between overall sperm parameters and pregnancy rates after IUI, others suggest that a normal sperm count is important for maintaining pregnancy, or that only progressive motile sperm count is effective for IUI success [10,11]. Research on the effect of semen parameters on pregnancy outcomes in IUI treatment for male infertility has yielded highly variable results. This inconsistency underscores the need for more comprehensive studies on this topic [12]. Based on this information, the aim of our study was to investigate the effects of semen parameters on pregnancy outcome in couples presenting to Gaziantep Cengiz Gökcek Maternity and Children's Hospital Assisted Reproductive Treatment Centre for unexplained infertility and male infertility and undergoing IUI.

MATERIALS AND METHODS

In our study, we used the data of all patients who applied to the ARTC (Assisted Reproductive Treatment Centre) Polyclinic of Gaziantep Cengiz Gökçek Gynaecology and Obstetrics and Paediatrics Hospital and underwent IUI between July 2021 and July 2023. In our study, spermiogram data and patient demographic characteristics of 251 couples diagnosed with unexplained infertility and 57 couples diagnosed with male infertility were used; data of couples with chronic diseases and those who did not want to participate in the study were not included in our study. In women, couples with ovulatory cycles and normal hysterosalpingography (HSG) were included in our study. Cases with a sperm count less than $20x10^6$ (oligozoospermia), a motility assessment of sperm percentage with fast progressive motile sperm less than 25% or the sum of fast and slow progressive motile sperm less than 50% (asthenozoospermia) or a morphology assessment of less than 4% normal sperm (teratozoospermia) according to Kruger criteria were classified as having a male infertility, and cases in which a male infertility was not identified were classified as having 'unexplained infertility'.

Ovulation Induction (OI)

Aromatase inhibitor (letrozole) and recombinant FSH (rFSH) preparations were used together for ovulation induction (OI). For ovulation induction with rFSH, the treatment dose was determined according to age, weight, and antral follicle count on day 2 of menstruation. Letrozole 2.5 mg 2x1 tb for 3 days and rFSH were started at doses of 50-150 IU. On day 7 of treatment, follicular development was assessed and recorded by serum estradiol measurement and transvaginal ultrasound. If no follicles larger than 10 mm were seen in the ovaries on the 7-day scan, the daily dose was increased to 37.5-75-112.5-150 IU. The maximum dose was set at 225 IU. The days on which patients were to be called for control were determined according to follicle size. If follicles >10 mm were observed at the check-ups, the same dose was continued until the follicle diameter reached 18 mm. When the follicle diameter reached 18 mm, 10,000 IU of human chorionic gonadotropin (hCG) was administered to induce follicular maturation and ovulation. IUI cycles with >3 follicles on hCG day >16 mm were cancelled due to the risk of multiple pregnancy and hyperstimulation. Cycles cancelled in this way were not included in the study. Ovulation was assessed in all patients by progesterone measurement on day 21 of the cycle.

Sample collection, Semen analysis, and Preparation protocol

On the day of the procedure, the couple to be inseminated was called approximately 3 hours before the procedure. After 2-5 days of abstinence by the male patient, semen samples were collected by masturbation. The semen sample was kept in the incubator until the semen liquefied (minimum 20 min, maximum 60 min), and the liquefaction time was calculated. After the liquefaction phase, the semen was homogenised by pipetting, its volume was recorded and evaluated with the Makler camera. Semen analysis was performed according to WHO criteria, and pre-preparation values were recorded. Motility assessment included the number of progressive motile spermatozoa, the number of in situ motile spermatozoa, and the number of immotile spermatozoa. The density-gradient washing method was used to prepare semen for intrauterine insemination in almost all cases; in a few cases of low sperm concentration, only the washing method was used. The amounts of density-gradient solution were determined according to the amount of semen, and the solutions were heated in an oven to 37 ºC for half an hour. 2 ml of the heated lower phase was added to a sterile disposable centrifuge tube using a sterile glass Pasteur pipette. Using the same pipette, 2 ml of the upper phase was added drop by drop to the centrifuge tube at an angle of 45 degrees to avoid mixing with the lower phase. 2 ml of liquefied spermatozoa was added to the upper phase. The tube was centrifuged at 400g (45-90% density) for 15 minutes, and the supernatant was removed from the pellet. Then 5 ml of sperm wash solution (SpermRinse™), previously heated in an oven at 37ºC, was added to the pellet and pipetted without foaming. This solution was centrifuged at 400g for 5 minutes, and 0.5- 1 mL of the pellet was prepared for insemination, and the sperm count

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was recorded after preparation by counting in a machine camera. The pellet filled into the insulin syringe was kept in the oven until the time of insemination.

Insemination technique

The mean follicular diameter was calculated for each follicle greater than 16 mm during transvaginal ultrasound monitoring between days 11 and 13 of the menstrual cycle. IUI was planned in the presence of at least 1 follicle with a mean diameter greater than 18 mm. Intrauterine insemination was performed 36-40 hours after hCG administration. Female patients were asked to urinate during insemination so that the uterus could be easily seen on transabdominal imaging. The cervix was washed with 2-3 ml saline and the insemination catheter (TechnoCath) was gently inserted into the uterus, advanced through the cervix and stopped ~1 cm from the fundus. The prepared specimen from the male patient, stored at 37 C, was slowly inserted through the cervix with the catheter. Patients were rested in a lying position for 15-30 minutes after the procedure. All patients received progesterone to support the luteal phase.

Patients were evaluated for pregnancy by serum beta-hCG measurement on day 14 after the procedure.

Statistical analysis

Descriptive statistics of the variables used in the study are presented as median and interquartile range. The Kolmogorov-Smirnov test was used to test whether the quantitative variables conformed to a normal distribution, and it was found that the variables did not conform to a normal distribution. Therefore, the Mann-Whitney U test was used to compare variables according to pregnancy outcome for male infertility and unexplained infertility. The relationship between the cause of infertility and pregnancy outcome was examined using chi-squared analysis. Analyses were performed using IBM SPSS Statistics 25.0, and the significance level was set at $p < 0.05$.

RESULTS

In our study, we evaluated 252 couples with unexplained infertility and 57 couples with male infertility who underwent intrauterine insemination (IUI). We assessed the male patients' spermiogram parameters and compared these with the couples' pregnancy rates.

Within the male infertility cohort, 51 patients had negative pregnancy results, while 6 achieved positive pregnancy results after IUI. We observed no significant differences in mean age, semen volume, total sperm count, or total progressive motile sperm count (TPMSC) based on pregnancy outcome. However, a statistically significant difference was found in TPMSC/semen volume (representing total progressive motile sperm (TPMS) density) and post-wash TPMSC values (p=0.035, p=0.017, respectively). For couples with male infertility, pregnancy success was higher in those with greater progressive motile sperm density and progressive motile sperm count after sperm preparation (Table 1).

Among couples undergoing IUI for unexplained infertility, 217 achieved negative pregnancy outcomes and 34 positive outcomes. In this group, age, semen volume, total sperm count, sperm density, motile sperm count per millimeter, and post-wash TPMSC showed no difference according to pregnancy outcome. Nevertheless, couples with a positive pregnancy outcome in the unexplained infertility group had a significantly higher progressive motile sperm count (p=0.048). Table 2 indicates that pregnancy outcomes in unexplained infertility cases are independent of male factors.

Overall, 89.5% of patients with male infertility and 86.5% of those with unexplained infertility experienced negative pregnancy outcomes. No statistically significant relationship was found between pregnancy success in patients with unexplained and male infertility who underwent IUI (p=0.665) (Table 3).

When comparing groups by the cause of infertility, no significant differences were observed in male age, female age, or semen volume (p=0.456, p=0.454, p=0.472, respectively). However, significant differences based on infertility status were found for total sperm count, sperm count per milliliter, progressive motile sperm count, patient's TPMSC/semen volume, and post-wash TPMSC values (all p=0.000). Despite higher values for total sperm count, sperm count per milliliter, progressive motile sperm count, motile sperm density, and post-wash progressive motile sperm count in the unexplained infertility group, pregnancy success following IUI did not differ significantly from that in male infertility (p=0.665) (Table 3, Table 4).

DISCUSSION

Intrauterine insemination (IUI) is a common first-line assisted reproductive technique (ART) for various indications, including cervical infertility, minimal or mild endometriosis, ovulatory dysfunction, moderate male infertility, and unexplained infertility [13, 14]. However, reported IUI pregnancy success rates vary widely across studies. For instance, Mohammadi et al. reported a 15.7% pregnancy rate after IUI for different infertility causes, while another study found 18.2% [11, 15]. Specifically for male infertility, rates have ranged from 12.95% (Zhang et al.) to 5.3% (Luco et al.) [16, 17], with Sinha P et al. reporting 14.28% for male infertility and 33.33% for unexplained infertility [18]. Another study documented a 29.9% pregnancy rate for unexplained infertility [19].

In our study, the pregnancy success rate was 10.5% for male infertility and 13.5% for unexplained infertility, which aligns with findings in the literature. Historically, IUI pregnancy success rates have ranged from 5% to 70%. This considerable variability is influenced by numerous factors, including the cause of infertility, population heterogeneity, evolving ovarian stimulation protocols, differences in sperm preparation and

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Table 1. Comparison of variables according to pregnancy outcome in male factor infertility.

	Pregnancy Outcome		
	β-hCG Negative (n=51)	β-hCG Positive (n=6)	
	Median (Interquartile Range)	Median (Interquartile Range)	p-value
Male Patient Age	34 (7)	35.5 (9.75)	0.114 $^{\Psi}$
Female Patient Age	27 (7)	30.5 (8.5)	0.064 $^{\Psi}$
Semen Volume (ml)	2.5 (1.75)	2.25 (1.67)	0.365$^{\Psi}$
Total Sperm Count (million)	10.5 (24.2)	11.76 (21.75)	0.391 $^{\Psi}$
Sperm count per millilitre (million/ml)	5 (6.70)	7 (4.60)	0.149$^{\Psi}$
TPMSC (million)	3.90 (7)	5.25 (8.34)	0.203$^{\Psi}$
TPMSC /Semen Volume(million/ml)= TPMS density	1.14 (2.63)	2.59 (3.18)	0.035 $^{\Psi*}$
Post-wash TPMSC	0.6 (1.84)	4.25 (3.95)	0.017 $^{\Psi*}$

*p<0.05; Ψ: Mann-Whitney U test.

Table 2. Comparison of variables according to pregnancy outcome for unexplained infertility.

	Pregnancy Outcome		
	β-hCG Negative (n=217)	β-hCG Positive (n=34)	
	Median (Interquartile Range)	Median (Interquartile Range)	p-value
Male Patient Age	32 (6)	32 (7.5)	0.556$^{\Psi}$
Female Patient Age	28 (8)	29.5 (7)	0.826 $^{\Psi}$
Semen Volume (ml)	2.5 (2)	3 (1.78)	0.099 $^{\Psi}$
Total Sperm Count (million)	126 (174)	156.5 (129.25)	0.134 $^{\Psi}$
Sperm count per millilitre (million/ml)	55 (58)	51 (55.5)	0.856$^{\Psi}$
TPMSC (million)	69.03 (118.25)	97.69 (108.59)	0.048 $^{\Psi*}$
TPMSC /Semen Volume(million/ml)= TPMS density	29 (37.3)	30.08 (33.77)	0.344$^{\Psi}$
Post-wash TPMSC	17 (38.5)	20.4 (29.01)	0.158 $^{\Psi}$

*p<0.05; Ψ: Mann-Whitney U test.

Table 3. Relationship between the cause of infertility and pregnancy outcome.

		Pregnancy Outcome		
		Negative	Positive	p-value
Cause of infertility	Male factor	51 (89.5%)	6 (10.5%)	0.665$^{\chi}$
	Unexplained	217 (86.5%)	34 (13.5%)	

*p<0.05; χ: Chi square test.

IUI techniques, and a lack of well-controlled prospective randomized trials [20, 21].The use of IUI in couples with male infertility remains a contentious topic. While some studies suggest that in vitro fertilization (IVF) should be the first-line treatment for patients with very low semen volume, total sperm count, and progressive motile sperm count, IUI is generally accepted as a first-line option for moderate male infertility [20]. Nevertheless, persistently low pregnancy rates have prompted researchers to evaluate specific semen parameters as predictors of pregnancy. Among these, the total motile sperm count has been identified as an important prognostic factor for IUI success, with other parameters often showing no significant relationship with pregnancy [22].

Specifically in male infertility, IUI success has been linked to a pre-wash Total Progressive Motile Sperm Count (TPMSC) exceeding 5×10^6, suggesting that patients below this threshold should be referred for IVF [16, 23, 24]. Some studies advocate for a total motile sperm count above 10×10^6 before proceeding to IVF [25, 26]. Yavuzcan et al. emphasized that a pre-wash TPMSC $\geq10\times10^6$ was the sole factor contributing to IUI success across all infertile couples in their clinic [27].

In our study, the pre-wash TPMSC for male infertile couples with positive pregnancies was $(8.57\pm9.14)\times10^6$, but this did not show a statistically significant difference in terms of pregnancy success. Conversely, the post-wash TPMSC of $(3.41\pm1.90)\times10^6$ showed a significant relationship with pregnancy success. Furthermore, TPMS density was $(3.68\pm2.59)\times10^6$ and positively influenced pregnancy, although no relationship was found between other semen parameters and pregnancy success. These results suggest that post-wash sperm count and pre-wash sperm density can predict IUI success in couples with male infertility.

For patients with unexplained infertility, where the underlying cause remains unknown, a course of ovarian stimulation-IUI is commonly recommended, followed by IVF if IUI is unsuccessful. While semen parameters have been evaluated for their predictive value in IUI pregnancy success in this group, many studies indicate that parameters other than TPMSC are not reliable markers. Hajder et al. found higher IUI preg-

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Table 4. Comparison of variables according to infertility status.

	Pregnancy Outcome		
	β-hCG Negative (n=252)	β-hCG Positive (n=57)	
	Median (Interquartile Range)	Median (Interquartile Range)	p-value
Male Patient Age	32 (6)	34 (6)	0.456^{Ψ}
Female Patient Age	28 (7.75)	27 (7)	0.454^{Ψ}
Semen Volume (ml)	2.8 (2)	2.5 (1.75)	0.472^{Ψ}
Total Sperm Count (million)	137.5 (169)	10.5 (24.26)	$0.000^{\Psi*}$
Sperm count per millilitre (million/ml)	54.5 (57.75)	6 (6.70)	$0.000^{\Psi*}$
TPMSC (million)	74 (115.13)	4 (6.64)	$0.000^{\Psi*}$
TPMSC /Semen Volume(million/ml)= TPMS density	29.03 (37.06)	1.88 (2.55)	$0.000^{\Psi*}$
Post-wash TPMSC	17.75 (36.02)	0.7 (2.22)	$0.000^{\Psi*}$

*p<0.05; Ψ: Mann-Whitney U test.

nancy rates than spontaneous rates in patients with a TPMSC above 5×10^6 [19]. Another study on unexplained infertility cases undergoing IUI reported significantly higher live birth rates in those with a post-wash TPMSC of $15–20\times10^6$ compared to those with 5×10^6 [28]. Conversely, Lin et al. found that TPMSC did not affect IUI success rates in patients with unexplained infertility [29]. Another study concluded that couple's age, infertility duration, follicle number and size, number of treatment cycles, and all semen parameters were not significant predictors of pregnancy success in this patient group [30].

Our study found no association between semen parameters and pregnancy success in patients with unexplained infertility. Although semen volume was higher in those with positive pregnancies, this difference was not statistically significant. Interestingly, total and per milliliter sperm count, sperm concentration, sperm density, and post-wash sperm concentration were higher in couples with negative pregnancies. Our results confirm that semen parameters are not related to pregnancy success in cases of unexplained infertility, implying they cannot be used for pregnancy prediction in these situations.

CONCLUSION

Our study, which evaluated the effects of semen parameters on pregnancy outcomes in couples undergoing IUI for unexplained and male infertility, revealed no significant difference in positive pregnancy rates between these two groups. Furthermore, we found no relationship between semen parameters and pregnancy success in cases of unexplained infertility.

However, in male infertility, pregnancy rates were observed to increase in patients with higher post-wash TPMSC and, notably, higher pre-wash progressive motile sperm density. We believe that evaluating post-wash TPMSC and pre-wash total progressive motile sperm density will be effective in predicting pregnancy before IUI in male infertility, potentially avoiding unnecessary IUI cycles. Comprehensive studies are still needed in this area to refine pregnancy prediction.

Additional Information: Preliminary data of this study were presented orally at NICHE2024; 16th National and 2nd International Histology and Embryology Congress on 26-28 September 2024.

Ethics Committee Approval: Our study received approval from the Ethics Committee for Non-Interventional Clinical Studies of Gaziantep Islam, Science and Technology University (numbers 2023/342 and 342.33.08). Additionally, institutional approvals were obtained from Gaziantep Cengiz Gökçek Maternity and Child Diseases Hospital and Gaziantep Provincial Health Directorate.

Informed Consent: Written informed consent was obtained from the legal guardians of all participating patients.

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Colorectal tumor-related intestinal obstruction: Surgical approaches and treatment strategies

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MAIN POINTS

- Colorectal tumor-related intestinal obstruction most commonly occurs in the sigmoid colon, necessitating emergency surgical intervention.
- Resection with stoma formation was the most frequently performed surgical procedure (70.7%), especially in sigmoid colon tumors.
- Tumor localization showed a significant linear association with the type of surgical intervention (p=0.019).
- No statistically significant difference was found between age groups and surgical strategies, highlighting tumor features as more decisive than age.
- The study supports the need for personalized surgical approaches based on tumor location and clinical presentation in colorectal emergencies.

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ABSTRACT

Aim: This study aims to evaluate the treatment approaches and management strategies applied in patients with colon tumor-related intestinal obstruction in colorectal emergencies. The efficacy of treatment methods and the types of surgical interventions based on tumor localization were analyzed.

Materials and Methods: A total of 45 patients diagnosed with intestinal obstruction due to colorectal tumors at Erciyes University Department of General Surgery between 01.08.2022 and 01.08.2024 were retrospectively reviewed. The demographic data, tumor localizations, and treatment methods were analyzed.

Results: The study included patients with an average age of 65.09 (± 12.65) years, of whom 57.8% were male and 42.2% were female. The most common tumor location was the sigmoid colon (66.7%). Emergency surgery was performed in 91.1% of cases, with tumor resection and stoma creation being the most frequent procedures (70.7%). A significant linear relationship was observed between tumor location and the type of surgical procedure (p=0.019).

Conclusion: Surgical intervention is the preferred treatment method for colorectal cancer-related intestinal obstruction. While resection with stoma creation is frequently performed for sigmoid colon tumors, the final treatment strategy depends on both the specific location of the tumor and the overall health of the patient.

Keywords: Colon tumor, Colorectal emergencies, Intestinal obstruction treatment, Surgical intervention, Tumor localization

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INTRODUCTION

Colorectal cancers rank third among the most common malignancies worldwide and are considered a significant public health issue in both developed and developing countries [1]. Most colorectal cancers progress slowly and can remain asymptomatic for an extended period, but once the disease advances or becomes complicated, severe clinical manifestations may arise [1]. One of these complications is intestinal obstruction, defined as bowel obstruction caused by colorectal tumors, a critical condition that often requires emergency surgical intervention [2]. Tumor-related intestinal obstruction typically occurs in the advanced stages of the disease, significantly impacting both the treatment process and patient survival [1].

The management of intestinal obstruction due to colorectal tumors varies depending on tumor localization, the patient's general condition, tumor size, and its extent [3]. While treatment options primarily involve surgical intervention, in some cases, medical management may also be pursued. Surgical options include tumor resection with anastomosis, resection with stoma formation, or stoma without resection [4]. These options are determined based on factors such as the patient's clinical condition, tumor size, and location [5]. However, determining the most appropriate treatment approach for tumor-related intestinal obstruction remains a topic of ongoing debate [6]. The literature on this subject is limited, and there is no consensus regarding which treatment strategies are the most effective [3].

In cases of colorectal intestinal obstruction, emergency surgical intervention is typically the first line of treatment. However, the outcomes of these interventions vary depending on factors such as patient age, tumor location, and overall health status. Factors such as advanced age, comorbidities, and tumor localization can influence surgical outcomes and play a critical role in treatment selection [7]. Therefore, the management of intestinal obstruction due to colorectal tumors necessitates the application of personalized treatment strategies.

In this study, we aimed to retrospectively evaluate the treatment approaches and management strategies applied in cases of colon tumor-related intestinal obstruction in colorectal emergencies. Our study aims to contribute to clinical practice and address the gap in the literature regarding the treatment outcomes of patients with tumor-related intestinal obstruction. Additionally, we aimed to provide more data on the types of surgical interventions tailored according to the tumor localization and age groups.

Therefore, this study aims to retrospectively evaluate the treatment approaches and surgical strategies used in patients with intestinal obstruction due to colorectal tumors, with a particular focus on the type of surgical interventions concerning the tumor localization and patient characteristics. This study also seeks to provide practical data that can guide future personalized treatment planning in emergency colorectal surgery.

MATERIALS AND METHODS

Patient selection

This retrospective study was conducted to evaluate the treatment approaches and management strategies for cases of intestinal obstruction due to colon tumors in colorectal emergencies between August 1, 2022, and August 1, 2024, at the Department of General Surgery, Erciyes University School of Medicine. A total of 45 patients who were treated and followed up in the department of general surgery during this period were included in the study.

Patients included in the study were those over 18 years of age, diagnosed with intestinal obstruction due to colorectal tumors, requiring either emergency surgical intervention or medical treatment, and followed up at the General Surgery Clinic of Erciyes University. Exclusion criteria included intestinal obstruction due to causes other than colorectal tumors, patients previously treated in another clinic and only followed up at Erciyes University, and patients with incomplete or insufficient medical data.

As this was a retrospective observational study, a formal sample size calculation was not conducted prior to data collection. We employed a non-probability purposive sampling method, including all eligible patients who were diagnosed and treated for intestinal obstruction caused by colorectal tumors at the Department of General Surgery, Erciyes University, during the study period from August 1, 2022, to August 1, 2024.

Data collection

The data collected included the demographic characteristics of the patients (age, gender), tumor localizations, and treatment methods applied. Tumors were localized in various segments, including the rectum, sigmoid colon, left colon, transverse colon, and right colon. Treatment methods were categorized into two main groups: emergency surgical intervention and medical management. Surgical interventions were further classified into resection with anastomosis, resection with stoma formation, and stoma formation without resection.

Statistical analysis

Descriptive statistics were used to summarize the data. Categorical (qualitative) variables, such as gender, tumor localization, and treatment types, were expressed as frequencies and percentages. Continuous (quantitative) variables, such as age, were expressed as mean, standard deviation, minimum, and maximum values. Data analysis was performed using IBM SPSS 22.0 (Statistical Package for the Social Sciences). Demographic data were presented as mean, standard deviation, minimum, and maximum values. Categorical variables were expressed as frequencies and percentages. The Pearson Chi-Square test was used to analyze differences between groups, and Fisher's exact test was applied for low-frequency data. Additionally, a linear-by-linear association test was conducted to evaluate the relationship between tumor localization and surgical procedures according to age categories. A p-value of less than 0.05 was considered statistically significant.

The primary outcome measure of this study was the type of surgical intervention (resection with anastomosis, resection with stoma formation, or stoma formation without resection) performed in patients with intestinal obstruction due to colorectal tumors, evaluated in relation to tumor localization. Secondary outcomes included age- and gender-based distribution of tumor locations and treatment methods. The assumptions for statistical tests were evaluated prior to hypothesis testing. For the Pearson Chi-Square test, the expected frequency assumption was checked, and Fisher's Exact Test was applied in cases where the expected cell frequency was below 5. For the linear-by-linear association test, the assumption of ordinal variables was met based on the ordered categorization of age groups and surgical procedures. All statistical analyses were two-tailed, and a p-value < 0.05 was considered statistically significant.

RESULTS

A total of 45 patients were evaluated in this study, with a mean age of 65.09 (± 12.65) years, ranging from 36 to 87 years. The

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Table 1. Demographic, Tumor Localization, and Treatment Characteristics of patients undergoing.

Characteristic	Number (n)	Percentage (%)
Total Number of Patients	45	
Gender Distribution	Male: 26 Female: 19	Male: 57.8% Female: 42.2%
Mean Age	65.09 years ± 12.65 (Min: 36, Max: 87)	
Mean Age of Male Patients	64.04 years ± 10.41 (Min: 36, Max: 80)	
Mean Age of Female Patients	66.53 years ± 15.38 (Min: 38, Max: 87)	
Tumor Location	Rectum: 6 Sigmoid Colon: 30 Left Colon: 3 Transverse Colon: 1 Right Colon: 5	Rectum: 13.3% Sigmoid Colon: 66.7% Left Colon: 6.7% Transverse Colon: 2.2% Right Colon: 11.1%
Type of Treatment	Emergency Surgery: 41 Follow-up with Medical Treatment: 4	Emergency Surgery: 91.1% Follow-up with Medical Treatment: 8.9%
Type of Surgery Performed (Total: 41 surgeries)	Resection with Anastomosis: 5 Resection with Stoma: 29 Stoma without Resection: 7	Resection with Anastomosis: 12.2% Resection with Stoma: 70.7% Stoma without Resection: 17.1%
		p-value
Surgical Procedure vs Age Group Surgical Procedure vs Tumor Location Trend between Tumor Location and Surgical Procedure		p = 0.535* p = 0.131* p = 0.019**

** Pearson Chi-Square test, ** Linear-by-Linear Association test.*

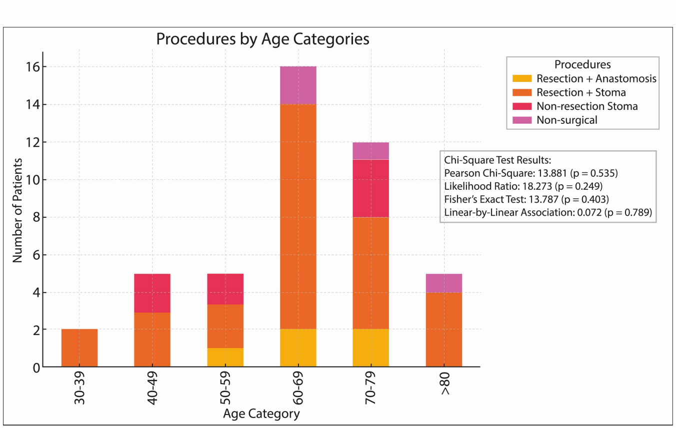

Figure 1. Distribution of surgical procedures by age categories in colorectal ileus cases.

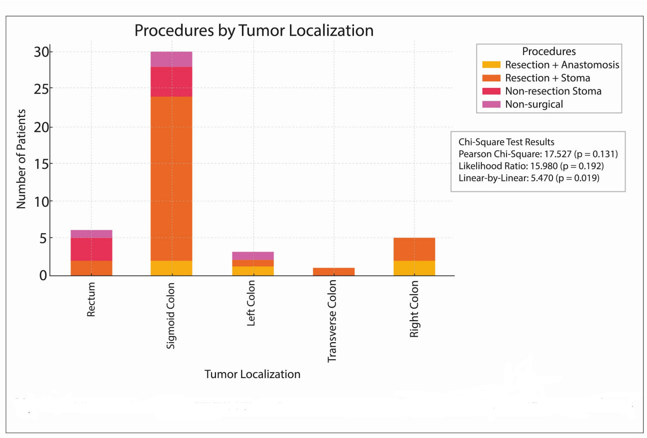

Figure 2. Distribution of surgical procedures by tumor localization in colorectal ileus cases.

mean age of male patients was 64.04 (± 10.41) years, while the mean age of female patients was 66.53 (± 15.38) years. Regarding gender distribution, 57.8% of the patients were male (n=26), and 42.2% were female (n=19). The demographic data of the patients, tumor localizations, and types of treatments administered are presented in the table.

When examining tumor localizations, sigmoid colon tumors were found to be the most common, observed in 66.7% of patients (n=30). Rectal tumors were present in 13.3% of patients (n=6), right colon tumors in 11.1% (n=5), left colon tumors in 6.7% (n=3), and transverse colon tumors in 2.2% (n=1). These data provided a basis for evaluating the relationship between tumor localizations and treatment approaches.

In terms of treatment approaches, 91.1% of patients (n=41) underwent emergency surgical intervention, while 8.9% (n=4) were managed with medical treatment. The most frequent surgical procedure among the 41 patients was tumor resection followed by stoma formation, which was performed in 70.7% of cases (n=29). Additionally, 17.1% (n=7) underwent stoma formation without tumor resection, and 12.2%

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(n=5) had resection followed by anastomosis. The distribution of these surgical interventions was also analyzed based on age categories.

In terms of age distribution, the 60-69 age group had the highest number of patients, with 16 individuals, of whom 75% underwent tumor resection followed by stoma formation. When analyzing the relationship between age groups and surgical interventions, it was observed that most patients in the 70-79 age group also underwent tumor resection, followed by stoma formation. In the 50-59 age group (n=5), 2 underwent tumor resection followed by stoma, 2 underwent stoma formation without resection, and 1 underwent resection followed by anastomosis. In the 40-49 age group, 3 out of 5 patients underwent tumor resection followed by stoma, while 2 underwent stoma formation without resection. Among the youngest age group (30-39 years), 2 patients underwent tumor resection followed by stoma. In the group aged 80 years and older, 4 out of 5 patients underwent surgical intervention. These data are illustrated in the graph presented in Figure 1.

When analyzing the surgical procedures based on tumor localization, we observed that 75.9% (n=22) of the 30 patients with sigmoid colon tumors underwent tumor resection followed by stoma, while 13.3% (n=4) had stoma formation without resection, and 6.7% (n=2) underwent resection followed by anastomosis. Of the 6 patients with rectal tumors, 50% (n=3) had stoma formation without resection, 33.3% (n=2) underwent tumor resection followed by stoma, and 16.7% (n=1) did not require emergency surgical intervention. Among the 5 patients with right colon tumors, 60% (n=3) underwent tumor resection followed by stoma, and 40% (n=2) underwent resection followed by anastomosis. Among the 3 patients with left colon tumors, 1 underwent resection followed by anastomosis, 1 underwent tumor resection followed by stoma, and 1 was managed with medical treatment. The patient with a transverse colon tumor underwent tumor resection followed by stoma formation. These data are illustrated in the graph shown in Figure 2, which provides a visual representation of the surgical procedures performed according to tumor localization.

Statistical analysis using the Pearson Chi-Square test found no significant difference between age groups and surgical procedures (p=0.535). Similarly, when evaluating the relationship between tumor localization and types of surgical intervention, no significant difference was found (p=0.131). However, a linear association between tumor localization and the type of surgical procedure was detected (p=0.019). This suggests that as the tumor localization shifts distally (e.g., from right colon to sigmoid colon or rectum), there is an increasing trend in favor of stoma formation rather than anastomosis. In contrast, proximal tumors are more frequently treated with resection and primary anastomosis. This pattern highlights the importance of tumor localization in determining surgical strategies.

DISCUSSION

Intestinal obstruction caused by colorectal tumors is a complication that can lead to severe clinical conditions in patients, and its management remains a topic of debate [3,8]. In our study, surgical intervention was found to be the most preferred treatment method for intestinal obstruction due to colorectal tumors. Emergency surgery was performed in 91.1% of the patients, with tumor resection followed by stoma formation being the preferred approach in 70.7% of these cases. These findings are consistent with similar studies in the literatüre [9]. For instance, it has been frequently highlighted that tumor resection followed by stoma formation is one of the common methods used in cases of sigmoid colon tumors [10].

The management of intestinal obstruction caused by colorectal tumors involves various surgical options, including tumor resection with anastomosis, tumor resection followed by stoma, and stoma formation without resection. In our study, as observed, tumor resection followed by stoma formation was the most common procedure for sigmoid colon tumors (75.9%). This finding is attributable to the anatomical characteristics of the sigmoid colon. The sigmoid colon is a narrow part of the colon, making tumors in this region more prone to causing obstructions, thus necessitating emergency surgical intervention more frequently [11].

In our study, a statistically significant relationship was also found between tumor localization and the type of surgical procedure performed. This result indicates that tumor localization is a key determinant in treatment strategies. The literature also supports that tumor localization influences surgical treatment decisions, with tumor resection followed by stoma being more common in sigmoid colon tumors, while diversion stoma without resection is more frequently preferred in rectal tumors [12]. This observation may be related to the more complex nature of surgical interventions in rectal tumors and the increased risk of anastomotic complications [13].

However, no significant difference was found between age groups and types of surgical procedures. This suggests that surgical treatment decisions are not based solely on patients' age or age-related comorbidities, but rather on factors such as tumor localization, the extent of tumor spread, and the patient's overall clinical condition at the time. This finding is also supported by studies in the literature, which indicate that while surgical outcomes in elderly patients should be carefully evaluated, age alone is not a decisive factor in surgical decisions [14]. Although comorbidities increase with age and can negatively affect surgical outcomes, tumor stage and localization remain the primary factors influencing surgical management in cases of colorectal tumor-related intestinal obstruction.

The impact of comorbidities on surgical outcomes in cases of intestinal obstruction caused by colorectal tumors is another aspect that must be considered. Although our study did not include information on comorbidities, it is generally

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accepted that comorbidities increase with age and can have a negative effect on surgical outcomes. The literature demonstrates that comorbidities, particularly in elderly patients, increase the risk of surgical complications and raise postoperative mortality rates [15]. Therefore, when making surgical treatment decisions, a patient's comorbid condition, in addition to their age, should be carefully considered.

The findings of our study demonstrate that tumor localization is a significant determinant in the selection of surgical procedures, independent of factors such as age and comorbidities. For example, tumor resection followed by stoma formation is more commonly preferred in patients with sigmoid colon tumors, whereas this procedure is less frequent in rectal tumors. Similarly, the rate of anastomosis is higher in right and transverse colon tumors. These results highlight the influence of tumor localization on the choice of surgical intervention.

Current literature emphasizes that treatment strategies for intestinal obstruction caused by colorectal tumors remain controversial, and personalized treatment approaches should be applied in each case [16]. Our study supports this conclusion. Factors such as tumor localization and stage are pivotal in surgical decision-making. While advanced age and the presence of comorbidities increase surgical risks, the biological characteristics of the tumor are ultimately more determinative in formulating treatment strategies. Consequently, the optimal treatment approach must be tailored to the individual patient.

The findings of our study align with those reported in the review by Grigorean et a. [2], which analyzed colorectal cancer as a leading cause of low bowel obstruction (LBO). In their analysis, colorectal tumors accounted for 60–80% of all LBO cases, and in 20% of patients, bowel obstruction was the first clinical manifestation of the malignancy. In our study, all patients presented with intestinal obstruction due to colorectal tumors, and the most common localization was the sigmoid colon, consistent with the review's finding that nearly 80% of left-sided colorectal obstructions are attributable to sigmoid tumors. Additionally, Grigorean et al. [2] reported that emergency surgery is required in 8–29% of cases, with Hartmann's procedure and resection with stoma formation being the most frequently preferred surgical approaches. Similarly, in our cohort, 91.1% of patients underwent emergency surgery, and resection followed by stoma formation was the most commonly performed procedure (70.7%). The review further noted postoperative complication rates of 35–40% and mortality rates of 15–20%, particularly in older patients with comorbidities. While our study did not focus on postoperative outcomes, the demographic profile of our patients—most commonly in the 60–69 age group—supports the clinical importance of early surgical decision-making in elderly populations with tumor-related obstruction.

CONCLUSION

In the management of intestinal obstruction secondary to colorectal tumors, surgical intervention is principally dictated by tumor localization and stage. Although patient-specific variables such as age and comorbidities are considered, the tumor's intrinsic characteristics are paramount in guiding treatment. The present study provides valuable data regarding surgical strategies for this condition, contributing to the field's knowledge base and underscoring the need for further research on the influence of comorbidities in geriatric populations.

Ethics Committee Approval: Ethics committee approval was received for this study from the Health Sciences Research Ethics Committee of Erciyes University (Date: 09/10/2024, Number:194).

Informed Consent: The study was designed retrospectively, and no data that would violate patient confidentiality were used in the study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that there is no conflict of interest.

Author Contributions: Concept-MK; Design-MK, SC; Supervision-SC; Resources-MK, SC; Materails-MK, SC; Data Collection and/or Processing-SC; Analysis and/or Interpretation- MK,; Literature Search- MK,SC; Writing Manuscript- MK; Critical Review- SC.

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Diagnostic performance of simplified intravoxel incoherent motion DWI for breast lesions

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MAIN POINTS

- This study evaluated the diagnostic utility of simplified IVIM (SI-IVIM) with three b-values in distinguishing malignant from benign breast lesions, showing comparable but not superior accuracy to conventional ADC.
- Median and minimum perfusion fraction (f) values yielded the highest AUCs (0.79 and 0.76), indicating potential as supplementary markers when diffusion imaging results are inconclusive.
- Despite advantages like shorter scan time and lower complexity, SI-IVIM's clinical utility is limited due to variability in perfusion estimates, necessitating validation in larger, diverse populations.

ABSTRACT

Aim: To assess the success of 3b-value simplified intravoxel incoherent motion (SI-IVIM) diffusion-weighted imaging (DWI) in distinguishing malignant from benign breast lesions.

Materials and Methods: Sixty-four breast lesions in 59 women were retrospectively analyzed. Patients with MRI-negative lesions, lesions smaller than 8 mm, poor-quality DWI, or indeterminate lesions without surgical excision were excluded. All MRIs scans were conducted using a 1.5 T MRI scanner, including DWI (b values: 0, 100, 800, and 1500 s/mm^2), and dynamic contrast-enhanced sequences (DCE-MRI). Lesions were segmented manually using the ITKsnap program with the help of DCE-MRI, and volumetric mask images (VOI) were generated. Different apparent diffusion coefficient (ADC) values and IVIM parameters, D=ADC (100,1500) and f= f(0, 50, 800), were computed. The diagnostic performances of different ADC values and IVIM parameters were compared to define sensitivity, specificity and the optimal cut-off values.

Results: Maximum (max) ADC100, median (med) ADC800, med ADC1500, med f and minimum (min) f values showed significant differences between benign and malignant breast lesions. Med D and min D were lower in the malignant group; however, this difference did not reach statistical significance. The diagnostic performances of med f (AUC= 0.79) and min f (AUC= 0.76) were superior to those of the conventional ADC value (ADC800, AUC= 0.74) in the ROC curve analysis. However, in the DeLong test analysis, neither med f nor min f demonstrated statistically significant diagnostic superiority over the other parameters.

Conclusion: The SI-IVIM parameters showed no significant diagnostic superiority over the ADC value in differentiating malignant breast lesions.

Keywords: Breast neoplasms, Diffusion magnetic resonance imaging, Simplified IVIM, Intravoxel-incoherent motion

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INTRODUCTION

The most sensitive imaging method for breast cancer detection is dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) [1]. However, its specificity is generally less than 80% [2]. Advanced imaging techniques are crucial in the era of precision medicine, because they play a central role in directing therapeutic decisions, improving diagnostic accuracy, and customizing treatment options. Diffusion-weighted imaging (DWI) has emerged as a promising noninvasive method for distinguishing between breast cancer and benign lesions, differentiating between in situ and invasive lesions, and predicting the efficacy of neoadjuvant therapy using apparent diffusion coefficient (ADC) values [3-6]. However, breast cancer typically exhibits a high number of cells (low diffusivity) and a high number of blood vessels (high perfusion), which may have opposite effects on ADC values [7].

Intravoxel incoherent motion (IVIM) MRI can reveal details regarding the diffusion and perfusion properties of tissues, particularly in the context of blood flow in the microvasculature, by using multi-b-value DWI [8, 9]. It provides separate measurements of pure diffusion (D), representing the mobility of water molecules in tissue; pseudodiffusion (D^*), which depends on the length of the microvessel segments and blood velocity; and the microvascular volume fraction (f), which reflects the contribution of microvascular blood flow without the use of a contrast agent [7].

In the IVIM technique, nonlinear least-squares fitting procedures without any constraints are generally used. employed to determine the values of D, D^*, and f simultaneously. To utilize fitting algorithms, multiple DWI sequences with a wide range of b values are needed to be acquired, which leads to prolonged acquisition durations [10]. Furthermore, these methods frequently result in numerical instabilities, inadequate repeatability, and incorrect parameter values for D^* and f in tissues having low perfusion [11]. SI-IVIM operates under the assumption of the pseudodiffusion has diminished to zero in b values that exceed a sufficiently large threshold, which may overcome the instability of the multi-b value IVIM. To achieve SI-IVIM analysis, acquiring DWI sequences with three or four distinct b values is necessary [12]. SI-IVIM offers reduced computational complexity and faster data analysis, which benefits clinical settings by improving patient comfort and compliance through quicker data acquisition [13]. However, simplified models may compromise accuracy and reliability in parameter estimation by overlooking complex tissue interactions, leading to variability and reduced precision in distinguishing tissue types or pathologies.

Few studies have investigated the efficacy of SI-IVIM in distinguishing between malignant and benign breast lesions [13, 14]. To address this problem, the primary objective of this study was to assess SI-IVIM to distinguish malignant from benign breast lesions.

MATERIALS AND METHODS

Patient population

This retrospective study was approved by the local institutional review board (Protocol no: KA23/73). The requirement for informed patient consent was waived because of the retrospective nature of the study. We retrospectively reviewed patients between April 2021 and March 2023 who have suspicious breast lesions on ultrasound, mammography or MRI and had biopsy (ACR BI-RADS scores of 4 or 5 breast lesions). The primary indications for breast MRI encompassed preoperative staging, surveillance of high-risk patient populations, and the assessment of indeterminate findings detected on mammography or ultrasound. Patients with MRI-negative lesions, lesions smaller than 8 mm to prevent the influence of partial volume effects, low DWI quality, and lesions with unknown malignant potential (papillary lesions, flat epithelial atypia, lobular neoplasia, atypical ductal hyperplasia, radial scar) without surgical excision were excluded from patient population of the study (Figure 1). A total of 64 breast lesions in 59 women (five patients with 2 suspicious breast lesions), with ages between 24 to 99 years and a mean age of 53.38±15.17 years, were included in the study.

MRI data acquisition and DWI parameters

All MRIs were conducted with the patient lying face down using a breast coil with four channels with a 1.5 T MRI scanner (MAGNETOM Avanto, Siemens Healthcare, Erlangen, Germany). The following sequences were acquired as part of the routine clinical protocol: axial turbo spin-echo (TSE) T1, axial turbo inversion recovery magnitude (TIRM), axial spin-echo echo-planar imaging (EPI), and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) using a 3D fat-saturated gradient echo axial sequence (TR/TE: 4.60/1.42 ms; flip angle: 6°; NEX: 1 slice thickness:1 mm; matrix size: 358 × 448; FOV: 340 × 100), six phases after injection of intravenous 0.2 mL/kg gadoterate meglumine (Dotarem).

Four b-values (0, 100, 800, and 1500 s/mm^2) in three orthogonal orientations were obtained for an EPI sequence using fat suppression (SPAIR) with the following parameters: acquisition time of 6.5 minutes, TR/TE of 7400/78 ms, matrix size of 63 × 164, FOV of 340 × 390 mm, slice thickness of 4 mm, slice gap of 4 mm, and NEX of 5.

Postprocessing and Image analysis

In previous research, the IVIM method employed the following equation to calculate its parameters in a streamlined manner [12, 13, 15].

$$ADC(i,j) = \frac{ln(S(b_i)) - ln(S(b_j))}{j-i}$$

Utilizing this specified equation, the different ADC values were calculated.

D and f were estimated using the method proposed by Le Bihan [15]. Previous studies have suggested that b-values > 200 s/mm^2 should be used to minimize the influence of perfusion effects [11]. Based on this information, we calculated the f values using b-values of b0=0, b_1=800, and b_2=1500 s/mm^2.

$$D = ADC(100,1500) = \frac{ln(S(b_1)) - ln(S(b_2))}{b2-b1}$$

$$f = f(0.800,1500) = 1 - \frac{S(b_2)}{S(0)}.exp^{D.b_2}$$

Volume of interest (VOI)

DWI images were registered with post-contrast images using ITK-SNAP (http://www.itksnap.org) software. A proficient breast radiologist with four years of expertise in breast radiology manually delineated the lesions seen on the post-contrast second phase of DCE-MRI scans (Figure 2). The segmentation process involved outlining the outer boundary of the tumor on each image slice, while excluding areas of hemorrhage, necrosis, or cystic elements. In cases of multifocal or

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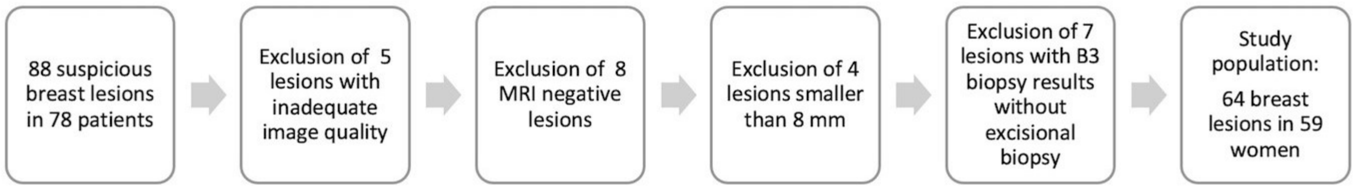

Figure 1. Flow chart of study population.

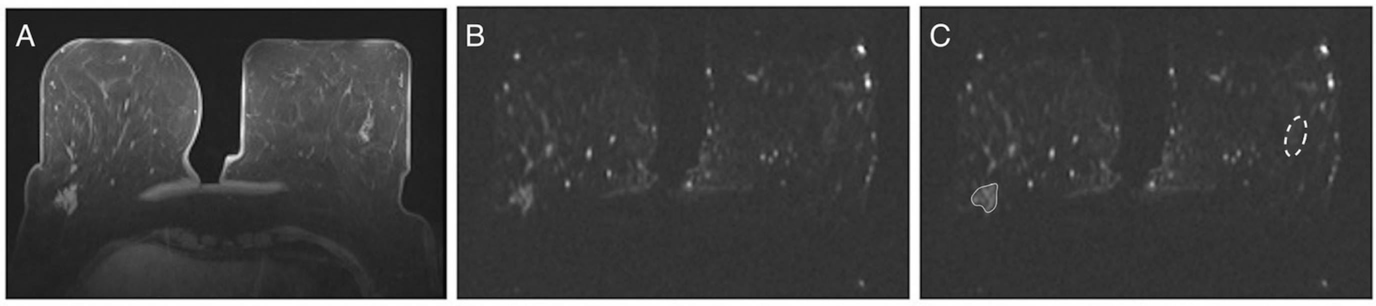

Figure 2. Segmentation of the mass and the contralateral normal breast tissue. An irregular contoured mass with invasive ductal carcinoma diagnosis in the outer-lower quadrant of the right breast is visible in the contrast-enhanced axial image (A) and the b = 0 DWI map (B). The segmentation of the mass (outlined with white line) and the contralateral normal breast (outlined with dashed white line) in the b = 0 DWI sequence which is used to create the mask image is seen (C). The contralateral normal breast was segmented ensure a volume comparable to the mass lesion.

multicentric tumors, only the primary lesion with the largest size was segmented. Volumetric mask images were generated for both lesions and normal fibroglandular structures of the contralateral breast using the VOI method based on DCE images and b=0 images in the ITKsnap. Following visual confirmation to ensure correct anatomical alignment between DCE images and images with varying b values, the VOI was transferred to the parameter maps. Subsequently, the average intensity values of the various ADC values, D, and f, were automatically computed from the mask images using the fslstats command.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.) and R Studio (version 2023.06.1+524; Posit, PBC, Boston, MA, USA). Post-test power analysis was performed using Cohen's d effect size calculations and two-sided t-tests with α=0.05 to evaluate the achieved statistical power for each radiological parameter. Continuous data are presented as mean standard deviation or median and interquartile range (IQR, 25–75th percentile). Kolmogorov-Smirnov (K-S) test was used to analyze the normal distribution assumption of the quantitative outcomes. The student's t-test was used to compare normally distributed variables, while the Mann–Whitney U test was applied for non-normally distributed variables. The Delong test was used to compare area under the curve (AUC) values to investigate whether any parameter exhibited diagnostic superiority. The diagnostic performance of different IVIM parameters was evaluated using receiver operating characteristic (ROC) curve analysis. The optimal cut-off values, for the parameters that showed statistically significant differences, in the ROC analysis were determined using the Youden Index, which maximizes the sum of sensitivity and specificity to achieve the best diagnostic threshold. For each parameter, the sensitivity and specificity were calculated along with their 95% confidence intervals (CI). Differences in IVIM parameters among different immunohistochemical subtypes were analyzed using the Kruskal-Wallis test for non-normally distributed variables and one-way ANOVA for normally distributed variables. Correlations between IVIM parameters and tumor immunohistochemical features were assessed using the Pearson correlation coefficient (r) for normally distributed data and the Spearman correlation coefficient (ρ) for non-normally distributed data. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 64 breast lesions were analyzed, comprising 35 (54.7%) malignant and 29 (45.3%) benign lesions. The descriptive statistics of the lesions are presented in Table 1.

Several parameters showed statistically significant differences between the malignant and benign groups (Figure 3). Among these, the median (med) f and minimum (min) f had the lowest p-values ($p< 0.001$) (Table 2).

Med D and min D were lower in the malignant group, but this difference was not significant (p= 0.184 and p= 0.210, respectively).

The diagnostic performances of med f (AUC= 0.79) and min f (AUC= 0.76) were superior to that of the conventional

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Table 1. Demographics of the patients and lesion characteristics.

	Malignant lesions	Benign lesions
Breast side (% in columns)		
Right	24 (68.6)	18 (62.1)
Left	11 (31.4)	11 (37.9)
Mean age of the patient	58.37±14.88	47.34±13.42
Mean diameter (mm) (min-max)	28.26±15.93 (9-80)	14.38± 6.40 (8-33)
Mean volume(cm^3) (min-max)	5.92±6.98 (0.20-30.21)	0.616± 1.18 (0.05-6.51)
Shape (% in columns)		
Mass	31 (88.6)	23 (79.3)
Non-mass	4 (11.4)	6 (20.7)
Histopathological subtype (% in columns)	Invasive carcinoma of no special type (NOS) 21 (60) Invasive lobular carcinoma (ILC) 4 (11.4) Mixed IDC/ILC 2 (5.7) Mucinous carcinoma 1 (2.9) Tubular carcinoma 1 (2.9) Mucoepidermoid carcinoma 1 (2.9) Ductal carcinoma in situ 4 (11.4) Focal microinvasive carcinoma on a background of papillary DCIS1 (2.9)	Fibroadenoma 12 (41.4) Fibrocystic changes 10 (34.5) Apocrine metaplasia 1 (3.4) Florid ductal hyperplasia 1 (3.4) Mastitis 3 (10.3) Papilloma 2 (6.9)
Grade (% in columns)		-
1	3 (8.6)	
2	15 (42.9)	
3	12 (34.3)	
HER-2 status (% in columns)		-
Positive	5 (14.3)	
Negative	26 (74.3)	
Hormone receptor status (% in columns)		
Positive	31 (100)	
Negative	0 (0)	-
Number of lesions (% in columns)		
Multifocal	10 (28.6)	
Multicentric	4 (11.4)	-
One mass	14 (40)	
Immunohistochemical subtypes (% in columns)		
Luminal A	9 (25.7)	
Luminal B	17 (48.6)	
HER-2 positive	5 (14.3)	
Triple negative	0 (0)	

ADC value (ADC800, AUC= 0.74) in the ROC curve analysis (Table 3) (Figure 4). However, in the DeLong test analysis, neither med f nor min f demonstrated statistically significant diagnostic superiority over the other parameters.

The optimal cutoff value for med f was 304.28 × 10^{-3} mm^2/s, yielding a sensitivity of 86.2% and a specificity of 65.7%, with a positive predictive value (PPV) of 85.2% and a negative predictive value (NPV) of 67.6%. (95% CI 68–91%). For min f, the optimal cut-off value was 65.78 × 10^{-3} mm^2/s, resulting in a sensitivity of 82.7% and a specificity of 57.1% with a PPV of 80% and an NPV of 61.5% (95% CI 64–88%). Similarly, for ADC800, the optimal cut-off value was 1.3 × 10^{-3} mm^2/s, achieving a sensitivity of 65.5% and a specificity of 85.7% , with a PPV of 75.7% and an NPV of 74.1% (95% CI 60-88%).

Min f, and med f among different immunohistochemical subtypes, no significant differences were found between the groups. Upon evaluating the correlation of these values with the receptor status and Ki-67, a negative correlation was observed between min f and Ki-67 (r_s = -0.45, p = 0.012). No significant correlations were detected for any other parameters.

Post-test power analysis revealed strong statistical power (>0.80) for medianADC800 (power=0.88), median$f$ (power=0.99), and min$f$ (power=0.98). Moderate power was observed for medianADC1500 (power=0.71) and maxADC100 (power=0.66). The remaining parameters showed lower statistical power (<0.60) (Figure 5).

DISCUSSION

In this study, the diagnostic efficacy of SI-IVIM parameters using three different b values was assessed to distinguish malignant from benign breast lesions. Although the AUC value

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Table 2. Comparison of IVIM parameters.

Parameter	Benign'	Malignant'	p value
Med ADC100*	1.80 (0.44-3.46)	1.75 (0.96-2.55)	0.677
Min ADC100 *	0.79 (0.06-3.18)	0.394 (0.008-1.56)	0.161
maxADC100 *	**2.87 (1.47-6.67)**	**6.65 (2.05-6.84)**	**0.007**
Med ADC800 t	**1.31 ±0.42**	**1.03±0.27**	**0.001**
Min ADC800 *	0.84 (0.008-1.72)	1.01 (0.21-1.56)	0.118
Max ADC800 t	1.81±037	1.83±0.35	0.863
Med ADC1500 t	**1.02±0.36**	**0.83±0.23**	**0.018**
Min ADC1500 *	0.62(0.03-1.42)0.4	0.44 (0.03-0.95)	0.104
Max ADC1500 t	1.44±0.36	1.43±0.33	0.919
Med D *	0.61 (0.07-1.38)	0.57 (0.05-1.20)	0.184
Min D *	0.29 (0.002-1.09)	0.20 (0.004-0.63)	0.210
Max D t	1.1±0.39	1.09±0.31	0.911
Med f *	**386.34 (157.60-586.99)**	**280.37 (155.16-457.98)**	**< 0.001**
Min f *	**193.08 (13.25-488.87)**	**55.63 (4.03-260.87)**	**< 0.001**
Max f *	521.58 (336.49-790.12)	560.87 (396.87-717.75)	0.240

Med: median, min: minimum, max: maximum. 'ADC, D, f values are given in units of 10^{-3} mm^2/s.*:median(min-max) value and p value of Mann–Whitney U test, t : mean SD and p value of Student's t-test.

Table 3. ROC curve analysis.

Test Variables	AUC	Std. Error[a]	P value	Lower Bound	Upper Bound
Med f	0.79	0.06	<0.001	0.68	0.91
Min f	0.76	0.06	<0.001	0.64	0.88
Med ADC800	0.74	0.07	0.001	0.60	0.88
Max ADC100	0.70	0.07	0.010	0.56	0.83
Med ADC1500	0.70	0.07	0.005	0.57	0.84

of med f (AUC=0.79) and min f (AUC= 0.76) were superior to that of the conventional ADC (ADC800 AUC=0.74), this difference was not statistically significant in the Delong test. Therefore, simplified IVIM with a 3-b value did not show diagnostic superiority to the ADC value in differentiating malignant breast lesions from benign ones.

This indicates that SI-IVIM could serve as a complementary imaging tool in breast lesion evaluation, potentially offering additional diagnostic insights in cases where conventional DWI findings are inconclusive. However, its clinical utility remains limited, and further studies with larger, more diverse patient populations are needed to validate its role in routine breast cancer assessment.

There are limited studies evaluating the diagnostic performance of simplified IVIM in breast lesions [13, 14]. Mürtz et al. studied the effectiveness of S-IVIM in the detection of breast lesions. They analyzed DWI data (b = 0, 50, 250, and 800 s/mm^2) of 126 patients. They claimed that ADC, $D1$, and $D2$ were significantly smaller, and $f1$, $f2$, and D^* were significantly larger in malignant breast lesions than in benign lesions. Their findings also indicated that using DWI with b = 800 s/mm^2 as a standalone tool, the combination of $D1+f1$ achieved the highest discriminability with an accuracy of 93.7%, that was significantly higher than ADC at 86.9%, $D1$ alone at 88.0%, and $f1$ alone at 87.4%. When DWI was used as adjunct to DCE-MRI, $D1$ (92.6%) showed the highest diagnostic accuracy as the single parameter, which was slightly, but not significantly, better than ADC (91.1%) and $D2'$ (88.1%).

Li et al. compared the effectiveness of a 12-b-value traditional biexponential fitting model IVIM with a 3-b-value method in addition to DCE-MRI in 28 suspicious breast lesions. The study found that the 3-b-value method provided imaging parameters that were more accurate and had comparable or superior diagnostic values compared to traditional biexponential IVIM fitting [14].

In a meta-analysis by Arian et al. D and f values were significantly different between benign and malignant lesions, whereas D^* did not show any significant difference [16]. Malignant lesions had lower D and higher f values. MA et al. evaluated the diagnostic value of IVIM in breast lesions in a meta-analysis, they showed that D had the highest diagnostic performance with pooled sensitivity and specificity of 0.85 and 0.87, respectively [17]. Previous studies mostly showed lower D values and higher f values in malignant breast lesions than benign lesions [13, 18].

In our study, to eliminate the influence of perfusion in light of previous research, IVIM parameters were calculated using three values, specifically b values of 0, 800, and 1500 s/mm^2 [11]. Consequently, the D^* value could not be determined.

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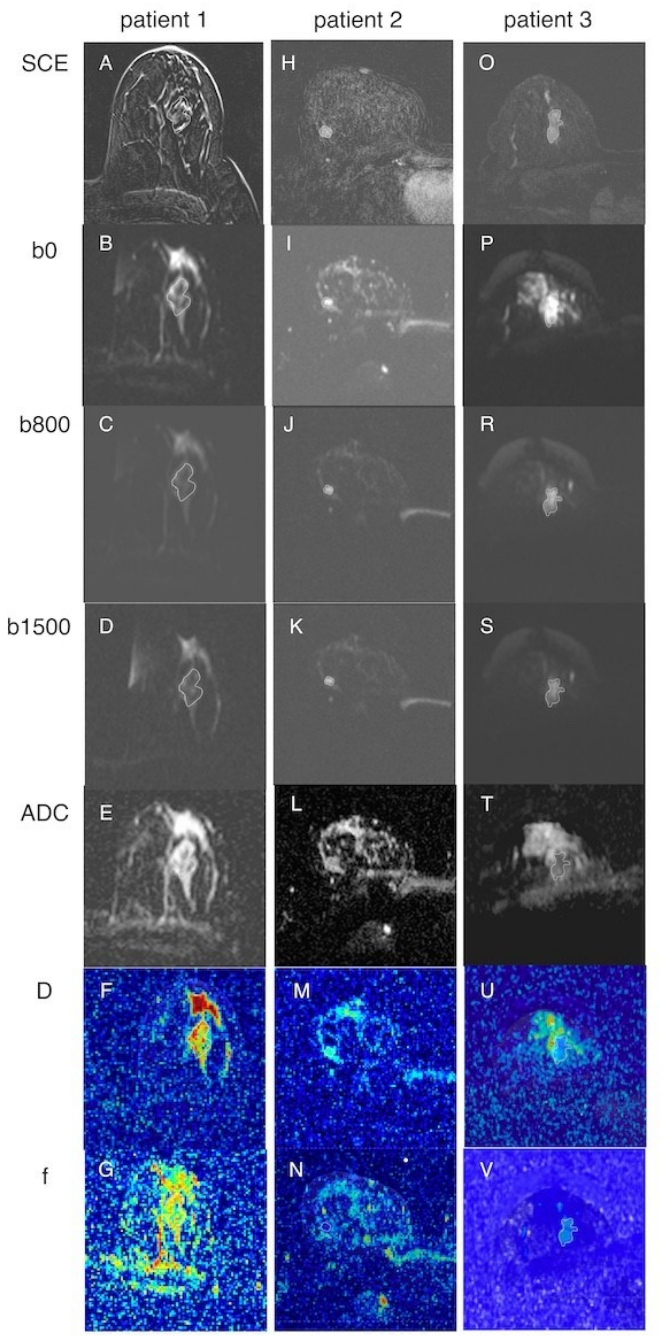

Figure 3. Axial MRI images of 3 different patients with following diagnosis: Lesion 1 (patient 1), fibroadenoma; lesion 2 (patient 2); invasive carcinoma of the no special type (grade 2 ER:60%, PR:55%, Her-2: negative, ki-67:40%); lesions 3 (patient 3), invasive lobular carcinoma (grade 2 ER, 95%; PR, 25%; Her-2, negative; ki-67:14%). First lesion appears with low signal intensity on the diffusion maps (C, D). It has high median ADC1500 (E, 1.21 x 10^{-3} mm^2/s), median D (F, 0.69 x 10^{-3} mm^2/s), and median f (G, 512.36 x 10^{-3} mm^2/s) values. Lesion 2 appeared hyperintense on diffusion maps (I, J). It has low median ADC1500 (L, 0.67 x 10^{-3} mm^2/s), median D (M, 0.55 x 10^{-3} mm^2/s), and f (N, 173.26 x 10^{-3} mm^2/s) values. Lesion 3 appeared hyperintense on the diffusion maps (R, S). It has low median ADC1500 (T, 0.79 x 10^{-3} mm^2/s), median D (U, 0.58 x 10^{-3} mm^2/s), and f (V, 131.18 x 10^{-3} mm^2/s) values.

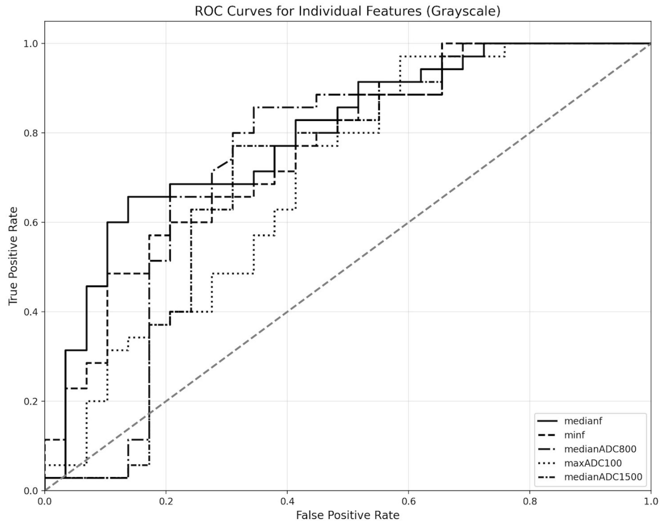

Figure 4. ROC curve analysis.

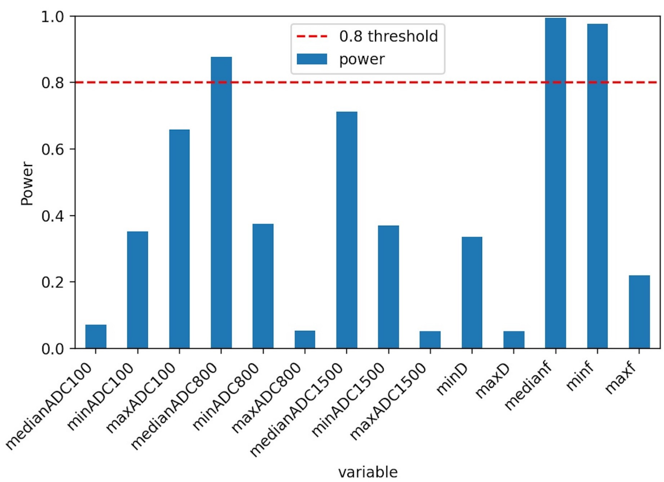

Figure 5. Post-test power analysis of IVIM parameters.

The D values were lower in the malignant group, but this difference was not significant. Surprisingly, the med f and min f values were significantly lower in malignant lesions. Although med f (AUC=0.79) showed a better diagnostic performance than conventional ADC (ADC800 AUC=0.74), this difference was not statistically significant. The reason for the reduced f can be explained by several factors. First, blood vessels in malignant tumors can be in abnormal structures that tend to be disorganized and leaky, so the overall blood flow within the tumor is lower than that in healthy tissue [19]. The dense cellular structure in malignant tumors may limit the movement of water molecules and the space available for blood perfusion, resulting in lower D and f values [11]. The heterogeneity of perfusion in breast tumors is a well-known issue. In one study, malignant lesions had an average of 27% of voxels with no perfusion at all [20]. Similarly, even more than 50% of the voxels exhibited no perfusion in another study [21]. Therefore, voxel-wise parameter calculations could be more accurate for perfusion analysis. Furthermore, unlike other simplified IVIM studies on the breast, the maximum b value in our study was b=1500, which is more susceptible to noise effects and Gaussian influences [22, 23]. Additionally, tumor

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perfusion values represent a parameter that reflects tumor aggressiveness. In the present study, there were no cases of triple-negative breast tumors, and the number of HER-2-positive, which are characterized by aggressive immunohistochemical profiles, patients was limited. This may have contributed to the lower perfusion values [24].

Perucho et al. designed an IVIM study to optimize b values in patients with cervical cancer. They stated that, although three *b*-values were sufficient for a simplified model, *Dlinear* and *f linear* had error rates of 1% and 8%, respectively, failing to maintain discriminative capability [25].

Several studies have shown that DWI demonstrates significant diagnostic value in characterizing breast tumors and may offer higher specificity compared to traditional MRI techniques [17, 26]. DWI is performed with 2-*b* values and is based on the assumption of a mono-exponential fit to obtain a decay constant. However, the signal attenuation observed in mono-exponential DWI is not always linear. DWI images fail to account for the microcirculation of blood. Le Bihan et al. introduced IVIM as a technique to differentiate the effects of diffusion and perfusion by applying a bi-exponential model to the signal decay using multiple *b*-values without requiring a contrast agent [15]. The traditional biexponential fitting model IVIM with multiple *b* values has some disadvantages, such as longer scanning time, increased complexity of execution and processing period, sensitivity to noise, and patient compliance [12]. SI-IVIM offers several advantages, such as reduced computational complexity and quicker and more straightforward data analysis, which are particularly advantageous in the clinical setting. Furthermore, the reduced time required to acquire data enhances patient comfort and compliance, which are essential considerations for regular clinical applications [13]. However, these methods have some disadvantages. An important drawback is the possible loss of accuracy and reliability in parameter estimation, because simplified models generally neglect the complex interactions between diffusion and perfusion within tissues. This may result in variability of parameters and decreased accuracy in differentiating tissue types or pathologies [27]. In IVIM imaging, the use of varying *b*-value ranges leads to inconsistencies in the IVIM parameters. There is no established consensus on the optimal *b* values, which may lead to variability in the results. Perfusion effects are generally more pronounced at b-values below 200 s/mm^2, and different thresholds can significantly alter IVIM parameters. Additional challenges, lack of standardized acquisition protocols, and different algorithms for analysis and motion artifacts, further affect the reliability and reproducibility of IVIM measurements [26, 28].

Limitations

The primary limitations of this study were the small number of patients and inadequate tumor diversity from an immunohistochemical perspective. Results of post-test power analysis suggests that larger sample sizes might be needed for more definitive conclusions about these metrics. Another limitation was that the segmentations were performed by a single individual, and neither the reproducibility of the VOIs nor the inter-observer variability was evaluated. In our study, a *b*-value of 1500 s/mm^2 was employed as the maximum *b*-value. This may result in higher non-Gaussian effects and noise-related biases [22, 23].

CONCLUSION

SI-IVIM parameters showed no significant diagnostic superiority over the ADC value in differentiating malignant breast lesions. Future studies conducted on larger and more diverse patient populations, as well as evaluating reproducibility and inter-observer variability, could further enhance the reliability and reproducibility of SI-IVIM for breast lesions.

Ethics Committee Approval: This study was approved by Baskent University Institutional Review Board and Ethics Committee (Protocol no: KA23/73).

Informed Consent: As the study was retrospective, the requirement for informed consent was waived.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Bing-Neel syndrome as a rare neurological complication of Waldenström macroglobulinemia: A case report

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ABSTRACT

Waldenström macroglobulinemia (WM) is a lymphoproliferative disorder characterized by lymphoplasmacytic infiltration and Immunoglobulin M (IgM) monoclonal gammopathy. Bing-Neel syndrome (BNS), a rare complication of WM, arises from direct infiltration of malignant lymphoplasmacytic cells into the central nervous system (CNS). This report presents a 66-year-old female patient who developed BNS 15 years after the initial diagnosis of WM. The patient presented with neurological symptoms including dizziness, imbalance, memory impairment, and speech disturbances. Brain magnetic resonance imaging (MRI) revealed leptomeningeal and dural enhancement accompanied by vasogenic edema. Laboratory findings showed IgM lambda monoclonal gammopathy and lymphoplasmacytic infiltration. Although histopathological confirmation could not be obtained, the clinical and radiological findings supported the diagnosis of BNS. Following treatment with a combination chemotherapy regimen of rituximab and bendamustine (R-BENDA), along with high-dose methotrexate, clinical and radiological regression was observed. This case highlights that BNS may develop years after the initial diagnosis of WM and should be considered in the differential diagnosis.

Keywords: Bing-Neel syndrome, Waldenström macroglobulinemia, Central nervous system, Magnetic resonance imaging, Case report

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INTRODUCTION

Waldenström macroglobulinemia (WM) is considered a lymphoplasmacytic lymphoma characterized by bone marrow involvement and Immunoglobulin M (IgM) monoclonal gammopathy [1]. WM most frequently presents with clinical features such as anemia and lymphoplasmacytic infiltration, primarily affecting the bone marrow, lymph nodes, and spleen, with occasional involvement of other organs.

In WM, neurological involvement typically manifests in two primary ways. Peripheral nerve infiltration (10–15%) usually presents as a distal, symmetrical, and slowly progressive sensorimotor neuropathy, whereas symptoms such as visual and hearing loss, vertigo, and ataxia may occur due to hyperviscosity syndrome (10–30%) [2]. However, infiltration of the central nervous system (CNS) by malignant cells is a rare condition and poses diagnostic challenges [3]. The condition was initially identified in 1936 by Jens Bing and Axel Valdemar Neel, who characterized it as a distinct neurological manifestation now known as "Bing-Neel syndrome (BNS)" [4].

Neuroradiological evaluations play a crucial role in the diagnosis of Bing-Neel syndrome. Magnetic resonance imaging (MRI) is a valuable diagnostic tool, particularly for detecting leptomeningeal involvement and parenchymal infiltrative lesions. In this report, we compare the clinical and radiological features of BNS in a patient previously diagnosed with WM to cases reported in the literature.

CASE REPORT

A 66-year-old female patient presented with complaints of dizziness, imbalance, memory loss, and word-finding difficulties persisting for approximately three months. Additionally, she reported a single episode of a suspected seizure lasting about 15 minutes. Over the past month, she also experienced fatigue, loss of appetite, and recurrent fever episodes reaching up to 38.5°C. Her medical history revealed a diagnosis of WM, for which she had been under follow-up for 15 years.

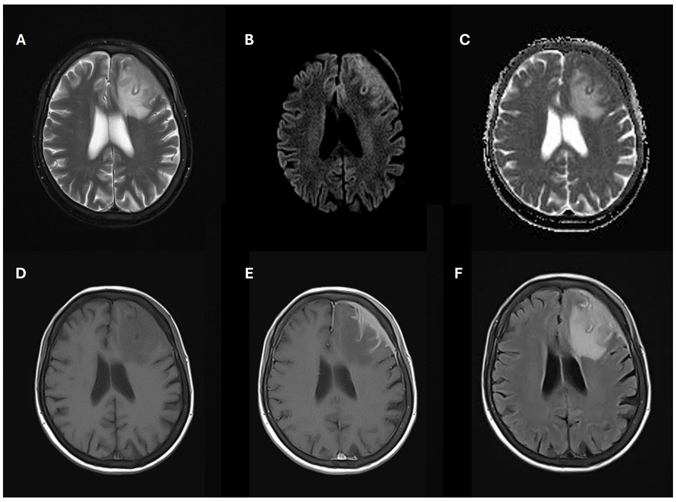

Figure 1. Magnetic resonance imaging findings at the time of diagnosis. On T2-weighted (A) and FLAIR (F) images, vasogenic edema adjacent to the lesion in the left frontal lobe is observed as a hyperintense signal. Diffusion-weighted imaging (B) and apparent diffusion coefficient map (C) demonstrate restricted diffusion within the lesion. The lesion appears hypointense on non-contrast T1-weighted image (D), while prominent contrast enhancement is seen on contrast-enhanced T1-weighted image (E).

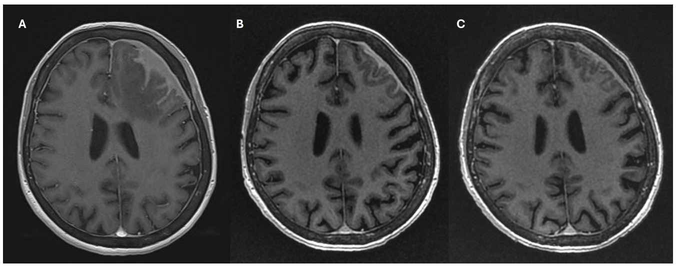

Figure 2. Contrast-enhanced thin-slice axial T1-weighted image at the time of BNS diagnosis is shown on the left (A). Follow-up images at 4 months (B) and 6 months (C) demonstrate marked regression of dural and leptomeningeal infiltration, with complete resolution of vasogenic edema.

The patient was in good general condition, cooperative, and oriented. Complete blood count: Mild anemia (Hb: 10.9 g/dL), lymphocytosis (LYM%: 51.8%), leukopenia (WBC: 3.4 K/μL), neutropenia (NEU: 1.08 K/μL). Elevated lactate dehydrogenase (LDH: 286 U/L) and hypergammaglobulinemia Serum immunofixation electrophoresis: IgM lambda monoclonal gammopathy. Bone marrow biopsy: Consistent with lymphoplasmacytic infiltration, confirming the diagnosis of WM.

Brain MRI revealed leptomeningeal enhancement with finger-like extensions into the left frontal parenchyma and prominent dural infiltration with contrast enhancement. On T2-weighted (T2W) images, signal hyperintensity consistent with vasogenic edema was observed in the adjacent left frontal lobe parenchyma, along with compression of the frontal horn of the left lateral ventricle. Diffusion-weighted imaging and apparent diffusion coefficient (ADC) maps demonstrated diffusion restriction in the areas of dural infiltration (Figure 1). Given the patient's known diagnosis of WM, the findings were considered consistent with Bing-Neel syndrome

The patient received alternating cycles of a combination chemotherapy regimen consisting of rituximab and bendamustine (R-BENDA), along with high-dose methotrexate (HD-MTX). In addition, dexamethasone therapy was initiated. We observed a marked improvement in the patient's neurological symptoms, alongside a noticeable recovery in cognitive function. Follow-up MRI at 4 and 6 months demonstrated partial regression of dural infiltration and complete resolution of the edema (Figure 2).

A signed informed consent form was obtained from the patient on June 18, 2024.

DISCUSSION

While neurological complications can occur in patients with Waldenström macroglobulinemia (WM), central nervous system (CNS) infiltration by malignant cells, known as Bing-Neel syndrome (BNS), is exceptionally rare [2,3,5,6]. Due to its scarcity, the radiological features of BNS aren't yet fully defined.

Imaging findings in BNS are generally categorized into two subtypes: the diffuse infiltrative form and the tumoral form. The infiltrative type most commonly appears in the brainstem, periventricular white matter, and leptomeninges. In contrast, the tumoral form presents as single or multifocal mass lesions, typically in deep hemispheric regions [7].

Another study noted that leptomeningeal involvement was the most frequent imaging finding in BNS. Dural involvement was seen in over one-third of cases, and parenchymal infiltration was more often in the brain than the spinal cord. Approximately 40% of cases showed increased signal intensity on T2-weighted images, with diffusion restriction detected in about a quarter [3].

In our patient, we observed dural and leptomeningeal infiltration with contrast enhancement. The differential diagnosis included meningioma, dural and leptomeningeal metastatic tumors, primary dural lymphoma, and non-neoplastic dural lesions like tuberculosis. However, given the patient's known WM diagnosis and supportive laboratory findings, BNS was considered the most probable diagnosis. While histopathological confirmation wasn't obtained, the observed regression in clinical and radiological findings after treatment strongly supports this diagnosis, emphasizing the importance of imaging-based diagnosis in selected cases.

Recent literature highlights the diagnostic value of MRI in BNS, especially using contrast-enhanced T1-weighted and FLAIR sequences to detect leptomeningeal and parenchymal involvement. Schep et al. recommend systematic brain and spine imaging, particularly when a biopsy isn't feasible [8]. Our imaging findings align with these recommendations, underscoring MRI's critical role in the early recognition of BNS.

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A 2015 study by Simon et al., which evaluated 44 reported cases, found that approximately one-third of patients presented with BNS as their initial clinical manifestation before a WM diagnosis. The study also revealed that BNS can develop at highly variable intervals, up to 25 years after the initial WM diagnosis [9]. Another study reported the mean interval from WM diagnosis to BNS onset was around 7 years [10]. In our case, BNS developed approximately 15 years after the WM diagnosis, consistent with existing literature.

CONCLUSION

Bing-Neel syndrome is a rare but clinically significant complication of Waldenström macroglobulinemia. Careful evaluation of radiological findings, interpreted within the clinical context, is paramount for early diagnosis and effective treatment.

Informed Consent: Written informed consent was obtained from the patient for publication and accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared by the authors.

Financial Disclosure: None declared by the authors.

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