

RESEARCH ARTICLE

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Association of Abdominal Aortic Calcification with Pathological Response to Neoadjuvant Chemotherapy in Locally Advanced Gastric Cancer: A Retrospective Exploratory Study

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Abstract

Background: Pathological response to neoadjuvant chemotherapy is an important prognostic determinant in patients with locally advanced gastric cancer (LAGC). However, reliable pretreatment biomarkers for predicting treatment response remain limited. Abdominal aortic calcification (AAC), an imaging marker of systemic atherosclerosis, can be readily assessed on routine computed tomography (CT). This study investigated the association between baseline AAC and pathological response to neoadjuvant chemotherapy in patients with LAGC. **Methods:** This retrospective exploratory study included patients with histologically confirmed LAGC who received neoadjuvant FLOT chemotherapy followed by curative-intent gastrectomy between January 2024 and January 2025. Pretreatment CT images were reviewed to quantify AAC using the abdominal aortic calcification index (ACI). Pathological response was evaluated according to the Mandard tumor regression grade (TRG) system. Receiver operating characteristic (ROC) curve analysis and logistic regression analyses were performed to evaluate the association between ACI and pathological response. **Results:** A total of 47 patients were included, with a median age of 64 years, and 70.2% were male. Patients with higher ACI values were significantly older than those with lower values. ROC analysis demonstrated limited discriminatory performance of ACI for predicting pathological response. Using an optimal cutoff value of 3.28, the sensitivity and specificity of ACI were 60.0% and 60.4%, respectively. Older age, hyperlipidemia, and clinical T stage were significantly associated with poorer pathological response in univariate analyses. However, ACI was not independently associated with pathological response in multivariable logistic regression analysis. **Conclusions:** Baseline AAC was not independently associated with pathological response to neoadjuvant chemotherapy in patients with LAGC. AAC may reflect host-related vascular aging rather than tumor-specific treatment sensitivity and may contribute to future exploratory risk-stratification models.

Keywords: Gastric cancer, Neoadjuvant chemotherapy, Abdominal aortic calcification, Tumor regression grade

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Introduction

Gastric cancer is among the most common gastrointestinal malignancies and continues to represent a major cause of cancer-related mortality worldwide. Given that the majority of patients present with advanced disease, overall prognosis remains poor. In patients with locally advanced gastric cancer (LAGC), neoadjuvant therapy followed by radical surgery constitutes the current standard of care. Several large randomized trials, including the UK MAGIC, French FNCLCC/FFCD, German FLOT4-AIO, and Chinese RESOLVE trials, have demonstrated significant survival benefits associated with

perioperative chemotherapy in this patient population [1-4]. Although neoadjuvant chemotherapy improves R0 resection rates and prolongs disease-free survival (DFS) and overall survival (OS), not all patients derive equal benefit. Reported pathological response rates remain variable, highlighting substantial interindividual heterogeneity in treatment sensitivity. Response to neoadjuvant therapy is a critical prognostic determinant, and identifying factors associated with treatment responses is essential for optimizing patient selection and improving clinical outcomes.

Recently, treatment strategies for LAGC have rapidly evolved with the incorporation of immunotherapy

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into perioperative and neoadjuvant settings [5]. Emerging randomized studies have demonstrated improved pathological response rates with perioperative chemoimmunotherapy combinations in selected patient populations [6].

Despite these advances, cytotoxic chemotherapy remains a cornerstone of treatment for the majority of patients with LAGC, especially in microsatellite-stable disease, and reliable biomarkers for predicting response to chemotherapy alone are still lacking. Moreover, in real-world clinical practice, a substantial proportion of patients continue to receive chemotherapy without immunotherapy due to molecular profile, availability, or clinical considerations.

Histopathological tumor regression grading remains the gold standard for assessing response to neoadjuvant therapy; however, it can only be evaluated postoperatively. Therefore, there is a clear clinical need for readily available, pre-treatment predictive markers that may help anticipate response to neoadjuvant chemotherapy in patients with LAGC.

Cardiovascular disease and cancer are the two leading causes of morbidity and mortality worldwide, and accumulating epidemiological evidence suggests that they share common risk factors and biological mechanisms [7, 8]. Atherosclerosis is a chronic inflammatory vascular disease characterized by lipid-rich plaques in large- and medium-sized arteries. Inflammatory processes involving macrophages and T lymphocytes play a key role in the development and progression of vascular calcification. Abdominal aortic calcification (AAC) represents a clinically relevant manifestation of systemic atherosclerosis and can be easily assessed using routine abdominal computed tomography (CT).

Prior research has indicated that vascular calcification in the aorta and iliac arteries correlates with negative postoperative results, such as anastomotic leakage after colorectal and gastric surgery [9, 10]. Moreover, emerging evidence suggests that a high AAC burden is associated with poor prognosis in patients with colorectal and pancreatic cancers [9-11]. However, the relationship between AAC and response to neoadjuvant chemotherapy in LAGC has not been well established.

Therefore, this exploratory study aimed to investigate whether abdominal aortic calcification assessed on routine baseline CT imaging is associated with pathological response to neoadjuvant chemotherapy in patients with LAGC.

Materials and Methods

Study Design and Ethics Statement

A total of 47 patients with LAGC were included in the study. Patient information was retrospectively collected from a single tertiary referral center, including cases diagnosed between January 2024 and January 2025. Patients diagnosed with LAGC and operated on after neoadjuvant chemotherapy were included in the study. Locally advanced stage was considered as patients with clinical stage $\geq$ cT2 and/or positive lymph nodes (cN+) confirmed by contrast-enhanced CT/MRI of the chest,

abdomen, and pelvis and ultrasound gastroscopy without clinical evidence of distant metastasis according to the 8th American Joint Committee on Cancer staging system. Patients whose CT images were not available at the time of diagnosis were not included in the study. Patients whose image quality was not suitable for evaluation and those in whom metastases were detected during surgery were not included in the study. One patient was excluded because CT image quality was inadequate for AAC assessment, and two patients were excluded because metastatic disease was detected intraoperatively.

This study was approved by the Izmir City Hospital Ethical Review Board in accordance with the Declaration of Helsinki (Date: 20 November 2024; Decision no: 2024/223). Due to the retrospective design of the study, ethical approval was obtained before retrospective data extraction and analysis.

Study Population and Treatment

All patients received neoadjuvant chemotherapy with the FLOT regimen, consisting of docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil, administered every two weeks according to institutional protocols. Only patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 were included; no patients with ECOG performance status 2 were enrolled. Two patients received three cycles due to treatment-related considerations, while the remaining patients completed four planned cycles. No patients received neoadjuvant radiotherapy or immunotherapy.

Evaluation of AAC and neoadjuvant chemotherapy response

Abdominal aortic calcification index (ACI) was measured with the technique described by Tatami [12]. Based on the axial CT sections taken from the level of the renal artery to the bifurcation of the aorta, the aorta was divided into 12 sectors in each section, and the number of calcifications in the sectors was calculated (Figure 1). Values above 130 Hounsfield units with a minimum area of 1 mm³ were considered indicative of calcification. The abdominal aortic calcification index (ACI) was calculated as the total number of calcified sectors divided by the total number of evaluated sectors (12 sectors per slice $\times$ number of slices) and expressed as a percentage.

All measurements were primarily performed by one radiologist blinded to the patients' clinical characteristics and subsequently cross-checked by a second radiologist for consistency. Because measurements were not independently obtained in parallel by two blinded observers, formal interobserver agreement analysis was not performed.

Histopathologically, response to neoadjuvant therapy was evaluated according to the Mandard tumor regression grade (TRG), which is a semi-quantitative system [13]. The TRG classification by Mandard is TRG 1, complete response with no residual cancer; TRG 2, rare residual cancer; TRG 3, fibrosis outgrowing residual cancer; TRG 4, residual cancer outgrowing fibrosis; and TRG 5, absence of regression changes. Patients with TRG 1–3 were classified as response group, whereas those with

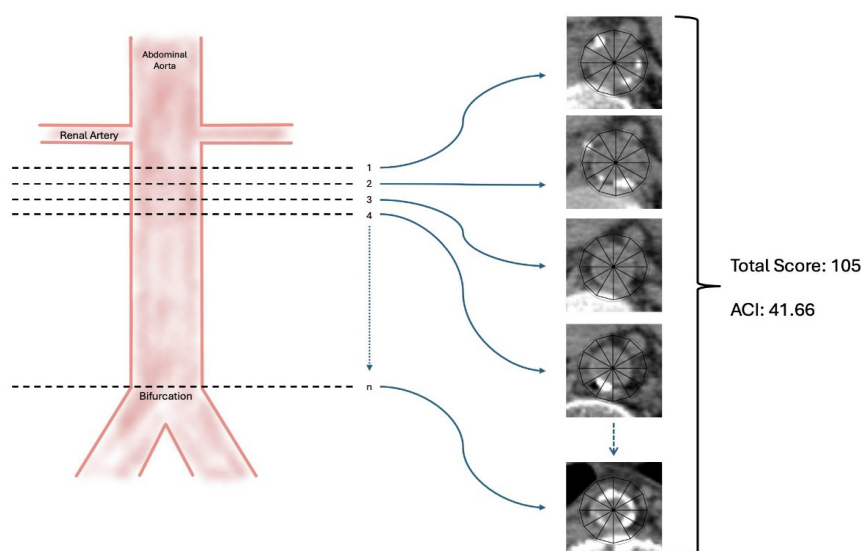


Figure 1. Assessment of Abdominal Aortic Calcification Index (ACI). Legend: Each axial CT slice between the renal arteries and aortic bifurcation was divided into 12 sectors. The abdominal aortic calcification index (ACI) was calculated as the proportion of calcified sectors relative to the total evaluated sectors.

TRG 4–5 were classified as non-response group.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (Statistical Package for the Social Sciences; IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as frequencies and percentages for categorical variables and as mean $\pm$ standard deviation or median (minimum–maximum) for continuous variables, as appropriate. ROC curve analysis was performed to evaluate the discriminatory performance of ACI for TRG response. Comparisons of categorical variables were conducted using the Pearson chi-square test or Fisher's exact test, as appropriate. For comparisons between two independent groups, the Mann–Whitney U test was used. Finally, multivariate logistic regression analysis was performed to identify independent factors associated with TRG response. Given the limited sample size, multivariable analyses were considered exploratory and interpreted cautiously. Results were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). A two-sided p-value of < 0.05 was considered statistically significant.

Results

Patient Characteristics According to Abdominal Aortic Calcification

Patients were stratified according to the ACI using a cut-off value of 3.28. Patients with $ACI > 3.28$ were significantly older than those with $ACI \leq 3.28$ (mean age: 67.26 ± 6.58 vs. 59.09 ± 7.52 years, $p = 0.003$). In addition, the proportion of patients aged ≥ 60 years was significantly higher in the high-ACI group (78.3% vs. 50.0%, $p = 0.044$).

No significant differences were observed between the ACI groups with respect to sex, smoking status, alcohol use, comorbidities, body mass index (BMI), clinical tumor

stage, or clinical nodal stage. Adenocarcinoma histology was more frequent among patients with $ACI > 3.28$ compared with those with $ACI \leq 3.28$ (87.0% vs. 54.2%, $p = 0.034$) (Table 1). Pathological characteristics, TRG, and recurrence rates did not differ significantly between the two ACI groups (Table 2).

Clinicopathological Features According to TRG

Patients were classified into the TRG response group ($n=24$) and TRG non-response group ($n=23$). Patients in the TRG non-response group were significantly older than those in the response group (65.03 ± 7.32 vs. 61.00 ± 8.49 years, $p = 0.039$), and the proportion of patients aged ≥ 60 years was higher among the non-response group (82.6% vs. 45.8%, $p = 0.009$) (Table 1). Hyperlipidemia was more common in the TRG non-response group (43.5% vs. 16.7%, $p = 0.045$). In terms of clinical tumor stage, cT3 disease was more frequent among non-response group, whereas cT2 disease was more common among the response group ($p = 0.039$). No significant differences were observed between the TRG groups with respect to sex, lifestyle factors, comorbidities, tumor location, or histological subtype (Table 1). Similarly, no significant differences were found in pathological nodal status, MSI or HER2 status, resection margin, lymphovascular invasion, perineural invasion, or recurrence between the two groups (Table 2).

Predictive Performance of ACI for Tumor Regression Grade

Receiver operating characteristic (ROC) curve analysis demonstrated limited discriminatory performance for TRG response, with an area under the curve (AUC) of 0.624 (95% CI: 0.462–0.786; $p = 0.045$). Using an optimal cut-off value of 3.28, ACI predicted TRG response with a sensitivity of 60.0% and a specificity of 60.4%.

Age, hyperlipidemia, and clinical T stage were significantly associated with TRG response in univariate

Table 1. Baseline Clinicopathological Characteristics According to Abdominal Aortic Calcification Index (ACI) and Tumor Regression Grade (TRG)

Variable	Total (N=47)	ACI > 3.28 (N=23)	ACI ≤ 3.28 (N=24)	p value	Response (N=24)	Non-Response (N=23)	p value
Age							
Mean±SD	62.72 ± 8.26	67.26 ± 6.58	59.09 ± 7.52	0.003 ^c	61.00 ± 8.49	65.03 ± 7.32	0.039 ^c
<60	17 (36.2)	5 (21.7)	12 (50)	0.044 ^a	13 (54.2)	4 (17.4)	0.009 ^a
≥60	30 (63.8)	18 (78.3)	12 (50)		11 (45.8)	19 (82.6)	
Sex							
Male	33 (70.2)	14 (60.9)	19 (79.2)	0.170 ^a	18 (75)	15 (65.2)	0.464 ^a
Female	14 (29.8)	9 (39.1)	5 (20.8)		6 (25)	8 (34.8)	
BMI							
Mean±SD	23.18 ± 4.75	22.73 ± 4.31	23.57 ± 5.17	0.472 ^c	22.31 ± 3.29	24.19 ± 5.95	0.628 ^c
Smoking							
No	20 (51.3)	8 (44.4)	12 (57.1)	0.429 ^a	11 (57.9)	9 (45)	0.421 ^a
Yes	19 (48.7)	10 (55.6)	9 (42.9)		8 (42.1)	11 (55)	
Alcohol							
No	38 (97.4)	17 (94.4)	21 (100)	0.462 ^b	19 (100)	19 (95)	1.000 ^b
Yes	1 (2.6)	1 (5.6)	0		0	1 (5)	
Comorbidities							
DM	13 (27.7)	9 (39.1)	4 (16.7)	0.085 ^a	5 (20.8)	8 (34.8)	0.285 ^a
HT	17 (36.2)	10 (43.5)	7 (29.2)	0.370 ^a	7 (29.2)	10 (43.5)	0.307 ^a
HL	14 (29.8)	9 (39.1)	5 (20.8)	0.170 ^a	4 (16.7)	10 (43.5)	0.045 ^a
CAD	8 (17.0)	4 (17.4)	4 (16.7)	1.000 ^b	3 (12.5)	5 (21.7)	0.461 ^b
cT							
T2	8 (17.0)	3 (13)	5 (20.8)	0.798 ^b	6 (25)	2 (8.7)	0.039 ^b
T3	22 (46.8)	12 (52.2)	10 (41.7)		7 (29.2)	15 (65.2)	
T4	17 (36.2)	8 (34.8)	9 (37.5)		11 (45.8)	6 (26.1)	
cN							
N0	11 (23.4)	6 (26.1)	5 (20.8)	0.398 ^b	5 (20.8)	6 (26.1)	0.971 ^b
N1	20 (42.6)	8 (34.8)	12 (50)		11 (45.8)	9 (39.1)	
N2	12 (25.5)	8 (34.8)	4 (16.7)		6 (25)	6 (26.1)	
N3	4 (8.5)	1 (4.3)	3 (12.5)		2 (8.3)	2 (8.7)	
Stage							
Stage 1	2 (4.3)	1 (4.3)	1 (4.2)	0.520 ^b	2 (8.3)	0	0.077 ^b
Stage 2	27 (57.5)	11 (47.8)	16 (66.7)		10 (41.7)	17 (73.9)	
Stage 3	10 (21.3)	7 (30.4)	3 (12.5)		5 (20.8)	5 (21.7)	
Stage 4A	8 (17.0)	4 (17.4)	4 (16.7)		7 (29.2)	1 (4.3)	
Histology							
Adenocarcinoma	33 (70.2)	20 (87)	13 (54.2)	0.034 ^b	19 (79.2)	14 (60.9)	0.571 ^b
Signet ring cell carcinoma	8 (17.0)	2 (8.7)	6 (25)		3 (12.5)	5 (21.7)	
Others	6 (12.8)	1 (4.3)	5 (20.9)		2 (8.4)	4 (17.3)	
Signet ring							
No	28 (59.6)	15 (65.2)	13 (54.2)	0.440 ^a	17 (70.8)	11 (47.8)	0.108 ^a
Yes	19 (40.4)	8 (34.8)	11 (45.8)		7 (29.2)	12 (52.2)	
Tumor location							
GEJ	4 (8.5)	3 (13)	1 (4.2)	0.793 ^b	3 (12.5)	1 (4.3)	
Proximal	9 (19.2)	4 (17.3)	5 (20.9)		4 (16.7)	5 (21.7)	
Middle	18 (38.3)	9 (39.1)	9 (37.5)		9 (37.5)	9 (39.1)	0.744 ^b
Distal	16 (34.1)	7 (30.4)	9 (37.5)		8 (33.3)	8 (34.8)	

Footnotes: Smoking and alcohol use data were unavailable for 8 patients. a: Pearson chi-square test; b: Fisher's exact test; c: Mann-Whitney U test. P < 0.05 was considered statistically significant. Abbreviations: ACI, abdominal aortic calcification index; BMI, body mass index; DM, diabetes mellitus; HT, hypertension; HL, hyperlipidemia; CAD, coronary artery disease; cT, clinical tumor stage; cN, clinical nodal stage; GEJ, gastroesophageal junction.

Table 2. Patient Post-Treatment Characteristics and Clinicopathological Features by Abdominal Aortic Calcification Index (ACI) and Tumor Regression Grade (TRG)

Variable	Total (N=47)	ACI > 3.28 (N=23)	ACI ≤ 3.28 (N=24)	p value	Response (N=24)	Non-Response (N=23)	p value
Operative method							
Subtotal	10 (21.3)	3 (13)	7 (29.2)	0.286 ^b	5 (20.8)	5 (21.7)	1.000 ^b
Total	37 (78.7)	20 (87)	17 (70.8)		19 (79.2)	18 (78.3)	
Dissection							
D1	6 (12.8)	2 (8.7)	4 (16.7)	0.660 ^b	4 (16.7)	2 (8.7)	0.666 ^b
D2	41 (87.2)	21 (91.3)	20 (83.3)		20 (83.3)	21 (91.3)	
ypT							
ypT0	2 (4.3)	0	2 (8.3)	0.328 ^b	2 (8.3)	0	0.054 ^b
ypT1	4 (8.5)	3 (13)	1 (4.2)		4 (16.7)	0	
ypT2	7 (14.9)	2 (8.7)	5 (20.8)		5 (20.8)	2 (8.7)	
ypT3	11 (23.4)	7 (30.4)	4 (16.7)		4 (16.7)	7 (30.4)	
ypT4	23 (48.9)	11 (47.8)	12 (50)		9 (37.5)	14 (60.9)	
ypN							
ypN0	15 (31.9)	6 (26.1)	9 (37.5)	0.521 ^b	11 (45.8)	4 (17.4)	0.204 ^b
ypN1	6 (12.8)	3 (13)	3 (12.5)		2 (8.3)	4 (17.4)	
ypN2	10 (21.3)	7 (30.4)	3 (12.5)		4 (16.7)	6 (26.1)	
ypN3	16 (34.0)	7 (30.4)	9 (37.5)		7 (29.2)	9 (39.1)	
Resection							
R0	44 (93.6)	22 (95.7)	22 (91.7)	1.000 ^b	23 (95.8)	21 (91.3)	0.609 ^b
R1	3 (6.4)	1 (4.3)	2 (8.3)		1 (4.2)	2 (8.7)	
LVI							
No	28 (68.3)	14 (70)	14 (66.7)	0.819 ^a	14 (66.7)	14 (70)	1.000 ^a
Yes	13 (31.7)	6 (30)	7 (33.3)		7 (33.3)	6 (30)	
PNI							
No	30 (73.2)	14 (70)	16 (76.2)	0.655 ^a	15 (71.4)	15 (75)	0.796 ^a
Yes	11 (26.8)	6 (30)	5 (23.8)		6 (28.6)	5 (25)	
MSI							
MSS	41 (93.2)	20 (95.2)	21 (91.3)	1.000 ^b	20 (95.2)	21 (91.3)	1.000 ^b
MSI-H	3 (6.8)	1 (4.8)	2 (8.7)		1 (4.8)	2 (8.7)	
Her2							
Negative	41 (91.1)	18 (85.7)	23 (95.8)	0.326 ^b	20 (87)	21 (95.5)	0.608 ^b
Positive	4 (8.9)	3 (14.3)	1 (4.2)		3 (13)	1 (4.5)	
Recurrence							
No	31 (75.6)	16 (80)	15 (71.4)	0.719 ^b	18 (85.7)	13 (65)	0.159 ^b
Yes	10 (24.4)	4 (20)	6 (28.6)		3 (14.3)	7 (35)	

Footnotes: MSI status was unavailable for 3 patients, HER2 status for 2 patients, and recurrence data for 6 patients. LVI and PNI could not be evaluated in six patients with complete or near-complete pathological response due to insufficient residual tumor tissue for assessment.. a: Pearson chi-square test; b: Fisher's exact test; c: Mann-Whitney U test. $P < 0.05$ was considered statistically significant. Abbreviations: ACI, abdominal aortic calcification index; ypT, pathological tumor stage after neoadjuvant therapy; ypN, pathological nodal stage after neoadjuvant therapy; MSI, microsatellite instability; MSS, microsatellite stable; MSI-H, microsatellite instability-high; HER2, human epidermal growth factor receptor 2; LVI, lymphovascular invasion; PNI, perineural invasion; TRG, tumor regression grade.

analyses and were therefore included in the multivariate logistic regression model. Given the limited sample size, the multivariate model should be interpreted cautiously and primarily as an exploratory analysis. Because the dependent variable in the logistic regression model was defined as TRG response (TRG 1–3), odds ratios below 1 indicated a lower likelihood of response. As shown in Table 3, age ≥ 60 years was associated with lower TRG

response rates in multivariable analysis, although the association did not reach statistical significance (OR = 0.23; 95% CI: 0.05–1.01; $p = 0.052$). Hyperlipidemia was not independently associated with TRG response (OR = 0.41; 95% CI: 0.09–1.79; $p = 0.235$). Compared with cT2, cT3 disease was not significantly associated with TRG response (OR = 0.20; 95% CI: 0.02–1.46; $p = 0.114$), and cT4 disease was also not significant (OR = 0.78; 95% CI:

Table 3. Multivariate Logistic Regression Analysis of Factors Associated with TRG Response

Variable	Multivariate	
	OR (95% CI)	p
Age ≥60 years	0.23 (0.05–1.01)	0.052
Hyperlipidemia	0.41 (0.09–1.79)	0.235
cT3 vs T2	0.20 (0.02–1.46)	0.114
cT4 vs T2	0.78 (0.10–6.11)	0.813
ACI (continuous)	0.994 (0.946–1.044)	0.804

Footnotes: Dependent variable in the logistic regression model was TRG response (TRG 1–3). –2 Log-likelihood = 51.44; Nagelkerke R^2 = 0.337; Hosmer–Lemeshow p = 0.721. Abbreviations: ACI, abdominal aortic calcification index; HL, hyperlipidemia; cT, clinical tumor stage.

0.10–6.11; p = 0.813). Overall model fit was assessed using the –2 log-likelihood (51.44), and the explanatory power of the model was indicated by a Nagelkerke R^2 value of 0.337. When ACI was additionally analyzed as a continuous variable in the multivariable model, it was not independently associated with TRG response (OR = 0.994; 95% CI: 0.946–1.044; p = 0.804). Model calibration was further evaluated using the Hosmer–Lemeshow goodness-of-fit test, which demonstrated acceptable calibration (χ^2 = 3.671, p = 0.721).

Discussion

This study aimed to investigate the association between AAC and response to neoadjuvant chemotherapy in patients with LAGC. Contrary to our initial hypothesis, AAC was not identified as an independent predictor of pathological response following neoadjuvant treatment. Although AAC demonstrated a limited discriminatory performance for tumor regression response in ROC analysis, this association did not persist in multivariate analysis after adjustment for relevant clinical factors. Importantly, the absence of an independent association between AAC and pathological response should not be interpreted as a negative or clinically irrelevant finding. Rather, it highlights the complex and multifactorial nature of treatment response in gastric cancer, in which host-related factors, tumor biology, and treatment-related variables interact dynamically. Taken together, these findings suggest that AAC alone does not function as a direct predictor of neoadjuvant chemotherapy response in this patient population.

Rather than functioning as a strong predictive biomarker, AAC may reflect host-related vascular characteristics, particularly vascular aging, rather than tumor-specific treatment sensitivity. To our knowledge, this is the first study to explore AAC in the context of neoadjuvant chemotherapy response in gastric cancer, providing novel insight into the potential role of systemic vascular health in oncologic outcomes. Given that AAC can be readily assessed on routine staging CT scans, it may still be considered as part of a broader, exploratory risk stratification framework rather than as a stand-alone predictive marker in patients with LAGC.

Vascular arterial calcification is associated with an increase in arterial stiffness, diastolic heart failure,

impaired perfusion of high-flow organs such as the brain, kidney, and liver, and chronic ischemia [14, 15]. It also increases the risk of vascular interventions and related complications. Studies have mostly focused on the relationship between vascular calcification and surgical complications. Calcification of the aorta and iliac arteries has been associated with poorer prognosis and postoperative complications, including anastomotic leakage, in gastrointestinal malignancies. In the present study, however, AAC was not independently associated with pathological response to neoadjuvant chemotherapy, suggesting that its impact may be mediated through systemic rather than tumor-specific mechanisms.

Currently, there is no universally accepted standardized method for the assessment of AAC. Various anatomical regions and evaluation techniques have been employed across different studies, with some focusing solely on the celiac trunk or iliac bifurcation or providing a total calcification score. The Agatston score, originally introduced by Agatston et al. in 1990, remains the reference standard for quantifying coronary artery calcification [16]. However, its application necessitates additional measurements and specialized workstations. In contrast, the ACI is a semi-quantitative method that enables evaluation of the entire abdominal aorta without the need for supplementary imaging protocols or dedicated software systems. This practicality supports its potential use in routine oncologic assessment, particularly in retrospective or real-world clinical settings. Alternative quantitative calcification scoring methods, such as Agatston or calcium volume scoring, may provide additional information and should be evaluated in future prospective studies.

The stomach is supplied by a rich system of arteries derived from the celiac trunk, the first major visceral branch of the abdominal aorta. Vascular calcification impairs blood flow and causes hypoxia. Hypoxia within the tumor microenvironment was associated with poorer response to radiotherapy [17]. The level of Hypoxia-Induced Factor (HIF)-1 increases as the body responds to low oxygen concentrations or hypoxia. HIF-1 promotes angiogenesis and plays a critical role in tumor proliferation [18, 19]. Increased hypoxia and HIF-1 activation may reduce sensitivity to chemotherapy and radiotherapy. However, our findings suggest that macrovascular calcification alone may not adequately capture the complexity of tumor oxygenation and treatment response, which are influenced by multiple systemic and local factors. Systemic conditions such as anemia may further impair oxygen delivery, and macrovascular flow disturbances may exacerbate the effects of both systemic and tumor-related hypoxia. Future studies incorporating hypoxia-related biomarkers, such as HIF-1 α expression or perfusion-based imaging parameters, may help clarify the biological relationship between vascular calcification and treatment response.

AAC is a well-known risk marker of cardiovascular diseases and is associated with hyperlipidemia, diabetes, chronic inflammation, and chronic kidney disease. In our cohort, higher AAC values were strongly associated with advanced age, supporting the concept that AAC reflects

biological aging rather than an isolated pathological process. This age-related association may partly explain why AAC did not retain independent predictive value for treatment response in multivariate analysis. In addition, the association between AAC and pathological response may have been influenced by confounding host-related factors and comorbidities that are closely linked to vascular aging. Future studies integrating AAC with other host-related biomarkers, including sarcopenia, visceral adiposity, and systemic inflammatory markers, may improve risk stratification and predictive models for neoadjuvant treatment response.

There are limited data in the literature examining the relationship between vascular calcification and chemotherapy response. More recently, increasing attention has been directed toward host-related imaging biomarkers, radiomics, and vascular imaging features as potential predictors of treatment response in gastric cancer and other solid tumors, although their clinical utility remains investigational. Knight et al. [20] reported that neither proximal nor distal aortic calcification was associated with response to neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer. However, in that study, response was dichotomized as pathological complete response (pCR) versus non-pCR, with only a small proportion of patients achieving pCR. Therefore, the limited sample size and imbalance between response groups may have reduced the statistical power of the analysis.

From a clinical perspective, these findings suggest that AAC should not be used to withhold or delay neoadjuvant chemotherapy. Rather, AAC may serve as a readily available imaging marker of host vulnerability that could be integrated into broader risk stratification models and warrants further investigation in larger, prospective cohorts.

This study has several limitations that should be acknowledged. The retrospective and non-randomized design may introduce selection bias, and the relatively small sample size from a single center limits the generalizability of the findings. Given the relatively small sample size, the study may have been underpowered to detect modest independent associations between AAC and pathological response, increasing the possibility of type II error. Moreover, the ROC-derived ACI cut-off value was both generated and evaluated within the same cohort without internal or external validation, which may increase the risk of overfitting and limit generalizability. Although ACI provides a practical method for assessing AAC, it remains a semi-quantitative and observer-dependent technique. In addition, formal interobserver reproducibility analysis was not performed because ACI measurements were not independently obtained in parallel by two blinded observers. Furthermore, the absence of patients treated with neoadjuvant immunotherapy limits extrapolation of our results to contemporary chemoimmunotherapy regimens. Prospective studies with larger cohorts are warranted to clarify the role of vascular calcification in treatment response and to explore its potential interaction with emerging therapeutic strategies. Additionally, the relatively homogeneous treatment

approach, consisting of FLOT chemotherapy alone, may have limited the ability to detect differential predictive effects across treatment modalities.

Our findings suggest that abdominal aortic calcification reflects host-related vascular aging rather than serving as an independent predictor of pathological response to neoadjuvant chemotherapy in patients with locally advanced gastric cancer. Although AAC demonstrated limited discriminatory performance, its predictive value diminished after adjustment for clinical variables. As a readily available radiological parameter, AAC may contribute to exploratory risk stratification models when interpreted alongside other host-related and tumor-specific factors. These findings should be considered hypothesis-generating and warrant validation in larger prospective studies.

Author Contribution Statement

Conceptualization: Özlem Kutlu, Cemre Özenbaş; Data curation: Özlem Kutlu, Gürkan Gül, Feyza Arslan Tan; Radiological evaluation: Cemre Özenbaş, Raşit Eren Büyüktoka; Pathological evaluation: Asuman Argon; Statistical analysis: Özlem Kutlu; Supervision: Mehmet Nuri Başer, Halil Taşkaynatan, Özlem Özdemir; Writing – original draft: Özlem Kutlu; Writing – review and editing: all authors. All authors read and approved the final manuscript.

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Ethics Approval

This study was approved by the Izmir City Hospital Ethical Review Board in accordance with the Declaration of Helsinki (Date: 20 November 2024; Decision No: 2024/223).

Availability of Data and Materials

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

Registration Statement

This study was not registered because of its retrospective observational design.

Conflict of Interest

The authors declare no conflicts of interest.

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