Research Square

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Larger Mesorectal Fat Area Predicts Better Response to Neoadjuvant Chemotherapy in Locally Advanced Rectal Cancer：A Real-World Retrospective Study

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Abstract

Objective

To investigate whether the mesorectal fat area (MFA) measured on pretreatment CT independently predicts neoadjuvant chemotherapy response in locally advanced rectal cancer (LARC), and to evaluate whether its predictive performance varies by tumor height.

Methods

We retrospectively analyzed 134 patients with LARC receiving neoadjuvant chemotherapy. MFA and subcutaneous fat area (SFA) were measured on pretreatment pelvic CT. Patients were classified by RECIST 1.1 into responders (n = 66) and non-responders (n = 68), and stratified by tumor height into low (< 5 cm), mid (5–10 cm), and high (> 10 cm) groups. Associations were assessed using logistic regression, ROC analysis, and variance inflation factor (VIF).

Results

Responders had significantly higher MFA than non-responders (20.91 vs. 15.62 cm², P < 0.001). MFA predicted response with an AUC of 0.751; at the Youden-derived cutoff of 17.02 cm², sensitivity was 77.3% and specificity 60.3%. On multivariate analysis, MFA was the strongest independent predictor. MFA did not differ across tumor height strata (P = 0.997), although discrimination was stronger in low and mid tumors than in high tumors. MFA correlated weakly with SFA (r = 0.254); all VIF values were below 1.32; and the partial correlation between MFA and response remained significant after controlling for SFA and waist circumference (P < 0.001).

Conclusions

MFA independently predicts neoadjuvant chemotherapy response in LARC, with predictive value beyond systemic adiposity indices. An MFA ≥ 17.02 cm² may serve as a clinically useful threshold for identifying patients likely to benefit from neoadjuvant chemotherapy.

1.Introduction

Colorectal cancer ranks third in global cancer incidence, with rectal cancer accounting for approximately 30%–40% of cases; the proportion is higher in East Asian countries, including China, than in Western populations [1]. For locally advanced rectal cancer (LARC), neoadjuvant chemoradiotherapy followed by total mesorectal excision (TME) constitutes the standard of care, substantially reducing local recurrence rates and improving R0 resection rates [2, 3]. However, the response to neoadjuvant therapy is markedly

heterogeneous: only 15%–38% of patients achieve pathological complete response (pCR), whereas 15%–20% show minimal or no response, or even disease progression — deriving no benefit while enduring treatment toxicity and a delay to definitive surgery [4, 5]. This heterogeneity in treatment response underscores the pressing need for pretreatment predictive biomarkers. Multiple candidate markers have been explored, including clinicopathological features (T/N stage, CEA), functional imaging parameters (e.g., ADC values, mrTRG), molecular markers (MSI status, RAS/BRAF mutations), and circulating tumor DNA [6, 7]; However, these markers have yet to demonstrate sufficient predictive accuracy or cost-effectiveness to exert an impact in clinical practice. Accordingly, identifying imaging biomarkers that are simple, noninvasive, and possess independent predictive value holds considerable translational significance.

The mesorectum is a fibrofatty tissue complex situated between the muscularis propria of the rectum and the parietal pelvic fascia. Anatomically, the mesorectum exhibits an inverted-cone morphology in the coronal plane — abundant in fat superiorly and tapering inferiorly [8]. Historically, the mesorectal fat was regarded as an inert surgical anatomical structure. More recent evidence, however, has established adipose tissue as a metabolically active endocrine organ that secretes adipokines — including leptin, adiponectin, IL-6, and TNF-α — which modulate the inflammatory state and immune surveillance of the tumor microenvironment [9–11]. In rectal cancer, the mesorectal fat is enveloped by an intact fascial layer, forming a relatively compartmentalized local microenvironment in which adipokines can attain and sustain high local concentrations, directly influencing the chemosensitivity of the adjacent tumor [12]. Thus, MFA represents not merely an anatomical descriptor but potentially a functional surrogate marker reflecting the state of the local tumor microenvironment.

Several recent studies have examined the relationship between body fat distribution and chemoradiotherapy response in rectal cancer. Qin, S.Y et al. [13] reported that the characteristics of mesorectal vessels and lymph nodes are predictors of nCRT in LARC patients. An exploratory study by De Nardi, P. et al. [14] noted limited consistency across studies and highlighted an "obesity paradox," suggesting that further investigation in this field is warranted.

Building on this body of work, the present study focuses on the mesorectal fat — an anatomically discrete fat compartment with a well-defined fascial boundary — complementing prior studies that have predominantly used the visceral fat area (VFA) as a global metric. We prospectively incorporate tumor height stratification to systematically evaluate the potential modifying effect of anatomical factors on the predictive performance of MFA. Methodologically, we introduce the variance inflation factor (VIF) and partial correlation analysis to quantitatively assess the degree of collinearity between MFA and systemic adiposity indices — including subcutaneous fat area (SFA), body mass index (BMI), and waist circumference — thereby confirming the independent incremental predictive value of MFA from a methodological standpoint.

2.Materials and Methods

2.1 Patients and Study Design

This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University. It was conducted in full accordance with the guidelines of the Declaration of Helsinki. Patients with LARC admitted to the Department of General Surgery, The First Affiliated Hospital of Nanchang University, between April 2020 and July 2023 were retrospectively enrolled. Inclusion criteria were: (1) histopathologically confirmed rectal adenocarcinoma; (2) clinical stage T2–4N0–2M0; (3) receipt of a complete course of neoadjuvant chemotherapy; (4) pretreatment high-resolution pelvic CT; and (5) complete clinicopathological data. Exclusion criteria were: (1) concurrent other malignancy; (2) prior pelvic radiotherapy; (3) suboptimal CT image quality; (4) failure to complete the prescribed chemotherapy regimen; (5) surgical treatment or patients with previous abdominal surgery. A total of 134 patients were ultimately included, the enrollment flowchart is shown in Fig. 1.

All patients received the CAPOX regimen: oxaliplatin 130 mg/m² administered as an intravenous (IV) infusion on day 1, plus capecitabine 850–1000 mg/m² taken orally twice daily on days 1–14, repeated every 3 weeks.

2.2 Data Collection

The following data were collected: age, sex, height, weight, waist circumference, distance from the lower tumor margin to the anal verge, T stage, N stage, maximum tumor diameter, histological type, and degree of differentiation, pretreatment serum CEA, SFA and MFA measured on CT, chemotherapy regimen.

2.3 Cohort Stratification

Response assessment: according to RECIST 1.1 criteria [15], during the treatment, the images were reviewed regularly (e.g.every 6–8 weeks). With CR/PR classified as responders and SD/PD as non-responders; Patients were stratified into three groups based on the distance from the lower tumor margin to the anal verge: low rectal cancer (< 5 cm), mid rectal cancer (5–10 cm), and high rectal cancer (> 10 cm).

2.4 CT-Based Fat Area Measurement

Pretreatment pelvic contrast-enhanced CT images were acquired and reviewed using the Carestream Vue PACS system (version 11.4.1.1102). Measurements of the mesorectal area were performed on CT images using a soft-tissue window setting (WW/WL = 350/50 HU; On axial CT images at the level of the maximum tumor diameter and the immediately adjacent superior and inferior slices, regions of interest (ROIs) were manually delineated to measure the SFA and MFA. MFA was defined as the fat area enclosed within the mesorectal fascia. The mean of the three slice-level measurements was used for analysis (Fig. 1). In order to control the measurement bias, the mesorectal area of all patients was measured independently by an imaging physician without knowing the patient 's chemotherapy response grouping. After all the measurements were completed, the correlation analysis was performed with the clinical follow-up data.

2.6 Statistical Analysis

Continuous variables are expressed as mean ± standard deviation and were compared between groups using the independent-samples t-test or one-way analysis of variance (ANOVA). Categorical variables were compared using the chi-squared test. Univariate and multivariate logistic regression analyses were performed to identify factors associated with chemotherapy response, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated. Receiver operating characteristic (ROC) curve analysis was used to evaluate predictive performance, and the optimal cutoff was determined by the Youden index. Pearson correlation analysis was used to assess inter-variable relationships. The variance inflation factor (VIF) was calculated to assess multicollinearity (VIF < 5 considered acceptable; VIF ≥ 10 indicating serious collinearity). Partial correlation analysis was performed to evaluate the net correlation between MFA and response after controlling for confounders. A two-side $P < 0.05$ was considered statistically significant.

3.Results

3.1 Baseline Patient Characteristics

The final cohort comprised 134 patients (82 men, 52 women) with a mean age of 58.9 ± 10.2 years (range, 28–84). The majority of tumors were located in the mid rectum (n = 95, 70.9%), followed by low (n = 24, 17.9%) and high (n = 15, 11.2%) locations. T stage distribution was as follows: T2 in 7 patients (5.2%), T3 in 87 (64.9%), and T4 in 40 (29.9%). According to RECIST 1.1 criteria, 66 patients (49.3%) achieved a response (CR/PR), while 68 (50.7%) had stable or progressive disease. The two groups were well balanced with respect to age, sex, BMI, tumor height, tumor size, N stage, CEA level, and lymphovascular invasion (Table 1). However, responders had a significantly lower proportion of T4 disease (22.7% vs. 36.8%) and a lower rate of perineural invasion (22.7% vs. 48.5%) compared with non-responders, suggesting more favorable baseline tumor biology in the responder group.

Table 1
Baseline characteristics of responders and non-responders

Variable	Responders (n = 66)	Non-responders (n = 68)	P
Age (years)	58.31 ± 10.07	59.94 ± 9.74	0.346
Sex (M/F)	39/27	43/25	0.928
BMI (kg/m²)	22.68 ± 3.40	21.91 ± 3.23	0.177
Distance from anal verge (cm)	6.81 ± 3.13	7.45 ± 3.03	0.232
Tumor size (cm)	3.25 ± 1.32	3.67 ± 1.79	0.131
T stage (T2/T3/T4)	6/45/15	1/42/25	**0.038**
N stage (N0/N1/N2)	19/28/19	14/32/22	0.578
CEA (ng/mL)*	5.73 (2.68–13.48)	7.42 (4.03–24.13)	0.106
Perineural invasion (yes/no)	15/51	33/35	**0.004**
Lymphovascular invasion (yes/no)	22/44	30/38	0.239

*CEA is presented as median (IQR) and was compared using the Mann–Whitney U test.

3.2 Comparison of Fat Areas Between Responders and Non-Responders

Responders had a substantially larger mesorectal fat area than non-responders (20.91 ± 5.59 cm² vs. 15.62 ± 5.19 cm², P < 0.001; Fig. 3), corresponding to an absolute difference of approximately 5.3 cm² — a 34% increase in mean MFA. In contrast, no significant between-group differences were observed for subcutaneous fat area (119.59 ± 61.83 cm² vs. 106.45 ± 61.66 cm², P = 0.221), waist circumference (83.00 ± 10.08 cm vs. 81.84 ± 9.74 cm, P = 0.502), or BMI (22.68 ± 3.40 kg/m² vs. 21.91 ± 3.23 kg/m², P = 0.177) (Table 2).

Table 2
Comparison of fat areas and anthropometric indices between the two groups

Parameter	Responders (n = 66)	Non-responders (n = 68)	P
MFA (cm²)	20.91 ± 5.59	15.62 ± 5.19	**< 0.001**
SFA (cm²)	119.59 ± 61.83	106.45 ± 61.66	0.221
Waist circumference (cm)	83.00 ± 10.08	81.84 ± 9.74	0.502
BMI (kg/m²)	22.68 ± 3.40	21.91 ± 3.23	0.177

3.3 ROC Curve Analysis of MFA for Predicting Chemotherapy Response

MFA discriminated between responders and non-responders with an AUC of 0.751 (95% CI: 0.658–0.823, Fig. 4A), indicative of moderate discriminatory ability. The Youden index identified an optimal threshold of 17.02 cm², at which MFA achieved a sensitivity of 77.3% and a specificity of 60.3%, with a positive predictive value of 65.4% and a negative predictive value of 73.2%.

Applying this threshold partitioned the cohort into two groups with markedly different outcomes: patients with an MFA at or above 17.02 cm² (n = 78) demonstrated a response rate of 65.4%, more than double the 26.8% observed among those below the cutoff (n = 56; P < 0.001;Figure 4B).

3.4 Stratified Analysis by Tumor Height

3.4.1 Comparison of MFA Across Tumor Height Strata

Given the potential influence of the inverted-cone mesorectal anatomy on MFA across different rectal tumor locations, we examined MFA among patients with tumors at different heights. Across the low (n = 24), mid (n = 95), and high (n = 15) rectum, MFA values were virtually superimposable (18.16 ± 7.43 cm², 18.26 ± 5.58 cm², and 18.16 ± 6.40 cm², respectively; P = 0.997; Fig. 5B), with no significant pairwise differences (all P > 0.96). Thus, despite the anatomical gradient in mesorectal volume, the fat area measured at the level of the tumor-bearing slice is not confounded by tumor height.

3.4.2 Association Between MFA and Chemotherapy Response After Stratification

Although MFA was constant across height strata, the strength of the MFA–response association varied (Fig. 6). In the low group, responders had a mean MFA of 21.41 ± 7.80 cm² compared with 14.33 ± 4.93 cm² in non-responders (P = 0.016), yielding an AUC of 0.776 and an optimal cutoff of 20.18 cm². The mid group showed the most robust discrimination: responders 21.10 ± 4.30 cm² vs. non-responders 15.47 ± 5.32 cm² (P < 0.001), with an AUC of 0.788 and a cutoff of 17.02 cm² that coincided with the overall cohort threshold. In contrast, among the 15 patients with high rectal tumors, MFA was nearly identical between responders and non-responders (18.40 ± 9.06 cm² vs. 18.00 ± 4.50 cm²; P = 0.910; AUC = 0.426), indicating a loss of predictive discrimination.

3.5 Logistic Regression Analysis

To determine whether MFA independently predicted response after accounting for established clinical variables, we performed logistic regression (Table 3). In univariate analysis, four factors were significantly associated with response: MFA (OR = 2.797, 95% CI: 1.979–4.439, P < 0.001), T stage (OR = 0.501, P = 0.023), perineural invasion (OR = 0.389, P = 0.004), and degree of differentiation (OR = 2.158, P = 0.016). SFA, waist circumference, BMI, age, and sex did not reach statistical significance.

In the multivariate model adjusting for age, sex, T stage, N stage, tumor size, and perineural invasion, MFA remained the dominant independent predictor (OR = 3.048, 95% CI: 2.071–5.407, P < 0.001), with a model AUC of 0.823 (Fig. 7). Male sex (OR = 2.482, P = 0.015) and lower T stage (OR = 0.455, P = 0.019) were also independently associated with response. MFA remained the dominant independent predictor (OR = 3.048, 95% CI: 2.071–5.407, P < 0.001), with a model AUC of 0.823 (Fig. 7). Male sex (OR = 2.482, P = 0.015) and lower T stage (OR = 0.455, P = 0.019) were also independently associated with response. After adding SFA to the model, the OR of MFA increased to 3.215 (AUC = 0.824), while SFA itself remained non-significant (OR = 0.997).

Table 3
Logistic regression analysis of factors associated with chemotherapy response

Variable	Univariate OR (95% CI)	P	Multivariate OR (95% CI)*	P
MFA (standardized)	2.797 (1.979–4.439)	< 0.001	3.048 (2.071–5.407)	**< 0.001**
Age	0.980 (0.947–1.016)	0.233	0.978 (0.936–1.023)	0.336
Sex (male)	1.146 (0.648–2.215)	0.671	2.482 (1.263–5.469)	**0.015**
T stage	0.501 (0.278–0.875)	0.023	0.455 (0.223–0.860)	**0.019**
N stage	0.854 (0.535–1.335)	0.483	1.014 (0.565–1.791)	0.962
Tumor size	0.841 (0.658–1.048)	0.123	0.864 (0.627–1.135)	0.331
Perineural invasion	0.389 (0.207–0.743)	0.004	0.474 (0.209–0.966)	0.056
SFA	1.003 (0.998–1.009)	0.239	—	—
Waist circumference	1.015 (0.981–1.050)	0.408	—	—
Lymphovascular invasion	0.681 (0.364–1.274)	0.233	—	—

3.6 Multicollinearity and Independence Assessment

3.6.1 Correlation Analysis

MFA correlated moderately with body weight (r = 0.445), waist circumference (r = 0.397), BMI (r = 0.347), and height (r = 0.301), consistent with the expectation that mesorectal fat reflects, in part, overall body habitus. In contrast, the correlation between MFA and SFA was notably weak (r = 0.254, R^2 = 0.064; Figs. 5A and 8A), with only 6.4% of the variance in MFA explained by subcutaneous adiposity, indicating that these represent relatively independent fat compartments.

3.6.2 Variance Inflation Factor (VIF) Analysis

To formally exclude collinearity as a concern, we calculated VIF values for all covariates in the multivariate model. Every variable had a VIF well below 1.31 (Table 4, Fig. 8B), far beneath the conventional warning thresholds of 5 or 10. When MFA and SFA were simultaneously included in the same model, their VIF values were 1.26 and 1.28, respectively — numerically confirming the lack of redundancy between the two fat measurements.

Table 4
Variance inflation factor (VIF) assessment

Variable	VIF	VIF (Model with SFA)	Assessment
MFA	1.10	1.26	No collinearity
SFA	—	1.28	No collinearity
Age	1.04	1.04	No collinearity
Sex	1.11	1.31	No collinearity
T stage	1.14	1.14	No collinearity
N stage	1.12	1.13	No collinearity
Tumor size	1.07	1.08	No collinearity
Perineural invasion	1.12	1.12	No collinearity

3.6.3 Partial Correlation Analysis

After controlling for SFA and waist circumference, the partial correlation coefficient between MFA and chemotherapy response was r = 0.457 (P < 0.001), further confirming that the predictive capacity of MFA for chemotherapy response is independent of systemic adiposity indices.

4.Discussion

This study systematically analyzed the relationship between MFA and the response to neoadjuvant chemotherapy in LARC. The principal findings are as follows: (1) MFA was significantly higher in responders than in non-responders (20.91 vs. 15.62 cm^2, P < 0.001), and MFA was an independent predictor of chemotherapy response (multivariate OR = 3.048); (2) MFA predicted chemotherapy response with an AUC of 0.751, and a cutoff of 17.02 cm^2 effectively discriminated between high- and low-benefit populations; (3) MFA showed no significant variation across tumor height strata (P = 0.997), yet the predictive performance was more pronounced in low and mid rectal cancer; and (4) both VIF analysis and partial correlation analysis confirmed that MFA provided incremental predictive value beyond SFA, BMI, and waist circumference.

Our initial hypothesis posited that the inverted-cone anatomy of the mesorectum would result in inherently larger MFA values in patients with high rectal cancer compared with those with low tumors. However, the data definitively refuted this hypothesis — mean MFA values were nearly identical across

the three height strata (approximately 18.2 cm²; ANOVA P = 0.997). A plausible explanation is that MFA was uniformly measured at the level of the maximum tumor diameter, where mesorectal expansion may be influenced by the mass effect of the tumor itself, offsetting height-related anatomical differences. Moreover, the high rectal cancer subgroup comprised only 15 patients, limiting statistical power. The mesorectal fat area may also be governed more by individual metabolic factors (e.g., systemic adiposity) than by anatomical location. We consider this negative finding to carry important methodological implications, suggesting that when MFA is used as a predictive biomarker, separate adjustment for tumor height may be unnecessary.

A key contribution of this study lies in its systematic evaluation of multicollinearity between MFA and other anthropometric adiposity indices. MFA exhibited only a weak correlation with SFA ($r = 0.254$, $R^2 \approx 6\%$), and VIF analysis confirmed the absence of collinearity between the two in the primary regression model (VIF_MFA = 1.26, VIF_SFA = 1.28). More importantly, partial correlation analysis revealed that, after controlling for SFA and waist circumference, MFA remained significantly and positively correlated with chemotherapy response ($r_{partial} = 0.457$, $P < 0.001$). These convergent findings indicate that the mesorectal fat area carries predictive value that extends beyond systemic adiposity indices, and that MFA reflects characteristics of the local tumor microenvironment rather than merely global obesity status.

The mesorectal adipose tissue possesses active metabolic and endocrine functions and may influence chemosensitivity through several pathways: (1) adipokines such as adiponectin exert insulin-sensitizing and anti-inflammatory effects, and a larger MFA may reflect a local anti-inflammatory microenvironment [16, 17]; (2) the rich capillary network within the mesorectal fat may facilitate the delivery of chemotherapeutic agents to the tumor tissue [12]; and (3) a smaller MFA may indicate a cachexia-prone or malnourished state, which is associated with poor chemotherapy tolerance. The weak correlation between MFA and SFA ($R^2 = 6.4\%$) suggests that the mesorectal and subcutaneous fat compartments are functionally distinct and metabolically divergent, consistent with the paradigm that visceral and subcutaneous adipose tissue play different roles in metabolic syndrome.

The AUC of MFA for predicting chemotherapy response in this study (0.751) is comparable to that reported by Dilek et al. (AUC = 0.757) [18]. Notably, the predictive performance of MFA in the present study substantially exceeded that of waist circumference (AUC = 0.542), BMI (non-significant univariate predictor), and SFA (AUC = 0.564), further underscoring the superiority of localized fat measurement over systemic indices. The loss of predictive performance of MFA in the high rectal cancer subgroup (AUC = 0.426), while potentially attributable to the limited sample size (n = 15), may also suggest that high rectal cancer involves distinct chemoresponse mechanisms, warranting further investigation in future studies.

5.Conclusion

The mesorectal fat area (MFA) is an independent predictor of the response to neoadjuvant chemotherapy in locally advanced rectal cancer. MFA does not differ significantly across tumor height

strata; therefore, adjustment for tumor position is not required. Collinearity between MFA and systemic adiposity indices — including SFA, BMI, and waist circumference — is minimal (VIF < 1.31), and the predictive value of MFA is independent of systemic fat distribution. An MFA ≥ 17.02 cm^2 may serve as a threshold for identifying patients likely to derive greater benefit from neoadjuvant chemotherapy. As a simple, noninvasive CT-derived imaging biomarker, MFA holds substantial promise for guiding precision treatment decisions in rectal cancer.

Declarations

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request. The research data is stored in the case data query system of the First Affiliated Hospital of Nanchang University.

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Conflict of interest

The authors have no conflicts of interest to disclose.

Ethical approval statement

The study protocol was approved by the Institutional Review Board of the the first affiliated hospital of nanchang university. Written informed consent was obtained from all participants, and all personal identifiers were removed.

Author contributions

Wei Zhou: Data curation; Writing – original draft.

Xin Ge: Formal analysis.

Yuli Yuan: Quality control of data and algorithms

Yahang Liang: Quality control of data and algorithms

Taiyuan Li: Supervision.

Xiong Lei: Supervision; Writing – review & editing.

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Figures

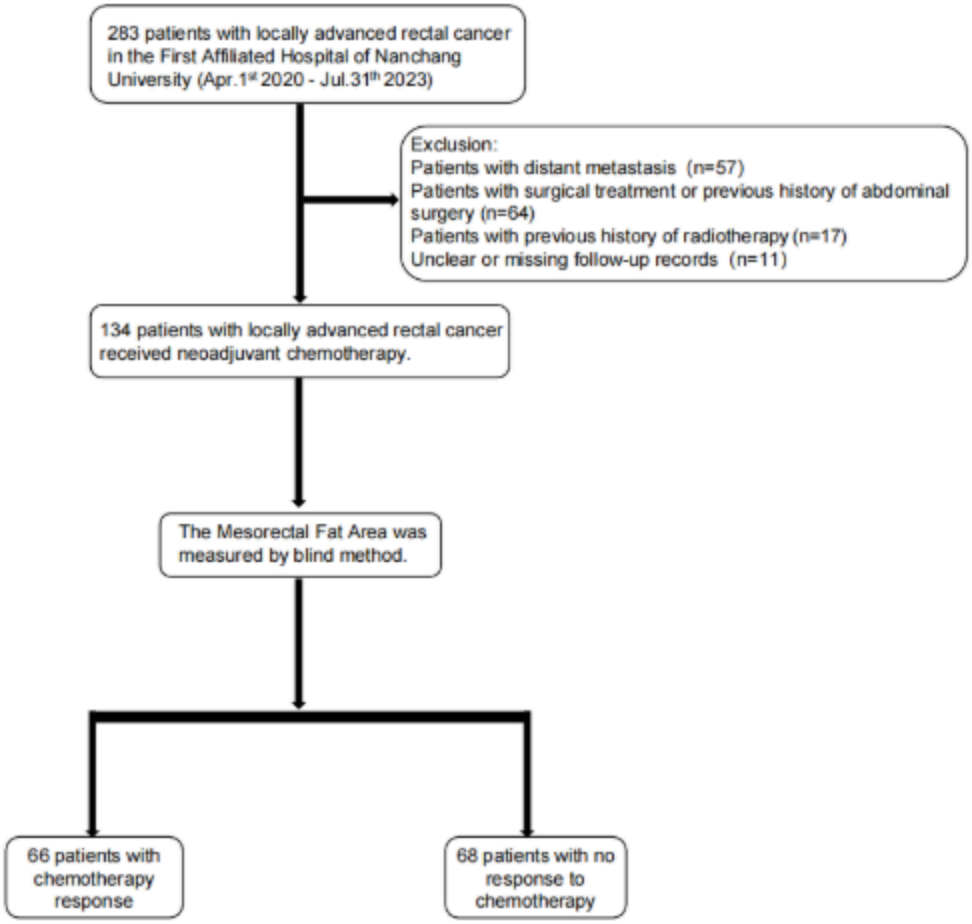


Figure 1

The patient enrollment process.

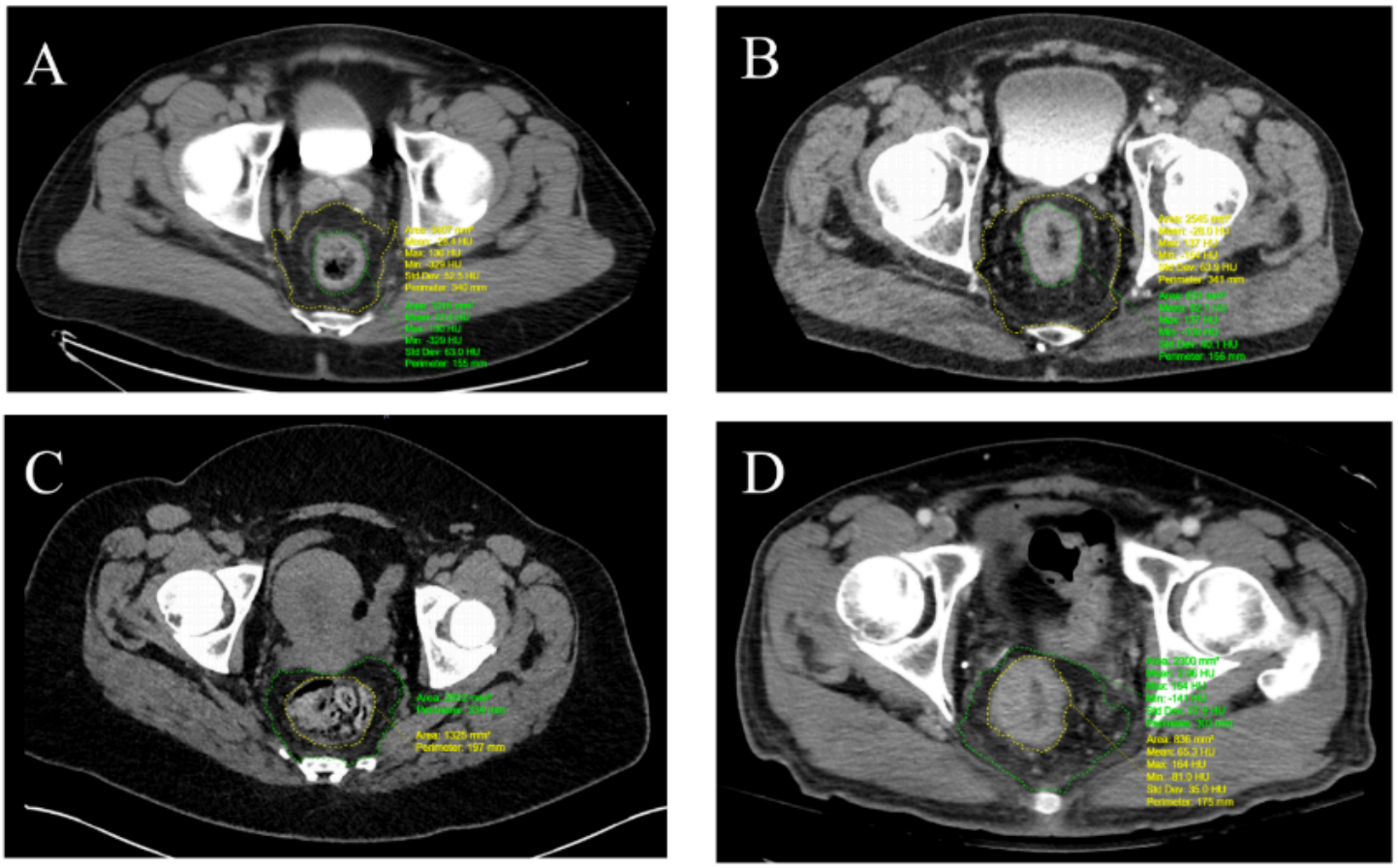


Figure 2

Axial tomographic images showed the measurement of mesorectal adipose tissue. Mesenteric fat area, two patients with neoadjuvant chemotherapy response(A,B); Two patients with no response to neoadjuvant chemotherapy(C,D)

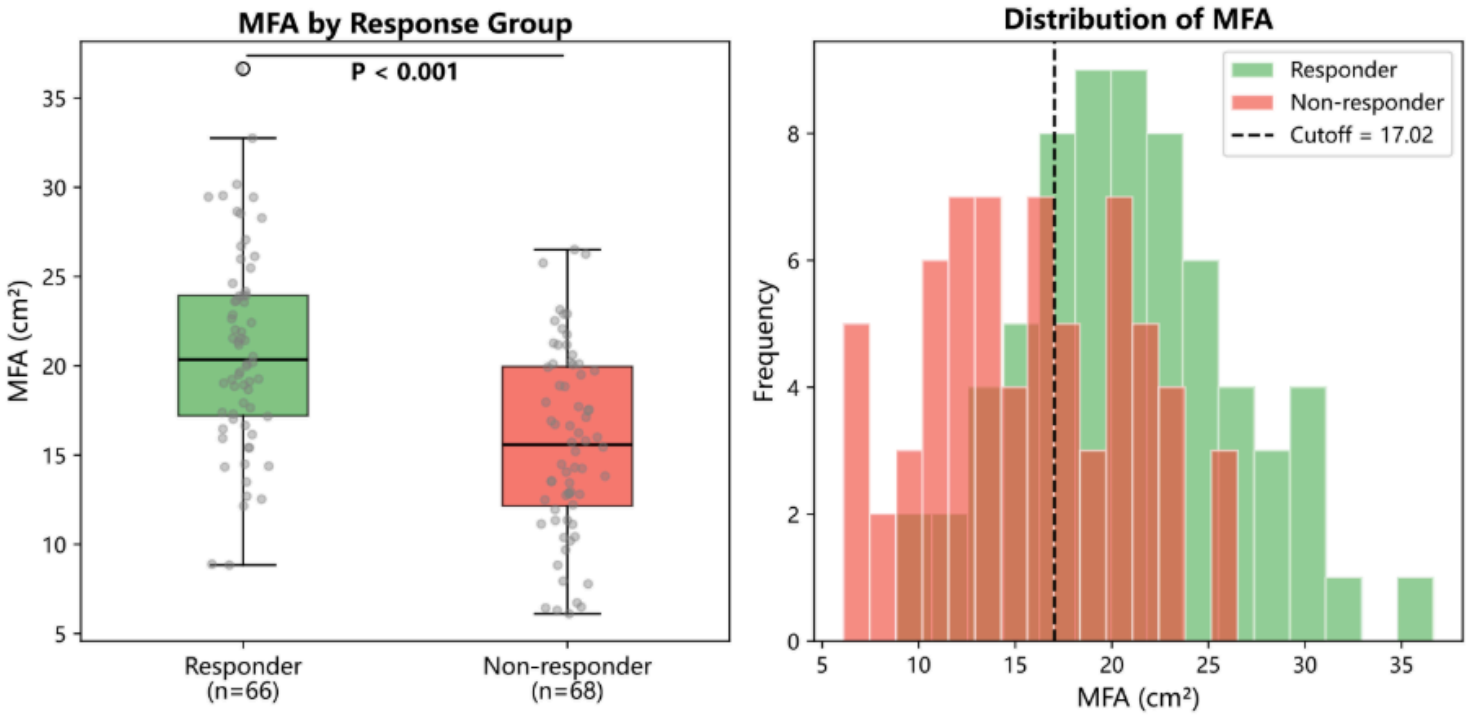


Figure 3

Comparison of MFA between responders and non-responders.

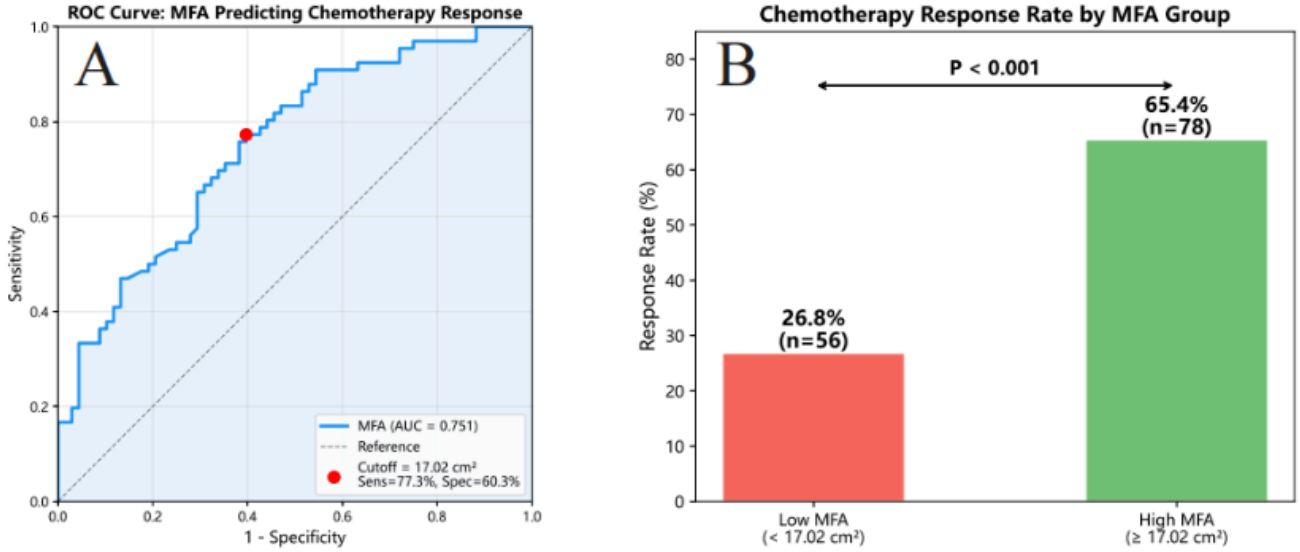


Figure 4

ROC curve of MFA for predicting chemotherapy response(A); Response rates in the high-MFA and low-MFA groups(B).

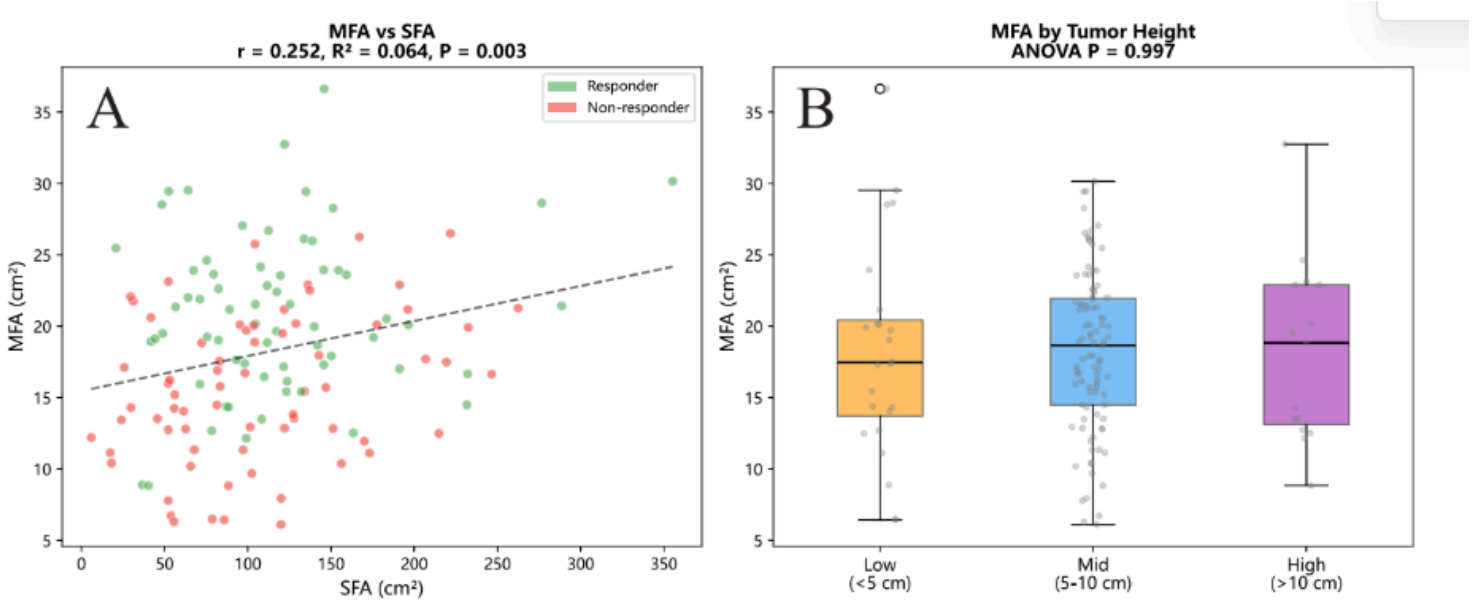


Figure 5

Scatter plot of MFA vs. SFA (A); MFA distribution by tumor height (B).

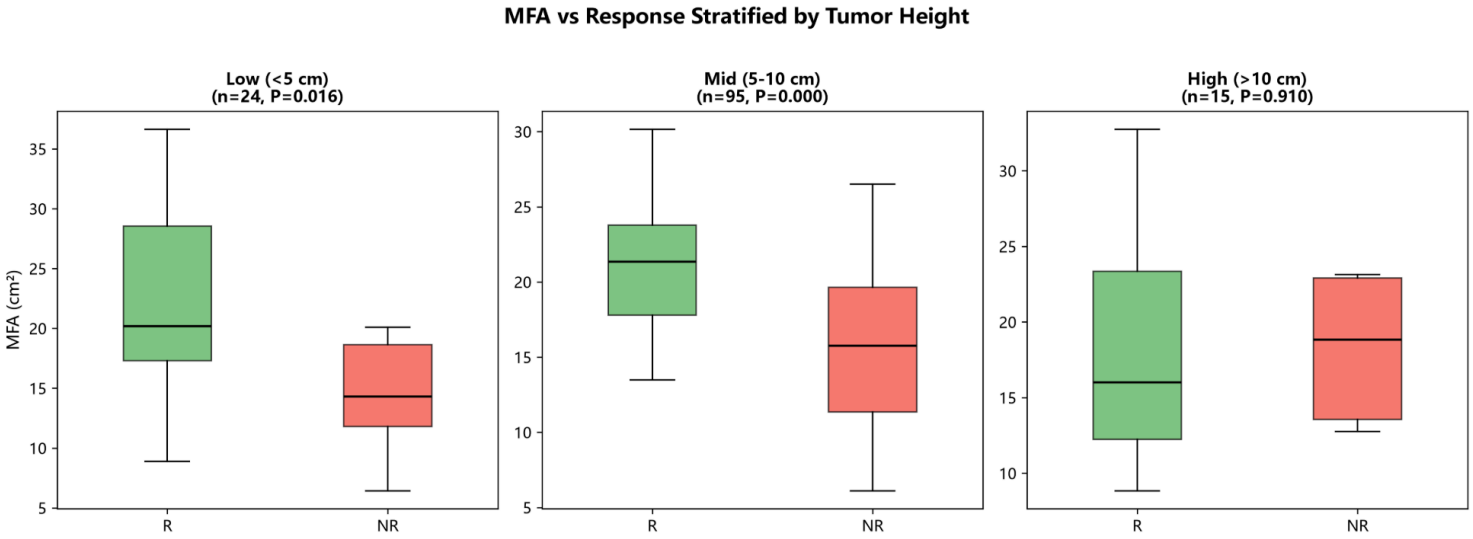


Figure 6

MFA vs. response stratified by tumor height.

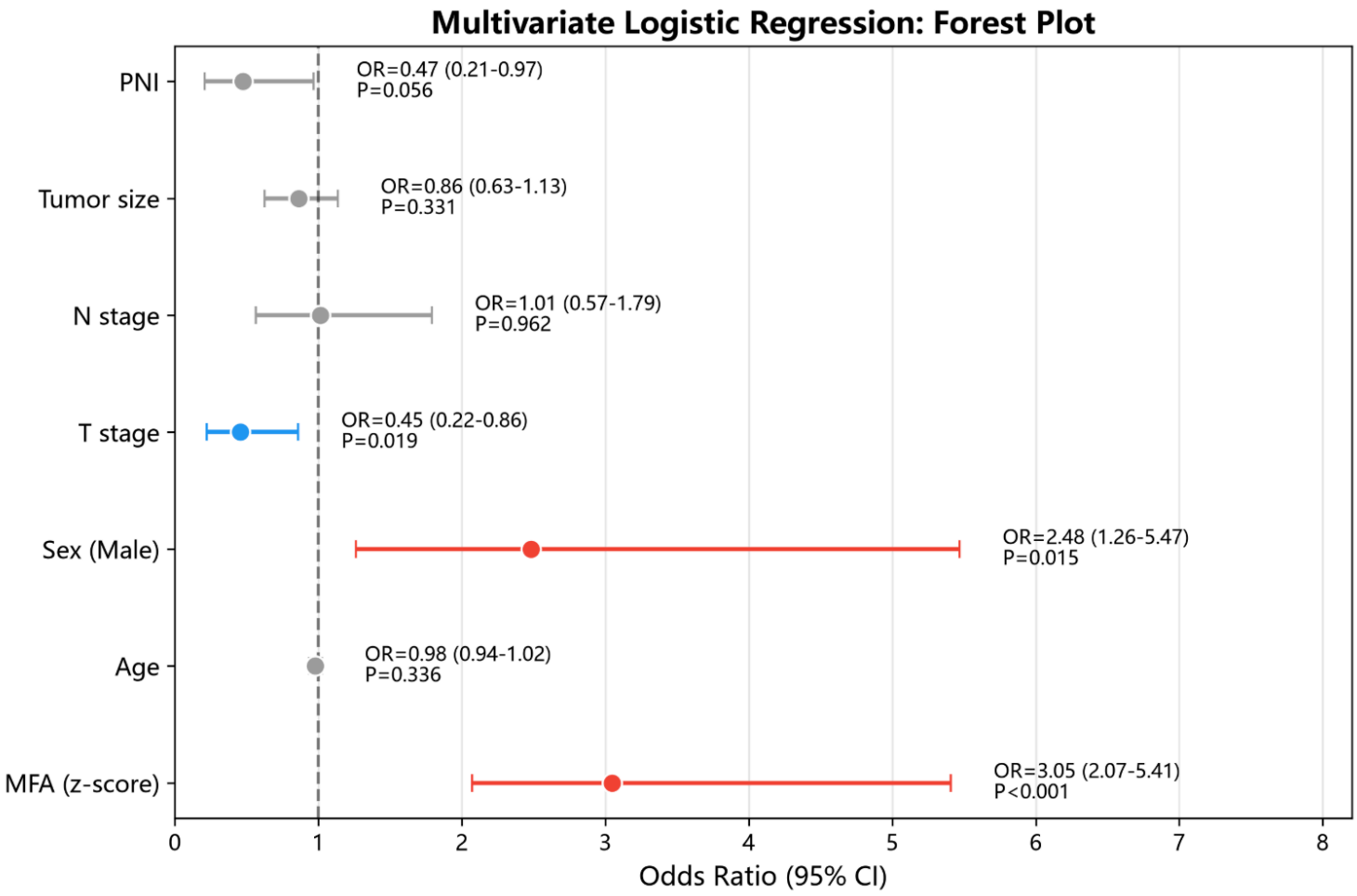


Figure 7

Forest plot of the multivariate logistic regression analysis.

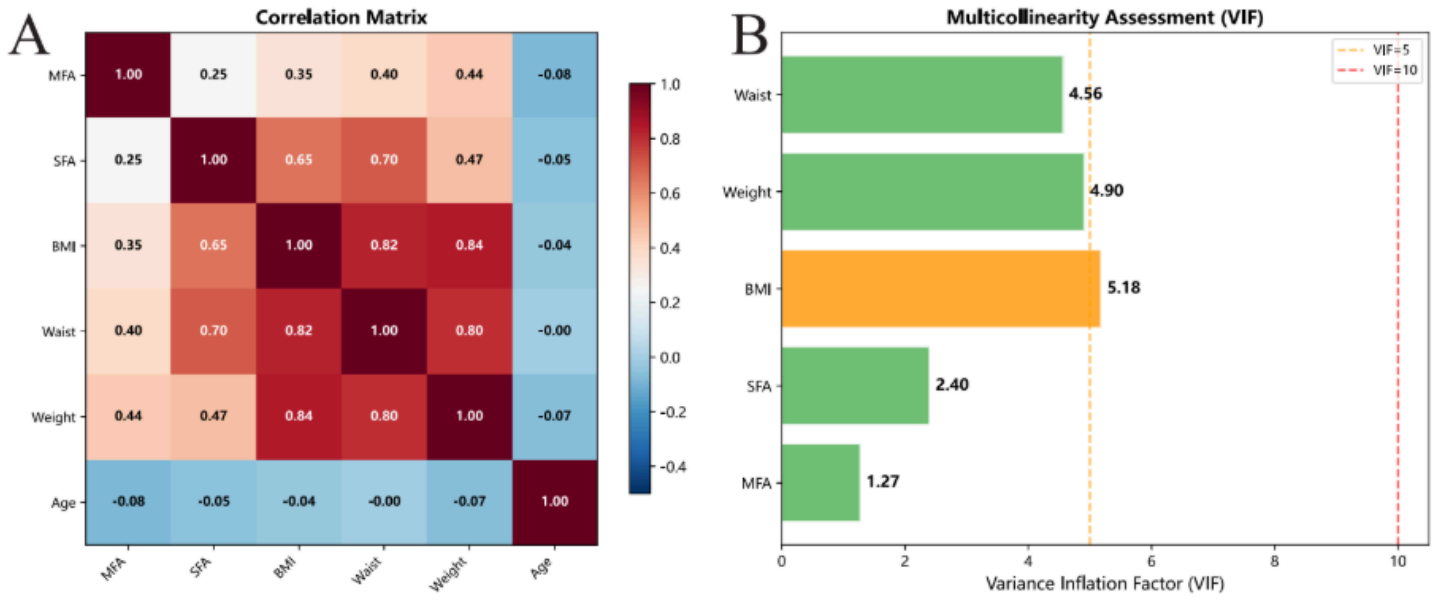


Figure 8

Correlation matrix(A); Variable multicollinearity assessment(B).