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Beyond Weight Loss: The Promise and Predicament of Incretin-Based Therapies

✉ Feray Akbaş

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For decades, lifestyle modification—including dietary changes, physical activity and behavioral interventions—has remained a cornerstone of obesity management. However, growing recognition of obesity as a complex, chronic and multifactorial disease has highlighted the limitations of relying on lifestyle interventions alone for many patients (1). Metabolic and bariatric surgery has provided an effective treatment option, particularly for individuals with more severe obesity or obesity-related complications, yet it is not suitable for or acceptable to every patient (2). Consequently, effective and sustainable pharmacological therapies have become an increasingly important component of comprehensive obesity care.

The development of obesity management medications has been marked by both therapeutic advances and significant setbacks. Although several agents have offered clinically meaningful weight reduction, others have been withdrawn because of serious adverse effects, while the efficacy, tolerability or clinical applicability of available treatments has remained variable (3,4). Against this background, incretin-based therapies—particularly glucagon-like peptide-1 (GLP-1) receptor agonists and more recently, dual glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonists—have substantially reshaped the pharmacological landscape of obesity treatment (5,6).

Beyond their substantial weight-loss efficacy, incretin-based therapies have demonstrated clinically meaningful benefits across several cardiometabolic and obesity-related conditions. These include improvements in glycemic control and selected lipid parameters, as well as reductions in major adverse cardiovascular events with specific agents in defined high-risk populations (5,7). Evidence has also expanded into obesity-related heart failure with preserved ejection fraction, metabolic dysfunction-associated steatohepatitis, obstructive sleep apnea and symptomatic knee osteoarthritis (8-11). Although the magnitude and certainty of benefit vary by agent, indication, and patient population, these findings highlight the potential of incretin-based therapies to address multiple complications of obesity beyond body-weight reduction.

Despite these advances, important challenges remain. Gastrointestinal adverse effects are common, and although many are manageable, the safety profiles of these agents differ across drugs and patient

populations (12). Furthermore, their expanding use raises concerns regarding long-term treatment durability, equitable access, affordability, and appropriate prescribing. The high cost of these medications and limited reimbursement in some healthcare systems may prevent eligible patients from accessing treatment, potentially widening existing health inequalities (13). At the same time, social-media promotion and the availability of non-prescription access through unregulated channels may contribute to inappropriate use and expose patients to misleading information or potentially unsafe products and may encourage demand among individuals without an established clinical indication or appropriate medical assessment (14,15). When treatment is initiated without adequate evaluation, individualized prescribing, and appropriate follow-up, opportunities to identify contraindications, to manage adverse effects, and to ensure continuity of care may be missed.

Addressing these challenges requires a coordinated approach that balances equitable access with appropriate clinical use. Incretin-based therapies should be reimbursed for eligible patients with a clear clinical indication, as part of comprehensive obesity care, to reduce financial barriers and health inequalities. Their sale without a valid prescription, including through unregulated online channels, should be prevented by effective regulatory oversight and enforcement. Public education should emphasize that incretin-based therapies are evidence-based medications to manage obesity and its complications, not cosmetic or quick-fix solutions for weight loss. Treatment should be initiated following an individualized clinical assessment by an appropriately qualified healthcare professional, with specialist input when indicated, and be supported by appropriate prescribing, monitoring, and long-term follow-up. Ultimately, the success of incretin-based therapies should be measured not only by their efficacy in reducing body weight but also by our ability to ensure their safe, appropriate and equitable long-term use in the management of obesity.

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Antimicrobial Resistance Trends in *Acinetobacter* spp. and *Pseudomonas* spp. Across the Pre-, Pandemic, and Post-COVID-19 Periods

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ABSTRACT

Introduction: The Coronavirus Disease-2019 (COVID-19) pandemic substantially changed healthcare delivery and may have influenced antimicrobial resistance (AMR) through increased empirical antibiotic prescribing, prolonged intensive care admissions, and extensive use of invasive interventions. As leading causes of healthcare-associated bloodstream infections, *Acinetobacter* spp. and *Pseudomonas* spp. represent important indicators for evaluating changes in resistance patterns over time. This study investigated temporal variations in AMR among these pathogens before, during, and after the COVID-19 pandemic.

Methods: A retrospective observational study was conducted at University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital using blood culture isolates collected from January 2017 to December 2023. Adult hospitalized patients with non-fermentative Gram-negative bloodstream isolates were included. Antimicrobial susceptibility testing was interpreted according to the European Committee on Antimicrobial Susceptibility Testing breakpoints applicable at the time of analysis, and resistance profiles were compared across the pre-pandemic, pandemic, and post-pandemic periods.

Results: Overall, 740 *Acinetobacter* spp. and 268 *Pseudomonas* spp. isolates were evaluated. *Acinetobacter* spp. demonstrated a progressive increase in resistance to meropenem, colistin, gentamicin, and amikacin, with the highest resistance rates observed after the pandemic (all $p < 0.001$). Meropenem resistance reached 98%, whereas colistin resistance increased to 32.2%. In contrast, *Pseudomonas* spp. exhibited significantly lower resistance to amikacin, gentamicin, ciprofloxacin, and imipenem during the post-pandemic period (all $p < 0.05$), although the proportion of isolates with intermediate susceptibility increased for several antimicrobial agents.

Conclusion: Distinct changes in AMR patterns were observed following the COVID-19 pandemic, and these changes differed between bacterial species. The substantial increase in resistance among *Acinetobacter* spp., compared with the relatively favorable susceptibility profile of *Pseudomonas* spp., reinforces the need for ongoing local resistance surveillance, effective antimicrobial stewardship programs, and strengthened infection prevention measures.

Keywords: Antimicrobial resistance, gram-negative bacteria, bloodstream infection, COVID-19

Introduction

Bloodstream infections caused by Gram-negative pathogens rank among the most clinically significant healthcare-associated infections and present substantial therapeutic challenges because they are associated with elevated morbidity and mortality, particularly in critically ill patients. Among non-fermentative Gram-negative bacteria, *Acinetobacter* spp. and *Pseudomonas* spp. have a prominent role in hospital-acquired bloodstream infections owing to their ability to persist in the healthcare environment and to develop resistance to multiple antimicrobial agents (1-3).

The global expansion of antimicrobial resistance (AMR) has substantially complicated the management of infections caused by these pathogens. Several factors, including excessive antimicrobial consumption, prolonged hospitalization, invasive medical procedures, and persistent selective antimicrobial pressure, have accelerated the emergence and dissemination of resistant strains. As a result, increasing resistance to last-line therapeutic agents, particularly carbapenems and colistin, has become a major obstacle to effective treatment (4-6).



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The Coronavirus Disease-2019 (COVID-19) pandemic profoundly affected healthcare systems worldwide and introduced conditions that may have further influenced AMR patterns. Widespread empirical administration of broad-spectrum antibiotics, increased intensive care unit occupancy, prolonged hospital stays, and extensive use of invasive devices created favorable conditions for the selection and transmission of resistant microorganisms. Although the World Health Organization declared the end of the COVID-19 Public Health Emergency of International Concern on May 5, 2023, the consequences of these changes on AMR are likely to extend beyond the pandemic period (7,8).

Accumulating evidence indicates that the impact of the pandemic on AMR has not been uniform across bacterial species. Differences in ecological characteristics, resistance mechanisms, and responses to antimicrobial pressure may have resulted in distinct resistance trajectories among clinically important non-fermentative Gram-negative pathogens. Therefore, evaluating species-specific resistance trends is essential to better understand the long-term effects of the pandemic on hospital epidemiology (9,10).

Drawing on this reasoning, our working hypothesis was that the COVID-19 pandemic exerted differential effects on the resistance profiles of *Acinetobacter* spp. and *Pseudomonas* spp. To test this hypothesis, the current study sought to examine shifts in antimicrobial susceptibility among bloodstream isolates obtained across the pre-pandemic, pandemic, and post-pandemic timeframes at a tertiary-care hospital.

Methods

This retrospective observational study was conducted at University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital Training and Research Hospital, a tertiary-care institution with a capacity of 700 inpatient beds, including 100 intensive care unit beds. The study period extended from January 2017 through December 2023. Hospitalized patients aged ≥ 18 years with blood cultures yielding non-fermentative Gram-negative bacteria were eligible for inclusion. To avoid duplicate sampling, only the first bloodstream isolate obtained from each patient was analyzed.

Among all non-fermentative Gram-negative organisms identified during the study period, only *Acinetobacter* spp. and *Pseudomonas* spp. were included because these species had complete microbiological data and sufficient isolate numbers for reliable statistical analysis.

The study protocol was approved by the University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (decision number: 66-2024, approval date: August 29, 2024). As this is a retrospective study, informed consent was waived.

Patient characteristics, including age, sex, hospital ward, intensive care unit admission, bacterial species, and antimicrobial susceptibility results, were retrieved retrospectively from the Hospital Information Management System and the Laboratory Information System.

Blood culture bottles were processed using the automated BACTEC FX blood culture system (BD Diagnostics, USA). Positive cultures were subcultured; bacterial identification and antimicrobial susceptibility testing were then performed using the VITEK® 2 automated identification system (bioMérieux, France). Susceptibility interpretations

were based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints that were applicable at the time each isolate was tested (11). Colistin susceptibility was determined by the reference broth microdilution method in accordance with current EUCAST recommendations. Isolates with incomplete or inaccurate microbiological records were excluded from the analysis.

For temporal comparisons, the study interval was divided into three predefined periods: the pre-pandemic period (January 2017-March 2020), the pandemic period (March 2020-December 2022), and the post-pandemic period (January 2023-December 2023).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was evaluated with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables are presented as mean $\pm$ standard deviation, while median values were additionally provided in the tables to facilitate interpretation of data distribution. Categorical variables are expressed as frequencies and percentages.

Comparisons of categorical variables between study periods were performed using the chi-square test or Fisher's exact test when appropriate. Continuous variables were compared using the Kruskal-Wallis test. When statistically significant overall differences were identified, pairwise comparisons were conducted using the Mann-Whitney U test with Bonferroni correction. All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant.

Results

A total of 740 *Acinetobacter* spp. isolates were included in the study: 191 from the pre-pandemic period, 369 from the pandemic period, and 180 from the post-pandemic period. The mean age of patients differed significantly between periods ($p = 0.007$). No statistically significant differences were found between periods with respect to gender distribution or patient admission location ($p > 0.05$).

When antibiotic susceptibility results were evaluated, resistance rates to amikacin, colistin, gentamicin, and meropenem showed significant differences between periods ($p < 0.001$). In particular, a marked increase in resistance rates to these antibiotics was observed in the post-pandemic period (Table 1).

When *Pseudomonas* spp. isolates were examined, 77 were evaluated in the pre-pandemic period, 113 in the pandemic period, and 78 in the post-pandemic period. The mean age of patients differed significantly between periods ($p < 0.001$). In contrast, no significant differences were found between the periods regarding gender distribution and patient admission locations ($p > 0.05$).

Analysis of antibiotic susceptibility results indicated that the resistance rates for amikacin, gentamicin, ciprofloxacin, and imipenem differed significantly between periods ($p < 0.05$). Rates of resistance to these antibiotics decreased, particularly in the post-pandemic period. In contrast, no statistically significant differences were found between periods for ceftazidime and colistin ($p > 0.05$) (Table 2).

Table 1. Demographic characteristics of patients with *Acinetobacter* spp. growth and antibiotic susceptibility of isolates

Variable	Pre-pandemic (n=191)	Pandemic period (n=369)	Post-pandemic (n=180)	p value/test
Age (mean ± SD)	68.4±18.7	64.7±16.6	66.7±16.8	0.007 (Kruskal-Wallis)
Median age	72.0	67.0	69.0	
Female, n (%)	86 (45.0%)	150 (40.7%)	72 (40.0%)	0.535 (chi-square)
Male, n (%)	105 (55.0%)	219 (59.3%)	108 (60.0%)	
Hospital ward, n (%)	44 (23.0%)	58 (15.7%)	31 (17.2%)	0.097 (chi-square)
ICU, n (%)	147 (77.0%)	311 (84.3%)	149 (82.8%)	
Amikacin-susceptible, n (%)	73 (38.2%)	118 (32.0%)	12 (6.7%)	p<0.001 (chi-square)
Amikacin-intermediate, n (%)	3 (1.6%)	1 (0.3%)	0 (0.0%)	
Amikacin-resistant, n (%)	115 (60.2%)	250 (67.8%)	168 (93.3%)	
Colistin-susceptible, n (%)	184 (96.3%)	353 (96.2%)	87 (59.6%)	p<0.001 (chi-square)
Colistin-intermediate, n (%)	0 (0.0%)	1 (0.3%)	12 (8.2%)	
Colistin-resistant, n (%)	7 (3.7%)	13 (3.5%)	47 (32.2%)	
Gentamicin-susceptible, n (%)	80 (41.9%)	88 (23.9%)	12 (9.4%)	p<0.001 (chi-square)
Gentamicin-intermediate, n (%)	0 (0.0%)	5 (1.4%)	0 (0.0%)	
Gentamicin-resistant, n (%)	111 (58.1%)	275 (74.7%)	116 (90.6%)	
Meropenem-susceptible, n (%)	38 (20.0%)	55 (14.9%)	3 (2.0%)	p<0.001 (chi-square)
Meropenem-intermediate, n (%)	1 (0.5%)	30 (8.2%)	0 (0.0%)	
Meropenem-resistant, n (%)	151 (79.5%)	283 (76.9%)	147 (98.0%)	

K: Kruskal-Wallis test (Mann-Whitney U for post-hoc comparisons), X²: Chi-square test (Fisher's exact test when appropriate)
SD: Standard deviation, ICU: Intensive care unit

Table 2. Demographic characteristics of patients with *Pseudomonas* spp. growth and antibiotic susceptibility of isolates

Variable	Pre-pandemic (n=77)	Pandemic period (n=113)	Post-pandemic (n=78)	p value/test
Age (mean ± SD)	70.1±16.9	60.3±17.4	69.3±14.4	p<0.001 (Kruskal-Wallis)
Median age	70.0	64.0	71.0	
Female, n (%)	32 (41.6%)	42 (37.2%)	34 (43.6%)	0.650 (chi-square)
Male, n (%)	45 (58.4%)	71 (62.8%)	44 (56.4%)	
Hospital ward, n (%)	19 (24.7%)	31 (27.4%)	31 (39.7%)	0.087 (chi-square)
ICU, n (%)	58 (75.3%)	82 (72.6%)	47 (60.3%)	
Amikacin-susceptible, n (%)	21 (29.2%)	46 (51.7%)	63 (90.0%)	p<0.001 (chi-square)
Amikacin-intermediate, n (%)	3 (4.2%)	1 (1.1%)	0 (0.0%)	
Amikacin-resistant, n (%)	48 (66.7%)	42 (47.2%)	7 (10.0%)	
Colistin-susceptible, n (%)	69 (95.8%)	84 (94.4%)	36 (72.0%)	0.204 (chi-square)
Colistin-intermediate, n (%)	0 (0.0%)	0 (0.0%)	8 (16.0%)	
Colistin-resistant, n (%)	3 (4.2%)	5 (5.6%)	6 (12.0%)	
Gentamicin-susceptible, n (%)	31 (41.3%)	51 (51.0%)	13 (86.7%)	0.005 (chi-square)
Gentamicin-intermediate, n (%)	0 (0.0%)	3 (3.0%)	0 (0.0%)	
Gentamicin-resistant, n (%)	44 (58.7%)	46 (46.0%)	2 (13.3%)	
Ceftazidime-susceptible, n (%)	12 (52.2%)	30 (49.2%)	29 (39.7%)	0.280 (chi-square)
Ceftazidime-intermediate, n (%)	0 (0.0%)	13 (21.3%)	17 (23.3%)	
Ceftazidime-resistant, n (%)	11 (47.8%)	18 (29.5%)	27 (37.0%)	
Ciprofloxacin-susceptible, n (%)	19 (25.3%)	20 (20.6%)	10 (13.2%)	p<0.001 (chi-square)
Ciprofloxacin-intermediate, n (%)	0 (0.0%)	29 (29.9%)	46 (60.5%)	
Ciprofloxacin-resistant, n (%)	56 (74.7%)	48 (49.5%)	20 (26.3%)	
Imipenem-susceptible, n (%)	20 (27.0%)	26 (26.5%)	9 (13.0%)	0.008 (chi-square)
Imipenem-intermediate, n (%)	0 (0.0%)	15 (15.3%)	27 (39.1%)	
Imipenem-resistant, n (%)	54 (73.0%)	57 (58.2%)	33 (47.8%)	

K: Kruskal-Wallis test (Mann-Whitney U for post-hoc comparisons), X²: Chi-square test (Fisher's exact test when appropriate)
SD: Standard deviation, ICU: Intensive care unit

Discussion

This study revealed that the AMR profiles of non-fermentative Gram-negative bloodstream isolates underwent notable shifts across the pre-pandemic, pandemic, and post-pandemic timeframes. While *Acinetobacter* spp. exhibited a substantial increase in resistance to several last-line antimicrobial agents, *Pseudomonas* spp. showed more variable susceptibility profiles, with reduced resistance to selected antibiotics. These findings indicate that the impact of the COVID-19 pandemic on AMR differed between these two major non-fermentative Gram-negative pathogens.

The clinically significant escalation in resistance among *Acinetobacter* spp., particularly to meropenem and colistin, is concerning because these agents constitute critical therapeutic pillars for managing severe nosocomial bloodstream infections. Several factors associated with the pandemic may have contributed to this increase, including the widespread empirical use of broad-spectrum antibiotics, prolonged stays in intensive care units, more frequent invasive procedures, and disruptions in antimicrobial stewardship and infection prevention practices. Moreover, the well-established ability of *Acinetobacter* spp. to survive in the hospital environment and to readily acquire resistance mechanisms may have promoted the persistence and dissemination of multidrug-resistant strains during and after the pandemic.

Previous studies have identified *Acinetobacter* spp. and *Pseudomonas* spp. as the predominant non-fermentative Gram-negative pathogens causing hospital-acquired bloodstream infections, particularly in intensive care units. The EUROACT-2 and VIRAPERU studies also reported high carbapenem resistance rates among *Acinetobacter* isolates and highlighted the considerable burden of multidrug-resistant Gram-negative bacteria in critically ill patients (12,13). Similarly, Müderris et al. (14) reported that *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were among the most frequently isolated pathogens causing superinfections in patients with COVID-19, whereas Özçelik et al. (15) identified these microorganisms as the predominant non-fermentative Gram-negative isolates recovered from blood cultures of intensive care unit patients. Our findings are consistent with these reports; however, they further demonstrate that AMR evolved differently in the two species over time. Specifically, resistance increased markedly in *Acinetobacter* spp. during the post-pandemic period, whereas *Pseudomonas* spp. showed relatively stable or even reduced resistance to several antimicrobial agents.

The effects of the COVID-19 pandemic on resistance patterns have been similarly documented in the literature. Etiz et al. (16) and Araj et al. (17) both noted a rise in resistance among hospital-acquired Gram-negative organisms during and following the pandemic, attributing these trends to modifications in antibiotic prescribing behaviors and the overwhelming strain placed on healthcare infrastructure. Our results agree with these observations but also suggest that the magnitude of these changes may vary by bacterial species. The pronounced increase in resistance among *Acinetobacter* spp., together with a more heterogeneous response observed in *Pseudomonas* spp., indicates that the ecological consequences of the pandemic were not uniform across non-fermentative Gram-negative pathogens.

A systematic review focusing on *Pseudomonas aeruginosa* bloodstream infections among COVID-19 patients highlighted extended ICU stays, dependence on mechanical ventilation, and broad-spectrum antibiotic exposure as key predisposing factors in critically ill individuals (18). Although our findings confirm the continued clinical importance of *Pseudomonas* spp. in this setting, the reduction in resistance observed for several antimicrobial agents during the post-pandemic period suggests that antimicrobial stewardship practices, infection control measures, or changes in patient characteristics may have influenced resistance patterns differently from those observed in *Acinetobacter* spp. This underscores the importance of conducting pathogen-specific analyses rather than grouping all non-fermentative Gram-negative bacteria together when evaluating resistance dynamics.

Overall, our findings indicate that the COVID-19 pandemic was associated with species-specific changes in AMR among non-fermentative Gram-negative bloodstream isolates. The marked increase in resistance observed in *Acinetobacter* spp., particularly against last-line antimicrobial agents, highlights the ongoing need for local resistance surveillance, effective antimicrobial stewardship, and robust infection prevention strategies to preserve the efficacy of currently available treatment options.

Study Limitations

This study has several limitations. First, the study was conducted at a single center, and the findings may not be generalizable to other hospitals and healthcare settings. Second, due to the retrospective design of the study, data on some clinical variables may be limited, and potential information bias may have occurred. Furthermore, the lack of detailed antibiotic consumption data for the study period limited the direct assessment of the relationship between antibiotic use and AMR trends. Finally, the lack of analysis of parameters such as mortality, length of hospital stay, or clinical outcomes limited the assessment of the clinical impact of the observed resistance changes.

Another limitation of this study is the unequal duration of the study periods. While the pre-pandemic and pandemic periods covered several years, the post-pandemic period included only one year (2023). Therefore, the findings related to the post-pandemic period should be interpreted with caution, as the shorter observation period may have influenced the observed AMR trends.

Changes in EUCAST breakpoint definitions and the reclassification of the “I” category as “Susceptible, increased exposure” may have influenced susceptibility categorization across the study period.

Conclusion

The COVID-19 pandemic was associated with pathogen-specific changes in AMR among non-fermentative Gram-negative bloodstream isolates. While *Acinetobacter* spp. demonstrated a marked post-pandemic increase in resistance to several last-line antimicrobial agents, *Pseudomonas* spp. exhibited more favorable susceptibility trends to selected antibiotics. These observations underscore that the pandemic's influence on resistance was not homogeneous across bacterial species and reinforce the critical role of sustained local surveillance,

antimicrobial stewardship initiatives, and robust infection prevention protocols in guiding empirical treatment decisions and safeguarding remaining therapeutic options.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (decision number: 66-2024, approval date: August 29, 2024).

Informed Consent: As this is a retrospective study, informed consent was waived.

Footnotes

Authorship Contributions: Concept - E.Z., M.K.T., H.T., H.E., Ü.A.; Design - E.Z., H.T., H.E., Ü.A.; Data Collection or Processing - M.K.T., H.T.; Analysis or Interpretation - H.T.; Literature Search - E.Z., M.K.T., H.E., Ü.A.; Writing - E.Z., M.K.T.

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The Relationship Between Load-Capacity Index and Common Geriatric Syndromes

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ABSTRACT

Introduction: The body mass index (BMI) does not accurately reflect changes in fat and muscle with age. The metabolic load-capacity framework identifies fat as “load” and muscle as “capacity”; this is measured by the load-capacity index (LCI), defined as the fat-mass-to-fat-free-mass ratio (FM/FFM). This study examined the relationship between LCI and health outcomes in older adults across obesity levels defined by BMI.

Methods: This study included adults aged 65 years and older who visited the Geriatric Outpatient Clinic from January 2024 to April 2025. A total of 113 participants were divided into two groups based on the number of geriatric syndromes: low (0-2 syndromes; 55 participants) and high (3 or more syndromes; 58 participants). The study used statistical tests to compare the groups and to examine the association between LCI and the frailty index, the SARC-F score, and the total number of geriatric syndromes.

Results: The high syndrome burden group demonstrated significantly worse physical performance, higher LCI, greater FM, lower lean body mass, poorer nutritional status, reduced functional independence, and higher rates of depression, polypharmacy, falls, urinary incontinence, and obesity compared with the low burden group, whereas age, sex, walking speed, and cognitive status did not differ between groups. In the obesity subgroup, objective performance measures and functional independence were comparable to those of the non-obese group, yet frailty, sarcopenia risk, syndrome burden, and LCI were significantly elevated, underscoring the limitations of BMI alone. LCI showed significant, moderate positive correlations with the frailty index, the SARC-F score, and the total number of geriatric syndromes.

Conclusion: Elevated LCI values were significantly associated with increased frailty, higher SARC-F scores, and a greater prevalence of geriatric syndromes. This finding supports the use of FM/FFM as a practical, biologically meaningful adjunct to CGA for screening and risk stratification in older adults.

Keywords: Geriatric syndromes, load-capacity index, body composition, frailty

Introduction

The aging trend of the global population has redirected the focus of geriatric medicine from addressing individual diseases to the comprehensive management of complex health conditions in older adults (1). Geriatric syndromes, including falls, urinary incontinence, cognitive impairment, malnutrition, and frailty, are considered clinical indicators that better reflect the overall health status of older adults than isolated diagnoses (2). The fundamental mechanism underlying these syndromes is the reduction in physiological reserves and narrowing of homeostatic capacity that occurs with aging. Because frailty represents heightened susceptibility to adverse outcomes when homeostatic reserves are depleted, body composition-centered models have emerged

as a promising avenue for clarifying the biological substrate of the aging phenotype (3).

Aging is accompanied by opposing shifts in tissue distribution: skeletal muscle steadily declines while adipose accumulation continues, and standard anthropometry, most notably body mass index (BMI), fails to register this reciprocal remodeling. Consequently, even patients whose weight and BMI remain within the reference ranges may exhibit a sarcopenic-obese phenotype in which reduced lean mass and expanded fat depots coexist. Research has consistently shown that BMI is insufficient for assessing the relationship between body composition and frailty, highlighting the need for more comprehensive indices (4).



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The load-capacity model of body composition provides a conceptual framework to address this limitation. Within this framework, visceral adiposity acts as a metabolic burden driving impaired insulin signaling, persistent low-grade inflammatory activity, and oxidative injury, whereas skeletal muscle constitutes the compensatory reserve that offsets these deleterious inputs (5,6). When the metabolic load exceeds the available capacity, the risk of adverse health outcomes increases. The load capacity index (LCI), operationally defined as the ratio of fat-mass to fat-free mass (FM/FFM), quantifies this balance as a single, continuous, dimensionless metric derived from body composition parameters (7). Several load-to-capacity ratios have been proposed in the literature, including the appendicular skeletal muscle mass to total body fat ratio (ASM/TBF) and trunk FM to ASM mass ratio (TrFM/ASM). Among these, the FM/FFM ratio was selected for the present study because it can be readily calculated from any bioelectrical impedance analysis (BIA) device without requiring segmental or regional body composition data, thereby offering broader clinical applicability in settings where advanced imaging modalities such as dual-energy X-ray absorptiometry (DXA), computed tomography or magnetic resonance imaging are not feasible (8).

Clinical studies have demonstrated that higher load-to-capacity ratios are associated with physical limitations, reduced walking speed, diabetes, metabolic syndrome, and cardiovascular disease (8). However, the relationship between LCI and common geriatric syndromes, including frailty, sarcopenia, falls, cognitive impairment, and malnutrition, has not been sufficiently explored.

This study aimed to investigate the relationship between the FM/FFM ratio, a BIA-derived metabolic LCI, and common geriatric syndromes, and to evaluate the potential utility of this ratio as a practical screening and risk-stratification tool that reflects metabolic imbalance in the context of comprehensive geriatric assessment (CGA). We hypothesized that higher LCI values would be positively associated with a greater burden of geriatric syndromes, and sought to explore whether this association persists across BMI-defined obesity categories.

Methods

Study Design

This retrospective, observational, cross-sectional study included individuals aged ≥ 65 years who attended at Istanbul University-Cerrahpaşa Faculty of Medicine, Department of Geriatrics Outpatient Clinic between January 2024 and April 2025. The protocol conformed to the ethical principles set out in the Declaration of Helsinki. The Istanbul University-Cerrahpaşa Faculty of Medicine Ethics Committee granted retrospective institutional review and approval for the analysis of anonymized outpatient records on 01 October 2025 (decision number: 2025/646). Sample size estimation was performed a priori using G*Power software (version 3.1.9.7). The calculation was based on an independent-samples t-test comparing obese and non-obese older adults. Assuming a two-sided α level of 0.05, a statistical power ($1-\beta$) of 80%, an allocation ratio of 1:1, and a moderate effect size (Cohen's d : 0.48), derived from

previous studies on body composition in older adults, the minimum required sample size was calculated to be 110 participants (55 per group). The statistical power achieved for this sample size was 80.4%.

Participants were stratified by obesity status, as obesity affects body composition, physical performance, and the prevalence of geriatric syndromes. Stratification permitted examination of the association between the LCI and geriatric outcomes within more homogeneous subgroups. Because only de-identified data collected during routine outpatient care were analyzed, the Ethics Committee waived the requirement for individual informed consent.

Inclusion and Exclusion Criteria

Patients aged ≥ 65 years who underwent CGA and body composition analysis during the study period were deemed eligible for inclusion. The following exclusion criteria were applied: presence of a pacemaker, defibrillator, or active electronic or metal implants; limb amputation; a diagnosis of active malignancy or receipt of oncological treatment within the last 6 months; terminal organ failure (advanced heart, liver, or kidney failure); and severe cognitive impairment that would prevent completion of the survey forms. From the eligible patient pool with complete data records, those meeting the inclusion criteria were selected for analysis.

The study population was divided into two groups according to the median value of the total number of geriatric syndromes: "Low Syndrome Burden" (0-2 syndromes) and "High Syndrome Burden" (≥ 3 syndromes). Additionally, participants were categorized and compared as patients with obesity (BMI ≥ 30 kg/m²) and patients without obesity (BMI < 30 kg/m²) based on their BMI values.

Comprehensive Geriatric Assessment

A CGA was conducted by a specialist geriatrician using standardized, validated tools (Table 1). Body composition was evaluated using BIA. FM and FFM were measured, and the LCI was calculated as the FM/FFM ratio. All CGA components, including nutritional screening, sarcopenia risk, cumulative deficit frailty, cognition, functional independence, and objective physical performance, were assessed using the validated instruments and cut-offs summarized in Table 1. Body composition indices (FM, FFM, and LCI) were derived from bioimpedance analysis, and standard demographic and clinical variables were extracted from medical records.

In addition, demographic and clinical data, including age, sex, medication use, history of falls, urinary incontinence, and comorbidities, were recorded using a standard data collection form (9).

Physical Performance and Body Composition Measurements

Handgrip strength was quantified using a Takei TKK 5401 dynamometer (Takei Scientific Instruments, Tokyo, Japan) in a seated position with 90° elbow flexion; the best of three trials per hand was retained. Physical performance testing comprised the 6-meter gait speed measurement and the five-repetition sit-to-stand test, both timed to the nearest second.

Table 1. Geriatric Assessment

Category	Tool/parameter	Cut-off values and interpretation
Obesity status	BMI	BMI ≥ 30 kg/m²: Patient with obesity BMI < 30 kg/m²: Patient without obesity
Probable sarcopenia	SARC-F and handgrip	SARC-F ≥ 4 Low handgrip strength
Medication	Polypharmacy	≥ 5 medications: Polypharmacy present
Nutrition	MNA (SF/LF)	SF < 12: Malnutrition risk; LF < 17: Malnutrition
Frailty	FRAIL scale	0: Robust; 1-2: Pre-frail; 3-5: Frail
Depression	GDS-15	≥ 5 points: Presence of depressive symptoms
Cognition	SMMSE	< 24 points: Cognitive impairment suspicion
Functionality	IADL/Katz ADL	IADL 17/Katz 0: Full independence
Muscle strength	Handgrip (HGS)	Male < 27 kg; female < 16 kg: Low strength
Performance	Gait speed/5xSTS	≤ 0.8 m/s/> 15 sec: Low physical performance

BMI: Body mass index, SARC-F: Strength, assistance with walking, rise from a chair, climb stairs, and falls, MNA: Mini nutritional assessment, SF: Short form, LF: Long form, FRAIL: Fatigue, resistance, ambulation, illness, and loss of weight, GDS-15: Geriatric depression scale (short form), SMMSE: Standard mini-mental state examination, ADL/IADL: Activities of daily living/ Instrumental activities of daily living, HGS: Handgrip strength, 5xSTS: 5 times sit-to-stand test

Body composition was assessed using BIA with the Tanita Body Composition Analyzer TBF-300 (Tanita Co., Tokyo, Japan) after a 12-hour fast; FM and FFM were obtained. The main focus of the study, the LCI, was calculated by dividing FM, which represents metabolic load, by FFM, which represents functional capacity ($LCI = FM/FFM$) (10).

Statistical Analysis

Analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Distributional characteristics of continuous variables were first assessed using Shapiro-Wilk and Kolmogorov-Smirnov tests. Variables meeting normality assumptions are reported as mean $\pm$ standard deviation; otherwise, median with interquartile range is given. Two-group comparisons relied on Student's t-test when parametric assumptions held, and on the Mann-Whitney U test otherwise, whereas categorical variables were contrasted using Pearson's chi-square test. The associations of LCI with the FRAIL score, SARC-F, and cumulative geriatric syndrome count were examined using Spearman's rank correlation. Significance was defined as a two-tailed p-value below 0.05. Where appropriate, effect sizes and 95% confidence intervals accompany the primary comparisons to convey both magnitude and precision.

Results

A total of 113 individuals aged ≥ 65 years, who were evaluated in terms of functionality and multimorbidity, and whose CGA were completed, were included in the study. Accordingly, participants were divided into the low syndrome burden group (0-2 syndromes, $n=55$) and the high syndrome burden group (≥ 3 syndromes, $n=58$). In the subgroup analysis, participants were also categorized into two groups according to the World Health Organization BMI classification: patients with obesity ($BMI \geq 30$ kg/m², $n=45$) and patients without obesity ($BMI < 30$ kg/m², $n=68$).

No significant differences were found between the groups with low and high syndrome burdens in terms of age ($p=0.07$), sex ($p=0.21$), walking speed ($p=0.09$), or cognitive status ($p=0.12$). In the group with a high

syndrome burden, handgrip strength was lower ($p=0.0004$), sit-to-stand times were longer ($p=0.01$), LCI values were significantly higher ($p=0.007$), and mobility scores were worse ($p<0.0001$). Compared with the low syndrome burden group, the high syndrome burden group had GDS scores ($p<0.0001$), sleep problems ($p=0.002$), polypharmacy rates ($p=0.0001$), and FM ($p=0.04$). Similarly, the number of falls ($p=0.0003$), the presence of urinary incontinence ($p=0.0001$), and the prevalence of obesity ($p=0.002$) were significantly elevated in this cohort. Conversely, functional independence ($p=0.005$), nutritional status ($p=0.002$), and lean body mass ($p=0.01$) were significantly lower in individuals with a high syndrome burden (Table 2).

When the obesity group was compared with the non-obesity group, no significant differences were observed in age ($p=0.21$), gender distribution ($p=0.35$), handgrip strength ($p=0.30$), sit-to-stand time ($p=0.22$), walking speed ($p=0.67$), cognitive status ($p=0.61$), or functional independence ($p=0.20$). The SARC-F score ($p=0.0006$), frailty index ($p<0.0001$), FM ($p<0.0001$), lean body mass ($p=0.03$), and geriatric syndrome burden ($p=0.003$) were higher in the obesity group. LCI was significantly higher in the obese group ($p<0.0001$). No significant differences were observed between the groups in terms of handgrip strength, sit-to-stand time, walking speed, prevalence of sarcopenia, nutritional status, instrumental activities of daily living, cognitive status, polypharmacy, incontinence, antidepressant use, or mobility score (Table 3).

The analysis of the relationship between LCI values and clinical parameters revealed moderate, statistically significant positive correlations with the frailty index ($r: 0.4046$, $p<0.0001$), SARC-F scores ($r: 0.3666$, $p<0.0001$), and the total number of geriatric syndromes ($r: 0.3250$, $p=0.004$). The findings are summarized in Table 4.

Discussion

The primary finding of this study was that an increase in the LCI, which represents the ratio of FM to lean body mass, was independently associated with a higher prevalence of geriatric syndromes. Our results demonstrate that individuals with an elevated LCI exhibit significantly higher frailty indices and SARC-F scores, suggesting that an unfavorable

Table 2. Comparison of demographic data and anthropometric measurements based on the number of geriatric syndromes

	Number of geriatric syndromes (0-2) n=55	Number of geriatric syndromes (≥3) n=58	p
Age (years)*	74.20±6.42	76.29±5.34	0.07
Gender (male/female)***	9/46 (83.6% female)	5/53 (91.3% female)	0.21
HGS** (kg)	24 (20-30)	20 (16-24.5)	0.0004
5xSTS** (s)	14.3 (12-16.27)	16 (13.55-20)	0.01
Gait speed* (m/s)	0.64±0.20	0.58±0.21	0.09
BMI** (kg/m ²)	27.7 (25.68-30.03)	30.30 (24-33.15)	0.18
SARC-F**	1 (0-2)	4 (2-5)	<0.0001
Frailty index**	1 (0-2)	2 (2-3)	<0.0001
GDS-15**	1 (0-2.25)	4 (2-8)	<0.0001
Sleep problem***	7/55 (12.7%)	26/58 (44.8%)	0.002
Polypharmacy***	20/55 (36.3%)	42/58 (72.4%)	0.0001
FM (kg/m ²)**	8.93 (7.93-10.54)	10.33 (8.16-12.08)	0.04
FFM (kg/m ²)**	5.83 (5.7-6.56)	5.45 (5.3-6.16)	0.01
Load capacity index**	1.55 (1.23-1.85)	1.79 (1.50-2.12)	0.007
Waist-to-hip ratio**	0.906 (0.82-0.95)	0.891 (0.83-0.97)	0.87
Sarcopenia***	8/55 (14.5%)	28/58 (48.2%)	0.0001
MNA-SF**	14 (11-14)	12 (10-14)	0.007
MNA total**	26.75 (24.38-28)	24.50 (21-27)	0.002
Lawton IADL**	16 (13.75-17)	14 (10-16.5)	0.005
SMMSE**	28 (27-29)	27 (25-29)	0.12
Antidepressant usage***	8/55 (14.5%)	12/58 (20.6%)	0.39
Number of falls**	0 (0-1)	1 (0-2)	0.0003
Incontinence***	11/55 (20%)	32/58 (55.17%)	0.0001
Mobility score (0-6)**	6 (5-7)	5 (3-6)	<0.0001
Number of drugs**	4 (2-5)	6 (4-8)	<0.0001
Obesity**	14/55 (25.4%)	31/58 (53.4%)	0.002

*mean ± standard deviation, **median (25th percentile-75th percentile), ***n (%). BMI: Body mass index, SARC-F: Strength, assistance with walking, rise from a chair, climb stairs, and falls, MNA: Mini nutritional assessment, SF: Short form, GDS-15: Geriatric depression scale (short form), SMMSE: Standardized mini-mental state examination, IADL: Instrumental activities of daily living, HGS: Handgrip strength, 5xSTS: 5 times sit-to-stand test, FM (kg/m²): Fat mass, FFM (kg/m²): Free fat mass

balance between metabolic load and physiological reserve may be a key driver of the frailty phenotype in advanced age (8). This observation is coherent with the load-capacity framework, in which fat compartments impose metabolic stress while lean mass sustains functional reserve; accordingly, the clinical consequences of body composition emerge not from absolute amounts but from the equilibrium or lack thereof between these two axes (11). Recent evidence corroborates this concept, showing that higher LCIs are superior to traditional anthropometric measurements in predicting adverse cardiometabolic outcomes and overall risks (12).

Our findings are consistent with existing literature, showing that a disproportionate fat-to-lean mass ratio is associated with adverse health outcomes. Previous studies have established that a diminished muscle-to-visceral-fat ratio is associated with metabolic syndrome and vascular stiffness, and that increases in the fat-to-muscle ratio are accompanied by parallel increases in cardiovascular event rates and mortality risk. While these studies primarily focused on metabolic and prognostic outcomes, our study extends these observations to geriatric syndromes by demonstrating significant associations between LCI, frailty,

sarcopenia risk, and the burden of geriatric syndromes (13). Notably, participants with high LCI values demonstrated lower grip strength and prolonged sit-to-stand durations, reinforcing the notion that LCI reflects a simultaneous state of increased metabolic stress and depleted physiological reserve (14).

An especially informative finding emerged within the obese stratum, where LCI elevations tracked closely with frailty and the burden of geriatric syndromes, despite the absence of any meaningful correlation between BMI and performance, suggesting that BMI-based categorization systematically fails to detect functionally vulnerable obese older adults. Thus, LCI may serve as a more sensitive surrogate for identifying “at-risk” older adults with obesity who possess hidden functional deficits (13).

Interestingly, no significant association was found between the LCI and cognitive assessment scores, which contradicts some reports linking skeletal muscle depletion to cognitive impairment (15). This discrepancy should be interpreted with caution. The relatively low sensitivity of brief screening tools in detecting mild cognitive impairment and the potential “ceiling effect” in our sample may have obscured this relationship (16).

Table 3. Comparison of demographic and anthropometric measurements between patients with and without obesity

	Patient with obesity (n=45)	Patient with obesity (68)	p
Age (years)*	74.41±5.4	75.84±6.19	0.21
Gender (male/female)***	4/41 (91% female)	10/58 (85% female)	0.35
HGS** (kg)	22 (16-28)	22.6 (18-28)	0.30
5xSTS** (s)	15 (13.85-19.15)	14.85 (12-17.96)	0.22
Gait speed* (m/s)	0.62±0.23	0.60±0.20	0.67
BMI** (kg/m ²)	33.3 (31.6-36.4)	25.85 (23.2-27)	<0.0001
SARC-F**	3 (2-5)	2 (1-3)	0.0006
Frailty index**	2 (1-3)	1 (0-2)	<0.0001
GDS-15**	3 (0.5-8)	2 (1-3.75)	0.20
Sleep problem***	17/45 (37.78%)	17/68 (25%)	0.14
Polypharmacy***	29/45 (64.4%)	36/68 (52.94%)	0.22
FM (kg/m ²)**	35 (32-38)	25 (21-27)	<0.0001
FFM (kg/m ²)**	18.10 (16.65-19.15)	17.26 (16.40-17.70)	0.03
Load capacity index**	2.04 (1.8-2.2)	1.46 (1.18-1.68)	<0.0001
Waist-to-hip ratio**	0.906 (0.86-0.98)	0.89 (0.81-0.95)	0.06
Sarcopenia***	18/45 (40%)	18/68 (26.47%)	0.13
MNA-SF**	13 (11-14)	13 (10-14)	0.75
MNA total**	26 (23.75-28)	25.25 (22.13-27.5)	0.28
Lawton IADL**	15 (11-17)	15 (12.25-17)	0.20
SMMSE**	28 (25.5-29)	28 (26-29)	0.61
Antidepressant usage***	9/45 (20%)	10/68 (14.71%)	0.46
Number of falls**	1 (0-2)	0 (0-1)	0.09
Incontinence***	20/45 (44.4%)	23/68 (38.82%)	0.25
Mobility score (0–6)**	5 (3-6)	6 (4-6)	0.11
Number of drugs**	5 (3-7.5)	4 (3-6)	0.17

*mean ± standard deviation, **median (25th percentile-75th percentile), ***n (%). BMI: Body mass index, SARC-F: Strength, assistance with walking, rise from a chair, climb stairs, and falls, MNA: Mini nutritional assessment, SF: Short form, LF: Long form, FRAIL: Fatigue, resistance, ambulation, illness, and loss of weight, GDS-15: Geriatric depression scale (short form), SMMSE: Standardized mini-mental state examination, IADL: Instrumental activities of daily living, HGS: Handgrip strength, 5xSTS: 5 times sit-to-stand test, FM (kg/m²): Fat mass, FFM (kg/m²): Free fat mass

Table 4. Spearman correlation in frailty index-load capacity index and SARC-F score-load capacity index

	Correlation coefficient (r)	p	95% CI
Frailty index-LCI	0.4046	<0.0001	(0.232-0.552)
SARC-F score-LCI	0.3666	<0.0001	(0.187-0.518)
Number of geriatric syndrome-LCI	0.3250	0.004	(0.144-0.485)

LCI: Load capacity index, SARC-F: Strength, assistance with walking, rise from a chair, climb stairs, and falls, CI: Confidence interval.

Nevertheless, the consistent correlation between the LCI, frailty, and SARC-F scores suggests that this index is a more sensitive marker of global geriatric vulnerability than isolated cognitive domains. Clinically, this underscores the need for the assessment of older adults to transcend weight-centric models (17). As a biologically grounded and easily calculable tool, the LCI can facilitate the early recognition of frailty and guide targeted interventions in geriatric outpatient settings (18).

Taken together, these findings support the consideration of LCI as a complementary body composition measure rather than a stand-alone diagnostic or prognostic instrument. Previous research on pre-frail older adults has similarly indicated that BMI may not adequately capture the distinct contributions of FM and FFM to physical function

and sarcopenia risk. Therefore, evaluating these compartments jointly within a load-capacity framework may provide a more integrated representation of body composition-related vulnerability than assessing BMI or either compartment in isolation. As LCI requires only a single BIA measurement, it is accessible in settings lacking DXA or cross-sectional imaging facilities. This is particularly beneficial for low- and middle-income countries.

Prospective longitudinal studies are required to determine whether the LCI provides incremental prognostic value for clinically relevant outcomes, including disability, falls, hospitalization, and mortality, beyond the established components of a CGA (19).

Study Limitations

Several caveats should temper the interpretation of these findings. Because the study design is cross-sectional and relies on retrospective chart data, we cannot infer causal direction between LCI and any specific geriatric syndrome. Recruitment was restricted to a single tertiary center, and women accounted for a disproportionate share of the cohort; both features limit the generalizability of our estimates to other populations. Body composition was captured by BIA rather than DXA or cross-sectional imaging. Although BIA is the pragmatic choice for outpatient settings, its readings are known to shift with hydration status, which is unpredictable in older adults with variable diuretic use or subclinical fluid overload. Finally, with 113 participants, some of the null findings—cognitive status in particular—may reflect insufficient statistical power rather than a true absence of an effect.

Although we found significant associations between the LCI and several geriatric syndromes, the LCI is a relatively new body composition metric, and evidence supporting its use in geriatric populations is limited. Therefore, these findings should be viewed as early supporting evidence rather than proof of clinical utility. They suggest that LCI may act as a complementary marker of metabolic imbalance within CGA and may provide a basis for future validation in geriatric populations.

Conclusion

In conclusion, higher LCI values were significantly associated with increased frailty, higher SARC-F scores, and a greater burden of geriatric syndromes. These findings suggest that the imbalance between metabolic load and physiological capacity is a fundamental component of frailty that is not adequately represented by BMI. The LCI is simple and inexpensive to obtain and may serve as a complementary tool in CGA. It provides information beyond that obtained from conventional anthropometric measurements for evaluating body composition and the burden of geriatric syndromes.

Ethics

Ethics Committee Approval: The İstanbul University-Cerrahpaşa Faculty of Medicine Ethics Committee granted retrospective institutional review and approval for the analysis of anonymized outpatient records on 01 October 2025 (decision number: 2025/646).

Informed Consent: Because only de-identified data collected during routine outpatient care were analyzed, the Ethics Committee waived the requirement for individual informed consent.

Footnotes

Authorship Contributions: Surgical and Medical Practices - G.K.A., A.D., D.S.E.; Concept - G.K.A., S.B., D.Ö., Ü.D., S.A., A.D., D.S.E.; Design - G.K.A., S.B., D.Ö., Ü.D., S.A., A.D., D.S.E.; Data Collection or Processing: G.K.A., D.Ö., K.Ç.A., Ü.D., S.A., A.D., D.S.E.; Analysis or Interpretation - G.K.A., S.B., D.Ö., K.Ç.A., A.D., D.S.E.; Literature Search: G.K.A., S.B., D.Ö., S.A., D.S.E.; Writing: G.K.A., S.B.

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Analysis of Effective Risk Factors and Comparison of Treatment Methods in Instabilities Following Total Knee Arthroplasty

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ABSTRACT

Introduction: This study aimed to investigate the significant risk factors for instabilities following total knee arthroplasty (TKA) and to develop a treatment algorithm by evaluating the efficacy of treatments described in the literature.

Methods: Seventeen patients diagnosed with instability after TKA performed in University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Orthopaedics and Traumatology, between 2012 and 2017 were retrospectively evaluated. Preoperative data and radiological examinations were obtained from the hospital database, while postoperative data were recorded through direct outpatient follow-ups. Factors causing instability were identified from radiological examinations, physical findings, and intraoperative observations. Patients were classified into three groups: flexion instability, extension instability, and global instability. Ten patients received a total condylar constrained prosthesis, four received a hinged knee prosthesis, two underwent polyethylene (PE) insert exchange, and one patient was managed conservatively. Postoperative outcomes were assessed using the American Knee Society Clinical and Functional Scores, Lysholm score, pre- and post-treatment pain scores, and range-of-motion measurements.

Results: Obesity and age were found to be the most significant risk factors for post-TKA instability. Patients who underwent revision of all components showed statistically significant improvements in all scores postoperatively. No significant improvement was observed in patients treated with PE insert exchange or conservative management. There were no statistically significant differences in treatment outcomes among the different instability groups.

Conclusion: Early primary knee arthroplasty and obesity are risk factors for postoperative instability. Identifying the underlying cause and selecting an appropriate implant are crucial for successful treatment. The best outcomes were observed in patients who underwent revision of all components.

Keywords: tibiofemoral instability, total knee arthroplasty, revision knee arthroplasty

Introduction

Total knee arthroplasty (TKA) is a surgical procedure that provides good or excellent outcomes in 92–97% of patients at 10–15 years of follow-up (1). Revisions of TKA are most commonly performed due to septic or aseptic loosening. However, instability has emerged as an important cause of early revisions. Among revision arthroplasty procedures performed within the first four years after TKA, those due to instability account for 10–22% of all cases (2).

Instability can be defined as excessive or abnormal motion of the structures forming the joint (2). It may occur immediately after TKA or develop progressively due to soft tissue deficiency, inadequate soft tissue or joint space balance, malalignment of components, or the use of

implants with inappropriate size or type (3). Various approaches, ranging from conservative methods to surgical techniques, are available for the treatment of instability following TKA. In this study, we aimed to identify risk factors contributing to instability following TKA. Additionally, we sought to evaluate the effectiveness of various surgical techniques employed in the treatment of this condition.

Methods

Between 2012 and 2018, 978 primary TKAs were performed in our clinic; of these, 60 patients who underwent revision TKA were evaluated. Of these, 17 patients required revision surgery due to instability. One patient was excluded from the study due to the development of periprosthetic infection during follow-up.



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All patients were followed for a minimum of six months. Preoperative data for revision surgery were obtained retrospectively from hospital archives, while postoperative data were collected through direct outpatient follow-up visits. Informed consent regarding the study process was obtained from all patients included in the study. The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval number: 1107, date: 09.11.2017). Patients with septic or aseptic loosening; those with signs of periprosthetic infection without loosening; patients with neuromuscular diseases, extra-articular deformities, or patellofemoral instability were excluded from the study.

Patient age, sex, comorbidities, medical history, and smoking habits were recorded. Symptoms recorded in the patients' histories included anterior knee pain, a sensation of sliding or instability, catching or locking, difficulty going up or down stairs, weakness, and recurrent effusions. The type of implant used in the primary surgery and the indication for the primary procedure were noted. The presence of instability was assessed using anterior and posterior drawer tests, as well as varus/valgus stress tests at 15°, 30°, and 90° of knee flexion. Hyperextension instability was evaluated by forcibly extending the knee. Range of motion (ROM) and the presence of contractures were recorded. Gait was observed for varus/valgus drift, sagittal plane translation and hyperextension. Patellar tracking in the trochlear groove was examined. The integrity of the extensor mechanism was assessed by evaluating knee extension strength against resistance. Hip joint movements were assessed to investigate possible joint pathologies. The presence of foot and ankle deformities was noted. Patient height and weight were measured to calculate body mass index (BMI).

In all patients, C-reactive protein, erythrocyte sedimentation rate, and complete blood count were measured to rule out infection. Joint fluid was aspirated and cultured in patients with effusion or suspected infection. Radiological evaluation included weight-bearing anteroposterior (AP) and lateral knee radiographs. All patients underwent full-length orthoroentgenograms to assess the mechanical alignment of the lower extremities and to rule out additional deformities. Radiographs were evaluated using the American Knee Society Radiographic Evaluation and Scoring System (4).

The type of instability was determined based on physical examination and radiological evaluation. Patients were categorized into three groups: extension instability, flexion instability, and global instability. Patient histories and physical examination data, both preoperative and postoperative were assessed using the Knee Society Score (KSS) for knee and functional evaluations. Additionally, the Lysholm Scoring System (LSS) was used to evaluate knee stability. The visual analog scale (VAS) was employed to assess pain. ROM measurements were recorded.

The treatment methods applied to the patients were as follows: isolated polyethylene (PE) insert exchange in 2 patients; revision surgery with a rotating hinge knee prosthesis (RT-Plus Modular Rotating Hinged, Smith & Nephew, USA) in 4 patients; and revision with a total condylar constrained prosthesis (Vanguard SSK 360, Biomet, Inc., Warsaw, IN, USA) in 10 patients. In some patients, offset options were used to achieve proper alignment. In cases of bone defects, cement, allograft,

or metal augments were used depending on the size of the defect. No patients received a patellar component. All patients were discharged on postoperative day 4 or 5, after stabilization of vital signs and achievement of a 90° ROM. During outpatient follow-up, infection parameters were monitored and weight-bearing AP/lateral knee radiographs were obtained.

Statistical Analysis

The Shapiro-Wilk test indicated that the data did not follow a normal distribution; therefore, non-parametric tests were used in the analysis. Results were presented as median (range) values. The Wilcoxon signed-rank test was used to compare preoperative and postoperative outcomes across all groups, while the Mann-Whitney U test was used to evaluate the relative success among different implant types. Statistical analyses were performed using IBM SPSS version 20.0 (IBM Corp, New York, NY, USA), with a significance level set at $p < 0.05$.

Results

Between 2012 and 2017, our clinic performed 978 primary TKA and 60 revision knee arthroplasties. Among all surgeries, the 17 patients included in our study represented a 1.7% incidence of instability following primary TKA; among all revision surgeries, 28.3% were performed due to instability. All patients included in the study were female. The mean age at the time of revision surgery was 70.1 years (range, 57–84), while the mean age at the time of primary surgery was 62.9 years (range, 55–80). Five patients (31.25%) underwent right knee surgery, while 11 patients (68.75%) underwent left knee surgery. Twelve patients (75%) had undergone TKA in the contralateral knee. The mean BMI was 36.7 ± 5.1 kg/m² (range, 31–47). The mean follow-up duration was 16.4 ± 10.1 months. None of the patients had a history of smoking. No hip, foot, or extra-articular deformities were observed in any patient. The indications for primary surgery were primary osteoarthritis in 14 patients (87.5%), post-traumatic arthritis and rheumatoid arthritis in one patient each. Regarding the primary implant type, 14 patients (87.5%) received cruciate-retaining (CR) implants, while the remaining two patients received a posterior-stabilized (PS) implant and a constrained condylar implant, respectively.

Postoperative evaluations in all patients demonstrated significant improvements in all scores and in ROM values compared with the preoperative period (Table 1). The mean increase in KSS was 60 points; the mean increase in KSS functional scores was 40 points; and the mean increase in LSS was 60 points. An average reduction of 5 points was observed in VAS pain scores. The mean increase in ROM was 20 degrees.

In the group that underwent PE insert exchange, KSS clinical scores increased from 38.5 to 58.5, functional scores increased from 12.5 to 25, Lysholm scores increased from 16 to 19.5, and ROM increased from 95° to 100°. When the preoperative and postoperative values of the patients in this group were compared, no statistically significant differences were observed. When evaluated by implant type, the group that received a total condylar constrained knee prosthesis had higher KSS clinical and functional scores than the hinged knee prosthesis group, whereas the hinged knee prosthesis group had better Lysholm scores, VAS values, and ROM. However, the differences between the two groups were not

statistically significant ($p>0.05$, Table 2). No postoperative complications were encountered in any of the patients.

Discussion

The findings of the study can be summarized as follows: All patients who developed instability after TKA were obese, underwent primary surgery under the age of 65, and had primary implants that were CR prostheses. Successful outcomes in the treatment of instabilities following TKA can be achieved with surgical techniques. The benefits of isolated PE-insert exchange are limited. There is no difference in postoperative success between constrained condylar knee prostheses and hinged prostheses for the treatment of tibiofemoral instabilities after TKA.

Obesity is one of the most prevalent problems of our time and is considered a risk factor for the development of osteoarthritis. In studies by Vazquez-Vela Johnson (6) and Kerkhoffs (5), the presence of obesity was associated with poor clinical scores and early loosening following TKA. In a study by Can et al. (7) focusing on patients who developed instability after TKA, obesity was suggested as a risk factor for the development of instability. According to the World Health Organization classification, among the patients in our study, one was overweight, seven were class 1 obese, five were class 2 obese, and four were class 3 obese (8). The distribution of patients in our study supports the hypothesis suggested in the literature that obesity may act as a risk factor for instability.

TKA is becoming increasingly common and is now also being sought by younger patients. In a study by Khan et al. (9) investigating causes of TKA failure and revision, younger age was identified as a major risk factor for early revision. Other studies have reported higher TKA failure rates in younger patients, likely due to their higher expectations for daily activity levels (6,10). The age distribution of patients in our study supports the finding in the literature that being under 65 years of age is a major risk factor for revision knee surgery.

Gender is considered a major risk factor for early knee revisions. In our study, however, all patients were female. In this respect, our study presents data that are inconsistent with the existing literature.

The relationship between factors causing osteoarthritis and surgical outcomes has been investigated in multiple studies. El-Galaly et al. (11) found that surgical outcomes for post-traumatic osteoarthritis were less successful compared to those for primary osteoarthritis, with higher rates of early revision in these patients. When comparing revision causes between the two groups, revision due to instability was higher in the post-traumatic osteoarthritis group (23%) compared to the primary osteoarthritis group (17%). In our study, the majority of patients had primary osteoarthritis. Our contribution to the literature on this point is limited because of the small sample size and unequal distribution.

Implant design in TKA affects postoperative outcomes. In Can et al. (7)'s study, all patients who developed instability had received CR

Table 1. Results of the statistical analysis including all groups

Group	Score	Preoperative				Postoperative				p
		n	Med	Range		n	Med	Range		
				Min	Max			Min	Max	
All groups (patients undergoing revision knee surgery)	KSS knee score	16	21.0	-13.0	49.0	16	79.0	48.0	95.0	0.000*
	KSS functional score	16	27.5	-20.0	60.0	16	70.0	-10.0	90.0	0.000*
	Lysholm score	16	21.5	10.0	59.0	16	80.5	19.0	95.0	0.001*
	VAS	16	7.0	5.0	9.0	16	2.0	0.0	7.0	0.001*
	Range of motion	16	75.0	45.0	120.0	16	95.0	70.0	120	0.002*

* $p<0.05$ indicates a statistically significant difference between groups. Med: Median, Min: Minimum, Max: Maximum, KSS: Knee Society Score, VAS: visual analog scale

Table 2. Results of the statistical analysis according to implant types

Group	Score	Preoperative				Postoperative				p
		n	Med	Range		n	Med	Range		
				Min	Max			Min	Max	
Constrained condylar knee prosthesis	KSS knee score	10	21.0	1	46.0	10	86.5	63.0	95.0	0.831
	KSS functional score	10	27.5	-20.0	60.0	10	70.0	-10.0	90.0	0.615
	Lysholm score	10	21.5	10.0	59.0	10	79.5	60.0	95.0	0.553
	VAS	10	7.0	5.0	9.0	10	2.0	0.0	4.0	0.257
	Range of motion	10	75.0	45.0	120.0	10	92.5	70.0	120.0	0.660
Hinged knee prosthesis	KSS knee score	4	0.0	-13.0	34.0	4	81.5	56.0	94.0	-
	KSS functional score	4	27.5	-10.0	45.0	4	67.5	50.0	80.0	-
	Lysholm score	4	7.5	19	37.0	4	1.5	80.0	90.0	-
	VAS	4	25.0	6	9.0	4	88.0	1.0	2.0	-
	Range of motion	4	57.5	55	120.0	4	95.0	70.0	120.0	-

* $p<0.05$ indicates a statistically significant difference between groups. Med: Median, Min: Minimum, Max: Maximum, KSS: Knee Society Score, VAS: visual analog scale

prostheses during their primary surgery, and successful outcomes were reported after revision with PS prostheses. Another study by Hao et al. (12) observed that among patients with instability, more were in the PS prosthesis group compared to the CR system group. In our study, the majority of patients had CR systems implanted. Due to the small sample size and unequal distribution, our contribution to the literature on this point is limited.

Various surgical approaches exist to treat instability following TKA. PE insert exchange is one of the revision options and is a low-morbidity, technically simple procedure. Patel et al. (13) performed only PE insert exchanges in 93 revision surgeries for post-TKA instability and reported that 10% of patients required early component revision during follow-up. In another study by Tetreault et al. (14) reported a 15.5% risk of rerevision in 143 unstable knees treated with PE exchange. In our study, two patients underwent PE-insert exchange. Neither patient showed significant improvement in KSS knee scores, KSS functional scores, or Lysholm scores. VAS scores also did not show a meaningful improvement. We consider PE insert exchange alone insufficient to eliminate the underlying factor causing the instability.

The appropriate level of constraint for the implant used to treat post-TKA instability is another topic of debate. In a study by Luttjeboer et al. (15), KSS functional scores were significantly lower in the hinged group compared to the condylar knee prosthesis group. No significant differences were observed in KSS clinical scores or VAS scores. In this study, the condylar constrained group experienced more frequent postoperative complications and required reoperations due to recurrent instability compared to the hinged group (15). Houfani et al. (16) reported that, at five years of follow-up, hinged knee prosthesis revisions achieved good clinical outcomes in 77% of patients, whereas postoperative complications were observed in 29% of cases. In our study, total condylar constrained systems demonstrated higher clinical and functional KSS scores than the hinged group. The hinged group showed a minimal positive difference in VAS scores. Unlike other studies, we included the Lysholm score in our evaluation. The hinged knee prosthesis group had a higher mean Lysholm score than the condylar constrained system group. Similarly, compared with preoperative values, hinged systems were associated with greater postoperative improvements in ROM. However, no statistically significant differences were found between the two groups in any of these scores or values. In our study, two patients had complete loss of the LCL, and two had complete loss of the MCL. All four patients underwent revision with a hinged knee prosthesis and achieved successful outcomes. Clinical evaluations indicated that hinged systems provided better stability, although no difference in patient satisfaction was observed between the two groups. We recommend hinged-knee prostheses for patients whose advanced bone loss or ligamentous instability cannot be corrected with condylar-constrained systems. Although no significant differences were observed between the two groups in clinical and functional scores, we believe that condylar-constrained systems may be a better primary choice because they require less bone resection than revisions with hinged systems.

Study Limitations

Our study has several limitations. First, because this was a retrospective study, we encountered challenges in accessing historical data. The demographic characteristics of our patients were largely homogeneous: all were female and obese. Therefore, we could not compare groups with different demographic characteristics. When determining risk factors, we had to interpret our data in the context of the literature rather than by directly comparing two groups. Additionally, the presence of greater instability in the hinged prosthesis group may have introduced a bias against this group. No inconsistencies between our results and the literature were observed.

Conclusion

In this study, patients who developed instability after TKA were predominantly in the obese category and had undergone primary surgery before age 65 years. The effectiveness of isolated PE insert exchange in revisions for instability was limited. In cases of tibiofemoral instability, no significant difference in postoperative success was observed between total condylar constrained systems and hinged knee prostheses. Therefore, except when the use of a hinged knee prosthesis is indicated, such as in cases of excessive bone or soft-tissue loss, less-constrained systems are more appropriate.

Ethics

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval number: 1107, date: 09.11.2017).

Informed Consent: The patients were first informed about the study, and their consent to participate was obtained.

Footnotes

Authorship Contributions: Surgical and Medical Practices - A.T., Y.Ö.; Concept - A.T., Y.Ö.; Design - A.T., A.Ş., Z.D., A.Z.B.; Data Collection or Processing - Z.D., M.E., A.Z.B.; Analysis or Interpretation - A.Ş., M.E., A.Z.B.; Literature Search - A.Ş., Z.D., M.E.; Writing - A.T., Y.Ö.

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

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Breast Manifestations of Hematologic Malignancies: Imaging Spectrum and Clinicopathologic Correlation in a Two-Center Retrospective Cohort

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ABSTRACT

Introduction: To characterize the clinicopathologic features and multimodality imaging spectrum of breast involvement by hematologic malignancies and to identify imaging findings that may facilitate differentiation from primary breast carcinoma.

Methods: This retrospective two-center study included consecutive patients with histopathologically confirmed breast involvement by hematologic malignancies between January 2015 and December 2025. Clinical records, pathology reports, mammography, ultrasonography, magnetic resonance imaging (MRI), and fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) examinations were reviewed. Imaging findings were analyzed with emphasis on lesion morphology, distribution pattern, laterality, nodal involvement, and systemic disease burden.

Results: Seventeen patients with breast involvement by hematologic malignancies were identified among approximately 5,300 malignant breast biopsy specimens (0.3%). Mean age was 52.8 years (range, 18-86 years), and 15 patients (88.2%) were female. Histopathologic diagnoses included lymphoma (76.5%), leukemia/chronic lymphocytic leukemia (17.6%), and plasma cell neoplasm (5.9%). Solitary breast lesions were observed in 52.9% of patients, multiple lesions in 47.1%, and bilateral involvement in 41.2%. Associated nodal disease was present in 47.1% of cases. Mammographically suspicious calcifications were absent in all patients. The predominant imaging presentation consisted of oval, round, or mildly lobulated masses with circumscribed or partially circumscribed margins. Three principal sonographic patterns were identified: solitary nodular lesions, multifocal or bilateral nodular disease, and diffuse infiltrative involvement. MRI frequently demonstrated enhancing masses with diffusion restriction or extensive non-mass enhancement, whereas FDG PET/CT commonly revealed concurrent nodal and systemic disease.

Conclusion: Breast involvement by hematologic malignancies demonstrates substantial imaging heterogeneity. Multifocal or bilateral disease, circumscribed nodular lesions, absence of suspicious calcifications, associated lymphadenopathy, and concurrent systemic involvement should raise suspicion for a hematologic origin and prompt appropriate clinicopathologic correlation.

Keywords: Hematologic malignancies, breast involvement, lymphoma, leukemia, breast imaging.

Introduction

Breast involvement by hematologic malignancies is an uncommon clinical entity that encompasses a heterogeneous group of disorders, including lymphomas, leukemias, and, less frequently, plasma cell neoplasms. Although hematologic malignancies represent one of the most common non-mammary malignancies involving the breast, breast manifestations remain rare compared with primary breast carcinoma and account for only a small proportion of all malignant breast lesions (1-4). Breast involvement may occur either as the initial manifestation of an underlying hematologic malignancy or as secondary involvement in patients with known systemic disease. Accurate recognition is clinically important because management strategies differ fundamentally from

those used for primary breast cancer, and misdiagnosis may result in unnecessary surgery, inappropriate staging, and delays in hematologic treatment (5,6).

The imaging appearance of hematologic malignancies involving the breast is heterogeneous and frequently overlaps with that of primary breast carcinoma (2,7-10). Lesions may present as solitary or multifocal masses, diffuse infiltrative disease, or bilateral breast involvement, and often demonstrate a relatively circumscribed morphology without suspicious calcifications. Consequently, histopathologic confirmation and clinic radiologic correlation remain essential for accurate diagnosis (5,11).



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Among hematologic malignancies, lymphoma represents the most frequently reported breast manifestation, whereas breast involvement by leukemia is considerably less common and remains largely described in isolated case reports and small series (2,3,9). Furthermore, hematologic malignancies may involve the breast through diverse biological mechanisms, including hematogenous dissemination, lymphatic spread, diffuse stromal infiltration, or direct extension from adjacent lymphatic structures. Despite increasing recognition of this entity, the available literature remains limited. Most published studies have focused on primary breast lymphoma, isolated leukemia cases, pictorial reviews, or mixed cohorts of secondary breast involvement from various extramammary malignancies (1-3,10-12). Comprehensive studies evaluating the multimodality imaging spectrum of both lymphoma and leukemia with detailed clinicopathologic correlation remain scarce.

Therefore, the aim of this study was to characterize the clinicopathologic features and the multimodality imaging spectrum of breast involvement by hematologic malignancies in a two-center retrospective cohort.

Methods

Study Design and Patient Population

Patients were identified through a systematic search of institutional pathology databases, radiology information systems, picture archiving and communication systems (PACSs), and electronic medical records. Search terms included the following: “lymphoma,” “leukemia,” “hematologic malignancy,” “breast involvement,” “breast infiltration,” and related diagnostic terminology. Consecutive patients with histopathologically confirmed breast involvement by hematologic malignancies, diagnosed between January 2015 and December 2025, were eligible for inclusion.

Breast involvement was defined as histopathologically confirmed infiltration of breast tissue by lymphoma, leukemia, or other hematolymphoid neoplasms. Both patients with previously established hematologic malignancies and patients in whom breast involvement represented the initial manifestation of disease were included. Cases with insufficient imaging examinations, indeterminate pathologic diagnosis, inadequate clinicopathologic information, or unavailable pathology material for review were excluded. The final cohort included patients with lymphoma, leukemia/chronic lymphocytic leukemia (CLL), and plasma cell neoplasms involving the breast.

Clinical and Pathologic Evaluation

Clinical information was retrospectively retrieved from electronic medical records and pathology archives. Recorded variables included age, sex, presenting symptoms, lesion laterality, lesion multiplicity, largest lesion diameter, history of hematologic malignancy, breast involvement as the initial manifestation of the disease, and concurrent systemic disease.

Histopathologic diagnoses were established using ultrasound-guided core needle biopsy, vacuum-assisted biopsy, excisional biopsy, surgical specimens, or lymph node biopsy when clinically indicated. All available pathology reports, histologic slides, and immunohistochemical findings

were reviewed by dedicated hematopathologists and breast pathologists at the participating institutions.

Histologic classification was performed according to the 5th edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours. Breast involvement by a hematologic malignancy was diagnosed based on characteristic morphologic findings and immunophenotypic confirmation.

For lymphoma cases, the diagnosis was established through morphological assessment and immunophenotypic characterization using lineage-specific markers when appropriate, including CD20, CD3, CD5, CD10, CD23, BCL2, BCL6, MUM1, Cyclin D1, CD30, ALK, and Ki-67. Lymphoma subtypes were classified according to current WHO criteria.

In cases of leukemia, the diagnosis was established using morphologic findings together with immunophenotypic and immunohistochemical markers, including CD45, TdT, MPO, CD34, CD117, CD13, CD33, CD19, CD79a, CD10, and other lineage-specific markers, according to the underlying leukemia subtype. When available, bone marrow biopsy findings, flow cytometry results, and cytogenetic analyses were reviewed to support the diagnosis.

Particular attention was paid to differentiating hematologic malignancies from primary breast carcinoma and from secondary breast involvement by solid tumors. Cases demonstrating atypical morphology, bilateral disease, diffuse infiltration, multiple lesions, or clinic radiologic-pathologic discordance underwent expanded immunohistochemical evaluation. Breast-specific markers, including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2, GATA3, mammaglobin, and gross cystic disease fluid protein-15, were used when clinically indicated. In all evaluated cases, the absence of mammary epithelial marker expression supported a hematolymphoid origin rather than a primary mammary origin. Pathologists were specifically informed that the biopsy specimens originated from breast lesions suspicious for either primary breast carcinoma or hematologic involvement, and clinic radiologic correlation was systematically performed in all cases.

The final diagnosis was established through the integration of histopathologic findings, immunophenotypic profile, clinical history, imaging findings, and multidisciplinary clinicopathologic correlation.

Imaging Analysis

Available mammography (MG), ultrasonography (US), breast magnetic resonance imaging (MRI), and fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) examinations were retrospectively reviewed. All imaging studies were independently evaluated by two fellowship-trained breast radiologists with more than 10 years of experience. The review was performed using the institutional PACS. Any discrepancies were resolved by consensus.

Imaging findings were assessed according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) lexicon, where applicable. Mammographic variables included breast density, lesion type, shape, margins, calcifications, architectural distortion, skin thickening, nipple retraction, and associated axillary findings.

Ultrasonographic assessment included lesion size, shape, orientation, margins, echogenicity, posterior acoustic features, internal vascularity, lesion distribution, skin involvement, chest wall extension, and regional lymph node status.

MRI examinations were reviewed for lesion morphology, mass vs. non-mass enhancement, internal enhancement characteristics, T2-weighted signal intensity, diffusion restriction, apparent diffusion coefficient values, dynamic enhancement kinetics, time-to-peak enhancement, multifocality, multicentricity, skin involvement, chest wall invasion, and associated regional nodal disease.

FDG PET/CT examinations were assessed for the presence, distribution, and intensity of FDG uptake in the breast. Maximum standardized uptake values (SUVmax) were recorded when available. Additional variables evaluated included regional nodal involvement, extranodal disease burden, bone marrow involvement, extranodal organ involvement, and disseminated systemic disease.

Based on overall imaging appearance, breast involvement was categorized into four major imaging patterns: solitary mass-forming lesion, multiple lesions, diffuse infiltrative involvement, and bilateral involvement.

Study Endpoints

The primary endpoint of the study was to characterize the clinicopathologic and multimodality imaging spectrum of breast involvement by hematologic malignancies.

Secondary endpoints included evaluation of lesion distribution patterns, systemic disease burden, and imaging features potentially suggestive of hematologic breast involvement.

Statistical Analysis

Descriptive analyses were performed using IBM SPSS Statistics, version 30.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean (range) or median (range), as appropriate, and categorical variables as frequencies and percentages. Given the small cohort size, no formal hypothesis testing was performed.

Ethics Statement

This study was conducted under ethics approval granted for a broader retrospective investigation of breast involvement by non-primary breast malignancies (Approval No: 2026-60; Date: 04.02.2026). The current analysis represents the hematologic malignancy subgroup of the approved study. The study was conducted in accordance with the Declaration of Helsinki.

Results

Patient Characteristics

During the study period, approximately 5,300 breast biopsy specimens demonstrating malignant involvement were identified across the two participating institutions. Among these cases, 17 patients were diagnosed with breast involvement from hematologic malignancies, corresponding to approximately 0.3% of all malignant breast biopsy specimens. A total

of 17 patients with breast involvement by hematologic malignancies were included in the final study cohort. The mean age at diagnosis was 52.8 years (range, 18–86 years). Fifteen patients (88.2%) were female, and two (11.8%) were male. Detailed demographic, clinical, and pathologic characteristics are summarized in Table 1.

Histopathologic diagnoses included lymphoma in 13 patients (76.5%), chronic lymphocytic leukemia (CLL) in three patients (17.6%), and plasma cell neoplasm (multiple myeloma) in one patient (5.9%) (Table 1). The lymphoma subgroup comprised diffuse large B-cell lymphoma, follicular lymphoma, mucosa-associated lymphoid tissue lymphoma, plasmablastic lymphoma, high-grade B-cell lymphoma, lymphoblastic lymphoma, non-Hodgkin lymphoma, and lymphoma not otherwise specified.

Breast involvement occurred both in patients with previously established hematologic malignancies and in those in whom breast findings represented the initial manifestation of disease. Notably, no patient demonstrated isolated breast-confined lymphoma in the absence of regional nodal or systemic disease. Both male patients had lymphoma and presented with bilateral multifocal breast involvement. Overall, breast manifestations most commonly occurred in association with regional lymphadenopathy and/or concurrent systemic disease.

Distribution Pattern

Breast involvement demonstrated a heterogeneous spectrum of imaging findings. Solitary breast lesions were observed in 9 of 17 patients (52.9%), whereas multiple lesions were observed in 8 patients (47.1%). Bilateral breast involvement was present in 7 patients (41.2%), while unilateral disease was observed in 10 patients (58.8%). In three patients, the dominant manifestation was nodal involvement rather than a conventional breast mass pattern. Detailed lesion distribution patterns and imaging characteristics are summarized in Table 2.

Associated nodal disease was common, occurring in at least 8 patients (47.1%). Regional lymphadenopathy frequently accompanied breast

Table 1. Clinicopathologic characteristics of patients with breast involvement by hematologic malignancies (n=17)

Variable	n	%
Female	15	88.2
Male	2	11.8
Mean age, years (range)	52.8 (18–86)	
Histopathology		
Lymphoma	13	76.5
Leukemia/CLL	3	17.6
Plasma cell neoplasm (multiple myeloma)	1	5.9
Distribution pattern		
Unilateral involvement	10	58.8
Bilateral involvement	7	41.2
Solitary lesion	9	52.9

Lymphoma subtypes included diffuse large B-cell lymphoma, follicular lymphoma, MALT lymphoma, plasmablastic lymphoma, high-grade B-cell lymphoma, lymphoblastic lymphoma, non-Hodgkin lymphoma, and lymphoma not otherwise specified. CLL: Chronic lymphocytic leukemia, MALT: Mucosa-associated lymphoid tissue

Table 2. Multimodality imaging characteristics of breast involvement by hematologic malignancies

Imaging finding	n	%
Overall imaging pattern		
Predominantly nodular (mass-forming) pattern	14	82.4
Diffuse infiltrative/non-mass pattern	3	17.6
Distribution characteristics		
Bilateral involvement	7	41.2
Multiple lesions	8	47.1
Nodal-type breast involvement	3	17.6
Associated axillary lymphadenopathy	8	47.1
Mammographic findings		
Suspicious calcifications	0	0
Architectural distortion	Rare	—
Spiculated margins	Rare	—
Ultrasonographic findings*		
Hypoechoic echotexture	9	69.2
Heterogeneous echotexture	4	30.8
Circumscribed or partially circumscribed margins	8	61.5
Non-circumscribed margins	5	38.5

*Percentages were calculated from available examinations for each imaging modality

lesions and in several cases represented the dominant imaging manifestation. Representative examples of solitary nodular disease, multifocal or bilateral involvement, and nodal-type breast lesions are illustrated in Figures 1-3.

Mammographic and Ultrasonographic Findings

The predominant imaging presentation was nodular disease. Most lesions appeared as oval, round, or mildly lobulated masses with circumscribed or partially circumscribed margins. Multifocal nodular disease and bilateral involvement were particularly frequent among lymphoid neoplasms.

Suspicious mammographic calcifications were absent in all patients (0/17, 0%). Likewise, architectural distortion and spiculated margins were uncommon. Consequently, many lesions lacked the classic mammographic appearance of primary invasive breast carcinoma.

On US, lesions were predominantly hypoechoic and frequently demonstrated internal vascularity on Doppler evaluation. Several lesions exhibited an intramammary nodal appearance, characterized by oval, hypoechoic masses resembling lymph nodes.

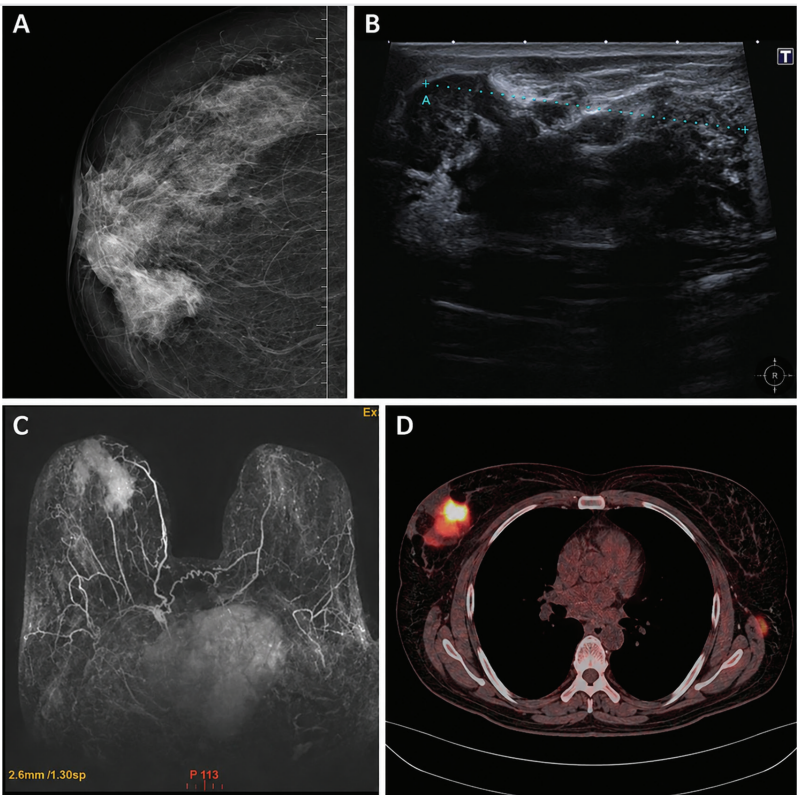


Figure 1. Solitary nodular breast involvement by diffuse large B-cell lymphoma. A 48-year-old woman presented with histopathologically confirmed diffuse large B-cell lymphoma involving the breast. (A) The craniocaudal mammogram demonstrates an irregular, high-density mass in the right breast without associated suspicious calcifications. (B) Targeted ultrasonography reveals a heterogeneous hypoechoic solid lesion with lobulated and partially indistinct margins. (C) Maximum-intensity-projection contrast-enhanced breast MRI demonstrates avid enhancement corresponding to the breast lesion. (D) An axial fused FDG PET/CT image demonstrates intense hypermetabolic uptake within the breast mass and associated metabolically active nodal disease. Histopathologic examination confirmed diffuse large B-cell lymphoma. MRI: Magnetic resonance imaging, FDG PET/CT: Fluorodeoxyglucose positron emission tomography/computed tomography

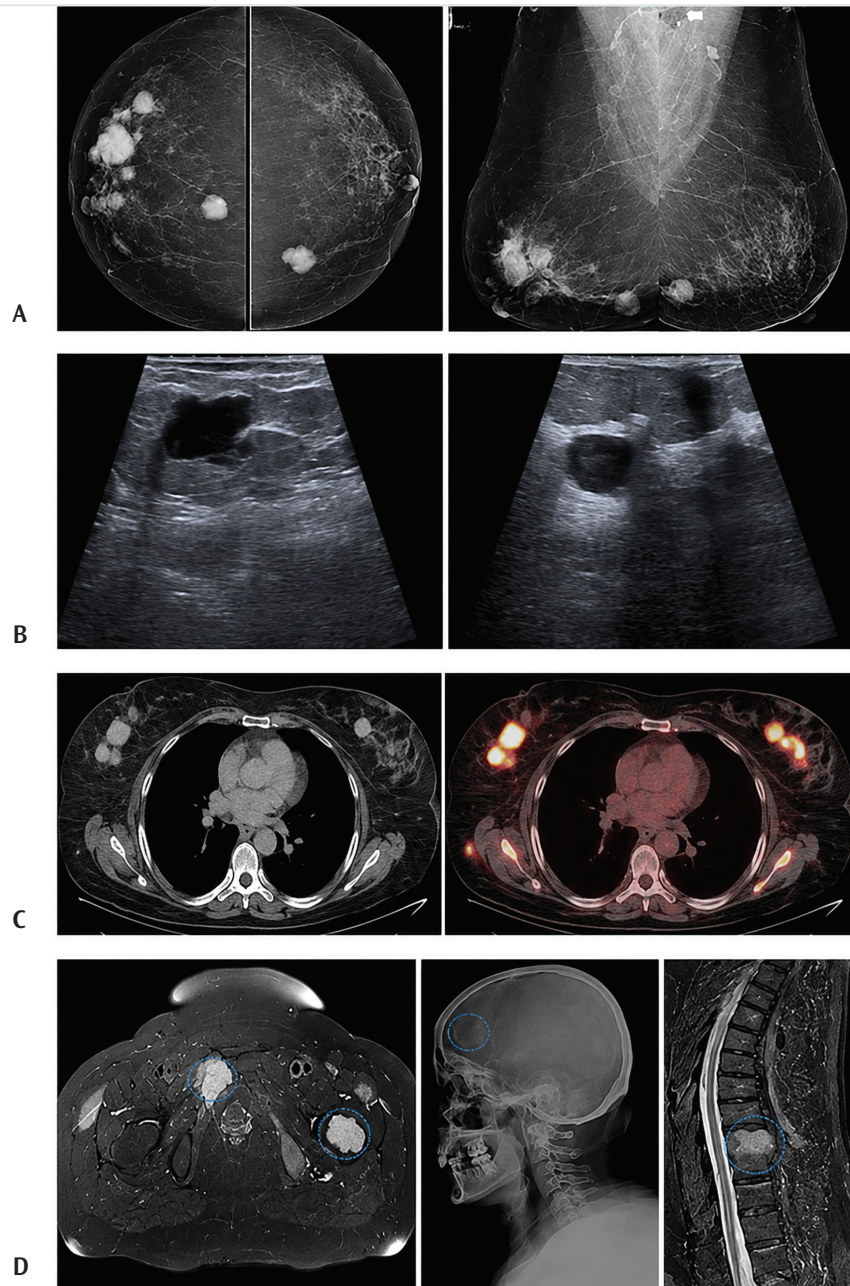


Figure 2. A 58-year-old woman with known multiple myeloma presenting with bilateral breast involvement. (A) Bilateral craniocaudal and right mediolateral oblique mammograms demonstrate multiple circumscribed high-density masses in both breasts without suspicious calcifications. (B) Targeted ultrasonography reveals multiple oval hypoechoic solid lesions with predominantly circumscribed margins. (C) Axial CT and fused FDG PET/CT images demonstrate multifocal bilateral breast lesions with associated metabolic activity. (D) Additional imaging demonstrates extramammary manifestations of systemic disease, including soft-tissue plasmacytomas and skeletal involvement. Histopathologic examination confirmed breast involvement by a plasma cell neoplasm (multiple myeloma). FDG PET/CT: Fluorodeoxyglucose positron emission tomography/computed tomography

Three principal sonographic patterns were identified:

1. Solitary nodular lesions
2. Multifocal and/or bilateral nodular lesions
3. Diffuse heterogeneous infiltrative involvement without a dominant mass

Diffuse infiltrative disease, observed in a minority of patients, was characterized by heterogeneous parenchymal echotexture, ill-defined hypoechoic infiltration, trabecular thickening, and skin thickening.

MRI Findings

Breast MRI was performed in 12 patients and demonstrated variable imaging appearances depending on the pattern of involvement. Nodular disease was the predominant MRI presentation, observed in 10 of 12 patients (83.3%); diffuse infiltrative involvement was identified in 2 patients (16.7%). Nodular lesions typically appeared as oval, round, or mildly lobulated, enhancing masses with circumscribed margins and associated restricted diffusion. Dynamic contrast-enhanced MRI frequently demonstrated rapid early enhancement, with variable

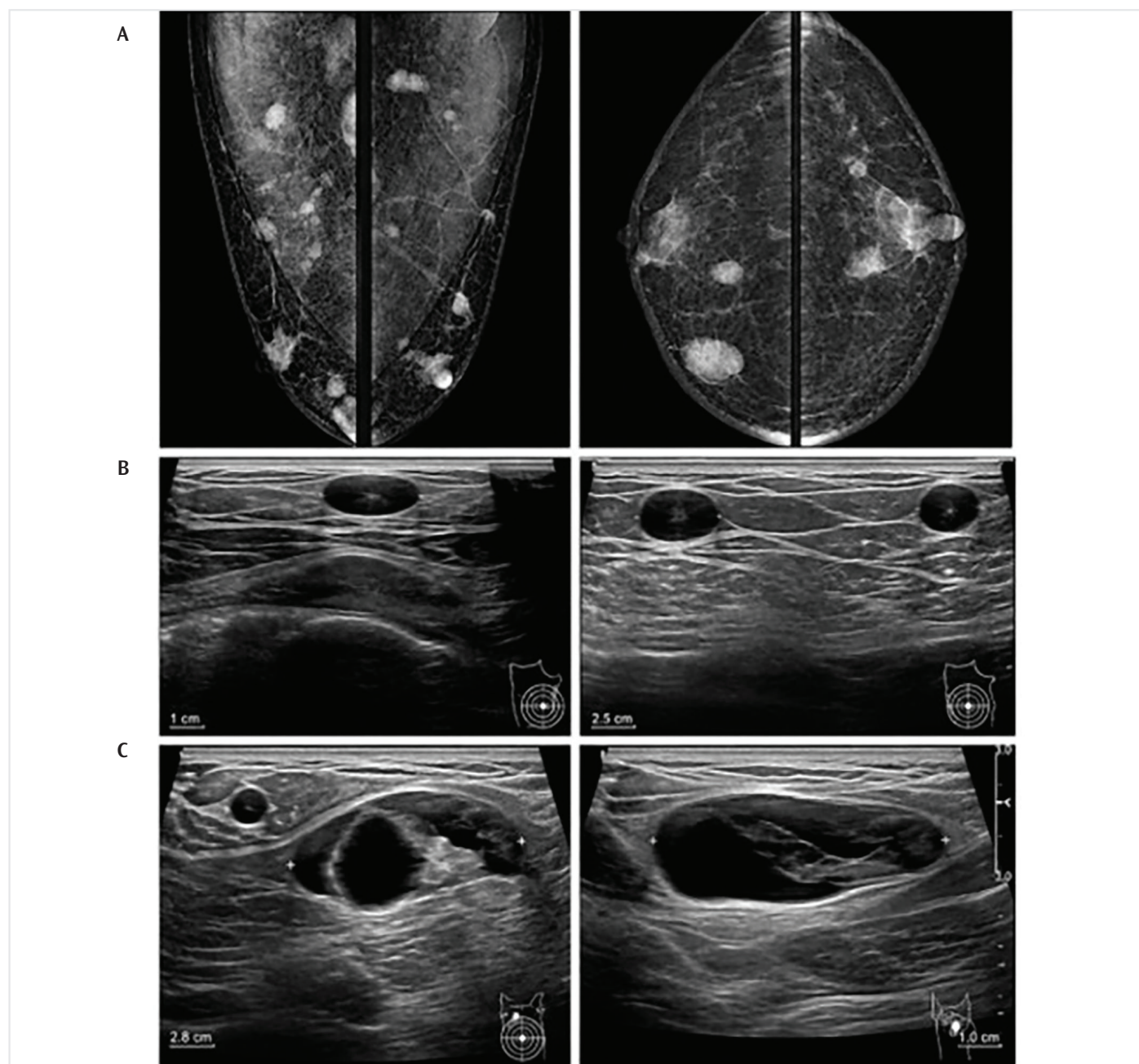


Figure 3. A 70-year-old man presented with secondary breast involvement by non-Hodgkin lymphoma. (A) Bilateral craniocaudal and mediolateral oblique mammograms demonstrate multiple circumscribed nodules in both breasts without associated suspicious calcifications. (B) Targeted breast ultrasonography reveals multiple superficial oval hypoechoic nodules with predominantly circumscribed margins. (C) Axillary ultrasonography demonstrates abnormal lymph nodes with cortical thickening and hilar effacement. Histopathologic examination confirmed lymphomatous involvement.

delayed-phase kinetic patterns. Diffusion restriction was observed in all MRI-evaluated lesions.

Several nodular lesions demonstrated imaging features resembling those of pathologic lymph nodes, including cortical thickening, deformity, and partial or complete loss of the fatty hilum.

In patients with diffuse infiltrative disease, MRI demonstrated extensive heterogeneous non-mass enhancement involving large portions of the breast parenchyma, occasionally extending toward the skin and subcutaneous tissues. MRI was particularly useful for assessing

disease extent, multifocality, bilateral involvement, skin extension, and associated regional nodal disease.

FDG PET/CT Findings

Among patients with available PET/CT examinations, breast lesions demonstrated moderate FDG avidity (mean SUVmax, 6.3; range, 3.8–10.0). In addition to breast involvement, PET/CT frequently identified regional lymphadenopathy, extranodal organ involvement, bone marrow infiltration, skeletal lesions, and disseminated systemic disease. No patient presented with breast-confined lymphoma; breast

manifestations were invariably associated with nodal and/or systemic disease. Accordingly, the principal contribution of FDG PET/CT was comprehensive whole-body staging and assessment of disease burden, rather than detailed characterization of breast lesions.

Summary of Imaging Findings

Overall, hematologic malignancies involving the breast demonstrated substantial imaging heterogeneity. The most frequently encountered patterns included nodular breast lesions, multifocal or bilateral disease, intramammary nodal-type lesions, diffuse infiltrative involvement, and associated axillary lymphadenopathy. Suspicious calcifications were absent in all patients, and the classic spiculated desmoplastic morphology typical of primary invasive breast carcinoma was rarely observed. Rather than presenting as an isolated breast-confined disease, breast involvement most commonly occurred in association with regional nodal or systemic hematologic disease.

Discussion

Breast involvement by hematologic malignancies is uncommon and poses a diagnostic challenge because imaging findings frequently overlap with those of primary breast carcinoma and benign breast lesions. In the present two-center cohort, hematologic breast involvement accounted for approximately 0.3% of all malignant breast biopsy specimens and was predominantly associated with lymphoma, followed by leukemia/CLL and plasma cell neoplasms. These findings are consistent with previous reports demonstrating that lymphoid neoplasms constitute the majority of hematologic malignancies involving the breast and remain substantially less common than primary breast carcinoma. Previous series by Talwalkar et al. (3), Surov et al. (6), and Guilbert et al. (4) similarly identified lymphoma as the predominant histologic subtype among breast hematologic malignancies, highlighting the rarity of leukemic and plasma cell infiltrates within breast tissue (5,12-14).

The histopathologic distribution observed in our cohort also deserves attention. Lymphoma accounted for more than three-quarters of all cases, whereas leukemia/CLL and plasma cell neoplasms were substantially less frequent. This distribution closely mirrors previous clinicopathologic series, in which lymphoid neoplasms consistently represented the predominant form of hematologic breast involvement, while leukemic infiltration and breast plasmacytoma remained distinctly uncommon entities (3-6,12-14). The predominance of lymphoma likely reflects both the greater overall incidence of lymphoid neoplasms involving extranodal sites and the propensity of breast tissue to serve as a site of secondary lymphomatous involvement. Conversely, breast manifestations of leukemia and plasma cell neoplasms are typically reported in small institutional series or isolated case reports, underscoring their rarity in routine breast imaging practice (12-13). Although breast lymphoma should remain the primary diagnostic consideration when evaluating hematologic breast lesions, radiologists should be aware that a broader spectrum of hematomphoid neoplasms may occasionally involve the breast and mimic primary breast malignancy.

One of the most important observations in our study was the heterogeneous pattern of breast involvement. Although solitary lesions

represented the most common presentation, nearly half of patients demonstrated multiple lesions, and more than 40% exhibited bilateral disease. These findings closely parallel previous imaging studies by Surov et al. (6), Yang et al. (9), Wienbeck et al. (10), Durhan and Demirkazık (11), and the recently published series by Pehlivan and Ozdemir (15), all of which reported a relatively high frequency of multifocal and bilateral breast involvement compared with primary breast carcinoma (8).

Recently, Pehlivan and Ozdemir (15) reported a contemporary series of breast involvement by hematologic malignancies and similarly demonstrated frequent multifocal disease together with imaging features that often differed from those typically encountered in primary breast carcinoma. Our findings are consistent with these observations and further support the applicability of contemporary BI-RADS terminology in describing the heterogeneous imaging spectrum of hematologic breast involvement (16). Beyond imaging characterization, our study incorporated comprehensive clinicopathologic correlation, evaluation of disease distribution patterns, and assessment of systemic disease burden. This multimodal approach allowed a broader characterization of hematologic involvement of the breast across lymphoma, leukemia/CLL, and plasma cell neoplasms. Notably, multifocality, bilateral disease, and associated nodal involvement were common findings, supporting the concept that breast manifestations of hematologic malignancies frequently represent part of a broader systemic disease process rather than isolated breast-confined pathology. In daily practice, the presence of bilateral or multifocal breast lesions, particularly when accompanied by regional lymphadenopathy or a known history of hematologic malignancy, should prompt consideration of hematologic involvement. Furthermore, FDG PET/CT frequently demonstrated concurrent nodal, extranodal, and bone marrow involvement, underscoring that breast manifestations are often one component of disseminated systemic disease rather than an isolated breast process (2,6).

Our results further emphasize that hematologic involvement of the breast often lacks several classic imaging hallmarks of primary invasive breast carcinoma. Suspicious calcifications were absent in all patients, while spiculated margins and architectural distortion were uncommon. Instead, most lesions appeared as oval, round, or mildly lobulated masses with circumscribed or partially circumscribed margins. Similar observations have been consistently reported by Glazebrook et al. (1), Raj et al. (2), Yang et al. (9), Surov et al. (6), Wienbeck et al. (10), and Durhan and Demirkazık (11), who demonstrated that hematologic malignancies frequently exhibit relatively non-aggressive morphologic features despite representing malignant disease (10). The absence of a pronounced desmoplastic response may partially explain these imaging characteristics. Consequently, reliance solely on conventional morphologic criteria may lead to under-recognition of hematologic breast involvement, underscoring the importance of clinical history and pathologic confirmation (5,17). Similar observations have also been reported in broader series evaluating secondary breast malignancies from extramammary tumors, where circumscribed morphology, absence of calcifications, and multifocal disease patterns were more common than in primary breast carcinoma (18).

Another noteworthy finding was nodal-type breast involvement in approximately one-fifth of patients (17.6%). These lesions demonstrated

imaging features resembling those of pathologic intramammary lymph nodes, including cortical thickening, loss of the fatty hilum, and oval morphology. Although intramammary nodal involvement has been described previously, it remains underemphasized in most radiologic reviews (1,2,6,9). Recognition of this pattern is important because the pattern may represent a manifestation of systemic lymphoid disease rather than a true primary breast mass. Awareness of this presentation may facilitate earlier consideration of hematologic malignancy and guide appropriate tissue sampling strategies.

MRI demonstrated considerable heterogeneity in the pattern of involvement. Among the 12 patients who underwent breast MRI, nodular disease was the predominant presentation (10/12, 83.3%), whereas diffuse infiltrative involvement was observed in 2 patients (16.7%). Nodular lesions frequently showed avid enhancement and diffusion restriction despite maintaining a relatively circumscribed morphology. In contrast, diffuse infiltrative cases demonstrated extensive, heterogeneous, non-mass enhancement involving large portions of the breast parenchyma and, occasionally, extending toward the skin. Raj et al. (2) described similar MRI appearances in both primary and secondary breast lymphoma, emphasizing the value of MRI in depicting both focal mass-forming lesions and diffuse infiltrative patterns of disease. Notably, diffusion restriction was consistently observed in all patients who underwent MRI, supporting the high cellularity typically associated with hematologic malignancies. Despite their often benign-appearing morphology on MG and US, these MRI findings underscore the biologically aggressive nature of the underlying disease.

A particularly important observation in our cohort was the close association between breast lesions and systemic disease burden. No patient demonstrated truly isolated breast-confined lymphoma without regional nodal or systemic involvement. Regional lymphadenopathy, extranodal disease, or disseminated hematologic manifestations were frequently identified, supporting the concept that breast involvement often represents one component of a broader systemic disease process rather than an isolated organ manifestation. Similar observations have been reported by Talwalkar et al. (3), Surov et al. (6), and Pehlivan and Ozdemir (15), who noted that disseminated disease is substantially more common than localized breast-confined involvement. Notably, approximately two-thirds of the patients in the series reported by Surov et al. (6) were classified as having secondary breast lymphoma, further supporting the close association between breast involvement and systemic disease burden. Although primary breast lymphoma has been well described in the literature, our findings further support the concept that breast involvement by hematologic malignancies frequently represents part of a broader systemic disease process rather than a truly organ-confined entity.

Perhaps the most important finding of our study was the apparent discrepancy between lesion morphology and overall disease burden. Many lesions demonstrated relatively benign morphological characteristics, including an oval shape, circumscribed margins, and absence of suspicious calcifications. Nevertheless, these findings frequently coexisted with multifocal disease, lymphadenopathy, and disseminated hematologic malignancy. Therefore, radiologists should

be cautious when interpreting apparently benign breast lesions in patients with known hematologic malignancies or with accompanying systemic findings. Radiologic-pathologic correlation remains particularly important because secondary breast malignancies may mimic both benign lesions and primary breast cancer, resulting in potential diagnostic delay or inappropriate management (19).

Study Limitations

The present study has several limitations. First, its retrospective design limited the standardization of imaging acquisition protocols, staging evaluations, and clinical assessments across the study period. Second, although this study represents one of the larger contemporary two-center cohorts specifically focused on hematologic breast involvement, the sample size remained limited because of the rarity of the condition. Third, not all patients underwent the full spectrum of imaging modalities, particularly breast MRI and FDG PET/CT, which limited comprehensive modality-to-modality comparisons and may have led to underestimation of certain imaging features or systemic disease manifestations. Fourth, the heterogeneity of histologic subtypes precluded meaningful subtype-specific statistical analyses and limited the direct comparison among lymphoma, leukemia/CLL, and plasma cell neoplasms. Finally, the descriptive nature of the study and the limited sample size restricted the ability to perform robust multivariable analyses. Nevertheless, the study provides a comprehensive, contemporary clinicopathological and multimodality imaging assessment of hematologic malignancies involving the breast and offers valuable insights into their patterns of presentation, imaging spectrum, and association with systemic disease burden.

Conclusion

Breast involvement by hematologic malignancies is a rare manifestation of systemic disease and demonstrates a broad and often deceptive imaging spectrum. Multifocal or bilateral disease, circumscribed nodular masses, intramammary nodal-type lesions, diffuse infiltrative involvement, and the absence of suspicious mammographic calcifications were the most characteristic imaging findings in our cohort. Importantly, breast lesions were almost invariably associated with regional nodal or systemic disease rather than representing isolated breast-confined involvement. Recognition of these imaging patterns, combined with clinicopathologic correlation and comprehensive systemic evaluation, may facilitate earlier diagnosis, guide appropriate tissue sampling, prevent unnecessary breast-directed surgery, and promote timely hematologic management.

Ethics

Ethics Committee Approval: The study protocol was approved by the Başakşehir Çam and Sakura City Hospital Scientific Research Ethics Committee No. 2 (protocol no. 2026-60; decision no. 60; approval date: 04.02.2026).

Informed Consent: The informed consent was waived because of the retrospective nature of the study.

Footnotes

Authorship Contributions: Concept - M.A.N., E.E., C.K.T.; Design - M.A.N.; Data Collection or Processing - M.A.N., E.E., C.K.T.; Analysis or Interpretation - M.A.N.; Literature Search - M.A.N., E.E., C.K.T.; Writing - M.A.N.

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

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Prevalence of Cerebral Microbleeds in Active Amateur Boxers: A 3T Susceptibility-Weighted Imaging Study

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ABSTRACT

Introduction: To estimate the prevalence of cerebral microbleeds (CMBs) on 3T susceptibility-weighted imaging (SWI) in active amateur boxers and compare findings with healthy controls.

Methods: Thirty active male amateur boxers and 30 healthy male volunteers (18-29 years) underwent brain magnetic resonance imaging including SWI on a 3T system. Boxing exposure variables (age, boxing duration, self-reported number of matches, knockouts, and history of concussion) were recorded via structured interviews. Two experienced neuroradiologists, blinded to group allocation, independently reviewed SWI datasets for CMBs using magnitude and phase information to confirm susceptibility and exclude mimics. Group differences in CMB prevalence were assessed using Fisher's exact test. For zero-event data, 95% confidence intervals (CIs) for prevalence were reported.

Results: Boxers had a mean boxing career duration of 6.04 years, with a total of 1,152 self-reported matches (38.4 per boxer), 47 knockouts, and 8 traumatic concussions. No CMBs were observed on SWI in either the boxer or control group (0/30 vs. 0/30; Fisher's exact test, $p=1.00$). For each group, the two-sided 95% CI for CMB prevalence was 0% to 11.6%. Inter-reader agreement was complete.

Conclusion: No CMBs were observed on 3T SWI in this cohort of young active amateur boxers. However, given the sample size and zero-event outcome, clinically relevant low prevalences cannot be excluded; larger studies enriched for higher cumulative head-impact exposure are needed to provide tighter prevalence estimates and clarify clinical significance.

Keywords: Amateur boxing, cerebral microbleeds, susceptibility weighted imaging (SWI)

Introduction

Trauma-related brain injury has become a major global public health problem, disproportionately affecting young and economically productive individuals and leading to substantial disability and mortality (1). Common causes of traumatic brain injury (TBI) include traffic and occupational accidents, sports-related trauma, falls from height, and physical violence. TBI-related disturbances are typically categorized as primary and secondary (2). Primary injury refers to damage occurring at the moment of impact, including hemorrhage, vascular injury, cranial fractures, and diffuse axonal injury (DAI). Secondary injury encompasses biochemical, physiological, and vascular processes that develop minutes to days after trauma as a consequence of homeostatic disruption.

Interest and participation in close-contact combat sports such as boxing have increased at both amateur and professional levels, accompanied by a rise in sports-related head injuries (3). Because the head is a frequent target in boxing, repetitive impacts are thought to contribute to both acute and chronic brain injury. Acute injuries span a wide clinical

spectrum, ranging from concussion and intracranial hemorrhage to cerebral white matter axonal damage. Behavioral disturbances and later-life motor and cognitive impairments have been reported after athletic careers end (4). The delayed and cumulative neural effects of repetitive blows may become more apparent after retirement from boxing.

Brain computed tomography (CT) and conventional magnetic resonance imaging (MRI) are widely used to evaluate athletes with suspected mild TBI (mTBI). However, these examinations frequently yield normal or non-specific findings, limiting their sensitivity for detecting subtle injury (5). This limitation has motivated increased interest in advanced neuroimaging techniques to better characterize TBI mechanisms and identify brain changes that may precede overt clinical findings, potentially enabling earlier risk stratification and preventive interventions.

Susceptibility-weighted imaging (SWI) is an advanced MRI technique first described for clinical implementation by Haacke et al. (6) in 2004. SWI leverages the magnetic susceptibility effects of blood products (e.g., deoxyhemoglobin, intracellular hemoglobin, and hemosiderin) and



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minerals such as iron and calcium by combining magnitude and phase information to enhance the detection of small hemorrhagic lesions, including cerebral microbleeds (CMBs). Given the established sensitivity of SWI for microhemorrhagic foci and the relevance of repetitive head trauma in boxing, this technique represents a particularly suitable tool for investigating subclinical brain injury in this population.

The aim of this study was to evaluate the presence and prevalence of CMBs on SWI in active amateur boxers exposed to repetitive head impacts, by comparing findings with those of healthy controls.

Methods

Study Design and Ethical Approval

This study was conducted between September 2021 and September 2022, after approval was obtained from the Selçuk University Ethics Committee (approval number: 2020/103, date: 04.03.2020). MRI-related costs were supported by Selçuk University's Scientific Research Projects Unit. Written informed consent was obtained from all participants before enrollment. All participants were informed of the study procedures, potential risks and benefits, the confidentiality of personal data, and their right to withdraw at any time without consequences. The consent process complied with the principles of the Declaration of Helsinki.

Participants

A total of 60 individuals were included: 30 active amateur boxers and 30 healthy male volunteers. The control group was recruited from the same age range as the boxer group and matched to the boxer group for age and sex. No significant difference in age was observed between the two groups (boxer group: median age 23 years, range 18-29 years; control group: median age 23 years, range 18-29 years; $p > 0.05$). All participants were male. For the boxer group, the following variables were recorded via structured interviews: age, duration of boxing career, total number of matches, mean number of matches per boxer, total number of knockouts, and number of prior traumatic concussions.

Exclusion Criteria

Participants were excluded if they had any of the following: a known neurological disease; a history of head trauma (except boxing-related trauma in the boxer group); epilepsy; metabolic disorders; perinatal asphyxia; active or prior central nervous system disease; a history of drug or substance use; or hypertension.

Clinical Assessment

All participants underwent a standardized neurological examination. The neurological evaluation assessed the presence of focal neurological deficits, tremor, nystagmus, speech disturbances, and subjective memory complaints. Data were collected using standardized forms and predefined evaluation protocols throughout the study period.

MRI Acquisition

MRI examinations were performed using a 3-Tesla scanner (Magnetom Aera, Siemens Healthcare, Erlangen, Germany) with a dedicated head coil. Initial sagittal localizer images were obtained. SWI was acquired

with the following parameters: repetition time, 49 ms; echo time, 40 ms; in-plane resolution, 0.9×0.9 mm; section thickness, 1.6 mm; base resolution, 320; flip angle, 15° ; phase field of view, 75%; image matrix, 247×320 (Figure 1). SWI images were reviewed for artifacts; no participant was excluded due to imaging artifacts.

Image Analysis

All images were evaluated independently by two academic radiologists with 10 and 12 years of neuroradiology experience, respectively. Readers were blinded to participant group and to each other's assessments. SWI magnitude images were reviewed together with corrected phase images to confirm susceptibility effects and to help exclude mimics. CMBs were defined as small, rounded or ovoid hypointense foci on SWI magnitude images (typically within the microbleed size range) that showed corresponding susceptibility on phase images and were not attributable to venous structures, calcifications, or artifacts. Microbleeds were recorded as present or absent. If present, the number of foci was counted. Any potential disagreements would be resolved by consensus; however, no disagreements occurred.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA). The prevalence of

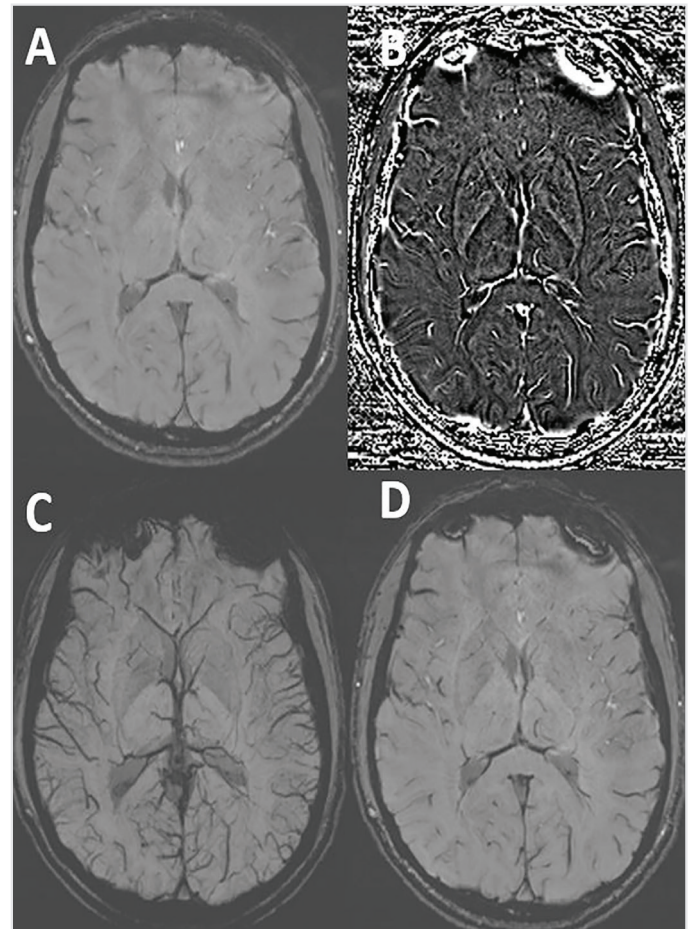


Figure 1. SWI examples: (A) magnitude image; (B) filtered phase image; (C) minIP image; (D) processed SWI image. SWI: Susceptibility-weighted imaging

microbleeds was compared between groups using Fisher's exact test. Age, as a demographic variable, was compared between groups using the Mann-Whitney U test. A two-sided p value of <0.05 was considered statistically significant. For each group, two-sided 95% confidence intervals (CIs) for microbleed prevalence were calculated. When the event count was zero, the upper bound of the CI was derived using the exact binomial (Clopper-Pearson) method.

Results

Study Population

A total of 60 male participants were included in the study: 30 active amateur boxers and 30 healthy controls. The overall age range was 18-29 years, and the median age in both groups was 23 years. No statistically significant difference in age was found between the boxer and control groups ($p>0.05$).

Boxing Exposure Characteristics

In the boxer group, the mean duration of boxing participation was 6.04 years. The total number of matches was 1,152, corresponding to a mean of 38.4 matches per boxer. There were 47 knockouts and 8 documented traumatic concussions. Systematic data on sparring frequency and training-related head impacts were not collected as part of the structured interview; this represents a recognized limitation of the exposure assessment, as discussed below.

SWI Findings

All SWI datasets were considered diagnostically adequate. SWI magnitude and corrected phase images generated through post-processing were independently evaluated by two academic radiologists with 10 and 12 years of neuroradiology experience. Both readers were blinded to the participant group and to each other's assessments.

Neither reader identified lesions suggestive of microbleeds in any participant in either group. Accordingly, the observed prevalence of SWI-detected microbleeds was 0/30 (0%) in the boxer group and 0/30 (0%) in the control group (Fisher's exact test, $p=1.00$). For each group, the two-sided 95% CI for microbleed prevalence was 0% to 11.6%.

Inter-reader Agreement

Inter-reader agreement was complete, with 100% concordance between the two radiologists regarding the presence or absence of microbleeds.

Discussion

Repetitive head impacts in boxing have been associated with a broad spectrum of TBI-related findings, including cerebral and cerebellar atrophy, ventricular enlargement, post-traumatic cysts, contusions, intraparenchymal and extra-axial hematomas, axonal injury, and white matter microhemorrhages. TBI may manifest as focal lesions or DAI. Importantly, microhemorrhages related to mTBI and DAI are most frequently located in deep subcortical white matter and the brainstem, and they may remain occult on cranial CT and conventional MRI sequences (7). Because the number, size, and anatomical distribution of microhemorrhages can correlate with clinical severity and may inform

prognosis, reliable detection of these lesions is clinically meaningful in populations exposed to repetitive head trauma (8).

SWI leverages magnetic susceptibility differences to enhance the conspicuity of venous structures and blood products. In SWI processing, phase information is filtered and combined with magnitude data to generate images with increased contrast for susceptibility effects, thereby improving the visualization of hemorrhagic foci and certain mineral deposits compared with conventional MRI (6). Prior work has demonstrated the added value of SWI in a variety of intracranial pathologies. For example, İkizceli and Mutlu Değer (9) evaluated SWI on a 1.5-T system across a heterogeneous cohort and reported that SWI increased lesion conspicuity and facilitated detection of micro- and macrohemorrhages, venous malformations, and mineral accumulation relative to conventional sequences. Similarly, in a large cohort study comparing T2* and SWI at 1.5 T, SWI was reported to be highly sensitive for slow-flow vascular lesions, hemorrhagic foci, mineral deposition, internal characteristics of cerebral masses, and hemorrhagic transformation in ischemic stroke, while preserving anatomic detail (10).

Earlier imaging studies of boxers using CT and lower-field MRI frequently reported normal findings or only subtle abnormalities, likely reflecting limited sensitivity and technical constraints. In a CT-based study of 338 active professional boxers, 93% had normal findings, while borderline atrophy was identified in 6% (7). In an MRI study including 12 active and 40 retired boxers, mild cerebral atrophy was reported in eight cases, and reduced size of the mammillary bodies and optic chiasm was described in 30 cases (11). However, early MRI studies often used low-field systems and thick slices, which likely limited detection of small lesions and constrained the interpretation of negative results. Consistent with this, a 1992 MRI study of 13 amateur boxers acquired on a 0.5-T system with 10-mm slice thickness reported no abnormalities and no cerebral microhemorrhages (12).

In contrast to these earlier reports, the present study employed SWI to investigate microbleeds potentially related to repetitive head trauma in active amateur boxers. We also recorded exposure-related variables that may influence injury burden (e.g., number of matches, knockouts, and documented concussions). Despite these measures, no SWI-detected microbleeds were observed in either the boxer group or the control group, and inter-reader agreement was complete.

Our findings align with studies using contemporary MRI approaches in boxing populations, suggesting low rates of detectable microbleeds in amateur cohorts. In one study of 24 professional boxers using current MRI techniques, diffusion values did not differ significantly between boxers and controls (13). In another study of 49 professional boxers, conventional MRI was normal in 42 participants; the remaining seven showed non-specific white matter lesions. Notably, diffusion tensor metrics differed between boxers and controls, findings interpreted as potential preclinical indicators of brain injury (14). Neither of these diffusion-focused studies specifically assessed microbleed burden. In a 3-T MRI study of 42 male amateur boxers and 37 healthy male controls, microhemorrhages were more frequent in boxers, but the difference did not reach statistical significance (15). Similarly, in a 1.5-T study including 21 amateur boxers and 21 controls, microhemorrhage was identified in 2 of 21 boxers, and these foci were not seen on conventional sequences (16).

Several factors may explain the absence of microbleeds in our boxer cohort. First, participants were young, active amateurs rather than long-retired athletes with decades of exposure, which may have reduced the cumulative risk of detectable hemorrhagic sequelae. Second, the observed burden of severe events (e.g., knockouts and documented concussions) may have been insufficient to yield SWI-visible lesions in this sample. Third, depending on the timing and biological evolution of microbleeds, some lesions may become less conspicuous over time. Finally, improvements in protective equipment, medical supervision, and stricter enforcement of safety regulations in boxing may have contributed to lower rates of microhemorrhagic injury in contemporary amateur athletes (17).

An important interpretive caveat must be emphasized: the absence of SWI-detected microbleeds does not exclude the presence of subtle microstructural or functional brain alterations in this cohort. SWI is specifically sensitive to blood products and susceptibility effects; it is not designed to detect DAI, white matter microstructural changes, or functional connectivity alterations. Advanced neuroimaging techniques such as diffusion tensor imaging, functional MRI, and magnetic resonance spectroscopy may reveal abnormalities in athletes with repetitive head trauma even when SWI findings are negative (13,14). Furthermore, the 95% CI for microbleed prevalence in the boxer group extended as high as 11.6%, indicating that a low but potentially clinically relevant prevalence cannot be excluded on the basis of this study alone. These considerations underscore the need for multimodal imaging approaches in future research, and caution against interpreting a negative SWI result as evidence of the absence of brain injury.

Study Limitations

This study has limitations that warrant careful consideration. First, the sample size was modest ($n=30$ per group), which substantially limits statistical power for detecting rare outcomes; with 0/30 observed microbleeds, the 95% CI upper bound was 11.6%, indicating that a low but potentially clinically relevant prevalence cannot be excluded. The small sample size is, therefore, a critical constraint on interpreting the negative finding; future studies with larger cohorts are needed to provide more definitive estimates. Second, the lack of longitudinal follow-up means that the temporal evolution of potential microstructural changes cannot be assessed; cross-sectional imaging at a single time point may miss lesions that develop or become more conspicuous with continued exposure. Third, although match exposure was recorded, unmeasured sparring and training-related head impacts may have led to exposure misclassification and underestimation of cumulative trauma—sparring sessions in particular, can involve substantial repetitive subconcussive impacts that are not captured by official match statistics. Fourth, SWI is sensitive to blood products, but very small or remote chronic foci may become less conspicuous over time due to resorption and tissue remodeling. Fifth, findings from a young amateur cohort may not generalize to professional or high-risk subgroups, particularly athletes with repeated knockouts or suspected chronic traumatic encephalopathy.

Conclusion

SWI is a robust method for detecting CMBs, an imaging correlate of TBI. In this study, however, SWI did not show an increased prevalence of microbleeds in active amateur boxers compared with healthy controls. Importantly, this negative finding should not be interpreted as evidence of the absence of brain injury; SWI does not capture the full spectrum of brain changes related to repetitive head trauma, and the upper bound of the 95% CI (11.6%) indicates that a clinically relevant prevalence of microbleeds cannot be definitively excluded. Larger prospective studies—ideally enriched for higher cumulative head-impact exposure, with longitudinal follow-up and integration of clinical outcomes and advanced microstructural imaging metrics—are needed to define the role of SWI in monitoring repetitive head trauma and to identify athletes at risk for long-term neurological sequelae.

Ethics

Ethics Committee Approval: This study was conducted between September 2021 and September 2022, after approval was obtained from the Selçuk University Ethics Committee (approval number: 2020/103, date: 04.03.2020).

Informed Consent: The written informed consent was obtained from all participants before enrollment.

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Footnotes

Authorship Contributions: Concept - M.Ö., H.C., Design - M.Ö., A.B., O.Ç., K.D., H.C.; Data Collection or Processing - M.Ö., A.B., O.Ç., K.D., H.C.; Analysis or Interpretation - A.B., O.Ç., H.C.; Literature Search - A.B., H.C.; Writing - M.Ö.

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The Hidden Role of Undernutrition in Geriatric Syndromes Among Prefrail Older Adults

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ABSTRACT

Introduction: Undernutrition frequently coexists with geriatric syndromes in older adults and may share common pathophysiological mechanisms, particularly among prefrail individuals. However, evidence regarding these associations in prefrail older adults remains limited. This study aimed to investigate the relationship between undernutrition and specific geriatric syndromes in this population.

Methods: This cross-sectional study included 624 community-dwelling prefrail adults aged ≥ 65 years evaluated at University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Clinic of Geriatrics between 2018 and 2025. Prefrailty was defined according to Fried's physical frailty phenotype. Nutritional status was assessed using the Mini Nutritional Assessment-Short Form (MNA-SF), with scores ≤ 11 indicating undernutrition. Geriatric syndromes, including polypharmacy, depression, insomnia, urinary incontinence, falls, cognitive impairment, and functional decline, were evaluated. Binary logistic regression analyses were performed to examine associations between geriatric syndromes and undernutrition, with sensitivity analyses restricted to participants with severe undernutrition (MNA-SF ≤ 7).

Results: The mean age was 77.6 ± 4.9 years, and 61.5% were women. Undernutrition was present in 8.5% of participants. Although depression, falls, cognitive impairment, and functional decline were more common among undernourished individuals, only insomnia remained independently associated with undernutrition after adjustment for age, sex, and education [odds ratio (OR): 2.27, 95% confidence interval (CI): 1.23-4.17, $p=0.008$]. This association persisted in sensitivity analyses of severe undernutrition (OR: 2.48, 95% CI: 1.39-4.44, $p=0.002$).

Conclusion: Insomnia was independently associated with undernutrition among prefrail older adults. These findings highlight the importance of incorporating sleep assessment into the comprehensive geriatric evaluation and suggest that targeting insomnia may represent a clinically relevant strategy to improve nutritional status and to prevent the progression to frailty.

Keywords: Undernutrition, prefrailty, geriatric syndromes, insomnia, comprehensive geriatric assessment

Introduction

The global increase in the proportion of older adults represents a major demographic transformation (1). A longer life expectancy is frequently accompanied by a gradual decline in overall health status and physical functioning, which contributes to the development of conditions such as cognitive impairment and frailty (2). Frailty is widely defined in clinical practice as a complex, multidimensional condition marked by diminished physiological reserves and an increased susceptibility to external stressors. This state of vulnerability is associated with a higher incidence of adverse health outcomes and a substantial increase in healthcare utilization, particularly in geriatric populations (3). Current clinical perspectives widely acknowledge frailty as a strong predictor of reduced survival (4).

The concept of prefrailty, defined as an intermediate stage between robust health and established frailty, has gained recognition as an important component of comprehensive geriatric assessment (5). Prefrailty is defined by the presence of one or two of the five components of the Fried frailty phenotype: weakness, self-reported exhaustion, low physical activity, slow gait speed, and unintentional weight loss (6). Identifying individuals at this transitional stage is crucial, as prefrailty represents a potentially reversible condition and offers an opportunity for early preventive interventions.

Over the past two decades, there has been a marked increase in research examining the link between nutritional status and frailty in older adults. Nutritional interventions are increasingly recognized as a promising strategy for improving the management of frailty and potentially reversing its course (7). Moreover, the impact of nutritional



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interventions on prefrail older adults remains unclear (8). Current systematic reviews highlight the limited evidence regarding the effects of nutritional interventions on a range of outcomes in frail and prefrail older adults (9). Consequently, this limitation hinders the ability to draw definitive conclusions about their effectiveness. Considering the potential of targeted interventions to prevent, delay, or even reverse frailty, the heterogeneity of study outcomes and intervention strategies poses significant challenges for clinicians and policymakers seeking to implement evidence-based practices (10).

Undernutrition in older adults is strongly linked to the onset and progression of geriatric syndromes (11). Conditions such as functional impairment, falls, urinary incontinence, depression, and polypharmacy share common underlying mechanisms with undernutrition, including sarcopenia, chronic inflammation, and a diminished physiological reserve (12,13). Undernutrition may accelerate the onset and severity of these syndromes by impairing muscle strength, immune response, and overall functional capacity. Conversely, the presence of geriatric syndromes may further deteriorate nutritional status through reduced mobility, loss of appetite, cognitive decline, and increased dependency (14). This bidirectional relationship underscores the clinical importance of evaluating undernutrition within the broader context of geriatric syndromes, particularly in vulnerable populations such as prefrail older adults.

Despite the growing body of evidence linking nutritional status to frailty and geriatric syndromes, data specifically focusing on prefrail older adults are scarce. Since prefrailty is considered a transitional and potentially reversible condition, identifying factors linked to unfavorable outcomes in this population carries significant clinical relevance. Within this context, the present study aimed to investigate, using a comprehensive geriatric assessment approach, the relationship between undernutrition and geriatric syndromes in prefrail older adults. By elucidating these associations, this study seeks to contribute to the early identification of high-risk individuals and to inform targeted multidisciplinary interventions that may help prevent the progression to frailty and the associated negative health outcomes.

Methods

Study Design and Sample

Participants were community-dwelling individuals aged ≥ 65 years who were consecutively assessed at a specialized geriatric outpatient center from 2018 to 2025. During the initial screening process, individuals with conditions that could introduce substantial clinical heterogeneity and potentially affect the validity of the analyses were excluded. These exclusion criteria included a documented diagnosis of dementia; total functional dependence; advanced-stage malignancy; advanced chronic obstructive pulmonary disease (COPD); severe heart failure; terminal conditions; or anticipated survival of less than three months. All eligible participants were subsequently assessed using a standardized protocol based on a comprehensive review of medical records and patient documentation. As shown in Figure 1, 857 prefrail older adults were initially evaluated. Among these, 171 individuals aged >85 years and 23 individuals with incomplete assessments were excluded. The

remaining 663 participants were evaluated for eligibility. Subsequently, 39 individuals were excluded due to missing key outcome or covariate data. The final study cohort comprised 624 prefrail older adults who were included in the analysis.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the University of Health Sciences Türkiye, Gülhane Training and Research Hospital Ethics Committee (decision number: 2026/107, date: 07.05.2026). Due to the retrospective design of the study and the use of anonymized medical records, the requirement for written informed consent was waived by the ethics committee. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Data were derived from Comprehensive Geriatric Assessments conducted by a multidisciplinary team under the supervision of a geriatrician. Each assessment included a structured clinical evaluation encompassing vital signs, comorbidities, and current medication use, along with standardized measures of cognitive function, psychological status, and functional capacity. These assessments provided the basis for evaluating the nutritional status and geriatric syndromes within the study population.

Frailty Screening

Frailty status was determined according to the physical frailty phenotype described by Fried et al. (15), which consists of five domains. Unintentional weight loss was defined as a decrease of at least 5% in body weight within the previous year. Muscle strength was assessed by measuring handgrip strength in the dominant hand using a Jamar hydraulic dynamometer (Patterson Medical Ltd.), and the results were interpreted according to sex- and body mass index (BMI)-specific thresholds. Exhaustion was evaluated using two items from the 20-item Center for Epidemiologic Studies-Depression scale ("I felt that everything I did was an effort" and "I could not get going"), with responses of "moderate" or "most of the time" considered indicative of exhaustion (16). Slowness was assessed by measuring gait speed over a 15-foot distance, using threshold values adjusted for gender and height. Physical activity level was determined using the International Physical Activity Questionnaire, and participants in the lowest tertile were classified as having low physical activity levels (17). Individuals meeting one or two of these criteria were categorized as prefrail and constituted the study population.

Undernutrition

Nutritional status was assessed using the Mini Nutritional Assessment-Short Form (MNA-SF; score range, 0-14). In accordance with established cut-off values, participants with a score of ≤ 11 were classified as having undernutrition (12).

Geriatric Syndromes

The geriatric syndromes examined in this study included polypharmacy, depression, insomnia, urinary incontinence, falls, cognitive impairment, and functional decline. Polypharmacy was defined as the concurrent use of five or more medications (18). Depressive symptoms were assessed using the Patient Health Questionnaire-2, which evaluates

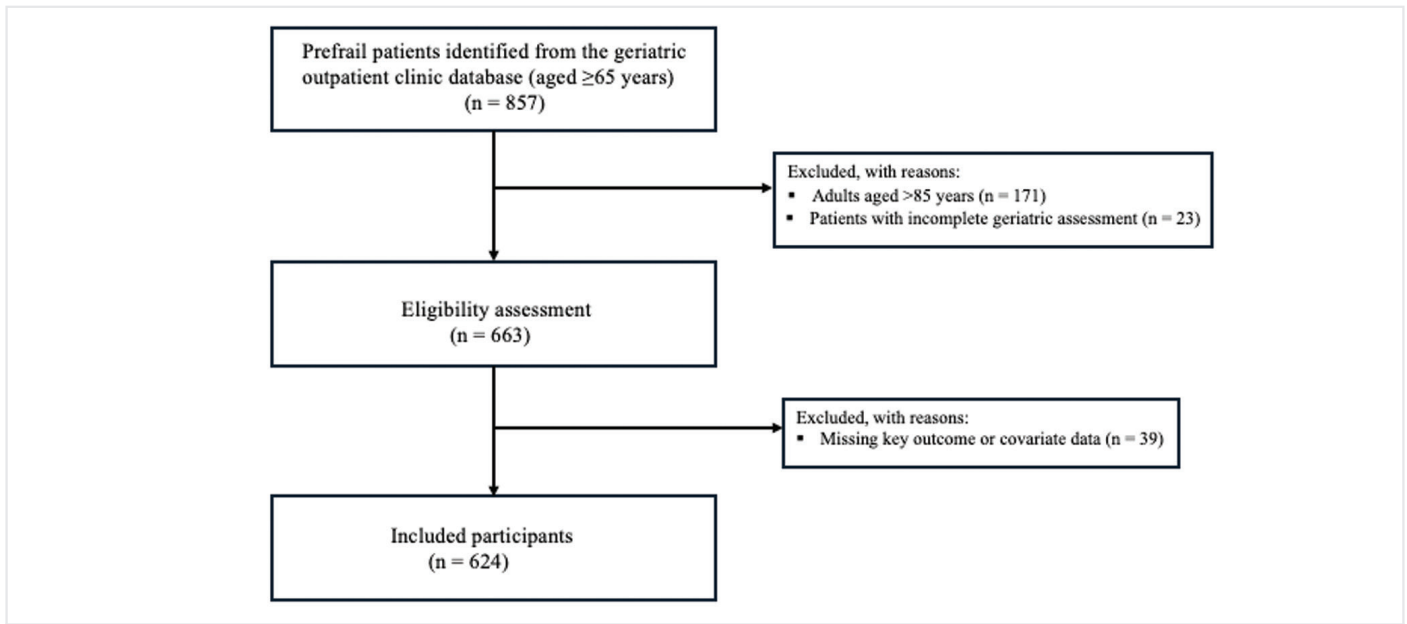


Figure 1. Flow diagram of sample selection process

mood-related symptoms over the preceding two weeks. A score of ≥ 3 (range 0-6) or current use of antidepressant therapy was considered indicative of depression (19). Sleep disturbances were evaluated through four items addressing difficulty initiating sleep, difficulty resuming sleep after nocturnal awakenings, early morning awakenings, and the need for daytime napping. Participants reporting at least one of these symptoms were classified as having insomnia (20). Urinary incontinence was determined from dichotomous (yes/no) questionnaire items regarding involuntary urine leakage. Information on falls was obtained from the participants' relatives or extracted from medical records, and individuals reporting at least one fall within the previous year were categorized as having a history of falls (21). Cognitive impairment was defined as a Mini-Mental State Examination score <24 and recorded as a binary variable (present/absent) (22). Functional status was assessed using the Barthel Index (range 0-100), with scores <90 indicating functional impairment (23). Additionally, for each participant, the total burden of geriatric syndromes was quantified by summing the individual conditions. Participants were further categorized based on the presence of at least two geriatric syndromes.

Other Variables

Baseline characteristics (age, gender, BMI, marital and educational status, smoking status, alcohol consumption, and comorbid conditions) were obtained from patient self-report and electronic health records. Participants' height and weight were recorded during outpatient visits, and BMI was calculated as weight divided by height squared. Routine blood analyses were conducted to measure laboratory parameters such as glucose, hemoglobin, and the levels of vitamins B12 and D.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 29.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as frequencies and percentages,

whereas continuous variables were expressed as mean $\pm$ standard deviation or as median values according to their distribution. The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Comparisons between groups were conducted using the chi-square (χ^2) test for categorical variables and the Mann-Whitney U test for continuous variables when the assumption of normality was not met.

The relationship between undernutrition and geriatric syndromes was first assessed using chi-square analysis. Subsequently, binary logistic regression analyses were performed to further examine the relationship between undernutrition and the presence of geriatric syndromes. Unadjusted models were constructed for each variable. Variables that were found to be statistically significant in the univariate analyses ($p < 0.05$) were included in the multivariable models. Adjusted analyses were performed, controlling for age, gender, and level of education.

The results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). A two-sided p value < 0.05 was considered statistically significant. To evaluate the stability of the results, sensitivity analyses were conducted by re-running all regression models in a subgroup limited to participants with more pronounced undernutrition, defined as an MNA-SF score ≤ 7 . Model calibration was assessed with the Hosmer-Lemeshow goodness-of-fit test, while overall model performance was evaluated using the omnibus test of model coefficients.

Results

Sample Characteristics

Baseline demographic and clinical characteristics of the study population are summarized in Table 1. A total of 624 older adults were included in the analysis, with a mean age of 77.6 ± 4.9 years, and 61.5% were women. The mean BMI was 28.0 ± 4.2 kg/m², and 65.1% of participants were married. Most individuals had a low educational level (≤ 5 years) (60.6%), and smoking and alcohol use were relatively uncommon

(6.7% and 2.1%, respectively). Hypertension was the most common chronic condition (74.4%), followed by diabetes mellitus (35.6%) and cardiovascular diseases (26.3%). Other comorbidities, including COPD (7.5%), cerebrovascular disease (4.6%), chronic kidney disease (3.8%), and Parkinson's disease (1.6%), were less frequent. With respect to geriatric syndromes, polypharmacy was the most prevalent condition (47.4%), followed by depression (32.4%), insomnia (27.2%), and urinary incontinence (26.1%). Falls were reported in 18.3% of individuals, while cognitive impairment and functional decline were present in 9.0% and 4.2% of the sample, respectively. Undernutrition was identified in 8.5% of the participants. The median number of geriatric syndromes was 2 (range, 0-6), and more than half of the participants (51.1%) had two

or more geriatric syndromes. In laboratory assessments, the median glucose level was 97.5 mg/dL, hemoglobin was 13.6 g/dL, vitamin B12 was 331 pg/mL, and vitamin D was 24.0 ng/mL.

Association Between Undernutrition and Geriatric Syndromes

The prevalence of geriatric syndromes stratified by undernutrition status is summarized in Table 2. Depression and insomnia were significantly more common among individuals with undernutrition than among those without (47.2% vs. 31.0%, $p=0.01$; 45.3% vs. 25.6%, $p=0.002$, respectively). Similarly, falls, cognitive impairment, and functional decline were more frequent in participants with undernutrition (28.3% vs. 17.3%, $p=0.04$; 17.0% vs. 8.2%, $p=0.03$; and 11.3% vs. 3.5%, $p=0.01$, respectively). In contrast, no significant differences were observed for polypharmacy and urinary incontinence between the groups. Binary logistic regression analyses evaluating the association between geriatric syndromes and undernutrition are presented in Table 3. In the unadjusted analyses, insomnia was significantly associated with higher odds of undernutrition (OR: 2.17; 95% CI: 1.19-3.96; $p=0.01$). This association remained significant after adjustment for age, gender, and education level (OR: 2.27; 95% CI: 1.23-4.17; $p=0.008$). Although falls, cognitive impairment, and functional decline showed higher ORs in both unadjusted and adjusted models, these associations did not reach statistical significance. Depression was not significantly associated with undernutrition in either model. The adjusted associations are summarized in Figure 2, which demonstrates that insomnia was the only geriatric syndrome independently associated with undernutrition among prefrail older adults.

Sensitivity Analyses

The main findings remained consistent in sensitivity analyses restricted to participants with MNA-SF scores ≤ 7 , supporting the robustness of the results. In this analysis, insomnia remained independently associated with a higher likelihood of undernutrition (OR: 2.48; 95% CI: 1.39-4.44; $p=0.002$).

Model diagnostics indicated good calibration and satisfactory overall performance. The Hosmer-Lemeshow test was non-significant (χ^2 : 5.733; $p=0.677$), supporting an adequate model fit. Furthermore, the Omnibus test confirmed that the model was statistically significant ($-2LL$: 346.186; $\chi^2(2)$: 16.561; $p=0.002$).

Discussion

This study examined the association between undernutrition and geriatric syndromes in a sizable cohort of prefrail older adults, employing a comprehensive geriatric assessment framework. The principal finding was that insomnia was independently associated with undernutrition, even after adjustment for key sociodemographic variables and in sensitivity analyses restricted to individuals with more severe nutritional impairment. Although several geriatric syndromes, including falls, cognitive impairment, and functional decline, were more prevalent among undernourished individuals, these associations did not remain statistically significant in multivariable models. These findings highlight insomnia not merely as a coexisting geriatric syndrome but as a potentially central determinant of nutritional

Table 1. Demographic and clinical characteristics of the study sample

Variables	Total (n=624)
Age (years), mean $\pm$ SD	77.6 $\pm$ 4.9
Gender (female), n (%)	384 (61.5)
BMI (kg/m ²), mean $\pm$ SD	28.0 $\pm$ 4.2
Marital status, married, n (%)	406 (65.1)
Education, ≤ 5 y, n (%)	378 (60.6)
Smoking, n (%)	42 (6.7)
Alcohol, n (%)	13 (2.1)
Chronic diseases	
Hypertension, n (%)	464 (74.4)
Diabetes mellitus, n (%)	222 (35.6)
Cardiovascular disease, n (%)	164 (26.3)
COPD, n (%)	47 (7.5)
Cerebrovascular disease, n (%)	29 (4.6)
Chronic kidney disease, n (%)	24 (3.8)
Parkinson's disease, n (%)	10 (1.6)
Geriatric syndromes	
Polypharmacy, n (%)	296 (47.4)
Depression, n (%)	202 (32.4)
Sleep disorder, n (%)	170 (27.2)
Urinary incontinence, n (%)	163 (26.1)
Fall, n (%)	114 (18.3)
Cognitive impairment, n (%)	56 (9.0)
Malnutrition risk, n (%)	53 (8.5)
Functional decline, n (%)	26 (4.2)
Geriatric syndrome count, median (min-max)	2 (0-6)
Geriatric syndrome burden, n (%)	
<2	305 (48.9)
≥ 2	319 (51.1)
Laboratory assessments	
Glucose (mg/dL), median	97.5
Complete blood count (CBC), median	13.60
Vitamin B12 level, median	331.0
Serum 25-hydroxyvitamin D levels, median	24.0
Results are mean $\pm$ SD, median (minimum-maximum), or percentage. Missing data: Vitamin B12 level (49), serum 25-hydroxyvitamin D levels (58). SD: Standard deviation, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease	

Table 2. Association between undernutrition and geriatric syndromes in prefrail older adults (n=624)

Geriatric syndromes	Undernutrition		p
	No	Yes	
Polypharmacy, n (%)	271 (47.5)	25 (47.2)	0.96
Depression, n (%)	177 (31.0)	25 (47.2)	0.01
Insomnia, n (%)	146 (25.6)	24 (45.3)	0.002
Urinary incontinence, n (%)	147 (25.7)	17 (32.1)	0.31
Fall, n (%)	99 (17.3)	15 (28.3)	0.04
Cognitive impairment, n (%)	47 (8.2)	9 (17.0)	0.03
Functional decline, n (%)	20 (3.5)	6 (11.3)	0.01

Table 3. Binary logistic regression analysis of geriatric syndromes associated with undernutrition

Variables	Unadjusted		Adjusted	
	OR (95% CI)	p	OR (95% CI)	p
Depression	1.44 (0.78-2.65)	0.23	1.45 (0.79-2.69)	0.22
Insomnia	2.17 (1.19-3.96)	0.01	2.27 (1.23-4.17)	0.008
Fall	1.75 (0.91-3.36)	0.09	1.74 (0.90-3.35)	0.09
Cognitive impairment	1.85 (0.78-4.34)	0.15	1.63 (0.69-3.87)	0.26
Functional decline	2.37 (0.82-6.81)	0.11	2.12 (0.73-6.12)	0.16

Note: Adjusted for age, gender and education. OR: Odds ratio, CI: Confidence interval

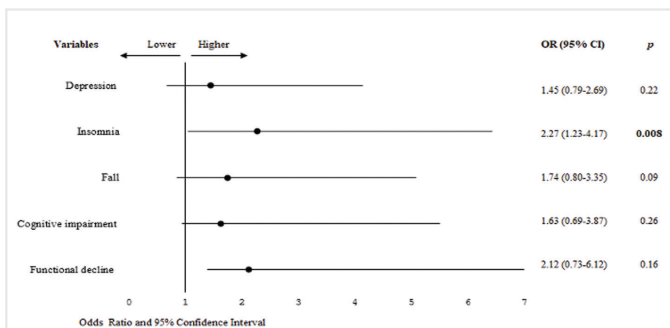


Figure 2. Forest plot of adjusted odds ratios for geriatric syndromes associated with malnutrition risk. The model was adjusted for age, sex, and educational level, OR: Odds ratio, CI: Confidence interval

vulnerability in the prefrail state. These findings suggest that insomnia represents a particularly important and potentially modifiable factor in this vulnerable population.

The relationship identified between insomnia and undernutrition aligns with prior evidence highlighting a strong interaction between sleep disturbances and nutritional status among older adults. Sleep problems have been associated with diminished appetite, disrupted eating behaviors, and insufficient energy intake, which may collectively contribute to nutritional decline (24,14). In addition, earlier studies have linked poor sleep quality to frailty and unfavorable health outcomes, indicating that sleep disturbances may serve as an early indicator of physiological vulnerability (25). However, most existing literature has focused on frail individuals or the broader older adult population, with relatively limited data on prefrail individuals. The present findings extend current knowledge by demonstrating that this association is already detectable during the prefrail stage, an intermediate and potentially reversible phase within the frailty continuum.

Inflammatory processes also play a pivotal role in the link between sleep disturbances and malnutrition. Chronic sleep disorders have been associated with elevated levels of systemic inflammatory markers, particularly interleukin-6 and C-reactive protein, whereas findings regarding tumor necrosis factor-alpha remain less consistent. These inflammatory pathways may contribute to muscle catabolism and appetite suppression (26). In prefrail older adults, who already exhibit reduced physiological reserves, this state of chronic low-grade inflammation may further exacerbate nutritional vulnerability and accelerate the progression to frailty (27).

Beyond biological mechanisms, behavioral and functional factors may also contribute to this association. Insomnia is frequently accompanied by daytime fatigue, reduced physical activity, and diminished motivation, which may adversely affect an individual's ability to maintain an adequate nutritional intake. Furthermore, sleep disturbances are often associated with depressive symptoms and cognitive decline, both of which have been linked to irregular eating patterns and reduced food consumption. In prefrail individuals, the interaction of these factors may exert a cumulative effect, contributing to deterioration in nutritional status, as reflected by the lower MNA-SF scores observed in our study.

In our study, falls, cognitive impairment, and functional decline were more common among participants with undernutrition; however, these associations did not persist after further analysis. This suggests that the link between undernutrition and these geriatric syndromes may not represent a direct, independent relationship but may rather operate through complex, multifactorial pathways. For example, Yu et al. (28) demonstrated a significant association between undernutrition and an increased risk of cognitive impairment; the difference compared with our findings may be explained by the prefrail characteristics of our cohort, in which cognitive decline is likely to be at an earlier

stage. In contrast, a narrative review has suggested that malnutrition contributes to a higher risk of falls and loss of functional independence through mechanisms such as decreased muscle mass and strength, impaired balance, and reduced physical performance (29). However, these associations are often mediated by intermediate factors, including frailty, sarcopenia, comorbidity burden, and physical inactivity (30). This may explain why the observed relationships in our study did not retain statistical significance after adjustment. Overall, these results suggest that the effects of undernutrition on geriatric syndromes may become more evident in advanced stages of frailty or in older populations with greater heterogeneity.

Study Limitations

Several limitations should be considered when interpreting these findings. The cross-sectional design of the study limits the ability to determine the directionality of the association between insomnia and undernutrition. However, the inclusion of comprehensive geriatric assessment data, along with adjustment for important confounding factors, strengthens the credibility of the findings. Although the study was conducted in a single tertiary care center, which may restrict generalizability, the inclusion of a well-defined and relatively large prefrail cohort supports the clinical relevance of our results. Moreover, evaluating insomnia based on self-reported symptoms rather than objective measures may have introduced reporting bias. However, the use of a standardized evaluation approach and consistent application of the assessment method across all participants likely mitigated this effect. Furthermore, the consistency of findings across the sensitivity analyses strengthens the robustness of the observed association and reinforces the internal validity of the study.

Conclusion

Insomnia emerged as an independent correlate of undernutrition among prefrail older adults. This finding underscores the importance of incorporating sleep assessments into comprehensive geriatric evaluations. These findings support the integration of sleep assessment into routine comprehensive geriatric evaluation and suggest that targeting insomnia may represent a novel and clinically relevant strategy for mitigating undernutrition and preventing progression to frailty. Future longitudinal studies are warranted to further elucidate the underlying causal mechanisms and evaluate the impact of sleep-focused interventions on nutritional and functional outcomes.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, Gülhane Training and Research Hospital Ethics Committee (decision number: 2026/107, date: 07.05.2026).

Informed Consent: Due to the retrospective design of the study and the use of anonymized medical records, the requirement for written informed consent was waived by the ethics committee.

Footnotes

Authorship Contributions: Surgical and Medical Practices - Z.S.D., M.I.N.; Concept - Z.S.D., M.I.N.; Design - Z.S.D., M.I.N.; Data Collection

or Processing - Z.S.D., M.I.N.; Analysis or Interpretation - Z.S.D., M.I.N.; Literature Search - Z.S.D., M.I.N.; Writing - Z.S.D., M.I.N.

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Effects of Hydroxyurea Therapy on Inflammatory Markers and Indices in Patients with BCR-ABL Negative Myeloproliferative Neoplasms

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ABSTRACT

Introduction: Chronic inflammation plays a central role in the pathogenesis and progression of Breakpoint Cluster Region- Abelson murine leukemia viral oncogene homolog 1 (BCR-ABL)-negative myeloproliferative neoplasms (MPNs). Although hydroxyurea is widely used as a cytoreductive agent in this patient population, its impact on systemic inflammation remains unclear. This study aimed to evaluate the effect of hydroxyurea on inflammatory markers and indices in patients with MPNs.

Methods: In this retrospective study, 298 patients diagnosed with BCR-ABL-negative MPNs who were followed between 2010 and 2022 were analyzed. Patients were classified as polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), or MPN-unclassifiable (MPN-u) according to the 2016 World Health Organization criteria. Laboratory parameters including leukocyte, neutrophil, lymphocyte, and platelet counts, C-reactive protein (CRP), and lactate dehydrogenase (LDH) were recorded at baseline and at months 3, 6, and 12. Inflammatory indices, including the neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII), were calculated. Statistical analyses were performed using non-parametric tests.

Results: Of the 298 patients, 59.4% were male, with a median age of 57 years. The cohort included PV (32.5%), ET (35.2%), PMF (8.7%), and MPN-u (23.5%). Hydroxyurea was used in 158 patients, while 126 patients were followed without cytoreductive therapy. Significant reductions in leukocyte and neutrophil counts were observed in the hydroxyurea group at months 0-3, 0-6, and 0-12 ($p<0.001$). NLR decreased significantly at months 0-3 and 0-6, while SII showed significant reductions at months 0-3, 0-6, and 0-12. CRP and LDH levels remained unchanged. No significant inflammatory changes were detected in patients not receiving hydroxyurea.

Conclusion: Hydroxyurea treatment was associated with early reductions in inflammatory indices in BCR-ABL-negative MPN patients, possibly reflecting either its myelosuppressive or its potential anti-inflammatory effects. Further prospective studies incorporating cytokine profiling are needed to clarify the mechanisms underlying hydroxyurea's impact on inflammation.

Keywords: Hydroxyurea, BCR-ABL-negative myeloproliferative neoplasms, systemic inflammation, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index

Introduction

Myeloproliferative neoplasms (MPNs) comprise a heterogeneous group of clonal hematopoietic disorders characterized by dysregulated proliferation of myeloid lineage cells within the bone marrow (1). These disorders are traditionally categorized based on the predominant cell lineage involved and include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Following the identification of the Philadelphia chromosome and the Breakpoint Cluster Region- Abelson murine leukemia viral oncogene homolog 1 (BCR-ABL) fusion gene, MPNs lacking this molecular abnormality have been classified as BCR-ABL-negative entities (1).

Driver mutations involving Janus kinase 2 (JAK2), calreticulin (CALR), and the thrombopoietin receptor (MPL) play a central role in disease pathogenesis by promoting constitutive activation of intracellular signaling pathways (2). These molecular alterations not only drive clonal expansion but also contribute to a pro-inflammatory microenvironment.

Beyond uncontrolled myeloid proliferation, MPNs are associated with a spectrum of clinical complications, including extramedullary hematopoiesis, leukemic transformation, and progressive bone marrow fibrosis (3). Increasing evidence suggests that chronic inflammation is a fundamental component of MPN biology. Malignant and non-malignant cells within the tumor microenvironment interact to sustain the release



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of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor- α (TNF- α), which in turn contribute to symptom burden and disease progression (4,5). This persistent inflammatory milieu has been linked to constitutional symptoms and fibrotic evolution.

Hydroxyurea remains one of the most frequently utilized cytoreductive agents in the management of MPNs. Its mechanism of action is primarily mediated through inhibition of ribonucleotide reductase, leading to depletion of deoxyribonucleotide pools and interruption of DNA synthesis during the S phase of the cell cycle (6). However, prolonged exposure or higher cumulative doses may result in increased oxidative stress and cytotoxic effects, ultimately causing bone marrow suppression and cytopenias (7).

Although hydroxyurea has long been established as a cornerstone in the treatment of MPNs, its influence on systemic inflammation remains incompletely understood. Evidence from studies in sickle cell disease suggests that hydroxyurea may modulate inflammatory pathways by reducing pro-inflammatory cytokines such as TNF- α while enhancing anti-inflammatory mediators such as IL-10 (8). Nevertheless, data specifically addressing this relationship in MPN patients are limited.

In the present study, we investigated the impact of hydroxyurea on systemic inflammatory status in patients with BCR-ABL-negative MPNs by evaluating commonly used inflammatory indices, including the neutrophil-to-lymphocyte ratio (NLR) and the systemic immune-inflammation index (SII). These indices, derived from routine hematologic parameters, have emerged as accessible and reproducible markers of systemic inflammation and have been increasingly utilized in both prognostic and predictive settings (9).

Methods

This retrospective study included patients admitted to the hematology outpatient clinic between January 1, 2010, and January 1, 2022. Patients were classified as PV, ET, PMF, or MPN-unclassifiable (MPN-u) according to the 2016 World Health Organization criteria. Baseline demographic and clinical data, including diagnosis, age at diagnosis, gender, underlying genetic mutations, and treatment preferences, were recorded. Laboratory parameters, such as neutrophil, lymphocyte, leukocyte and platelet counts, C-reactive protein (CRP), and lactate dehydrogenase (LDH), were evaluated at 0, 3, 6, and 12 months and compared across these time points. Changes in NLR and SII, derived from these values, were also monitored. Analysis of treatment preferences revealed that patients were either under active surveillance or were receiving cytoreductive therapy, including hydroxyurea, anagrelide, or ruxolitinib. The formula has been calculated as follows: NLR: neutrophil count/lymphocyte count (9) and SII: (neutrophil count x platelet count)/lymphocyte count (10).

Ethical Approval

Ethical approval was obtained from the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Institutional Review Board (approval number: 328; date: 27 October 2022), and the study was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to participation.

Inclusion Criteria

- Patients aged ≥ 18 years were eligible for inclusion.
- Patients diagnosed with BCR-ABL negative MPN in our clinic
- Patients who had completed at least one year of follow-up and treatment in our clinic

Exclusion Criteria

- Patients younger than 18 years or with pregnancy
- Patients diagnosed with BCR-ABL positive MPN
- Patients with another disease or on medication affecting the systemic inflammatory response
- Patients without regular follow-up for at least one year

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was applied to assess the normality of patient data. For comparisons between two groups, the Mann-Whitney U test was used, while comparisons among three or more groups were performed using the Kruskal-Wallis test, followed by Dunn-Bonferroni post-hoc correction. For within-group comparisons of repeated measurements across the four time points (baseline, 3, 6, and 12 months), the Friedman test was used. When the Friedman test was significant, pairwise comparisons between time points were performed using the Wilcoxon signed-rank test, and p values were adjusted for multiple comparisons using the Bonferroni correction. Two-sided $p < 0.05$ was considered statistically significant.

Results

Of the 298 patients included in our study, 177 were male (59.4%) and 121 were female (40.6%). The median age at diagnosis was 57 years (range: 19.2-82.4). When divided into subgroups, the patients were classified as follows: 97 (32.5%) as PV, 105 (35.2%) as ET, 26 (8.7%) as PMF, and 70 (23.5%) as MPN-u. Analysis of treatment regimens showed that 126 patients were under active surveillance without cytoreductive therapy, whereas 158 patients were treated with hydroxyurea, 11 with anagrelide, and 3 with ruxolitinib (Table 1).

Genetic mutation results were obtained for 144 of the 298 BCR-ABL-negative MPN patients included in our study. Among them, 142 patients carried the JAK2 V617F mutation; 1 patient in the ET group had the MPL mutation, and 1 patient in the unclassified group had the CALR mutation.

When patients receiving cytoreductive therapy were stratified into those treated with hydroxyurea and those not, a statistically significant reduction in leukocyte and neutrophil counts was observed in the hydroxyurea group over months 0-3, 0-6, and 0-12 ($p < 0.001$). In contrast, no significant reductions were detected between 3 and 6, 3 and 12, and 6 and 12 months.

Upon evaluation of inflammatory indices, the NLR showed a statistically significant decrease from month 0 to month 3 and from month 0 to month 6 in patients receiving hydroxyurea ($p<0.001$ and $p=0.01$). Analysis of SIII showed a significant decrease in the hydroxyurea group at months 0-3, 0-6, and 0-12 ($p<0.001$, $p<0.05$, and $p<0.05$) (Graphics 1 and 2). However, no significant changes were found in CRP and LDH levels within the hydroxyurea-treated group ($p>0.05$).

No statistically significant decrease was found in leukocyte, neutrophil, CRP, LDH, NLR, and SIII values in patients who were under active follow-up or who received cytoreductive therapies other than hydroxyurea ($p>0.05$).

Discussion

In our study, which included 298 BCR-ABL–negative MPN patients, the cohort was classified into the following subgroups: PV (32.5%), ET

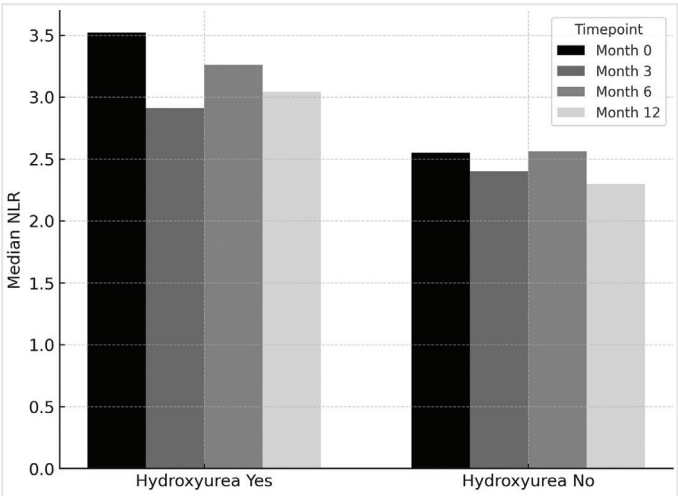
(35.2%), PMF (8.7%), and MPN-unclassified (23.5%). While 126 patients were followed without cytoreductive therapy, the remaining patients mostly received hydroxyurea, and a smaller number received anagrelide or ruxolitinib. Among 144 patients with available genetic data, the JAK2 V617F mutation was found in 142; only one MPL mutation and one CALR mutation were detected. Hydroxyurea treatment led to significant reductions in leukocyte and neutrophil counts at months 0-3, 0-6, and 0-12, and significant decreases in NLR and SIII during early follow-up, although CRP and LDH levels remained unchanged. This result suggests that the neutropenic effect caused by hydroxyurea is more prominent during the early stages of treatment. No significant changes were found in inflammatory indices in patients who were followed without treatment or who received treatments other than hydroxyurea.

It is known that chronic inflammation plays an important role in the pathophysiology of abnormal clonal proliferation, which forms the basis of MPNs (11). Somatic mutations underlying abnormal clonal proliferation such as JAK2 (V617F and exon12), MPL and CALR continuously activate signaling receptor pathways that trigger inflammatory responses (12). The continuous activation of these signaling receptor pathways plays a role in disease progression and development of constitutional symptoms through the release of inflammatory cytokines from both neoplastic cells and normal cells (13). In addition, inflammation is also involved in the development of premature atherosclerosis and thrombotic events in these patients (13). Therefore, controlling the inflammatory microenvironment is an important therapeutic goal in the MPNs (12,13).

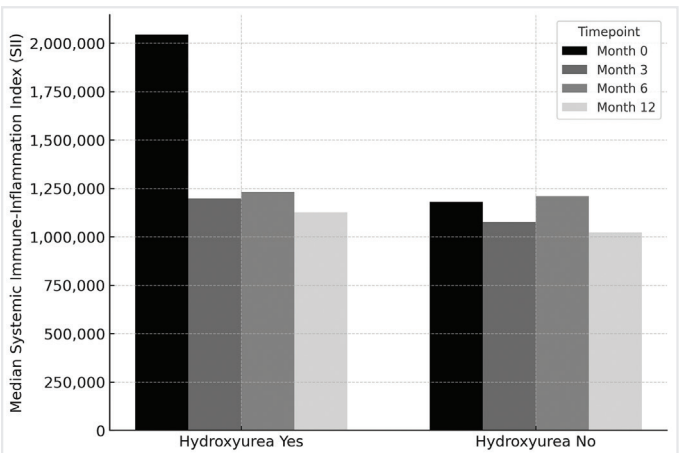
In our study, we investigated the effects of hydroxyurea in the MPN cohort, particularly its anti-inflammatory properties. A literature review indicates that similar investigations have been conducted in patients with sickle cell anemia. In the study conducted by Lanaro and colleagues, it was demonstrated that hydroxyurea treatment in the sickle cell anemia group resulted in a decrease in TNF-alpha levels, while leading to an increase in IL-10 levels, an anti-inflammatory cytokine (8). In an *in vitro* endothelial model carrying the JAK2 V617F mutation, it has been demonstrated that HU treatment prevents thrombosis development by

Table 1. Distribution of patients included in the study according to patient characteristics		
	n	%
Gender		
Male	177	59.4%
Female	121	40.6%
Diagnosis		
PV	97	32.5%
ET	105	35.2%
PMF	26	8.7%
MPN-u	70	23.5%
Treatment		
Surveillance	126	42.3%
Hydroxyurea	158	53%
Anagrelide	11	3.7%
Ruxolitinib	3	1%
Total	298	100%

PV: Polycythemia vera, ET: Essential thrombocythemia, PMF: Primary myelofibrosis, MPN-u: Myeloproliferative neoplasm-unclassifiable



Graphic 1. Median NLR at baseline and at months 3, 6, and 12 according to hydroxyurea treatment. In patients receiving hydroxyurea, NLR decreased significantly from baseline to month 3 ($p<0.001$) and from baseline to month 6 ($p=0.010$), whereas the baseline-to-month-12 difference was not statistically significant. No significant longitudinal changes were observed in patients not receiving hydroxyurea. NLR: Neutrophil-to-lymphocyte ratio



Graphic 2. Median SIII at baseline and at months 3, 6, and 12 according to hydroxyurea treatment. In patients receiving hydroxyurea, SIII decreased significantly from baseline to month 3 ($p<0.001$), to month 6 ($p<0.05$), and to month 12 ($p<0.05$). No significant longitudinal changes were observed in patients not receiving hydroxyurea

reducing P-selectin expression on the endothelium (14,15). In a study similar to ours that evaluated the NLR, the parameters of 35 children diagnosed with sickle cell anemia who were monitored while receiving hydroxyurea treatment for one year and those of 20 healthy controls were examined. It was observed that hydroxyurea treatment resulted in a significant decrease in NLR, accompanied by a concurrent reduction in inflammatory cytokine levels (15,16). In a different study, the effectiveness of hydroxyurea was evaluated in adult patients with sickle cell anemia by examining two distinct cohorts: those receiving hydroxyurea and those not receiving hydroxyurea. The hydroxyurea cohort was further divided into two subgroups based on dosage: individuals receiving a daily dose of 1 gram and those receiving a daily dose of 1.5–2 grams. Levels of inflammatory markers (myeloperoxidase, TNF- α , and IL-10) and oxidative markers (superoxide dismutase, glutathione peroxidase, and malondialdehyde) were significantly altered ($p < 0.05$) in these cells, demonstrating notable differences between the hydroxyurea subgroups and the non-hydroxyurea group. Treatment with HU restored the levels of all markers to concentrations similar to those observed in healthy individuals, indicating a positive dose-effect relationship (16). In a study of patients with sickle cell anemia, researchers analyzed the association between monocyte subsets and hydroxyurea treatment. Significant alterations in monocyte subsets were observed, with classical monocytes (CD14⁺⁺CD16⁻) being highly prevalent in individuals not receiving hydroxyurea, whereas those with a patrolling phenotype (CD14^{dim}CD16⁺) were more abundant in patients undergoing therapy. Furthermore, hydroxyurea was found to reduce the production of TNF- α , IL1- β , IL-6 and IL-8 (17).

A review of the literature shows that the number of studies investigating the relationship between hydroxyurea and inflammation, particularly in MPNs, is limited. In this research, MPN patients who were started on hydroxyurea treatment experienced an early decrease in neutrophil count, NLR, and SII. It is known that hydroxyurea causes myelosuppression through inhibition of DNA synthesis, which may lead to neutropenia, and that this side effect can resolve upon discontinuation of the drug (18,19). Thrombotic events are common complications in MPNs and arise through a complex interplay of blood cell activation, endothelial dysfunction, inflammation, and coagulation abnormalities. Leukocytes are key drivers of this thromboinflammatory process, releasing pro-inflammatory and pro-thrombotic mediators that amplify clot formation (19). Hydroxyurea has been shown to reduce thrombosis, particularly in high-risk ET and when combined with aspirin in MPNs (20,21). Therefore, its influence on inflammatory markers is clinically important. In this context, our study evaluates the effect of hydroxyurea on inflammatory parameters, changes in which may contribute to its protective role against thrombotic complications.

The observed reductions in NLR and SII may suggest attenuation of the circulating inflammatory milieu during hydroxyurea treatment (10). However, neutrophils constitute the numerator of both indices, while platelet counts are also incorporated into the calculation of SII. Therefore, the observed changes may largely represent a mathematical consequence of hydroxyurea-induced cytoreduction and myelosuppression rather than an independent anti-inflammatory effect (19). The absence of a significant change in CRP further limits

the interpretation of these findings as evidence of a systemic anti-inflammatory response. Although previous studies have reported that hydroxyurea may modulate inflammatory cytokines and immune-cell subsets (18), the present data cannot distinguish true immunomodulation from the numerical effects of reduced circulating blood cell counts. Moreover, thrombotic events, symptom burden, disease progression, and survival outcomes were not evaluated. Accordingly, these findings should be interpreted as changes in cell-count-derived inflammatory indices rather than definitive evidence of an independent anti-inflammatory effect or of clinical benefit.

We believe that, to more clearly demonstrate the impact of hydroxyurea on inflammation in patients with MPNs, future studies should evaluate inflammatory markers and cytokine profiles concurrently throughout the course of treatment in larger patient cohorts. Such comprehensive and longitudinal assessments will not only help clarify the mechanisms underlying hydroxyurea's anti-inflammatory effects, but also contribute valuable insights to future research and the development of more targeted therapeutic strategies.

Study Limitations

This study has several limitations that should be acknowledged. First, the retrospective study design inherently limits the ability to establish causal relationships between inflammatory indices and clinical outcomes. Second, as the analysis was conducted at a single institution, the findings may not be fully generalizable to broader, more diverse patient populations.

Although inflammatory parameters were assessed at predefined time points, potential confounding variables that could influence systemic inflammatory status may not have been fully controlled. The absence of detailed longitudinal cytokine profiling further restricts the ability to comprehensively interpret the underlying biological mechanisms.

Conclusion

Finally, molecular and genetic data were not uniformly available for all patients, which may have limited the ability to perform a more in-depth evaluation of disease heterogeneity and its potential impact on inflammatory markers.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Institutional Review Board (approval number: 328; date: 27 October 2022), and the study was performed in accordance with the Declaration of Helsinki.

Informed Consent: All participants provided written informed consent prior to participation.

Footnotes

Authorship Contributions: Surgical and Medical Practices - O.A., I.S., O.Y.; Concept - O.A., I.S.; Design - O.A., O.Y.; Data Collection or Processing - O.A., I.S., O.Y.; Analysis or Interpretation - O.A., I.S., O.Y.; Literature Search - O.A., Writing - O.A.

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Diagnostic Accuracy of 12-Lead Electrocardiographic Algorithms in Predicting the Origin of Idiopathic Premature Ventricular Complexes: Comparison with Ablation Outcomes

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ABSTRACT

Introduction: Accurate preprocedural localization of the origin of idiopathic premature ventricular complexes (PVCs) using the 12-lead electrocardiogram (ECG) may facilitate procedural planning for catheter ablation. However, the diagnostic performance of ECG criteria and localization algorithms remains variable. We aimed to evaluate the diagnostic accuracy of five ECG-based criteria or algorithms in predicting the successful ablation site in idiopathic PVCs.

Methods: This study included 32 patients who underwent successful catheter ablation for idiopathic PVCs. The successful ablation site served as the reference standard. Intraprocedural ECG recordings were analyzed to calculate the ratio of S-wave amplitude in lead V2 to R-wave amplitude in lead V3 (V2S/V3R) index, V2 transition ratio, and R-wave duration index (RwDI) and to apply two previously published regional localization algorithms. For binary algorithms, diagnostic performance metrics were calculated; for regional algorithms, exact regional concordance was assessed.

Results: Among the outflow tract discrimination tools, the V2S/V3R Index showed the best performance, with 80.8% accuracy, 85.7% sensitivity, and 75.0% specificity. The V2 Transition Ratio showed modest performance, whereas the RwDI had low sensitivity (16.7%) but perfect specificity (100.0%) for identifying aortic cusp origins. For comprehensive localization, the Yamada algorithm achieved 87.5% accuracy for left-vs.-right ventricular outflow tract (LVOT-RVOT) lateralization and 81.3% exact regional concordance, while the Enriquez algorithm achieved 56.3% accuracy and 31.3% exact regional concordance, respectively. Exact regional performance was significantly better with Yamada ($p=0.0004$).

Conclusion: ECG algorithms showed variable performance for predicting the successful ablation site. The V2S/V3R index was the most useful for discriminating RVOT from LVOT, whereas the Yamada algorithm showed the best overall performance for whole-heart localization. These hypothesis-generating findings warrant external validation in larger, multicenter cohorts before clinical adoption.

Keywords: Premature ventricular contractions, catheter ablation, electrocardiography, arrhythmia localization

Introduction

Premature ventricular contractions (PVCs) observed in patients without structural heart disease are defined as idiopathic PVCs. In the presence of PVCs, the main indications for treatment are symptoms and impaired cardiac function. While beta-blockers, calcium channel blockers, certain class IC antiarrhythmic agents, and rarely amiodarone constitute the medical treatment options, catheter ablation is superior to antiarrhythmic therapy because of its low complication rates and relatively high success expectation (1,2). Compared with right ventricular outflow tract (RVOT) PVCs and left fascicular PVCs, idiopathic PVCs arising from other sites are less well studied and are generally associated with

lower ablation success rates and higher complication rates, particularly when originating from the aortic cusps, summit, or left ventricular outflow tract (LVOT). Therefore, in addition to the patient's symptoms and findings of cardiac dysfunction, the predicted PVC origin should also be taken into consideration when deciding on ablation therapy (1). The ability to predict the probable localization can, on the one hand, provide information during decision-making for the procedure and during the patient's informed consent process, and on the other hand, guide procedural planning (3). To date, many parameters and algorithms have been studied to predict the origin of PVCs from the 12-lead ECG. While some of these aims to predict RVOT/LVOT differentiation, others aim to predict the precise location of the PVCs (3-10).



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We aimed to evaluate the ability of five ECG algorithms to predict the successful ablation site using preprocedural surface ECG morphology in patients who underwent catheter ablation for idiopathic PVCs and in whom the successful ablation site was definitively identified. The ratio of S-wave amplitude in lead V2 to R-wave amplitude in lead V3 (V2S/V3R) index and the V2 transition ratio were primarily assessed for RVOT-LVOT discrimination, the R-wave duration index (RwDI) for differentiating aortic sinus cusps (ASC) from RVOT origins, and the algorithms proposed by Enriquez et al. (10) and Yamada et al. (3) for predicting all possible anatomical localizations.

Methods

Study Population

This single-center retrospective accuracy study included 32 patients who underwent successful catheter ablation of idiopathic PVCs at İzmir City Hospital, Department of Cardiology between June 2025 and February 2026. The data analyzed in the study were derived from intracardiac electrograms, 12-lead ECG recordings, and three-dimensional activation maps obtained during the procedure; all were recorded and stored using the EnSite X EP System (Abbott, Abbott Park, IL, USA), which is routinely used at İzmir City Hospital. Clinical and demographic data were obtained from the hospital information management system records. Patients were included in the study if they had an evaluable 12-lead ECG recording of the clinical PVC before ablation, if the clinical PVC could be mapped during the electrophysiological study, and if the successful ablation site could be definitively identified from the procedural records. Patients with structural heart disease, baseline bundle branch block, ventricular-paced rhythm, or conduction abnormalities that could interfere with ECG interpretation and those in whom adequate mapping could not be performed because of insufficient PVC frequency or limited anatomical access were excluded. For the purposes of this study, the term “idiopathic PVCs” was operationally defined as focal, monomorphic PVCs whose 12-lead electrocardiogram (ECG) morphology was consistent with an origin in anatomically defined idiopathic foci (outflow tracts, aortic cusps, aortomitral continuity, papillary muscles, fascicles, annular regions, or the cardiac crux), in the absence of ECG, echocardiographic, or imaging evidence of a scar-related arrhythmogenic substrate. Patients with a history of coronary artery disease were not excluded a priori; however, patients with prior myocardial infarction, regional wall-motion abnormalities consistent with an arrhythmogenic scar, or PVC morphology suggesting a scar-related origin were excluded. Reductions in left ventricular ejection fraction in this cohort were considered consistent with PVC-induced cardiomyopathy rather than primary structural heart disease, given the focal PVC morphology and the absence of a defined ischemic or non-ischemic substrate.

Clinical Characteristics, Symptoms, and Comorbidities

The patients' demographic (age, sex, diabetes, hypertension, chronic obstructive pulmonary disease, coronary artery disease, smoking), clinical (presence of palpitations, irregular heartbeat, or syncope), and echocardiographic (LV end-diastolic/end-systolic diameters, left atrial diameter, and LV ejection fraction) data were collected from the hospital information management system records.

Ablation Procedure

Catheter ablation of PVCs is routinely performed using the EnSite™ X EP System (Abbott, Abbott Park, IL, USA). According to the ECG findings and operator preference, mapping is initially undertaken from either the right or the left ventricle. When the earliest activation site cannot be identified or effective ablation cannot be achieved from the initial chamber, mapping is continued from the contralateral ventricle. Activation mapping and, when necessary, pace mapping are performed using a TactiCath™ Contact Force Ablation Catheter, Sensor Enabled™ (Abbott), and radiofrequency energy is delivered at the site of earliest activation of the clinical PVC. Radiofrequency energy was delivered in power-controlled mode at a power of 35 W (20 W in the coronary venous system), with a target contact force of 10-20 g and irrigation at 17mL/min. If aortic cusp or LV summit origins were suspected, selective coronary angiography was performed to delineate the proximity of the coronary arteries. Acute procedural success defined as abolition of the targeted PVC with no spontaneous or inducible ($\pm$ isoproterenol) recurrence during a 30 minute observation period.

Electrocardiographic Assessment

A PVC was identified as an ectopic ventricular beat occurring earlier than expected, displaying widened QRS complexes (>120 ms) and QRS/T-wave morphologies that differed from those of sinus beats. ECG data, such as PVC QRS duration, coupling interval, and post-PVC interval type (compensatory, non-compensatory, or interpolated) were obtained from the patients' 12-lead ECGs during the procedure. PVC burden (the percentage of heartbeats that are PVCs over a specified monitoring period), mean heart rate, and presence of ventricular tachycardia were obtained from ambulatory ECG recordings and hospital information management system recordings. ECG time intervals, QRS durations, and amplitudes were manually measured using the integrated digital caliper tools of the EnSite™ X EP System, enabling precise ECG waveform annotation and interval calculation.

First, all parameters to be used in the algorithms were analyzed and entered into the data collection form. For this purpose, the following were recorded for each PVC: the bundle branch block pattern in lead V1, frontal axis, lead I polarity, QRS patterns in aVL, aVR, and V6, presence of positive concordance, QRS voltage in the inferior leads, precordial transition location during sinus rhythm and during PVC, and QRS durations and amplitudes in leads V1, V2, and V3. The maximum deflection index (MDI) was calculated as the shortest time from QRS onset to the maximum deflection in any precordial lead divided by the total QRS duration.

To minimize observer bias, all 12-lead ECG measurements and algorithmic classifications were independently performed by two reviewers blinded to the successful ablation site, intraprocedural three dimensional mapping data, and ablation outcome. The ECG analyses were completed and recorded before the reviewers had access to procedural data.

ECG Algorithms and Indices Evaluated in the Study

The parameters obtained from the 12-lead surface ECG were used to predict the localization according to 5 different indices or algorithms.

1. The V2S/V3R index: The V2S/V3R index was calculated by dividing the S-wave amplitude in lead V2 by the R-wave amplitude in lead V3 measured during a clinical PVCs or ventricular tachycardia. A value of 1.5 or lower was considered suggestive of an origin in the LVOT. This index was applied only to cases showing left bundle branch block (LBBB) morphology with an inferior axis (4).

2. The V2 transition ratio was assessed in patients with LBBB morphology, an inferior axis, and precordial transition at lead V3. For this calculation, the R-wave proportion in lead V2 during ventricular arrhythmia was compared with that during sinus rhythm. Origins were then classified according to the previously defined threshold for this criterion (6). For this index, only PVCs/VTs with an LBBB morphology, an inferior axis, and a transition in V3 were included in the analysis.

3. RwdI was evaluated in the appropriate outflow tract subgroup. The index was obtained by measuring the longer R-wave duration between leads V1 and V2 and expressing it as a percentage of the total QRS duration of the PVC. In addition, the R/S amplitude index was determined using the largest R/S amplitude ratio in leads V1 or V2. This criterion was used to differentiate ASC origins from RVOT origins in patients with LBBB morphology and inferior axis (9). For this index, only PVCs/VTs with an LBBB morphology and an inferior axis were included in the analysis.

4. Four step algorithm proposed by Enriquez et al. (10): The four-step algorithm described by Enriquez et al. (10) was applied to classify the likely site of origin. In this algorithm, ventricular arrhythmias are initially categorized into broad anatomical regions using frontal plane axis and lead I polarity. Localization is further refined by incorporating precordial transition, QRS duration, V1 morphology, and aVL/aVR patterns. This method enables assessment of both outflow tract and non-outflow tract regions, including the aortic cusps, aortomitral continuity, atrioventricular annuli, papillary muscles, para-Hisian region, and cardiac crux (10).

5. The algorithm proposed by Yamada et al. (3), the Yamada localization approach, was used as a comprehensive ECG framework for whole-heart PVC localization. This approach integrates multiple ECG features, including bundle branch block pattern, frontal axis, lead V6 polarity, precordial transition, QRS duration, MDI, and region-specific QRS morphologies. It was used to assign probable origins across a wide range of anatomical sites, including the outflow tracts, aortic sinuses, aortomitral continuity, left ventricular summit, mitral and tricuspid annuli, papillary muscles, fascicular regions, moderator band, and other right ventricular muscular structures (3).

Follow-Up and Recurrence Assessment

Follow-up data were obtained retrospectively from the hospital information management system. Recurrence was defined as either documentation on surface ECG of PVCs with a morphology consistent with the ablated clinical PVC, or a PVC burden greater than 5% on ambulatory Holter monitoring during follow-up. Because follow-up was based on available clinical records rather than a prespecified prospective follow-up protocol, recurrence data should be interpreted as representing clinically documented recurrence.

Statistical Analysis

All statistical analyses were conducted using standard computational libraries in Python. Continuous variables are presented as medians (minimum-maximum), and categorical variables are expressed as absolute frequencies and percentages. The diagnostic performance of each surface ECG algorithm was evaluated against the electrophysiology-confirmed site of origin, which served as the gold standard.

For algorithms designed to differentiate systemic left-sided from right-sided origins (V2S/V3R index, V2 Transition Ratio, and RwdI), predictive utility was quantified using overall accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). For algorithms predicting precise regional sub-structures [Yamada et al. (3) and Enriquez et al. (10)], performance was reported as the overall regional concordance rate.

To evaluate differences in diagnostic accuracy between algorithms tested on the same patient cohort, paired comparisons of correct classification rates were performed using the exact McNemar test. When comparing the binary differentiating algorithms, McNemar's test was restricted to the overlapping subsets of patients for whom both algorithms in each pairing were clinically applicable. A two-tailed p value of less than 0.05 was considered to indicate statistical significance. Ninety-five percent confidence intervals for all proportions (accuracy, sensitivity, specificity, and predictive values) were calculated using the Wilson score method. Cohen's kappa coefficient was calculated to assess chance-corrected agreement between each algorithm and the electrophysiology-confirmed reference standard.

To address potential selection bias from algorithm-specific applicability criteria, we performed a complete-case sensitivity analysis limited to patients in whom all three binary ECG indices were applicable. In this overlapping subset, each algorithm was classified as correct or incorrect according to its predefined diagnostic target, and paired comparisons were performed using the exact McNemar test.

Ethics Approval

The study complied with the Declaration of Helsinki and received approval from the İzmir City Hospital Institutional Review Board (decision number: 2025/522, date: 16.10.2025). Due to the retrospective nature of the study, informed consent was not obtained from the patients.

Results

A total of 32 patients underwent successful catheter ablation for symptomatic PVCs. Baseline demographic, clinical, and ECG characteristics of the cohort are summarized in Table 1. The study flow, algorithm applicability, and summary diagnostic performance are presented in Figure 1. The electrophysiology-confirmed sites of origin encompassed a diverse range of systemic left- and right-sided structures, with the definitive anatomical distribution presented in Table 2 and Figure 2. Notably, a significant proportion of the targeted arrhythmias originated from complex anatomical border zones, including the left ventricular summit, the aortic coronary cusps, and the posterior RVOT. With the ground-truth locations definitively established

by successful ablation, we evaluated the diagnostic accuracy and predictive performance of the five surface ECG algorithms. No major procedural complications (cardiac tamponade, coronary arterial injury, atrioventricular block, thromboembolism, or vascular complications requiring intervention) occurred.

During follow-up, recurrence was observed in 10 patients (33.3%). Recurrence was identified either by surface ECG documentation of PVCs

with a morphology consistent with the ablated PVC or by a PVC burden greater than 5% on follow-up Holter monitoring.

Algorithm Performance Metrics

The V2S/V3R Index

The method uses ECG indices specifically designed to differentiate left- vs. right-ventricular outflow tract origins in patients presenting with LBBB-morphology PVCs. Accordingly, 6 patients with an RBBB PVC morphology were excluded from this step, leaving a cohort of 26 patients for evaluation.

The V2 Transition Ratio

This index uses specific surface ECG criteria (such as V2 transition ratio and R-wave characteristics) to predict the site of origin, particularly to differentiate left from right outflow tracts. Based on the dataset, 11 patients were excluded from this analysis due to the absence of a V3 R/S transition.

R-wave Duration Index

This method utilizes R-wave indices in the precordial leads, such as R-wave duration and R/S amplitude ratios, to differentiate arrhythmias originating in the ASC from those arising in the RVOT.

Because of the algorithm’s highly specific anatomical focus, 14 patients were deemed not applicable to this algorithm, as their arrhythmias originated from regions outside the classical RVOT/ASC dichotomy (e.g., Summit, Papillary muscles) or exhibited an RBBB morphology, leaving an applicable cohort of 18 patients.

Performance of Outflow Tract Differentiating Algorithms

When evaluating the algorithms designed primarily to differentiate systemic left-sided from systemic right-sided origins, the V2S/V3R Index achieved the highest diagnostic utility, yielding an overall accuracy of 80.8% (21 of 26 applicable patients). It demonstrated a sensitivity of 85.7% and a specificity of 75.0% for left-sided origins, with a PPV of 80.0% and a NPV of 81.8%. The V2 transition ratio and RwDI yielded lower overall diagnostic accuracies of 61.9% (13 of 21 patients) and 72.2% (13 of 18 patients), respectively. The V2 transition ratio algorithm demonstrated a sensitivity of 61.5% and a specificity of 62.5% for left-sided targets. The RwDI exhibited low sensitivity (16.7%) but perfect specificity (100.0%) for aortic cusp origins (PPV 100.0%, NPV 70.6%).

To rigorously evaluate the relative performance of these differentiating models, pairwise exact McNemar tests were performed on the strictly overlapping patient subsets in which both algorithms in each pair were clinically applicable. Despite the observed absolute differences in overall accuracy, pairwise comparisons of their correct classification rates did not reach statistical significance for V2S/V3R index vs. V2 transition ratio (p=0.289, n=21), V2S/V3R index vs. RwDI (p=1.000, n=18), or V2 transition ratio vs. RwDI (p=1.000, n=14). These non-significant pairwise comparisons must be interpreted cautiously. Because both the overall sample and the strictly overlapping applicable subsets were small (n=14-21), the McNemar tests were markedly underpowered; therefore, the absence of a statistically significant difference does not

Table 1. Baseline demographic and clinical characteristics

Variable	Total (n=32)
Demographics	
Age (years)	54 (23-82)
Women (%)	13 (40.6%)
Comorbidities	
Diabetes	4 (12.5%)
Chronic obstructive pulmonary disease	1 (3.1%)
Coronary artery disease	4 (12.5%)
Hypertension	7 (21.9%)
Smoking	5 (15.6%)
Symptom	
Palpitation	15 (46.9%)
Skipped beats	6 (18.8%)
Syncope	3 (9.4%)
Asymptomatic	8 (25%)
Echocardiography	
LVEF (%)	55 (25-60)
LVEDD (mm)	51 (40-68)
LVESD (mm)	37 (22-60)
Left atrium diameter (mm)	35 (27-53)
Post-PVC interval	
Compensatory	28 (87.5%)
Non-compensatory	2 (6.25%)
Interpolated	2 (6.25%)
PVC QRS pattern	
LBBB	26 (81.3%)
RBBB	6 (18.8%)
PVC burden on Holter ECG	
Percent	16 (6-50)
Beats	17000 (5000-40000)
PVC QRS duration (ms)	137 (119-184)
Ablation procedure metrics	
Procedure duration (min)	73 (38-180)
Fluoroscopy time (seconds)	340 (62-890)
Number of RF applications	6 (3-17)
Cumulative RF time (seconds)	480 (120-950)
Recurrence	10/30* (33.3%)

*Two patients were lost to follow-up; recurrence percentages are calculated using the available cohort (n=30). Continuous variables are reported as median (minimum-maximum); categorical variables as n (%). LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, PVC: Premature ventricular complex, LBBB: Left bundle branch block, RBBB: Right bundle branch block, ECG: Electrocardiogram, RF: Radiofrequency ablation

constitute evidence of equivalent diagnostic performance (i.e., absence of evidence is not evidence of absence). No formal equivalence or non-inferiority testing was undertaken, and the observed absolute

differences in accuracy should be regarded as exploratory. The diagnostic performance metrics of the V2S/V3R index, the V2 transition ratio, and the RwDI are summarized in Table 3.

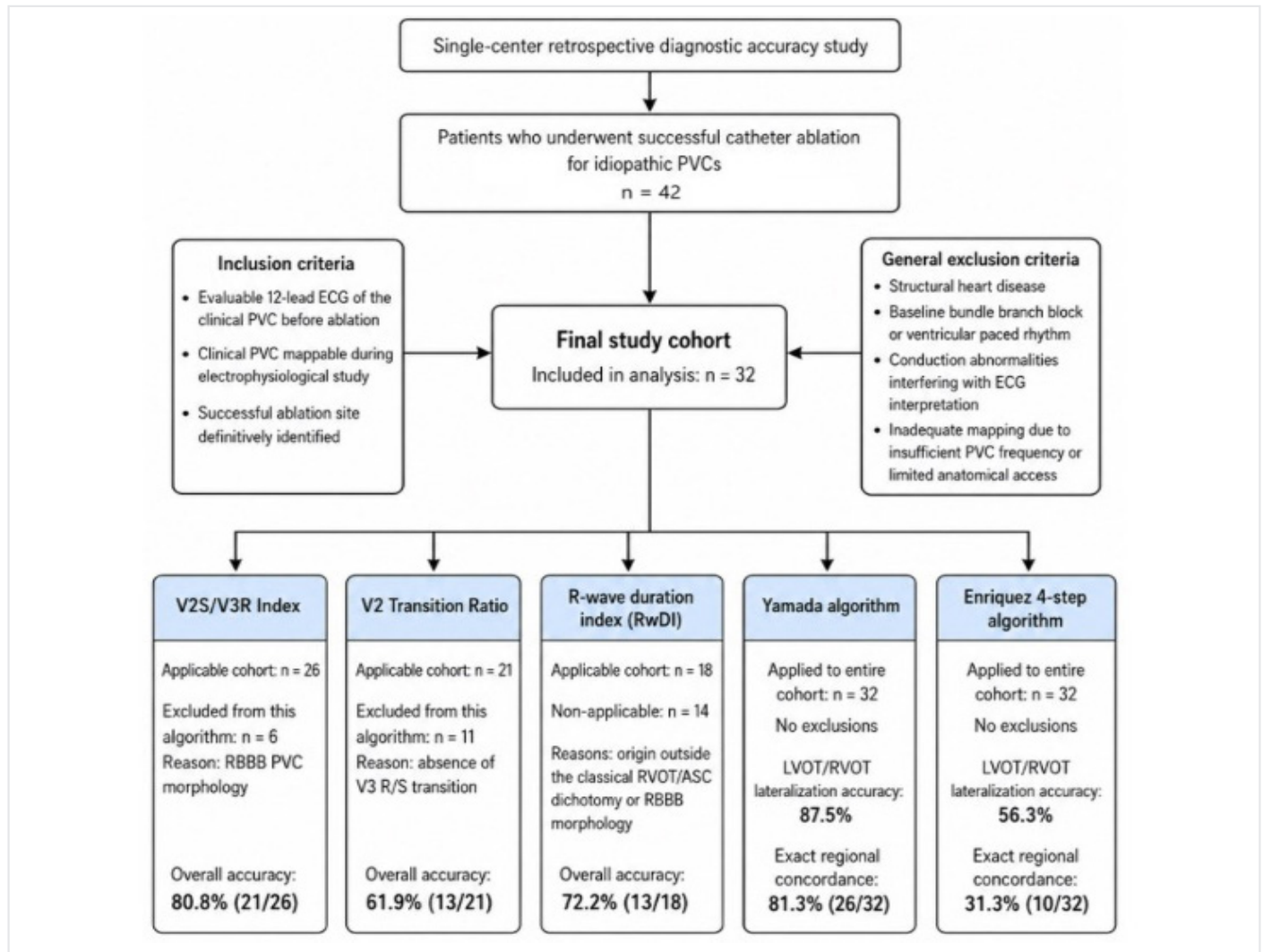


Figure 1. Study flow diagram. The flowchart summarizes the single-center, retrospective, diagnostic-accuracy design; patient eligibility; inclusion and exclusion criteria; final study cohort; algorithm-specific applicable cohorts, and summary diagnostic performance metrics. PVC: Premature ventricular complex, ECG: Electrocardiogram, V2S/V3R: Ratio of S-wave amplitude in lead V2 to R-wave amplitude in lead V3, RBBB: Right bundle branch block, RVOT: Right ventricular outflow tract, ASC: Aortic sinus cusp, LVOT: Left ventricular outflow tract, RVOT: Right ventricular outflow tract

Table 2. Anatomical distribution of successful ablation sites

Ablation side	Successful ablation location	Total
LVOT	Summit	8 (25%)
LVOT	L-RCC commissure	5 (15.6%)
LVOT	Left coronary cusp	2 (6.3%)
LVOT	Aortomitral continuity	1 (3.1%)
RVOT	Anterior RVOT	6 (18.8%)
RVOT	Posterior RVOT	5 (15.6%)
Right ventricle (other)	Parahisian	1 (3.1%)
Left ventricle (other)	Top of mitral valve	2 (6.3%)
Left ventricle (other)	Left posterior fascicle	1 (3.1%)
Left ventricle (other)	Posteromedial papillary muscle	1 (3.1%)

LVOT: Left ventricular outflow tract, RVOT: Right ventricular outflow tract

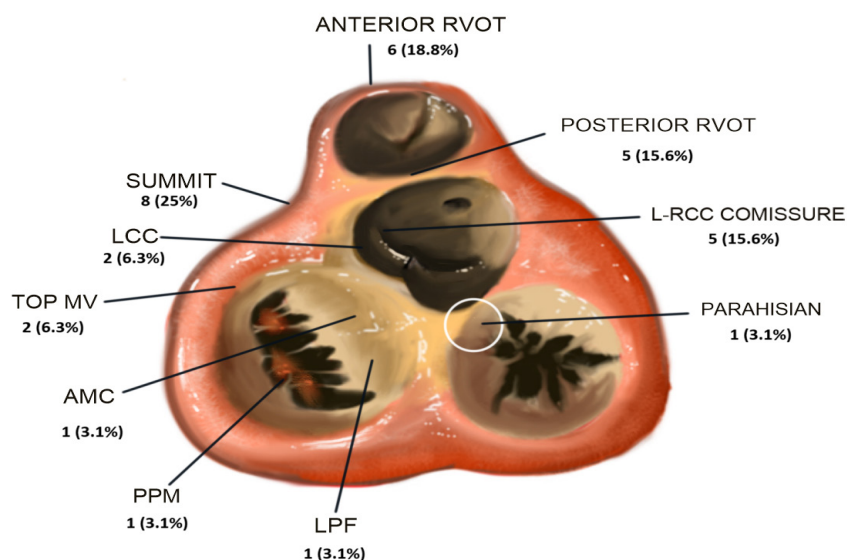


Figure 2. Anatomical distribution of electrophysiologically confirmed premature ventricular complex origins. The schematic illustrates the successful ablation sites in the final study cohort, with case numbers and percentages for each anatomical region. Percentages are based on the final analyzed cohort (n=32). LVOT: Left ventricular outflow tract, RVOT: Right ventricular outflow tract, LCC: Left coronary cusp, MV: Mitral valve, AMC: Aortomitral continuity, PPM: Posteromedial papillary muscle, LPF: Left posterior fascicle, L-RCC: Left-right coronary cusp commissure

Table 3. Diagnostic performance of algorithms targeting RVOT-LVOT distinction

	The V2S/V3R index n=26	The V2 transition ratio n=21	R-wave duration index n=18	
Metric	Value (95% CI)			
Overall accuracy	80.8% (62.1–91.5)	61.9% (40.9–79.2)	72.2% (49.1–87.5)	
Sensitivity	85.7% (60.1–96.0)	61.5% (35.5–82.3)	16.7% (3.0–56.4)	
Specificity	75.0% (46.8–91.1)	62.5% (30.6–86.3)	100.0% (75.8–100)	
Positive predictive value	80.0% (54.8–93.0)	72.7% (43.4–90.3)	100.0% (20.7–100)	
Negative predictive value	81.8% (52.3–94.9)	50.0% (23.7–76.3)	70.6% (46.9–86.7)	
Cohen's kappa	0.61	0.23	0.21	
	Count			Description
True positives	12	8	1	Algorithm predicted LVOT (ASC/LVOT in RwDI); EP confirmed LVOT (ASC/LVOT in RwDI)
True negatives	9	5	12	Algorithm predicted RVOT ("Not aortic cusp" in RwDI); EP confirmed RVOT (RVOT/other in RwDI)
False positives	3	3	0	Algorithm predicted LVOT (ASC/LVOT in RwDI); EP confirmed RVOT (RVOT/other in RwDI)
False negatives	2	5	5	Algorithm predicted RVOT ("Not aortic cusp" in RwDI); EP confirmed LVOT (ASC/LVOT in RwDI)

LVOT: Left ventricular outflow tract, RVOT: Right ventricular outflow tract, V2S/V3R: Ratio of S-wave amplitude in lead V2 to R-wave amplitude in lead V3, CI: Confidence interval, ASC: Aortic sinus cusp, RwDI: R-wave duration index, EP: Electrophysiological

A complete-case sensitivity analysis was performed in the 14 patients in whom the V2S/V3R index, V2 Transition ratio, and RwdI were all applicable. In this matched subset, the V2S/V3R index remained the most numerically accurate algorithm, with 78.6% accuracy, 83.3% sensitivity, and 75.0% specificity. The V2 Transition ratio showed 57.1% accuracy, 50.0% sensitivity, and 62.5% specificity. The RwdI demonstrated an accuracy of 64.3%, a sensitivity of 16.7%, and a specificity of 100.0% in identifying aortic cusp origins. Pairwise exact McNemar comparisons did not show significant differences between the V2S/V3R index and V2 transition ratio ($p=0.453$), V2S/V3R index and RwdI ($p=0.688$), or V2 transition ratio and RwdI ($p=1.000$).

Chance-corrected agreement was substantial for the V2S/V3R index (κ : 0.61) and fair for both the V2 transition ratio (κ : 0.23) and the RwdI (κ : 0.21).

The Algorithm Proposed by Yamada et al. (3)

Unlike the previously analyzed models, which were restricted to differentiating between outflow tracts or identifying specific aortic cusps, this algorithm is a comprehensive 12-lead ECG tool designed to

localize idiopathic PVC origins across the entire heart. As a result, all 32 patients in our cohort were eligible for this analysis. The diagnostic performance of Yamada et al.'s (3) algorithm for left (LVOT) vs. right (RVOT) localization, including accuracy, sensitivity, specificity, PPV, and NPV, is presented in Table 4.

Because the algorithm predicts highly specific sub-regional locations (e.g., distinguishing between anterior RVOT, specific cusps, or mitral valve regions), we evaluated its performance at two distinct levels: binary lateralization (left-sided/LVOT vs. right-sided/RVOT) and exact sub-regional localization.

4-Step Algorithm Proposed by Enriquez et al. (10)

The final model in our analysis is the 4-step algorithm proposed by Enriquez and colleagues. Similar to Yamada, this algorithm attempts to predict the specific regional origin of the PVC and is evaluated based on strict regional concordance. In our dataset, it was applied to all 32 patients without exclusions. The diagnostic performance of the Enriquez et al. (10) algorithm for left-/LVOT vs. right-/RVOT localization, including accuracy, sensitivity, specificity, PPV, and NPV, is presented in Table 5.

Table 4. Diagnostic performance of the Yamada et al. (3) algorithm for left-/LVOT vs. right-/RVOT localization

Yamada et al. (3) (n=32)		
Metric	Value (95% CI)	Description
Overall Accuracy	87.5% (71.9–95.0)	
Sensitivity	90% (69.9–97.2)	
Specificity	83.3% (55.2–95.3)	
Positive predictive value	90.0% (69.9–97.2)	
Negative predictive value	83.3% (55.2–95.3)	
Cohen's kappa	0.73	
Classification	Count	
True positives	18	Algorithm predicted left/LVOT; EP confirmed left/LVOT
True negatives	10	Algorithm predicted right/RVOT; EP confirmed right/RVOT
False positives	2	Algorithm predicted left/LVOT; EP confirmed right/RVOT
False negatives	2	Algorithm predicted right/RVOT; EP confirmed left/LVOT

LVOT: Left ventricular outflow tract, RVOT: Right ventricular outflow tract, CI: Confidence interval, EP: Electrophysiological

Table 5. Diagnostic performance of the Enriquez et al. (10) algorithm for left-/LVOT vs. right-/RVOT localization

Enriquez et al. (10) (n=32)		
Metric	Value (95% CI)	Description
Overall accuracy	56.3% (39.3–71.8)	
Sensitivity for left/LVOT origins	30% (14.5–51.9)	
Specificity for right/RVOT origins	100% (75.8–100)	
Positive predictive value (PPV)	100% (61.0–100)	
Negative predictive value (NPV)	46.2% (28.8–64.5)	
Cohen's kappa	0.24	
Classification	Count	
True positives (TP)	6	Algorithm predicted left/LVOT; EP confirmed left/LVOT
True negatives (TN)	12	Algorithm predicted right/RVOT; EP confirmed right/RVOT
False positives (FP)	0	Algorithm predicted left/LVOT; EP confirmed right/RVOT
False negatives (FN)	14	Algorithm predicted right/RVOT; EP confirmed left/LVOT

LVOT: Left ventricular outflow tract, RVOT: Right ventricular outflow tract, CI: Confidence interval, EP: Electrophysiological

Performance of Regional Prediction Algorithms

For exact regional localization, the Yamada algorithm demonstrated an overall accuracy of 81.3%, correctly identifying the specific substructural origin in 26 of 32 patients. In contrast, the Enriquez algorithm yielded a significantly lower overall accuracy of 31.3% (10 of 32 patients). A pairwise comparison using the exact McNemar’s test in the matched cohort revealed that the diagnostic performance of the Yamada algorithm was statistically superior to that of the Enriquez algorithm ($p=0.0004$). The exact regional concordance of the Enriquez et al. (10) and Yamada et al. (3) algorithms with the electrophysiologically confirmed site of origin is presented in Table 6.

For binary lateralization (left/LVOT vs.right/RVOT), agreement was substantial for the Yamada algorithm (κ : 0.73) and fair for the Enriquez algorithm (κ : 0.24).

Discussion

In this retrospective study assessing accuracy among patients who underwent successful catheter ablation for idiopathic PVCs, several important findings emerged. First, among the ECG tools primarily designed for outflow tract discrimination, the V2S/V3R index demonstrated the best overall diagnostic performance in our cohort. Second, although the RwDI demonstrated lower sensitivity, it provided excellent specificity for identifying a non-aortic cusp origin. Third, among the two comprehensive localization approaches, the algorithm proposed by Yamada et al. (3) substantially outperformed the 4-step algorithm proposed by Enriquez et al. (10) for exact regional localization.

Among the right–left outflow tract discrimination algorithms, the V2S/V3R index showed the best overall diagnostic performance in our cohort. On closer examination of the data, the algorithm predicted an LVOT origin in three patients, but their successful ablation sites were right-sided. Two of these sites were located in the posterior RVOT, and one was located in the right para-Hisian region. Anatomically, these right-sided structures lie close to the septal border of the LVOT, which may produce pseudo-left-sided ECG patterns. In the original study by Yoshida et al. (4), a cut-off value of ≤ 1.5 predicted an LVOT origin with 89% sensitivity and 94% specificity. In our cohort, however, the V2S/V3R index demonstrated a sensitivity of 85.7% and a specificity of 75.0% for left-sided origins, with a PPV of 80.0% and a NPV of 81.8%. Although both sensitivity and specificity were lower than those reported in the original study, the V2S/V3R index remained the most accurate parameter among those evaluated in our analysis, which is consistent with the findings of the original report (4). The complete-case sensitivity analysis reduced the potential bias introduced by unequal algorithm-specific denominators.

In this matched subset, the V2S/V3R index remained numerically higher, consistent with the main analysis. However, the absence of statistically significant pairwise differences should be interpreted with caution, because only 14 patients were eligible for all three binary indices.

The physiological basis of this index is that the aortic sinuses and the LVOT are located deeper and more posteriorly than the RVOT, resulting in a relatively higher R-wave amplitude in lead V3 and relatively lower S-wave amplitudes in leads V1 and V2. Although the V2 transition ratio was developed as an anatomically refined index that accounts for cardiac rotation, respiratory variation, and interindividual anatomical differences, its performance in our cohort was modest. While Betensky et al. (6) reported that a V2 transition ratio ≥ 0.6 predicted an LVOT origin with 95% sensitivity and 100% specificity in their original article, Yoshida et al. (4) found lower values, with a sensitivity of 81% and a specificity of 61%. In our series limited to patients with a V3 transition pattern, the corresponding sensitivity and specificity were 61.5% and 62.5%, respectively. It proved particularly unreliable for predicting RVOT for structures deep within the LVOT [left-right coronary cusp commissure (L-RCC), left coronary cusp (LCC), and summit], resulting in a very low NPV (50.0%). Detailed analysis of our data revealed that most false-positive and false-negative classifications originated in anatomically challenging regions near the contralateral side, particularly the posterior RVOT, the coronary cusps, and the summit.

The RwDI, first described by Ouyang et al. (9) in a 15-patient study, was found by Yoshida et al. (4) to have a sensitivity of 45% and a specificity of 92%. In the subgroup of patients with a precordial PVC transition at V3, sensitivity was shown to decline further to 31% (4,9). Although our results were broadly consistent with previous findings, the RwDI showed notably low sensitivity in our cohort, despite a specificity of 100%. The main limitation of this index was its inability to identify true aortic cusp origins: five patients with electrophysiologically confirmed cusp foci—three from the L-RCC commissure and two from the left coronary cusp—were misclassified as having an RVOT origin. Therefore, while a positive RwDI finding strongly supports an aortic cusp origin, a negative result does not reliably exclude it.

The Yamada algorithm performed exceptionally well in our cohort. It not only successfully lateralized the arrhythmia in 87.5% of patients but also achieved exact regional concordance in 81.3% of the cohort. As with prior algorithms, the primary vulnerability of this algorithm lies at the deep septal border (posterior RVOT masquerading as left/summit structures and vice versa). An additional noteworthy aspect of our findings is that, to our knowledge, the review-based whole-heart localization scheme proposed by Yamada et al. (3) has not previously been validated as a

Table 6. Exact regional concordance of the Enriquez et al. (10) and Yamada et al. (3) algorithms with the electrophysiologically confirmed site of origin			
	Overall accuracy	Value (n=32)	Description
Enriquez et al. (10)	Exact regional concordance	10 (31.3%)	Algorithm exactly matched the EP-confirmed site
	Discordance (error)	22 (68.8%)	Algorithm missed the exact sub-regional origin
Yamada et al. (3)	Exact regional concordance	26 (81.3%)	Algorithm exactly matched the EP-confirmed site
	Discordant cases	6 (18.8%)	Algorithm missed the exact sub-regional origin
EP: Electrophysiological			

single, comprehensive diagnostic algorithm with globally reported sensitivity, specificity, or accuracy. The 2019 publication by Yamada et al. (3) is a review that summarizes ECG approaches for localizing idiopathic PVC origins and discusses their caveats, rather than being an original validation study reporting unified performance metrics for the entire algorithmic framework. In this context, our study provides clinically relevant validation data for the Yamada approach (3).

Among the localization tools evaluated in this study, the four-step algorithm proposed by Enriquez et al. (10) showed the lowest performance, with an exact regional accuracy of 31.3%. Its principal weakness was a marked underdetection of left-sided origins, particularly LVOT cusps and LV summit foci, which were frequently misclassified as anterior RVOT or other right-sided structures. Although left-sided predictions were highly reliable when explicitly made, the algorithm demonstrated a clear tendency to default challenging left-sided substrates to right-sided categories. This pattern suggests that the algorithm may be more useful for broad bedside orientation than for precise preprocedural localization in anatomically complex idiopathic PVCs (10).

Recurrence occurred in 10 of 30 patients with available follow-up (33.3%). This is higher than the ~15–25% long-term recurrence commonly reported after idiopathic PVC ablation, and most plausibly reflects the anatomically complex composition of our cohort, which was enriched for technically demanding origins, LV summit, coronary cusps, and papillary muscles, that carry lower acute success and higher recurrence than the RVOT (11,12). Notably, late recurrence in this setting frequently arises from a site remote from the index focus rather than from the originally targeted region (13).

Clinical Utility and Incremental Value

Beyond their diagnostic metrics, preprocedural ECG algorithms have practical implications for procedural planning and patient counseling. Reliable lateralization informs the anticipated access strategy (retrograde aortic or transseptal access for left-sided origins vs. a right-sided approach), prompts pre-emptive coronary angiography when an aortic cusp or LV summit origin is suspected, and flags cases in which an epicardial or coronary-venous approach may be required, thereby indicating the need for referral to a high-volume center. It also enables individualized counseling, because expected acute success and complication risk differ substantially between, for example, the RVOT and the LV summit (12). That said, the incremental value of these algorithms over an experienced operator's gestalt was not directly assessed in the present study; structured algorithms are likely most useful for less-experienced operators, for trainee education, and as reproducible adjuncts, and may be further augmented by emerging automated and machine-learning-based localization tools and noninvasive ECG imaging (14). Prospective evaluation is warranted to determine whether algorithm-guided planning measurably changes access strategy, procedure duration, or outcomes.

Although the overall cohort size in our study ($n=32$) may appear modest, this is consistent with historical methodology used in

ventricular arrhythmia localization research. Many of the pioneering and now widely accepted ECG criteria for idiopathic PVC localization were originally derived and validated in similarly sized or even smaller cohorts. For example, the seminal study by Ouyang et al. describing ECG characteristics for ablation of repetitive monomorphic ventricular tachycardia from the ASC was based on only 15 patients (9). Subsequent foundational work, including early descriptions of the precordial transition zone, the V2 transition ratio, and the R-wave deflection interval, was likewise derived from cohorts of fewer than 50 patients (6,7). This precedent reflects the focal and relatively uncommon nature of these arrhythmias and the considerable time and procedural resources required to assemble series that are accurately localized and ablation-confirmed. While these historical considerations do not eliminate the limitations of a small cohort, they support the validity of small, well-characterized validation studies, a recognized methodological tradition in this field, and justify the role of the present study as a hypothesis-generating contribution to the comparative evaluation of established algorithms.

Study Limitations

This study has several limitations. It was a single-center retrospective study with a relatively small sample size ($n=32$). Moreover, because several of the evaluated algorithms were applicable only to specific morphological subgroups, individual analyses were based on as few as 14 patients. As a result, the diagnostic performance estimates are imprecise, with correspondingly wide 95% confidence intervals (Tables 3-5), and the present findings should be regarded as hypothesis-generating rather than confirmatory. In particular, the absence of external validation in an independent, ideally multicenter, cohort is a key limitation. Only five ECG algorithms were assessed, and the inclusion of a broader range of previously proposed ECG criteria might have allowed a more comprehensive evaluation. Prospective validation in larger multicenter populations is therefore required before these comparative observations can be translated into routine clinical practice.

Conclusion

In patients undergoing catheter ablation for idiopathic PVCs, ECG algorithms differed substantially in their ability to predict the successful ablation site. The V2S/V3R index was the most useful discriminator for right-left outflow tract origin, whereas the R_wDI provided excellent specificity but poor sensitivity for aortic cusp identification. The Yamada algorithm demonstrated the best overall performance for comprehensive localization and may represent a useful preprocedural whole-heart ECG tool. These findings support selective rather than uniform use of ECG algorithms, depending on the specific clinical localization question.

Ethics

Ethics Committee Approval: The study complied with the Declaration of Helsinki and received approval from the Izmir City Hospital Institutional Review Board (decision number: 2025/522, date: 16.10.2025).

Informed Consent: Due to the retrospective nature of the study, informed consent was not obtained from the patients.

Footnotes

Authorship Contributions: Surgical and Medical Practices - S.E., H.G.U.; Concept - S.E.; Design - S.E.; Data Collection or Processing - S.E., H.G.U.; Analysis or Interpretation - S.E., H.G.U.; Literature Search - S.E.; Writing - S.E., H.G.U.

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

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Direct Vision Cardiac Surgery via Minimal Lateral Thoracotomy: Which Procedure is it Most Suitable for?

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ABSTRACT

Introduction: Minimal approaches have become popular in cardiac surgery in recent years worldwide; as in other surgical specialties, minimal right anterior thoracotomy (RAT) and minimal right lateral thoracotomy (RLT) techniques can be used for some cardiac procedures. This study compares and presents the operative and postoperative advantages and disadvantages of both techniques.

Methods: Between March 2021 and July 2024, a total of 40 patients underwent cardiac surgery via direct vision minimally invasive right thoracotomy approach at Cardiovascular Surgery Center of University of Health Sciences Türkiye, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital. Eight of these patients underwent surgery with the RAT technique, and 32 underwent surgery with the RLT technique. Operative and postoperative outcomes were compared.

Results: One patient who underwent RAT died during the operative period, and two patients who underwent RLT died during the postoperative period. Cross-clamp and cardiopulmonary bypass times were longer for RAT during the operative period. While there was no difference in extubation times or intensive care stay durations, tube drainage times and hospital stays were shorter for RLT in the postoperative period.

Conclusion: These findings suggest a potential clinical advantage of direct-vision RLT; however, they require further validation in large-scale, prospective studies. The situation may be different in camera-assisted approaches.

Keywords: Cardiac surgery, minimal invasive, right anterior thoracotomy, direct vision, mitral valve surgery

Introduction

Over the past 70 years, various cardiac surgical techniques have been successfully used to treat cardiac pathologies, facilitated by cardiopulmonary bypass (CPB) and advances in myocardial protection (1). As in other surgical specialties, cardiac surgical techniques have been revised over time to reduce surgical trauma and to address cosmetic concerns (2). The number of patients undergoing minimally invasive cardiac surgery techniques has been steadily increasing. This trend can be attributed to both increased patient demand and physician preference (3). Today, minimal left anterior thoracotomy and robotic surgery can be used for coronary artery bypass grafting instead of a full median sternotomy (4,5). Minimal right anterior thoracotomy (RAT), minimal right lateral thoracotomy (RLT), and robotic surgery can be used for valvular and other cardiac pathologies [e.g., atrial septal defect (ASD), anomalous pulmonary venous return, cardiac myxoma, etc.] (2,5,6). Recently, transcatheter methods have also been used to treat coronary or valvular pathologies, or both (7). Numerous methods and technologies are currently available for the treatment of heart disease. This represents

a new situation, especially for cardiac surgery, where there were few practical alternatives in the early stages (1).

In this study, cardiac surgical procedures performed with RAT and RLT were described, and their results were compared. The areas of use of these procedures in cardiac surgery, the CPB cannulation techniques, and their advantages and disadvantages were presented.

Methods

Between March 2021 and July 2024, a total of 40 patients underwent cardiac surgery via direct vision minimally invasive right thoracotomy approach at Cardiovascular Surgery Department of University of Health Sciences Türkiye, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital. The mean age of the operated patients was 52.70 ± 16.99 years, and 11 of the patients (27.5%) were male. The mean ejection fraction of the patients was $57.13 \pm 4.22\%$. Of these patients, 33 underwent [mitral valve replacement (MVR); mechanical MVR: 32 mechanical valves, 1 biological valve], 3 underwent ASD repair, and the remaining 4 patients each underwent one of the following



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procedures: ASD repair combined with correction of partial anomalous pulmonary venous return, left atrial myxoma excision, supracoronary aortic replacement (SCAR), and mitral valve repair (Table 1). Among the 34 patients who underwent mitral valve surgery, 24 had severe mitral regurgitation, 3 had severe mitral stenosis, and 7 had combined mitral regurgitation and stenosis. Of these patients, 8 underwent surgery via the RAT approach (7 for MVR and 1 for SCAR), while 32 underwent surgery via the RLT approach. In patients who underwent surgery via the RAT approach, arterial cannulation was performed via the right femoral artery, while venous cannulation was performed via both the right femoral vein and the right internal jugular vein. Only peripheral cannulation techniques were used for the RAT procedure; in contrast, some RLT cases required only central cannulation, while others required a combination of central and peripheral cannulation. The substantial difference between the numbers of patients undergoing RAT and RLT was primarily attributable to our preference to avoid routine peripheral cannulation, which is required for the RAT approach. Most patients were reluctant to undergo an additional femoral incision unless it was considered absolutely necessary. Consequently, our preference for central cannulation resulted in more patients being treated with the RLT approach. The operative and postoperative outcomes of the two minimally invasive techniques were compared.

Surgical Techniques

In the RLT approach, a 6-7-cm skin incision is made along the right mid-axillary line. Subsequently, a thoracotomy is performed through the 4th or 5th intercostal space at a 90° angle to the incision. The surgical field is accessed using two thoracic retractors placed perpendicularly to each other (Figure 1).

For the RAT approach, a 5-6 cm skin incision is made over the 5th intercostal space, beginning 5-6 cm lateral to the right sternal border, under the breast. The surgical intervention is performed through this intercostal space using a single thoracic retractor (Figure 2).

In both techniques, standard surgical instruments available at our institution were used rather than dedicated minimally invasive surgical equipment.

Table 1. Distribution of surgical procedures performed via minimally invasive right thoracotomy (March 2021-July 2024)

Procedure	Number of patients
Mitral valve replacement	33
ASD repair	3
ASD repair + correction of partial anomalous pulmonary venous return	1
Left atrial myxoma excision	1
Supracoronary aortic replacement	1
Mitral valve repair	1
Total	40

ASD: Atrial septal defect



Figure 1. Postoperative right lateral thoracotomy incision (consent of the patient is taken)



Figure 2. Postoperative right anterior thoracotomy incision (consent of the patient is taken)

Ethics Committee Approval

Our study received ethical approval from the Istanbul Medipol University Ethics Committee on 30.04.2026 (decision number: 688). As our institution does not have an institutional ethics committee, ethical approval for this study was obtained from the Istanbul Medipol University Ethics Committee.

Informed Consent

As this was a retrospective study, informed consent was not required.

Statistical Analysis

Statistical analyses of the study were conducted using the trial version of the SPSS 22.0 software package (SPSS Inc., Chicago, IL, USA). The normality of the distribution of quantitative variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For normally distributed variables, comparisons between independent groups were made using the independent samples t-test. For non-normally distributed variables, the Mann-Whitney U test was employed. Paired measurements that were normally distributed were analyzed using the paired-samples t-test, whereas those that were not normally distributed were analyzed using the Wilcoxon signed-rank test. The relationship between categorical variables was examined using the chi-square test. Descriptive statistics for normally distributed quantitative variables were presented as mean $\pm$ standard deviation, while those not normally distributed were presented as median (minimum-maximum). Descriptive statistics for categorical variables were expressed as frequencies (%). A p value of <0.05 was considered statistically significant.

Results

A total of 32 patients underwent surgery using the RLT technique, while 8 underwent surgery using the RAT approach. The mean age of patients who underwent the RLT procedure was 57.5 years, and 25 (78.1%) were female. The mean age of patients who underwent the RAT procedure was 60.0 years; 4 (50%) were female (Table 2). The mean cross-clamp time for the RLT and RAT techniques was 77.44 ± 27.03 minutes (min.) and 94.25 ± 26.90 min., respectively. The mean CPB times were 124.41 ± 39.00 min. and 171.13 ± 84.44 min., respectively. The mean cross-clamp and CPB times were shorter with the RLT technique. However, this difference was statistically significant only for CPB time. The preferred techniques for arterial-venous cannulation and left atrial approaches are presented in Table 3. Of the 34 patients with mitral valve disease, 32 underwent mechanical MVR, 1 underwent biological MVR, and 1 underwent mitral valve repair. Concomitant tricuspid De Vega annuloplasty was performed in 15 of these patients (Table 3).

Two patients who underwent surgery with the RLT technique died in the postoperative period, while one patient who underwent surgery with the RAT technique died intraoperatively.

In our study, no statistically significant differences were observed between the two techniques for extubation time and length of stay in the intensive care unit (ICU). Furthermore, the RLT technique was statistically superior in terms of postoperative chest-tube drainage duration and

overall length of hospital stay. Additionally, no significant differences were detected in implanted valve sizes between the groups (Table 4).

When comparing preoperative and postoperative atrial diameters and pulmonary artery pressures for each technique separately, the RLT group demonstrated statistically significant reductions in left atrial apico-basal and medio-lateral diameters, as well as in pulmonary artery pressure. In the RAT group, no statistically significant changes were observed in atrial diameters and pulmonary artery pressures (Table 5).

Discussion

Mitral valve disease is a common cardiac condition requiring surgical intervention. Traditional sternotomy, while effective, is associated with significant morbidity and prolonged recovery (8). Minimally invasive approaches, such as RLT and RAT, have gained popularity due to reduced trauma and faster recovery (9). However, the optimal approach remains debated.

This research demonstrates that both RLT and RAT are safe and effective options for MVR. RLT provides greater visibility than RAT. On the other hand, although other previous studies have found that “By minimizing muscle dissection, RAT may facilitate more rapid postoperative recovery and consequently reduce both operative duration and length of

Table 2. Baseline demographic and clinical characterization

Total number of patients	40
Age, years, mean $\pm$ SD; [min-max]	52.70 $\pm$ 16.99 [19-76]
Sex, male/female, n (%)	11 (27.5)/29 (72.5)
Presence of MS, n (%)	14
Grade 1	4
Grade 2	1
Grade 3	1
Grade 4	8
Presence of MR, n (%)	33
Grade 1	3
Grade 2	5
Grade 3	10
Grade 4	15
Presence of mitral pathology	34
• Degenerative	17 (50)
• Rheumatic	17 (50)
Ejection fraction, %, mean $\pm$ SD; [min-max]	57.13 $\pm$ 4.22 [45-60]
Left atrium AP diameter, mm, mean $\pm$ SD; [min-max]	45.95 $\pm$ 10.09 [30-50]
Left atrium AB diameter, mm, mean $\pm$ SD; [min-max]	58.43 $\pm$ 12.41 [35-90]
Left atrium ML diameter, mm, mean $\pm$ SD; [min-max]	48.38 $\pm$ 9.79 [29-77]
Right atrium AB diameter, mm, mean $\pm$ SD; [min-max]	44.08 $\pm$ 10.90 [25-70]
Right atrium ML diameter, mm, mean $\pm$ SD; [min-max]	35.45 $\pm$ 9.01 [19-59]
PAP, mmHg, mean $\pm$ SD; [min-max]	39.50 $\pm$ 17.01 [12-78]
Presence of AF, n (%)	13 (32.5)
Presence of TR	30
Grade 1	17
Grade 2	6
Grade 3	7

Data presented as n (%), mean $\pm$ SD and median (IQR) as appropriate. SD: Standard deviation, MS: Mitral stenosis, MR: Mitral regurgitation, AP: Anterior-posterior, AB: Apical-basal, ML: Medial-lateral, PAP: Pulmonary artery pressure, AF: Atrial fibrillation, TR: Tricuspid regurgitation, IQR: Interquartile range, min-max: Minimum, maximum

Table 3. Operational outcomes

n=40	RAT (n=8)	RLT (n=32)	p value
Age, years, median (min-max)	60.5 (5-72)	57.5 (19-76)	0.342**
Sex, female, n (%)	4 (50.0)	25 (78.1)	0.182*
Arterial cannulation, n (%)			
• Peripheral	8 (100)	7 (21.9)	<0.001*
• Central	0 (0)	25 (78.1)	
Superior vein cannulation, n (%)			
• Peripheral	7 (87.5)	1 (3.1)	<0.001*
• Central	1 (12.5)	31 (96.9)	
Inferior vein cannulation, n (%)			
Peripheral	8 (100)	2 (6.3)	<0.001*
Central	0 (0)	30 (93.8)	
Atriotomy type, (n=39)			
Right, n (%)	0 (0)	5 (15.6)	0.101*
Left, n (%)	4	13 (40.6)	
Left + right, n (%)	3	7 (21.9)	
Transseptal, n (%)	0	7 (21.9)	
Mitral valve type, n (%)			
• Mechanical	7	25	N/A
• Biological	0	1	
• Repair	0	1	
Mitral valve size, mm, median (min-max)	29 (27-29)	29 (25-33)	0.232**
TDV, n (%)	3 (37.5)	12 (37.5)	0.999*
Xclamp time, min, mean $\pm$ SD	94.25 $\pm$ 26.90	77.44 $\pm$ 27.03	0.062***
CPB time, min, mean $\pm$ SD	171.13 $\pm$ 84.44	124.41 $\pm$ 39.00	0.025***

*chi square test, **Mann-Whitney U test, ***Independent sample t-test. RAT: Right anterior thoracotomy, RLT: Right lateral thoracotomy, TDV: Tricuspid De Vega annuloplasty, SD: Standard deviation, CPB: Cardiopulmonary bypass, min-max: Minimum-maximum, N/A: Not applicable

Table 4. Postoperative outcomes

n=37	RAT (n=7)	RLT (n=30)	p value
Extubation time, days, median (min-max)	0 (0-14)	0 (0-22)	0.212*
ICU stay, days, median (min-max)	2 (1-14)	1 (1-24)	0.185*
Drain time, days, median (min-max)**	5 (3-7)	3 (2-12)	0.005*
Hospital stay, days, median (min-max)	8.5 (6-98)	6.0 (4-17)	0.004*

*Mann-Whitney U test, **Duration of postoperative chest tube drainage. RAT: Right anterior thoracotomy, RLT: Right lateral thoracotomy, min-max: Minimum-maximum, ICU: Intensive care unit

Table 5. Comparison of preoperative and postoperative changes in atrial diameters

n=37	RAT (n=7)			RLT (n=30)		
	Preop	Postop	p value	Pre-op	Post-opp	p value
EF	57.50 (50-60)	60 (50-60)	0.560*	60 (45-60)	60 (45-60)	0.520*
Left atrium AP diameter, mm, mean $\pm$ SD; (min-max)	44.67 $\pm$ 6.02	44.33 $\pm$ 9.22	0.942**	45.90 $\pm$ 10.94	42.43 $\pm$ 5.56	0.063**
Left atrium AB diameter, mm, mean $\pm$ SD; (min-max)	59.50 $\pm$ 9.05	54.00 $\pm$ 14.51	0.422**	57.97 $\pm$ 13.26	53.13 $\pm$ 10.73	0.014**
Left atrium ML diameter, mm, mean $\pm$ SD; (min-max)	48.00 $\pm$ 5.47	43.17 $\pm$ 9.08	0.280**	47.50 (29-77)	44.00 (29-66)	0.013*
Right atrium AB diameter, mm, mean $\pm$ SD; (min-max)	49.33 $\pm$ 3.44	42.50 $\pm$ 8.28	0.051**	42.77 $\pm$ 11.79	40.17 $\pm$ 9.75	0.200**
Right atrium AB diameter, mm, mean $\pm$ SD; (min-max)	37.83 $\pm$ 4.46	34.00 $\pm$ 7.29	0.252**	36 (19-57)	33 (22-60)	0.341*
PAP	48.83 $\pm$ 19.65	37.33 $\pm$ 18.04	0.329**	38.53 $\pm$ 16.94	24.33 $\pm$ 6.86	<0.001**

*Wilcoxon t test, **Paired sample t-test. RAT: Right anterior thoracotomy, RLT: Right lateral thoracotomy, min-max: Minimum-maximum, EF: Ejection fraction, PAP: Pulmonary artery pressure, AP: Anterior-posterior, AB: Apical-basal, ML: Medial-lateral

hospital stay” (10,11) our study showed the opposite. Unlike previous studies, our findings show that RLT is associated with significantly shorter Xclamp and CPB times and a shorter hospital stay compared with RAT. This observation may be attributed to several intraoperative and postoperative factors that distinguish between the two techniques. These situations can be considered: CPB cannulation and decannulation



Figure 3. Surgical exposure of the right anterior thoracotomy (consent of the patient is taken)

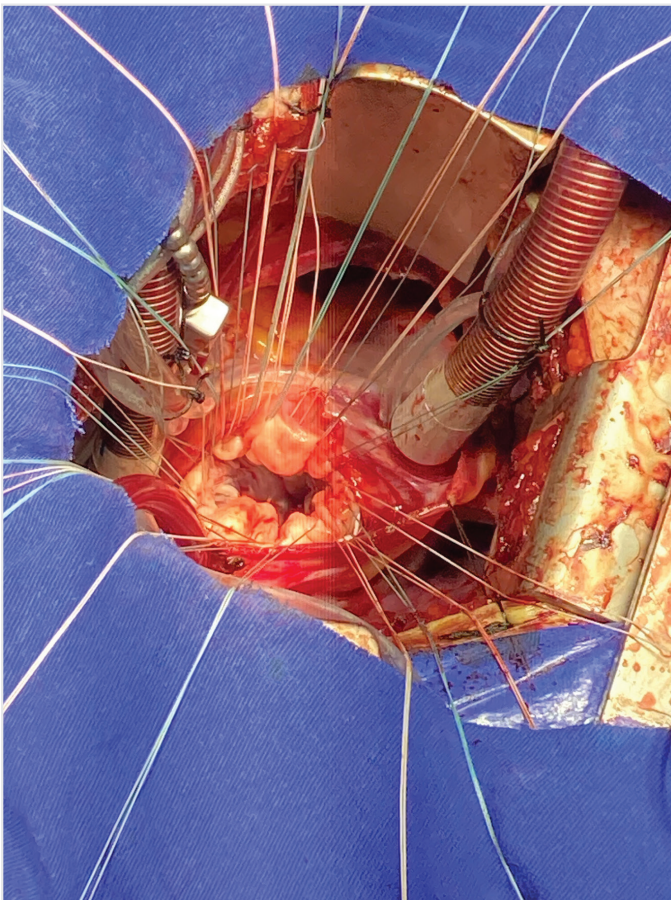


Figure 4. Surgical exposure of the right lateral thoracotomy (consent of the patient is taken)

for RAT being peripheral; RLT exposure being more visible compared to RAT; hemostasis being more difficult to achieve by direct vision in RAT since no camera is used; and being associated with longer tube drainage and hospital stay in the postoperative period. Although no statistically significant differences were observed between the groups in terms of extubation time or ICU stay, the prolonged chest tube duration in RAT patients appears to play a crucial role in extending hospitalization. One plausible explanation for this difference lies in the limitations of direct vision techniques employed in RAT. Without the enhanced visual assistance provided by a camera system, identifying minor bleeding foci that can contribute to prolonged drainage may be more challenging (Figure 3). RLT, on the other hand, offers superior visualization and exposure, allowing the surgeon to detect and manage even minimal sources of bleeding more effectively. This intraoperative advantage may lead to reduced postoperative drainage, thereby facilitating earlier chest tube removal and subsequent hospital discharge (12).

Direct cannulation of the ascending aorta for the RLT technique (Figure 4) is effective in overcoming the challenges associated with peripheral cannulation, particularly in patients with peripheral artery disease. In situations where transesophageal echocardiography is not available in the operating room, blind peripheral cannulation may pose significant risks. However, the RLT technique eliminates this concern by enabling direct cannulation of the aorta and vena cava (13). Peripheral arterial cannulation is mandatory for the RAT technique. In contrast, peripheral arterial cannulation in RLT is at the discretion of the surgeon. If the surgeon believes that it will not hinder exposure and the patient's anatomy is suitable, central arterial cannulation may be performed. Peripheral arterial cannulation, in addition to the inherent complications of cardiac surgery, can introduce further risks. The most significant of these are femoral wound infection, seroma, hematoma, peripheral arterial stenosis, and peripheral venous thrombosis (14).

The decision to use RLT or RAT should be based on factors such as the patient's anatomy, the surgeon's expertise, and the institution's available resources. For instance, RAT might be the preferred option for patients with a high body mass index (the association of obesity with respiratory pathologies is particularly common in society) (15), where lateral exposure is difficult (16). On the other hand, RLT could be more beneficial in reoperative cases or those requiring extensive mitral valve repair (17).

Study Limitations

This study has several limitations that should be considered. First, its retrospective, non-randomized, single-center design introduces potential selection bias, as the choice of surgical approach was based on surgeon preference and patient-specific anatomical factors. In addition, the relatively small sample size—particularly in the RAT group—limits the statistical power of intergroup comparisons and may have reduced the ability to detect clinically meaningful differences.

Second, procedural heterogeneity and technical differences between the two approaches may have influenced the perioperative outcomes. Variations in cannulation strategies, exposure quality, and the use of

direct vision without camera assistance, particularly with the RAT technique, may have affected operative times, control of hemostasis, and postoperative drainage. These factors should be taken into account when interpreting the comparative results of the two minimally invasive approaches.

The relatively small number of patients in the RAT group, compared with that in the RLT group, represents one of the major limitations of this study.

Conclusion

The superior intraoperative hemostasis and improved visualization provided by RLT during direct vision operations without camera assistance seem to contribute significantly to reduced postoperative drainage and shorter hospital stay compared with RAT. These findings suggest a potential clinical advantage of direct vision RLT and require further validation in large-scale, prospective studies. The situation may be different in camera-assisted approaches. It would be beneficial for the surgeon to choose the technique he believes will be more successful and to complete the learning curve for that technique.

Ethics

Ethics Committee Approval: Our study received ethical approval from the İstanbul Medipol University Ethics Committee on 30.04.2026 (decision number: 688). As our institution does not have an institutional ethics committee, ethical approval for this study was obtained from the İstanbul Medipol University Ethics Committee.

Informed Consent: As this was a retrospective study, informed consent was not required.

Footnotes

Authorship Contributions: Surgical and Medical Practices - Y.Ö., M.Ş., Y.Ş., İ.K.; Concept - Y.Ö., Y.Ş.; Design - Y.Ö., M.Ş., İ.K.; Data Collection or Processing - Y.Ö., E.S.; Analysis or Interpretation - Y.Ö., M.Ş., Y.Ş.; Literature Search - Y.Ö., E.S., İ.K.; Writing - Y.Ö., E.S.

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The Effect of Conventional Versus Pleth Variability Index-Guided Goal-Directed Intraoperative Fluid Management on Renal Function in Patients Undergoing Elective Total Abdominal Hysterectomy

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ABSTRACT

Introduction: Intraoperative fluid management is a critical component of anesthetic practice, aiming to maintain tissue perfusion and electrolyte balance. Inadequate or excessive fluid administration may cause complications, thereby affecting postoperative outcomes. This study aimed to assess the impact of pleth variability index (PVI)-based goal-directed fluid therapy (GDFT), compared with a conventional fluid strategy, on renal function during elective total abdominal hysterectomy (TAH).

Methods: This prospective, non-randomized, comparative study included 68 participants (American Society of Anesthesiologists I-II) who underwent TAH. Patients were followed in two parallel clinical cohorts according to the fluid management strategy applied: Group P (GDFT monitored via PVI) and Group G (conventional fluid therapy). Heart rate (HR), mean arterial pressure (MAP), urine output, blood loss, and fluid volumes were recorded every 30 minutes for up to 150 minutes post-intubation. Blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), urine specific gravity, and calculated osmolality were evaluated preoperatively, postoperatively, and on postoperative day 3.

Results: No statistically significant differences were observed between the groups in HR, MAP, or urine output. Group G received more fluids and experienced greater intraoperative blood loss than Group P. Postoperatively, BUN levels and calculated osmolality decreased in both groups, while eGFR and creatinine remained unchanged from baseline. Urine specific gravity increased significantly only in Group P.

Conclusion: Conventional and PVI-guided GDFT protocols exert similar effects on postoperative renal function after elective TAH. PVI-guided GDFT achieves robust hemodynamic stabilization with a significant reduction in intraoperative fluid volumes compared to conventional management, representing a reliable fluid-sparing approach for routine clinical practice.

Keywords: PVI, goal directed fluid management, renal function, traditional fluid therapy

Introduction

Intraoperative fluid therapy represents an essential component of routine anesthetic management. The main goals of fluid administration are to sustain tissue perfusion, ensure adequate oxygen delivery, preserve normal electrolyte concentrations, and achieve normoglycemia (1).

Various fluid therapy regimens are being used in the intraoperative setting, including traditional, restrictive, and goal-directed approaches. Inadequate fluid administration during the perioperative period may lead to impaired tissue perfusion and acute kidney injury (AKI), whereas excessive fluid administration may cause complications such as pulmonary edema, pneumonia, postoperative ileus, anastomotic

leakage, and impaired wound healing. Therefore, perioperative fluid replacement is of critical significance for postoperative morbidity and mortality (2,3).

Goal-directed fluid therapy (GDFT) aims to optimize intraoperative cardiac output and oxygen delivery based on individual needs, particularly in patients with limited cardiopulmonary reserve or hemodynamic instability. In patients undergoing major surgery, standard anesthetic monitoring may be insufficient to assess intraoperative hypovolemia or hypervolemia. To ensure individualized fluid therapy and optimal oxygen delivery in the perioperative period, advanced hemodynamic monitoring is recommended. Dynamic parameters such as pulse pressure variation (PPV), stroke volume variation (SVV), and pleth variability index (PVI),



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which are based on cardiopulmonary measurements, are recognized as accurate predictors of fluid responsiveness (4).

Due to its non-invasive nature and cost-effectiveness, PVI has gained prominence among dynamic hemodynamic monitoring tools, and has been shown to provide fluid optimization comparable to that of invasive monitors (5).

The primary objective of this study was to determine whether PVI-guided GDFT results in superior preservation of renal function compared with conventional fluid therapy in patients undergoing elective total abdominal hysterectomy (TAH), as assessed by perioperative changes in serum creatinine, estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), urine specific gravity, and calculated osmolality.

Methods

This study was conducted with the approval of the University of Health Sciences Türkiye, Istanbul Training and Research Hospital Ethics Committee (decision number 257, date: October 13, 2023). The 12 months period between ethics approval and initiation of patient enrollment was attributable to institutional logistics and the procurement timeline for the specific non-invasive hemodynamic monitoring equipment (Masimo Rainbow ROOT). The study included participants aged 18 to 65 years who underwent TAH under general anesthesia between October 16, 2024, and April 16, 2025. The study was registered on the UMIN-CTR website (UMIN000058074). We acknowledge that this registration was completed retrospectively, following the conclusion of the study, due to mandatory institutional administrative workflows and formal registry approval timelines. This investigation was structured as a prospective, non-randomized, comparative study (quasi-experimental design) and reported in accordance with the STROBE guidelines. Patients were followed in a 1:1 parallel design based on the clinical fluid management approach selected by the attending anesthesia team, resulting in two distinct cohorts: Groups P and G. Because group assignments were determined by the institutional clinical pathway and the specific monitoring protocol chosen by the clinician, no randomization sequence or allocation concealment methods (such as sealed envelopes) were used. Due to the practical nature of the intraoperative interventions and the visibility of the monitoring screens, the clinical anesthesia team, the participants, and the data analysts could not be blinded to the group allocations. The flow of participants through the screening, exclusion, and final analysis stages is detailed in the provided Participant Flow Diagram. Written informed consent was obtained from each participant after they were fully briefed on the protocol and prior to their inclusion in the study.

Patients with American Society of Anesthesiologists (ASA) physical status $\geq$ III, a known history of renal failure, diabetes mellitus, diuretic use, ischemic heart disease, arrhythmias, severe peripheral arterial disease or congestive heart failure were excluded from the study. Additional exclusion criteria included patients with blood loss exceeding 20%, patients who received blood transfusions, patients who required more than 500 mL of colloid solutions, patients who required vasopressor support, and patients with psychiatric conditions impairing their ability to provide informed consent.

The required sample size was estimated through a power analysis performed with G*Power 3.1.9.4 software (Heinrich Heine University Düsseldorf, Düsseldorf, Germany). Based on a medium effect size (d : 0.5) for early postoperative fluid-driven renal variables (such as eGFR changes), a 5% significance level, and 80% statistical power, at least 63 participants were required. To account for potential dropouts, the final cohort was maintained at 68 participants and was analyzed using an independent t-test.

All patients who completed preoperative preparations and were eligible for the study were followed in one of two groups: Group P (receiving GDFT guided by PVI) and Group G (receiving conventional fluid therapy). Anesthesia was administered according to the group assignment.

Preoperative evaluation was performed for each patient included in the study, and demographic data such as age, sex, height, weight, ASA score, and comorbidities were recorded. Upon transfer to the operating room, routine monitoring, including electrocardiography, peripheral oxygen saturation, and non-invasive blood pressure, was applied, along with hemodynamic monitoring using the Masimo Rainbow ROOT device (Masimo Corp., Irvine, CA, USA) to assess PVI, perfusion index (PI), and Oxygen Reserve Index.

At induction, propofol 2 mg/kg, fentanyl 1-1.5 mcg/kg, and rocuronium 0.6-0.7 mg/kg were administered. For maintenance of anesthesia, intravenous remifentanyl and sevoflurane were administered. Ventilation parameters were adjusted to 40% FiO₂ with a flow rate of 2 L/min, tidal volume based on ideal body weight, and end-tidal CO₂ between 35-45 mmHg.

Following intubation, heart rate (HR), mean arterial pressure (MAP), peripheral oxygen saturation, urine output, blood loss, and the volume of fluids administered were recorded for all patients at 30, 60, 90, 120, and 150 minutes. The duration of surgery was also documented. Serum urea, creatinine, and eGFR levels, as well as urine specific gravity (measured using the Laboquick urine analysis strip), were assessed preoperatively, postoperatively, and on postoperative day 3. The eGFR was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equation, which incorporates serum creatinine, age, and sex, without race adjustment. Serum osmolality was calculated using the conventional formula: $[2 \times (\text{Na}) + (\text{Glucose}/18) + (\text{BUN}/2.8)]$, with values expressed in mOsm/L. We acknowledge that calculated osmolality is an estimate, and measured serum osmolality may differ due to an osmolar gap. In Group P, PVI values were also recorded. According to the routine preoperative protocol at our obstetrics and gynecology clinic, all patients received 2000 mL of Ringer's lactate solution, as confirmed by medical records.

Group P: Following induction, 250 mL crystalloid boluses were administered based on the PVI value, and fluid replacement was continued until the target PVI threshold of 14% was achieved. Throughout the surgical procedure, a maintenance infusion of crystalloids was administered at a rate of 2 mL/kg/h.

The intraoperative management protocol was as follows:

When PVI >14% and MAP <65 mmHg, patients were administered a 250 mL crystalloid solution as a bolus. If MAP did not increase above

65 mmHg, 5 mg IV ephedrine was administered. A total bolus dose of 15 mg of ephedrine was permitted. Patients requiring norepinephrine infusion were excluded from the study.

PVI <14% and MAP >65 mmHg: Maintenance infusion of crystalloids at 2 mL/kg/h was continued.

When PVI <14% and MAP <65 mmHg, 5 mg IV ephedrine was administered and repeated as needed, up to a total dose of 15 mg. Patients who required norepinephrine infusion were excluded from the study.

Group G: Patients received crystalloid replacement based on preoperative fasting duration, calculated basal fluid requirements (using the 4-2-1 rule), and maintenance plus insensible fluid losses (4 mL/kg/h). Of the total calculated basal fluid requirement, 50% was administered during the first hours, 25% in the second hours, and the remaining 25% in the third hours.

In cases where MAP was below 65 mmHg or decreased more than 25% from baseline, a 250 mL crystalloid solution was given as a bolus. If hypotension persisted, 5 mg IV ephedrine was administered. Patients who required norepinephrine infusion were excluded from the study.

Statistical Analysis

Descriptive statistics were expressed as mean, standard deviation, median, minimum and maximum values, and as frequencies and percentages. The distributions of the variables were assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The independent samples t-test was used for normally distributed independent quantitative data, whereas the Mann-Whitney U test was applied to non-normally distributed data. The Wilcoxon test was used to analyze dependent quantitative variables. The chi-square test was used to analyze independent categorical (qualitative) variables. All statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 70 patients were initially enrolled in the study; however, 2 were excluded because they required intraoperative blood product transfusion. Consequently, 68 patients were included in the final analysis.

The patients were assigned to two groups: Group P (n=34), who received GDFT guided by PVI, and Group G (n=34), who received conventional fluid therapy.

There were no statistically significant differences between Group P and Group G in terms of age, height, weight, body mass index (BMI), duration of surgery, baseline PVI value, ASA score, and the total of patients who needed ephedrine ($p>0.05$) (Table 1).

In both groups, postoperative and postoperative day 3 hemoglobin (HGB) and hematocrit (HCT) levels showed significant decreases compared with preoperative values ($p<0.05$), while white blood cell counts increased significantly ($p<0.05$); however, there were no significant differences between groups ($p>0.05$) (Table 2).

In both Group P and Group G, postoperative BUN and creatinine levels and those on postoperative day 3 were significantly lower than preoperative measurements ($p<0.05$), while eGFR increased significantly ($p<0.05$). The decrease in creatinine and the increase in eGFR did not differ significantly between groups ($p>0.05$). However, in Group G, both postoperative BUN levels and postoperative day 3 BUN levels were significantly lower than those in Group P ($p<0.05$) (Table 3). To evaluate the precision of the observed equivalence in primary renal outcomes, between-group mean differences with 95% confidence intervals (CIs) and observed effect sizes (Cohen's d) were calculated for overall perioperative changes on Postoperative Day 3 (Δ_{day3} : postoperative day 3-preoperative). For Δ_{day3} eGFR, the between-group mean difference was -1.20 mL/min (95% CI: -4.66 to 2.26; Cohen's d: 0.17). For Δ_{day3} creatinine, the mean difference was +0.01 mg/dL (95% CI: -0.03 to 0.05; Cohen's d: 0.11). For Δ_{day3} BUN, the mean difference was +1.50 mg/dL (95% CI: -1.62 to 4.62; Cohen's d: 0.23). These small effect sizes ($d\leq 0.23$) and narrow 95% CIs bound around zero confirm that true clinically meaningful differences in renal outcomes were not missed due to statistical power constraints.

In both groups, postoperative osmolality levels were significantly lower than preoperative levels ($p<0.05$); however, the between-group decrease in osmolality was not statistically significant ($p>0.05$). Postoperative urine specific gravity in Group G was significantly lower than that in Group P ($p<0.05$). In Group P, urine specific gravity showed a significant

Table 1. Comparison of demographic and clinical characteristics between the groups

		Group P (n=34)			Group G (n=34)				p
		Mean $\pm$ SD/n-%			Mean $\pm$ SD/n-%			Median	
Age (years)		49.1	$\pm$	5.7	48.0			47.5	0.615
Height (cm)		162.4	$\pm$	6.5	161.0			160.0	0.279
Weight (kg)		73.3	$\pm$	10.8	75.0			74.5	0.672
BMI (kg/m ²)		27.6	$\pm$	4.2	27.0			28.0	0.364
ASA score	I	14		41.2%	21		61.8%		0.089
	II	20		58.8%	13		38.2%		
Duration of operation (min)		133.2	$\pm$	28.8	120.0			120.0	0.985
Baseline PVI (%)		13.2	$\pm$	2.1	13.0			13.0	0.467
Ephedrine	(-)	31		91.2%	32		94.1%		0.642
	(+)	3		8.8%	2		5.9%		

Independent samples t-test/Mann-Whitney U test/chi-square test. BMI: Body mass index, ASA: American Society of Anesthesiologists, PVI: Pleth variability index, SD: Standard deviation

increase both immediately postoperatively and on postoperative day 3 compared with preoperative values ($p<0.05$). In Group G, there was no significant change in urine specific gravity immediately postoperative compared to preoperative values ($p>0.05$); however, a significant increase was observed on postoperative day 3 ($p<0.05$) (Table 4).

No significant differences were observed between Group P and Group G in serial measurements of MAP and HR ($p>0.05$).

The volume of fluids administered in Group G was significantly higher than that in Group P ($p<0.05$). At 30, 60, and 90 minutes, bleeding was

Table 2. Comparison of HCT, HGB and WBC levels between the groups

	Group P (n=34)				Group G (n=34)				p
	Mean ± SD			Median	Mean ± SD			Median	
HCT (%)									
Preoperative	37.2	±	5.6	37.2	37.0	±	3.5	36.8	0.868
Postoperative	34.7	±	4.4	34.9	33.4	±	3.3	32.3	0.103
Postoperative day 3	30.4	±	4.0	30.4	29.6	±	3.6	29.4	0.294
Preop/postop change	-2.5	±	4.3	-2.2	-3.7	±	2.2	-3.7	0.056
Preop/postop day 3 change	-6.7	±	3.7	-6.5	-7.4	±	3.0	-7.7	0.259
HGB (g/dL)									
Preoperative	12.2	±	1.8	12.4	12.1	±	1.3	12.1	0.778
Postoperative	11.5	±	1.6	11.5	11.0	±	1.2	10.8	0.134
Postoperative day 3	9.8	±	1.4	9.8	9.8	±	1.3	9.7	0.835
Preop/postop change	-0.8	±	0.9	-1.0	-1.1	±	0.8	-1.1	0.165
Preop/postop day 3 change	-2.4	±	1.0	-2.4	-2.3	±	1.0	-2.3	0.768
WBC (mcl)									
Preoperative	7.3	±	3.1	6.0	7.1	±	1.8	7.0	0.673
Postoperative	13.6	±	3.0	13.5	13.0	±	3.4	14.0	0.390
Postoperative day 3	8.7	±	2.2	8.5	8.2	±	2.3	8.0	0.325
Preop/Postop change	6.3	±	2.9	7.0	5.9	±	2.7	6.0	0.269
Preop/postop day 3 change	1.4	±	2.6	2.0	1.1	±	2.0	1.0	0.151
Mann-Whitney U test/Wilcoxon test. HCT: Hematocrit, HGB: Hemoglobin, WBC: White blood cell, SD: Standard deviation									

Mann-Whitney U test/Wilcoxon test. HCT: Hematocrit, HGB: Hemoglobin, WBC: White blood cell, SD: Standard deviation

Table 3. Comparison of BUN, creatinine and eGFR levels between the groups

	Group P (n=34)				Group G (n=34)				p
	Mean ± SD			Median	Mean ± SD			Median	
BUN (mg/dL)									
Preoperative	25.9	±	6.4	26.0	25.0	±	7.0	25.0	0.480
Postoperative	18.9	±	4.1	18.0	15.7	±	5.3	14.5	0.002
Postoperative day 3	17.5	±	5.3	16.0	15.2	±	5.9	14.0	0.027
Preop/postop change	-7.0	±	6.5	-5.5	-9.3	±	6.0	-9.0	0.078
Preop/postop day 3 change	-8.4	±	6.5	-8.5	-9.9	±	6.4	-9.0	0.555
Creatinine (mg/dL)									
Preoperative	0.62	±	0.09	0.60	0.60	±	0.10	0.60	0.324
Postoperative	0.57	±	0.10	0.60	0.53	±	0.09	0.50	0.151
Postoperative day 3	0.58	±	0.10	0.60	0.55	±	0.10	0.55	0.302
Preop/postop change	-0.05	±	0.08	0.00	-0.07	±	0.10	-0.10	0.506
Preop/postop day 3 change	-0.04	±	0.09	0.00	-0.05	±	0.09	-0.05	0.713
eGFR (mL/min)									
Preoperative	102.9	±	7.9	104.0	105.0	±	8.3	107.0	0.156
Postoperative	108.7	±	7.6	108.5	111.4	±	7.9	111.5	0.158
Postoperative day 3	108.0	±	8.4	109.5	111.3	±	8.6	112.0	0.206
Preop/postop change	5.8	±	6.5	5.0	6.4	±	7.6	4.5	0.966
Preop/postop day 3 change	5.1	±	7.7	5.0	6.3	±	6.6	5.0	0.649

Mann-Whitney U test/Wilcoxon test. BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, SD: Standard deviation

significantly greater in Group G than in Group P ($p < 0.05$). Although the final bleeding volume was greater in Group G, the difference between the groups was not statistically significant ($p > 0.05$). There was no significant difference in urine output between Group P and Group G ($p > 0.05$) (Table 5).

Discussion

The optimal intraoperative fluid administration volume remains a topic of widespread investigation in the literature. In major surgeries, liberal fluid administration was found to be linked to an increased incidence of pulmonary complications (3).

Conversely, restrictive regimens, while not shown to increase mortality or morbidity, were associated with a greater risk of AKI (6).

In our study, we investigated the effects of conventional fluid therapy and PVI-guided GDFT on renal function. GDFT aims to optimize hemodynamic stability based on individual patient needs, and studies by Muñoz et al. (7) and Gómez-Izquierdo et al. (8) have shown that it reduces intraoperative fluid volume and shortens hospital stay; in our study, we further evaluated its effects on urine specific gravity, serum urea and creatinine levels, as well as intraoperative fluid administration and blood loss.

To maintain normovolemia, current recommendations emphasize avoiding both overly restrictive and overly liberal fluid strategies. Instead, individualized fluid therapy guided by advanced hemodynamic monitoring should be applied to optimize oxygen delivery during the perioperative period (9).

Table 4. Comparison of osmolarity and urine specific gravity levels between the groups

	Group P (n=34)				Group G (n=34)				p
	Mean ± SD			Median	Mean ± SD			Median	
Osmolarity (mOsm/L)									
Preoperative	286.0	±	3.7	286.0	285.3	±	4.4	284.5	0.153
Postoperative	283.8	±	3.9	284.0	281.7	±	5.3	283.0	0.099
Postoperative day 3	286.8	±	4.3	286.0	285.3	±	3.5	286.0	0.217
Preop/postop change	-2.2	±	5.2	-2.0	-3.6	±	5.5	-3.5	0.271
Preop/postop day 3 change	0.8	±	5.1	2.0	0.0	±	5.7	1.0	0.543
Urine specific gravity									
Preoperative	1010.9	±	4.2	1010.0	1010.4	±	4.2	1010.0	0.860
Postoperative	1015.7	±	4.1	1015.0	1011.6	±	3.6	1010.0	< 0.001
Postoperative day 3	1016.0	±	5.0	1015.0	1017.4	±	7.4	1015.0	0.659
Preop/postop change	4.9	±	3.6	5.0	1.2	±	3.9	0.0	< 0.001
Preop/postop day 3 change	5.1	±	6.7	5.0	6.9	±	8.3	5.0	0.555
Mann-Whitney U test/Wilcoxon test. SD: Standard deviation									

Mann-Whitney U test/Wilcoxon test. SD: Standard deviation

Table 5. Comparison of intraoperative fluid administration, blood loss, and urine output between the groups

	Group P (n=34)				Group G (n=34)				p
	Mean ± SD		Median	Mean ± SD		Median			
Intraoperative fluid administration volumes (mL)									
30 th minutes	244.3	±	133.5	177.5	410.3	±	100.6	400.0	< 0.001
60 th minutes	461.2	±	172.5	475.0	802.9	±	189.9	800.0	< 0.001
90 th minutes	706.8	±	228.8	700.0	1142.6	±	264.3	1200.0	< 0.001
Total	1012.1	±	319.5	1000.0	1700.0	±	409.2	1550.0	< 0.001
Intraoperative bleeding volumes (mL)									
30 th minutes	27.2	±	30.4	12.5	45.6	±	32.8	50.0	0.018
60 th minutes	78.7	±	46.9	50.0	105.9	±	48.9	100.0	0.006
90 th minutes	139.7	±	72.6	100.0	168.4	±	67.2	150.0	0.049
Total	213.8	±	97.2	200.0	253.6	±	120.9	225.0	0.250
Urine output (mL)									
30 th minutes	128.7	±	106.6	100.0	113.2	±	52.7	100.0	0.797
60 th minutes	225.7	±	162.2	200.0	207.4	±	76.0	200.0	0.570
90 th minutes	324.3	±	194.7	275.0	298.5	±	90.9	300.0	0.696
Total	465.5	±	289.4	400.0	494.6	±	172.3	475.0	0.211

Mann-Whitney U test. SD: Standard deviation

Dynamic cardiopulmonary parameters such as the PPV, PVI, and SVV are considered useful indicators for assessing fluid responsiveness, offering greater accuracy than static measures for guiding fluid management (4,10).

PVI, obtained by analyzing respiration-related changes in the PI, has been shown to correlate strongly with invasive indices such as PPV and SVV, making it an effective dynamic marker of fluid sensitivity (5,11).

Considering these advantages, we assessed intraoperative fluid responsiveness using PVI, a non-invasive measure. In a study by Çevikkalp et al. (12), PVI-based fluid therapy allowed better estimation of patients' intravascular volume than central venous pressure-based monitoring. In that protocol, patients with a PVI value above 14% received 250 mL of crystalloid replacement, and no significant changes were observed in HR or MAP (12).

Similarly, Cannesson et al. (5) and Demirel et al. (13) demonstrated that a PVI threshold of 14% could effectively distinguish fluid responders from non-responders. Based on these findings, we also adopted a PVI threshold value of 14% in our study.

To minimize the risk of postoperative AKI, intraoperative management should aim to maintain MAP above 60-65 mmHg, or above 75 mmHg in individuals with a history of hypertension (14).

In a study of 3,300 non-cardiac surgery patients, the cumulative duration of hypotension was independently associated with AKI, with MAP <55 mmHg for more than 10 minutes or <60 mmHg for more than 20 minutes significantly increasing risk (15,16).

Although tachycardia has traditionally been considered a classic sign of hypovolemia, contemporary evidence reaffirms that its clinical sensitivity and specificity remain highly limited, as compensatory mechanisms and anesthetic depth frequently confound HR variations during acute volume shifts (17).

In our study, MAP and HR measurements showed no statistically significant differences between groups P and G.

Excessive fluid administration is another well-recognized contributor to AKI in critically ill patients (18,19).

At our hospital, the obstetrics and gynecology clinic routinely administers 2000 mL of intravenous Ringer's lactate the night before surgery as part of standard preoperative hydration. Consequently, baseline PVI values in our patient population averaged around 13%. Because this standardized protocol does not account for individual characteristics, such as BMI or fasting duration, some patients may have received unnecessary or excessive fluid loading. This high-volume preoperative fluid loading represents a methodological limitation, as it likely induced a baseline volume expansion, thereby masking the potential renal-protective benefits of the PVI-guided GDFT. This ceiling effect explains why postoperative renal markers remained equivalent across the two groups.

In a study by Muñoz et al. (7) on patients undergoing laparoscopic sleeve gastrectomy, the volume of crystalloids and total fluids administered was significantly lower in the GDFT group.

Similarly, in our study, the total fluid volumes given at 30, 60, and 90 minutes, as well as overall were significantly higher in Group G than in Group P. On average, patients in Group G received 1550 mL of total fluid during the operation, while those in Group P received 1000 mL of total fluid. It was found that patients managed with the GDFT protocol required significantly less fluid infusion compared to those treated with conventional fluid therapy, consistent with findings in the literature (11,20).

Our findings regarding fluid volume reduction without compromising renal function align with the physiological frameworks highlighted in landmark multicenter trials. In the RELIEF trial by Myles et al. (21), a strictly restrictive fluid regimen was shown to significantly increase the risk of AKI compared to a liberal approach, underscoring the dangers of unguided fluid limitation. Conversely, our protocol used dynamic PVI monitoring, which allowed explicit fluid conservation (1000 mL in Group P vs. 1550 mL in Group G) without exposing patients to subclinical renal hypoperfusion. Furthermore, the contemporary OPTIMISE II trial (2024) demonstrated that structured, goal-directed fluid protocols offer a safe and reliable approach to clinical optimization without causing fluid overload (22). By implementing PVI-guided GDFT, we individualize fluid delivery to prevent both the restrictive-induced renal risks shown in the RELIEF trial (21) and the dilutional or volume-overload complications associated with conventional liberal strategies.

Rapid intravenous fluid infusion can increase atrial pressure, stimulate atrial natriuretic peptide release, and disrupt the glycocalyx, thereby promoting fluid extravasation and potentially contributing to AKI. In our study, intraoperative fluid boluses of 250 mL were administered over 10 minutes to avoid these effects. In the study of Bihari et al. (23), fluid overload may compromise endothelial integrity and dilute coagulation factors.

Group G in our study showed higher intraoperative and total bleeding volumes, which might be secondary to dilutional coagulopathy resulting from increased fluid administration. However, reverse causality cannot be ruled out, as clinical teams may have administered more fluids to Group G in response to increased bleeding, to maintain hemodynamic stability. Other factors such as individual surgeon variability or specific uterine pathologies, including fibroid size, might have influenced blood loss. Since routine perioperative coagulation profiles (prothrombin time, international normalized ratio, platelets) were not monitored as part of our study protocol, it is not possible to definitively attribute this difference to a single mechanism. In both groups, P and G, HGB and HCT values measured postoperatively and on postoperative day 3 were significantly decreased compared with preoperative values. However, there were no statistically significant differences between the two groups in the decreases in HGB and HCT values from preoperative to postoperative measurements or from preoperative to postoperative day 3 measurements.

Cannesson et al. (24) demonstrated that urine output is frequently relied upon to guide volume expansion, with 83% of ASA and 77% of ESA respondents administering fluids in response to decreased urine output.

Another study of low intraoperative urine output during laparoscopic abdominal surgery reported that patients who received 3300 mL (high-volume group) or 1325 mL (low-volume group) had nearly identical urine outputs (100 mL vs. 107 mL). The mean surgery durations were approximately 180 and 190 minutes. No significant differences were observed in preoperative or perioperative creatinine values, although HCT levels decreased significantly on postoperative days 1 and 3. The researchers concluded that oliguria was not indicative of postoperative renal function and that intraoperative fluid replacement of 4-10 mL/kg had no significant effect on urine output. Thus, intraoperative oliguria during laparoscopic abdominal surgery was neither responsive to fluid administration nor associated with postoperative renal insufficiency (25). In our study, although the fluid volume administered in Group G was higher than that in Group P, there were no significant differences in urine output between the two groups at 30, 60, and 90 minutes or at the final measurement. Intraoperative oliguria was not observed in either group. Despite significant differences in intraoperative fluid volumes, no significant effect on urine output was noted. Therefore, we consider urine output monitoring alone an insufficient indicator for guiding additional fluid administration.

Postoperative and postoperative-day-3 serum urea levels decreased significantly compared with preoperative values in both Groups P and G. However, urea levels in Group G were significantly lower than those in Group P at both postoperative measurements. We believe that the significantly lower postoperative and postoperative-day-3 urea values in Group G, compared with Group P, were due to the greater amount of intraoperative fluid replacement administered to Group G. However, both values remained entirely within the normal physiological range, indicating a lack of clinical significance. This dilutional effect might have partially masked early postoperative creatinine increases in Group G, while alternative perioperative factors such as fasting duration, tissue catabolism, and surgical stress on hepatic urea synthesis could also have influenced these levels, despite a formal BUN/creatinine ratio not being routinely tracked.

In most clinical settings, endogenous filtration markers measured in blood are routinely used to eGFR. The most common endogenous biomarker remains serum creatinine; however, contemporary consensus from the KDIGO initiative reemphasizes that serum creatinine concentrations demonstrate a significant diagnostic delay, often rising only after a substantial reduction—frequently estimated up to 50%—in functional nephron capacity or glomerular filtration (26). As detailed in recent critical evaluations of renal classification milestones, this inherent physiological limitation heavily restricts the real-time detection of the acute injury phase of perioperative renal impairment (27). This clinical “blind spot” is particularly pronounced in cohorts where healthy baseline kidneys and preserved renal functional reserve are present preoperatively, wherein minor or subclinical filtration shifts fail to trigger immediate creatinine spikes despite active physiological stress (28).

In patients with high-grade obesity scheduled for laparoscopic Roux-en-Y gastric bypass surgery, no difference was observed in preoperative and postoperative creatinine values between the group monitored with PVI and the group managed with a standard fluid regimen (13).

In our study, there were no significant differences between groups P and G in preoperative, postoperative, and postoperative day 3 eGFR values, including increases in eGFR. Similarly, comparisons of preoperative, postoperative, and postoperative day 3 serum creatinine values revealed no significant differences; according to AKI criteria, no meaningful postoperative changes were observed. Therefore, we consider that, in elective TAH surgery, although the intraoperative fluid volume was lower in the PVI-guided GDFT group, its effects on renal function were comparable to those of conventional fluid therapy.

Routinely administering excessive preoperative fluids in critically ill patients may mask postoperative increases in creatinine, leading to delayed or more difficult early detection of AKI compared to preoperative creatinine levels (15).

In our study, osmolarity values in both groups decreased significantly postoperatively compared with preoperative values; however, osmolarity on postoperative day 3 did not differ significantly from preoperative levels. The observed postoperative decrease in osmolarity in both groups may be attributable to the routine preoperative administration of 2000 mL Ringer’s lactate, according to our obstetrics and gynecology clinic’s standard preparation protocol. Similarly, the lack of significant change in osmolarity on postoperative day 3 is likely attributable to the routine use of Isolen-S as postoperative maintenance IV fluid therapy. We also consider that differences in osmolarity between preoperative, postoperative, and postoperative day 3 measurements may be related to variations in balanced crystalloid solutions administered.

The endothelial glycocalyx layer plays a key role in preventing excessive vascular fluid extravasation, thereby limiting tissue edema. Therefore, in intraoperative fluid regimens, any additional fluid should be carefully considered as it may impair glycocalyx function (29).

In a study by Hahn et al. (30), it was demonstrated that preoperative dehydration and high urine specific gravity may be strongly associated with postoperative increases in plasma creatinine.

For this reason, we measured urine specific gravity both preoperatively and postoperatively in our study. In Group P, urine specific gravity measured postoperatively and on postoperative day 3 increased significantly compared with preoperative values, with no significant difference between the postoperative and day 3 measurements. In Group G, postoperative urine specific gravity did not change significantly from preoperative values, whereas on postoperative day 3 it showed a significant increase relative to those values. Postoperative urine specific gravity in Group G was significantly lower than that in Group P. The mean preoperative urine-specific gravity in both groups was 1010, close to the lower limit of the normal range. We attribute this to the routine preoperative administration of 2000 mL of Ringer’s lactate, according to our obstetrics and gynecology clinic’s standard preparation protocol. The lower postoperative urine specific gravity in Group G, compared with that in Group P, is likely due to the higher volume of intraoperative crystalloid fluids administered to Group G. Even a 500 mL difference in intraoperative fluid administration was sufficient to affect urine-concentrating ability in ASA I-II patients assumed to have healthy kidneys.

The increase in postoperative urine specific gravity in the P group may reflect the avoidance of excessive fluid administration due to PVI-guided GDFT. In the G group, the absence of a postoperative increase in urine specific gravity and the observed lower urine specific gravity may be attributed to the higher fluid volumes administered according to the conventional fluid therapy protocol. We consider monitoring urine specific gravity a valuable parameter for assessing renal concentrating ability in the postoperative period.

Previous studies have shown that postoperative serum creatinine elevation is associated with preoperative and postoperative concentrated urine; in our study, urine specific gravity remained within normal limits, and postoperative creatinine levels were normal (30).

Study Limitations

Our study has several limitations. First, it was conducted at a single center with a relatively small sample size, which may limit the generalizability of our findings. Second, we excluded high-risk patients (ASA physical status $\geq$ III, diabetes mellitus, or pre-existing renal insufficiency) to maintain a homogeneous sample, limiting the external validity of our results to more vulnerable cohorts who might benefit most from GDFT. Therefore, future well-designed trials should focus on ASA III-IV patients or on those with pre-existing renal insufficiency, in whom GDFT is anticipated to yield a greater clinical impact. Third, intraoperative events such as major blood loss ($>20\%$) or requirement for vasopressors led to post-allocation exclusions. Although this per-protocol approach prevented confounding, it potentially introduced attrition bias. Long-term postoperative follow-up was not performed because measurements were limited to the first three postoperative days. Fourth, the routine 2000 mL preoperative hydration protocol served as a confounding factor, inducing a baseline state of volume fullness and thereby reducing the study's statistical power to detect subtle fluid-driven differences in renal outcomes. Furthermore, standard eGFR equations are validated for steady-state chronic conditions; thus, dynamic perioperative fluid shifts and subsequent hemodilution may have artificially influenced early postoperative creatinine and eGFR kinetics. Fifth, subclinical renal injury markers such as NGAL or cystatin C, which are more sensitive than serum creatinine and urea, were not evaluated due to cost constraints. Urine specific gravity was evaluated using semi-quantitative reagent strips rather than refractometry, which is a limitation in measurement precision for detecting minor between-group differences.

Conclusion

In our study comparing the effects of a traditional fluid replacement strategy and a PVI-guided fluid optimization protocol on kidney function in individuals scheduled for elective TAH, no significant differences were observed between groups in hemodynamic parameters or urine output. The total fluid volume administered and intraoperative blood loss were significantly higher in the G group. Postoperatively, both groups showed decreases in serum urea and osmolality compared to preoperative values, while eGFR and creatinine levels remained unchanged compared to preoperative values. In the P group, postoperative urine specific gravity increased significantly compared with preoperative values, whereas the G group showed no significant change.

The study reported no significant differences in postoperative renal function between conventional and PVI-guided GDFT protocols in patients undergoing elective TAH. Our findings suggest that PVI-guided GDFT achieves hemodynamic stabilization while minimizing total fluid volumes, indicating fluid conservation, in contrast to conventional fluid management. Given the equivalent postoperative renal profiles across groups, we consider it a reliable, fluid-sparing approach applicable in routine clinical practice.

Following adequate hydration, postoperative measurement of urine specific gravity, along with hourly intraoperative urine output monitoring, provides valuable information for assessing renal concentrating capacity. This postoperative increase in urine specific gravity in Group P is considered a physiological response to more tailored fluid administration. Given that serum creatinine and eGFR levels remained stable in both groups, this stability indicates that adequate renal perfusion was maintained. Consequently, this finding supports the clinical safety of the GDFT protocol in maintaining balanced renal function.

Ethics

Ethics Committee Approval: This study was conducted with the approval of the University of Health Sciences Türkiye, Istanbul Training and Research Hospital Ethics Committee (decision number 257, date: October 13, 2023).

Informed Consent: Written informed consent was obtained from each participant after they were fully briefed on the protocol and prior to their inclusion in the study.

Footnotes

Authorship Contributions: Surgical and Medical Practices - O.K.A., Y.C.A.; Concept - İ.N., Y.C.A.; Design - İ.N., Y.C.A.; Data Collection or Processing - O.K.A.; Analysis or Interpretation - Y.C.A.; Literature Search - O.K.A.; Writing - O.K.A., İ.N.

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Effect of Malignancy on Morbidity and Mortality in Left-Sided Emergency Colorectal Resections

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ABSTRACT

Introduction: Despite technological developments, morbidity and mortality in emergency colorectal surgery remain high. Despite efforts to diagnose colorectal cancer early, more than 20% of patients still undergo emergency surgery. How do outcomes in these patients differ from outcomes in patients with benign disease? Very few studies provide information on this subject; therefore, the aim of our study was to determine the effects of malignancy in patients who have undergone left-sided emergency colorectal resections.

Methods: Patients undergoing emergency left-sided colectomy at a single tertiary hospital were included in this observational study. Demographics, Charlson comorbidity index, perforation, duration of surgery, preference for primary anastomosis or end colostomy, and benign or malignant etiologies were all examined. Morbidity was defined as a Clavien–Dindo grade III or higher complication. Risk factors for both morbidity and mortality were first evaluated using univariate analyses. Multivariable logistic regression analyses were then performed for both morbidity and mortality.

Results: The study included 76 patients, 46 (60.5%) of whom were men. The mean age was 61.5 years, and the most common cause was colorectal cancer (n=46, 60%). Perforation was observed in 32.8% of patients (n=25), and obstruction in 38.1% of patients (n=29). The morbidity rate was 27.6% and the 90-day mortality rate was 15.7%. In univariate tests and multivariable regression analyses, malignancy was not associated with morbidity (p=0.879, p=0.711) or mortality (p=0.416, p=0.453). In both univariate and multivariable analyses, perforation was the only factor significantly related to morbidity and mortality.

Conclusion: Malignancy was not identified as a direct cause of morbidity and mortality in emergency left-sided colectomies. Perforation was significantly associated with morbidity and mortality. In these high-risk surgeries, multicenter studies with larger patient groups are needed to detect causes of deterioration and to improve outcomes.

Keywords: Colorectal cancer, emergency surgery, morbidity, mortality, diverticulitis

Introduction

Emergency colorectal surgery occupies a prominent place in the emergency practice of general surgery (1,2). Despite technological and other recent advancements in emergency colorectal surgery, the high morbidity and mortality rates remain a subject of numerous studies (3-5). Naturally, patients in emergency service due to colorectal etiologies are not a uniform category and include various disease processes such as diverticulitis, ischaemia, volvulus, cancer etc., each of which possesses distinct characteristics (6).

Colorectal cancer constitutes a critical subgroup within these etiologies. Despite the efforts made for early diagnosis, approximately 20% of the colorectal cancer patients are still operated on under emergency

conditions (7-9). Since the principles of oncological surgery are also applied when addressing the urgent problem of the patient taken to emergency surgery for colorectal cancer, the procedure may differ in some respects from other surgeries. These include high ligation, attempts to obtain sufficient negative surgical margins, and efforts to perform resection without compromising the integrity of the mesocolon. However, it is also noted that a significant proportion of mortality in colorectal surgery occurs in patients who require emergency surgery (10,11).

Overall, can it be concluded that the presence of malignancy in emergency left colorectal surgery results in worse outcomes? Or inversely, as mentioned in another study, do benign groups which include



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etiologies such as ischaemia, have worse outcomes? (2). The objective of the present study was to ascertain the impact of malignancy on the morbidity and mortality rates among patients who had undergone left-sided emergency colorectal resection.

Methods

This retrospective observational study was conducted at University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital between January 2023 and May 2024. The study population included, consecutively during the study period, patients aged 18 years or older who underwent emergency left-sided colorectal resection for isolated colorectal pathology. Patients with diseases originating from a colonic segment proximal to the left colon or from a rectal segment distal to the rectosigmoid junction, patients who underwent surgery for combined organ pathologies of various benign and malignant causes, and those undergoing reoperation due to complications of elective abdominal surgery were excluded from the study.

Patients were operated on by general surgeons, two of whom specialized in colorectal surgery. Assistant surgeons provided support during all surgeries. The majority of surgeries were performed outside of regular working hours. The decision to perform end colostomy or an anastomosis after resection was made by the surgeon based on the patient's overall condition. Sepsis, the need for vasopressor support, advanced age, and the presence of numerous comorbidities are among the leading factors influencing the operating surgeon's decision.

The data from patients were obtained via the hospital software system. The demographic data, Charlson comorbidity index score, baseline characteristics, operative and postoperative results, type of surgery (primary anastomosis or end colostomy), length of hospital stay, presence of perforation, and benign vs. malignant etiologies were investigated. Morbidity was defined as a Clavien-Dindo (CD) grade III or higher complication.

Ethical approval for this study was obtained from University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital Scientific Research Ethics Committee (decision number: 166, date: 07.08.2024). Informed consent was obtained from all the patients participating in the study, which was registered with the Clinical Trials Protocol Registration and Results System (Trial ID: NCT06958900, registration date: 07.04.2025). The study also adhered to the STROBE Statement and complied with the principles of the World Medical Association's Declaration of Helsinki.

Statistical Analysis

Univariate analyses were employed to evaluate risk factors for morbidity and mortality. For univariate analysis of morbidity, patients were divided into two subgroups: those who experienced morbidity and those who did not. Following this initial categorisation, a comprehensive comparison was conducted between the two subgroups across all variables. A similar approach was adopted for univariate mortality analysis, with patients once again divided into two subgroups: those who succumbed within the first 90 days postoperatively and those who survived. These mortality and survival subgroups were then investigated across all variables. The

appropriate statistical tests employed were Pearson chi-square, the independent-samples t-test, and Mann-Whitney U test. The Kolmogorov-Smirnov test was utilised to assess the normality of the variables. For variables with a normal distribution, the mean $\pm$ standard deviation was reported. Categorical variables were expressed as numbers and percentages. Variables with non-normal distributions were reported as medians and interquartile ranges (25th-75th percentiles). The effects of risk factors on morbidity and mortality were expressed as odds ratios with 95% confidence intervals. The statistical significance level was set at 0.05. After univariate analyses, multivariable logistic regression tests were performed. The data were compiled and analysed using SPSS for Windows, version 29.0 (SPSS, Chicago, IL, USA).

Results

The study included 76 patients, of whom 46 (60.5%) were male. The morbidity rate was 27.6%, and the 90-day mortality rate was 15.7%. The mean age was 61.5 years. The most common cause was colorectal carcinoma (n=46, 61%) (Figure 1); diverticulitis was the most common benign etiology (Table 1). Perforation was observed in 32.8% of patients (n=25), while obstruction was detected in 38.1% (n=29) (Table 1).

The Hartmann procedure was preferred for 41 patients (53.9%). Primary anastomosis was performed in 46% of patients (n=35). The procedures were: extended left hemicolectomy (n=4), left hemicolectomy (n=3), anterior resection (n=22), and low anterior resection (n=6). A diverting loop ileostomy was performed in 20% of patients (n=7). The anastomotic leak rate was 11% (n=4).

Two patients underwent laparoscopic surgery; one of these was converted to open surgery to complete the procedure. All other procedures were performed using conventional open surgery techniques. The overall complication rate was 35.5% (n=27). Six patients experienced CD Grade II complications [surgical site infection (n=4), pneumonia (n=2)].

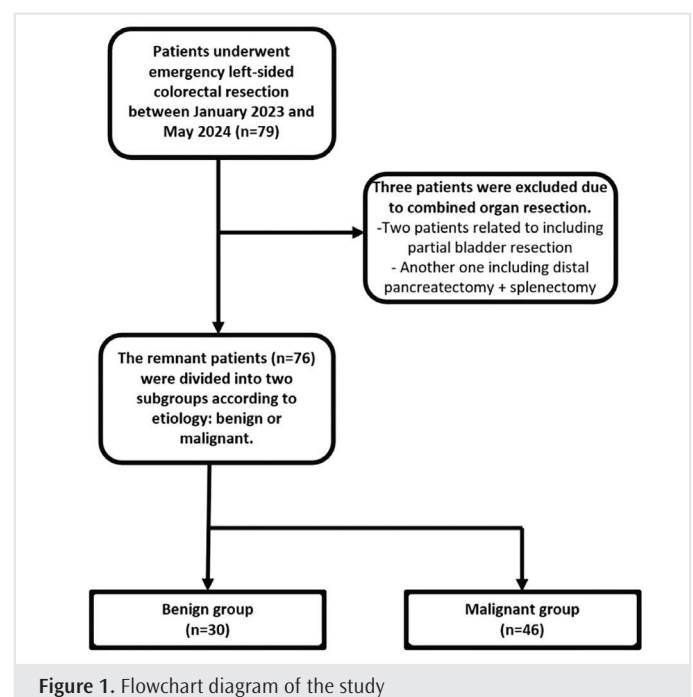


Figure 1. Flowchart diagram of the study

CD Grade III complications were detected in 9 patients: anastomotic leak (n=4), evisceration (n=3), and stoma retraction with intra-abdominal abscess (n=2). Two cases of anastomotic leakage were managed non-operatively using endoscopic interventions. Twelve patients died within the first 90 days after surgery, primarily due to sepsis related to their late arrival at the hospital (CD Grade 5).

By tumor stage, the stage 3 group included the most patients; tumor characteristics are presented in Supplementary Table 1. The majority of colorectal cancer patients (76%) were Grade II (Supplementary Table 1).

In both univariate and multivariable analyses, malignancy was not associated with morbidity: $p=0.879$ and $p=0.711$, respectively (Table 2),

and $p=0.416$ and $p=0.453$, respectively (Table 3). The type of surgery was significantly related to morbidity in the univariate analysis; however, this was not supported by the multivariable logistic regression analysis. The impact of the type of surgery was found to be non-significant in both univariate and multivariable mortality analyses.

The duration of the operation was not significantly associated with either morbidity ($p=0.369$) (Table 2) or mortality ($p=0.932$) (Table 3). Mortality was not related to the type of surgery ($p=0.111$). Length of hospital stay did not change significantly between groups ($p=0.208$).

Both univariate and multivariable analyses revealed a significant relationship between perforation and morbidity ($p=0.025$ and $p=0.027$, respectively). Similarly, univariate and multivariable logistic regression analyses for mortality showed that perforation was significantly associated with outcomes ($p=0.007$ and $p=0.015$, respectively).

Discussion

In the present study, colorectal cancer was identified as the most common indication for emergency colorectal resections, a finding that aligns with the findings of other studies (5,12). However, malignancy was not found to be associated with statistically different rates of morbidity and mortality in both univariate and multivariable analyses. Although cancer itself is a more complicated disease, it did not result in worse perioperative outcomes. Although the characterization of “benign” may suggest a simpler disease presentation to some, inflammatory conditions that follow many benign etiologies are closely related to patient morbidity and mortality. This “worsening” inflammatory background may play a role in balancing possible negative outcomes because of the effects of the extensive dissection required for oncological resection and of findings secondary to obstructive symptoms, which may be more frequently encountered in the cancer subgroup. However postoperative course following emergency colorectal resection may be influenced more by the severity of acute illness, than by the complexity of the underlying disease process itself and its surgical requirements (13). Patients presenting with perforation, sepsis, diffuse peritoneal contamination, or hemodynamic compromise are exposed to substantial operative risk, regardless of whether the underlying pathology is benign

Table 1. Baseline characteristics of patients

Variable	n (%)
Age, mean $\pm$ SD	61.5 $\pm$ 14.5
Sex	
Male	46 (60.5)
Female	30 (39.4)
Charlson comorbidity index, median (IQR ²⁵⁻⁷⁵)	2 (1-4)
Duration of operation (min), median (IQR ²⁵⁻⁷⁵)	120 (100-172)
Perforation	25 (32.8)
Length of hospital stay (days), median (IQR ²⁵⁻⁷⁵)	10 (8.2-15.7)
Type of surgery	
Resection + end stoma	41 (53.9)
Resection + anastomosis	35 (46.0)
Etiology	
Malignancy	46 (61.3)
Diverticulitis	15 (19.7)
Volvulus	12 (15.7)
Iatrogenic	2 (2.6)
Trauma	1 (1.3)
Stage of malignancy patients	
I	1 (2.1)
II	16 (34.7)
III	18 (39.1)
IV	11 (23.9)

SD: Standard deviation, IQR: Interquartile range

Table 2. Univariate analyses and multivariable logistic regression for morbidity

Variable	No-morbidity (n=55)	Morbidity (n=21)	Univariate p value	Multivariable p value	OR (CI 95%)
Age mean $\pm$ SD	61.7 $\pm$ 13.7	61.0 $\pm$ 16.8	0.847	0.818	0.99 (0.95-1.04)
Sex					
Male	35 (63.6)	11 (52.4)	0.369	0.535	1.41 (0.47-4.20)
Female	20 (36.4)	10 (47.6)			
Charlson comorbidity index median (IQR ²⁵⁻⁷⁵)	2 (2)	2 (5)	0.604		
Duration of operation (min) median (IQR ²⁵⁻⁷⁵)	130 (80)	120 (48)	0.369	0.243	0.99 (0.98-1.01)
Perforation	14 (26.4)	11 (52.4)	0.025	0.027	3.60 (1.15-11.26)
Length of hospital stay (days) median (IQR ²⁵⁻⁷⁵)	10 (6)	10 (8)	0.604		
Type of surgery					
Resection + end stoma	26 (47.3)	15 (71.4)	0.046	0.947	0.96 (0.30-3.01)
Resection + anastomosis	29 (52.7)	6 (28.6)			
Malignancy	33 (60)	13 (61.9)	0.879	0.711	1.25 (0.37-4.16)

CI: Confidence interval, IQR: Interquartile range, OR: Odds ratio, SD: Standard deviation

Table 3. Univariate analyses and multivariable logistic regression for mortality

Variable	No-mortality (n=64)	Mortality (n=12)	Univariate p value	Multivariable p value	OR (95% CI)
Age mean $\pm$ SD	61.2 $\pm$ 13.9	63.0 $\pm$ 17.6	0.688	0.422	1.02 (0.97-1.07)
Sex					
Male	39 (60.9)	7 (58.3)	0.866	0.867	0.88 (0.22-3.51)
Female	25 (39.1)	5 (41.7)			
Charlson comorbidity index median (IQR ²⁵⁻⁷⁵)	2 (2)	3.5 (5)	0.236		
Duration of operation (min) median (IQR ²⁵⁻⁷⁵)	120 (100-180)	135 (105-172)	0.932	0.921	1.00 (0.98-1.01)
Perforation	17 (26.4)	8 (66.7)	0.007	0.015	5.07 (1.40-23.8)
Length of hospital stay (days) median (IQR ²⁵⁻⁷⁵)	10.5 (7)	10 (12)	0.208		
Type of surgery					
Resection + end stoma	32 (50)	9 (75)	0.111	0.974	1.02 (0.24-4.36)
Resection + anastomosis	32 (50)	3 (25)			
Malignancy	40 (62.5)	6 (50)	0.416	0.453	0.57 (0.13-2.44)

CI: Confidence interval, IQR: Interquartile range, OR: Odds ratio, SD: Standard deviation

or malignant. Our finding that perforation remained an independent predictor of both morbidity and mortality supports this interpretation. In another studies by Ellensen et al. (3) and Leong et al. (14), similarly to our findings, morbidity and mortality rates did not differ significantly depending on whether the aetiology was benign or malignant. In the study by Leong et al. (14), this was interpreted as a contribution of much greater involvement on the part of a consultant surgeon to the surgery, in the event of challenging operations. Despite the presence of similar outcomes (15-17), there remains other investigators who have reported worse outcomes among patients with colorectal malignancy, in the emergency colorectal surgery (4).

Our study found that perforation development was the most influential factor on morbidity and mortality among the variables and literature data supports this finding (7,18). Colonic perforation can result in bacterial translocation and faecal contamination of the peritoneal cavity. This triggers a profound systemic inflammatory response that can rapidly progress to sepsis, septic shock and multiple organ dysfunction syndromes (19). In addition to the physiological burden imposed by sepsis itself, perforation is often associated with delayed presentation, severe disturbances of fluid and electrolyte balance, and impaired nutritional status. These factors can all negatively impact postoperative recovery. Furthermore, extensive intra-abdominal contamination often necessitates more complex surgical procedures and may limit the feasibility of primary anastomosis, thereby influencing operative strategy and postoperative outcomes (20,21). Taken together, these factors may explain why perforation is a consistent predictor of mortality in emergency colorectal surgery. In the study conducted by Leong et al. (14), the presence of perforation was observed in 80% of postoperative deaths, while in our study, this rate was detected at 50% (n=6). The perforation rate in our study was 32%, which is similar to the 31% rate reported in another study of emergency colorectal surgery (22). However, the WSES guidelines state that the perforation rate in colorectal cancer is 20% (7). The higher rate of perforation in patients with benign disease is likely related to complicated diverticulitis. That the prognostic importance of perforation exceeds that of malignancy suggests that the

severity of the acute surgical presentation may outweigh disease-specific factors in determining short-term outcomes. This is consistent with previous reports indicating that physiological status and acute clinical deterioration are stronger predictors of outcomes following emergency colorectal surgery, than the underlying diagnosis (23,24).

Emergency colorectal surgery can be performed for etiologies such as malignant or benign such as diverticulitis, volvulus, etc. and the outcome may depend on many factors such as comorbidities and preferred surgical approach (22,25). As previously mentioned, a significant proportion of colorectal surgeries performed in emergency condition achieve a high morbidity and mortality (7,15). Notwithstanding this, a significant percentage of surgeons in a Delphi process endorsed the benefit of formal cancer resection in emergencies for improving disease-free and overall survival. Although the strengthening of antibiotic options and the increase in centers and equipment, where patients can be closely monitored, have increased the possibility of conservative follow-up in benign diseases such as ischemic colitis and diverticulitis, surgery continues to play an inevitable role for many benign patients in whom serious peritoneal contamination occurs (25).

The overall morbidity rate was 27.6%, and the 90-day mortality rate was 15.7% in our study, while postoperative morbidity and mortality rates were found to be 48% and 15.3%, respectively, in another multicenter study (10). Similar rates have been reported in other studies (26). In general, emergency colorectal surgery represents a high-risk for a patient (3). Various factors have been identified as contributing to increased morbidity and mortality in emergency colorectal surgery. These include age and co-morbidities, then the preoperative health status, the surgeon who performs the surgery, the type of surgery, and the time at which the surgery is performed are some factors mentioned as the leading causes (2). Insufficient time for patient optimisation and lack of bowel preparation have also been identified as contributing factors to high morbidity in emergency colorectal surgery. In this study, the anastomotic leak rate was 11% (n=4). This outcome is consistent with that of a large multicenter trial that included patients who underwent colorectal resection (27).

In the present study, age was not found to significantly change morbidity and mortality in multivariable analyses, which is similar to other reports (1,14,15,25). Indeed, one point that has been emphasized frequently is that chronological age alone is not a sufficient predictor of mortality and morbidity; age-related changes across multiple physiological systems provide more meaningful information (13). The lack of an independent association between chronological age and adverse outcomes further supports the notion that physiological reserve and acute clinical status may be more relevant than demographic characteristics when assessing operative risk. Physiological reserve clearly illustrates that chronological age alone is not an independent factor apart from other causes and effects. This concept, defined as the organism's ability to cope with stress factors, should be considered as a patient characteristic that we do not have the opportunity to improve prior to emergency surgery (28). Male patients constituted the majority in our study, as in a Norwegian study (3), with a contrasting finding in a similar Korean study (15). Sex was not found to be directly associated with morbidity or mortality in either univariate or multivariable analyses results in our study, similar to some other reports in the literature (29,30).

Anastomotic leakage remains one of the most dreaded complications following colorectal surgery and is associated with substantial increases in postoperative morbidity, mortality, length of hospital stay, reoperation rates and healthcare costs (31). The risk may be even greater in emergency settings, where patients frequently present with bowel obstruction, perforation, peritoneal contamination, sepsis, malnutrition and physiological derangement (32). These factors can impair tissue perfusion and healing, thereby increasing the likelihood of anastomotic failure. Although the anastomotic leak rate in the present study was comparable to rates reported in large multicentre series (32), the potential consequences of leakage often influence intraoperative decision-making and contribute to a more cautious approach regarding primary anastomosis. Recent studies suggest that, in carefully selected patients with adequate physiological reserve and limited contamination, primary anastomosis can be performed safely, even in emergency situations (33). Nevertheless, surgeons must balance the benefits of avoiding a likely permanent stoma against the potentially devastating consequences of an anastomotic leak. This dilemma continues to represent one of the most challenging aspects of emergency colorectal surgery and highlights the importance of individualized patient assessment and risk stratification (34).

Although the majority of patients in our study underwent the Hartmann procedure, an anastomosis was performed in almost half of the cohort (46%). This rate is compatible with other literature examples (25,35). However, this finding may be affected by a relatively high perforation rate at initial presentation. It should be noted that including only left-sided colorectal diseases in our study is an obvious contributing factor to the preference for the Hartmann procedure in this context. It is also noted as beneficial in terms of preventing delay to systemic therapy, particularly among metastatic patients (35). The possibility that critically ill patients may be more severely affected and that life-threatening conditions may occur following a potential anastomotic leak, is compelling surgeons to contemplate their interventions in a

more scrutinized and protective manner (27). However, the decision to perform a Hartmann procedure should be made with caution and for in particular in patients with a clear indication, such as those with haemodynamic instability, multiple comorbidities or sepsis (36). It is noteworthy that fewer than half of patients may be eligible to eventually undergo a reversal of the colostomy (37). Additional risks of these stoma reversal procedures must also be kept in mind (7,35,38-40).

Study Limitations

The retrospective nature of the study constitutes its primary limitation. The relatively small number of patients constitutes another limitation, particularly for establishing a multivariable logistic regression model. The limited number of mortality events relative to the number of variables included in the multivariable model may have increased the risk of overfitting and thus reduced the reliability of the estimated associations. For these reasons, the results should be interpreted with caution. If qualifying details for the surgeon are not included, the surgeon's status as a trainee, a registrar, or a consultant can also be mentioned. Nevertheless, the emphasis on a problem associated with high morbidity, mortality, and significant costs enhances the significance of the content. Studies on this topic, which focus on one of the most demanding patient groups from the perspectives of the surgeon, the surgical team, and the entire emergency department, represent significant steps towards improving efficiency.

Conclusion

This study examined emergency colorectal surgeries performed on 76 patients. The total morbidity rate was found to be 27.6%, while the 90-day mortality rate was found to be 15.7%. Colorectal cancer was the most common malignant cause; diverticulitis was the most common benign cause. The study found no association between malignant etiology and morbidity or mortality. The presence of perforation was associated with morbidity and mortality in both univariate and multivariable analyses. These findings suggest that short-term outcomes after emergency colorectal resection are driven more by acute physiological derangement, particularly perforation, than by the underlying pathology itself. While the Hartmann procedure was preferred, a significant proportion of patients underwent an anastomosis. The study once again revealed the high-risk nature of emergency colorectal surgery. Randomised controlled studies involving larger, multicentric patient groups in our country would provide stronger evidence to determine the factors.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital Scientific Research Ethics Committee (decision number: 166, date: 07.08.2024). The study adhered to the STROBE Statement and complied with the principles of the World Medical Association's Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all the patients participating in the study, which was registered with the Clinical

Trials Protocol Registration and Results System (Trial ID: NCT06958900, registration date: 07.04.2025).

Footnotes

Authorship Contributions: Surgical and Medical Practices - Y.M.K., H.A., H.Y., E.S., S.Y., A.K.; Concept - Y.M.K., H.Y., E.S., S.Y.; Design - Y.M.K., H.A., E.S., A.K.; Data Collection or Processing - Y.M.K., H.A., H.Y.; Analysis or Interpretation - Y.M.K., H.A., H.Y., E.S., S.Y., A.K.; Literature Search - Y.M.K., H.A., H.Y., E.S., S.Y., A.K.; Writing - Y.M.K., H.A., H.Y., E.S., S.Y., A.K.

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Supplementary Table Link: <https://d2v96fxpocvxx.cloudfront.net/bfe6b059-1982-481c-8e2f-073cbc0b054a/content-images/cb4fe15d-f3c4-4a06-8c78-42ede770eb3b.pdf>

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Evaluation of Patient Numbers and Hospital Dynamics After The Establishment of The Oncology Follow-Up Unit

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ABSTRACT

Introduction: This retrospective study aimed to evaluate the contribution of the oncology follow-up unit to the follow-up of cancer patients and its impact on hospital treatment rates and overall survival (OS).

Methods: This study was conducted on 5,042 patients diagnosed with any kind of cancer via pathology between January 2022 and February 2025. Data were compared between the before establishment period (January 2022-July 2023) and the after establishment period (August 2023-February 2025) of the oncology follow-up unit. The patient characteristics and follow-up data were obtained from patients' database.

Results: A total of 5042 cancer patients were included in this study. After the unit's establishment, the number of patients receiving treatment at our hospital increased from 2,053 to 2,989 ($p=0.001$). The rate of patients lost to follow-up or went to other oncology centers for treatment decreased from 18.99% to 11.43% ($p=0.001$). Furthermore, comparison of OS before and after the establishment of the oncology follow-up unit showed a significant increase in median OS from 12 months to 14 months ($p=0.002$).

Conclusion: The establishment of an oncology follow-up unit has made the follow-up process more patient-centred and appropriate in terms of preventing patients' loss from follow up. This was associated with significantly improved patient retention, reduced loss to follow-up, and improved OS.

Keywords: Hospital administration, cancer, survival

Introduction

Ischemic heart disease is the leading cause of death worldwide, accounting for approximately 13% of global deaths. Oncological diseases rank second and are responsible for 12% of global mortality. According to the Global Cancer Incidence, Mortality and Prevalence report, 20 million new cancer cases worldwide and 10 million cancer deaths globally, in 2022 (1). With rising cancer rates and continuously evolving cancer treatment methods in recent years, the need for structured follow-up and treatment care has increased significantly in recent decades (2). Research in this field examines various aspects such as how oncology clinics are organized and staffed, how they inform and manage treatment methods for patients diagnosed with cancer, the impact on patients' quality of life and satisfaction, and cost-effectiveness compared to traditional follow-up approaches (3). Therefore, making

appropriate decisions regarding treatment and follow-up after a cancer diagnosis is essential.

The initiation of the Healthcare Information and Management Systems Society (<https://www.himss.org/maturity-models/>) process at İstanbul Training and Research Hospital in 2022 revealed a lack of guidance regarding the department to which cancer patients should be referred and the factors influencing treatment and follow-up decisions. This process enabled analysis of the reasons these patients dropped out of follow-up. This process has enabled improved monitoring and evaluation of care pathways for patients diagnosed with cancer.

Our study aimed to ensure continuity in the post-diagnosis treatment planning, implementation, and follow-up for patients diagnosed with cancer.



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Methods

A total of 5,042 patients who received a cancer diagnosis from the pathology department between January 1, 2022, and February 28, 2025 were included in the study. The timeline for data comparison was set based on the implementation of the Oncology Follow-up Unit, with January 2022 to July 2023 defined as the pre-implementation period and August 2023 to February 2025 as the post-implementation period (Figure 1). The numbers of patients on follow-up and those lost to follow-up were compared across these periods. Patients' data obtained from the Probel Data Analysis Application (Hospital Data Software System) were recorded in Microsoft Excel.

The oncology follow-up unit consists of three physicians (one oncological surgeon and two clinical radiation oncologists) and one nurse. Throughout this process, the nurse plays a key role in communicating treatment decisions to patients and their relatives and in accompanying patients during the relevant stages of care. Every patient diagnosed with cancer is assessed by the oncology follow-up unit, whose responsibilities include referring patients to multidisciplinary tumor boards and informing them about treatment decisions. Based on the oncology board's decisions, patients are referred to the relevant clinical departments.

The inclusion criteria of the study were (1) presence of histopathological proven cancer (2) patient diagnosed at the age of ≥ 18 years (3) presence of hospital records including treatment parameters and follow-up information. The exclusion criterion of the study was the presence of inconclusive histopathological results. The study was approved by the Ethics Committee of University of Health Sciences Türkiye, İstanbul Training and Research Hospital, (approval number: 216, approval date: 26.06.2026). Informed consent was not obtained because of the retrospective nature of the study.

Outcomes and Follow-up

For the purposes of this study, loss to follow-up was defined as patients with a pathologically confirmed primary cancer diagnosed at our hospital who declined all oncological treatment (surgery, radiotherapy, or chemotherapy) and did not attend subsequent oncology follow-up visits at our hospital, excluding patients whose follow-up was interrupted due to death. The expected primary endpoint of this study was to ensure that, with the establishment of the oncology follow-up unit, cancer patients could continue their entire treatment at our hospital. The secondary endpoint was improvement in survival. Overall survival (OS) was defined as the time from cancer diagnosis to death.

Statistical Analysis

Normality of the variables was examined using the Kolmogorov-Smirnov test. Mean, standard deviation, and median values were used to present descriptive analyses. Categorical variables were compared using the Pearson chi-square test. Age was compared between the groups using the independent-samples student's t-test. The OS was examined by Kaplan-Meier analysis. All analyses were performed a 95% confidence level and a 0.05 significance level using SPSS 26.0 (SPSS Inc., Chicago, IL, USA) for Windows.

Results

A total of 5042 cancer patients were included in the study. The baseline clinicopathological characteristics of the patients before and after the establishment of the oncology follow-up unit are summarized in Table 1.

The number of patients who received treatment and follow-up care at our hospital increased significantly, from 2,053 before to 2,989 after the establishment of the oncology follow-up unit ($p=0.001$).

The median age at the time of cancer diagnosis was 63.43 ± 14.17 year before, while it was found to be 62.80 ± 13.73 year after the establishment of oncology follow-up unit ($p=0.001$).

Comparative analyses showed that the sex distribution was similar before and after the establishment of the oncology follow-up unit. Female patients accounted for 44.7% (917/2,053) and 45.3% (1,353/2,989) of the cohorts before and after the unit was established, respectively, while male patients accounted for 55.3% (1,136/2,053) and 54.7% (1,636/2,989). The difference was not statistically significant ($p \geq 0.05$).

Comparing all cancer types (including head and neck, upper gastrointestinal, lower gastrointestinal, gynecological, urological, skin, soft tissue, and breast cancers) before and after the establishment of the Oncology Follow-up Unit revealed an increase in patient numbers for all cancer types. This increase was statistically significant ($p=0.001$).

During the 18-month period before the establishment of the oncology follow-up unit, 1,356 (66.3%) patients were alive, while 688 (33.7%) had died. After the unit was established, 2,269 (76.1%) patients were alive and 711 (23.9%) were deceased. Compared with the pre-establishment period, the post-establishment period showed a significantly higher proportion of surviving patients and a lower proportion of deaths ($p=0.001$).

We also compared the proportion of patients who were lost to follow-up or who sought treatment at other oncology centers. Before the establishment of the oncology follow-up unit, 18.99% of patients were

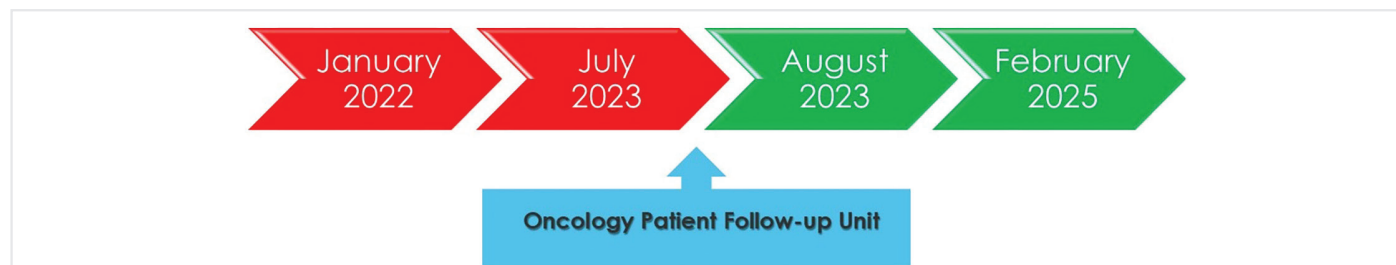


Figure 1. Time to set up the oncology follow-up unit (missing data n=9 for each group)

lost to follow-up or were transferred to other oncology centers for treatment. After the unit was established, this proportion decreased significantly to 11.43% (Table 2, $p=0.001$).

OS was evaluated using Kaplan-Meier analysis (Figure 2). A statistically significant difference in OS was observed between the two groups (log-rank $p=0.002$). Patients treated after establishment of the oncology follow-up unit had significantly longer OS than those treated before its establishment. The median OS increased from 12 months before the unit's establishment to 14 months afterward.

Discussion

In this study, we evaluated the impact of establishing an oncology follow-up unit on patient volume, clinicopathological characteristics, follow-up outcomes, and survival. We also investigated whether the implementation of the unit reduced the number of patients who were lost to follow-up or who sought treatment at other oncology centers.

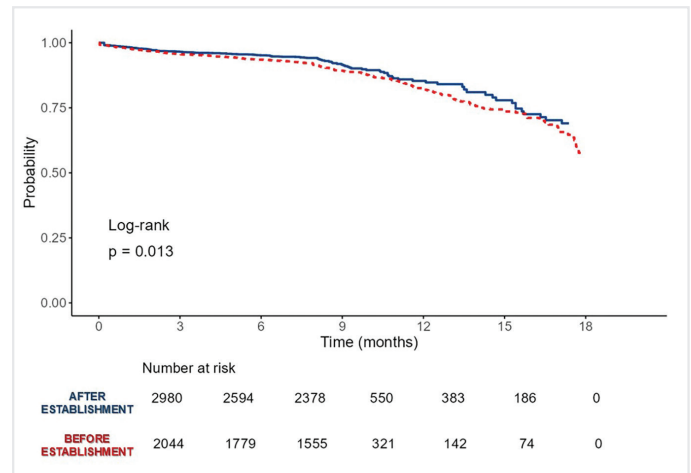


Figure 2. Kaplan-Meier curve for overall survival

Table 1. The baseline clinicopathological parameters of patients

	Before establishment of unit n=2053 n (%)	After establishment of unit n=2989 n (%)	p value	Change
Age (years)	63.43±14.17	62.80±13.73	0.001**	↓ Decreased
Sex				
• Female	917 (44.67%)	1353 (45.29%)	N.S.*	↑ Increased
• Male	1136 (55.33%)	1636 (54.71%)		↓ Decreased
Location of cancer			0.001*	
• Urinary system	478 (23.29%)	666 (22.29%)		↓ Decreased
• Breast	400 (19.50%)	605 (20.24%)		↑ Increased
• Lower GIS	233 (11.35%)	360 (12.06%)		↑ Increased
• Upper GIS	191 (9.30%)	302 (10.11%)		↑ Increased
• Skin	128 (6.23%)	201 (6.73%)		↑ Increased
• Hematological	230 (11.20%)	192 (6.42%)		↓ Decreased
• Head and neck	88 (4.29%)	147 (4.92%)		↑ Increased
• Thyroid	98 (2.44%)	133 (4.42%)		↑ Increased
• Gynecological	50 (4.77%)	132 (4.45%)		↓ Decreased
• Lung	31 (1.51%)	100 (3.35%)		↑ Increased
• Brain	54 (2.63%)	49 (1.64%)		↓ Decreased
• Soft Tissue	11 (33.3%)	22 (66.7%)		↑ Increased
• Multiple focus	16 (0.54%)	15 (0.74%)		↓ Decreased
• Unknown	45 (2.19%)	65 (2.18%)		↓ Decreased
Alive	1356 (66.34%)	2269 (76.14%)	0.001*	↑ Increased
Exitus	688 (33.65%)	711 (23.86%)		↓ Decreased

*chi-square test, **student-t test. GIS: Gastrointestinal system, N.S.: Not significant

Table 2. Comparison of the number of patients under follow-up and those lost to follow-up before and after the establishment of the oncology follow-up unit, including monthly median loss-to-follow-up rates

	Number of patients remained on follow-up	Number of patients lost to follow-up	Median rate of loss per month*
Before establishment of the unit January 2022-July 2023	2053	717	18.99%
After establishment of the unit August 2023-February 2025	2989	555	11.43%

*Mann-Whitney U test $p=0.001$

We found that both the number of patients receiving cancer treatment and the duration of follow-up increased in the 18 months after the unit's establishment compared with the preceding 18 months. By contrast, the proportion of patients lost to follow-up or transferred to other oncology centers for treatment decreased significantly. These findings suggest that the oncology follow-up unit improved continuity of care by facilitating timely access to oncology services, enhancing patient retention, and ensuring that patients receive appropriate treatment and follow-up at the right time.

In the literature, the median age at cancer diagnosis globally is around 65-67 years, with incidence rising sharply after age 50 (4). In our study, the age at diagnosis before and after establishment was in accordance with the literature.

One of the most important indicators of the effectiveness of an oncology follow-up unit is its ability to improve continuity of care by increasing the number of patients who remain under regular follow-up. In our study, patient retention improved significantly following the establishment of the oncology follow-up unit. The number of patients receiving treatment and follow-up at our institution increased from 2,053 to 2,989, while the proportion of patients who were lost to follow-up or transferred to other oncology centers for treatment decreased significantly from 18.99% to 11.43%.

Treatment decisions and monitoring of cancer patients have traditionally been carried out by cancer specialists (i.e., medical oncologists, surgical oncologists, radiation oncologists, and hematologists) (5). In addition, a nurse has been added to our oncology follow-up unit as a "clinical anchor" between patients and their families for treatment and follow-up. Oncology follow-up units and oncology nurses, by streamlining the transition from the pathology department to multidisciplinary tumor boards, function as "clinical anchors," ensuring that the hospital's diagnostic capabilities are matched by its therapeutic retention. The pivotal role of the oncology nurse within this unit cannot be overstated. Literature consistently shows that patient-centered communication reduces "decisional conflict" in oncology. The pivotal role of the oncology nurse as a consistent liaison likely contributed to this improvement, consistent with reports that navigation and nurse-led coordination reduce treatment defaulter rates and improve continuity (6,7). Literature supports oncology follow-up systems effect: structured follow-up and rapid-access oncology services divert care away from emergency departments and inpatient wards, improving throughput and preserving capacity (8,9).

The improvement in OS in our cohort—from 12 to 14 months—could be explained by a reduction in time to treatment, a factor frequently highlighted as influencing oncology outcomes. While delays in initiating chemotherapy, radiotherapy, or surgery have been reported as independent risk factors for mortality, it remains possible that timely follow up contributed to fewer readmissions and more efficient use of bed capacity, as suggested in the literature (10-13). Our study demonstrated that effective patient follow-up was associated with improved prognostic outcomes, as reflected by an increase in the proportion of surviving patients from 66.3% to 76.1% and a corresponding decrease in mortality. Furthermore, the median

OS improved from 12 months before the establishment of the oncology follow-up unit to 14 months after its implementation.

Comparative study designs are recommended to strengthen the assessment (12,14). Our single-center study provides direct evidence of improved patient retention and survival; future studies should extend the assessment to include long-term quality of life and economic sustainability.

Study Limitations

Despite the positive outcomes, this study has several limitations. First, the 18-month pre- and post-establishment follow-up periods may be insufficient to provide reliable long-term survival estimates. Longer follow-up periods, such as 3-, 5-, and 10-year assessments, are more clinically meaningful for oncology patients. Second, the patient population evaluated by the oncology follow-up unit was heterogeneous, including patients with diverse cancer types (e.g., solid tumors and hematological malignancies), which could have introduced variability in clinical outcomes. Third, the retrospective design of the study and the absence of key prognostic factors, particularly disease stage, limited the ability to conduct more accurate prognostic evaluations and may have affected the interpretation of survival outcomes, precluding causal inference.

Conclusion

According to the study findings and the most recent available data, the implementation of an oncology follow-up unit was associated with a significant increase in the number of patients maintained under oncological surveillance, prolonged survival, and a reduction in loss-to-follow-up rates. As cancer incidence continues to rise and therapeutic approaches become increasingly complex, the role of dedicated oncology follow-up units has gained substantial importance in recent decades. These units address the growing need for personalized, structured, and continuous care throughout the cancer treatment trajectory.

The establishment of the oncology follow-up unit represents a valuable healthcare intervention that effectively addresses the "guidance gap" frequently encountered after a cancer diagnosis. By enhancing continuity of care, improving patient retention, reducing loss to follow-up, and contributing to improved OS, this model provides a potential framework for secondary and tertiary healthcare institutions seeking to optimize oncology care delivery.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Türkiye, İstanbul Training and Research Hospital, (approval number: 216, approval date: 26.06.2026).

Informed Consent: Informed consent was not obtained because of the retrospective nature of the study.

Footnotes

Authorship Contributions: Surgical and Medical Practices - M.Ş., G.Ü.; Concept - Y.Ö.K., M.Ş., G.Ü., M.T.; Design - B.Y., Ç.U.A., G.Ü., M.T.; Data Collection or Processing - Y.Ö.K., M.Ş., S.Z.S.; Analysis or Interpretation

- B.Y., Ç.U.A., S.Z.S., M.T.; Literature Search - B.Y., Ç.U.A., Y.Ö.K., S.Z.S.; Writing - B.Y.

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Prediction of Radiology Appointment Cancellations Using Machine Learning Models: A Comparison of City and State Hospitals

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ABSTRACT

Introduction: Although the Central Physician Appointment System (MHRS) implemented in Türkiye in 2010 improved access to healthcare services, patients cannot directly schedule radiological imaging appointments. This study aims to predict the likelihood of radiology appointment cancellations at city and state hospitals using machine learning algorithms.

Methods: Radiology appointment data recorded between January 2021 and June 2024 at a city hospital and a state hospital were analyzed. The dataset contained more than 3 million rows, with independent variables including age, gender, International Classification of Diseases-10 diagnosis codes, and imaging type. Logistic regression, random forest, and support vector machine (SVM) models were developed and evaluated using accuracy, precision, recall, and F1-score.

Results: Appointment cancellations were less frequent at the city hospital than at the state hospital. Logistic regression achieved 82% accuracy and demonstrated the best performance among the conventional models. Following additional validation procedures with different train-test splits, random forest and SVM achieved accuracies of approximately 97.66% and 97.69%, respectively. Higher cancellation rates were observed among patients aged 18-30 and for non-urgent procedures. Most cancellations occurred either 3-5 days before the scheduled date or on the same day.

Conclusion: Predicting radiology appointment cancellations with machine learning supports efficient use of hospital resources. Developing tailored strategies based on hospital type can improve capacity management, patient satisfaction, and overall service quality.

Keywords: Appointment system, health informatics, healthcare system, prediction, machine learning models

Introduction

Digital transformation enhances the quality of healthcare services and has become an essential component of modern healthcare management. Compared to traditional appointment scheduling methods, online appointment systems provide faster and more practical solutions for both patients and healthcare providers (1,2). Studies indicate that web-based services are increasingly preferred over conventional methods. Traditional appointment systems generally involve direct interaction with scheduling personnel via phone or in person. While these methods offer flexibility, they are time-consuming and constrained by staff availability. On the other hand, online appointment systems automate scheduling and integrate the process into a single accessible platform. This not only reduces the workload on administrative staff but also minimizes patients' waiting times (3).

Online appointment systems are widely used in healthcare to improve scheduling coordination and facilitate patient access to services.

Compared with traditional appointment methods, these systems may reduce administrative workload, support more efficient resource utilization, and improve operational workflow through centralized scheduling and automated processes (4-7).

Recent studies have demonstrated that machine learning models can effectively predict radiology appointment no-shows with moderate to high accuracy, typically achieving area under the curve (AUC) values ranging from approximately 0.75 to 0.93 depending on the dataset and clinical context (8-13).

However, evidence also suggests that model performance may vary across healthcare settings and often declines when transitioning from retrospective analyses to real-world deployment, highlighting the need for context-specific evaluation and continuous recalibration (8).

Prior research consistently identifies several key predictors of appointment cancellations, including previous no-show behavior,



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scheduling characteristics such as lead time and appointment timing, imaging modality and exam type, and socioeconomic factors such as insurance status and access to care (9-13). These findings suggest that both patient-related and system-level variables play a critical role in shaping attendance behavior.

The adoption of patient-centered applications has been shown to reduce appointment no-show rates. Allowing patients control over appointment scheduling enhances their commitment to the system. However, online appointment systems are not equally accessible to all demographic groups (8). Particularly, older adults, those with lower levels of education and income, and those residing in rural areas often face challenges in effectively utilizing digital healthcare services. Consequently, many still rely on phone-based appointment systems (9).

Managing waiting times in healthcare is a critical issue that affects patient satisfaction and access to care. The increasing demand for medical services, coupled with the limitations of traditional appointment scheduling methods, has made waiting times a major concern for both patients and healthcare providers (10). The implementation of technology, particularly online appointment systems, has introduced new ways to improve patient access and reduce waiting times in hospitals. The advantage of leveraging online appointment systems lies in their potential to streamline operations, enhance the efficiency of healthcare service delivery, and improve overall patient experience (11).

Globally, various countries have implemented digital appointment management platforms to facilitate patient access to healthcare services and improve scheduling efficiency. Examples include Türkiye's Central Physician Appointment System (MHRS), the United Kingdom's NHS online services, and widely used patient portal systems such as MyChart and Zocdoc (12-19). These platforms primarily serve as operational tools for appointment coordination and digital access management within healthcare systems.

It is well established that online appointment systems significantly reduce patient waiting times (14). These systems allow patients to efficiently schedule and manage doctor appointments while also enabling healthcare providers to better organize patient flow. Previous studies have shown that digital appointment systems may contribute to improved scheduling coordination, reduced administrative burden, and more efficient management of healthcare resources (14-17). These systems are particularly valuable in high-demand clinical settings where workflow optimization and appointment management are critical for operational efficiency.

A study conducted by AlHajeri et al. (20) in 2021 demonstrated that the adoption of online patient appointment systems significantly improved the quality of healthcare services. These findings align with other studies reporting a decrease in average patient waiting times (14). For instance, a study conducted by Maeder and Martin-Sanchez in 2012 highlighted that web self-service applications in primary healthcare settings led to improved patient perceptions and reduced waiting times (18).

Previous studies have suggested that digital appointment systems may improve scheduling coordination and operational workflow in healthcare settings (20,21). The study, conducted across multiple

geographical regions, further supported the benefits of such systems. Cao et al. (22) also demonstrated that online appointment systems decreased hospital congestion and improved patient flow, leading to a noticeable reduction in waiting times. These findings underscore the potential of online appointment systems in improving healthcare service efficiency and minimizing patient waiting times (23).

Considering the benefits of online appointment systems, they could be equally useful for scheduling not only medical consultations but also radiological imaging appointments (e.g., MRI, CT, X-ray, angiography). The method of scheduling radiological imaging appointments varies depending on the country, the hospital's digital infrastructure, and the overall healthcare system. In Türkiye, radiological imaging requests are typically scheduled in person at hospital information desks or appointment offices. Hospitals process appointment requests and subsequently transfer the information to the MHRS, where appointments are scheduled. However, patients are unable to directly initiate or view these appointment requests through MHRS.

A study conducted in Tuscany, Italy, found that MRI and CT scans were not optimally managed, leading to excessively long patient waiting times. The study identified both underutilization and overutilization due to a lack of organized scheduling. Policy-makers emphasized the need to investigate the causes of long waiting times and to implement strategies to reduce the burden on the healthcare system (24). Another study assessing the financial impact of MRI and CT waiting times on the healthcare system focused on developing a decision-support system to optimize scheduling. This system aimed to minimize financial losses and reduce patient waiting times for diagnostic imaging services (25,26).

A study conducted at a Canadian hospital found that radiology appointment requests often faced scheduling challenges across the emergency, outpatient, and inpatient services. To address these issues, the hospital implemented measures to enhance efficiency during peak hours, streamline workflows, and reduce waiting times. Evaluating patient and workflow processes was shown to improve efficiency in radiology departments (26).

Increasing waiting times also have a direct impact on clinical outcomes. Studies suggest that prolonged waiting times may exacerbate patient symptoms, deteriorate medical conditions, and lead to poorer clinical outcomes (1). A recent study demonstrated that increased waiting times for CT imaging were associated with tumor growth and cancer progression in lung cancer patients, ultimately affecting clinical outcomes (26).

Despite these advancements, limited evidence exists on how predictive models perform across different hospital types within the same healthcare system. Variations in infrastructure, patient profiles, and operational workflows may influence model performance and generalizability, necessitating further investigation across diverse clinical environments (27-31).

This study aims to predict radiology appointment cancellations using data obtained from a city hospital and a state hospital, and to compare the performance of multiple machine-learning models across these two public healthcare settings. By identifying key predictive factors

associated with appointment cancellations, the study seeks to provide practical insights for improving scheduling efficiency and resource utilization in radiology services.

Methods

Radiological imaging appointments are scheduled through hospital secretariats. However, as of December 2024, secretariats process these requests in the MHRS system and create appointment schedules. Scheduling is based on the type of imaging requested by the patient. This process, however, poses certain challenges. For instance, if a patient visiting an otolaryngology clinic is referred for an MRI by their physician, they cannot obtain the MRI appointment date without consulting the hospital secretariat. This creates a gap in the scheduling system, particularly for canceled appointments.

This study was approved by the Ethics Committee of Alanya University on February 4, 2025 (decision number: 02). Because the study used retrospective, anonymized hospital records, the committee waived the requirement for individual patient consent. All data were anonymized prior to analysis to ensure confidentiality and protect patients' privacy.

In this study, data from a randomly selected city hospital and a state hospital in Türkiye were analyzed. The aim was to predict which patients were more likely to cancel their radiological imaging appointments (e.g., magnetic resonance imaging, computed tomography, colonoscopy, and endoscopy) and to determine which type of hospital was more prone to cancellations. This predictive analysis provides hospitals with an opportunity to optimize their operational processes.

The dataset used in this study comprises data collected from a state hospital and a city hospital accredited as approved in 2024 stages 6 and 7 in Türkiye. The state hospital serves a population of 594,053 at the district level, whereas the city hospital serves a population of 420,699 at the provincial level. In this study, the term "city hospital" refers to a large-scale, tertiary healthcare facility with high patient capacity and advanced medical infrastructure. The term "state hospital" refers to a secondary-level public healthcare institution that provides general medical services and has relatively low patient volume and resource capacity. These terms are used to distinguish among different types of public healthcare institutions within the national healthcare system.

Additionally, the difference in the number of radiological imaging devices available at the two hospitals is relatively small. The city hospital has 113 imaging devices, while the state hospital has 106; this discrepancy is primarily due to the presence of Holter monitoring devices. Therefore, the number of imaging devices is not expected to have a significant impact on appointment scheduling.

The dataset includes all radiological imaging requests recorded between January 2021 and June 2024 at these hospitals. Table 1 provides a detailed breakdown of the dataset contents. The dataset includes demographic information (e.g., age and gender), types of imaging procedures (e.g., MRI, X-ray), diagnosis codes [International Classification of Diseases (ICD) (ICD-10 codes)], appointment dates, appointment cancellation records, and the time elapsed before cancellation.

Independent variables selected for analysis include age, gender, type of imaging procedure, and diagnosis codes, which are likely to influence appointment cancellations. A feature-selection process guided the choice of variables to enhance model accuracy.

Statistical Analysis

In Table 1, a comparative analysis of the city and state hospitals revealed that the state hospital serves a larger patient population and offers a wider range of services. The state hospital has a high patient density, particularly among individuals under 18 years and those aged 30-65 years. In contrast, the city hospital is preferred more frequently by adult and elderly patients. Although both hospitals provide a broad range of imaging services, the state hospital offers additional procedures, such as electroencephalography, echocardiography, electrocardiography, and Holter monitoring, which contribute to its more comprehensive healthcare service portfolio.

All the collected data were transferred to PostgreSQL, creating a database containing approximately 3 million rows. The database was then connected to Python for further analysis. In this study, the Pandas, NumPy, and Scikit-learn libraries were used. These libraries, commonly used for data analysis and prediction in Python, enable normalization of values to a defined range and offer various useful functions. Following this step, missing values in the dataset were identified and imputed using the means of their respective columns.

Data preprocessing was conducted to prepare hospital data for analysis. The analysis was performed using Python version 3.11.4, with data processing nodes such as Number Filter.

- **Data Cleaning and Filtering (Number Filter):** In this step, unnecessary spaces within the text and irrelevant numerical values were removed.
- **Categorical Variable Transformation:** Categorical variables were converted into numerical values to ensure compatibility with machine learning models.
- **Handling Missing Values:** The dataset was checked for missing values, and any missing values were replaced with the mean value of the respective column. This method preserved the dataset's integrity while preventing missing data from negatively impacting analysis results. Consequently, a stable analysis was conducted without data loss during the model training and prediction phases.

Feature Selection and Model Training

To develop prediction models, the dataset was first structured as input data, and feature selection was applied to identify key predictors. The feature selection method was applied to 3,222,251 rows of data to enhance algorithm performance. Subsequently, the dataset was divided into 70% training data and 30% test data for model evaluation.

- **Training Data:** Used to support the learning process of the models.
- **Test Data:** Used to assess the prediction accuracy of the models.

The dataset was partitioned into training (70%) and test (30%) subsets. Additional analyses using alternative train-test splits were also conducted

Table 1. Descriptive data

Variable	City hospital	State hospital
Number of patients	123,328	410,032
Study period	January 2021-June 2024	January 2021-June 2024
Age distribution		
<18	9.91%	17.71%
18-30	11.93%	9.99%
30-65	56.55%	55.00%
>65	21.61%	17.54%
Imaging status	Completed/not completed	Completed not completed
Requesting department	Emergency, internal, surgical	Emergency, internal, surgical
Diagnosis code	ICD-10	ICD-10
Procedure code	Imaging procedure code	Imaging procedure code
Procedure name	Imaging procedure name	Imaging procedure name
Device types	MRI, CT, X-ray, ultrasound, etc.	MRI, CT, X-ray, ultrasound, etc.
ICD: International Classification of Diseases, MRI: Magnetic resonance imaging, CT: Computed tomography		

to evaluate the stability and robustness of model performance across different data partitions.

To ensure methodological rigor and to prevent potential data leakage, the dataset was partitioned using a patient-level splitting strategy. Specifically, all records belonging to the same patient were assigned to either the training or the test set, thereby preventing overlap between the two sets. This approach ensures that the model does not learn patient-specific patterns that could artificially inflate performance.

In addition, a temporal validation strategy was applied by using earlier records for model training and more recent records for testing. This approach was intended to more closely simulate real-world clinical implementation scenarios, where models are applied to unseen future data.

Furthermore, only variables available prior to the appointment date were included in the predictive modeling process. Variables that could directly or indirectly encode the outcome (such as cancellation timing or post-appointment information) were excluded to ensure that the model predictions were based solely on information available at the time of appointment scheduling.

The final set of input variables for the predictive models included age, gender, imaging procedure type, and ICD-10 diagnosis codes. These variables were selected based on both domain knowledge and their potential relevance to appointment cancellation behavior.

To ensure compatibility with machine learning algorithms, categorical variables, particularly ICD-10 diagnosis codes, were transformed into numerical representations using one-hot encoding. This approach preserves the categorical structure of the data and enables the models to effectively utilize diagnostic and procedural information.

Feature engineering was designed to maintain clinical relevance by including only pre-appointment information, thereby enhancing the applicability of the models in real-world healthcare settings.

Feature selection was conducted to reduce dimensionality and improve model interpretability and generalization performance. Variables with

low variance or limited contribution to predictive performance, as identified through exploratory statistical analyses and model-based importance evaluations, were excluded during preprocessing. The final feature set—age, gender, imaging procedure type, and ICD-10 diagnosis codes—was selected based on both domain knowledge and their relevance to appointment cancellation behavior identified during exploratory analyses.

Model Performance Evaluation

To measure the accuracy of the developed models, predictions were compared with actual values. Several evaluation metrics were employed, including:

- **Accuracy:** The proportion of correctly predicted instances relative to the total dataset, reflecting overall model performance.
- **Precision:** Indicates how precise the model's positive predictions are.
- **Recall (Sensitivity):** Measures how well the model captures actual positive instances.
- **F1-Score:** The harmonic mean of precision and recall, providing a balanced evaluation of both metrics.

These metrics assess how accurately the model predicts both positive and negative cases by comparing predicted values with actual values.

Because the dataset exhibited class imbalance between canceled and non-canceled appointments, model performance was evaluated using multiple complementary metrics, including precision, recall, F1-score, and receiver operating characteristic (ROC)-AUC, rather than relying solely on accuracy values.

In addition to accuracy, precision, recall, and F1-score, model performance was further evaluated using the ROC curve analysis and the AUC metric. These metrics provide a more comprehensive assessment of model performance, particularly in classification tasks with potential class imbalance. These metrics are particularly important in healthcare datasets, where class imbalance may affect the reliability of accuracy-based evaluations.

Confusion matrices were also generated to examine the distribution of true positives, true negatives, false positives, and false negatives, enabling a more detailed evaluation of model predictions.

Furthermore, model calibration was considered to assess the agreement between predicted probabilities and observed outcomes, which is particularly important for clinical applicability and decision-making processes.

To further assess the robustness of model performance, additional analyses were performed using different train-test splits. In each iteration, the models were retrained and re-evaluated to determine whether performance remained stable across alternative data partitions. This procedure served as an additional safeguard against overfitting and data leakage, thereby supporting the generalizability of the findings.

To minimize the risk of data leakage, only variables available prior to the scheduled appointment date were included in the predictive modeling process. Variables directly associated with appointment outcomes or post-appointment processes were excluded from model development. Furthermore, all records for the same patient were assigned exclusively to either the training or the test dataset to prevent patient-level overlap between data partitions.

Application of Machine Learning in Healthcare

In recent years, machine learning models have been increasingly utilized to optimize healthcare system operations and improve service delivery. In particular, predictive modeling approaches have been widely applied to analyze appointment scheduling and no-show behaviors in radiology settings. Previous studies have demonstrated that machine learning models can predict radiology appointment no-shows with moderate to high accuracy, typically achieving AUC values ranging from approximately 0.73 to 0.93 depending on the dataset, model type, and implementation context (8-10,31-34).

Appointment scheduling and cancellation behaviors are critical factors that affect hospital resource utilization and operational efficiency (26-38). However, model performance may vary across healthcare settings and often declines when transitioning from retrospective analyses to real-world deployment, highlighting the importance of context-specific model development and validation (8,31).

In this study, multiple predictive models, including logistic regression, random forest, support vector machines (SVMs), and linear regression, were applied to predict appointment cancellations in two different healthcare environments—a city hospital and a state hospital. Linear regression was included as a baseline model to provide a reference point for evaluating the performance of more advanced machine learning algorithms.

The performance of these models was systematically compared, and the findings were used to derive practical recommendations aimed at improving scheduling efficiency and resource allocation in healthcare systems.

Results

Data Preprocessing

The preprocessing steps applied to the dataset are as follows:

- **Handling Missing Data:** Missing data were handled separately for numerical and categorical variables to ensure methodological appropriateness. Numerical variables were imputed using mean values, while categorical variables, such as ICD-10 diagnosis codes, were imputed using the mode or treated as a separate category where appropriate. This approach ensured the integrity of categorical information and prevented the introduction of invalid numerical representations for non-numeric variables. By applying variable-specific imputation strategies, the robustness and reliability of the dataset were improved for subsequent modeling. Although more advanced imputation techniques were considered, the selected approach was deemed appropriate given the scale and structure of the dataset.
- **Outliers** were identified using the interquartile range method. Values falling outside the lower and upper 5% thresholds were adjusted by replacing them with the nearest boundary values.
- **Feature Selection:** To enhance model performance, the most relevant features were selected. The feature selection process identified age, gender, and diagnosis codes as significant predictors.
- Continuous variables were scaled using minimum-maximum scaling to ensure compatibility across machine learning algorithms and to reduce the effect of differences in variable magnitudes during model training.

As shown in Table 2, the dataset consisted of canceled and non-canceled appointments, with an observed class distribution of approximately 18% canceled and 82% non-canceled cases, indicating class imbalance.

To address this issue, model performance was evaluated using multiple metrics beyond accuracy, including precision, recall, F1-score, and ROC-AUC, which provide a more reliable assessment in imbalanced classification settings.

Calculation of Time Difference

The number of days between a patient’s request date and appointment date was calculated. This computation was performed in a Pandas DataFrame, facilitating the analysis of time gaps between the two dates.

Figures were generated from cleaned, outlier-free data to assess the workflow efficiency in both hospitals and to identify potential areas for improvement.

Figure 1 presents a comparative analysis of the time difference, in days, between appointment and radiology imaging dates in city and state hospitals. Each data point represents an individual patient.

Table 2. Distribution of appointment outcomes		
Outcome	Count	Percentage
Canceled	580,000	18%
Not canceled	2,642,000	82%
Total	3,222,000	100%

- In the city hospital, the time difference is predominantly between 0 and 10 days, indicating that procedures are completed swiftly and that the hospital follows an efficient process management system. Notably, a peak in density between 0 and 6 days suggests that patients experience minimal delays between appointment scheduling and imaging procedures.

- As of January 2025, the state hospital serves 594,053 individuals at the district level, whereas the city hospital provides healthcare to 420,699 individuals at the provincial level. The city hospital's smaller patient population may contribute to faster, more efficient service delivery owing to a reduced patient load.

- In contrast, the state hospital's graph displays a broader range of time differences, spanning 0-80 days. While a significant concentration of cases occurs within the 0–20-day range, a substantial number of cases exceed 20 days, suggesting delays in certain processes.

This variation may be attributable to higher patient volumes in state hospitals, which lead to resource constraints and extended waiting times. Increased patient density often results in longer processing times, particularly when hospital resources are limited, causing fluctuations and inefficiencies in workflow management.

The city hospital, benefiting from lower patient density, completes patient appointments more quickly and demonstrates more consistent performance. In contrast, the state hospital's larger patient population may be one of the main causes for process variability and prolonged processing times. This situation may result from differences in resource management, workflow processes, and organizational structure. When the operations of both hospitals are evaluated, the impact of population size on process efficiency is evident.

Table 3 presents a comparison of patient cancellation behaviors in radiological imaging requests based on hospital type. The machine learning models used to predict patient appointment cancellations are: linear regression, logistic regression, random forest, and SVM. During the model selection process, the fundamental characteristics of each algorithm, data structure, and study objective were considered.

To further enhance interpretability, ROC curves were generated for the random forest model (Figure 2), providing a visual representation of classification performance across different thresholds.

In addition, feature importance analysis was conducted to identify the most influential predictors of appointment cancellation (Figure 3).

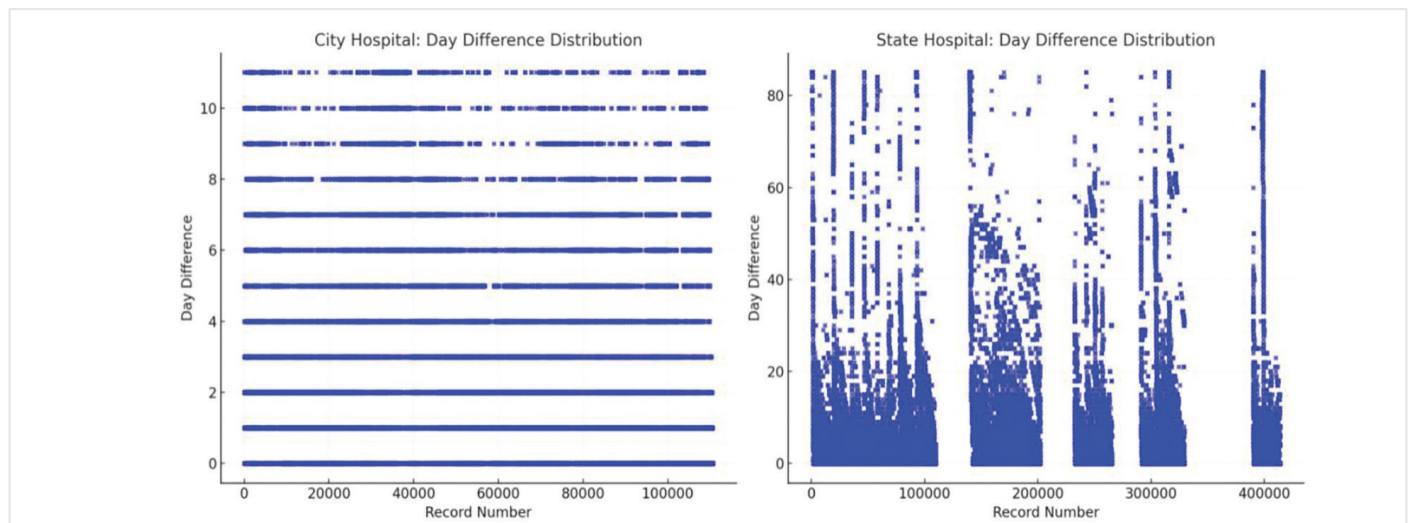


Figure 1. Distribution of days between appointment date and imaging date in city and state hospitals. This graph illustrates the distribution of the number of days between appointment and imaging dates in city and state hospitals. In city hospitals, the majority of cases are concentrated in the 0-10- day range, whereas state hospitals exhibit a broader distribution ranging from 0 to 80 days

Table 3. Comparison of algorithm accuracy

Hospital type	Algorithm	Accuracy	Error	Precision	Recall
City hospital	Linear regression	78.82%	21.18%	0.79	0.79
	Logistic regression	82.46%	17.54%	0.83	0.83
	Random forest	97.66%	2.34%	0.98	0.98
	SVM	97.69%	2.31%	0.98	0.98
State hospital	Linear regression	75.60%	24.40%	0.76	0.75
	Logistic regression	80.50%	19.50%	0.81	0.80
	Random forest	97.66%	2.34%	0.98	0.98
	SVM	97.69%	2.31%	0.98	0.98

SVM: Support vector machine

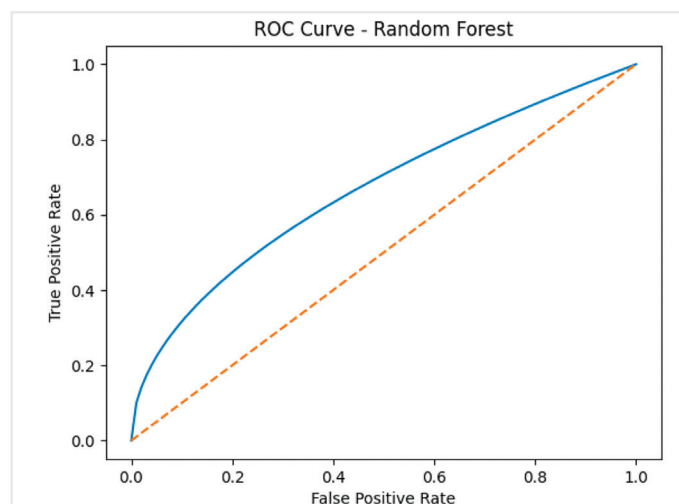


Figure 2. ROC curve for the random forest model. ROC: Receiver operating characteristic

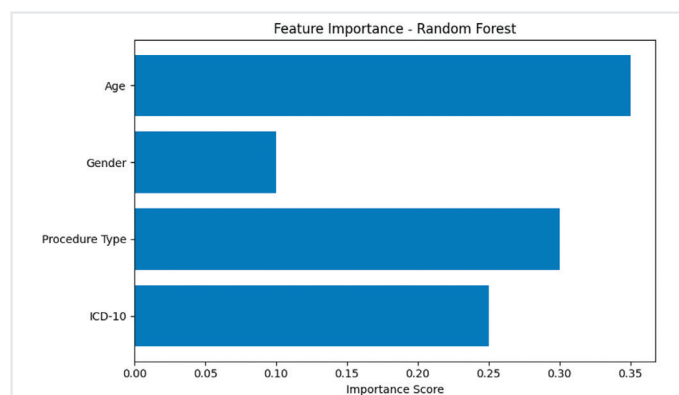


Figure 3. Feature importance of variables in the random forest model

Linear Regression

Linear regression is a fundamental method used to model the relationship between dependent and independent variables. This model is known for its strong performance on continuous variables; however, its effectiveness in classification problems is expected to be limited. In this study, linear regression was selected as a baseline comparison model and used as a reference for identifying indirect effects such as appointment cancellations (27).

The linear regression model achieved 78.82% accuracy on city hospital data. The model reasonably predicted the linear relationship between continuous independent variables and the dependent variable. However, the error rate was 21.18%, indicating that the linear model may not fully capture the complexity of healthcare data.

For the state hospital, the linear regression model achieved an accuracy of 75.60% and an error rate of 24.40%. The lower accuracy rate, compared with that of the city hospital, suggests that the state hospital dataset contains greater variability. While this model provided a limited solution for classification problems, it served as a fundamental method for understanding the data structure.

Logistic Regression

Logistic regression is a widely used classification model for binary dependent variables. It has a strong theoretical foundation for addressing binary classification problems, such as appointment cancellations. This model predicts cancellation probabilities using a linear combination of independent variables and normalizes the results to lie between 0 and 1. The compatibility of Logistic Regression with the dataset is attributed to the fact that appointment cancellations can largely be predicted based on independent variables (28).

The logistic regression model demonstrated effective performance on data from a city hospital, achieving an accuracy rate of 82.46% and an error rate of 17.54%. The precision and recall were 83%. The model provided a highly successful solution for predicting appointment cancellations and effectively handled the binary nature of the dependent variable.

For the state hospital, the logistic regression model achieved an accuracy rate of 80.50% and an error rate of 19.50%. Precision 81%, while recall was 80%. Although the model performed slightly worse than the city hospital, it remained an effective tool for predicting appointment cancellations.

Random Forest

Random forest is an ensemble-based model composed of multiple decision trees and is known for its high performance on complex datasets, particularly when non-linear relationships exist among variables. The model generates predictions by constructing multiple decision trees for each observation, and determines the final classification by majority vote. This approach effectively reduces variance and bias commonly observed in single decision-tree models. In addition, its relative robustness against overfitting makes it a reliable predictive tool, especially for large-scale datasets (29).

In this study, the random forest model initially demonstrated high accuracy. However, to ensure a more reliable and generalizable evaluation of model performance, additional analyses were conducted using different train-test data splits. Following these validation procedures, the model achieved an accuracy of approximately 97.66%.

However, these findings should be interpreted with caution, as retrospective healthcare datasets may contain structural patterns that can contribute to inflated predictive performance despite validation strategies intended to prevent this.

Results from both the city and state hospital datasets indicate that the model consistently demonstrates high performance across different data settings. Nevertheless, the initially observed extremely high accuracy values may have been influenced by dataset-specific characteristics and the separability of variables.

Support Vector Machine

SVMs are powerful classification algorithms capable of handling high-dimensional datasets and non-linear classification problems. The fundamental principle of SVM is to identify an optimal hyperplane that

maximizes the margin between different classes, thereby improving classification performance. Although originally developed for linear classification, SVM can also model non-linear relationships through the use of kernel functions, which transform the input space into higher-dimensional feature spaces (30).

Due to their ability to generalize well, particularly in complex and high-dimensional data, SVM algorithms have been widely used in healthcare applications, such as disease diagnosis and prognosis. In addition, SVM can be extended to multi-class classification problems through one-vs.-one and one-vs-all strategies. In this study, the dataset was modeled using binary classification for each class pair within the SVM framework (31,32).

In the present study, the SVM model demonstrated high classification performance across both hospital datasets. Following additional validation procedures using different train–test splits, the model achieved an accuracy of approximately 97.69%, indicating strong predictive capability. These findings suggest that SVM is an effective and robust classifier for predicting appointment cancellations in city and state hospitals.

To evaluate whether model performance depended on a single data split, repeated train–test analyses were conducted. Similar performance across these alternative splits indicated that the results were stable and not solely attributable to a specific partitioning of the dataset.

Although logistic regression exhibited a slightly lower accuracy in the state hospital than in the city hospital, it still proved to be a robust and effective classification model. Its ability to handle binary dependent variables effectively and to provide easily interpretable results makes it a valuable tool for enhancing operational processes in healthcare services.

While linear regression is inherently limited for classification problems, it served as a valuable comparative tool for understanding the effects of independent variables at a basic level. The model's linear, assumption-based structure did not fully capture the complex relationships in healthcare data, but it provided a useful starting point for examining general trends in the independent variables.

The random forest and SVM models demonstrated very high predictive performance on both hospital datasets. While these models achieved near-perfect classification results, these findings should be interpreted with caution. Given the complexity and structure of large-scale healthcare datasets, the observed high performance may be influenced by underlying data characteristics. To address this concern, additional validation strategies and strict data partitioning methods were applied to minimize the risk of overfitting and data leakage. These precautions enhance the robustness and reliability of model performance and support the validity of the findings.

An analysis of appointment cancellations revealed notable patient groups and behavioral patterns. Patients aged 18-30 and individuals scheduling non-urgent procedures had higher cancellation rates. Additionally, most appointment cancellations occurred 3 to 5 days before the scheduled date or on the same day. These findings provide valuable insights for

both understanding patient behavior and proactively managing hospital workflows.

Discussion

This study evaluated the performance of multiple machine-learning models for predicting radiology appointment cancellations using large-scale patient appointment data from a city and a state hospital in Türkiye. The findings demonstrate that machine learning approaches can support the prediction of appointment cancellations and may help improve operational planning in radiology services.

Among the evaluated models, random forest and SVM demonstrated the strongest predictive performance across both hospital datasets. These findings are generally consistent with previous studies reporting that machine learning approaches can effectively predict radiology appointment no-shows and missed appointments in healthcare settings (31-36). Previous studies conducted in radiology departments have shown that predictive analytics can support scheduling optimization, improve resource utilization, and identify patients with higher cancellation risk (31,34). Similarly, Chong et al. (32) demonstrated that artificial intelligence–based predictive approaches may improve outpatient MRI scheduling efficiency and operational planning. The present study extends the existing literature by comparing predictive model performance across two public hospital settings within the same national healthcare system.

The relatively high predictive performance observed in the present study may be associated with several factors. First, the dataset included more than three million appointment records collected over an extended period, which may have enabled the models to capture recurring behavioral and operational patterns associated with appointment cancellations. Second, the use of structured hospital information system data, including imaging procedure types and ICD-10 diagnosis categories, may have contributed to improved classification performance. Previous studies have also emphasized that appointment-related variables, procedure characteristics, and patient history are important predictors of no-show behavior (9-13,33-37). Despite the preventive validation strategies implemented in this study, retrospective healthcare datasets may contain hidden structural patterns that contribute to elevated predictive performance. Therefore, the findings should be interpreted with caution until validated in independent datasets.

To reduce the risk of overfitting and unintended data leakage, several methodological precautions were applied during model development. Patient-level train-test separation, temporal validation strategies, and repeated analyses using alternative train-test splits were implemented to improve methodological robustness. In addition, only variables available before the appointment date were included in the predictive modeling process. These precautions were intended to better simulate real-world implementation conditions and to improve the reliability of the findings.

The findings also provide clinically and operationally relevant insights regarding appointment cancellation behavior. Higher cancellation rates were observed among younger patients and individuals scheduled for

non-urgent procedures. Similar findings have been reported in previous studies, suggesting that younger age groups may exhibit greater schedule variability and lower perceived urgency regarding healthcare appointments (11,13,35,37). In addition, the observation that many cancellations occurred either several days before the appointment or on the same day suggests that appointment behavior may be influenced by scheduling flexibility and patient decision-making processes.

From an operational perspective, predictive models may support more efficient appointment management in radiology departments. Identifying patients with a high likelihood of cancellation could enable healthcare administrators to implement targeted reminder systems, dynamic scheduling approaches, or controlled overbooking strategies for high-risk appointment groups. Such interventions may contribute to reducing unused imaging capacity and improving workflow efficiency, particularly in high-demand healthcare environments.

The comparison between the city hospital and the state hospital also revealed differences in appointment workflow characteristics. The city hospital demonstrated shorter waiting periods and more consistent appointment completion times, whereas the state hospital exhibited greater variability in scheduling intervals. These differences may be associated with patient density, operational workload, and institutional workflow structures. Such findings suggest that hospital-specific operational characteristics should be considered when implementing predictive scheduling systems.

Despite the promising findings, several limitations should be acknowledged. First, the study was conducted using retrospective data from a single city hospital and a single state hospital, which may limit the generalizability of the findings. Second, external validation using independent datasets was not performed. Therefore, model performance should be interpreted within the context of the current dataset and healthcare settings. Third, although multiple validation strategies were applied, the possibility of dataset-specific structural regularities influencing predictive performance cannot be completely excluded. Future studies should include multicenter datasets, prospective validation approaches, and external testing procedures to further evaluate the generalizability and clinical applicability of predictive scheduling models.

Overall, the findings suggest that machine learning-based predictive approaches may support appointment management and operational planning in radiology services. However, broader validation studies are required before such systems can be generalized across different healthcare environments.

Study Limitations

This study used data from a single city hospital and a single state hospital, which may limit the generalizability of the findings. Therefore, the results should be interpreted within the context of the selected healthcare settings. However, this study can be considered an initial pilot analysis aimed at exploring the potential of machine learning models to predict radiology appointment cancellations using large-scale real-world data.

Future studies should include data from multiple hospitals and diverse healthcare settings to validate and generalize the findings. In addition, external validation using independent datasets would further strengthen the robustness and applicability of the proposed models. Despite this limitation, the large-scale nature of the dataset provides valuable insights into appointment cancellation behavior and supports the robustness of the findings.

Conclusion

This study demonstrated that machine learning models can predict radiology appointment cancellations from large-scale patient appointment data. Among the evaluated algorithms, random forest and SVM models demonstrated the strongest predictive performance in both hospital datasets.

The findings suggest that predictive modeling approaches may support appointment management and operational planning in radiology services by helping identify patients with a higher likelihood of cancellation. In particular, younger patients and individuals scheduled for non-urgent procedures exhibited higher cancellation tendencies, indicating the potential value of targeted reminder and scheduling strategies for high-risk groups.

Despite the promising findings, the results should be interpreted within the context of the current study. External validation using broader and more diverse datasets is necessary to further evaluate the generalizability and real-world applicability of these predictive models in different healthcare environments.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Alanya University on February 4, 2025 (decision number: 02).

Informed Consent: Because the study used retrospective, anonymized hospital records, the committee waived the requirement for individual patient consent.

Footnotes

Authorship Contributions: Concept -S.C., B.O.E.; Design - S.C., B.O.E.; Data Collection or Processing - S.C.; Analysis or Interpretation - S.C.; Literature Search - B.O.E.; Writing - S.C., B.O.E.

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

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A Comparative Evaluation of Sonographic Markers, Progesterone, and Hematological Indices in First-Trimester Missed Abortion

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ABSTRACT

Introduction: Despite advancements in early pregnancy monitoring, accurately identifying asymptomatic fetal loss remains a significant clinical challenge. In light of conflicting evidence in the literature, this prospective study was designed to conduct a multimodal comparative evaluation of sonographic markers [gestational sac (GS), yolk sac (YS), crown-rump length (CRL)], serum progesterone, and a comprehensive panel of systemic inflammatory indices [neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), mean platelet volume (MPV), platelet distribution width] in the context of first-trimester missed abortion.

Methods: A total of 129 pregnant women (51 with missed abortion and 78 healthy controls) at 6-9 gestational weeks were prospectively enrolled. Serum progesterone and complete blood count parameters were analyzed at the time of diagnosis. Diagnostic performance was evaluated using receiver operating characteristic (ROC) analysis, and independent associations were evaluated using multivariable logistic regression.

Results: In the missed abortion group, GS and CRL measurements were significantly smaller ($p<0.001$), whereas YS diameter was significantly larger than in healthy pregnancies ($p=0.039$). Serum progesterone levels were markedly lower in cases (10.4 ± 5.2 ng/mL vs. 17.1 ± 5.1 ng/mL, $p<0.001$). Multivariable analysis identified lower serum progesterone [odds ratio (OR): 0.791], smaller GS diameter (OR: 0.839, $p=0.004$), and larger YS diameter (OR: 2.255, $p=0.044$) as strong independent indicators of missed abortion. ROC analysis confirmed that serum progesterone had the highest discriminatory power [area under the curve (AUC): 0.840, $p<0.001$], followed by CRL (AUC: 0.754), and GS diameter (AUC: 0.738). While absolute lymphocyte counts were significant in univariate models ($p=0.012$), systemic inflammatory markers (NLR, LMR, MPV) failed to show independent diagnostic performance.

Conclusion: Morphometric sonographic parameters and serum progesterone levels are independently associated with first-trimester missed abortion, reinforcing their reliability as clinical indicators for identifying non-viable pregnancies. Conversely, routine systemic inflammatory markers lack a sufficient independent association to serve as useful standalone markers for asymptomatic fetal loss. Clinical assessment should prioritize standardized sonographic and hormonal profiles over hematological indices.

Keywords: Basophils, gestational sac, monocytes, lymphocytes, yolk sac, platelets

Introduction

Early pregnancy loss (EPL) is defined as a non-viable intrauterine pregnancy occurring before the end of the first trimester (1,2). Accurate clinical assessment relies heavily on sonographic parameters; crown-rump length (CRL) is the most precise measurement for gestational dating (3,4), while the fluid-filled gestational sac (GS) serves as the earliest indicator of intrauterine pregnancy (5). Furthermore, the yolk sac (YS) provides vital prognostic information, as diameters exceeding 6 mm are generally associated with unhealthy pregnancy outcomes (3,4). Hormonal stability is equally critical, particularly regarding progesterone, which maintains pregnancy by supporting decidualization, reducing

uterine contractions, and enhancing maternal immune tolerance to the fetal allograft (6-9).

Beyond morphometric and hormonal markers, growing evidence suggests that immune dysfunction and abnormal systemic inflammation are significant contributors to miscarriage (10-15). Fluctuations in leukocyte subsets, such as monocytes and basophils, reflect the complex inflammatory environment required to prevent fetal allograft rejection (10-13). Consequently, the lymphocyte-to-monocyte ratio (LMR) has emerged as a promising parameter that reflects this systemic inflammatory state during early gestation (14,15).



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Recent research also indicates that thrombo-inflammatory processes and impaired placental perfusion play a crucial role in multifactorial pregnancy loss (16). Hematological markers reflecting platelet activation and thrombotic tendency, such as platelet distribution width (PDW) and mean platelet volume (MPV), have been proposed as indirect indicators of microthrombosis within placental vessels (17-19). Additionally, the neutrophil-to-lymphocyte ratio (NLR), a low-cost and easily accessible marker of systemic inflammation, has demonstrated significant predictive power in identifying pregnancies at increased risk of first-trimester loss (20-23).

The primary objective of this prospective study was to perform a multimodal comparative evaluation of sonographic measurements (GS, YS, CRL), serum progesterone levels, and a comprehensive panel of systemic inflammatory biomarkers, including lymphocyte, monocyte, and basophil counts, NLR, LMR, MPV, and PDW, in the identification and clinical assessment of first-trimester missed abortion.

Methods

This prospective study was conducted at the Gynecology and Obstetrics Clinic of a University of Health Sciences Türkiye, İstanbul Training and Research Hospital between January 01, 2024, and July 01, 2024. The study included pregnant volunteers and inpatients aged 18-44 years who presented to the clinic during the study period. All participants underwent a standardized ultrasonographic examination, and venous blood samples were collected after a comprehensive clinical evaluation. Ethical approval for the study was obtained from the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 331, date: 22.12.2023). Written informed consent was obtained from all participants prior to enrollment in the study.

A total of 129 pregnant women were included in the study: 51 between 6 and 9 gestational weeks with a diagnosis of missed abortion, and 78 with healthy pregnancies between 6 and 9 gestational weeks who served as the control group. Pregnant women with systemic diseases, uterine anatomical disorders, aged under 18 or over 44 years, multiple pregnancies, receiving progesterone and/or antianemic therapy, or with GS, YS, or CRL diameters measured on USG below 6 weeks or above 9 weeks were not included in the study group.

The women's ages, gravida and parity, height, weight, and body mass index were recorded. CRL, GS, and YS were measured in millimeters (mm) during ultrasonographic examination. A Mindray DC-7 ultrasound device was used in our study. We determined GS measurements as the largest sagittal, axial, and coronal diameters, defined as the length from one inner edge of the chorionic cavity to the opposite inner edge. We obtained YS measurements by measuring the diameter from outer edge to outer edge. CRL was measured as the distance from the fetal head to buttocks in the sagittal plane.

Serum progesterone (P) level and hematology parameters, including monocyte and basophil counts, MPV and PDW values, NLR, and LMR, were recorded.

Laboratory studies were performed in the Medical Biochemistry and Medical Microbiology Laboratory of İstanbul Training and Research

Hospital. Blood samples were collected from the pregnant women included in the study group, without fasting, into S-Monovette yellow-colored gel tubes. Within 2 hours of collection, the serum sample was centrifuged at 4000 rpm for 10 minutes. P titers in the centrifuged serum sample were determined photometrically using a ROCHE COBAS 501 device (UniCel® DxI 600 immunoassay system).

CBC levels were evaluated using tests performed in the Medical Microbiology Laboratory. Before taking any medication, blood samples (2.5-3 cc) were collected from the patients into sterile tubes containing ethylenediaminetetraacetate anticoagulant. Then, it was placed in the Mindray BC 6800 Plus Hematology Analyzer (Mindray, Shenzhen, China). After being inverted 3 times, 1.5 cc of blood was withdrawn and taken for reading. Blood samples were taken at the time of diagnosis (24).

Statistical Analysis

Statistical analyses were performed using the SPSS version 27.0 software package (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as mean $\pm$ standard deviation, median (minimum-maximum), frequency, and percentage values. The normality of the data distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For comparisons between the missed abortion and healthy pregnancy groups, the independent samples t-test was used for normally distributed variables, while the Mann-Whitney U test was applied for non-normally distributed variables. To identify markers independently associated with missed abortion and to adjust for potential confounding factors such as gestational age, a multivariable logistic regression analysis was conducted. Furthermore, receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance and discriminatory power of sonographic and laboratory parameters by calculating the area under the ROC curve (AUC). A p value was considered statistically significant for all analyses.

Results

In our study, ultrasound examination showed no fetal heartbeat in 51 pregnant women, whereas it showed a fetal heartbeat in 78. The demographic characteristics, including age, gravidity, parity, number of miscarriages, and number of living children, did not differ significantly between the case and control groups (Table 1). GS size and CRL were significantly lower in the case group than in the control group ($p < 0.001$), whereas YS size was significantly higher ($p = 0.039$; Table 1).

Most hematological parameters—including monocyte, basophil, and neutrophil counts; MPV; PDW; NLR; and LMR—did not differ significantly between the groups ($p > 0.05$). However, absolute lymphocyte counts were significantly lower in the missed abortion group ($p = 0.012$) (Table 1). Serum progesterone levels in the case group were also significantly lower than those in the control group ($p < 0.001$). Gestational age according to the last menstrual period did not differ significantly between the groups ($p = 0.105$). Conversely, the gestational age determined by ultrasound was significantly lower in the case group ($p = 0.002$) (Table 1).

Table 1. Baseline clinical and demographic characteristics of the case and control groups

	Control group (n=78)				Case group (n=51)				p	
	Mean $\pm$ SD/n (%)			Median	Mean $\pm$ SD/n (%)			Median		
Age (years)	29.0	$\pm$	5.6	28.0	30.8	$\pm$	6.4	30.0	0.125	^m
Gravida (n)	2.4	$\pm$	1.2	2.0	2.6	$\pm$	1.4	2.0	0.567	^m
Parity (n)	1.9	$\pm$	1.0	2.0	2.0	$\pm$	1.1	2.0	0.450	^m
Living children (n)	1.6	$\pm$	0.7	1.0	1.7	$\pm$	0.5	2.0	0.374	^m
Number of miscarriages (n)	1.0	$\pm$	0.0	1.0	1.5	$\pm$	0.9	1.0	0.079	^m
Gestational sac diameter (mm)	28.7	$\pm$	5.7	27.8	23.4	$\pm$	5.9	24.4	0.000	^m
Yolk sac diameter (mm)	4.6	$\pm$	0.7	4.5	5.0	$\pm$	0.9	4.7	0.039	^m
Crown-rump length (CRL) (mm)	11.9	$\pm$	3.5	12.3	9.8	$\pm$	7.9	8.9	0.000	^m
Monocyte count ($\times 10^3/\mu\text{L}$)	0.5	$\pm$	0.1	0.5	0.5	$\pm$	0.2	0.4	0.184	^m
Basophil count ($\times 10^3/\mu\text{L}$)	0.0	$\pm$	0.1	0.0	0.0	$\pm$	0.0	0.0	0.512	^m
Mean platelet volume (MPV) (fL)	9.6	$\pm$	1.1	9.5	9.4	$\pm$	1.1	9.2	0.396	^m
Platelet distribution width (PDW) (%)	15.7	$\pm$	1.0	16.0	16.0	$\pm$	0.4	16.0	0.577	^m
Neutrophil count ($\times 10^3/\mu\text{L}$)	6.2	$\pm$	2.3	5.9	6.2	$\pm$	2.7	5.8	0.868	^m
Lymphocyte count ($\times 10^3/\mu\text{L}$)	2.3	$\pm$	0.6	2.2	2.0	$\pm$	0.7	1.9	0.012	^m
NLR	3.0	$\pm$	1.7	2.6	3.4	$\pm$	2.4	2.9	0.108	^m
LMR	4.5	$\pm$	1.3	4.4	4.6	$\pm$	1.8	4.5	0.654	^t
Serum progesterone (ng/mL)	17.1	$\pm$	5.1	16.9	10.4	$\pm$	5.2	9.2	0.000	^m
Gestational age by LMP (days)	56.4	$\pm$	2.3	56.0	58.0	$\pm$	0.0	59.0	0.105	^m
Gestational age by USG (days)	52.3	$\pm$	4.5	52.0	49.7	$\pm$	5.0	49.0	0.002	^m

^t: Independent samples t-test, ^m: Mann-Whitney U test. NLR: Neutrophil lymphocyte ratio, LMR: Lymphocyte monocyte ratio, USG: Ultrasonography, SD: Standard deviation

Multivariable logistic regression analysis was performed to identify factors independently associated with first-trimester missed abortion (Table 2). The analysis revealed that lower serum progesterone levels [odds ratio (OR): 0.791, $p < 0.001$], smaller GS diameter (OR: 0.839, $p = 0.004$), and larger YS diameter (OR: 2.255, $p = 0.044$) were strong, independent indicators of missed abortion. While absolute lymphocyte counts showed a significant association in the univariate model ($p = 0.025$), they did not retain independent significance in the multivariable analysis. Notably, systemic inflammatory markers—including NLR, LMR, MPV, and PDW—were not significantly associated with missed abortion in either univariate or multivariable models ($p > 0.05$; Table 2).

ROC analysis was performed to determine how effectively each parameter could distinguish between missed abortions and healthy pregnancies (Figure 1). Serum progesterone demonstrated the highest diagnostic accuracy, with an AUC of 0.840 (95% CI: 0.764-0.915, $p < 0.001$), indicating excellent discriminatory power. Among the ultrasound markers, CRL (AUC: 0.754, $p < 0.001$) and GS diameter (AUC: 0.738, $p < 0.001$) also showed significant accuracy in identifying non-viable pregnancies. While lymphocyte counts had a modest but statistically significant discriminatory value (AUC: 0.631, $p = 0.012$), other hematological markers—specifically NLR, LMR, and MPV—did not demonstrate diagnostic utility ($p > 0.05$) (Figure 1).

Discussion

This study presents a prospective multimodal analysis evaluating the comparative diagnostic and associative value of sonographic

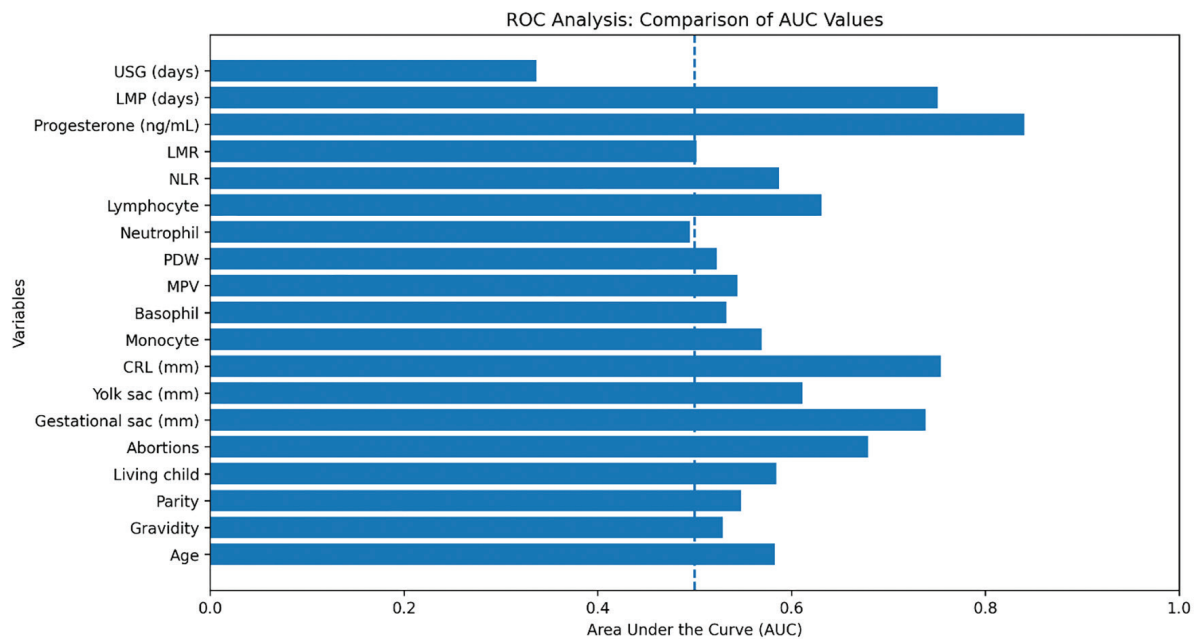
measurements, serum progesterone levels, and systemic inflammatory markers in first-trimester missed abortion. Our findings demonstrate that, in the missed abortion group, GS and CRL measurements were significantly diminished, whereas the YS diameter was significantly enlarged ($p < 0.001$ and $p = 0.039$, respectively). Serum progesterone levels were markedly lower in cases of EPL than in healthy controls ($p < 0.001$). Using multivariable logistic regression, we identified lower serum progesterone, smaller GS diameter, and larger YS diameter as strong independent indicators of missed abortion. Furthermore, ROC analysis confirmed that serum progesterone provides the highest discriminatory power with an AUC of 0.840, followed by CRL and GS diameter. Notably, despite the growing popularity of hematological indices such as NLR, LMR, and MPV in recent literature as potential indicators of pregnancy outcomes, these parameters did not demonstrate a significant independent association in our multivariable model.

Our literature search indicated that USG examinations and inflammatory biomarkers during early gestational weeks may vary. Marin et al. (25) in a study of 82 pregnant women, found that a YS size smaller or larger than normal was associated with pregnancy loss; similarly, a larger YS diameter was significantly associated with missed abortion in our study, further established as a strong independent indicator through multivariable analysis. Liu et al. (26) reported that small GS and CRL measurements were risk factors for EPL. Consistent with their findings, GS and CRL measurements in our case group were significantly smaller (26), and our findings were objectively validated by ROC analysis, demonstrating significant discriminatory power for both CRL and GS diameter. Suguna and Sukanya (27) demonstrated that while the

Table 2. Univariate and multivariable logistic regression analysis of factors associated with first-trimester missed abortion

	Univariate model					Multivariable model				
	OR	%95 CI			p	OR	%95 CI			p
Age (years)	1.052	0.991	-	1.118	0.097					
Gravida (n)	1.117	0.850	-	1.467	0.428					
Parity (n)	1.151	0.738	-	1.796	0.535					
Living children (n)	1.282	0.450	-	3.654	0.642					
Gestational sac diameter (mm)	0.847	0.786	-	0.913	0.000	0.839	0.746	-	0.944	0.004
Yolk sac diameter (mm)	1.860	1.107	-	3.124	0.019	2.255	1.022	-	4.975	0.044
CRL (mm)	0.906	0.821	-	1.000	0.050					
Monocyte count ($\times 10^3/\mu\text{L}$)	0.590	0.063	-	5.501	0.643					
Basophil count ($\times 10^3/\mu\text{L}$)	0.992	0.978	-	1.005	0.231					
Mean platelet volume (MPV) (fL)	0.854	0.608	-	1.200	0.363					
Platelet distribution width (PDW) (%)	1.677	0.948	-	2.965	0.076					
Neutrophil count ($\times 10^3/\mu\text{L}$)	1.002	0.869	-	1.155	0.977					
Lymphocyte count ($\times 10^3/\mu\text{L}$)	0.517	0.290	-	0.922	0.025					
NLR	1.117	0.928	-	1.343	0.241					
LMR	1.055	0.836	-	1.331	0.651					
Serum progesterone (ng/mL)	0.766	0.693	-	0.846	0.000	0.791	0.700	-	0.894	0.000
Gestational age by LMP (days)	1.208	1.109	-	1.317	0.000	1.358	1.171	-	1.574	0.000
Gestational age by USG (days)	0.886	0.817	-	0.961	0.003	0.805	0.702	-	0.922	0.002

OR: Odds ratio, CI: Confidence interval, NLR: Neutrophil lymphocyte ratio, LMR: Lymphocyte monocyte ratio

**Figure 1.** ROC analysis of sonographic and laboratory parameters for the identification of missed abortion. ROC: Receiver operating characteristic, USG: Ultrasonography, LMP: Last menstrual period, LMR: Lymphocyte-to-monocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, PDW: Platelet distribution width, MPV: Mean platelet volume, CRL: Crown-rump length

presence or absence of a YS has strong clinical value, its shape may be a more distinct indicator of poor outcomes than its diameter. In our study, we evaluated the diameter of the YS and found it to be significant in the comparative evaluation of missed abortion (27). Detti et al. (28) reported that small GS and large YS measurements were reliable indicators of pregnancy loss. Correspondingly, we found significantly smaller GS diameters and significantly larger YS diameters in patients with missed abortion (28), identifying both as independent associative factors in our multivariable model. Nayak et al. (29) reported that USG findings and lower progesterone levels play an important role in the identification of pregnancy loss. Unlike some of the aforementioned literature focusing on longitudinal prediction, our study performed a comparative evaluation of pregnancies diagnosed with missed abortion to healthy pregnancies, demonstrating significant differences in GS, YS, CRL measurements, and serum progesterone levels (29), with serum progesterone providing the highest diagnostic accuracy among all parameters evaluated.

Regarding hormonal markers, Kadam et al. (30) reported that higher progesterone levels were associated with viable pregnancies in women with threatened miscarriage, a finding corroborated by the significantly elevated progesterone levels observed in our control group, which was further established as the strongest independent indicator of missed abortion in our multivariable model and the parameter with the highest diagnostic accuracy. In terms of hematological profiles, Liu et al. (13) identified pre-pregnancy leukopenia and neutropenia in cases of spontaneous abortion; however, monocyte and basophil counts did not differ significantly between the groups in our study. Although the absolute lymphocyte count was significantly lower in our missed-abortion group, it did not retain independent significance in the multivariable analysis and demonstrated only modest discriminatory power. This lack of significant difference in other inflammatory parameters aligns with Kale et al. (31) who similarly reported that basophil and monocyte values did not differ significantly, reinforcing our finding that systemic inflammatory indices lack sufficient independent associative value for identifying first-trimester missed abortion.

The role of systemic inflammatory markers in missed abortion remains a subject of ongoing debate, characterized by conflicting results across various studies. While Feng et al. (15) suggested that a lower LMR correlates with an increased risk of pregnancy loss, our comprehensive analysis of basophil, monocyte, neutrophil counts, as well as MPV, PDW, NLR, and LMR, did not differ significantly between the groups. This lack of association was further confirmed by our multivariable analysis, which demonstrated that these hematological indices had no independent diagnostic value in our cohort. This result contrasts with the work of Topkara et al. (32), who found only the systemic immune-inflammatory index to be discriminative among various indices, including NLR, PLR, and MLR, in the clinical assessment of pregnancy outcomes for threatened miscarriage cases. Moreover, although Morisaki et al. (33) reported a gestational age-dependent decrease in LMR values, our study did not find LMR to be a significant indicator for missed abortion when comparing cases to healthy pregnancies, even after adjusting for gestational age in our multivariable model.

Discrepancies also extend to other well-studied indices, such as the NLR. A recent meta-analysis by Hantoushzadeh et al. (34) indicated significantly higher NLR values in women with recurrent miscarriage compared to healthy controls; however, our findings demonstrated that NLR lacked significant associative value for missed abortion in our specific study population, which was further supported by its lack of independent significance in our multivariable model and its failure to demonstrate significant discriminatory power in ROC analysis. Similarly, investigations into platelet indices have yielded inconsistent results. Yilmaz et al. (19) observed significantly elevated MPV levels in patients with recurrent miscarriage, whereas our data align more closely with Gürsoy et al. (16). Their study similarly reported that MPV, PDW, and their respective ratios did not differ significantly, a finding that remained consistent in our analysis even after adjusting for potential confounding factors. Overall, our results suggest that while these hematological parameters are cost-effective and easily accessible, they do not show a significant independent association with missed abortion in our cohort, particularly compared with the more consistent and robust differences observed in sonographic and hormonal markers.

A notable finding in our analysis was a significantly lower lymphocyte count in the missed abortion group compared with healthy controls ($p=0.012$). While this parameter demonstrated a modest but statistically significant discriminative ability in our ROC analysis (AUC: 0.631), it did not retain independent significance in multivariable analysis, suggesting that its role is likely secondary to other primary markers. This result is consistent with the established understanding that immune system dysfunction and abnormal inflammation are central to the pathophysiology of early pregnancy failure (34). Pregnancy requires a delicate balance of maternal-fetal immune tolerance to protect the fetal allograft; a decrease in peripheral lymphocytes may reflect a shift toward a pro-inflammatory state or a breakdown in this immunoprotective environment (15). Furthermore, while systemic indices like NLR did not reach statistical significance in our cohort, the observed lymphopenia aligns with the biological response where inflammation often leads to a rise in neutrophils and a corresponding fall in lymphocyte counts (34). This suggests that absolute lymphocyte counts may serve as sensitive, albeit non-specific, indicators of the altered immune milieu in missed abortion, potentially linked to the diminished immunomodulatory effects of lower progesterone levels observed in these cases (30).

Study Limitations

This study has several limitations that should be considered when interpreting the results. First, the sample size was relatively small, and the study was conducted at a single tertiary care center, which may limit the generalizability of our findings to more diverse populations. Second, missed abortion is a pathologically heterogeneous condition with multiple etiologies, including chromosomal abnormalities, embryonic factors, and maternal conditions, all of which were not investigated or differentiated in this cohort. This lack of etiological classification may limit the generalizability of our findings to specific subgroups of pregnancy loss. Third, hematological and hormonal parameters were assessed using single-point measurements taken at the time of diagnosis, precluding longitudinal analysis of subtle biological fluctuations during

early gestation. Fourth, although a statistically significant difference in gestational age was observed based on ultrasound measurements ($p=0.002$), we addressed this potential confounding effect by performing a multivariable logistic regression analysis. Our model confirmed that serum progesterone, GS diameter, and YS diameter remain strong, independent indicators of missed abortion even after adjusting for gestational age. Finally, although strict exclusion criteria were applied, certain unmeasured confounding factors, such as maternal subclinical infections, could have influenced systemic inflammatory markers. Despite these limitations, our study provides important prospective data to inform the comparative evaluation of multimodal markers for missed abortion.

Conclusion

Our study demonstrates that morphometric sonographic parameters (specifically GS and YS diameters) and serum progesterone levels are independently associated with first-trimester missed abortion. Multivariable logistic regression and ROC analysis confirm that these markers, particularly serum progesterone, which has high discriminatory power, serve as robust clinical indicators for assessing non-viable pregnancies at 6-9 weeks' gestation. Conversely, routine hematological indices, including NLR, LMR, and MPV, did not show a significant independent association in our multivariable model, indicating that they lack sufficient sensitivity to serve as reliable standalone markers for identifying asymptomatic fetal loss. While standardized sonographic and hormonal data provide more consistent diagnostic clarity, further large-scale multicenter prospective studies incorporating etiological subgrouping, such as chromosomal analysis, are warranted to validate these associations across the heterogeneous causes of pregnancy loss and to determine their clinical utility more definitively.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 331, date: 22.12.2023)

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

Footnotes

Authorship Contributions: Surgical and Medical Practices - S.A.K., N.İ.V., A.K.; Concept - N.İ.V.; Design - S.A.K., N.İ.V.; Data Collection or Processing - S.A.K., N.İ.V., A.K.; Analysis or Interpretation - S.A.K.; Literature Search - S.A.K., N.İ.V.; Writing - S.A.K., N.İ.V., A.K.

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