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ORIGINAL RESEARCH

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Microsatellite instability and survival outcomes in endometrial cancer: a comprehensive analysis of molecular subtypes and clinical implications

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Abstract

Background: Microsatellite instability (MSI) is a key biomarker in endometrial cancer, present in 20–30% of cases. The prognostic significance of MSI status, particularly MSI-high (MSI-H), remains under investigation, with conflicting reports on survival outcomes. This study aimed to evaluate the impact of MSI on overall and disease-free survival in endometrial carcinoma patients and compare characteristics between MSI-H and microsatellite stable (MSS) tumors. **Methods**: We retrospectively analyzed 100 patients with surgically treated endometrial carcinoma from March 2018 to March 2024. Patients were grouped as MSI-H or MSS based on immunohistochemical analysis of mismatch repair (MMR) proteins (MLH1 (mutL homolog 1), MSH2 (mutS homolog 2), MSH6 (mutS homolog 6), and PMS2 (postmeiotic segregation increased 2)) in formalin-fixed, paraffin-embedded (FFPE) tissue. We collected and analyzed clinicopathological data, including demographics, tumor features, molecular data, treatments, and survival outcomes. **Results**: Of the 100 patients, 34 (34%) were MSI-H and 66 (66%) were MSS. No significant differences were found in age, body mass index, or preoperative Cancer Antigen 125 (CA-125) levels. MSI-H tumors were significantly larger (median 65 mm *vs.* 45 mm, $p < 0.001$), had higher rates of mucinous differentiation (52.9% *vs.* 24.2%, $p = 0.008$), and more frequent poor differentiation (20.6% *vs.* 3.03%, $p = 0.003$). MSI-H status was also associated with more advanced-stage disease. The most common MMR protein losses were in PMS2 (79.2%) and MLH1 (67.6%). Over a median follow-up of 48 months, the 5-year overall and disease-free survival rates for the entire cohort were 71.3% and 67.9%, respectively. **Conclusions**: Although MSI-H endometrial carcinomas have distinct pathological features, MSI status did not significantly affect survival in this cohort. These findings suggest that MSI testing is more valuable as a predictive biomarker for immunotherapy than for prognostic purposes. Comprehensive molecular profiling, including p53 and DNA polymerase epsilon (POLE) analysis, is necessary for a complete understanding of prognosis in endometrial carcinoma.

Keywords

Microsatellite instability; Endometrial carcinoma; Mismatch repair deficiency; Molecular classification; Survival analysis; Immunotherapy

1. Introduction

Globally, endometrial carcinoma constitutes the fourth most prevalent malignant neoplasm affecting women and stands as the predominant gynecological malignancy within developed nations [1]. The occurrence of endometrial carcinoma has demonstrated a consistent upward trajectory, with approximately 417,000 newly diagnosed cases recorded internationally in 2020, contributing to roughly 97,000 fatalities per year [2]. This escalating pattern is primarily linked to the growing prevalence of obesity, diabetes mellitus, and demographic aging within industrialized countries [3]. The condition primarily impacts women in the postmenopausal period, with the median diagnostic age being 62 years; however, roughly one-quarter of all cases manifest in women of reproductive age [4]. In recent years, there have been major advances in understanding the molecular characteristics of endometrial carcinoma, significantly improving diagnostic approaches, prognostic assessment, and therapeutic strategies. The genomic investigation conducted by The Cancer Genome Atlas (TCGA) Research Network in 2013 delineated four distinctive molecular phenotypes of endometrial carcinoma: POLE-mutated (characterized by ultramutation), microsatellite instability-high (MSI-H), copy number low, and copy number high subtypes [5]. This molecular taxonomy has been subsequently enhanced through the establishment of the Proactive Molecular Risk

Classifier for Endometrial Cancer (ProMisE), which offers a practical framework for molecular subclassification within routine clinical settings [6]. Among these molecular subtypes, microsatellite instability represents one of the most clinically significant and therapeutically relevant categories. Microsatellites are short tandem repeats of one to five DNA bases distributed throughout the genome, predominantly occurring in non-coding regions [7]. When these repetitive sequences undergo length alterations due to insertion or deletion of repeating DNA bases, the phenomenon is termed microsatellite instability (MSI) [8]. MSI arises from defective DNA mismatch repair (MMR) systems that fail to rectify errors occurring during DNA replication, resulting in accumulation of mutations particularly in microsatellite regions that are susceptible to polymerase slippage during replication [9]. Microsatellite instability demonstrates an exceptionally elevated occurrence rate in endometrial carcinoma, manifesting in roughly 20–30% of all cases, which constitutes the most substantial frequency observed across prevalent malignant neoplasms [10]. This substantial occurrence rate presents a marked distinction when compared to colorectal carcinoma, wherein MSI is detected in merely 10–15% of sporadic instances and exceeds 90% in hereditary non-polyposis colorectal cancer (HNPCC) presentations [11]. The heightened incidence of MSI within endometrial carcinoma encompasses both inherited and spontaneous pathways of MMR dysfunction, with the predominant proportion of cases arising from somatic hypermethylation of the MLH1 promoter region rather than germline genetic mutations [12]. The underlying molecular pathways responsible for MSI development in endometrial carcinoma encompass impairment of essential MMR proteins, specifically MLH1, MSH2, MSH6, and PMS2 [13]. These proteins operate as heterodimeric complexes, wherein MLH1-PMS2 and MSH2-MSH6 partnerships serve critical functions in detecting and correcting DNA sequence errors and insertion-deletion anomalies [14]. Functional impairment of any constituent protein leads to in MMR deficiency (dMMR), subsequently promoting mutation accumulation and establishing the MSI phenotype [15]. Within endometrial carcinoma, MLH1 depletion secondary to promoter hypermethylation is the predominant pathogenic mechanism, accounting for approximately 70% of all dMMR presentations [16].

The clinical relevance of MSI in endometrial carcinoma transcends molecular categorization to incorporate prognostic ramifications and therapeutic implications. MSI-H endometrial carcinomas demonstrate characteristic clinicopathological attributes, encompassing correlations with decreased age at initial diagnosis, elevated tumor differentiation grade, enhanced lymphovascular space involvement, and distinctive histological characteristics including tumor-infiltrating lymphocytes and peritumoral lymphocytic infiltration [17]. These tumors also demonstrate characteristic molecular features, including high tumor mutational burden, increased neoantigen load, and enhanced immune infiltration, making them particularly susceptible to immune checkpoint inhibitor therapy [18]. Contemporary developments in immunotherapeutic interventions have transformed the therapeutic paradigm for MSI-H endometrial carcinoma. The regulatory authorization of pembrolizumab via the FDA (Food and Drug Administration) for MSI-H/dMMR solid malignancies, encompassing endometrial cancer (EC), signified a fundamental transition toward personalized medicine strategies [19]. Subsequent clinical investigations have established the exceptional therapeutic effect of immune checkpoint blockers in MSI-H EC, with objective response rates spanning from 48% to 57% in recurrent or advanced disease presentations [20]. The KEYNOTE-B21 clinical trial recently established substantial enhancement in disease-free survival utilizing adjuvant pembrolizumab combined with chemotherapy in high-risk dMMR endometrial carcinoma, demonstrating a hazard ratio of 0.31 (95% CI, 0.14–0.69) in favor of the pembrolizumab treatment arm [21]. Correspondingly, dostarlimab has established itself as an additional highly efficacious immunotherapeutic alternative for MSI-H endometrial carcinoma. The RUBY clinical trial established superior progression-free survival and overall survival outcomes with dostarlimab combined with a carboplatin-paclitaxel regimen compared to chemotherapy monotherapy in advanced or recurrent endometrial carcinoma [22]. The European Commission has recently broadened dostarlimab authorization to encompass all adult patients presenting with primary advanced or recurrent endometrial carcinoma, irrespective of MSI status, although the most substantial therapeutic benefit is documented in dMMR tumor presentations [23].

Despite these therapeutic advances, the prognostic significance of MSI status in endometrial cancer remains a subject of ongoing debate. While some studies suggest improved survival outcomes for MSI-H tumors, others report no significant prognostic difference or even worse outcomes in certain subgroups [24]. This controversy may reflect the heterogeneity within MSI-H endometrial cancers, differences in study populations, treatment protocols, and follow-up periods [25]. Additionally, the interaction between MSI status and other molecular features, such as POLE mutations or p53 abnormalities, may influence prognostic outcomes [26]. Advances in diagnostic testing have facilitated the integration of molecular classification into clinical practice. Immunohistochemical evaluation of MMR proteins remains the most widely used screening method, offering high sensitivity and specificity for detecting dMMR [27]. However, newer molecular approaches, including the Idylla MSI test, provide rapid, automated assessment of MSI status with high concordance to traditional methods [28]. These technological advances have made routine MSI testing feasible in clinical practice, enabling personalized treatment decisions based on molecular characteristics [29].

The current study aims to contribute to the understanding of MSI in endometrial cancer by providing a comprehensive analysis of survival outcomes and clinicopathological characteristics in a well-defined cohort of patients. By examining the relationship between MSI status and clinical outcomes, this research seeks to clarify the prognostic significance of MSI in endometrial cancer and inform evidence-based treatment decisions in the era of precision oncology.

2. Materials and methods

2.1 Study design and patient selection

This retrospective cohort investigation was conducted on 100 patients diagnosed with endometrial carcinoma who received surgical intervention between March 2018 and March 2024 at the Department of Oncology, Azerbaijan Medical University, Baku, Azerbaijan. The study protocol received approval from the Azerbaijan Medical University Clinical Research Ethics Committee (Decision No. 205, dated 05 April 2024). It was conducted in accordance with the principles of the Declaration of Helsinki. All patients included in this study had histologically confirmed endometrial carcinoma based on preoperative endometrial biopsy performed according to standard clinical protocols. The diagnosis was established by experienced gynecologic pathologists using WHO 2020 classification criteria. Subsequently, all hysterectomy specimens underwent comprehensive histopathological review to confirm the diagnosis and determine final tumor characteristics. Patients aged 18 years and older who underwent surgical treatment for endometrial cancer during the study period were identified through electronic medical files using International Classification of Diseases (ICD) codes for endometrial malignancy. Inclusion criteria comprised: (1) histologically confirmed endometrial adenocarcinoma, (2) complete surgical staging including total hysterectomy with bilateral salpingo-oophorectomy, (3) availability of MSI status evaluation through immunohistochemical assessment of MMR proteins, and (4) adequate follow-up data for survival analysis with minimum 6 months follow-up unless death occurred within this period. Exclusion criteria included: (1) preoperative evidence of distant metastatic disease, (2) synchronous primary malignancies, (3) incomplete surgical staging, (4) insufficient tissue for molecular analysis, and (5) patients lost to follow-up within the first six months post-surgery. Patients with isolated peritoneal metastases discovered during surgery were included in the analysis if complete cytoreductive surgery was achieved.

All surgical procedures were performed by gynecologic oncologists using standardized techniques. The standard surgical approach included total hysterectomy with bilateral salpingo-oophorectomy, with the extent of additional procedures determined by preoperative imaging, intraoperative findings, and tumor characteristics.

Comprehensive surgical staging was performed according to International Federation of Gynecology and Obstetrics (FIGO) 2023 guidelines and included:

- Total hysterectomy with bilateral salpingo-oophorectomy.
- Pelvic lymphadenectomy (when indicated based on risk factors).
- Para-aortic lymphadenectomy (for high-risk cases).
- Omentectomy (for serous or clear cell histology).
- Peritoneal biopsies and cytology (when indicated).

The decision for lymphadenectomy was based on established risk factors, including tumor grade, depth of myometrial invasion, lymphovascular space invasion, and histological subtype. A minimum of 12 lymph nodes was required for adequate pelvic lymphadenectomy, and a minimum of 5 nodes for para-aortic lymphadenectomy.

All surgical specimens were processed according to standardized protocols by experienced gynecologic pathologists. Histopathological evaluation included assessment of tumor histological subtype according to the WHO 2020 classification, FIGO grade (for endometrioid carcinomas), depth of myometrial invasion, lymphovascular space invasion (LVSI), cervical stromal invasion, adnexal involvement, peritoneal cytology, and lymph node status.

Tumor size was measured as the maximum dimension and recorded in millimeters (mm). Lymphovascular space invasion (LVSI) was assessed according to FIGO 2023 staging criteria and classified as absent, focal, or substantial based on the extent of vascular involvement. All cases were evaluated by experienced gynecologic pathologists using standardized criteria, and consensus was reached in cases of diagnostic uncertainty. The FIGO 2023 classification system was chosen as it represents the most current international standard for endometrial carcinoma staging and prognostic assessment.

Molecular Analysis and MSI Testing. Formalin-fixed, paraffin-embedded (FFPE) tissue blocks were retrieved from the institutional pathology archives for all cases included in this retrospective study. All specimens were stored under standard conditions and assessed for tissue quality before analysis. MMR immunohistochemistry was performed on FFPE sections, with some cases requiring retrospective analysis as routine MMR testing was not standard practice during the early study period. Fresh 4-μm sections were cut from archived FFPE blocks to ensure optimal staining quality and antigen preservation.

MSI status was determined through immunohistochemical evaluation of four mismatch repair (MMR) proteins: mutL homolog 1 (MLH1), mutS homolog 2 (MSH2), mutS homolog 6 (MSH6), and postmeiotic segregation increased 2 (PMS2). Immunohistochemistry was performed on 4-μm-thick formalin-fixed, paraffin-embedded (FFPE) tissue sections using automated immunostaining platforms. The following primary antibodies were utilized: MLH1 (clone M1, Ventana Medical Systems, Tucson, AZ, USA), MSH2 (clone G219-1129, Ventana Medical Systems, Tucson, AZ, USA), MSH6 (clone 44, Ventana Medical Systems, Tucson, AZ, USA), and PMS2 (clone EPR3947, Ventana Medical Systems, Tucson, AZ, USA). Staining was evaluated by two independent pathologists who were blinded to the clinical outcomes. Nuclear staining in tumor cells was assessed, with adjacent normal tissue and inflammatory cells serving as internal positive controls. Complete loss of nuclear staining in tumor cells with retained staining in normal cells was considered indicative of MMR deficiency. Patients were classified into two groups based on MMR protein expression:

- MSI-High (MSI-H): Loss of expression of one or more MMR proteins (MLH1, MSH2, MSH6, or PMS2).
- Microsatellite Stable (MSS): Retained expression of all four MMR proteins.

The MSI-Low (MSI-L) category was not utilized in this study as it is not routinely distinguished in clinical practice and has unclear clinical significance.

Molecular Subtyping Limitations. A significant limitation of this study is the lack of comprehensive molecular subtyping within the MSS cohort. p53 immunohistochemistry and POLE mutation analysis were not routinely performed during the study period, preventing stratification into p53-abnormal and

NSMP (No Specific Molecular Profile) subgroups according to the ProMisE classification system. This represents a significant limitation that should be addressed in future studies, as molecular subtyping has become essential for optimal endometrial carcinoma management.

Comprehensive clinical data were collected through review of electronic medical records using a standardized case report form. Variables collected included demographic characteristics (age at diagnosis, body mass index, menopausal status, parity and reproductive history, comorbidities), family history (personal or family history of Lynch syndrome-associated cancers, genetic counseling and testing when performed), preoperative assessment (CA-125 levels, imaging findings, endometrial biopsy results), treatment details (surgical approach, extent of surgical staging, adjuvant therapy, treatment complications), and follow-up outcomes (local recurrence, distant metastasis, disease-free survival, overall survival, cause of death). Patients were followed according to institutional guidelines with regular surveillance visits. The follow-up schedule included clinical examination every 3 months for the first 2 years, every 6 months for years 3–5, and annual follow-up thereafter. Surveillance imaging was performed based on clinical indication and risk factors. CA-125 monitoring was utilized in patients with elevated preoperative levels or high-risk features.

Follow-up duration was calculated from the date of surgery to the last clinical contact or death. Given the study period from March 2018 to March 2024, the maximum possible follow-up was 72 months for patients treated at the beginning of the study period. Patients with less than 6 months of follow-up were excluded from survival analysis unless death occurred within this period.

2.2 Statistical analysis

Statistical analysis was performed using R version 4.0.0 software. Descriptive statistics were presented as frequencies and percentages for categorical variables, and as mean ± standard deviation or median (interquartile range) for continuous variables, depending on data distribution.

Normal distribution was assessed using histograms, Q-Q (Quantile-Quantile) plots, and normality tests (Shapiro-Wilk test). Categorical variables were compared using Pearson's chi-square test or Fisher's exact test when expected cell counts were less than 5. For tables larger than 2×2 with multiple cells having expected counts <5, the Fisher-Freeman-Halton test was employed. Continuous variables were compared between two groups using an independent samples *t*-test for normally distributed data or a Mann-Whitney U test for non-normally distributed data. Survival analysis was performed using Kaplan-Meier methodology with log-rank tests for group comparisons. Overall survival was defined as the time from surgery to death from any cause or last follow-up. Disease-free survival was defined as the time from surgery to first recurrence (local or distant), death from disease, or last follow-up. Univariate and multivariate Cox proportional hazards regression analyses were performed to identify factors associated with survival outcomes. Variables with $p < 0.10$ in univariate analysis were included in multivariate models. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated.

One-, three-, and five-year survival probabilities were calculated using the Kaplan-Meier method. Statistical significance was defined as $p < 0.05$ for all analyses.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Azerbaijan Medical University Clinical Research Ethics Committee. Patient confidentiality was maintained throughout the study, and all data were de-identified prior to analysis. Since the study was retrospective and observational, the Clinical Research Ethics Committee waived the need for written informed consent.

3. Results

The final analytical cohort comprised 100 patients diagnosed with endometrial carcinoma. Demographic and clinicopathological features of the study population are detailed in Table 1. Immunohistochemical assessment of mismatch repair (MMR) proteins revealed microsatellite stability (MSS) in 66 patients (66%) and microsatellite instability-high (MSI-H) in 34 patients (34%) (Fig. 1). The median age at diagnosis was 72.5 years (IQR: 64.0–79.0) in the MSS group and 71.0 years (IQR: 63.0–79.2) in the MSI-H group, with no statistically significant difference between groups ($p = 0.519$). Body mass index (BMI) was comparable between groups, with median values of 25.1 kg/m^2 (IQR: 24.1–26.9) in the MSS group and 24.6 kg/m^2 (IQR: 23.5–25.6) in the MSI-H group ($p = 0.082$). Preoperative CA-125 levels showed no significant difference between groups, with median values of 2.60 ng/mL (IQR: 1.65–6.0) in the MSS group and 2.78 ng/mL (IQR: 1.18–5.39) in the MSI-H group ($p = 0.496$). Patient Demographics and Clinical Characteristics are presented in Table 1. No significant differences were observed between MSS and MSI-H groups regarding tumor location, surgery type, or adjuvant therapy administration.

The pathological parameters of endometrial carcinoma are shown in Table 2. Significant differences were detected between MSS and MSI-H groups in several key pathological features. Regarding histological subtypes, endometrioid adenocarcinoma was the predominant type in the MSS group (72.7%), while mucinous carcinoma was more common in the MSI-H group (52.9% *vs.* 24.2%, $p = 0.008$). Clear cell carcinoma occurred in 1.52% of MSS cases and 5.88% of MSI-H cases ($p = 0.266$), while carcinosarcoma occurred in 1.52% of MSS cases, 2.94% of MSI-H cases ($p = 1.000$).

Tumor differentiation showed significant differences between groups ($p = 0.003$). While moderately differentiated tumors were most common in both groups (93.9% in MSS *vs.* 70.6% in MSI-H), poorly differentiated neoplasms were significantly more common in the MSI-H cases (20.6% *vs.* 3.03%). Well-differentiated tumors comprised 3.03% of MSS cases and 8.82% of MSI-H cases.

Tumor size demonstrated a statistically significant difference, with MSI-H tumors being substantially larger than MSS tumors. The median tumor size was 65 mm (IQR: 50–80 mm) in the MSI-H group compared to 45 mm (IQR: 35–64 mm) in the MSS group ($p < 0.001$).

The total number of lymph nodes examined showed no critical difference between groups, with a median of 34.0

TABLE 1. Patient demographics and clinical characteristics total (n = 100).

Characteristic	MSS (n = 66)	MSI-H (n = 34)	*p* value
Age, median (IQR)	72.5 (64.0–79.0)	71.0 (63.0–79.2)	0.519
BMI (kg/m^2), median (IQR)	25.1 (24.1–26.9)	24.6 (23.5–25.6)	0.082
Preoperative CA-125 (ng/mL), median (IQR)	2.60 (1.65–6.0)	2.78 (1.18–5.39)	0.496
Tumor Location, n (%)			
Fundus	15 (22.7)	7 (20.6)	0.309
Corpus	24 (36.4)	9 (26.5)	
Lower Uterine Segment	14 (21.2)	10 (29.4)	
Cervical Involvement	13 (19.7)	6 (17.6)	
Adnexal Involvement	0 (0.0)	2 (5.88)	
Surgery Type, n (%)			
Emergency	15 (22.7)	4 (11.8)	0.292
Elective	51 (77.3)	30 (88.2)	
Adjuvant therapy, n (%)			
Yes	34 (51.5)	15 (44.1)	0.624
No	32 (48.5)	19 (55.9)	

MSS: Microsatellite Stable; MSI-H: Microsatellite Instability-High; BMI: Body Mass Index; IQR: Interquartile Range; CA-125: Cancer Antigen 125.

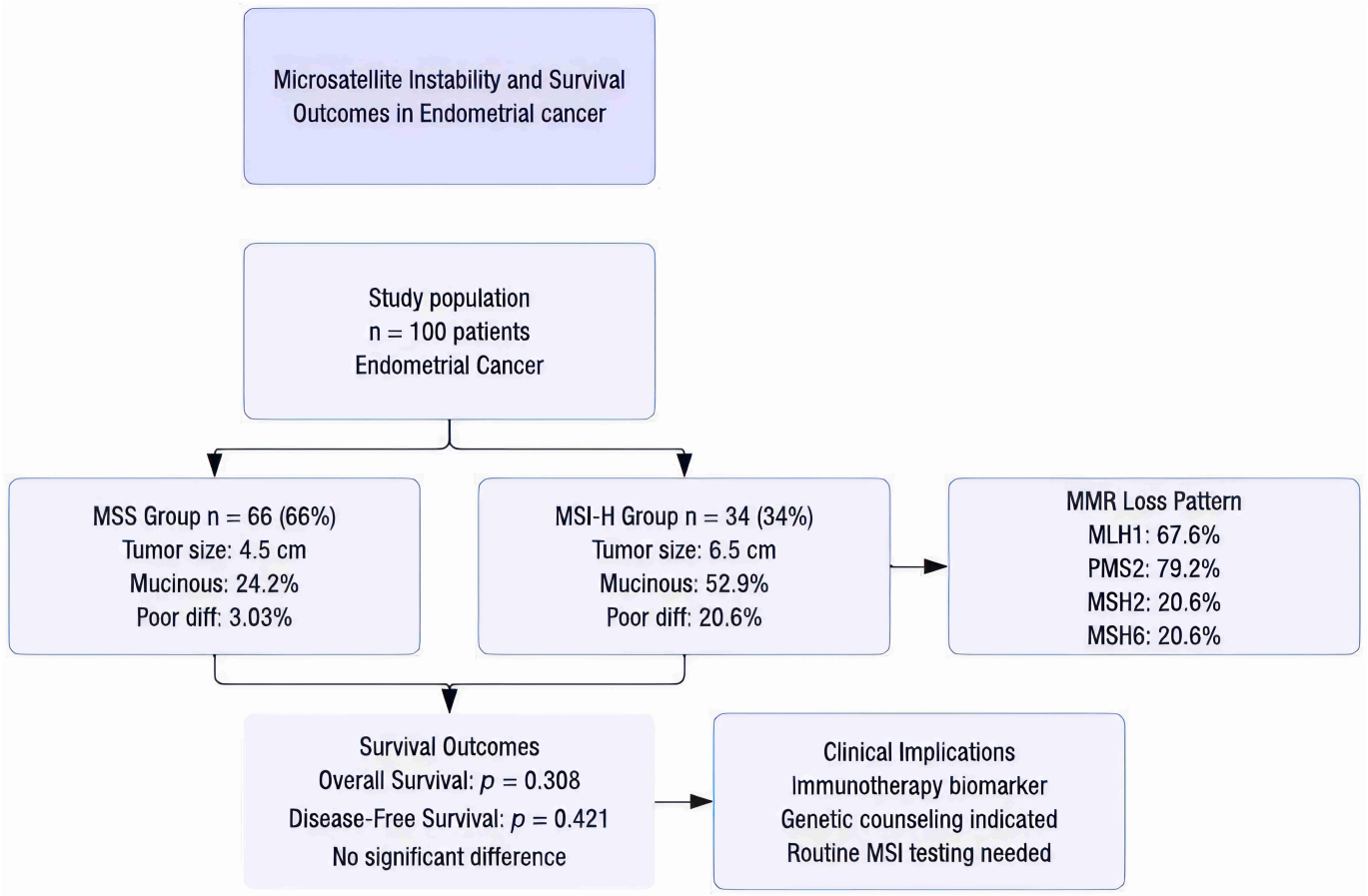

FIGURE 1. Microsatellite instability and survival outcomes in endometrial cancer. MSS: Microsatellite Stable; MSI-H: Microsatellite Instability-High; MMR: mismatch repair; MLH1: mutL homolog 1; MSH2: mutS homolog 2; MSH6: mutS homolog 6; PMS2: postmeiotic segregation increased 2.

TABLE 2. Pathological characteristics of endometrial tumors total (n = 100).

Characteristic	MSS (n = 66)	MSI-H (n = 34)	*p* value
Histological Subtype, n (%)			
Endometrioid Adenocarcinoma	48 (72.7)	13 (38.2)	0.002
Clear Cell Carcinoma	1 (1.52)	2 (5.88)	0.266
Mucinous Carcinoma	16 (24.2)	18 (52.9)	0.008
Carcinosarcoma	1 (1.52)	1 (2.94)	1.000
Tumor Size (mm), median (IQR)	45 (35–63)	65.0 (50–80)	<0.001
Tumor Differentiation, n (%)			
Well Differentiated	2 (3.03)	3 (8.82)	
Moderately Differentiated	62 (93.9)	24 (70.6)	0.003
Poorly Differentiated	2 (3.03)	7 (20.6)	
Total Lymph Nodes, median (IQR)	34.0 (24.2–49.0)	40.5 (23.8–52.0)	0.313
Metastatic Lymph Nodes, n (%)	24 (36.4)	8 (23.5)	0.281
Metastatic Lymph Node Count, median (IQR)	2 (1.00–3.25)	4.5 (2.75–5.50)	0.106
Lymphovascular Invasion, n (%)	19 (28.8)	13 (38.2)	0.463
Myometrial Invasion, n (%)	24 (36.4)	7 (20.6)	0.165
MMR Protein Loss, n (%)			
MLH1	0 (0.0)	23 (67.6)	
MSH2	0 (0.0)	7 (20.6)	<0.001
MSH6	0 (0.0)	7 (20.6)	
PMS2	0 (0.0)	27 (79.2)	

MSS: Microsatellite Stable; MSI-H: Microsatellite Instability-High; MMR: Mismatch Repair; IQR: Interquartile Range; MLH1: mutL homolog 1; MSH2: mutS homolog 2; MSH6: mutS homolog 6; PMS2: postmeiotic segregation increased 2.

nodes (IQR: 24.2–49.0) in the MSS group and 40.5 nodes (IQR: 23.8–52.0) in the MSI-H group ($p = 0.313$). Lymphatic metastasis was present in 24 patients (36.4%) in the MSS group and 8 cases (23.5%) in the MSI-H group, although the mentioned difference was insignificant ($p = 0.281$). Among patients with metastatic nodes, the median number of involved nodes was two (IQR: 1.00–3.25) in the MSS group, 4.5 (IQR: 2.75–5.50) in the MSI-H group ($p = 0.106$).

Lymphovascular invasion was detected in 28.8% of MSS cases and 38.2% of MSI-H cases ($p = 0.463$). Deep myometrial invasion (>50%) was present in 36.4% of MSS cases, 20.6% of MSI-H cases ($p = 0.165$).

MMR Protein Expression Patterns. Among MSI-H cases, PMS2 loss was observed in 79.2% (27/34) of cases, while MLH1 loss was detected in 67.6% (23/34) of cases. This pattern reflects the molecular dependency of PMS2 protein stability on MLH1 expression, where MLH1 deficiency leads to secondary PMS2 protein degradation even when PMS2 gene expression remains intact. MSH2 and MSH6 losses were each present in 7 patients (20.6%). The pattern of MMR protein loss showed significant correlation with MSI status ($p < 0.001$), as expected by the study design.

The higher frequency of PMS2 loss compared to MLH1 loss is consistent with the established molecular relationship between these proteins. PMS2 protein requires MLH1 for stabilization, and MLH1 deficiency whether due to promoter hypermethylation or other mechanisms results in rapid PMS2 protein degradation. This phenomenon explains why PMS2 immunohistochemistry may be more sensitive than MLH1 staining for detecting MLH1-related MMR deficiency.

The FIGO staging distribution showed significant differences between MSS and MSI-H groups (Table 3). No Stage I tumors were observed in the MSI-H group, while 15.2% of MSS tumors were Stage I ($p = 0.019$). Stage II tumors were most prevalent in the MSI-H group (67.6% *vs.* 47.0%), while Stage III tumors were more common in the MSS group (37.9% *vs.* 32.4%). No Stage IV tumors were observed in either group.

Family history assessment according to current criteria revealed significant differences between groups (Table 4). Positive family history was most common in the MSI-H group, with 16 patients (47.1%) meeting one or more criteria compared with 12 patients (18.2%) in the MSS group ($p = 0.004$). Genetic testing was performed in 12 patients (35.3%) in the MSI-H group and no patients in the MSS group ($p < 0.001$), reflecting clinical practice guidelines for genetic evaluation in patients with dMMR tumors.

Surgical complications were comparable between groups, with no significant differences in postoperative morbidity ($p = 0.399$). The most common complications were pulmonary complications (9 patients), urinary complications (7 patients), surgical site infections (5 patients), wound dehiscence (2 patients), intra-abdominal hematoma (1 patient), and postopera-

TABLE 3. FIGO staging distribution total (n = 100).

Stage	MSS (n = 66)	MSI-H (n = 34)	*p*-value
Stage I, n (%)	10 (15.2)	0 (0.0)	0.019
Stage II, n (%)	31 (47.0)	23 (67.6)	
Stage III, n (%)	25 (37.9)	11 (32.4)	
Stage IV, n (%)	0 (0.0)	0 (0.0)	

MSS: Microsatellite Stable; MSI-H: Microsatellite Instability-High.

TABLE 4. Family history assessment (n = 100).

Diagnostic Criteria	MSS (n = 66)	MSI-H (n = 34)	*p* value
Negative, n (%)	54 (81.8)	18 (52.9)	0.004
Criterion 1 Positive, n (%)	3 (4.55)	8 (23.5)	
Criterion 2 Positive, n (%)	7 (10.6)	4 (11.8)	
Criterion 3 Positive, n (%)	2 (3.03)	4 (11.8)	
Genetic Testing Performed, n (%)	0 (0.0)	12 (35.3)	<0.001

MSS: Microsatellite Stable; MSI-H: Microsatellite Instability-High.

tive cerebrovascular accident (1 patient). Adjuvant chemotherapy was administered to 49 patients (49%) overall, with no significant difference between MSS (51.5%) and MSI-H (44.1%) groups ($p = 0.624$). The decision for postoperative management was made according to pathological parameters, tumor stage, and molecular characteristics, in accordance with international guidelines.

During a median follow-up period of 48 months (range: 6–72 months), comprehensive survival analysis was performed for the entire cohort. Local recurrence occurred in 8 patients overall: 4 patients (6.06%) in the MSS group and 4 patients (11.8%) in the MSI-H group, with no statistically significant difference ($p = 0.439$). Distant metastasis developed in 10 patients: 6 patients (9.09%) in the MSS group and 4 patients (11.8%) in the MSI-H group ($p = 0.731$). The metastatic sites were the peritoneum (6 patients), lung (2 patients), and liver (2 patients). Five patients developed both locoregional and distant metastasis. Overall mortality occurred in 19 patients during the observation period: 11 patients (16.7%) in the MSS group and 8 patients (23.5%) in the MSI-H group ($p = 0.576$). The median overall survival was not reached for either group during the follow-up period.

The Kaplan-Meier survival curves demonstrated near superimposability of progression-free survival and overall survival. This pattern reflects the aggressive nature of recurrent endometrial carcinoma and the limited efficacy of salvage therapies during the study period. Among patients who experienced disease progression, the median time from progression to death was 8 months (range: 2–18 months), indicating rapid clinical deterioration following recurrence. Most patients who experienced disease progression had limited response to salvage therapies available during the study period, resulting in minimal separation between progression-free survival (PFS) and overall survival (OS) events.

Complete molecular subtyping according to the ProMisE classification was not available for this cohort. Within the MSS group (n = 66), molecular stratification into p53-abnormal and NSMP subgroups could not be performed due to a lack of p53 immunohistochemistry and POLE mutation data.

Univariate analysis identified several factors associated with overall survival and disease-free survival. Age, tumor size, lymph node status, and adjuvant chemotherapy showed significant associations with survival outcomes in univariate analysis. The 1-, 3-, and 5-year estimated survival outcomes for the entire cohort and by MSI status are presented in Table 5. While MSI-H patients showed numerically lower survival rates, these differences did not reach statistical significance ($p = 0.308$ for overall survival, $p = 0.421$ for disease-free survival).

TABLE 5. Survival probabilities by MSI status.

Time Point	Overall Survival (%)	Disease-Free Survival (%)
Entire Cohort (n = 100)		
1-year	89.2	86.4
3-year	78.5	74.8
5-year	71.3	67.9
MSS Group (n = 66)		
1-year	91.8	88.7
3-year	81.2	77.3
5-year	74.6	70.8
MSI-H Group (n = 34)		
1-year	84.7	81.5
3-year	73.1	69.2
5-year	65.4	61.8

MSS: Microsatellite Stable; MSI-H: Microsatellite Instability-High.

4. Discussion

This comprehensive analysis of microsatellite instability in endometrial cancer provides important insights into the clinicopathological characteristics and survival outcomes associated with MSI-H status. Our findings contribute to the ongoing discourse on the prognostic importance of MSI in endometrial carcinoma, highlighting the complex relationship between molecular features and clinical outcomes in this heterogeneous disease. The observed prevalence of MSI-H in our research group (34%) aligns closely with recent literature reports, which consistently demonstrate that endometrial cancer exhibits the highest frequency of MSI among common malignancies [30]. This finding is particularly significant when compared to colorectal cancer, where MSI occurs in only 10–15% of sporadic cases [31]. The prevalence of MSI in endometrial carcinoma reflects the unique molecular pathogenesis of this disease, with the majority of dMMR cases resulting from somatic MLH1 promoter hypermethylation rather than germline mutations [32].

Recent advances in molecular classification have further emphasized the clinical importance of MSI testing in endometrial cancer. The integration of molecular features into the FIGO 2023 staging system represents a paradigm shift toward precision medicine in gynecologic oncology [33]. This updated staging system recognizes the prognostic significance of molecular subtypes and their impact on treatment decisions, particularly in the era of immunotherapy [34].

Our observation that PMS2 loss was the most frequent MMR protein abnormality (79.2% of MSI-H cases) is consistent with the established understanding that PMS2 expression is dependent on MLH1 stability [35]. The co-occurrence of MLH1 and PMS2 loss in the numerous cases (67.6% MLH1 loss) supports the predominant role of MLH1 promoter hypermethylation in sporadic endometrial carcinoma [36]. The lower frequency of MSH2 and MSH6 losses (20.6% each) likely represents cases associated with Lynch syndrome or other hereditary mechanisms [37].

The higher frequency of PMS2 loss compared to MLH1 loss in our cohort is consistent with the established molecular relationship between these proteins. PMS2 protein requires MLH1 for stabilization, and MLH1 deficiency—whether due to promoter hypermethylation or other mechanisms results in rapid PMS2 protein degradation. This phenomenon has been consistently reported in endometrial carcinoma and explains why PMS2 immunohistochemistry may be more sensitive than MLH1 staining for detecting MLH1 promoter hypermethylation-related MMR deficiency [38].

Our study revealed several distinctive clinicopathological features associated with MSI-H endometrial cancers that warrant detailed discussion. The significantly larger tumor size observed in MSI-H cases (median 65 mm *vs.* 45 mm, $p < 0.001$) represents a novel finding that has not been consistently reported in previous studies. This observation may reflect the rapid growth potential of MSI-H tumors due to their high mutational burden and altered DNA repair mechanisms [39]. The increased frequency of mucinous differentiation in MSI-H tumors (52.9% *vs.* 24.2%, $p = 0.008$) aligns with previous reports suggesting that mucinous features are more common in dMMR endometrial cancers [40]. This histological pattern may reflect the underlying molecular alterations that characterize MSI-H tumors, including mutations in genes involved in mucin production and secretion [41]. The higher prevalence of poor differentiation in MSI-H tumors (20.6% *vs.* 3.03%, $p = 0.003$) appears paradoxical given the generally favorable prognosis associated with MSI-H status in other malignancies [42]. However, this finding aligns with recent research suggesting that the connection between MSI status and tumor grade in endometrial cancer is complex and may not follow the same patterns observed in colorectal cancer [43]. One of the most significant findings of our study is the absence of a statistically important difference in OS and DFS (diseasefree survival) between MSI-H and MSS endometrial carcinomas. This observation contrasts with the well-established prognostic benefit of MSI status in colon cancer and raises important questions about the clinical impact of MSI in endometrial carcinoma [44].

The near superimposability of PFS and OS curves observed in our study warrants specific discussion. This pattern reflects the aggressive nature of recurrent endometrial carcinoma during the study period, with limited effective salvage treatment options available. The minimal separation between PFS and OS events reflects the poor prognosis associated with recurrent disease and the lack of effective second-line treatments during our study period (2018–2024). This finding contrasts with more recent reports where immunotherapy has improved post-progression survival in MSI-H tumors, highlighting the evolving treatment landscape in endometrial carcinoma [45].

Recent clinical trials have demonstrated remarkable efficacy of immune checkpoint inhibitors in MSI-H endometrial carcinoma. The KEYNOTE-B21 trial results, published by Van Gorp T *et al*. [46], provide important context for interpreting our findings. This landmark study showed significant improvement in disease-free survival with adjuvant pembrolizumab plus chemotherapy in high-risk dMMR endometrial carcinoma, with a hazard ratio of 0.31 (95% CI, 0.14–0.69) favoring the pembrolizumab arm. The two-year disease-free survival rates were 92.4% in the pembrolizumab group versus 80.2% in the placebo group.

Similarly, the RUBY trial demonstrated superior outcomes with dostarlimab combined with carboplatin-paclitaxel compared to chemotherapy alone in advanced or recurrent endometrial carcinoma [47]. These results suggest that while MSI status may not independently predict prognosis, it serves as a crucial biomarker for treatment selection, particularly for immunotherapy [48].

The implementation of molecular classification into endometrial carcinoma treatment has fundamentally altered our approach to this disease [49]. The recent expansion of dostarlimab approval by the European Commission to include patients with primary advanced or recurrent endometrial carcinoma reflects the growing recognition of immunotherapy's role in treatment [50]. However, the greatest benefit is consistently observed in dMMR tumors, emphasizing the importance of accurate molecular characterization [51].

Recent advances in MSI testing methodology have improved the accessibility of molecular diagnosis. Studies

have shown that newer molecular approaches, including the Idylla MSI test, provide rapid, automated assessment of MSI status with high concordance to traditional immunohistochemical methods [52]. While these concordance rates highlight the need for continued refinement of testing approaches, they also underscore the clinical utility of current methods for treatment selection [53].

The integration of comprehensive molecular profiling into routine clinical practice represents a critical advancement in endometrial cancer management. The ProMisE classification system has been validated across multiple international cohorts and provides a practical framework for molecular subtyping [54]. Recent studies have demonstrated the prognostic value of complete molecular classification, with distinct survival outcomes observed across the four molecular subtypes [55].

A significant limitation of our study is the lack of comprehensive molecular subtyping within the MSS cohort. The absence of p53 immunohistochemistry and POLE mutation analysis prevented stratification into p53-abnormal and NSMP subgroups according to the ProMisE classification. This molecular heterogeneity within the MSS cohort may have masked important prognostic differences and contributed to the lack of significant survival differences between MSI-H and MSS groups. The MSS group likely contains both p53-abnormal and NSMP tumors, which have distinct prognostic implications. p53-abnormal endometrial carcinomas are associated with poor prognosis and aggressive behavior, while NSMP tumors generally have intermediate outcomes [56].

Our finding of significantly increased family history positivity in the MSI-H group (47.1% *vs.* 18.2%, $p = 0.004$) underscores the importance of genetic counseling and testing in patients with dMMR endometrial cancer [57]. The higher frequency of diagnostic criteria positivity in MSI-H patients reflects the association between hereditary cancer syndromes and MMR deficiency [58]. The fact that genetic testing was performed in 35.3% of MSI-H patients but no MSS patients reflects current clinical practice guidelines recommending genetic evaluation for all patients with dMMR tumors [59].

Lynch syndrome-associated endometrial cancers typically present at younger ages and may have different clinical behaviors compared to sporadic MSI-H tumors [60]. The distinction between hereditary and sporadic dMMR endometrial cancers has important implications for family counseling, surveillance recommendations, and risk-reducing strategies [61].

Several limitations of our study warrant acknowledgment. The retrospective design and single-institution experience may limit the generalizability of our findings. The relatively modest sample size, while adequate for the primary analysis, may have limited power to detect smaller survival differences between groups. Additionally, the heterogeneity in treatment approaches over the study period may have influenced survival outcomes, particularly regarding the limited availability of immunotherapy during the early study period.

The absence of standardized treatment protocols represents a significant limitation, particularly for progression-free survival analysis. Treatment decisions were made according to institutional guidelines and physician discretion based on individual patient factors. While this limits the comparability of survival outcomes, it reflects real-world clinical practice and provides valuable insights into the natural history of MSI-H endometrial carcinoma. Future prospective studies with standardized treatment protocols are needed to definitively establish the prognostic impact of MSI status.

The lack of comprehensive molecular profiling, including POLE mutation testing and p53 analysis, represents a significant limitation in the context of current molecular classification systems [62]. Future studies should incorporate complete molecular characterization to better understand the prognostic implications of different molecular subtypes [63]. The evolving treatment landscape, particularly the introduction of immunotherapy for MSI-H endometrial cancer, may alter survival outcomes in ways that are not captured in our historical cohort [64]. Despite the absence of significant survival differences in our cohort, MSI status remains a crucial biomarker for treatment selection in endometrial cancer [65]. The established efficacy of immunotherapy in MSI-H tumors necessitates routine MSI testing for all endometrial cancer patients, particularly those with advanced or recurrent disease [66]. The integration of molecular classification into staging systems, as reflected in the 2023 FIGO staging revision, emphasizes the clinical importance of molecular characterization [67]. Healthcare systems must adapt to incorporate routine molecular testing into standard care pathways while ensuring equitable access to these technologies [68]. The development of treatment algorithms incorporating molecular features alongside traditional clinicopathological factors will be essential for optimizing patient outcomes [69]. The ongoing evolution of treatment options, including novel immunotherapy combinations and targeted therapies, will require continuous refinement of these algorithms [70].

Several research priorities emerge from our findings and the current state of knowledge in endometrial cancer. Large-scale, prospective studies incorporating comprehensive molecular profiling are needed to definitively establish the prognostic significance of MSI status in the context of modern treatment approaches [71]. The development of predictive biomarkers beyond MSI status will be crucial for optimizing immunotherapy selection and identifying patients most likely to benefit from specific treatment approaches [72].

Emerging technologies, including liquid biopsies and artificial intelligence-based image analysis, may provide additional tools for patient stratification [73]. The investigation of resistance mechanisms to immunotherapy in MSI-H endometrial cancer will be essential for developing strategies to overcome treatment failure [74]. Understanding the molecular basis of primary and acquired resistance may lead to novel combination approaches and treatment sequencing strategies.

5. Conclusions

This study demonstrates that while MSI-H endometrial carcinomas exhibit distinctive pathological characteristics including larger tumor size, mucinous differentiation, and poor differentiation, MSI status alone did not significantly influence survival outcomes in our cohort. These findings emphasize the complexity of prognostic factors in endometrial carcinoma and highlight the importance of MSI testing primarily as a predictive biomarker for immunotherapy selection rather than

prognostic stratification.

The near superimposability of progression-free survival and overall survival curves reflects the limited efficacy of salvage therapies available during our study period and underscores the transformative potential of immunotherapy in the current treatment landscape. The significantly higher frequency of positive family history in MSI-H patients emphasizes the importance of genetic counseling and testing in this population. The absence of comprehensive molecular subtyping within the MSS cohort represents a major limitation that prevented complete ProMisE classification. This molecular heterogeneity may have masked important prognostic differences and highlights the critical need for routine p53 and POLE analysis in clinical practice. Future research priorities include large-scale prospective studies incorporating comprehensive molecular profiling to definitively establish the prognostic significance of MSI status in the context of modern immunotherapy-based treatment approaches. As the treatment landscape continues to evolve, the importance of accurate molecular diagnosis and personalized treatment selection will continue to grow.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request, subject to appropriate ethical approval and data sharing agreements.

AUTHOR CONTRIBUTIONS

AI—conceptualization; methodology; formal analysis and investigation; writing–original draft preparation; writing–review and editing; supervision.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol received approval from the Azerbaijan Medical University Clinical Research Ethics Committee (Decision No. 205, dated April 2024) and was conducted in accordance with the principles of the Declaration of Helsinki. Since the study was retrospective and observational, the Clinical Research Ethics Committee of Azerbaijan Medical University waived the need for written informed consent.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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