COMPARATIVE OVERALL SURVIVAL AND TIME TO PROGRESSION ACROSS FOUR HDR BRACHYTHERAPY FRACTIONATION REGIMENS IN LOCALLY ADVANCED CERVICAL CANCER: A RETROSPECTIVE COHORT STUDY AT UCH IBADAN, NIGERIA

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ABSTRACT

Background: Locally advanced cervical cancer represents the dominant presentation in sub-Saharan Africa, where radiotherapy remains the primary curative modality. High-dose-rate (HDR) intracavitary brachytherapy is an essential component of definitive chemoradiation; however, the optimal fractionation schedule in resource-limited settings remains a subject of ongoing debate. This study compared overall survival and time to disease progression across four distinct HDR brachytherapy fractionation regimens delivered alongside external beam radiotherapy at a tertiary radiotherapy centre in Nigeria.

Methods: A retrospective cohort analysis was conducted on 116 patients with histologically confirmed FIGO stage IIB–IIIB uterine cervical cancer treated at the University College Hospital (UCH), Ibadan. All patients received external beam radiotherapy of 45 Gy in 12 alternate-day fractions combined with HDR intracavitary brachytherapy using the intrauterine-and-ring applicator. Patients were stratified into Group I (3×4 Gy), Group II (3×5 Gy), Group III (3×6.5 Gy), and Group IV (3×7 Gy). Kaplan-Meier analysis, log-rank tests, and Bonferroni-corrected pairwise comparisons were performed using IBM SPSS Statistics version 25.

Results: The mean age of the patients was 53.9±11.3 years. The 32-month overall survival for the cohort (n=114) was 65.8%. Group-specific survival rates were 35.3%, 50.0%, 83.3%, and 85.7% for Groups I–IV, respectively ($p<0.05$). Pairwise comparisons confirmed significant survival differences between lower-dose HDR brachytherapy regimens and higher-dose HDR brachytherapy regimens. Median time to disease progression was 6.0, 8.0, 15.0, and 24.0 months across Groups I–IV ($p=0.144$).

Conclusion: Higher-dose HDR brachytherapy fractionation regimens conferred significantly superior overall survival. Group IV (3×7 Gy) achieved the best clinical outcomes with a total EQD2 meeting the American Brachytherapy Society recommended range of 80–90 Gy, supporting protocol revision toward higher-dose-per-fraction schedules in resource-constrained settings.

Keywords: Cervical Cancer, HDR Brachytherapy, Fractionation; Overall Survival, Nigeria, Kaplan-Meier

INTRODUCTION

Cervical cancer remains the leading cause of cancer-related mortality among women in developing nations, with over 75% of patients in Nigeria presenting with locally advanced disease at the time of diagnosis.[1] The standard of care for locally advanced uterine cervical cancer, spanning FIGO stages IIB through IVA, is concurrent chemoradiation, comprising external beam radiotherapy (EBRT) to the pelvis and intracavitary high-dose-rate (HDR) brachytherapy, typically with cisplatin-based sensitizing chemotherapy.[2,3]

Brachytherapy delivers a highly focused radiation dose to the primary tumour and parametria while sparing adjacent critical structures, including the bladder, rectum, and sigmoid colon.[4,5] Its omission from treatment regimens has been consistently associated with inferior local control and survival outcomes across multiple institutional and population-based series.[6] In high-income countries, image-guided adaptive brachytherapy based on MRI has largely supplanted conventional dosimetry; however, in sub-Saharan Africa, conventional X-ray-based planning remains the predominant standard of practice.[7,8]

The University College Hospital (UCH) in Ibadan, Nigeria, operates the single HDR brachytherapy unit in its region. Given the operational pressures of a single-machine facility—including high patient volumes, scheduling constraints, and machine downtime—four distinct HDR fractionation regimens have been applied in practice: 3×4 Gy, 3×5 Gy, 3×6.5 Gy, and 3×7 Gy, all combined with standardised EBRT of 45 Gy in 12 alternate-day fractions. The American Brachytherapy Society (ABS) recommends a minimum total EQD2 of 80–90 Gy; only the highest-dose regimen meets this target.[9] This study aimed to compare overall survival and time to disease progression across the four regimens.

MATERIALS AND METHODS

Study Setting

This study was conducted at the Department of Radiotherapy, UCH Ibadan, Nigeria, which served as the principal radiotherapy referral centre for south-western, south-eastern, and south-southern Nigeria. The department is equipped with one HDR brachytherapy machine (five-channel Gynesource, Eckert & Ziegler Bebig, Germany; Cobalt-60 source), one Cobalt-60 teletherapy machine, a simulator, and a treatment planning system.

Study Design and Population

A retrospective cohort study was conducted among all patients with histologically confirmed FIGO stage IIB–IIIB cervical cancer who received EBRT (45 Gy in 12 alternate-day fractions) and HDR intracavitary brachytherapy with the intrauterine-and-ring applicator at UCH. Patients with FIGO stage IVA disease, non-standard EBRT doses, or

inadequate documentation were excluded. A total of 116 patients were eligible.

Treatment Regimens

HDR brachytherapy was delivered as Group I (3×4 Gy), Group II (3×5 Gy), Group III (3×6.5 Gy), or Group IV (3×7 Gy). Scheduling was determined by machine availability and clinical judgement. BED and EQD2 were calculated using the linear-quadratic model.

Data Collection

Case notes, EBRT treatment cards, and HDR brachytherapy records were reviewed using standardised extraction forms. Variables included age, educational attainment, FIGO stage, histological subtype, treatment dates, disease progression, and vital status. Where records were incomplete, telephone contact was made with patients or next-of-kin.

Statistical Analysis

Data were analysed using IBM SPSS Statistics version 25. Continuous variables were described as means ± standard deviations; categorical variables as frequencies and proportions. Kaplan-Meier survival analysis was performed and group differences assessed with the log-rank test. Pairwise Bonferroni-corrected comparisons were conducted (threshold $p < 0.0125$). Patients lost to follow-up were censored at last contact.

Ethical Considerations and Informed Consent

Ethical clearance was obtained from the Joint Ethical Review Committee of the University of Ibadan and University College Hospital, Ibadan. Due to the retrospective nature of this cohort review using completely anonymized historical medical charts, the requirement for active patient informed consent was waived by the institutional review board. Strict data management measures were taken, and serial alphanumeric identifiers replaced patient names to maintain confidentiality throughout data extraction and statistical modeling.

RESULTS

Distribution of Patients across HDR Brachytherapy Fractionation Groups (Table 1, Table 2, Table 3)

A total of 116 patients with locally advanced uterine cervical cancer met the inclusion criteria, with two subsequently lost to follow-up (evaluable n=114 for survival analysis). The mean age at presentation was 53.9 ± 11.3 years, with the majority (67.2%) aged over 50 years (Table 1). Regarding disease stage, 47 patients (40.5%) presented with FIGO stage IIB, 42 (36.2%) with stage IIIA, and 27 (23.3%) with stage IIIB (Table 2). The distribution across brachytherapy fractionation groups was: Group I, 18 patients (15.5%); Group II, 39 patients (33.6%); Group III, 24 patients (20.7%); and Group IV, 35 patients (30.2%) (Table 3).

Table 1: Age Group Distribution of Study Participants (n=116)

Age Group (years)	Frequency (n)	Percentage (%)
< 40	13	11.2
40–50	25	21.6
> 50	78	67.2
Total	116	100.0
Mean ± SD	53.9 ± 11.3 years	

Table 2: Distribution of FIGO Disease Stages Across the Study Cohort (n=116)

FIGO Stage	Frequency (n)	Percentage (%)
IIB	47	40.5
IIIA	42	36.2
IIIB	27	23.3
Total	116	100.0

Table 3: Distribution of HDR Brachytherapy Fractionation Regimens (n=116)

Treatment Group	Regimen	Frequency (n)	Percentage (%)
Group I	3 × 4 Gy	18	15.5
Group II	3 × 5 Gy	39	33.6
Group III	3 × 6.5 Gy	24	20.7
Group IV	3 × 7 Gy	35	30.2
Total		116	100.0

Overall Survival by Treatment Group and FIGO Stage (Table 4, Table 5, Figure 1, Figure 2, Figure 3)

Within the 32-month follow-up period, 39 deaths were recorded among the 114 evaluable patients, corresponding to a cohort mortality of 34.2%. The 32-month overall survival for the entire cohort was 65.8% (Figure 1). Survival stratified by FIGO stage declined with advancing disease: 71.7%, 68.3%, and 51.9% at 36 months for stages IIB, IIIA, and IIIB respectively (Table 4). When stratified by brachytherapy fractionation regimen, Group I demonstrated the poorest outcome at 35.3%, Group II at 50.0%, while Groups III and IV achieved markedly superior rates of 83.3% and 85.7% respectively (Table 5). These differences were statistically significant ($p < 0.05$, log-rank test). The group-stratified Kaplan-Meier survival curves illustrate clear separation between low-dose and high-dose regimens (Figure 2), and the 32-month survival rates by group are shown in Figure 3.

Table 4: Thirty-Six-Month Overall Survival Rates Stratified by FIGO Disease Stage

FIGO Stage	36-Month Overall Survival (%)	Frequency (n)
IIB	71.7%	47
IIIA	68.3%	42
IIIB	51.9%	27

Table 5: Thirty-Two-Month Overall Survival Rates Stratified by Treatment Group (n=114)

Group	N	Deaths n (%)	Survived n (%)	32-Month OS (%)
Group I	17	11 (64.7)	6 (35.3)	35.3
Group II	38	19 (50.0)	19 (50.0)	50.0
Group III	24	4 (16.7)	20 (83.3)	83.3
Group IV	35	5 (14.3)	30 (85.7)	85.7
Overall	114	39 (34.2)	75 (65.8)	65.8

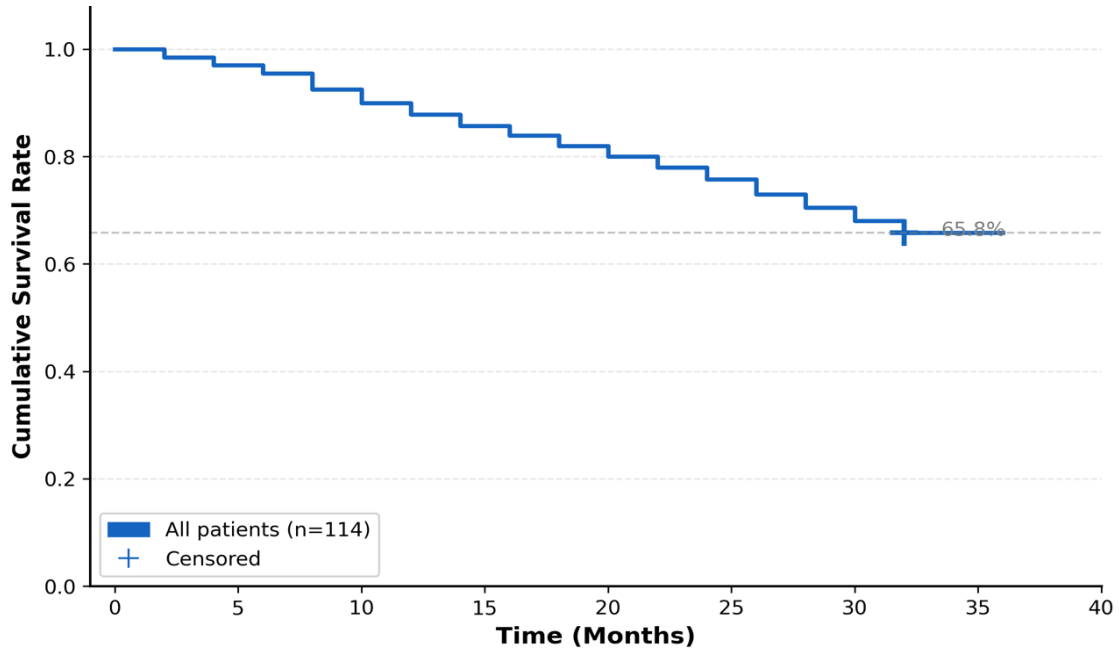
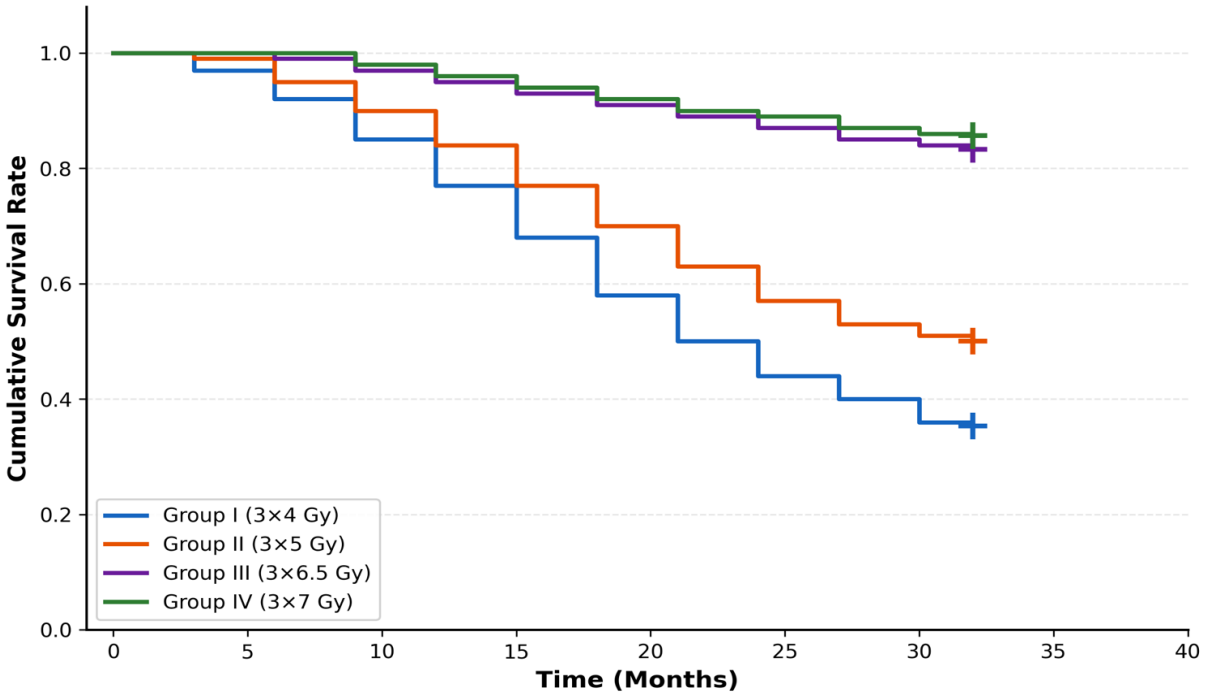


Figure 1: Kaplan-Meier Estimate of 32-Month Overall Survival for The Entire Evaluable Cohort (n=114)



1. **Figure 2:** Kaplan-Meier 32-Month Overall Survival Curves Stratified by HDR Brachytherapy Fractionation Regimen (Log-Rank p = 0.000057)

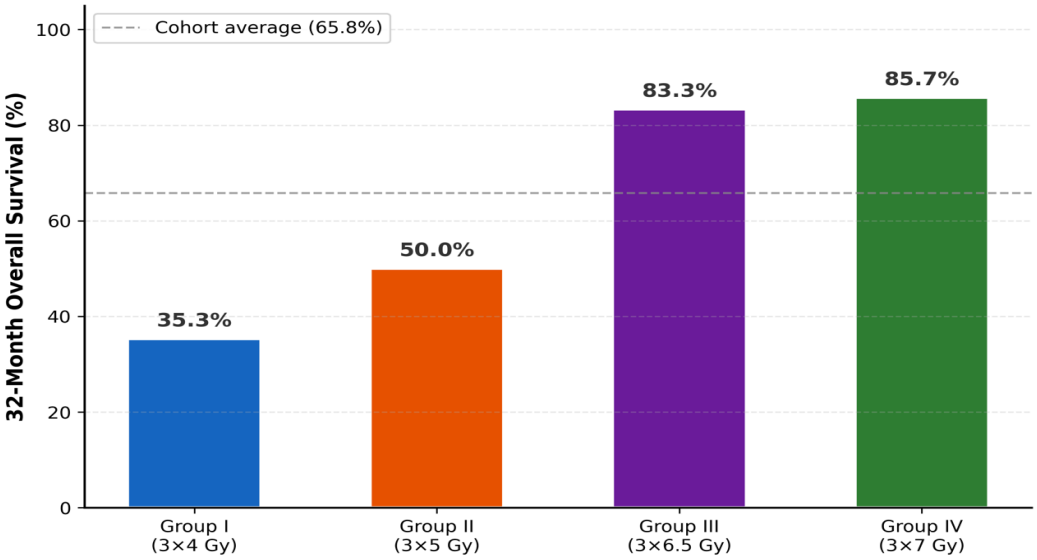


Figure 3: Thirty-Two-Month Overall Survival Rates by Treatment Group

Median Survival Time and Pairwise Comparisons (Table 6, Table 7)

Median survival times increased progressively with higher brachytherapy dose per fraction. Group IV demonstrated the longest median survival of 33.97 months (95% CI: 31.78–36.16), followed by Group III at 33.75 months, Group II at 31.53 months, and Group I at 27.41 months. Pairwise comparisons confirmed statistically significant differences between Groups I and III ($p = 0.001$), I and IV ($p < 0.001$), II and III ($p = 0.011$), and II and IV ($p = 0.002$). No significant difference was found between Groups I and II ($p = 0.141$) or Groups III and IV ($p = 0.812$).

Table 6: Median Survival Time Estimates with 95% Confidence Intervals by Treatment Group

Group	Median (months)	Std. Error	95% CI Lower	95% CI Upper
Group I	27.41	2.260	22.98	31.84
Group II	31.53	1.374	28.83	34.22
Group III	33.75	1.771	30.28	37.22
Group IV	33.97	1.116	31.78	36.16
Overall	32.13	0.747	30.67	33.60

Table 7: Pairwise Log-Rank Survival Comparisons with Bonferroni Correction (Threshold P< 0.0125)

Comparison	Chi-Square	p-value	Significant?
Group I vs II	2.162	0.141	No
Group I vs III	10.568	0.001	Yes*
Group I vs IV	14.785	< 0.001	Yes*
Group II vs III	6.512	0.011	Yes*
Group II vs IV	9.532	0.002	Yes*
Group III vs IV	0.056	0.812	No

*Statistically significant

Time to Disease Progression (Table 8, Figure 4)

Median time to disease progression extended from 6.0 months in Group I to 24.0 months in Group IV, with intermediate values of 8.0 and 15.0 months in Groups II and III, respectively (Table 8, Figure 4). Disease progression occurred in 66.7%, 50.0%, 16.7%, and 14.3% of patients in Groups I–IV. Despite clinically meaningful differences, the overall group comparison did not reach statistical significance ($p = 0.144$).

Table 8: Median time to disease progression stratified by brachytherapy fractionation group

Group	Progressed (n)	No Progression (n)	Progression %	Median TTP (months)	95% CI	p-value
Group I	12	6	66.7%	6.0	0.0–14.5	**0.144**
Group II	19	19	50.0%	8.0	4.8–11.2	
Group III	4	20	16.7%	15.0	9.4–20.6	
Group IV	5	30	14.3%	24.0	15.4–32.6	

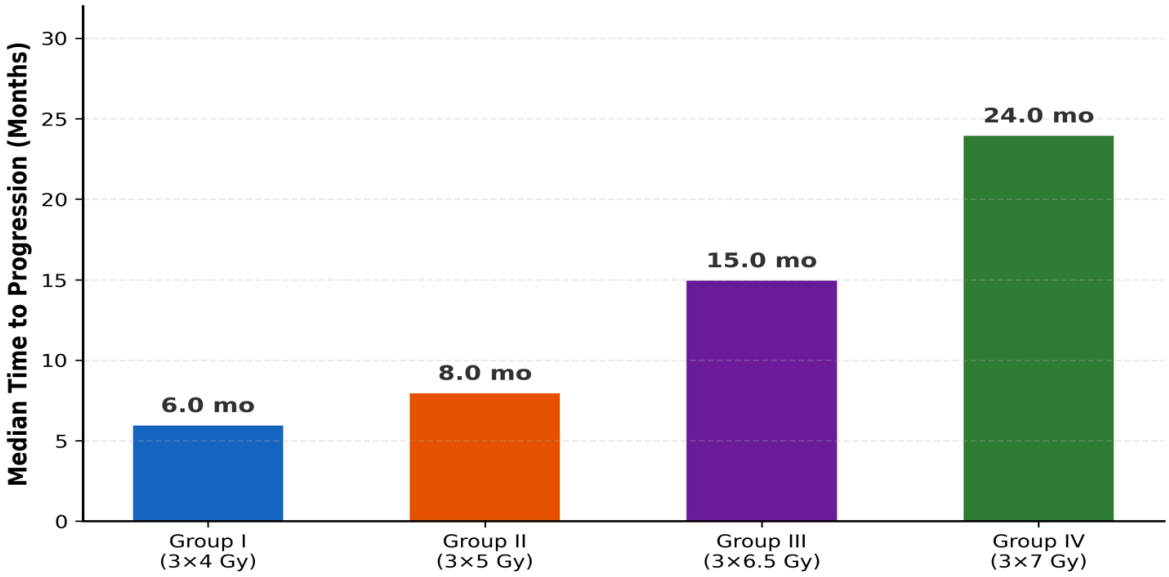


Figure 4: Median Time to Disease Progression by Treatment Group (p = 0.144)

DISCUSSION

This retrospective cohort study demonstrates a clear dose-response relationship between HDR brachytherapy fractionation and overall survival in locally advanced cervical cancer at UCH Ibadan. The 32-month overall survival of 65.8% is consistent with published African data for locally advanced cervical cancer managed with conventional radiotherapy.[10–12] The marked survival advantage in Groups III and IV is biologically coherent: their total EQD_2 values of 78.4 and 81.4 Gy approach or meet the ABS-recommended minimum of 80 Gy, whereas Groups I and II, with EQD_2 values of 65.6 and 70.4 Gy, deliver sub-therapeutic doses that are associated with inferior local tumour control. Several studies have demonstrated that survival deteriorates markedly when total EQD_2 falls below 75–80 Gy, consistent with the findings presented here.[13–15]

The pairwise comparison results reveal a threshold phenomenon: no statistically significant survival difference was observed between Groups I and II (p = 0.141) or between Groups III and IV (p = 0.812), indicating that

clinically meaningful separation occurs at the transition from sub-threshold to near-adequate dosing. The stage-specific survival pattern—71.7%, 68.3%, and 51.9% for stages IIB, IIIA, and IIIB—follows expected oncological principles, corroborating the representativeness of this cohort. While the time to disease progression difference was not statistically significant ($p = 0.144$), the fourfold difference in median TTP between Groups I and IV (6.0 vs. 24.0 months) reflects improved locoregional control at higher doses and carries important implications for follow-up scheduling.

An important contextual factor is the operational reality of a single-HDR-machine facility serving a large referral catchment. Machine downtime and scheduling constraints have historically driven fractionation heterogeneity at UCH. The survival data presented here argue strongly for prioritising the Group IV schedule (3×7 Gy), which is administratively equivalent to other three-fraction regimens in terms of machine time, while delivering the only EQD_2 value meeting international standards. This transition requires no additional capital expenditure, only a commitment to protocol standardisation and applicator placement quality assurance.

Limitations

This study has several limitations. The retrospective design precludes randomized allocation; baseline differences in patient or disease characteristics such as tumor stage and performance status between the subgroups may influence survival outcomes independently of the radiotherapy regimens. Fractionation assignment was driven by scheduling availability rather than clinical stratification.

Group sample sizes were modest however imbalance in subgroup distribution may limit statistical power for subgroup analyses and ultimately affect reliability of survival comparison.

Concurrent chemotherapy was incompletely documented and could not be adjusted for. The follow-up duration of 32 months is insufficient for a 5-year survival assessment.

Despite these constraints, this study provides direct locally derived evidence available on this clinically important question, and its findings are applicable to comparable resource-limited radiotherapy centres across sub-Saharan Africa.

CONCLUSION

Higher-dose HDR brachytherapy fractionation regimens are associated with significantly superior overall survival in locally advanced cervical cancer at UCH Ibadan, Nigeria. The 3 × 7 Gy regimen (Group IV), achieving a total EQD_2 of 81.4 Gy within the ABS-recommended range, demonstrated the best 32-month survival (85.7%) and the longest median time to disease progression (24.0 months). These results provide a strong evidence base for protocol revision toward higher-dose-per-fraction schedules in resource-constrained radiotherapy settings across sub-Saharan Africa, and highlight the urgent need for quality assurance investment, applicator training, and treatment completion monitoring at centres operating single HDR brachytherapy units.

Declarations

Conflict of Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work, analysis, or clinical recommendations described in this manuscript.

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This research did not receive any specific grant or financial support from funding agencies in the public, commercial, or not-for-profit sectors. The study was conducted using existing departmental resources and clinical records as part of routine institutional cohort verification.

Data Availability

All relevant data used in this study are readily available and can be obtained from the corresponding author upon request.

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