

Utility of intravoxel incoherent motion diffusion-weighted imaging in predicting pathological response to neoadjuvant immuno-chemotherapy for locally advanced gastric cancer

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Abstract

Background

To investigate the feasibility of intravoxel incoherent motion diffusion-weighted imaging (IVIM) for predicting pathological tumor regression grade (TRG) after neoadjuvant immuno-chemotherapy (NICT) in locally advanced gastric cancer (LAGC).

Methods

Between January 2022 and December 2024, consecutive patients with endoscopy-biopsy confirmed gastric adenocarcinoma undergoing NICT followed by curative gastrectomy were prospectively recruited. Stomach MRI examinations, including IVIM, were performed within one week before NICT initiation. Patients were classified as responders (TRG 0/1) or non-responders (TRG 2/3). The apparent diffusion coefficient (ADC), IVIM-derived true diffusion coefficient (D), pseudodiffusion coefficient (D*), and pseudodiffusion fraction (f) were measured and compared between the two groups. Independent predictors of non-responders were identified and used to establish a combined parameter. The performances of IVIM-derived parameters were assessed using receiver operating characteristic curve analysis. The relationship between the combined parameter and patient survival outcomes was explored using Kaplan–Meier survival analysis.

Results

Ninety-three patients (74 males, 19 females; mean age 59.0 ± 9.9 years) were finally recruited. ADC and D were significantly lower, whereas f was higher in non-responders compared with those in responders ($p < 0.05$). ADC, D, and f were independent predictors of non-responders. Their combination outperformed each individual parameter, achieving an area under the curve of 0.779, and was associated with patient disease-free survival (DFS) (hazard ratio = 3.624).

Conclusion

IVIM is feasible for early prediction of treatment response to the emerging NICT in LAGC; ADC, D, and f are equally useful and their combination demonstrated incremental benefit and prognostic value for patient DFS.

Introduction

Neoadjuvant therapy (NAT) is the standard treatment for locally advanced gastric cancer (LAGC) [1]. Recently, emerging clinical trials have focused on combining perioperative immunotherapy with chemotherapy (neoadjuvant immuno-chemotherapy, NICT). Although NICT improves pathological complete response rate and patient overall survival [2, 3], the immune-related adverse events remain a non-negligible concern. Furthermore, tumor regression grade (TRG), the gold standard for evaluating NICT response, is assessed postoperatively on surgical specimens. This limits its utility in guiding adjuvant therapy rather than allowing pre-surgical adaptation of the NICT regimens. Besides, the significant heterogeneity observed in individual responsiveness hinders advancement in personalized medical care [4], underscoring the necessity for reliable tools to accurately predict NICT efficacy. Consequently, there is an urgent need for early prediction of treatment response to NICT, which would enable clinicians to optimize therapeutic strategies by modifying or discontinuing the regimen among patients who do not respond.

Current in-vivo assessments during treatment cycles, based on the immune Response Evaluation Criteria in Solid Tumors (iRECIST), rely on CT to measure size changes in target lesions (e.g., lymph nodes > 15 mm short diameter, or organ lesions > 10 mm long diameter) [5, 6]. However, this approach is unsuitable for the hollow stomach and cannot distinguish residual tumor from treatment-induced fibrosis, leading to significant discrepancies with pathological evaluation [5]. Hence, novel imaging markers are critically needed for earlier and more accurate prediction of NICT efficacy.

Dual-energy CT (DECT), a functional CT imaging, shows potential in predicting NICT response [7, 8] but requires multiple contrast-enhanced scans, limiting use in patients with iodine allergy or renal impairment and raising radiation concerns. Positron Emission Tomography (PET) can predict treatment response [9], yet is not routine for GC due to radiation, cost, and false-positives. These limitations drive growing interest in magnetic resonance imaging (MRI) for evaluating treatment response in GC.

Diffusion-weighted imaging (DWI), the most widely used functional MRI technique, shows promise for assessing GC treatment response [10, 11]. However, the conventional ADC derived from a mono-exponential model assumes Gaussian diffusion, which is often violated in cancer tissues [12]. IVIM, an advanced DWI technique, uses a bi-exponential model to separate true molecular diffusion from perfusion-related pseudodiffusion, yielding three parameters: D , D^* , and f [13]. This provides insights into cellularity and microcirculation, key features altered during chemotherapy [14]. Recent studies highlight potential use of IVIM in predicting treatment responses across cancers [15–18], and have established its role in staging resectable GC and assessing post-chemotherapy response in advanced cases [17, 18]; however, its ability to predict NICT response in LAGC remains unclear.

Therefore, this study aimed to investigate the utility of IVIM-derived parameters for predicting pathological response to NICT in patients with LAGC.

Methods

Patient recruitment

This prospective study was approved by the institutional review board of our hospital (NCT:04028375). Informed consent was obtained from each patient (2021-KY-0023-001). Consecutive GC patients between January 2022 and Dec 2024 were prospectively recruited. The inclusion criteria were: (1) gastric adenocarcinoma confirmed by endoscopic biopsy-based pathology; (2) staged as LAGC (cT2 ~ 4a/N-any/M0) by the multidisciplinary team (MDT) and referred to NICT; (3) patients underwent MRI examination including IVIM and DWI before NICT initiation. The exclusion criteria were: (1) poor image quality due to severe artifacts or image distortion; (2) refusal to surgical resection after NICT. Patient recruitment flowchart was provided in Fig. 1. The eligibility of participants for NICT trials was determined by the MDT, see details of MDT framework in Supplementary material. All the NICT trials were supervised and approved by the GCP committee.

MRI acquisition protocols

IVIM-MRI scans were performed within 1 week (median: 4 days) before NICT initiation on two 3.0 T MR platforms (Skyra or Prisma, Siemens Healthineers) with an anterior 18-element body coil and in-built posterior 32-element spine coil array. The pre-examination preparation followed standardized protocols including: (1) patients fasted for at least 6 hours to empty the stomach; (2) respiration training to avoid unwanted artifacts; (3) patients drank at least 500 mL of warm water 10 min before acquisition to fill up the stomach cavity; (4) intramuscular administration of

raceanisodamine hydrochloride injection (10mg, Dahongying Pharmaceutical Co.) to eliminate gastric peristalsis. As shown in Table 1, the acquisition protocols included: (1) 3D volumetric interpolated breath-hold examination (VIBE) opp- in axial T₁WI, (2) axial respiratory triggered, fat-suppressed turbo spin echo (fs_TSE) T2WI, and (3) IVIM acquired using a prototyped integrated specific slice dynamic Shim (iShim) sequence. Twelve b values (0, 25, 50, 75, 100, 200, 400, 600, 800, 1000, 1200, and 1600 s/mm²) were applied ^[19], including six b value ≤ 200 s/mm² for accurate D* calculation ^[20], and four b value ≥ 800 s/mm² for tumor detection and comparison ^[19].

Table 1
MRI acquisition protocol

Parameters	T1WI axial	T2WI axial	IVIM (b = 0, 25, 50, 75, 100, 200, 400, 600, 800, 1000, 1200, 1600 s/mm ²)
TR (ms)	3.9	4500 ~ 7800	8000
TE (ms)	1.32/2.74	98	59
Slice thickness (mm)	5	5	5
Slice gap (mm)	NA	0.5	0.5
NEX	1	2	1 ~ 4
FOV (cm ²)	38×38	28.7×28.7	38×38
Resolution	180 ×288	193 × 384	83×128
Voxel size (mm ³)	1.47×1.32×4.23	1.49×1.04×5	3.28×2.66 5
Flip angle (°)	9	120	NA

TR: repetition time, TE: echo time, NEX: number of excitations, FOV: field of view. NEX for IVIM range from 1–4, NEX = 1 for b = 0, 25, 50, 75, 100, 200, 400 s/mm², NEX = 2 for b = 600, 800 s/mm², NEX = 3 for b = 1000 s/mm², NEX = 4 for b = 1200, 1600 s/mm².

Image interpretation

The IVIM raw data were processed using the MADC software in FuncTool software package. Two radiologists with 12 and 16 years of experience in gastrointestinal (GI) radiology reviewed the images and measured IVIM parameters independently. The image quality was scored using a 5-point Likert scale, point 1 represents poor image quality with severe artifacts or image distortion; 2, mild image quality; 3, moderate quality; 4, good image quality; 5, perfect image quality. Images with scores less than 3 by any of the radiologists were excluded. For IVIM parameters measurements, referring to T2WI and IVIM-DWI with b = 800 s/mm², the readers manually draw freehand ROIs encompassing the whole GC lesions on the maximal axial plane. The ADC from mono-exponential model was calculated following the formula: $S_b/S_0 = \exp(-b \times ADC)$ ^[20]. IVIM parameters were calculated with equation: $S_b/S_0 = (1-f) \times \exp(-bD) + f \times \exp[-b(D + D^*)]$ ^[21]. The b value threshold was 200 for the fitting ^[22].

Other assessments included: (1) Tumor thickness: defined as the maximal diameter vertical to the longest axis plane of the tumor ^[11]; (2) Clinical tumor staging (cT): defined as the invasion depth into the gastric wall and was assessed using multiple sequences including fs-T2WI, DWI, and DCE, following the diagnostic criteria described in a previous

report^[23]; (3) Clinical node staging (cN): defined as MRI-reported LN status, following the Node Reporting and Data System (Node-RADS) scheme v1.0, cN-positive was diagnosed when a regional lymph node scored ≥ 3 by any of the radiologists^[24]; (4) MRI-based Borrmann classification: GC lesions were categorized into four subtypes according to ulceration, infiltration scale and morphology as reported previously^[8, 11].

Quantitative parameters were measured three times, and their averages were used for subsequent analysis. Inter-observer agreements between the two readers' results on image interpretation and measurements were evaluated. If good agreements were achieved, the results from the more experienced reader were adopted. Otherwise, a third senior radiologist with 22 years of experience was consulted to make the final decision.

NICT regimens

Standard 3 cycles of NICT were performed in each participant and followed by radical gastrectomy. Specific regimens were determined through the MDT workshop (Supplementary material).

Pathological response evaluation

Two board-certified GI pathologists with 10 and 16 years of experience, blinded to MRI data, evaluated the pathologic responses in consensus according to the 8th AJCC TRG criteria^[25]. Responses were categorized as: TRG 0 (pathologic complete response, pCR), TRG 1 (near complete response), TRG 2 (partial response), or TRG 3 (poor or no response) (details are described in Supplementary material).

Follow up

Patients were regularly monitored every 3 months with 2 years after surgery, every 6 months thereafter. Disease relapse and metastasis were identified with endoscopy, enhanced CT, MRI, or PET, where eligible. Patient survival status was recorded. Disease relapse or metastasis and death were defined as clinical endpoint events. Disease-free survival (DFS) and overall survival (OS) were calculated by counting the days between surgery date and date of disease progression or death, respectively.

Statistical analyses

Statistical analyses were performed using Python 3.10. Two-tailed p value less than 0.05 stands for statistical significance. Interobserver agreement between readers was assessed using intraclass correlation coefficient (ICC) with 95% confidence interval (CI) for quantitative variables, and Kappa values for qualitative variables. Agreement levels were defined as follows: ICC or Kappa value ≤ 0.20 , poor; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, good; and 0.81–1.00, excellent. Quantitative data were compared using the student's t -test or Mann–Whitney U test. Categorical data were compared using the chi-square test or Fisher's exact test. Multivariable logistic regression was performed to screen independent predictors of non-responders. The receiver operating characteristic (ROC) curve analysis was employed to evaluate the performances of significant parameters. Decision curve analysis (DCA) was employed to assess the net clinical benefit of each parameter across a range of threshold probabilities, thereby quantifying their practical utility in clinical decision-making. To evaluate the stability and generalizability of the parameter, a five-fold cross-validation was further performed. Given the imbalanced distribution between responders and non-responders, weighted logistic regression with class weights set to "balanced" was fitted on each training fold, and the resulting model was then assessed on the corresponding validation fold to control for potential bias induced by class imbalance.

Results

Patient Clinicopathological Characteristics

Among 111 consecutive patients, 18 were excluded, including 3 patients who refused to do the surgery, 15 had poor MR images scored <3 by any of the radiologists. Thereafter, 93 were eventually recruited (74 males, 19 females), aged 59.0 ± 9.9 (26–78) years. After surgery, 13, 18, 38, 24 patients achieved TRG 0, TRG 1, TRG 2, or TRG 3, respectively; 31 were labelled as responders and 62 were non-responders (66.67%) accordingly. As shown in Table 2, no evidences of differences were identified in age, sex, location, histodifferentiation, Lauren subtype, and TLN between responders and non-responders ($p>0.05$). Significant differences were observed in terms of ypT, ypN, PLN, PLNR, PNI, and LVI between the two groups ($p < 0.05$).

Table 2
Clinicopathological characteristics of patients between responders and non-responders

Clinicopathologic characteristics		Overall (n = 93)	Responders (TRG = 0 + 1, n = 31)	Non-responders (TRG = 2 + 3, n = 62)	$\chi^2/ t/Z$ value	p value
Age(years) range: 26–78 yrs		59.0 ± 9.9	59.1 ± 9.9	58.8 ± 10.3	0.441	0.660
Sex	Male	74	24	50	0.132	0.716
	Female	19	7	12		
Location	Cardia/Fundus	54	16	38	—	0.105
	Body	27	13	14		
	Antrum	12	2	10		
Histodifferentiation	Poor	57	17	40	—	0.280
	Moderate	35	13	22		
	Well	1	1	0		
Lauren subtype	Intestinal	21	9	12	4.886	0.087
	Mixed	30	13	17		
	Diffused	42	9	33		
ypT	0	15	14	1	—	<0.001
	1	13	8	5		
	2	20	2	18		
	3	35	7	28		
	4a	10	0	10		
ypN	0	45	25	20	—	<0.001
	1	10	0	10		
	2	21	5	16		
	3a	11	1	10		
	3b	6	0	6		
PLN	Range: 0 ~ 22	1 (0, 5)	0 (0, 0)* ¹	2.5 (0, 6.25)* ²	3.683	<0.001
TLN	Range: 12 ~ 65	25 (19, 34.5)	31 (21, 38) ^{Δ1}	24 (17.75, 33) ^{Δ2}	1.203	0.229
PLNR (%)	Range: 0 ~ 94.12	2.08 (0, 23.06)	0 (0, 0) ^{#1}	7.95 (0, 35.61) ^{#2}	4.064	<0.001
Lymphoascular invasion	Negative	61	29	32	—	<0.001
	Positive	32	2	30		

Clinicopathologic characteristics		Overall (n = 93)	Responders (TRG = 0 + 1, n = 31)	Non-responders (TRG = 2 + 3, n = 62)	$\chi^2/ t/Z$ value	<i>p</i> value
Perineural invasion	Negative	66	28	38	—	0.004
	Positive	27	3	24		

PLN=Positive lymph node numbers, *1: range of 0 ~ 8 in responders; *2: range of 0 ~ 22 in non-responders; TLN=Total dissected lymph node numbers in surgery, Δ1: range of 12 ~ 54 in responders, Δ2: range of 12 ~ 65 in non-responders; PLNR=Positive lymph node ratio, ratio of positive lymph nodes to the total dissected lymph node numbers in surgery; #1: range of 0 ~ 50.00% in responders; #2: range of 0 ~ 94.12% in non-responders. ypT=Yielded pathologic tumor staging; ypN=Yielded pathologic node staging; PLN, TLN, PLNR was displayed as *M* (*Q1*, *Q3*).

Interobserver reproducibility

Interobserver reproducibility for the readers' assessments ranged from good to excellent. The kappa values were 0.813 (95% CI: 0.708–0.917) for image quality scoring, 0.786 (95% CI: 0.671–0.900) for cT, 0.795 (95% CI: 0.650–0.940) for cN, and 0.936 (95% CI: 0.874–0.999) for MRI-based Borrmann classification (see Supplementary Tables S1–S4). The ICC values for measuring ADC, D, D*, and *f* were 0.869 (95% CI: 0.809–0.914), 0.901 (95% CI: 0.854–0.933), 0.825 (95%CI: 0.747–0.881), 0.818(95%CI: 0.738–0.876), respectively. Corresponding Bland-Altman plots are provided in Supplementary Figure S2.

Comparison of MRI parameters

The tumor thickness was 20.9 ± 7.4 (range: 10.5–51.3) mm. As shown in Table 3, no significant differences were found in tumor thickness, cT, cN between the two groups ($p = 0.301$ – 0.429). There was significant difference of MRI-based Borrmann classification between responders and non-responders ($p = 0.036$). As shown in Fig. 2, the mean value of ADC, D in non-responders were statistically lower, whereas the mean value of *f* was higher compared with those in responders ($p < 0.05$). The mean value of D* in non-responders was non-significantly different with that in responders ($p = 0.094$). Figures 3 and 4 were representative baseline MR images of responders and non-responders, respectively.

Table 3
Comparison of MRI-based measurements between responders and non-responders

Parameters		Responders (n = 31)	Non-responders (n = 62)	t/Z value	p value
Thickness-pre (mm)	range:10.5 ~ 51.3	20.88 ± 7.44	22.74 ± 8.40	1.041	0.301
cT	2	2	4	—	0.429
	3	16	28		
	4a	13	30		
cN	Negative	6	17	0.722	0.395
	Positive	25	45		
Borrmann classification	Ⅰ	3	8	—	0.036
	Ⅱ	17	18		
	Ⅲ	11	36		
ADC (×10 ⁻³ mm ² /s)		1.29 ± 0.33	1.14 ± 0.29	2.146	0.035
D (×10 ⁻³ mm ² /s)		1.03 ± 0.05	0.78 ± 0.34	2.772	0.007
D* (×10 ⁻³ mm ² /s)		6.87 (2.40, 15.70)	4.21 (1.18, 10.75)	-1.675	0.094
f		0.44 ± 0.14	0.53 ± 0.16	2.780	0.007

cT: clinical tumor staging; cN: clinical node staging; ADC: apparent diffusion coefficient;D: true diffusion coefficientⅠD*: pseudodiffusion coefficient; f: pseudodiffusion fraction.

Diagnostic performances of MRI parameters

ADC, D, f, and MRI-reported Borrmann classification were associated with TRG outcomes. Multivariable regression analysis revealed that ADC, D and f were independent predictors for non-responders, with corresponding odds ratio (OR) being 0.243 (95%CI: 0.083–0.713), 0.203 (95%CI: 0.070–0.759), 1.058 (95%CI: 1.020–1.096) ($p = 0.010$, 0.011 , 0.002 , Table 4) and were used to build a combined parameter. Hosmer & Lemeshow test revealed good fitting between the predicted probability of non-responders by the combined parameter and the actual probability ($\chi^2 = 11.588$, $p = 0.172$).

Table 4
Univariable and multivariable regression analysis of MRI-based measurements

Variables	Univariable regression analysis		Multivariable regression analysis	
	OR (95% CI) value	P value	OR (95% CI) value	p value
ADC (×10 ⁻³ mm ² /s)	0.216 (0.051–0.916)	0.028	0.243 (0.083–0.713)	0.010
D (×10 ⁻³ mm ² /s)	0.222 (0.068–0.728)	0.013	0.203 (0.070–0.759)	0.011
f (%)	1.042 (1.010–1.074)	0.009	1.058 (1.020–1.096)	0.002
Borrmann Classification	1.353 (1.139–1.895)	0.038	1.192 (1.028–11.256)	0.494

OR: odds ratio; CI: confident interval; ADC: apparent diffusion coefficient;D: true diffusion coefficientD*: pseudodiffusion coefficient; f: pseudodiffusion fraction.

ROC analyses revealed that the combined parameter yielded the highest AUC of 0.779 (95% CI: 0.681–0.859) for identifying non-responders, followed by *f*, D, ADC, and MRI-reported Borrmann classification with AUC achieving 0.677(95%CI: 0.572–0.770), 0.653(95%CI: 0.547–0.748), 0.629 (95%CI: 0.522–0.726), and 0.571 (95% CI: 0.464–0.673), respectively (Fig. 5A, Table 5). Pair comparison revealed no significant differences were observed among the AUCs of individual parameters (all *p*>0.05); the combined parameter overweighed D, *f*, and ADC (Delong test, all *p*<0.05). Five-fold cross-validation with weighted logistic regression results showed a mean AUC of 0.726 ± 0.130 (Supplementary Material).

Table 5
Diagnostic performances of MRI-based measurements for identifying pathologic response

Parameters	AUC (95%CI)	Sensitivity (%)	Specificity (%)	PPV (%, 95%CI)	NPV (%, 95%CI)	Youden index	Cut off value	Z value	p value
ADC (×10 ⁻³ mm ² /s)	0.629 (0.522–0.726)	72.58	58.06	77.61 (64.76–87.51)	51.39 (33.95–68.58)	0.31	≤ 1.23	2.030	0.004
D (×10 ⁻³ mm ² /s)	0.653 (0.547–0.748)	62.90	61.29	74.50 (62.54–87.23)	45.20 (29.81–61.29)	0.24	≤ 0.081	2.583	0.010
<i>f</i>	0.677 (0.572–0.770)	58.06	74.19	81.84 (67.31–91.82)	46.90 (32.50–61.69)	0.30	>0.5	3.028	0.003
Borrmann classification	0.571 (0.464–0.673)	58.16	61.29	75.06 (64.48–86.40)	42.24 (27.66–57.88)	0.194	–	1.263	0.207
Combined parameter	0.779 (0.681–0.859)	69.35	77.42	86.02 (73.28–94.19)	55.77 (39.83–70.89)	0.468	>0.676	5.204	<0.001

CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; ADC: apparent diffusion coefficient;D: true diffusion coefficientD*: pseudodiffusion coefficient; *f*: pseudodiffusion fraction.

DCA results showed that the combined parameter provided greater net benefit than any other individual parameter across threshold probabilities of 0.50–0.85 (Fig. 5B). Using the cut-off value as of>0.676, the combined parameter detected 11 true responders out of 31 (pathologically confirmed responders), and 53 true non-responders out of 62 (pathologically confirmed non-responders), the overall accuracy was 68.8% (64/93).

Survival analysis

Till the end time point at 31th Dec 2025, 15 patients were lost during follow up. Among the remaining 78 patients, 2 died of accident within 3 months after surgery. Totally 76 patients were successfully followed up, 13 developed disease progression (5 with live metastasis, 4 with peritoneal metastasis, 3 with multiple lymph node metastasis, 1 with bone

metastasis in the third lumbar vertebra), and 12 of them have died. The overall follow up time duration was 43 (4 ~ 68) months.

Kaplan-Meier curves of survival analysis (Fig. 6) revealed that TRG status was associated with both DFS ($\chi^2 = 8.295, p = 0.004$) and OS ($\chi^2 = 8.494, p = 0.004$), with hazard ratio (HR) being 10.849 (95%CI: 4.118–28.583), 10.644 (95%CI: 4.033–28.094), respectively. The risk-category defined by the cut-off value of the combined parameter was associated with patient DFS [$\chi^2 = 4.345, p = 0.037$, HR: 3.091 (95%CI: 1.942–8.001)], but not with patient OS ($\chi^2 = 3.045, p = 0.081$). The median DFS in the high-risk category was significantly shorter than that in the low-risk category (38 vs. 45 months, $Z = 2.878, p = 0.042$).

Discussion

This study utilized functional IVIM-MRI and established useful imaging markers for identifying non-responders in advance. Individual parameter of ADC, D and f are associated with the TRG status and equally useful for indicating non-responders. Moreover, their combined use demonstrates improved non-responder identification (AUC = 0.779), with robust validation and prognostic relevance to DFS. These findings underscore the clinical feasibility of IVIM-MRI for early prediction of treatment response to NICT, thus, offering clinicians a practical tool to refine therapeutic strategies in real-time.

DWI-derived ADC, the most commonly used functional parameter, aids in characterizing, staging, and evaluating treatment response and prognosis of gastric cancer (GC) [17, 18, 26, 27]. We previously showed ADC outperformed DCE-MRI in predicting pathological response to NAC [11], and the present study confirms its utility in indicating TRG status after NICT, ADC < $1.23 \times 10^{-3} \text{ mm}^2/\text{s}$ indicates a higher likelihood of developing poor response. ADC inversely correlates with cellular density; lower values reflect active proliferation and narrowed extracellular space, thus leading to treatment resistance [28]. However, ADC alone yielded modest predictive performance (AUC: 0.629), partly because its mono-exponential model assumes ideal Brownian diffusion, which does not hold in cancerous tissue [12, 13]. This limitation underscores the need to integrate additional quantitative metrics.

D, derived from a bi-exponential diffusion model, reflects true molecular diffusion and has outperformed ADC in staging and systematic chemotherapy response evaluation in GC [15–18]. Our study confirms its non-significantly superior performance in predicting TRG after NICT. D correlates with differentiation, TNM stage, LVI, and PNI [17, 18, 29, 30]; lower D values indicate more aggressive disease and greater heterogeneity, which may contribute to poor response. Additionally, we used iShim for IVIM acquisition, which reduces geometric distortion and ensures reproducible measurements [16], allowing the reproducibility of measurements for D value.

D* represents perfusion-related incoherent microcirculation [13, 22]; however, based on established evidences, it was unable to predict treatment response in several cancers, including GC [15, 16, 18], and showed no utility in staging or characterization of GC [17, 29, 30]. Consistently, in the present study, D* values in non-responders were non-significantly lower than those in responders, and D* failed to predict TRG status after NICT. Theoretically, variations in microcirculation may affect drug delivery and thereby influence treatment response; nevertheless, this study did not demonstrate a significant difference in D* between response groups. This may be attributable to sample size, study design, or the fact that accurate D* measurement is influenced by multiple factors, such as the selection of low b-values [21, 22]. Therefore, the value of D* in predicting treatment response warrants further investigation.

The role of f in GC remains debated [17, 18, 29, 30]; it is useful for predicting LVI/PNI status [29, 30] but not for N staging [17]. Song et al. reported decreased f value is suggestive of good response after systemic chemotherapy in far advanced GC

[18]. However, whether baseline IVIM predicts NAT response in LAGC, including NICT, is unknown. We found f significantly higher in non-responders. Since f correlates positively with microvessel density [18], which promotes angiogenesis and invasiveness [31] and may reduce NICT sensitivity, this mechanism could partly explain our finding; however, validation is needed.

We found that non-responders had a higher proportion of advanced Bormann type (III/IV), which reflects larger, more aggressive lesions [26] and may affect response. However, Bormann type alone showed the lowest AUC and, as a subjective morphological assessment, is inadequate for early NICT response prediction. In contrast, quantitative ADC, D , and f were all effective, and their combination achieved superior performance, highlighting the advantage of functional IVIM over conventional morphology. The combined model also demonstrated stable performance in 5-fold cross-validation ($AUC = 0.726 \pm 0.130$) and higher net clinical benefit on decision curve analysis, underscoring its clinical potential.

Survival analysis revealed that the risk category defined by the combined parameter was significantly associated with patient DFS. This finding highlights the potential prognostic value of IVIM. Using the cutoff value of the combined parameter, clinicians can prospectively identify high-risk patients who are unlikely to respond to NICT treatment, thereby facilitating more appropriate treatment strategies (e.g., discontinuing NICT regimens or proceeding with timely surgery) and enabling more intensive postoperative surveillance for these patients.

This study has several limitations. First, the sample size is small and external validation is lacking; although cross-validation showed stable performance, reproducibility requires multi-center confirmation. Second, b-value settings for IVIM in GC lack consensus [14–18]; our 12-b-value sequence is center-specific. Third, the limited sample precluded adjustment for clinical heterogeneity (e.g., different NICT regimens). Finally, survival analyses are preliminary and need validation.

Conclusions

In summary, this study suggests that functional IVIM with quantitative parameters is feasible for early prediction of pathologic response after NICT in patients with LAGC.

Abbreviations

ADC

Apparent diffusion coefficient

AUC

Area under the curve

D

True diffusion coefficient,

D^*

Pseudodiffusion

f

Pseudodiffusion fraction

LAGC

Locally advanced gastric cancer

IVIM

Intravoxel incoherent motion diffusion-weighted imaging

NAC

Neoadjuvant chemotherapy
NICT
Neoadjuvant immuno-chemotherapy
NAT
Neoadjuvant therapy
TRG
Tumor regression grade

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board of the Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital (Zhengzhou, 450008, China) in accordance with the Declaration of Helsinki. All methods were carried out in accordance with relevant guidelines and regulations. Written informed consent was obtained from all individual patients included in the study (NCT: 04028375). Institutional Review Board approval was obtained at the Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital (2021-KY-0023-001).

Consent for publication

Not applicable, as the images were fully anonymized and do not contain identifiable information that could compromise patient anonymity

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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

QY and CLL contributed equally to this work and are co-first authors.

QY, CLL and JL conceived and designed the study. QY and CLL drafted the manuscript. XXL, DXY, YW, and SNX prepared the figures and contributed to data interpretation. JL conceived and designed the study, supervised the study, and critically revised the manuscript. All authors read and approved the final manuscript.

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Figures

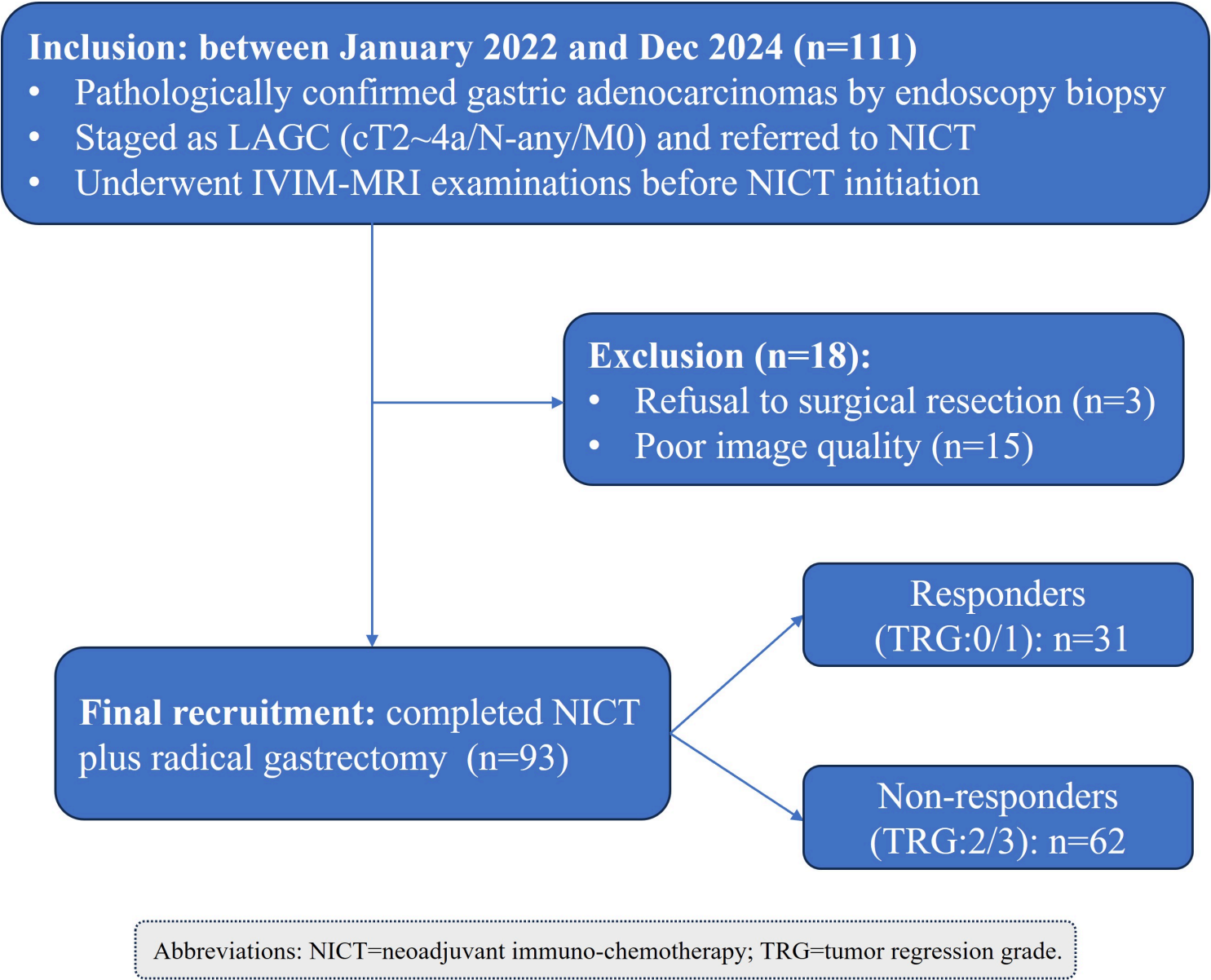


Figure 1

Flowchart of patient recruitment.

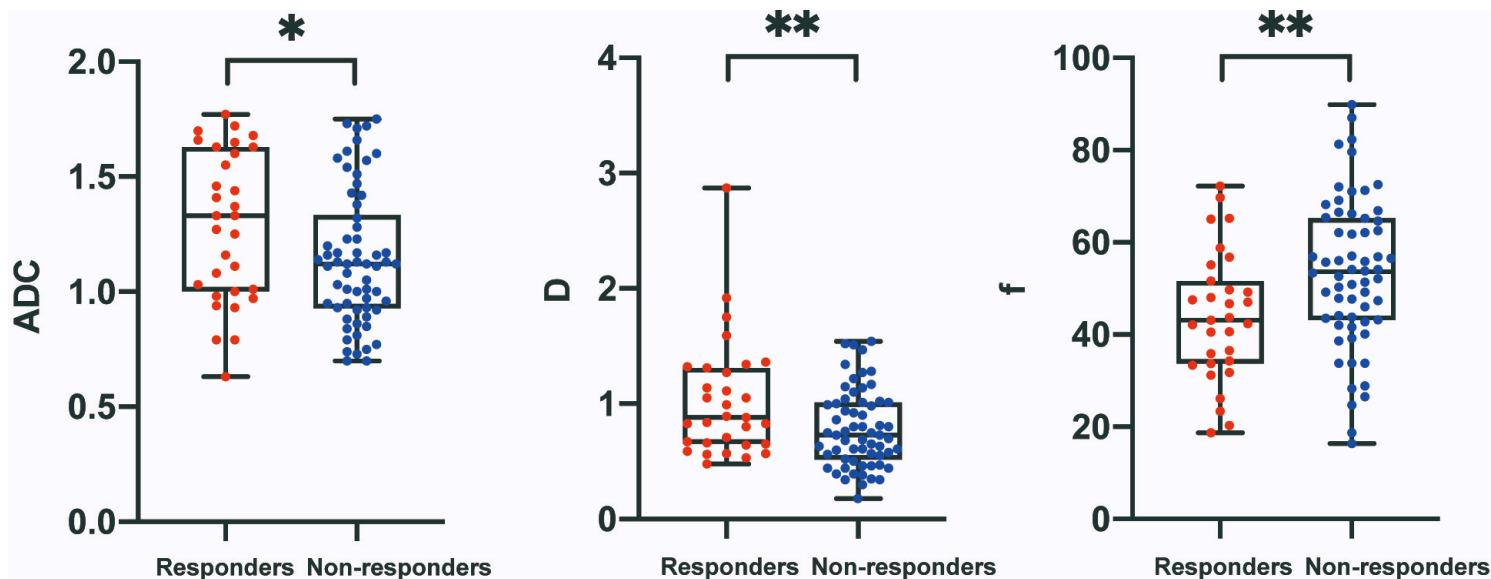


Figure 2

Box and whisker plots for comparison of IVIM-based parameters between responders and non-responders, including (A) ADC ($\times 10^{-3} \text{ mm}^2/\text{s}$), (B) D ($\times 10^{-3} \text{ mm}^2/\text{s}$), and (C) f. Abbreviations: ADC=apparent diffusion coefficient, D=true diffusion coefficient, f=pseudodiffusion fraction.

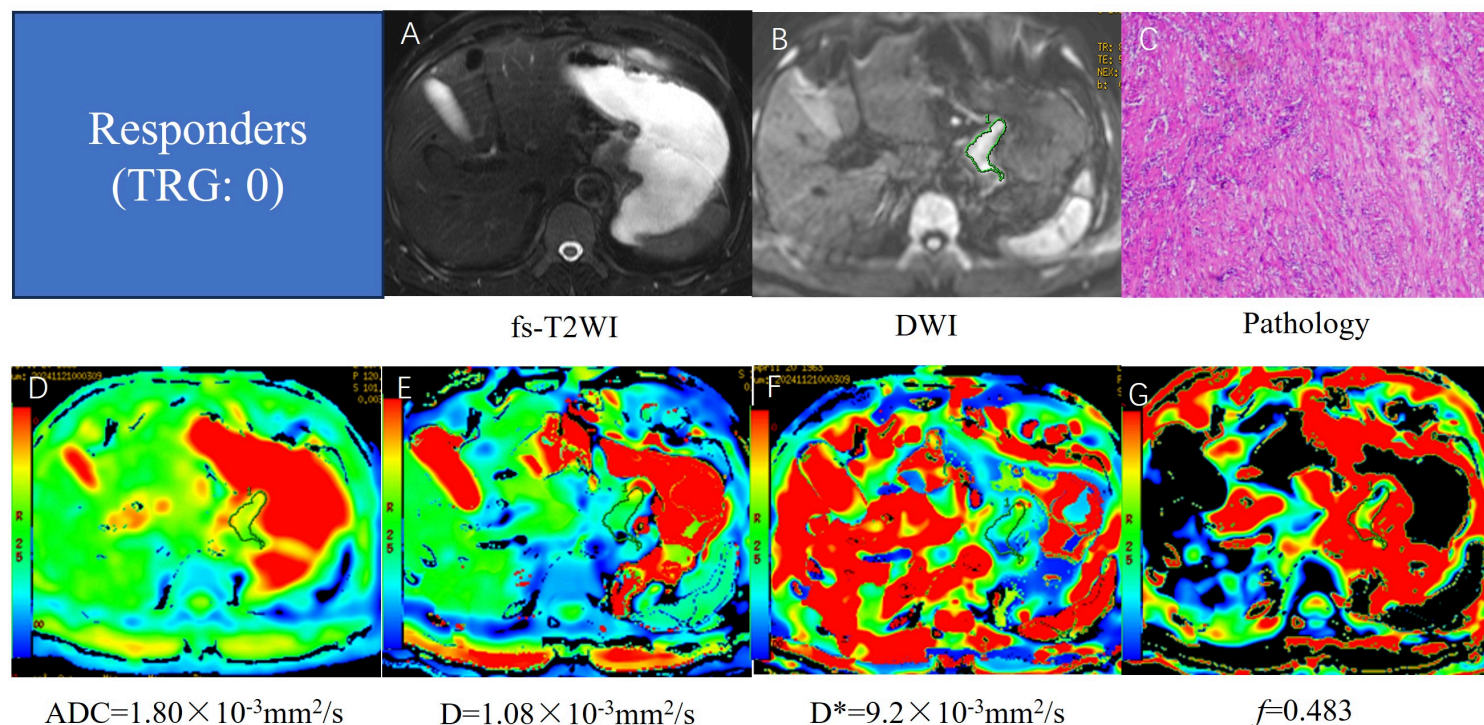


Figure 3

Baseline MR images and IVIM maps of a responder patient, who achieved pathological complete response (pCR) with TRG=0. (A) Axial fat-suppressed T2WI shows an ulcerative mass in the cardia; (B) A freehand ROI (green contour) is manually delineated along the margin of tumor (hyperintense) on reference image of DWI with $b=800 \text{ s/mm}^2$; (C) The histopathology (HE, magnification: $\times 40$) shows no residual tumor cells in the tumor bed, significant fibrosis is presented; (D-G) From the left to right was the ADC map, D map, D^* map, and f map, respectively; the corresponding

values are listed below. Abbreviations: ADC=apparent diffusion coefficient, D=true diffusion coefficient, f=pseudodiffusion fraction.

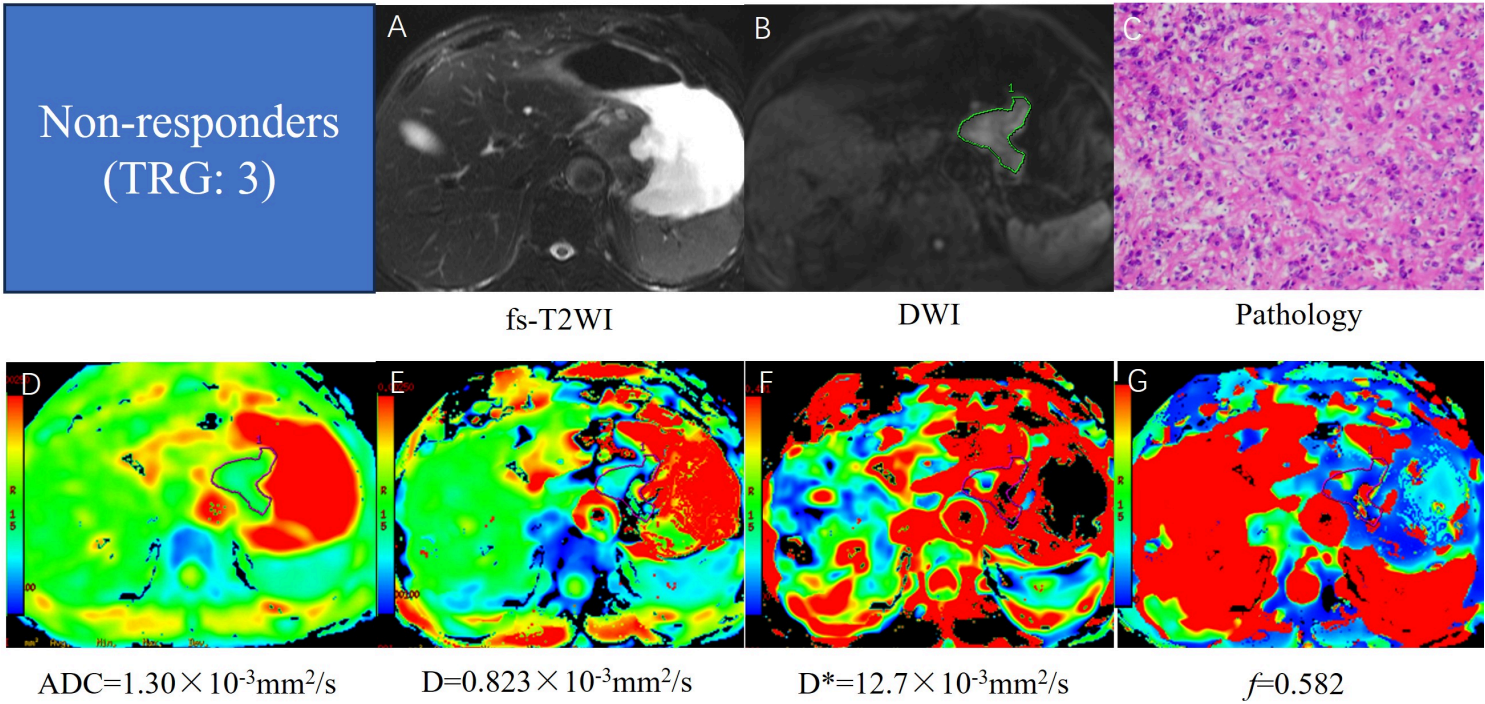


Figure 4

Baseline MR images and IVIM maps of non-responder patient, who achieved poor response with TRG=3. (A) Axial fat-suppressed T2WI shows an ulcerative mass in the cardia; (B) A freehand ROI (green contour) was manually delineated along the margin of tumor (hyperintense) on reference image of DWI with $b=800 \text{ s/mm}^2$; (C) The histopathology (HE, magnification: $\times 40$) shows massive residual tumor cells in the tumor bed; (D-G) From the left to right was ADC map, D map, D* map, and the f map, respectively; the corresponding values were listed below.

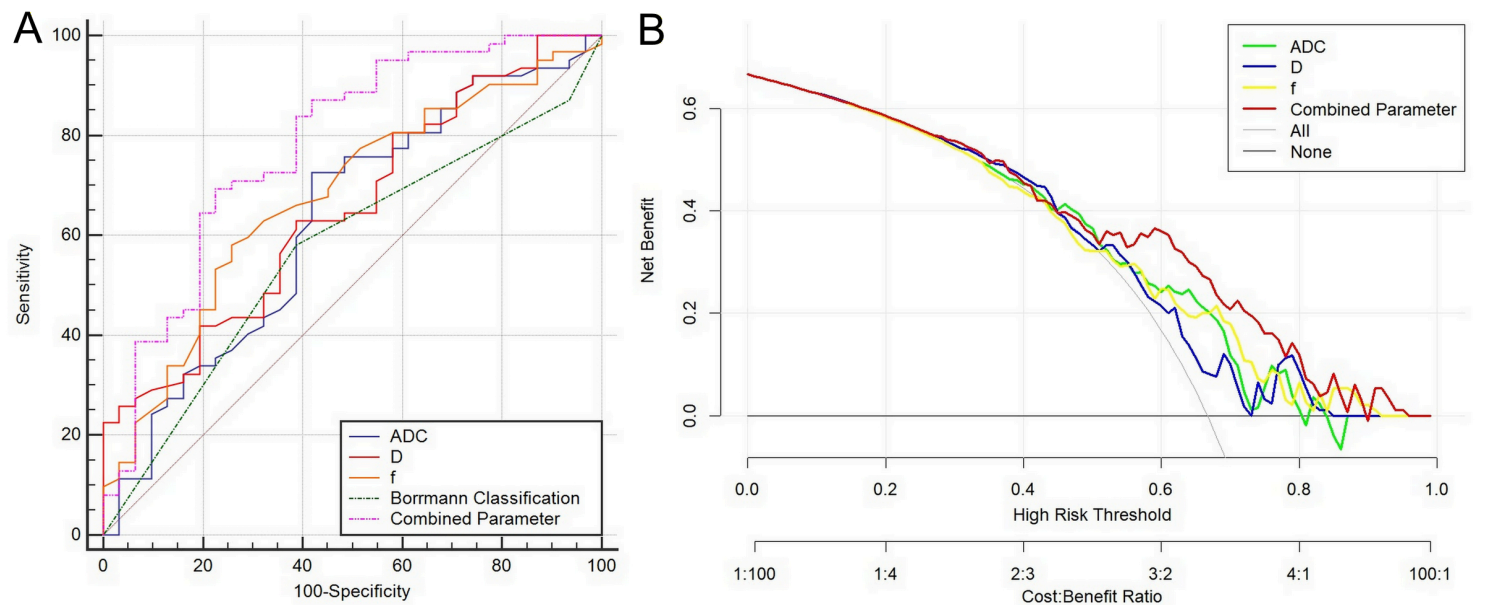


Figure 5

ROC analysis of Borrmann classification, ADC, D, f and the combined parameter (ADC+D+f) in dichotomizing pathological responsiveness categories.

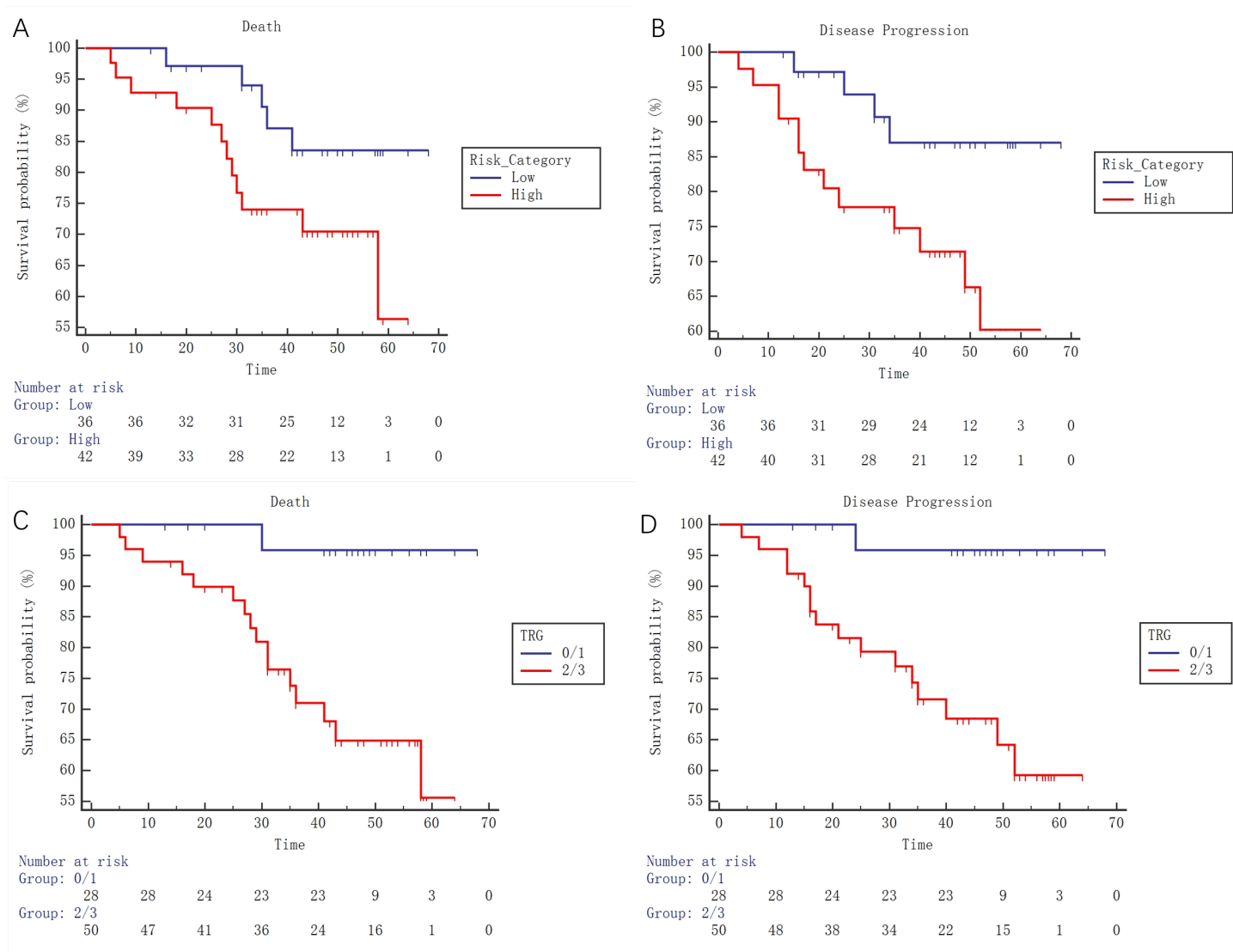


Figure 6

Kaplan-Meier (KM) survival analysis curves. (A, B) KM curves showing risk categories defined by the DECT-based combined parameter with OS (A) and DFS (B). (C, D) KM curves showing associations between TRG status and OS (C) and DFS (D). Abbreviations: OS = Overall survival; DFS = Disease-free survival; TRG = Tumor regression grade.

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