Asian Pacific Journal of Cancer Care
Vol 11 No 3 (2026), 419-427
Original Research

Factors Affecting Survival in Cervical Cancer Stage IIIB Treated with Radiation Therapy

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Introduction: To evaluate the factors affecting overall survival (OS) and local control (LC) rates in patients with uterine cervical cancer FIGO stage IIIB treated with radiation therapy (RT).

Materials and Methods: A retrospective study was conducted on 229 patients diagnosed with FIGO stage IIIB cervical cancer who received external beam RT (EBRT) followed by high-dose rate intracavitary brachytherapy (HDR-ICBT) at the Division of Radiation Oncology, Srinagarind Hospital, Khon Kaen University, Thailand, between January 1, 2009, and December 31, 2011. Key prognostic factors, including age, pre-treatment hemoglobin level, tumor size, histology, pelvic side wall involvement, concurrent chemoradiation (CCRT), equivalent dose in 2 Gy (EQD2) at point A, parametrial boost, and overall treatment time (OTT), were analyzed. Survival and local control rates were estimated using the Kaplan-Meier method; hazard ratios (HR) were calculated via Cox proportional hazards regression. Toxicities were recorded per CTCAE v4.03 and RTOG/EORTC criteria.

Results: A total of 229 patients were analyzed.The median age was 55 years (range 33-79). The 5-year OS rate was 41.9% and the 5-year LC rate was 71.4%. Multivariate analysis identified pre-treatment hemoglobin <10 vs. ≥10 g/dL (HR=1.565, p=0.017), tumor size <5 vs. ≥5 cm (HR=0.621, p=0.008), squamous cell carcinoma (SCCA) histology vs. non-SCCA (HR=0.62, p=0.035), unilateral vs. bilateral pelvic side wall involvement (HR=0.691, p=0.049), and RT alone vs. CCRT (HR=1.852, p=0.001) as significant prognostic factors for OS. For LC, significant factors included age ≥50 years, higher hemoglobin, squamous histology, and smaller tumor size. Grade 3-4 gastrointestinal toxicities were most common; no

grade 4 hematologic toxicity was seen.

Conclusion: Pre-treatment hemoglobin level, tumor size, pelvic side wall involvement, histology, and CCRT were significant predictors of survival in FIGO stage IIIB cervical cancer treated with EBRT plus HDR-ICBT. Optimizing these factors may improve outcomes.

Introduction

Cervical cancer remains a key public health issue worldwide, including in Thailand, where it is among the most prevalent cancers in women, with an estimated 8,662 new cases and 4,567 deaths per year, ranking 5th in cancer incidence and mortality [1-3]. The International Federation of Gynecology and Obstetrics (FIGO) defined cervical cancer stage IIIB as the tumor extending into the pelvic wall and/or causing hydronephrosis or non- functioning kidney [4, 5]. The National Comprehensive Cancer Network (NCCN) recommends external beam radiation therapy (EBRT) concurrent with platinum- based chemotherapy (CCRT) followed by high-dose rate intracavitary brachytherapy (HDR-ICBT) with or without immunotherapy as the standard treatment of choice [6]. However, the 5-year overall survival (OS) in cervical cancer stage IIIB was only 34 - 54.8%, which remains inferior to stage IIB at 61 - 80.3% [7-11]. This study aimed to clarify the factors influencing OS and local control (LC) in locally advanced cervical cancer FIGO stage IIIB treated at our institution, contributing evidence for optimizing treatment strategies.

Materials and Methods

Study Design and Population

A retrospective cohort of female patients with pathologically confirmed cervical cancer, the 2009 FIGO clinical stage IIIB, treated with EBRT with or without concurrent chemotherapy plus HDR-ICBT between January 2009 and December 2011 at the Division of Radiation Oncology, Srinagarind Hospital, Khon Kaen University, was collected and analyzed. Patients with prior pelvic radiation therapy (RT), other concurrent malignancies, recurrent disease, incomplete data, or unstaged disease were excluded from the study.

Data Collection

Patient demographics, clinical, and treatment characteristics were extracted from medical records, including age (<50 vs. ≥50 years), pre-treatment hemoglobin (<10 vs. ≥10 g/dL), tumor size (<5 vs. ≥5 cm), histology (Squamous cell carcinoma [SCCA] vs non-SCCA), pelvic side wall involvement (one vs. both sides), treatment modality (RT alone vs. CCRT), point A dose (<85 vs. ≥85 Gy EQD2), parametrial EBRT boost (yes/no), and overall treatment time (OTT) (<56 vs. ≥56 days). All patients were staged according to the 2009 FIGO clinical staging by per vaginal, per rectal examinations, intravenous pyelogram, cystoscope, and proctoscope in the tumor clinic of the multidisciplinary team, which consisted of radiation oncologists, gynecologic oncologists, and urologists. Routine pre-treatment cross-sectional imaging was not available due to the limitations of hospital facilities at the time of the study.

Treatment

All patients received whole pelvis EBRT (50-50.4 Gy, 1.8-2 Gy per fraction), with or without parametrial EBRT boost. HDR-ICBT (Ir-192, 6 Gy × 4 fractions at point A) was performed weekly

after the completion of EBRT. Prescribing to point A was used as a surrogate in the absence of 3D planning under the limited-resource circumstances. Chemotherapy (cisplatin 40 mg/m² IV weekly × 5–6 cycles) was offered unless contraindicated. The RT alone group was defined as patients receiving whole pelvis EBRT followed by HDR-ICBT. Patients receiving whole pelvis EBRT concurrent with chemotherapy, followed by HDR-ICBT, were categorized as the CCRT group.

Outcomes

The primary endpoint was 5-year OS, which was defined as the time from diagnosis to death/last follow-up. The secondary endpoint was 5-year LC, which was defined as the time from the end of primary treatment to local recurrence. Tumor recurrence was assessed by clinical examination, pap smear, and biopsy of the suspected lesions. Toxicities were reported according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and toxicity criteria from the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC).

Statistical Analysis

Baseline characteristics were described using frequencies with percentages for categorical data and means with standard deviations (SD) or medians with interquartile ranges (IQR) for continuous data. OS and LC rates were estimated using Kaplan-Meier analysis. The log-rank test was used to compare the Kaplan-Meier curves. The Cox proportional hazard model was used to perform the multivariable analysis to find the factors affecting OS and LC. Statistical significance was indicated by a p-value ≤ 0.05. Data analysis was performed with IBM SPSS Statistics Version 19 (IBM Inc., New York, NY).

Results

Patient and Treatment Characteristics

The medical records of 232 patients with the 2009 FIGO clinical stage IIIB cervical cancer were reviewed. Of these, 3 patients were excluded according to the exclusion criteria. Therefore, a total of 229 patients were included in the analysis. The median age was 55 years (range 33- 79). The median follow-up time was 20.7 months (range 1-86.5). Most patients (67.7%) had pre-treatment Hb ≥10 g/dL; 58.5% had tumor size ≥5 cm; SCCA comprised 83.4%; 62% had bilateral pelvic side wall involvement; 51.1% received CCRT; 82.1% received point A dose ≥85 Gy; 59% received parametrial EBRT boost. OTT ≥56 days occurred in 95.2%. Almost all patients were clinically assessed as stage IIIB by pelvic side wall involvement (99.6%) (Table 1).

Patient factors			Percentage
1. Age (years)		median = 55 (range 33-79)	
< 50	84		36.70
≥ 50	145		63.30
2. Pre-treatment Hb (g/dL)		mean = 10.6 (range 5.7-15.4)	
< 10	74		32.30
≥ 10	155		67.70
Disease factors			
3. Tumor size (cm.)		median = 5 (range 2-10)	
< 5	91		39.70
≥ 5	134		58.50

N/A	4		1.80
4. Histology			
Squamous cell carcinoma	191		83.40
Adenocarcinoma	32		14.00
Adenosquamous cell carcinoma	3		1.30
Small cell carcinoma	2		0.90
Sarcoma	1		0.40
5. Pelvic side wall involvement			
One side	86		37.60
Both sides	142		62.00
N/A	1		0.40
Treatment factors			
6. Treatment modality			
CCRT	117		51.10
RT alone	111		48.50
N/A	1		0.40
7. Point A dose (Gy)		median = 90.85 (range 55.4-98.4)	
< 85	41		17.90
≥ 85	188		82.10
8. Parametrial boost			
Yes	135		59.00
No	94		41.00
9. Overall treatment time (days)		median = 79 (range 35-164)	
< 56	11		4.80
≥ 56	218		95.20

Table 1. Baseline Characteristics.

Survival, Local Control, and Prognostic Factors

The 5-year OS rate was 41.9%. The Kaplan-Meier univariable analysis showed that the survival was statistically significant better in pre-treatment Hb ≥10 vs.<10 g/dL (5-year OS 50.0% vs. 24.7%, median survival 59.8 mo. vs. 25.4 mo., p-value <0.001), histology of SCCA vs. non-SCCA (5-year OS 45.5% vs. 27.3%, median survival 52.2 mo. vs 29.6 mo., p-value=0.006), tumor size <5 vs. ≥5 cm (5-year OS 52.7% vs. 34.3%, median survival 65.4 vs. 31.7 mo., p-value=0.003), and CCRT vs. RT alone (5-year OS 51.8% vs. 31.7%, median survival 66.9 vs. 33.9 mo., p-value <0.001), respectively (Fig.1 & Table 2).

Figure 1. Kaplan-Meier OS Curves of Five Significant Prognostic Factors: (a) pre-treatment Hb level of < 10 vs. ≥10 g/dL (log rank; p-value < 0.001), (b) tumor size < 5 vs. ≥ 5 cm. (log rank; p-value = 0.003), (c) Histology of SCCA vs. non-SCCA (log rank; p-value = 0.006), (d) RT alone vs. CCRT (log rank; p-value < 0.001), and (e) PSW involvement on one side vs. both sides (log rank; p-value = 0.053).

Factors		N	5-year survival (%)	Median survival (mo.)	p-value
1. Age (years)	< 50	84	41.7	36.2 (25.2-47.2)	0.936
	≥ 50	145	42	48.0 (33.8-62.2)	

2. Pre-treatment Hb (g/dL)	< 10	74	24.7	25.4 (17.3-33.5)	<0.001*
	≥ 10	155	50	59.8 (43.6-76.0)	
3. Tumor size (cm.)	< 5	91	52.7	65.4 (35.0-95.8)	0.003*
	≥ 5	134	34.3	31.7 (24.8-38.6)	
4. Histology	SCCA	191	45.5	52.2 (37.0-67.4)	0.006*
	Non-SCCA	38	27.3	29.6 (16.5-42.7)	
5. PSW involvement	One side	86	48.3	58.4 (45.2-71.6)	0.053
	Both sides	142	38.3	34.1 (26.6-41.6)	
6. Treatment modality	RT alone	111	31.7	33.9 (25.8-42.0)	<0.001*
	CCRT	117	51.8	66.9 (46.4-77.2)	
7. Point A dose (Gy)	< 85	41	43.6	37.6 (8.0-67.2)	0.742
	≥ 85	188	41.7	43.3 (31.9-54.7)	
8. Parametrial boost	No	94	37.5	38.7 (27.7-49.7)	0.542
	Yes	135	44.8	44.5 (23.8-65.2)	
9. OTT (days)	< 56	11	45.5	44.5 (14.1-75.0)	0.628
	≥ 56	218	41.9	40.9 (28.7-53.1)	

Table 2. Kaplan-Meier Analysis 5-year Survival and Median Survival Stratified by Factors.

For the multivariable analysis using the Cox proportional hazard model, all 4 factors above remained statistically significant for OS. The adjusted hazard ratio (HR) was 1.565 for pre-treatment Hb <10 g/dL (95%CI 1.090-2.247, p-value = 0.017), 0.620 for histology of SCCA (95%CI 0.408-0.968, p-value = 0.035), 0.621 for tumor size <5 cm. (95%CI 0.410-0.875, p-value= 0.008) and 1.852 for RT alone (95%CI 1.290-2.725,p-value = 0.001). One-sided pelvic side wall extension was the only factor that showed no statistical difference in univariable analysis (p-value = 0.053), but in the multivariable analysis, when adjusting with other factors, one-sided pelvic side wall extension was a significant positive prognostic factor for OS compared to both pelvic side wall extension with HR of 0.691 (95%CI 0.478-0.998, p-value = 0.049) (Table 3).

Factors	Adjusted HR	95% CI	p-value
Pre-treatment Hb (g/dL)			
< 10 vs. ≥ 10	1.565	1.090 - 2.247	0.017*
Tumor size (cm.)			
< 5 vs. ≥ 5	0.621	0.410 - 0.875	0.008*
Histology			
SCCA vs. non-SCCA	0.62	0.408 - 0.968	0.035*
PSW involvement			
One side vs. Both sides	0.691	0.478 - 0.998	0.049*
Treatment modality			
RT alone vs. CCRT	1.852	1.290 - 2.725	0.001*

Table 3. Multivariate Analysis of Prognostic Factor for Overall Survival by Cox Proportional Hazard Model.

Abbreviations: HR = hazard ratio, CI = confidence interval

For the secondary endpoint, the 5-year LC was 71.4%. Predictive factors for better LC from the univariable analysis were age ≥50 vs. <50 years (78.3% vs. 58.5%, p-value = 0.002), pre-treatment Hb ≥10 vs. <10 g/dL (79.5% vs. 46.0%, p-value <0.001), histology of SCCA vs. non-SCCA (76.8% vs.45.6%, p-value <0.001), and tumor size <5 vs. ≥5 cm (85.8% vs.60.2%, p-value<0.001) (Figure 2 and Table 4).

Figure 2. Kaplan Meier LC Curves of Four Significant Prognostic Factors: (a) Age of < 50 vs. ≥ 50 years (log rank; p-value = 0.002), (b) pre-treatment Hb level of < 10 vs. ≥ 10 g/dL (log rank; p-value < 0.001), (c) tumor size < 5 vs. ≥ 5 cm. (log rank; p-value < 0.001), and(d) Histology of SCCA vs. non-SCCA (log rank; p-value < 0.001).

Factors		N	5-year local control (%)	Median time to recurrence (mo.)	p-value
1. Age (years)	< 50	84	58.5	-	0.002*
	≥ 50	145	78.3	-	
2. Pre-treatment Hb (g/dL)	< 10	74	46	58.2	<0.001*
	≥ 10	155	79.5	-	
3. Tumor size (cm.)	< 5	91	85.8	-	<0.001*
	≥ 5	134	60.2	-	
4. Histology	SCCA	191	76.8	-	<0.001*
	Non-SCCA	38	45.6	16.5	
5. PSW involvement	One side	86	74.7	-	0.098
	Both sides	142	70.5	-	
6. Treatment modality	RT alone	111	66	-	0.43
	CCRT	117	75.7	-	
7. Point A dose (Gy)	< 85	41	73.4	-	0.72
	≥ 85	188	70.9	-	
8. Parametrial boost	No	94	70.8	-	0.834
	Yes	135	71.4	-	
9. OTT (days)	< 56	11	88.9	-	0.216
	≥ 56	218	70.5	-	

Table 4. Kaplan-Meier Analysis 5-year Local Control and Median Time to Recurrence Stratified by Factors.

The Cox proportional hazard model for multivariable analysis showed that all previously mentioned factors were significant predictors for better LC with the adjusted HR of 2.379 (age <50 vs.≥50 years; 95%CI 1.230-4.602, p-value =0.010), 1.896 (pre-treatment Hb <10 vs. ≥10 g/dL; 95%CI 1.054-3.408, p-value=0.033), 0.398 (tumor size <5 vs. ≥5 cm; 95%CI 0.194-0.817, p-value = 0.012) and 0.313 (histology of SCCA vs. non-SCCA; 95%CI 0.170-0.576, p-value=<0.001), respectively (Table 5).

Factors	Adjusted HR	95% CI	p-value
Age (years)			
< 50 vs. ≥ 50	2.379	1.230 - 4.602	0.010*
Pre-treatment Hb (g/dL)			
< 10 vs. ≥ 10	1.896	1.054 - 3.408	0.033*
Tumor size (cm.)			
< 5 vs. ≥ 5	0.398	0.194 - 0.817	0.012*
Histology			
SCCA vs. non-SCCA	0.313	0.170 - 0.576	<0.001*

Table 5. Multivariate Analysis of Prognostic Factor for Local Control by Cox Proportional Hazard Model.

Abbreviations: HR = hazard ratio, CI = confidence interval

Toxicity

The most common grade 3-4 complications were gastrointestinal toxicities (11.35%), such as diarrhea and radiation proctitis. No grade 4 hematologic toxicity occurred in CCRT patients. One patient had a severe urinary tract infection. Small bowel obstruction occurred in one patient who received CCRT with bilateral parametrial EBRT boost. Grade 4 radiation proctitis happened in one patient who received CCRT (EQD2 radiation dose at point A was 93.2 Gy) (Table 6).

Toxicity		Grade	
	3	4	5
Gastrointestinal toxicity	24	2	0
Genitourinary toxicity	4	1	0
Skin toxicity	4	0	0
Hematologic toxicity	4	0	0

Table 6. Grade 3-5 Toxicities.

Remark: Toxicities stratified by grading from both CCRT and RT alone groups

Discussion

This single-institution retrospective study of exclusive FIGO stage IIIB cervical cancer provided evidence that pre-treatment Hb, tumor size, histology, pelvic wall involvement, and CCRT were key predictors for overall survival. As for local control, age, pre-treatment Hb, tumor size, and histology were predictive factors.

The 5-year OS rate in this study was 41.9%, which was similar to the literature [7-11]. This study used the 2009 FIGO clinical staging at the time of the study, which may include stage IIIC patients as of the 2018 FIGO staging in the analysis. However, the survival in this study was almost identical to the study by Wright et al., which performed a prognostic performance comparing the 2009 and 2018 FIGO clinical staging. The literature found that the 2009 FIGO stage IIIB had a 5-year OS rate of 38.4% (37.2–39.6%) while the 2018 FIGO stage IIIB, IIIC1, and IIIC2 were 41.4% (39.9–42.9%), 60.8% (58.7–62.8%), and 37.5% (33.3–41.7%), respectively [10].

Young patients were associated with poor tumor response and higher local recurrence, which may be due to aggressive tumor biology, which was mostly found in the younger age group [12, 13]. Hong et al. documented that the age group of less than forty years correlated with lower tumor response [14]. Similarly, Saibishkumar et al. studied exclusive FIGO stage IIIB cervical cancer and found that an age of more than 50 years was associated with no residual tumor after whole pelvis EBRT [15]. This study also demonstrated poorer local control in the younger age group (<50 years) with an adjusted HR of 2.379, even after adjusting for the CCRT factor. Many studies have demonstrated a correlation between pre-treatment Hb level and overall survival, with the optimal cut point ranging from 10 to 12 g/dL [14, 16-19]. In this study, we demonstrated that a pre-treatment Hb level lower than 10 g/dL was a poor prognostic factor for overall survival (HR = 1.565, 95% CI 1.090 – 2.247, p-value = 0.017).

The larger tumor size was a poor prognostic factor for local control and overall survival in uterine cervical cancer at any stage [17–20]. Kudaka et al. found that squamous cell cervical cancer stage IIIB-IVA (92% IIIB) receiving CCRT had poorer overall survival when the tumor size was greater than 5.5 cm [17]. Similarly, this study found that tumor size less than 5 cm was associated with better overall survival (HR = 0.621, 95% CI 0.410 - 0.875, p-value = 0.008) and local control (HR = 0.398, 95%CI 0.194-0.817, p-value = 0.012).

Regarding pelvic side wall involvement, unilateral invasion was a better prognostic factor for overall survival compared to bilateral invasion (HR = 0.691, 95% CI 0.478-0.998, p-value = 0.049), which was similar to previous literature reporting that bilateral PSW extension had poorer OS than one side in uterine cervical cancer stage IIIB [19, 21]. This finding offered valuable clinical insight, which was often overlooked even in the current staging system.

Several trials showed better survival of SCCA than adenocarcinoma only in early-stage cervical cancer [13, 22, 23]. However, the number of patients with stage IIIB in those trials was very few (5.3% and 16.0% of patients in Kilgore et al. and Kleine et al. studies respectively). A study from Katanyoo et al. analyzing stage IIIB/IVA uterine cervical cancer (168 patients) also showed no survival difference between SCCA and adenocarcinoma in subgroup of stage IIIB/IVA [24]. Rose PG et al. retrospectively analyzed cervical cancer stage IB2-IVA demonstrating that adenocarcinoma and adenosquamous cell carcinoma had worse OS and PFS in RT alone group but similar in the platinum-based CCRT compared to SCCA group [25]. A recent retrospective study of Yokoi et al. in IB-IVA cervical cancer treated with both RT alone and CCRT with weekly nedaplatin showed that adenocarcinoma group had worse OS and PFS [26]. In this study, only stage IIIB was analyzed and the result showed statistically significant poorer OS and LC in non- SCCA group (mostly adenocarcinoma).

As for the overall survival, we found that only CCRT had statistically significant impact. This study showed that RT alone was a negative prognostic factor for OS with HR 1.852 (95%CI 1.290 – 2.725, p-value = 0.001).

In contrast to the subgroup analysis in stage III – IVA from Eifel et al., which reported that OS, local failure, and DFS were not different in CCRT compared to RT alone group [27]. However, a retrospective analysis of stage IIIB cervical cancer from Kuroda et al. reported that receiving CCRT was a good significant prognostic factor [28]. CCRT remains the standard of care in stage IIIB unless contraindicated. Prior literature had shown that the survival and local control outcomes would decrease if the OTT was more than 56 days [29-32]. Nevertheless, we found that the OS and LC rates were not statistically different between the 2 groups of OTT (p-value = 0.628 for OS and 0.216 for LC). However, this study could not effectively evaluate the impact of treatment delay due to most patients had prolonged OTT (N = 218), and only 11 patients had achieved OTT less than 56 days. The major cause of prolonged OTT in this study was the limitation in brachytherapy resources and the long waiting list. Therefore, this study could not evaluate the OTT impact effectively. Completion of EBRT plus ICBT within 56 days remains the standard of care.

The radiation dose at point A of 85-90 Gy (EQD2) was recommended in NCCN, ABS, and ASTRO guidelines for advanced-stage cervical cancer [6, 33, 34]. We used the cut point of 85 Gy and found that escalating point A dose over 85Gy did not show OS and LC benefit similar to the retrospective study from Saibishkumar et al. showing no survival difference even escalated point A dose more than 80 Gy [15].

According to parametrial boost, we found no benefit of LC with external beam parametrial boost, which was similar to Rajasooriyar et al. study documenting that parametrial boost after EBRT did not add benefit in pelvic control [35]. However, to define pelvic recurrence, the follow-up diagnostic imagings were not routinely done due to limited resource circumstances. We performed routine post-treatment per vaginal examination, per rectal examination, and pap smear. Cross-sectional imagings would only be done in selected patients in whom recurrence was clinically suspected.

Limitations of this study included inherent selection and information bias due to its retrospective design. Performance status could not be assessed properly. Lymph node involvement could not be systematically evaluated in the absence of routine pre-treatment cross-sectional imaging. The OTT could not be prospectively controlled. Recurrence was primarily monitored via clinical examination, cytology, and confirmed with pathology, without routine cross-sectional imaging, which may have potentially underestimated subclinical relapse and reflected real-world resource constraints.

In conclusion, in FIGO stage IIIB cervical cancer treated with EBRT plus HDR-ICBT, higher pre-treatment hemoglobin, smaller tumor size, squamous histology, unilateral pelvic wall involvement, and receipt of CCRT independently predict better survival. Optimizing these factors, where possible, should be the focus of clinical efforts to improve patient outcomes.

Declarations

Clinical trial registration

Not applicable

Conflicts of interest/Competing interests

The authors declared no conflict of interest.

Availability of data and material

The data used for this study are not available due to patient confidentiality.

Code availability

Not applicable

Authors' contributions

SK and MP contributed to the conception and supervision. NK contributed to data collection and primary drafting of the manuscript. NS, KT, CS, and SL contributed to formal analysis, data visualization, and resources. YN contributed to project administration. All authors approved the final version for submission.

Ethics approval

The protocol of this study was approved by the Center for Ethics in Human Research, Khon Kaen University (Ref. No: HE601019).

Consent to participate

Not applicable.

Consent for publication

Not applicable

Originality Declaration for Figures

All figures included in this manuscript are original and have been created by the authors

specifically for the purposes of this study. No previously published or copyrighted images have been used. The authors confirm that all graphical elements, illustrations, and visual materials were generated from the data obtained in the course of this research or designed uniquely for this manuscript.

Acknowledgments

The author would like to express sincere gratitude to all our staff for their support and share the cases that made this study possible.

Declaration on generative AI and AI-assisted technologies in the writing process

This article was edited with the assistance of a generative AI tool for proofreading and grammatical corrections. All original content, research, and conclusions are the work of the authors.

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