Additional chemoradiotherapy following endoscopic submucosal dissection in patients with esophageal squamous cell carcinoma: a narrative review

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This review offers a critical synthesis of additional therapeutic strategies following endoscopic submucosal dissection (ESD) for esophageal squamous cell carcinoma, providing evidence-based recommendations to optimize clinical decision-making. For pT1a-EP/LPM lesions, ESD alone demonstrates curative potential with lymph node metastasis rates ranging from 0.0% to 3.3%. In contrast, pT1b-MM tumors exhibiting lymphovascular invasion warrant adjuvant chemoradiation therapy, associated with 21.4% nodal metastasis rates. For pT1b-SM1 lesions, chemoradiation is indicated-particularly demonstrating 13.2% nodal involvement without lymphovascular invasion versus 60.0% metastasis risk in cases with vascular invasion during observation. Timing of additional chemoradiotherapy should be expedited, with immediate initiation (1–2 months post-ESD) showing superior outcomes. Radiation dosing optimization reveals equivalent efficacy between lower radiation doses (40-41.4 Gy) and higher doses (50-50.4 Gy), with reduced treatment-related toxicity. Target volume delineation should prioritize the ESD bed with appropriate margins over elective nodal coverage, maintaining therapeutic efficacy while minimizing radiation exposure. The role of concurrent chemotherapy remains controversial, with retrospective evidence suggesting definitive radiotherapy may provide comparable local control.

KEYWORDS

esophageal cancer, endoscopic submucosal dissection, ESD, surgery, radiotherapy, chemotherapy

1 Introduction

Esophageal cancer persists as a major global health challenge, ranked seventh among malignancies worldwide with over 470,000 annual diagnoses (1). Histologically classified cases reveal esophageal squamous cell carcinoma predominates in 90% of instances, exhibiting disproportionately high prevalence in East Asia. Notably, China bears half of the global squamous cell carcinoma burden (2). With advancements in screening technologies and early diagnostic modalities, a growing proportion of patients are identified at earlier disease stages (3).

Endoscopic submucosal dissection (ESD) has emerged as a cornerstone intervention for superficial esophageal carcinoma (4). This technique offers distinct clinical advantages, particularly its superior en bloc resection rates and capacity for precise histopathological assessment. By enabling localized tumor excision while concurrently evaluating critical lymph node metastasis risk factors, including invasion depth, lymphovascular invasion, and invasion pattern, ESD is poised to expand its role in minimally invasive esophageal cancer management.

Nevertheless, therapeutic misjudgment arising from inaccurate indication assessment or curability evaluation may lead to treatment failure, necessitating additional therapeutic interventions post-ESD (5). Current evidence remains insufficient regarding the efficacy of additional chemoradiotherapy following ESD, with several pivotal clinical questions requiring resolution. These clinical uncertainties specifically concern: (1) optimal patient selection criteria for additional chemoradiotherapy, (2) timing of additional chemoradiotherapy post-ESD, (3) radiation dose optimization strategies, (4) target volume delineation strategies, and (5) therapeutic value of concurrent chemotherapy.

To addressing these critical knowledge gaps, we conducted this review adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guidelines (6, 7), through comprehensive searches of Embase, PubMed, and Cochrane Library databases from inception through April 2025. Employing predefined search terms ("esophageal cancer", "endoscopic submucosal dissection", "radiotherapy"), we critically appraised relevant studies. Our synthesis of current evidence aims to provide evidence-based recommendations for optimizing post-ESD therapeutic protocols and guiding future clinical investigations.

2 Diagnostic accuracy

Current guidelines establish clear indications for ESD in esophageal squamous cell carcinoma: (1) clinical epithelial/lamina propria mucosae (T1a-EP/LPM) lesions, (2) circumferential T1a-EP/LPM lesions ≤50 mm, and (3) clinical muscularis mucosae (T1a-MM) or submucosa invasion ≤200 μm (T1b-SM1) (8–10).

While image-enhanced magnifying endoscopy and iodine staining reliably assess lateral lesion extension, accurate determination of invasion depth remains a critical challenge.

Standard diagnostic modalities for invasion depth evaluation include endoscopic ultrasound and magnifying endoscopy (10), with their diagnostic performance detailed in Table 1. Among lesions classified as cMM/SM1 through magnifying endoscopy (type B2 vessels), pathological staging demonstrated: 27.4% pEP/LPM, 55.7% pMM/SM1, and 17.0% submucosa invasion >200 μm (pSM2) (11–14). For those diagnosed via type V3 vessel patterns, corresponding pathological distributions were 29.8% pEP/LPM, 42.3% pMM/SM1, and 27.9% pSM2 (15). Notably, the corresponding pathological diagnoses were: 55.2% pEP/LPM, 29.3% pMM/SM1, and 15.5% pSM2 for endoscopic ultrasound-based cMM/SM1. Furthermore, 15.5%-27.9% of cMM/SM1 cases prove to be pSM2.

These findings reveal substantial discrepancies between preoperative assessments and postoperative findings. This disparity arises from operator-dependent interpretative variability in assessing deep invasion patterns, compounded by inherent limitations in current imaging modalities. Therefore, additional treatments following ESD should be primarily determined by pathological factors, particularly invasion depth and the presence of lymphovascular invasion.

3 Additional treatments

Patients with completely resected pEP/LPM carcinomas exhibit minimal lymph node metastasis risk (0.0-3.3%) (8). alone provides curative intent in these cases, with annual endoscopic surveillance recommended for early detection of metachronous lesions rather than additional therapy.

TABLE 1 Diagnostic accuracy of cancer invasion depth using endoscopy and endoscopic ultrasound.

cMM/SM1	pEP/LPM	pMM/SM1	pSM2
B2 vessels (11–14)	58/212 (27.4%)	118/212 (55.7%)	36/212 (17.0%)
V3 vessels (15)	31/104 (29.8%)	44/104 (42.3%)	29/104 (27.9%)
Endoscopic ultrasound (11)	32/58 (55.2%)	17/58 (29.3%)	9/58 (15.5%)

T1a-EP/LPM: Epithelial/lamina propria mucosae esophageal cancer, T1a-MM: muscularis mucosae esophageal cancer, T1b-SM1: submucosa invasion ≤ 200 μm, T1b-SM2: submucosa invasion > 200 μm.

B1 vessels: characterized by small, irregular, dot-like microvessels without loop formation, indicates tumor invasion confined to the T1a-EP/LPM.

B2 vessels: marked by severe irregularity in microvessel morphology, suggests invasion into the T1a-MM or T1b-SM1.

B3 vessels: characterized by complete destruction of microvessel structures, indicates deeper invasion into T1b-SM2.

V1 vessels: tumor adhesion to or indentation of a vessel without clear evidence of invasion into the vessel wall, suggests non-invasive or suspicious for invasion.

V2 vessels: tumor invasion into the vessel wall, up to the adventitia, indicates local tumor progression and increased risk of metastatic spread.

V3 vessels: tumor invasion through the vessel wall with luminal occlusion or thrombus formation, indicates invasion into T1b-SM1 or deeper.

Vn vessels: newly formed tumor vessels, indicates invasion into mid-to-deep submucosa or muscularis propria.

TABLE 2 Metastasis rates in patients with muscularis mucosae cancers underwent endoscopic submucosal dissection.

Lymphovascular invasion status	Observation (16–20)	Additional surgery (21–23)	Additional chemoradiotherapy (24–27)
Non-lymphovascular invasion	12/216 (5.6%)	0/6 (0.0%)	1/17 (5.9%)
Lymphovascular invasion	3/14 (21.4%)	1/20 (5.0%)	7/45 (15.6%)

CI, confidence interval.

In pMM carcinomas without lymphovascular invasion, (Table 2) nodal metastasis rates differ significantly across management strategies: 5.6% (95% confidence interval [CI]: 2.9-9.5%) under observation (16–20), 0.0% (95% CI: 0.0-46.0%) with surgical resection (21–23), and 5.9% (95% CI: 0.2–28.7%) following chemoradiotherapy (24–27).

For lymphovascular invasion positive pMM cases, corresponding rates increase to 21.4% (95% CI: 4.7-50.8) (18–20), 5.0% (95% CI: 0.1–24.9%) (21–23), and 15.6% (95% CI: 6.5–29.5%) (24–27). Given surgical mortality risks and chemoradiation-related grade ≥3 toxicities, additional treatments are not recommended in patients without lymphovascular invasion, but essential for lymphovascular invasion positive cases.

Submucosal invasive carcinomas demonstrate distinct metastatic patterns (Table 3). For pSM1 lesions without lymphovascular invasion, surveillance yields 13.2% metastasis (16–20), additional surgery shows 0.0% metastasis (21–23), and chemoradiation yields 2.9% metastasis (24–27). In contrast, lymphovascular invasion positive cases show 60.0%, 0.0%, and 17.9%, respectively.

In pSM2 cohorts, observation achieves 18.8% metastasis without lymphovascular invasion and 0.0% with lymphovascular invasion (16–20, 28). Additional surgery shows 8.3% and 0.0%, respectively (21–23). Additional chemoradiotherapy resulted in metastasis rates of 9.3% and 28.1%, respectively (24–27, 29).

The clinically elevated metastasis risk under observation versus additional interventions in lymphovascular invasion negative pSM carcinomas justifies adjuvant treatment despite potential side effects. Similarly, lymphovascular invasion positive subgroups require additional management, notwithstanding paradoxical outcome variations in pSM2 lymphovascular invasion cohorts. Based on these findings, recommendations for additional treatments are outlined in Figure 1.

4 Additional chemoradiotherapy vs. surgery

Both esophagectomy and chemoradiotherapy serve as primary additional interventions (16, 19). Esophagectomy demonstrates favorable 3-year disease-free survival (86%) (30), 5-year disease-free survival (100%) (31), and 5-year overall survival (90-100%) (22, 31). Compared to upfront esophagectomy, ESD followed by surgery achieves equivalent 3-year overall survival (91.6% vs. 90.9%, hazard ratio [HR] = 0.88, 95% CI: 0.24–3.21; P = 0.871) (32). Furthermore, esophagectomy allows for a more comprehensive assessment of the primary tumor site and regional lymph node status, addressing a limitation of ESD. These outcomes establish esophagectomy as the current therapeutic standard.

Nevertheless, surgical risks remain substantial, with 1.3% treatment-related mortality (95% CI: 0.7-2.2%) (33–37). Additionally, grade 3 and 4 adverse events were reported, including 6.3% anastomotic leaks, 7.7% pneumonia, 2.9% recurrent nerve palsy, and 1.9% fistulae (38). These complications, coupled with quality of life impairment, necessitate cautious patient selection, particularly in elderly or comorbid populations.

Additional chemoradiotherapy emerges an alternative to esophagectomy. The JCOG0508 trial reported a 3-year overall survival rate of 90.7% (90% CI: 84.0-94.7%) for cSM1/SM2 carcinomas managed with ESD plus chemoradiotherapy (39). Real-world evidence from Japanese multicenter studies reveals comparable 5-year overall survival (HR = 0.72, 95% CI: 0.31-1.68; P = 0.44), relapse-free survival (HR = 0.70, 95% CI: 0.34-1.41; P = 0.31), and cause-specific survival (HR = 0.86, 95% CI: 0.08–9.47; P = 0.90) between chemoradiotherapy and esophagectomy (5). Retrospective analyses consistently confirm equivalent survival benefits across both approaches (17, 21–23, 30, 40–43).

TABLE 3 Metastasis rates in patients with submucosa invasion cancers underwent endoscopic submucosal dissection.

Lymphovascular invasion status	Observation (16–20)	Additional surgery (21–23)	Additional chemoradiotherapy (24–27)
pSM1			
Non-lymphovascular invasion	5/38 (13.2%)	0/5 (0.0%)	1/35 (2.9%)
Lymphovascular invasion	3/5 (60.0%)	0/14 (0.0%)	5/28 (17.9%)
pSM2			
Non-lymphovascular invasion	3/16 (18.8%)	1/12 (8.3%)	8/86 (9.3%)
Lymphovascular invasion	0/4 (0.0%)	0/21 (0.0%)	23/82 (28.1%)

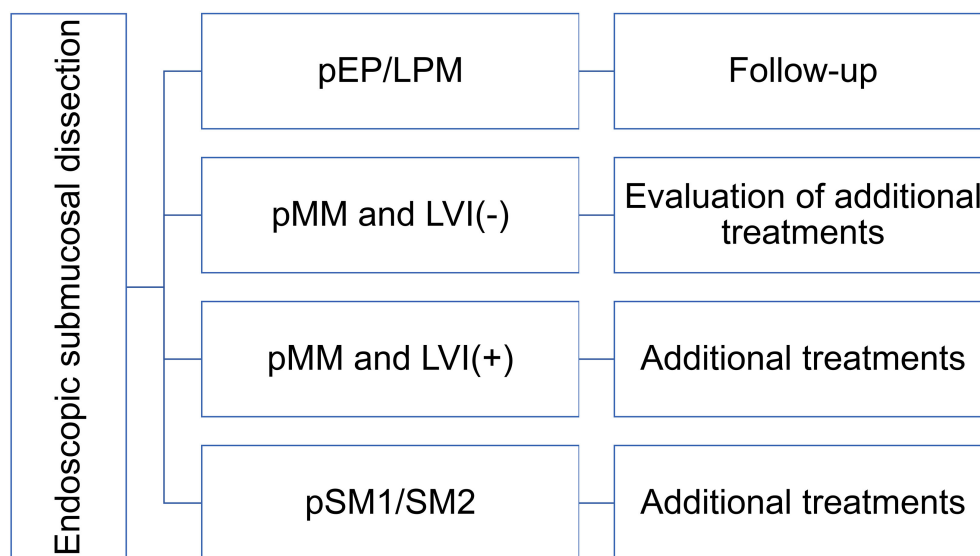SM1, submucosa invasion ≤ 200 μm; SM2, submucosa invasion > 200 μm.

FIGURE 1

Recommendations of additional treatments after endoscopic submucosal dissection. T1a-EP/LPM: epithelial/lamina propria mucosae esophageal cancer, T1a-MM: muscularis mucosae esophageal cancer, T1b-SM1: submucosa invasion ≤ 200 μm, T1b-SM2: submucosa invasion > 200 μm, LVI: lymphovascular invasion.

Notably, chemoradiotherapy demonstrates superior safety profiles, with grade ≥2 toxicities (dyspnea 11.1%, esophagitis 2.7%, cardiac events 2.7-1.4%) and grade ≥3 stenosis (0.6%) being significantly rarer than surgical complications (39, 44). Moreover, chemoradiotherapy further enhances quality of life metrics versus esophagectomy (45). Salvage surgery post-recurrence maintains comparable efficacy to primary esophagectomy, with 90-day mortality rates of 4% versus 5%.

Current clinical practice reflects these advantages, with 61.5% receiving chemoradiotherapy and 24.7% undergoing esophagectomy (5). The ongoing Ad-ESD randomized trial (NCT04616157) directly comparing chemoradiotherapy versus esophagectomy in cN0-pT1b esophageal squamous cell carcinoma will provide Level I evidence to optimize treatment algorithms (46).

5 Key clinical uncertainties of additional chemoradiotherapy

5.1 Optimal timing of chemoradiotherapy post-ESD

The optimal timing for initiating adjuvant chemoradiotherapy following ESD remains undefined. Current evidence supports initiating treatment within 1–2 months post-procedure, mirroring esophagectomy adjuvant therapy intervals (39, 47, 48). This empirical window demonstrates 3-year overall survival rates of 87.9-90.0% and 5-year survival of 85.1%. ESD is less invasive than surgical resection, chemoradiotherapy can be safely initiated once the esophageal scar has formed, with 6% grade ≥3 nonhematologic adverse events (23). The 2-year locoregional control rate and overall survival rate were both 100% with early intervention.

Notably, a multicenter Japanese real-world study revealed immediate post-ESD chemoradiation significantly reduced regional/distant recurrence risk (HR = 0.27, 95% CI: 0.15-0.47; P < 0.001) without increasing overall recurrence (HR = 0.76, 95% CI: 0.46-1.27; P = 0.30) (5). These outcomes contrast with post-esophagectomy adjuvant therapy patterns, confirming the safety and efficacy of early chemoradiation post-ESD.

Limited data exist regarding delayed chemoradiotherapy. A retrospective cohort study found that esophagectomy at a median of 3 months post-ESD resulted in comparable 3-year survival rates to immediate esophagectomy (91.6% vs 90.9%; HR = 0.88, 95% CI: 0.24-3.21; P = 0.817) (32). However, the distinct therapeutic mechanisms of surgery versus chemoradiation preclude direct extrapolation. Given the absence of contraindications, prompt chemoradiotherapy initiation post-ESD is recommended to maximize oncological control while maintaining procedural safety.

5.2 Radiation dose optimization

The phase III ARTDECO trial established that dose escalation to 61.6 Gy failed to improve local control versus 50.4 Gy (HR=1.03, 95%CI 0.73-1.44; P=0.85) across histological subtypes in definitive chemoradiotherapy (49). This dose-independent efficacy pattern was corroborated by a multicenter randomized trial showing comparable survival between 60 Gy and 50 Gy cohorts (50). Current guidelines accordingly recommend 50 Gy/25 fractions or 50.4 Gy/28 fractions as the standard.

Chinese multicenter data reveal 87.9% 3-year overall survival with 50 Gy post-ESD (47), albeit with elevated grade ≥3 pneumonitis rates and other radiation-induced adverse events (50). Conversely, neoadjuvant protocols (CROSS/NEOCRTEC5010 trials) employing

41.4 Gy/23 fractions or 40 Gy/20 fractions achieved 43-48% pathological complete response rates (51–54), suggesting potential for dose de-escalation in adjuvant settings.

Regional practices reflect this paradigm shift. Japanese cohorts receiving 41.4 Gy/23 fractions demonstrate a 3-year overall survival rate exceeding 90%, with a 5-year survival rate of 85.1% (39, 48). Similarly, Chinese study with 40 Gy/20 fractions reports a 2-year overall survival rate of 100% (23).

Despite these advances, the optimal radiation dose remains uncertain. Current clinical consensus recommends 41.4 Gy/23 fractions or 40 Gy/20 fractions are recommended based on comparable survival outcomes and superior safety profiles.

5.3 Target volume delineation strategies

Additional chemoradiotherapy following ESD aims to mitigate local recurrence through precise radiation field design, with ongoing debate regarding two critical aspects (1): inclusion of the primary tumor bed in gross tumor volume delineation, and (2) selection between involved-field irradiation versus elective nodal irradiation.

Current evidence diverges on gross tumor volume delineation. Several studies suggest encompassing the ESD resection bed as the gross tumor volume, typically irradiated with 50Gy/25 fractions to 60Gy/30 fractions (23, 47, 55). Conversely, some studies advocate omitting gross tumor volume delineation unless positive margins exist, focusing instead on prophylactic nodal coverage at 50.4 Gy/28 fractions to 60 Gy/30 fractions (39, 48, 56).

Regarding nodal irradiation strategies, elective nodal irradiation remains predominant in clinical practice, with field design dictated by tumor location (39, 48, 56). The upper thoracic lesions typically encompass supraclavicular, upper mediastinal, and subcarinal region. The middle esophageal tumors include mediastinal and perigastric regions. The lower esophageal cancers extend to celiac nodal stations.

However, emerging evidence from advanced disease studies challenges this paradigm. Involved-field irradiation demonstrates comparable survival rates to elective nodal irradiation (57–59). Furthermore, involved-field irradiation significantly reduces radiation-induced side effects incidence, attributed to reduction in normal tissues radiation exposure (60, 61). Similarly, involved-field irradiation, targeting the primary tumor with 3–5 cm craniocaudal margins and adjacent nodes regions, maintains efficacy for T1N0M0 lesions (62, 63).

Post-ESD involved-field irradiation data remains limited. A multicenter study delineated the clinical target volume as the gross tumor volume plus a 2–5 cm craniocaudal margin, with or without elective nodal irradiation (47). Due to the small sample size (47 patients), directly comparison between involved-field irradiation and elective nodal irradiation was performed, preventing definitive conclusions.

Current consensus increasingly favors involved-field irradiation for margin negative cases given its favorable toxicity profile, reserving elective nodal irradiation for multifocal lesions or high-risk histopathological features. Radiation oncologists must balance recurrence prevention against organ preservation benefits, particularly in patients with pre-existing cardiopulmonary compromise.

5.4 Role of concurrent chemotherapy

For patients with stage T1N0M0 disease, concurrent chemoradiotherapy yields significantly inferior 5-year progression-free survival compared to esophagectomy (71.6% vs. 81.7%), while 5-year overall survival remains comparable between modalities (85.5% vs. 86.5%; HR = 1.05, 95% CI: 0.67-1.64) (64). Real-world evidence corroborates the result (65), supporting its role as a viable alternative for surgically ineligible T1N0M0 cases.

Contrasting data emerge from the KROG 21–10 retrospective study, where chemotherapy failed to independently predict overall survival (HR=0.16, 95% CI: 0.02-1.11, P = 0.06), despite improving 3-year locoregional control (94.4% vs. 66.8%, P = 0.001) (63). These paradoxical outcomes, compounded by retrospective design and small sample size, underscore the need for cautious interpretation while highlighting critical knowledge gaps regarding chemotherapy necessity post-ESD.

Radiotherapy monotherapy demonstrates comparable survival outcomes to chemoradiation in select cohorts. A multicenter study reported that radiotherapy improved 5-year overall survival (91.7% vs 59.5%, P = 0.050) and disease-free survival (92.9% vs 42.6%, P = 0.010) compared to observation (47). Notably, these survival benefits mirrored those reported for chemoradiotherapy in contemporary series (39, 55, 66), suggesting radiotherapy monotherapy may provide comparable oncologic outcomes with reduced chemotoxicity.

However, these studies are constrained by methodological heterogeneity. The predominantly retrospective study designs lack direct comparative arms, resulting in a grade C level of evidence according to established classification systems. This heterogeneity in research methodologies significantly limits our ability to draw definitive conclusions regarding the therapeutic value of concurrent chemotherapy in this specific clinical context.

Furthermore, pharmacological evidence demonstrates that chemotherapeutic agents such as 5-fluorouracil and cisplatin may enhance radiosensitivity through synergistic mechanisms involving DNA damage stabilization, repair pathway inhibition, and tumor cell cycle synchronization during radiation exposure (67). Nevertheless, marked discrepancies in chemotherapeutic regimens across clinical trials compromise the therapeutic impact of concurrent chemotherapy on post-ESD survival outcomes.

Pending the availability of large-scale, multicenter prospective randomized controlled trials, clinicians should exercise prudence when considering additional chemotherapy recommendations. Decision-making frameworks should incorporate multidimensional risk assessment models integrating histopathological parameters (particularly tumor invasion depth), comorbidity profiles, and metastatic potential. Development of validated prognostic algorithms containing these variables may ultimately establish evidence-based recommendations for therapeutic escalation.

6 Conclusion

Our review highlights critical gaps between current practice patterns and evidence-based recommendations for post-ESD management. While guidelines prioritize esophagectomy after ESD with high-risk patients, our review suggests chemoradiotherapy achieves comparable survival with superior quality of life metrics (68). This discrepancy warrants urgent guideline updates to incorporate additional chemoradiotherapy as an alternative option for select patients. Furthermore, our review suggests that multidisciplinary decision-making should be performed in clinical practice based on risk-stratified recommendations and shared decision-making tools.

Several limitations must be acknowledged. First, the majority of included studies were retrospective observational analyses, which inherently carry selection bias and confounding risks. Second, significant heterogeneity exists in radiation dosing protocols, target volume definitions, and chemoradiotherapy regimens, limiting direct comparisons across studies. Third, the follow-up duration in many studies was relatively short, particularly for assessing late complications such as radiation-induced strictures or secondary malignancies. Fourth, the absence of randomized controlled trials comparing chemoradiotherapy with surgery directly after ESD leaves critical clinical questions unresolved, particularly regarding long-term quality of life and cost-effectiveness (46).

Future research should prioritize multicenter randomized controlled trials to compare chemoradiotherapy and surgery in terms of survival, toxicity, and patient-reported outcomes. Prospective studies are needed to standardize radiation dosing (40-41.4 Gy vs. 50-50.4 Gy), optimize target volume delineation strategies (involved-field irradiation vs. elective nodal irradiation), and evaluate the role of concurrent chemotherapy. Long-term follow-up studies are essential to assess recurrence patterns, metachronous cancer risks, late treatment-related morbidity, and patient-reported outcomes. Additionally, translational research should explore molecular mechanisms underlying chemoradiotherapy resistance, which may guide personalized adjuvant therapy.

Author contributions

YLin: Conceptualization, Writing – original draft. SW: Formal analysis, Methodology, Writing – original draft. HL: Formal analysis, Resources, Writing – original draft. YLiu: Methodology, Resources, Writing – original draft. WH: Formal analysis, Validation, Writing – original draft. XP: Writing – review & editing, Validation.

Funding

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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