

A modified ^{18}F -FDG PET/CT diagnostic criterion for regional lymph node metastasis in gastric cancer: a multicenter retrospective study

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Abstract

Background

Lymph-node metastasis represents the dominant metastatic pathway and a critical prognostic factor for gastric cancer. Therefore, accurate pre-treatment evaluation of regional lymph nodes is clinically essential. Nevertheless, preoperative ^{18}F -FDG PET/CT exhibits limited diagnostic performance in routine practice. This study hypothesized that such limitation partially originates from drawbacks of conventional diagnostic criteria, and proposed a modified hierarchical criterion combining metabolic and morphological features to improve PET/CT diagnostic performance for lymph-node metastasis.

Methods

Of 173 patients with histologically confirmed gastric adenocarcinoma initially enrolled from three tertiary hospitals, 166 patients with 507 evaluable lymph node groups were included in the final retrospective analysis. Analyses were performed at the lymph-node group level to account for within-patient clustering. Two diagnostic criteria were compared: Criterion 1 (conventional, purely SUVmax-based metabolic criterion) and Criterion 2 (modified hierarchical criterion integrating metabolic and contrast-enhanced CT morphological features). Diagnostic performance metrics including area under the receiver-operating-characteristic curve (AUC), accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Performance was further stratified by lymph-node groups and pathological subtypes.

Results

Compared with Criterion 1, Criterion 2 yielded significantly improved diagnostic performance for lymph-node metastasis (AUC: 79.80% vs. 62.70%; accuracy: 84.02% vs. 56.41%; sensitivity: 90.79% vs 47.62%; specificity: 69.59% vs 80.05%; PPV: 83.83% vs 78.30%; NPV: 78.67% vs 49.79%; DeLong test, $P < 0.01$). Subgroup analyses demonstrated superior performance of Criterion 2 across all Lauren subtypes ($P < 0.05$). For WHO pathological subtypes, Criterion 2 achieved higher AUC values relative to Criterion 1; the difference reached marginal statistical significance for tubular adenocarcinoma (TAC, adjusted DeLong test, $P = 0.053$), whereas statistically significant differences were observed for the remaining subtypes (DeLong test, $P < 0.05$). Regarding individual lymph-node group, Criterion 2 showed improved diagnostic efficiency for stations 1, 3A, 4SA, 7, 8, and 9 (DeLong test, $P < 0.05$).

Conclusions

The diagnostic performance of ^{18}F -FDG PET/CT for regional gastric-cancer lymph-node metastasis is strongly dependent on the applied diagnostic criteria. The proposed modified hierarchical criterion integrating metabolic and morphological features outperforms the conventional purely metabolic criterion and shows potential for preoperative clinical application.

Key points

- Lymph-node-group analysis with GEE accounted for within-patient clustering.
- A hierarchical PET/CT criterion integrated metabolic and morphological features.
- The modified criterion increased the AUC from 62.70% to 79.80%.
- Sensitivity improved from 47.62% to 90.79%, although specificity decreased.
- Diagnostic gains were maintained across Lauren and most WHO subtypes.

Introduction

Gastric cancer is one of the most common malignant tumors in the world [1]. Lymph-node metastasis is the main metastatic route and critical determinant of prognosis and therapeutic regimen of gastric-cancer patients [2–6]. Therefore, accurate lymph-node staging before treatment is especially important. While imaging methods including CT, MRI, and EUS are currently utilized, their performance is often limited by morphology-based diagnostic criteria which frequently fail to distinguish benign lymph nodes from metastases [7–10].

^{18}F -FDG PET/CT (PET/CT) has been widely adopted in oncological work for lesion detection, differential diagnosis, prognosis evaluation, and therapeutic evaluation of gastric cancer [3, 11]. However, its clinical value in nodal staging remains inadequate [12]. This limitation is primarily attributed to the conventional diagnostic criteria relying solely on SUV [3, 10, 13, 14], leading frequent false-negative findings, especially for small nodes < 4 mm (limited by PET resolution) or histological subtypes with low FDG avidity, including mucinous or signet-ring cell carcinomas driven by abundant mucinous content, low cellular density, and reduced GLUT-1 expression [2, 15]. We hypothesized that the diagnostic ability of PET/CT has been substantially underestimated due to this methodological shortcoming. To address this gap, we propose a modified comprehensive diagnostic criterion integrating metabolic and contrast-enhanced CT morphological features. Moving beyond conventional patient-level evaluation, we adopted lymph-node-group-level analysis requiring strict image-pathology correspondence within identical lymph-node stations, and stratified diagnostic performance by lymph-node groups and pathological subtypes. Venous-phase contrast-enhanced CT was applied to supply richer morphological information compared with unenhanced CT.

Materials and methods

Patients Inclusion Criteria

Patients with histologically confirmed gastric adenocarcinoma who underwent preoperative ^{18}F -FDG PET/CT followed by radical gastrectomy between January 2021 and December 2025 were consecutively enrolled from three tertiary hospitals. Inclusion criteria: (1) Interval between PET/CT and surgery ≤ 14 days; (2) no preoperative anti-tumor or tumor reducing treatment; (3) No prior upper-abdominal surgery or concurrent primary malignancy; (4) Absence of comorbidities (pneumoconiosis, tuberculosis, inflammatory bowel disease, rheumatoid disorders) predisposing to extensive abdominal lymph-node reactive hyperplasia.

Analyses were performed at lymph-node-group level. Eligible groups were those with pathologically confirmed metastasis or containing at least one lymph node with short-axis diameter > 0.3 cm in PET/CT image. In total, 173 patients were enrolled (107 from Sixth Affiliated Hospital of Sun Yat-sen University; 32 from Union Hospital of Fujian Medical University; 34 from Fujian Cancer Hospital), yielding 507 evaluable regional lymph-node groups.

TNM staging and lymph-node grouping followed the 8th AJCC manual. Pathological evaluation used WHO and Lauren classification systems. WHO subtypes: poorly differentiated adenocarcinoma (PAC, type 1), tubular adenocarcinoma (TAC, type 2), mucinous-rich adenocarcinoma (MRAC, type 3), poorly differentiated adenocarcinoma with partial signet-ring-cell carcinoma (PAC-MRAC, type 4), tubular adenocarcinoma with partial poorly differentiated adenocarcinoma (TAC-PAC, type 5). Lauren classification included diffuse (type 1), intestinal (type 2), and mixed (type 3).

Imaging machine and methods

All participants received whole-body ^{18}F -FDG PET/CT covering the skull base to proximal femur across three centers with three scanners: United Imaging uMI 780, GE Discovery MI, and Philips Gemini TF 64. The ^{18}F -fluorodeoxyglucose (^{18}F -FDG) radiotracer was supplied by Beijing Atomic High Tech Isotope Company (Guangzhou Branch) for examinations at the Sixth Affiliated Hospital of Sun Yat-sen University and by Fujian Andike Positron Technology Co., Ltd. (Fuzhou, China) for studies at Union Hospital of Fujian Medical University. For patients enrolled from Fujian Cancer Hospital, ^{18}F -FDG was produced in-house using a Sumitomo HM-10 cyclotron. All patients received standard preparation before imaging, involving 6 ~ 8 hours of fasting and blood-glucose controlled at 3.9 ~ 7.5 mmol/L. ^{18}F -FDG was administered via intravenous injection at a dose of 3.7 ~ 5.55 MBq/kg, with radiochemical purity exceeding 95%. After tracer injection, patients rested in a quiet and warm environment for approximately 1 hour. Oral intake of approximately 300 mL warm water was performed before scanning to distend the gastric lumen. All scans were acquired with patients in the supine position. The scanning range covered from the skull base to the proximal femur. The parameters for image acquisition and reconstruction are summarized in Supplementary Table 1.

Contrast-enhanced CT (CE-CT) was obtained to analyze lymph node morphological features. The primary center acquired venous-phase contrast-enhanced images synchronously on the integrated uMI 780 PET/CT scanner, while the other two centers adopted dedicated standalone abdominal CE-CT with GE Revolution CT and Philips Brilliance ICT, as PET/CT at these sites did not support synchronous contrast injection. To standardize imaging quality, identical iodinated contrast dosage, injection speed and 70s venous phase were applied in all subjects, with thin-slice reconstruction (1.25 mm) performed for precise nodal structural evaluation. The 70-second delay is consistent with established gastric-cancer CT imaging protocols [16]. Detailed scanner parameters are summarized in Supplementary Table 2.

Image Processing and Analysis

Two board-certified gastrointestinal-imaging nuclear-medicine physicians (5-year and 10-year experience) performed blinded independent reading. Both visual and semi-quantitative PET analyses were performed. For hypermetabolic nodes, hilar architecture was assessed; for non-hypermetabolic nodes, size, enhancement pattern, and cortical thickening were evaluated. Reader disagreements were resolved by consensus with a third senior physician.

Diagnostic Criterion 1 (the conventional, based on an SUVmax threshold) [12, 17]: Lymph-node-group classified as metastatic if FDG uptake exceeded abdominal-aorta activity; morphology was disregarded.

The diagnostic Criterion 2 (the modified, metabolic-morphological criterion):

1. Elevated FDG uptake (higher than that of abdominal aorta): metastatic unless existing of a clear and complete lymph node hilum structure;
2. No elevated FDG uptake: $\square$ Short-axis diameter > 0.8 cm: classified benign; $\square$ Short-axis diameter ≤ 0.8 cm: metastatic if heterogeneous enhancement or nodular cortical thickening; otherwise, benign.

The 0.8 cm short-axis threshold represents a clinically practical compromise derived from abdominal-lymph-node imaging literature [18, 19]. Nodes > 0.8 cm approach the 4–6 mm spatial-resolution limit of clinical PET scanners [20], allowing reliable metabolic assessment; nodes ≤ 0.8 cm are more susceptible to partial-volume effects and require morphological supplementation.

Final diagnosis

The lymph node metastasis was confirmed by postoperative histopathology as reference standard.

Statistical Analysis

Statistical analysis was conducted by SPSS 27. 0. Using chi square test to analyze the diagnostic ability of two diagnostic criteria based on PET/CT results, and the sensitivity (Se), specificity (Sp), accuracy (Acc), positive predictive value (PPV), and negative predictive value (NPV) were calculated and compared them according to different lymph node groups and pathological types including Lauren pathological types and WHO pathological types. The DeLong test adapted for clustered data Using Delong test to compare the diagnostic performance of AUC for Criterion 1 (C1) and Criterion 2 (C1). $p < 0.05$ indicates statistical significance, while $0.05 \leq p \leq 0.10$ indicates marginal significance. Cohen's Kappa test was used to evaluate the inter-observer agreement. Weighted κ was applied for ordinal-type visual ratings where appropriate. All indicators and p-values were corrected using generalized estimation equation (GEE) to eliminate intra-patient bias caused by the inherent clustering correlation between multiple groups of lymph node metastasis status and PET/CT interpretation results in the same patient. For individual lymph-node-station-stratified analyses without repeated measurements within each station, GEE correction was not applicable and conventional χ^2 test was adopted. Patient clustering Bootstrap (2000 resamples)) was used to obtain a 95% confidence interval.

Results

Patients and LN characteristics and correlation of data clustering

The study cohort comprised 173 patients with gastric cancer, including 60 with pathologically confirmed N0 disease and 113 with lymph node metastasis. Their clinical and pathological characteristics are summarized in Table 1. Lymph node groups were eligible for analysis if they contained pathologically confirmed metastases or lymph nodes measuring > 0.3 cm in short-axis diameter on imaging. Seven of the 60 patients with N0 disease had no lymph node groups meeting these criteria on imaging and therefore contributed no lymph node groups to the analysis. The final lymph-node-group-level analysis included 507 groups from 166 patients, comprising 352 pathologically positive groups and 155 pathologically negative groups. The diagnostic efficacy of C1 and C2 before and after correction is shown in Table 2 ~ 4.

Table 1
Baseline clinical characteristics of the patients (n = 173).

Clinical characteristics	n	Percentage (%)
Age (Mean $\pm$ SD)	61.7 $\pm$ 12.7	-
Gender		
Male	131	75.7
Female	42	24.3
T stage		
T1	27	15.6
T2	19	11.0
T3	74	42.8
T4	53	30.6
N stage		
N0	60	34.7
N1	30	17.3
N2	30	17.3
N3	53	30.6
M stage		
M0	143	82.7
M1	30	17.3
Lauren type		
Type 1(diffuse type)	65	37.6
Type 2(intestinal type)	52	30.0
Type 3(mixed type)	56	32.4
Pathological type		
Type 1 (PAC)	43	24.9
Type 2 (TAC)	51	29.5
Type 3 (MRAC)	15	8.7
Type 4 (PAC-MRAC)	16	9.2
Type 5 (TAC-PAC)	48	27.7

Table 2
Overall diagnostic performance of methods C1 and C2 (unadjusted vs GEE cluster-adjusted).

Overall				
Method	C1	C2	C1	C2
Correction	Unadjusted	Unadjusted	GEE-adjusted	GEE-adjusted
n (lymph node groups)	507	507	507	507
n (patients)	166	166	166	166
Sensitivity (%)	46.59	90.62	47.62	90.79
Specificity (%)	78.71	69.03	80.05	69.59
Accuracy (%)	56.41	84.02	56.41	84.02
FPR (%)	21.29	30.97	19.95	30.41
FNR (%)	53.41	9.38	52.38	9.21
PPV (%)	83.25	86.92	78.3	83.83
NPV (%)	39.35	76.43	49.79	78.67
AUC	62.65	79.83	62.65	79.83
AUC (95% CI)	57.58–67.72	76.01–83.64	57.04–68.04	75.45–84.21
Youden index	0.253	0.597	0.277	0.604
DeLong P-value		< 0.001	—	—
Adjusted P-value	—	—		< 0.001
Note: Note: AUC, area under the receiver operating characteristic curve; CI, confidence interval; GEE, generalized estimating equations; PPV, positive predictive value; NPV, negative predictive value; FPR, false positive rate; FNR, false negative rate. The unadjusted analysis did not account for within-patient correlation among lymph node groups. In the GEE-adjusted analysis, GEE was used to account for within-patient clustering when estimating diagnostic performance measures, whereas AUC inference was performed using patient-level cluster bootstrap resampling. “DeLong P-value” refers to the comparison of AUCs between C1 and C2 using the paired DeLong test without adjustment for within-patient clustering. “Adjusted P-value” refers exclusively to the cluster-adjusted comparison of AUCs between C1 and C2 using patient-level cluster bootstrap resampling, with paired C1 and C2 observations retained within each resampled patient. Neither P-value represents a comparison of sensitivity or accuracy. AUC estimates and their 95% confidence intervals are expressed as percentages.				

Corrected Diagnostic Efficacy of Two Diagnostic Criteria overall

Inter-observer agreement between the two readers was substantial, with a Cohen’s Kappa value of 0.759 (95% CI, 69.6% ~ 82.1%; raw agreement = 89.74%, $Z = 23.92$, $P < 0.001$). Corrected clustered DeLong test $P < 0.001$, indicates that statistically significant differences exists between Criteria overall.

Sensitivity and missed diagnosis rate: C1 achieved a sensitivity of only 47.62% with a false negative rate as high as 52.38% (Table 2), and more than half of metastatic lymph nodes were missed. The sensitivity of C2 increased to 90.79%, with a false negative rate of merely 9.21% (Table 2), which can greatly reduce the risk of missed diagnosis of metastatic lymph nodes.

Specificity and misdiagnosis rate: C1 had a higher specificity of 80.05% and a false positive rate of 19.95% (Table 2). The specificity of C2 slightly decreased to 69.59%, with a false positive rate of 30.41% (Table 2). C2 tends to cause mild increased misjudgment of inflammatory hyperplastic lymph nodes. Nevertheless, the benefit from reduced missed diagnoses far outweighs the slight loss in specificity.

Comprehensive efficacy indicators: C1 had an accuracy of only 56.41%, an AUC of 0.627 and a Youden index of 0.277 (Table 2), indicating poor overall discriminatory capacity. C2 reached an accuracy of 84.02%, an AUC of 0.798 and a Youden index of 0.604 (Table 2). Its comprehensive ability to identify lymph node metastasis was significantly superior to C1.

Predictive values: C2 yielded a positive predictive value (PPV) of 83.83% and a negative predictive value (NPV) of 78.67%, which were markedly improved compared with C1 (PPV = 78.30%, NPV = 49.79%) (Table 2). The improvement in negative predictive value was particularly prominent, suggesting that C2 possesses higher clinical value for ruling out lymph node metastasis. Figure 1 shows the overall diagnostic performance.

Comparison of Diagnostic Efficacy Stratified by WHO Pathological Classification

The sensitivity, AUC and Youden’s index of C2 were higher than those of C1 in all WHO subtypes (Table 3). Except for the TAC with adjusted Delong $P = 0.053$ (marginally significant) (Table 3), the differences in AUC of C2 compared with C1 in all other WHO pathological classifications were statistically significant. C2 of TAC classification had the highest Youden index (0.712, Table 3) compared with others, suggesting that the modified criterion achieved better comprehensive performance in identifying metastases for this pathological sub-type. Although C2 of the MRAC classification had the lowest sensitivity among the criteria compared (83.11%, Table 3), its sensitivity was still more than twice that of C1.

Table 3
Diagnostic performance by WHO pathological classification (unadjusted vs GEE cluster-adjusted).

Pathologic subtype	Method	Correction	n (lymph node groups)	n (patients)	Sensitivity (%)	Specificity (%)	Accuracy (%)	FPR (%)	FNR (%)	PPV (%)	NPV (%)	AUC	AUC (95% CI)
Type 1	C1	Unadjusted	170	42	52.9	87.5	59.41	12.5	47.1	94.81	30.11	70.2	61.1 79.2
Type 1	C2	Unadjusted	170	42	93.48	59.38	87.06	40.62	6.52	90.85	67.86	76.43	68.4 84.4
Type 1	C1	GEE-adjusted	170	42	53.18	87.26	59.41	12.74	46.82	92.95	39.5	70.2	57.8 79.3
Type 1	C2	GEE-adjusted	170	42	94.25	59.98	87.06	40.02	5.75	89.06	72.77	76.43	67.5 86.9
Type 2	C1	Unadjusted	96	50	59.09	73.08	66.67	26.92	40.91	65	67.86	66.08	55.0 77.0
Type 2	C2	Unadjusted	96	50	93.18	78.85	85.42	21.15	6.82	78.85	93.18	86.01	78.2 93.7
Type 2	C1	GEE-adjusted	96	50	60.15	72.88	66.67	27.12	39.85	58.5	75.47	66.08	55.8 77.0
Type 2	C2	GEE-adjusted	96	50	92.74	78.49	85.42	21.51	7.26	76.25	92.85	86.01	78.9 93.4
Type 3	C1	Unadjusted	54	15	11.9	83.33	27.78	16.67	88.1	71.43	21.28	47.62	28.7 66.4
Type 3	C2	Unadjusted	54	15	83.33	50	75.93	50	16.67	85.37	46.15	66.67	50.3 82.9
Type 3	C1	GEE-adjusted	54	15	13.26	83.88	27.78	16.12	86.74	—	29.12	47.62	34.0 57.9
Type 3	C2	GEE-adjusted	54	15	83.11	100	75.93	0	16.89	76.6	61.16	66.67	52.2 81.7
Type 4	C1	Unadjusted	39	14	40	71.43	51.28	28.57	60	71.43	40	55.71	36.9 74.4
Type 4	C2	Unadjusted	39	14	92	57.14	79.49	42.86	8	79.31	80	74.57	59.1 89.9
Type 4	C1	GEE-adjusted	39	14	38.15	72.39	51.28	27.61	61.85	63.23	44.2	55.71	39.3 72.8
Type 4	C2	GEE-adjusted	39	14	92.24	46.96	79.49	53.04	7.76	79.22	80.5	74.57	58.4 88.7
Type 5	C1	Unadjusted	148	45	48.54	80	58.11	20	51.46	84.75	40.45	64.27	55.0 73.5
Type 5	C2	Unadjusted	148	45	88.35	73.33	83.78	26.67	11.65	88.35	73.33	80.84	73.9 87.7
Type 5	C1	GEE-adjusted	148	45	49.23	87	58.11	13	50.77	84.56	43.64	64.27	54.3 74.5
Type 5	C2	GEE-adjusted	148	45	87.97	74.21	83.78	25.79	12.03	86.59	74.49	80.84	73.4 88.0

Note: AUC, area under the receiver operating characteristic curve; CI, confidence interval; GEE, generalized estimating equations; PPV, positive predictive value; FPR, false positive rate; FNR, false negative rate. Pathological subtypes were defined as follows: type 1, poorly differentiated adenocarcinoma (PAC); type 2, mucinous-rich adenocarcinoma (MRAC); type 3, mucinous-rich adenocarcinoma with partial mucin-rich adenocarcinoma (PAC-MRAC); and type 5, poorly differentiated adenocarcinoma (TAC-PAC). The unadjusted analysis did not account for within-patient correlation among lymph node groups. The GEE analysis accounted for within-patient clustering, with metric-specific estimation and inference procedures described in the Methods. "DeLong P-value" refers to the comparison of AUC estimates between two methods (C1 vs C2) using DeLong's test. Adjusted P-value is reported for the GEE-adjusted analysis (both compare method C1 vs C2). AUC estimates and P-values are expressed as percentages. Dashes in the P-value columns indicate that the corresponding test is not applicable to that analysis.

Comparison of Diagnostic Efficacy Stratified by Lauren Classification

Stratified results based on the Lauren classification (diffuse type, intestinal type, mixed type) demonstrated that C2 exhibited superior diagnostic performance compared with C1 across all subtypes (Table 4). The adjusted Delong *P* values of the three groups were all less than 0.05 indicating statistically significant differences (Table 4). Among them, the Youden's index of C2 for intestinal type reached 0.72 (Table 4), the highest among all stratifications. Severe missed diagnoses were observed with C1 for diffuse type, whereas C2 can markedly reduce the risk of missed diagnosis (Table 4), conferring prominent value for preoperative staging of this type. The AUCs of the different subtypes are compared in Fig. 2, whereas their sensitivities and specificities are presented in Fig. 3.

Table 4
Diagnostic performance by Lauren classification (unadjusted vs GEE cluster-adjusted).

Lauren classification	Method	Correction	n (lymph node groups)	n (patients)	Sensitivity (%)	Specificity (%)	Accuracy (%)	FPR (%)	FNR (%)	PPV (%)	NPV (%)	AUC	A (95% CI)
Type 1	C1	Unadjusted	222	62	43.37	82.14	53.15	17.86	56.63	87.8	32.86	62.76	57.71
Type 1	C2	Unadjusted	222	62	89.16	57.14	81.08	42.86	10.84	86.05	64.00	73.15	60.81
Type 1	C1	GEE-adjusted	222	62	43.84	81.25	53.15	18.75	56.16	83.76	42.90	62.76	57.71
Type 1	C2	GEE-adjusted	222	62	89.43	57.11	81.08	42.89	10.57	81.98	69.56	73.15	60.81
Type 2	C1	Unadjusted	104	51	56.86	73.58	65.38	26.42	43.14	67.44	63.93	65.22	57.71
Type 2	C2	Unadjusted	104	51	96.08	77.36	86.54	22.64	3.92	80.33	95.35	86.72	70.91
Type 2	C1	GEE-adjusted	104	51	59.85	73.54	65.38	26.46	40.15	61.62	74.45	65.22	57.71
Type 2	C2	GEE-adjusted	104	51	96.00	76.37	86.54	23.63	4	77.51	95.18	86.72	70.91
Type 3	C1	Unadjusted	181	53	46.67	80.43	55.25	19.57	53.33	87.5	33.94	63.55	57.71
Type 3	C2	Unadjusted	181	53	90.37	73.91	86.19	26.09	9.63	91.04	72.34	82.14	70.81
Type 3	C1	GEE-adjusted	181	53	46.07	88.23	55.25	11.77	53.93	86.07	37.92	63.55	57.71
Type 3	C2	GEE-adjusted	181	53	90.15	75	86.19	25	9.85	89.61	73.51	82.14	70.81

Note: AUC, area under the receiver operating characteristic curve; CI, confidence interval; GEE, generalized estimating equations; PPV, positive predictive value; NPV, negative predictive value; FPR, false positive rate; FNR, false negative rate. Lauren classification was coded as type 1 (diffuse), type 2 (intestinal), and type 3 (mixed). The unadjusted analysis did not account for within-patient correlation among lymph node groups. The GEE-adjusted analysis accounted for within-patient clustering, with metric-specific estimation and inference procedures described in the Methods. “DeLong *P*-value” refers to the comparison of AUCs between C1 and C2 within each Lauren subtype using DeLong’s test. Adjusted *P*-value is reported for the GEE-adjusted analysis (both compare method C1 vs C2). AUC estimates and their 95% confidence intervals are expressed as percentages.

Comparison of Diagnostic Efficacy Stratified by Regional Lymph Node Groups

There are no repeated observations within per-group and no within-patient clustering bias, leaving no room for adjustment via GEE. The result was calculated according to the ordinary chi square test. C2 achieved better performance for lymph node groups 4SA, 3A, 1, 7, 8 and 9, with AUC > 79% and Youden’s index > 0.59 (Table 5). Among them, groups 3A, 7, 8, 9 represent the most common metastatic regions of gastric cancer and serve as core target areas for clinical preoperative evaluation [13, 14, 21–25]. Rare lymph node subgroups including 4SB, 10, 11 and 12 exhibited insufficient test performance in some subgroups due to the limited sample size of individual lymph node groups, with Delong *P* > 0.05 (Table 5). Nevertheless, the sensitivity and AUC values of C2 remained consistently higher than those of C1 (Table 5), showing a trend consistent with that of the overall population. Although no statistically significant difference was observed in lymph node groups with small sample sizes, numerical evidence verified that C2 possessed superior discriminatory capacity (Table 5).

Table 5
Diagnostic performance of different lymph node groups (unadjusted).

Lymph node station	Method	n (lymph node groups)	n (patients)	Sensitivity (%)	Specificity (%)	Accuracy (%)	FPR (%)	FNR (%)	PPV (%)	NPV (%)	AUC	AUC (95% CI)	Youden index	D P
3A	C1	132	131	69.05	72.92	70.45	27.08	30.95	81.69	57.38	70.98	62.21–79.75	0.420	0
3A	C2	132	131	97.62	64.58	85.61	35.42	2.38	82.83	93.94	81.1	73.93–88.27	0.622	
3B	C1	23	23	63.16	50	60.87	50	36.84	85.71	22.22	56.58	25.99–87.17	0.132	0
3B	C2	23	23	89.47	50	82.61	50	10.53	89.47	50	69.74	43.58–95.90	0.395	
4D	C1	63	63	39.53	95	57.14	5	60.47	94.44	42.22	67.27	53.60–80.94	0.345	0
4D	C2	63	63	90.7	65	82.54	35	9.3	84.78	76.47	77.85	66.43–89.27	0.557	
4SA	C1	16	16	42.86	100	50	0	57.14	100	20	71.43	36.71–100.00	0.429	0
4SA	C2	16	16	71.43	100	75	0	28.57	100	33.33	85.71	62.94–100.00	0.714	
4SB	C1	7	7	42.86	–	42.86	–	57.14	100	0	–	–	–	–
4SB	C2	7	7	100	–	100	–	0	100	–	–	–	–	
1	C1	38	38	35.71	90	50	10	64.29	90.91	33.33	62.86	43.43–82.29	0.257	0
1	C2	38	38	89.29	70	84.21	30	10.71	89.29	70	79.64	65.06–94.22	0.593	
10	C1	3	3	0	–	0	–	100	–	0	–	–	–	–
10	C2	3	3	100	–	100	–	0	100	–	–	–	–	
11	C1	18	18	43.75	50	44.44	50	56.25	87.5	10	46.88	2.71–91.04	-0.063	0
11	C2	18	18	75	50	72.22	50	25	92.31	20	62.5	23.25–100.00	0.250	
12	C1	13	13	20	100	38.46	0	80	100	27.27	60	23.56–96.44	0.200	0
12	C2	13	13	50	100	61.54	0	50	100	37.5	75	45.37–100.00	0.500	
2	C1	17	17	33.33	50	35.29	50	66.67	83.33	9.09	41.67	0.00–86.48	-0.167	0
2	C2	17	17	86.67	0	76.47	100	13.33	86.67	0	43.33	0.00–88.07	-0.133	
5	C1	15	15	41.67	100	53.33	0	58.33	100	30	70.83	40.00–100.00	0.417	0
5	C2	15	15	91.67	66.67	86.67	33.33	8.33	91.67	66.67	79.17	53.37–100.00	0.583	
6	C1	30	30	36	80	43.33	20	64	90	20	58	31.24–84.76	0.160	0
6	C2	30	30	80	60	76.67	40	20	90.91	37.5	70	47.02–92.98	0.400	
7	C1	79	78	44	72.41	54.43	27.59	56	73.33	42.86	58.21	45.33–71.09	0.164	<
7	C2	79	78	100	72.41	89.87	27.59	0	86.21	100	86.21	78.29–94.13	0.724	
8	C1	34	34	35.71	80	61.76	20	64.29	55.56	64	57.86	37.97–77.74	0.157	0
8	C2	34	34	92.86	80	85.29	20	7.14	76.47	94.12	86.43	72.91–99.95	0.729	

Lymph node station	Method	n (lymph node groups)	n (patients)	Sensitivity (%)	Specificity (%)	Accuracy (%)	FPR (%)	FNR (%)	PPV (%)	NPV (%)	AUC	AUC (95% CI)	Youden index	D P
9	C1	19	19	25	85.71	47.37	14.29	75	75	40	55.36	28.18–82.53	0.107	0
9	C2	19	19	100	85.71	94.74	14.29	0	92.31	100	92.86	81.02–100.00	0.857	

Note: AUC, area under the receiver operating characteristic curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; FPR, false positive rate; FNR, false negative rate. Results are presented separately for each lymph node station. “DeLong *P*-value” refers to the comparison of AUCs between methods C1 and C2 within the same lymph node station using DeLong’s test; one *P* value is reported for each station. The analyses presented in this table were not adjusted for within-patient clustering. AUC estimates and their 95% confidence intervals are expressed as percentages.

C2 consistently achieves superior sensitivity, AUC, Youden index, and negative predictive value compared with C1 for the overall (Table 2), WHO pathological classification (Table 3), Lauren classification (Table 4), or regional lymph node subgroups (Table 5), the specificity shows only a mild decrease, at the cost of misidentifying a small number of benign lymph nodes, while substantially reducing missed diagnoses. Collectively, these findings verify that C2 effectively remedies the critical limitation of high missed diagnosis rates by C1, and markedly improves the preoperative diagnostic efficacy of ¹⁸F-FDG PET/CT for regional lymph node metastasis in gastric cancer. The results of the subgroup analyses evaluating diagnostic performance are presented in Fig. 4.

For rare lymph-node stations including 4SB, 10, 11, and 12, the number of evaluable lymph-node groups per station was limited (range 8 ~ 23 groups per station), resulting in insufficient statistical power for between-criterion comparisons (Table 5). Although DeLong *P*-values exceeded 0.05 for these stations, the sensitivity and AUC values of Criterion 2 were numerically consistently higher than those of Criterion 1 (Table 5), showing a directional trend consistent with the overall population and high-frequency stations.

Discussion

Intrinsic Limitations of Conventional PET/CT Diagnostic criterion

The vast majority of previous studies on PET/CT diagnosis of lymph nodes in gastric cancer have multiple limitations. Observation unit bias: Most studies adopt overall patient N0/N+ staging as the endpoint, which conceals the actual interpretation errors arising from coexisting benign and malignant lymph nodes within a single patient and leads to distorted results. Mechanical combination of imaging data: Only simple superposition of SUV and short-axis thresholds is performed without hierarchical logic. The diagnostic weight of morphological signs under different metabolic levels cannot be differentiated, resulting in poor discriminative ability for micro metastases with low metabolism. Insufficient stratified analysis: Stratification is mostly conducted only based on per-patient pathology, lacking performance comparisons across different lymphatic stations.

Meanwhile, the conventional criteria only accurately diagnoses lymph nodes with significantly high metabolism (Figure S1) and fails to identify low-activity lymph nodes associated with mucinous carcinoma/signet ring cell carcinoma and micro metastases too small to be detected by PET [26–31] (Figure S2). Which tends to cause under staging before treatment and interfere with the selection of treatment regimens. In this study, the overall sensitivity of C1 with 47.62% (Table 2) is consistent with that of 33.3% ~ 64.6% reported in previous studies [31].

Three Core Innovations of This Study

Taking individual lymph nodes as independent observation units

Unlike previous study designs based on patient-level analysis, this study matched each lymphatic group with independent imaging data and pathological diagnosis. Generalized Estimating Equations (GEE) were adopted to eliminate clustering bias of intra-patient observations. The data better conforms to the routine imaging reading practice of clinicians, leading to higher reliability of results.

Organic hierarchical integration of metabolic and morphological features (distinguished from the previous mechanical superposition strategy)

Previous studies mostly adopted a parallel diagnostic model defining metastasis as positivity in either SUV or short-axis diameter. This study established a progressive hierarchical interpretation approach: For hypermetabolic lymph nodes, benign and malignant lesions are differentiated primarily based on the portal structure. The logic behind this consideration is that high metabolism cannot be definitively attributed to malignancy, reactive inflammatory lymph nodes typically retain clear lymphatic gate adipose structures, whereas malignant nodes often exhibit lymphatic gate occlusion and fat disappearance. Therefore, the lymphatic portal structure is prioritized as the key discriminant sign to rapidly exclude benign high-metabolism lymph nodes and control false positives (Figure S3). For non-metabolic lymph nodes, a threshold of 0.8 cm is used for stratification [32]: it is considered benign with diameter ≥ 0.8 cm (Figure S4). The logic behind this consideration is that diameter of 0.8 cm reaches resolution of PET definitely and false negatives caused by exceeding PET resolution can be ruled out, which indicates no FDG uptake indeed by cells inside. Lymph nodes < 0.8 cm have low tumor burden and weak tracer uptake, and diagnosis solely relies on metabolism is prone to misdiagnosis. Further identification relies on subtle morphological changes such as uneven enhancement and nodular cortical thickening should be applied (Figure S5). The diagnostic weight of morphological indicators is dynamically adjusted centered on

metabolic status, specifically addressing two major clinical challenges: missed diagnosis of low-metabolism micro metastases and misdiagnosis of inflammatory lymph nodes.

Multidimensional stratified subgroup evaluation

Subgroup analyses were performed simultaneously based on the WHO pathological classification, Lauren classification and gastric lymph node stations. The results demonstrated that C2 achieved the optimal diagnostic performance for intestinal type gastric cancer and yielded the most prominent reduction in missed diagnoses for diffuse-type gastric cancer, especially tiny spot. High-metastasis core lymph node stations including 3A, 7 and 8 exhibited outstanding discriminatory capacity (Table 5), providing imaging evidence for regional surgical evaluation.

Imaging-Pathological Mechanisms and Clinical Trade-offs of the Modified Criteria

C2 enables complementarity between functional and anatomical images: small lymph nodes without metabolism are detected relying on subtle cortical and enhancement signs, which substantially reduce missed diagnoses; benign lymph nodes with high metabolism are rapidly ruled out based on distinct lymphatic portal, so as to control false positive results. The specificity of C2 shows a slight decline compared with C1 (Table 2). Nevertheless, underestimated staging and inadequate treatment caused by missed diagnoses exert greater harm to patients' prognosis, while a small number of false positive cases only require postoperative pathological confirmation. The clinical benefits outweigh the costs. Results from all subgroups verify that the modified criterion has consistently superior diagnostic performance compared with the conventional method.

Comparison with Similar Studies

Design innovation: taking individual lymphatic group as the observation unit combined with GEE cluster correction to avoid bias in findings of previous studies; Model innovation: Adopting hierarchical progressive fusion logic, which differs from simple threshold parallel connection, and providing standardized reading protocols with strong practicality and repeatability that require no complex quantitative modeling, which help radiologists to unify reading standards and reduce inter-reader variability; Comprehensive analysis: Triple subgroup stratification to refine diagnostic performance under diverse pathological and anatomical scenarios.

Clinical Application Value

Unify PET/CT reading process relying on imaging features without additional post-processing, facilitating popularization in hospitals at all levels; Reduce missed diagnoses of micro metastases and accurately guide the scope of preoperative lymph node dissection and the selection of neoadjuvant therapy for gastric cancer; Provide targeted imaging evaluation protocols for prevalent low-metabolic subtypes including diffuse and mucinous gastric cancer, as well as high-risk perigastric lymph node regions.

Limitations and improvement directions

The number of included patients is relatively small, and a multi-center prospective cohort is needed to validate the universality of the improved criterion. Rare lymph-node stations (4SB, 10, 11, 12) had limited sample sizes per station, which constrained the statistical power of subgroup analyses and precluded definitive between-criterion comparisons for these anatomical locations. Although numerical trends favored Criterion 2 in these stations (Table 5), the lack of statistical significance should not be interpreted as evidence of equivalent performance. Future studies with larger multi-center cohorts specifically enriched for these low-frequency stations are warranted to validate the generalizability of the modified criterion across all gastric lymph-node groups. Micro metastases and macro metastases were not distinguished, and machine learning was not used to optimize the optimal cut-off values of multiple parameters. Special populations prone to be extensive in lymphatic proliferation such as patients with tuberculosis and severe systemic inflammation were not included, and further verification regarding false positive results is required.

Additionally, a minor limitation of this multi-center cohort lies in that the source of CT enhanced images cannot be unified (Simultaneous scanning with PET/CT on the same scanner vs. standalone abdominal CT devices). Nevertheless, standardized contrast agent parameters, acquisition and reconstruction protocols were strictly implemented at all centers, which largely harmonized lymph node morphological features and reduced diagnostic bias introduced by different CT hardware.

We are well aware that the application of ^{18}F -FDG PET/CT in diagnosing regional lymph nodes of gastric cancer is still unsatisfactory. Although some research suggested that other tracers such as ^{68}Ga -FAPI and ^{18}F -FLT may compensate for the shortcomings of FDG to some extent [33, 34], with the introduction of PET/MR in our center, the combination of ^{18}F -FDG PET/CT with simultaneous abdominal PET/MR imaging may be more efficient.

Conclusions

Conventional diagnostic criterion relying solely on FDG metabolism for regional lymph node metastasis in gastric cancer results in serious misdiagnosis and insufficient diagnostic efficacy, making it difficult to meet the preoperative staging needs of gastric cancer;

This study innovatively takes single lymphatic group as the observation unit and corrects clustering bias to construct an improved interpretation criterion for metabolic stratification and organic fusion of multiple morphological features, which is different from the previous mechanical superposition mode. The sensitivity, AUC and the negative predictive value significantly increased, with only a slight decrease in specificity, which is clinically acceptable.

The improved criterion has stable diagnostic advantages in various WHO (Table 3), Lauren classification (Table 4), and gastric lymph node subgroups (Table 5), and have outstanding differential value for intestinal type, diffuse type gastric cancer, and lymphatic stations with high metastatic risk nodes such as 3A, 7, and 8 (Table 5). They are suitable as a recommended preoperative PET/CT lymph node staging scheme for gastric cancer. This diagnostic criterion

is easy to operate, and is easy to standardize clinical interpretation. It can be used as a recommended imaging diagnosis scheme for preoperative regional lymph node staging of gastric cancer.

Abbreviations

- Acc Accuracy
- AJCC American Joint Committee on Cancer
- AUC Area under the receiver-operating-characteristic curve
- C1 Diagnostic Criterion 1 (conventional purely metabolic criterion)
- C2 Diagnostic Criterion 2 (modified hierarchical metabolic-morphological criterion)
- CE-CT Contrast-enhanced computed tomography
- CT Computed tomography
- EUS Endoscopic ultrasonography
- FDG ¹⁸F-fluorodeoxyglucose
- FAPI ⁶⁸Ga-fibroblast activation protein inhibitor
- FLT 3'-deoxy-3'-¹⁸F-fluorothymidine
- GEE Generalized estimating equation
- GLUT-1 Glucose transporter type 1
- ICC Intra-class correlation coefficient
- MRAC Mucinous-rich adenocarcinoma group
- MRI Magnetic resonance imaging
- NPV Negative predictive value
- PAC Poorly differentiated adenocarcinoma
- PAC-MRAC Poorly differentiated adenocarcinoma with partial mucin-rich adenocarcinoma
- PET/CT Positron emission tomography/computed tomography
- PET/MR Positron emission tomography/magnetic resonance imaging
- PPV Positive predictive value
- Se Sensitivity
- Sp Specificity
- SUVmax Maximum standardized uptake value
- TAC Tubular adenocarcinoma group
- TAC-PAC Tubular adenocarcinoma with partial poorly differentiated adenocarcinoma
- TNM Tumor-node-metastasis
- WHO World Health Organization

Declarations

Ethics approval and consent to participate

This retrospective observational study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Research Ethics Committee of Fujian Medical University Union Hospital (approval number: 2025KY858). The requirement for written informed consent was waived by the ethics committee owing to the retrospective design of this study.

Consent for publication

All patients agreed to the publication of anonymized data.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

Conceptualization: SL, GF, CC; Data curation: SL, GF, LL, JY, AL, HJ; Formal analysis: SL, GF; Investigation: SL, GF, LL, JY, AL, HJ; Methodology: SL, GF, ZZ, ZJ, CC; Project administration: CC; Resources: LL, ZZ, ZJ, CC; Supervision: ZZ, ZJ, CC; Validation: SL, GF, JY, ZZ, ZJ; Visualization: SL, GF; Writing – original draft: SL, GF; Writing – review and editing: SL, GF, LL, JY, AL, HJ, ZZ, ZJ, CC.

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Figures

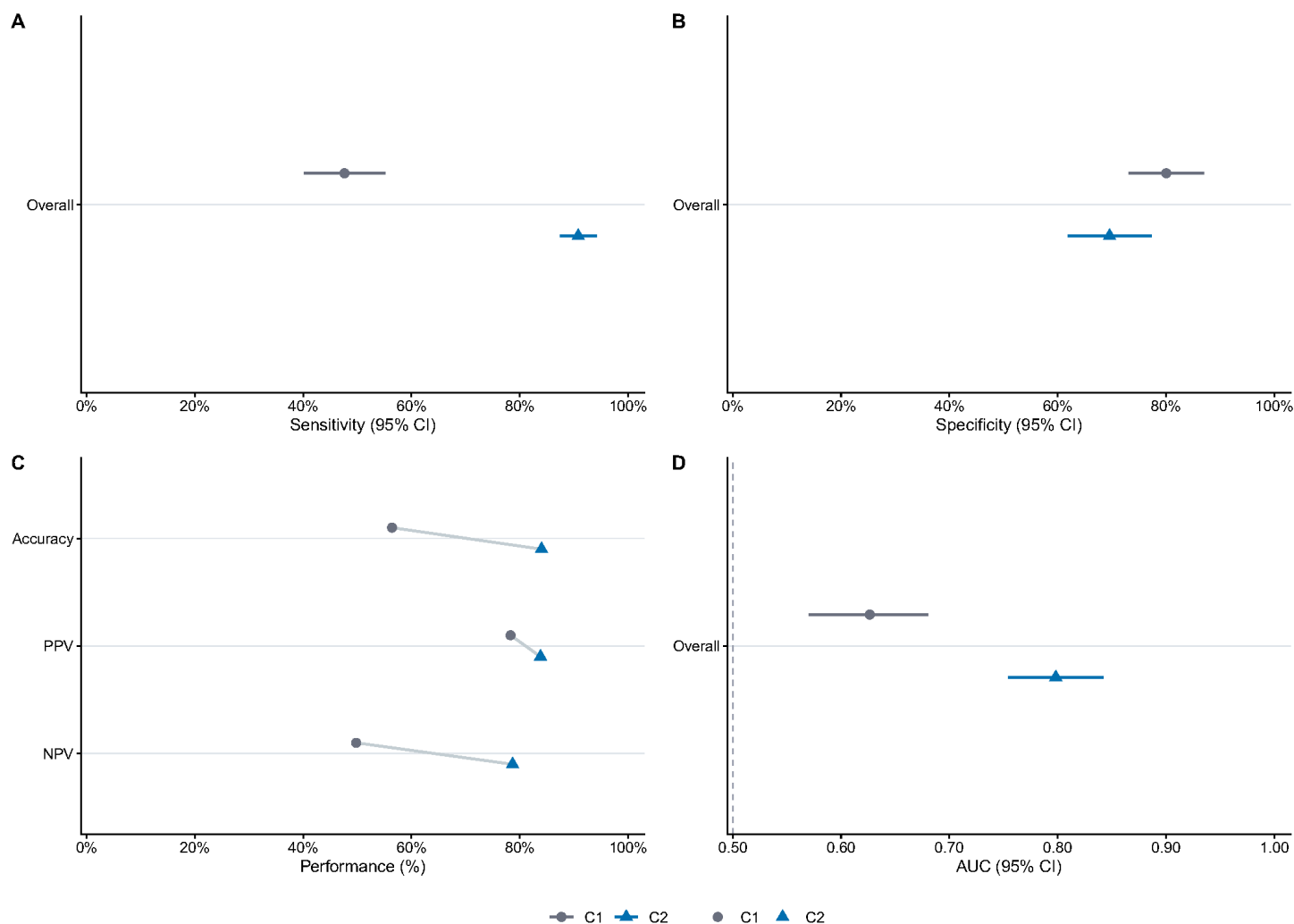


Figure 1

Overall diagnostic performance of Criterion 1 (C1) and Criterion 2 (C1) for regional metastases in the whole cohort. (A) Pooled sensitivity with 95% confidence intervals; (B) Pooled specificity with 95% confidence intervals; (C) Accuracy, positive predictive value (PPV) and negative predictive value (NPV); (D) Area under the receiver-operating-characteristic curve (AUC) with corresponding 95% confidence intervals. Estimates were adjusted for intra-patient clustering by generalized estimating equation (GEE).

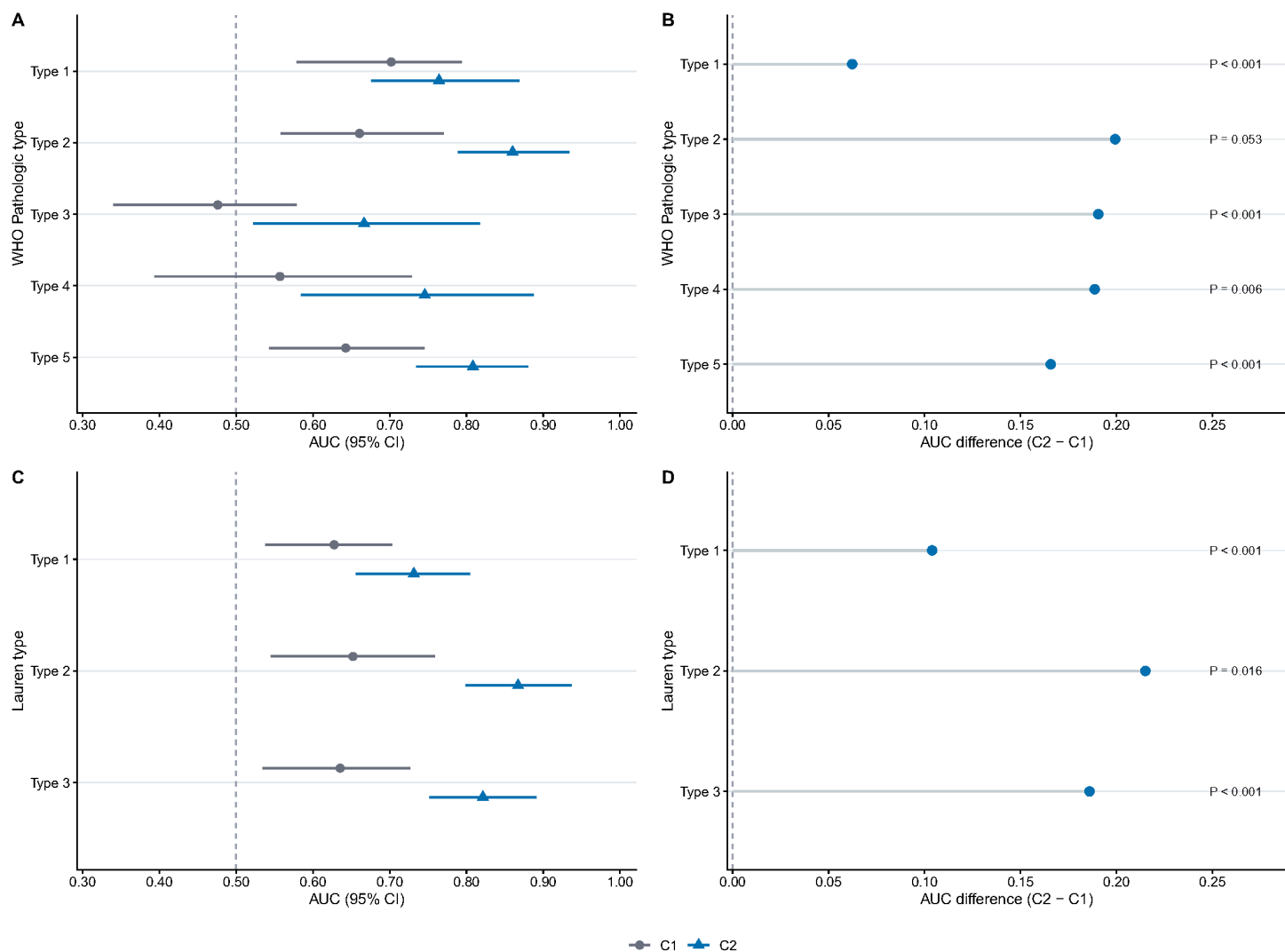


Figure 2

Subgroup comparison of diagnostic performance of Criterion 1 versus Criterion 2 stratified by gastric cancer pathological subtypes. (A) AUC (95% CI) across WHO pathological subtypes; (B) AUC difference (C2 - C1) and P -values for WHO subtypes; (C) AUC (95% CI) across Lauren subtypes; (D) AUC difference (C2 - C1) and P -values for Lauren subgroups. All metrics were adjusted for intra-patient clustering using GEE, and P -values were calculated by clustered DeLong test.

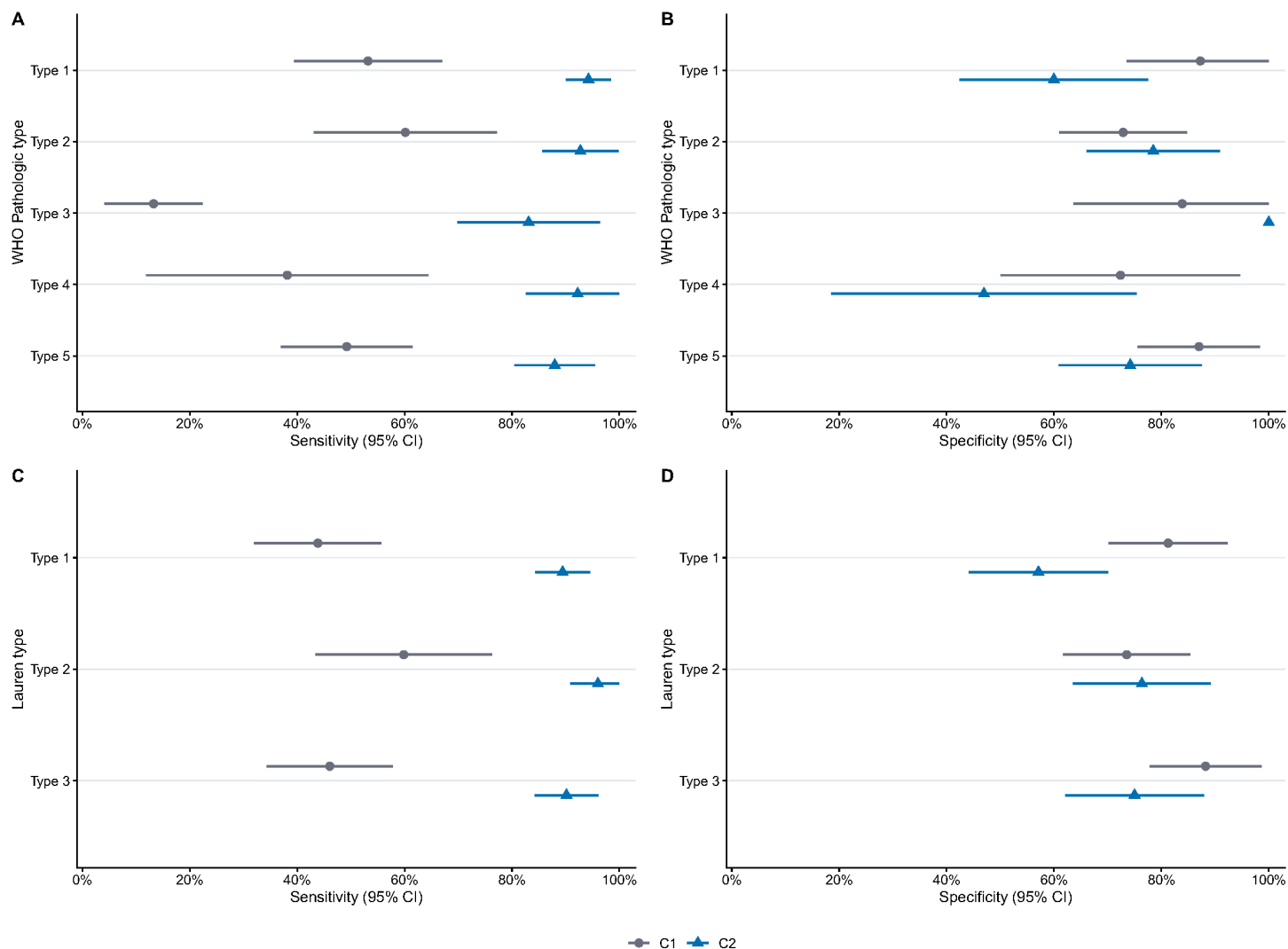


Figure 3

Comparison of sensitivity and specificity for Criterion 1 versus Criterion 2 stratified by pathological subtypes. (A) Sensitivity (95% CI) for WHO pathological subtypes; (B) Specificity (95% CI) for WHO pathological subtypes; (C) Sensitivity (95% CI) for Lauren subtypes; (D) Specificity (95% CI) for Lauren subtypes. All metrics were adjusted for intra-patient clustering using the generalized estimating equation (GEE).

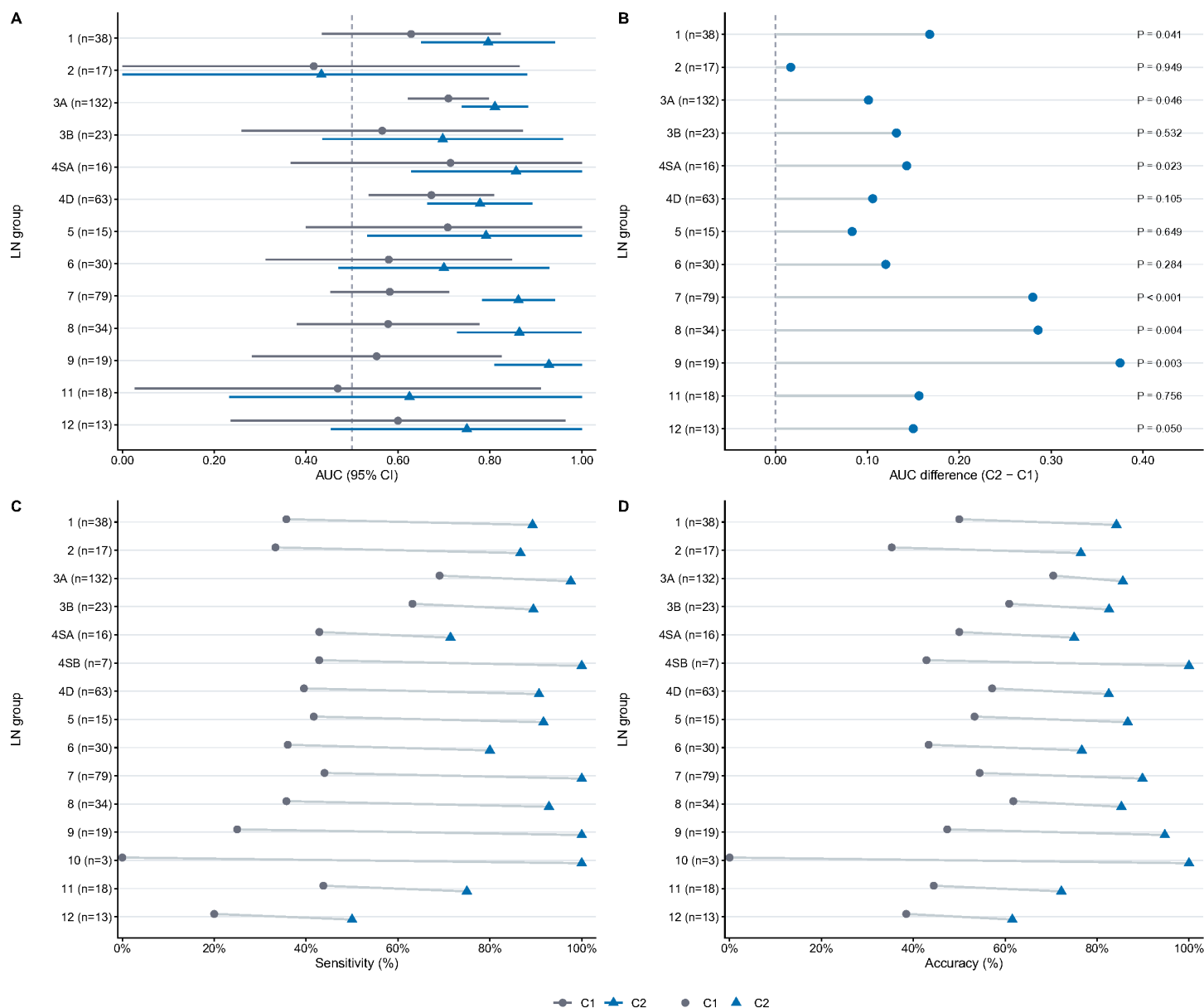


Figure 4

Diagnostic performance stratified by individual lymph-node groups for Criterion 1 versus Criterion 2. Parenthetical values represent sample size of evaluable lymph-node groups per station. (A) AUC (95% CI); (B) AUC difference (C2 - C1) and corresponding *P*-values; (C) Sensitivity; (D) Accuracy. Analyses within each lymph-node station did not require GEE correction; conventional χ^2 tests were used for between-criterion comparisons.

Supplementary Files

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