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Predictors for Recurrences Within One Year Following Radical Nephrectomy for Non-metastatic Renal Cell Carcinomas

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Abstract

Background/Aim: This study aimed to identify predictors of rapid recurrence following radical nephrectomy for non-metastatic renal cell carcinomas.

Patients and Methods: Patients with non-metastatic renal cell carcinoma who underwent radical nephrectomy between 2014 and 2024 at Okayama University Hospital were included. Rapid recurrence was defined as local or distant metastasis occurring within one year after radical nephrectomy, whereas recurrences occurring beyond one year were classified as non-rapid.

Results: Among a total of 194 patients, 37 (19%) experienced recurrence during a median follow-up of 37 months, with 16 (43%) being classified as experiencing rapid recurrence. The multivariate Cox hazard model revealed that microscopic venous invasion and a size of 60 mm or larger were predictors of rapid recurrence (hazard ratio=4.1, 95% confidence interval=1.5-11.4, p=0.006, and hazard ratio=8.0, 95% confidence interval=2.6-25.0, p<0.001, respectively). Dividing the entire cohort into four groups based on the presence of the two risk factors (0, 1: venous invasion, 1: tumor size, and 2), the median PFS was not estimable, 87, 67, and 7 months, respectively (p<0.001).

Conclusion: Microscopic venous invasion and tumor size of 60 mm or larger were identified as independent predictors of rapid recurrence following radical nephrectomy for non-metastatic renal cell carcinoma.

Keywords: Renal cell carcinoma, adjuvant therapy, radical nephrectomy, early recurrence, metastases.

Introduction

Renal cell carcinoma (RCC) is one of the most common urogenital malignancies. Extirpative surgeries, such as radical or partial nephrectomy, are the standard treatment for patients with non-metastatic localized RCC. However, some patients experience recurrences and/or distant metastases after surgery, with a reported

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5-year recurrence-free survival rate of approximately 70% (1, 2). Multiple trials have attempted to demonstrate the efficacy of adjuvant treatments utilizing immunotherapy and vascular endothelial growth factor receptor tyrosine kinase inhibitors (3-5). The pivotal phase III KEYNOTE-564 trial showed the superiority of one-year pembrolizumab administration over placebo as an adjuvant treatment for high-risk localized RCC (6). Currently, the treatment is solely approved as an adjuvant therapy for RCC after extirpative surgery and for patients with no evidence of disease following metastasectomy (7).

Previously, Leibovich *et al.* established an algorithm to predict the recurrences following the extirpative surgeries (8, 9). However, several studies have demonstrated the differences in clinicopathologic features between early and late recurrences following extirpative surgeries for non-metastatic RCCs (1, 10, 11). Patients with high-risk localized RCC often experience disease progression within five years post-surgery (8). While some recur soon after the surgery, others may experience much later recurrences, and the former group is more likely to benefit from adjuvant therapy.

This study aimed to identify predictors of early recurrence following radical nephrectomy (RN) for non-metastatic RCC.

Patients and Methods

Following approval from the local ethics committee, patients with non-metastatic RCC who underwent RN at Okayama University Hospital between January 2014 and March 2024 were included and assessed. Patients were excluded if they underwent partial nephrectomy (PN) as the extirpative surgery, had distant metastases at the time of surgery, bilateral kidney tumors, multiple tumors, or malignancies other than RCC on final pathology, or if they received adjuvant therapy, including participation in clinical trials. However, patients with locoregional lymph node metastases that were completely resected during surgery were included.

For clinical surveillance, computed tomography (CT) scans with or without contrast enhancement were commonly performed, depending on postoperative renal function or contrast agent allergies. Imaging was conducted every three to six months at the clinician's discretion.

Patient data collected included age at surgery, sex, laterality, tumor size on final pathology, surgical approach (open, laparoscopic, or robotic surgery), and pathological features such as T stage, histologic subtype, nuclear grade, presence of necrosis, sarcomatoid or rhabdoid dedifferentiation, venous invasion, sinus fat invasion, peritumoral fat invasion, and urinary tract invasion. Clinical lymph node metastases on the presurgical imaging or intraoperative findings were considered when complete resection was achieved. Surgery and recurrence dates were obtained from medical records. Rapid recurrence was defined as recurrence within one year of radical nephrectomy, while non-rapid recurrence referred to recurrence occurring beyond one year. Recurrence was classified as local recurrence at the primary site or distant metastasis, including locoregional lymph node metastases. Between the two groups, the clinicopathologic factors, such as T stage, and pathological features, were compared.

The progression-free survival (PFS) was defined as the time from surgery to the first recurrence or distant metastasis. The second or more progressions after the treatment for the first recurrence were ignored. The overall survival (OS) was defined as the time from surgery to all-cause death. The 2-year and 5-year PFS and OS were estimated.

Statistical analysis. All statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). Continuous variables were analyzed using the Mann-Whitney *U* test, while categorical variables were assessed using Fisher's exact test and the Chi-square test. Kaplan-Meier methods were used to estimate survival functions, with comparisons made using the log-rank test. Receiver operating characteristic (ROC)

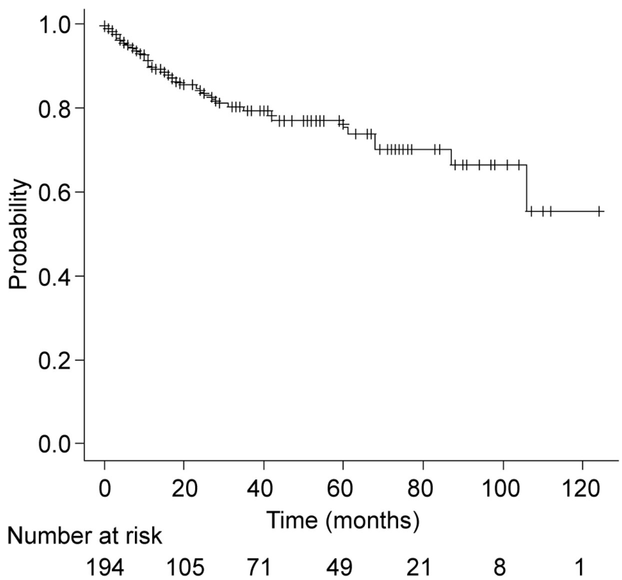

Figure 1. *Kaplan–Meier curve of recurrence-free survival of the entire cohort.*

Table I. *Patient baseline characteristics.*

Variables	N=194
Median age, years old (range)	68 (19-88)
Sex	Male 133
	Female 61
Median tumor size, mm (range)	44 (7-133)
Clinical lymph node positive	2
Surgical procedure	Laparoscopic 164
	Open 12
	Robot-assisted 18
Pathological T stage	T1 109
	T2 19
	T3a 61
	T3b 3
	T4 2
Pathological subtype	Clear-cell RCC 159
	Non-clear cell RCC 35
Pathological variant	Sarcomatoid dedifferentiation 4
Nuclear grade ≥3	Rhabdoid dedifferentiation 3
Microscopic venous invasion	42
Microscopic sinus fat invasion	50
Microscopic peritumoral fat invasion	10
Microscopic urinary tract invasion	6
Microscopic necrosis	4
Risk classification	34
Keynote 564 trial classification	Intermediate-poor risk 69
	Poor risk 2
Leibovich classification	Low risk 92
	Intermediate risk 89
	High risk 13

analysis was utilized to set the optimal cut-off point of a tumor size. Predictors of overall and rapid recurrence were evaluated using a multivariable Cox proportional hazards model.

Results

A total of 194 patients were included, with 37 (19%) experiencing recurrence or distant metastases during a median follow-up of 37 months. The median time to recurrence was 15 months (range=1-106 months). The 2-year and 5-year progression-free survival (PFS) rates were 84% and 75%, respectively (Figure 1). The most common site of recurrence or metastasis was the lung (n=25, 68%), followed by local recurrence (n=5, 14%), bone (n=3, 8%), and the liver and adrenal gland (n=2 each, 5%). During follow-up, 23 patients (12%) died from any cause; 10 of these deaths (43%) were due to RCC. The 2-year and 5-year overall survival (OS) rates were 98% and 84%, respectively. Pathological findings showed that 128 patients (66%) had pT2 or lower stage RCC, while 66 (34%) had pT3 or more advanced RCC. Most patients (159, 82%) had clear cell subtypes, with non-clear cell RCCs comprising the remainder. Among these, the most common non-clear cell subtype was papillary RCC (n=11), followed by chromophobe RCC (n=9), and transcription factor E-3 rearranged RCC (n=3). Additionally, 42 patients (22%) had nuclear grade 3 or higher, 50 (26%) exhibited microscopic venous invasion, 34 (18%) showed microscopic necrosis, four (3%) had sarcomatoid dedifferentiation, and three (2%) had rhabdoid dedifferentiation (Table I). There was no significant difference in PFS between clear cell and non-clear cell subtypes (Figure 2). ROC analysis determined that a tumor size of 59 mm was the optimal cut-off point, with an area under the curve of 0.78. The multivariable Cox hazard model identified microscopic

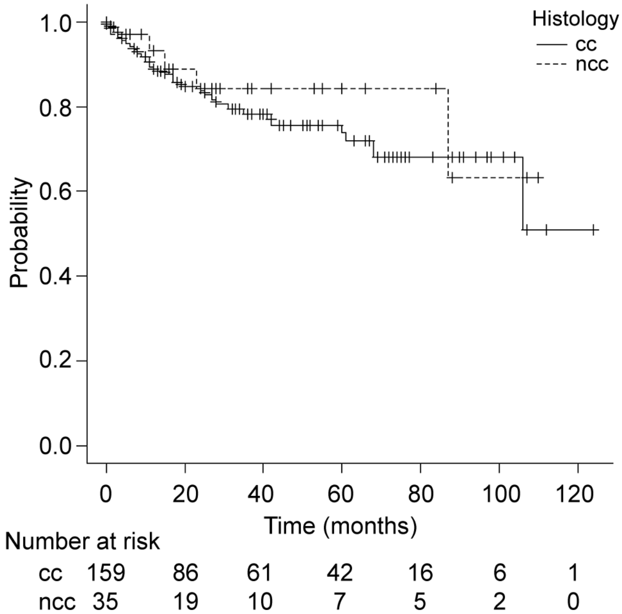

Figure 2. *Kaplan–Meier curve of recurrence-free survival stratified by the histological subtypes. There was no significant difference between the progression-free survival rate of clear-cell subtype (CC) and non-clear cell subtypes (NCC).*

Table II. *Multivariable cox hazard model for predicting overall recurrence.*

Variables	Hazard ratio (95% confidential interval)	*p*-Value
Nuclear grade ≥3	1.2 (0.8-1.9)	0.4
Microscopic necrosis	2.4 (1.1-5.1)	0.03
Microscopic venous invasion	3.0 (1.4-6.2)	0.004
Tumor size ≥70 mm	5.2 (2.5-10.7)	<0.001

necrosis [hazard ratio (HR)=2.4, 95% confidence interval (95%CI=1.1-5.1, p=0.03], microscopic venous invasion (HR=3.0, 95%CI=1.4-6.2, p=0.004), and tumor size of 60 mm or larger (HR=3.9, 95%CI=1.8-8.0, p<0.001) as independent predictors of recurrence after RN (Table II). Among patients with disease progression, 16 (43%) were classified as rapid recurrence, while 21 (57%) experienced non-rapid recurrence. The rapid recurrence group showed significantly higher rates of pathological T stage 3 or higher and microscopic venous invasion compared to the non-rapid recurrence group (87% *vs*. 19%, p<0.001, and 63% *vs*. 14%, p=0.005, respectively) (Table III). Univariable analysis revealed that nuclear grade 3 or higher (HR=2.9, 95%CI=1.0-7.9, p=0.04), microscopic venous invasion (HR=5.3, 95%CI=1.9-14.5, p=0.001), and tumor size of 60 mm or larger (HR=7.3, 95%CI=3.0-17.7, p<0.001) were independent predictors of rapid recurrence. The multivariable Cox hazard model confirmed that microscopic venous invasion and tumor size of 60 mm or larger independently predicted rapid recurrence (HR=4.1, 95%CI=1.5-11.4, p=0.006 and HR=8.0, 95%CI=2.6-25.0, p<0.001, respectively) (Table IV). Further multivariate analyses identified tumor size as the independent predictor for recurrences within two and within three years post-RN (Table V). When dividing the entire cohort into four groups based on the presence of two risk factors, venous invasion, tumor size, or both, the median PFS was not estimable in the group with no risk factors and with venous invasion, and was 68 and 17 months in the groups with larger tumor size or both factors present, respectively (p<0.001, Figure 3).

Discussion

Approximately 30% of RCCs develop recurrence or distant metastases following extirpative surgery for non-metastatic disease (1, 2). Interestingly, a considerable number of patients with RCC experience local recurrences or distant metastases even many years after surgery (12). However, the RCCs with early recurrence generally have aggressive potential and a worse prognosis compared to those with late recurrence. The KEYNOTE-564 trial demonstrated pembrolizumab's efficacy as an adjuvant treatment for localized RCC (6). The trial included RCC patients with high-risk features, pT2 with nuclear grade 4, pT3, pT4, and any pT stage with N1, and showed 75.2% recurrence-free survival in the pembrolizumab group. By contrast, over 20% of patients treated with pembrolizumab discontinued the treatment due to adverse events (6). Moreover, over 60% of the patients in the placebo group did not experience recurrences at the three-year follow-up (6), implying that not all the

Table III. A *comparison of patients' baseline characteristics between rapid and non-rapid recurrence groups.*

Variables	Rapid group (n=16)	Non-rapid group (n=21)	*p*-Value
Median age (range)	71 (23-80)	65 (27-81)	0.15
Sex			
Male	12 (75%)	14 (67%)	0.7
Female	4 (25%)	7(33%)	
Tumor size (range)	76 (27-130)	60 (27-115)	0.3
Surgical procedure			0.8
Laparoscopic	10 (63%)	13 (62%)	
Open	5 (31%)	5 (24%)	
Robot-assisted	1 (6%)	3 (14%)	
Pathological T stage			<0.001
T1	0 (0%)	10 (48%)	
T2	2 (13%)	7 (33%)	
T3	13 (80%)	4 (19%)	
T4	1 (7%)	0 (0%)	
Clear cell subtype	14 (88%)	18 (86%)	1
Nuclear grade ≥3	7 (44%)	9 (43%)	1
Microscopic necrosis	6 (38%)	9 (43%)	1
Microscopic venous invasion	10 (63%)	3 (14%)	0.005
Microscopic sinus fat invasion	0 (0%)	0 (0%)	1
Microscopic peritumoral fat invasion	2 (13%)	0 (0%)	0.2
Microscopic urinary tract invasion	0 (0%)	0 (0%)	1
Risk classification			
Keynote-564			<0.001
Intermediate-poor	14 (86%)	6 (29%)	
Poor	1 (7%)	0 (0%)	
Leibovich			0.06
Low	0 (0%)	5 (24%)	
Intermediate	10 (63%)	13 (62%)	
High	6 (37%)	3 (14%)	
Metastatic site			
Lung	13 (81%)	13 (62%)	
Lymph nodes	0 (0%)	2 (10%)	
Bone	3 (19%)	0 (0%)	
Liver	1 (6%)	1 (5%)	
Local recurrence	2 (12%)	3 (14%)	
Adrenal	0 (0%)	2 ((10%)	
Pancreas	0 (0%)	2 (10%)	
Others	0 (0%)	4 (19%)	

participants might be the right indication. A substantial proportion of patients in the present study overlapped with the high-risk population studied in the KEYNOTE-564 study. Therefore, our findings regarding early recurrence risk factors may provide useful insights for refining candidate selection for adjuvant immunotherapy.

Leibovich *et al.* reported a high-quality risk classification (8) and utilized it in considering the indications for adjuvant pembrolizumab. However, the study did not consider the timing of recurrences (8). For the recurrences that occurred a long time after the surgery, whether one-year adjuvant treatment following the surgery could be effective remains unknown. Therefore,

Table IV. *Multivariable cox hazard model for predicting rapid recurrence.*

Variables	Hazard ratio (95% confidence interval)	*p*-Value
Tumor size ≥60 mm	8.0 (2.5-25.0)	<0.001
Microscopic venous invasion	4.1 (1.5-11.4)	0.006

Table V. *Multivariable cox hazard model for predicting the recurrences within one, two, and three years following radical nephrectomy.*

	Within 1 year n=16	Within 2 years n=23	Within 3 years n=29
Tumor size ≥60 mm	8.0 (2.5-25.0)	6.6 (2.7-16.2)	5.8 (2.7-12.5)
Hazard ratio (95%CI)	p<0.001	p<0.001	p<0.001
Venous invasion	4.1 (1.5-11.4)	2.5 (1.1-5.8)	1.8 (0.8-3.8)
Hazard ratio (95%CI)	p=0.006	p=0.03	p=0.13

95%CI: 95% confidence interval.

the recurrences immediately following the surgery, especially within one year, seem to be the candidates for adjuvant treatment.

One study examined the risk factors for recurrence within one year; Choi *et al.* showed that Eastern Cooperative Oncology Group Performance Status of 1 or higher, pathological T stage, and tumor necrosis were independent predictors (13). However, the study included patients who underwent both PN and RN (13). Assessing the pathological findings after PN could be difficult when enucleation is performed and the tissue surrounding the tumors is not removed. Therefore, patients who had PN were excluded from this study.

Although several studies have reported differences in clinical features between early and late recurrences, the risk factors for each tend to overlap (10, 14). Fujii *et al*. demonstrated that high T stage (T2 or higher), positive lymphovascular invasion, and a nuclear grade of 3 or more were independent predictors of early recurrences (10). These findings are consistent with those of our study. Similarly, a pathological T stage of 3 or higher was also an independent predictor of late recurrence (10). However, this study showed that the proportion of patients with pathological T stage 3 was low in the non-rapid group. Although the T3 stage has been reported as a predictor of late recurrence (10, 14), our study showed the opposite trend, with T3 tumors being relatively less frequent in the non-rapid recurrence group. This finding suggests that the T3 category may include biologically heterogeneous tumors with varying features such as tumor size, venous invasion, and fat invasion (15). Therefore, we incorporated its individual components into the multivariable model to more precisely assess their respective impacts and to reduce the risk of multicollinearity instead of including the overall T stage in the analysis. Another study found that advanced age, male sex, lymphovascular invasion, Fuhrman grade 3 or higher, tumor size, advanced pathological T stage, and pN1 were independent predictors of recurrence within five years following surgery (13). Bozkurt *et al.* showed that high Fuhrman grade, lymphovascular invasion, and tumor necrosis were independent predictors of early recurrence (14). They also demonstrated that

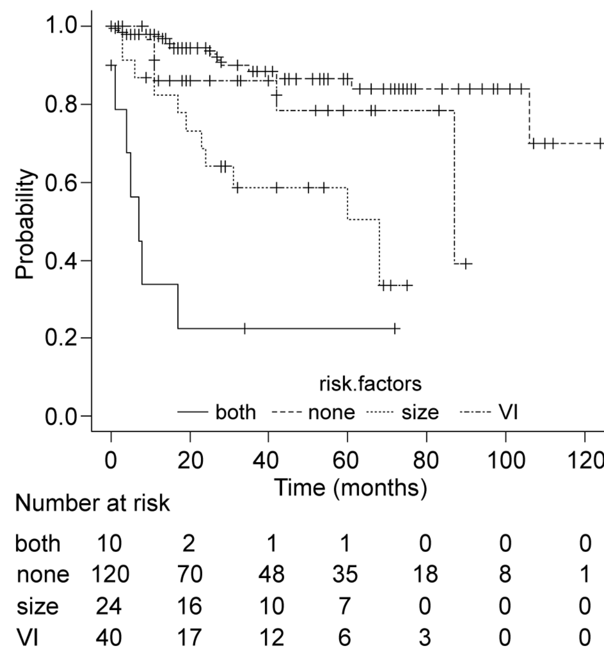

Figure 3. *Kaplan–Meier curve of recurrence-free survival stratified by the risk factors: 0, VI (venous invasion), tumor size, and both of them.*

favorable risk, according to the Memorial Sloan Kettering Cancer Center (MSKCC) classification, was significantly associated with recurrences occurring after five years post-surgery compared to those within five years (14). This suggests that late recurrence is difficult to predict, and long-term surveillance is necessary for all patients with localized RCC. Identifying predictors of early recurrence is particularly important for selecting suitable candidates for adjuvant therapy.

Neves *et al*. collected the patients with chromophobe RCC and demonstrated the clinicopathologic factors for detecting early recurrences (14). They detected that pathological T2b or more and sarcomatoid dedifferentiation were the risk factors for the recurrences within two years after extirpative surgeries (14). The results were similar to those in the studies that collected clear cell RCCs. In this study, no significant difference was found between clear cell and non-clear cell RCC in terms of PFS and OS, justifying the inclusion of both subtypes in our analyses.

Lymph node (LN) metastases are considered to be a common risk factor for recurrence. Yang *et al.* demonstrated that the timing of recurrence after extirpative surgery in the RCC patients with LN metastases was earlier than those without LN metastases (11). In this study, only two patients had regional LN metastases and were completely resected during the surgery, and one of those experienced recurrence. However, the sample size was too small to draw definitive conclusions regarding the prognostic impact of LN involvement.

The most common metastatic site in this study was the lung, with local recurrence being the second most common site. Interestingly, three patients in the rapid recurrence group experienced bone metastases, whereas none of the non-rapid recurrence patients did. Santini *et al*. demonstrated the natural history of bone metastasis in patients with RCC, showing that bone metastases occurred within 6 months for MSKCC intermediate- and poor-risk patients, while taking a median time of 24 months for low-risk patients (15). Fan *et al.* demonstrated that factors such as tumor size, T and N stage, and grade (16), also identified in our study, were predictors for developing bone metastases.

Study limitations. First, its retrospective and single-institutional design inherently introduces the possibility of selection bias and limits the generalizability of the findings to broader patient populations. Second, the sample size was relatively small, particularly in the subgroup of patients who experienced recurrence and those with rapid recurrence, which may have limited the statistical power of the multivariable analyses. Third, postoperative imaging surveillance was not standardized and was performed at the discretion of the treating physician, potentially introducing detection bias in determining the timing of recurrence. Additionally, the definition of rapid recurrence as occurring within one year of surgery, while clinically reasonable, is arbitrary and may not align with the criteria used in other studies. Fourth, the inclusion of both clear cell and non-clear cell RCCs, despite their biological differences (17), may have introduced heterogeneity that affected the analysis, although no significant differences in survival were observed. Fifth, certain relevant clinical variables, such as performance status, comorbidities, and preoperative inflammatory markers, were not available and therefore not included in the multivariable models (18). Finally, the study did not externally validate the identified predictors of recurrence or compare them against established risk models such as the Leibovich score (8), which may limit the applicability of these findings in clinical practice. Future prospective, multi-institutional studies with larger cohorts and integrated molecular data are warranted to confirm and refine the predictors of early recurrence following radical nephrectomy for non-metastatic RCC.

Conclusion

In this retrospective study of patients undergoing RN for non-metastatic RCC, we identified microscopic venous invasion and tumor size ≥60 mm as independent predictors of recurrence within one year of surgery. These clinicopathologic features may help identify patients at higher risk of early disease progression who could benefit most from adjuvant therapies utilizing pembrolizumab. While current risk stratification tools primarily focus on overall recurrence risk, incorporating the timing of recurrence could further improve patient selection for adjuvant treatment. Prospective validation and integration of these predictors into clinical decision-making frameworks are necessary to optimize postoperative management strategies in non-metastatic RCC.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Kensuke Bekku: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing-original draft. Tomoaki Yamanoi: Writing-review and editing. Tatsushi Kawada: Writing-review and editing. Yusuke Tominaga: Writing-review and editing. Takuya Sadahira: Writing-review and editing. Satoshi Katayama: Writing-review and editing. Takehiro Iwata: Writing-review and editing. Shingo Nishimura: Writing-review and editing. Motoo Araki: Supervision; Writing-review and editing. All Authors have read and agreed to the published version of the manuscript.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (Grammarly) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

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