Circulating miRNA-30a is associated with favorable therapeutic outcome in patients with gastric cancer treated with neoadjuvant chemotherapy

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Abstract. Neoadjuvant chemotherapy (NAC) represents a cornerstone in the management of locally advanced gastric cancer (GC); however, variability in therapeutic effect underscores the need for additional approaches to support post-operative risk stratification. The present study investigated circulating microRNA (miRNA)-30a as a potential post-treatment, response-associated indicator of therapeutic outcome in patients with GC undergoing NAC. Circulating miRNA-30a expression was measured in serum samples using quantitative real-time polymerase chain reaction (RT-qPCR). NAC-treated patients were stratified into responders (TRG 0-2) and non-responders (TRG 3-5) according to Mandards criteria, while chemotherapy-naive (CT-naive) patients were included as a control group. Circulating miRNA-30a levels were higher in responders compared to non-responders. Elevated miRNA-30a expression was associated with reduced pathological tumor burden, including lower T stage and absence of nodal involvement. ROC analysis demonstrated strong discriminatory performance for distinguishing treatment response. In both univariate and multivariable logistic regression analyses, increased miRNA-30a expression remained independently associated with treatment response. Furthermore, higher miRNA-30a levels were associated with improved overall survival. In conclusion, circulating miRNA-30a is associated with favorable therapeutic outcome in GC and may complement conventional assessment strategies in the post-treatment setting as a response-associated indicator. Further validation in larger, prospective cohorts is needed.

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Abbreviations: GC, gastric cancer; NAC, neoadjuvant chemotherapy; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; CT-naive, chemotherapy-naive

Key words: gastric cancer, microRNA-30a, neoadjuvant chemotherapy, liquid biopsy, treatment response

Introduction

Gastric cancer (GC) remains the fifth most common cancer diagnosis and a leading cause of cancer-related mortality worldwide (1). Despite advances in multimodal therapeutic approaches, overall prognosis remains poor (2). For patients with locally advanced disease, neoadjuvant chemotherapy (NAC) followed by radical surgery constitutes a cornerstone of curative management, with treatment response typically evaluated post-operatively through conventional imaging and histopathological assessment (3). Although standard clinical evaluation serves as an important surrogate of therapeutic efficacy and is associated with improved survival (4), clinical outcomes remain highly variable (5,6). Some patients with residual disease experience prolonged recurrence-free survival (5), whereas relapse may still occur in a subset of patients showing favorable pathological response (7). Together, these observations emphasize the complexity of therapeutic effectiveness and limitations of traditional evaluation methods in providing a complete picture, highlighting the need for additional approaches that can better reflect treatment-associated alterations, thereby enabling improved post-operative risk stratification in GC.

MiRNAs are small non-coding RNAs of approximately 19-24 nucleotides that regulate gene expression at post-transcriptional level (8). These epigenetic regulators modulate multiple cancer-related processes including proliferation, invasion, metastasis, and treatment response, functioning either as oncogenic genes or tumor suppressors (9). Importantly, miRNAs are detectable in stable cell-free forms in circulation, making them attractive candidates for non-invasive liquid biopsy

approaches (10). Among candidate miRNAs, miRNA-30a has been consistently implicated as a tumor-suppressive regulator across malignancies, with reduced expression linked to aggressive tumor behavior and treatment resistance (11,12). However, data regarding its role in GC, particularly in the neoadjuvant setting, remain limited.

Therefore, the aim of this study was to evaluate the association between circulating miRNA-30a levels and therapeutic effect in patients with GC treated with NAC, and to investigate whether miRNA-30a expression may further help stratify patients according to treatment-related patterns and clinical outcome.

Materials and methods

Patients and sample collection. A cohort of 67 patients with histologically confirmed GC was enrolled in the study between March 2022 and September 2023. Clinical data, including age and sex, were retrieved from hospital records. The median age of the patients was 67.0 years (IQR, 57.0-73.5 years), with a male-to-female ratio of 6:1. In 42 patients, blood samples were obtained following completion of NAC and prior to surgical resection. In the remaining 25 patients, samples were collected prior to surgery in the absence of NAC; these patients served as a treatment-naive (CT-naive) control group. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments, and was approved by the Research and Ethics Committee of Aretaieio Hospital, National and Kapodistrian University of Athens (approval no. 415/21-02-2022). Written informed consent was obtained from all participants.

Pre-operative chemotherapy and clinicopathological characteristics. Neoadjuvant chemotherapy with the FLOT regimen (5-fluorouracil, oxaliplatin, leucovorin, and docetaxel) was administered as the predominant treatment approach. Patients received four cycles of FLOT every two weeks prior to surgery, followed by gastrectomy within 4-6 weeks after completion. Pathological evaluation was performed by experienced pathologists. Tumors were staged according to the American Joint Committee on Cancer (AJCC) Staging Manual, 8th edition, with yTNM classification (13), and histological subtype was determined according to the Lauren classification. Histopathological tumor regression grade (TRG) of the primary tumor after therapy was assessed according to Mandards' system.

Patients were categorized into Responders (defined as TRG 0-2) and Non-responders (defined as TRG 3-5). Pathological tumor depth was categorized as Tx, T1-T2, or T3-T4, with Tx indicating absence of residual primary tumor. Nodal burden was categorized into low (N0) and high (N1-N3). All grouping strategies were selected to allow meaningful comparisons within the context of the limited cohort size. Patient and disease characteristics, along with associations between categorical variables, are summarized in Table I.

Blood sample preparation and Quantitative reverse transcription-polymerase chain reaction (RT-qPCR). Peripheral venous blood samples were collected using vacutainer tubes and processed immediately after collection to minimize the risk of hemolysis. Samples were centrifuged at 1,300 x g for 15 min, and then serum was aliquoted and stored at -80˚C until further analysis.

Total RNA extraction from 100 μl of serum samples was carried out with magnetic bead technology using the MagMAX™ mirVana™ Total RNA Isolation Kit (cat. # A27828; Thermo Fisher Scientific, USA) following the manufacturer's protocol. Synthetic cel-miR-39 was spiked at 10fmol concentration prior to extraction in each serum sample and served as an internal spike-in control. Total RNA was eluted in 50 μl RNase-free water.

Reverse transcription (RT) reaction was prepared according to the instructions of the TaqMan™ Advanced miRNA cDNA Synthesis Kit (cat. # A28007; Thermo Fisher Scientific, USA). Quantitative reverse-transcription polymerase chain reaction (RT-qPCR) was performed using the TaqMan™ Fast Advanced Master Mix (cat. # 4444557; Thermo Fisher Scientific, USA) followed by amplification with TaqMan™ Advanced microRNA assays (cat. # A25576; Thermo Fisher Scientific, USA) specific for miRNA-30a and cel-miR-39 (Table SI) on the StepOnePlus™ Real-Time qPCR System (Applied Biosystems, USA). The qRT-PCR reaction was performed as follows: 95˚C for 20 sec, then 40 cycles of 95˚C for 1 sec, and 60˚C for 20 sec.

Each assay was performed with two identical replicates, and a no-template control was included to assess the possibility of reaction contamination. Inter-assay variability was also assessed across independent runs to confirm consistency and reproducibility. Relative miRNA expression levels of interest were calculated using the $2^{-\Delta\Delta Cq}$ method (14).

Statistical analysis. Statistical analysis was performed using SPSS software (version 28.0; SPSS, Chicago, IL, USA) and GraphPad Prism (version 9.5.1; GraphPad Software, San Diego, CA, USA) was employed for visualization and generation of all graphical representations. Numerical variables were expressed as median and range as appropriate. Categorical variables were expressed as absolute frequencies and percentages.

Kolmogorov-Smirnov test was used to analyze the distribution of miRNA expression levels. Differences in miRNA expression between groups were evaluated using Mann-Whitney U test for two-group comparisons and Kruskal-Wallis test for comparisons involving more than two groups, followed by Dunn's post hoc test for multiple comparisons with Bonferroni correction. Associations between categorical variables were assessed with Fisher's exact test and comparisons of continuous variables and miRNA expression were assessed using Spearman's rank correlation coefficient. MiRNA discrimination potential was analyzed by computing receiver operating characteristic (ROC) curves and calculating areas under the curves (AUC) with corresponding 95% confidence intervals (CI), as well as the optimal specificity and sensitivity values. Overall survival (OS) and disease-free survival (DFS) were analyzed using the Kaplan-Meier method, and differences between groups were assessed with log-rank (Mantel-Cox) test. Univariate Cox proportional hazards regression analyses were additionally performed to estimate hazard ratios (HRs) and 95% confidence intervals for survival outcomes. Statistical significance was assumed at $P < 0.05$ (two-sided) for all analyses.

Table I. Baseline clinicopathological characteristics.

Variable	Responders TRG 0-2 (n=14)	Non-responders TRG 3-5 (n=28)	P-value
Sex, n (%)			
Male	14 (100.0)	22 (78.6)	0.083[a]
Female	0 (0.0)	6 (21.4)	
Tumor location, n (%)			
Stomach	5 (35.7)	12 (42.9)	0.747[a]
Gastroesophageal junction	9 (64.3)	16 (57.1)	
Lauren classification, n (%)			
Intestinal	2 (14.3)	10 (35.7)	<0.001[a]
Diffuse	2 (14.3)	13 (46.4)	
Mixed	3 (21.4)	5 (17.9)	
Other	7 (50.0)	0 (0.0)	
Tumor differentiation, n (%)			
Poor	3 (21.4)	20 (71.4)	<0.001[a]
Moderate	4 (28.6)	7 (25.0)	
Well	0 (0.0)	1 (3.6)	
No residual tumor	7 (50.0)	0 (0.0)	
T stage, n (%)			
Tx	7 (50.0)	1 (3.6)	<0.001[a]
T1–T2	6 (42.9)	7 (25.0)	
T3–T4	1 (7.1)	20 (71.4)	
N stage, n (%)			
N0	10 (71.4%)	9 (32.1%)	0.023[a]
N1-N3	4 (28.6%)	19 (67.9%)	
Age, years			
Median (IQR)	67 (58-74)	66 (57-73)	0.811[b]

Data are presented as n (%) for categorical variables and median (IQR) for continuous variables. [a]Fisher's exact test; [b]Mann-Whitney U test. IQR, interquartile range.

Results

Patients. A total of 67 patients with GC were included in the study, comprising NAC-treated patients (n=42, 62.7%) and patients who did not receive therapy (CT-naive) (n=25, 37.3%), who served as a treatment-naive reference group. Among NAC-treated patients, treatment response was assessed based on histopathological tumor regression grade (TRG), and patients were classified as Responders (TRG 0-2; n=14, 33.3%) or Non-responders (TRG 3-5; n=28, 66.7%).

Pathological tumor depth was classified as Tx in 8 patients (19.0%), T1-T2 in 13 patients (31.0%), and T3-T4 in 21 patients (50.0%). Low nodal burden was observed in 19 patients (45.2%), while high nodal burden was present in 23 patients (54.8%). Median follow-up was 24 months after completion of treatment.

Association of circulating miRNA-30a expression with treatment outcome and disease status. Circulating miRNA-30a was assessed following completion of NAC, reflecting post-treatment expression levels. No difference was observed between NAC-treated patients and CT-naive control group (Fig. S1). Stratification of NAC-treated patients according to treatment outcome revealed significant differences in circulating miRNA-30a levels (P<0.001), with Responders exhibiting higher levels compared to Non-responders (P<0.001) (Fig. 1). Notably, circulating miRNA-30a levels in patients without therapeutic effect were similar to those observed in patients who did not receive therapy, whereas Responders displayed comparatively higher expression levels, supporting the differentiation between treatment-responsive and non-responsive disease states.

Consistent associations were observed with pathological tumor burden, as higher miRNA-30a levels were detected in patients with lower pathological T stage (Tx vs. T1-T2 vs. T3-T4; P<0.001), showing a stepwise decrease across increasing tumor stage categories (Fig. 2A), and in patients without nodal involvement (N0 vs. N1-N3; P=0.004) (Fig. 2B). No associations were identified between miRNA-30a expression and other clinical and pathological variables, including age, sex, tumor location, Lauren classification, or differentiation status (Table SII).

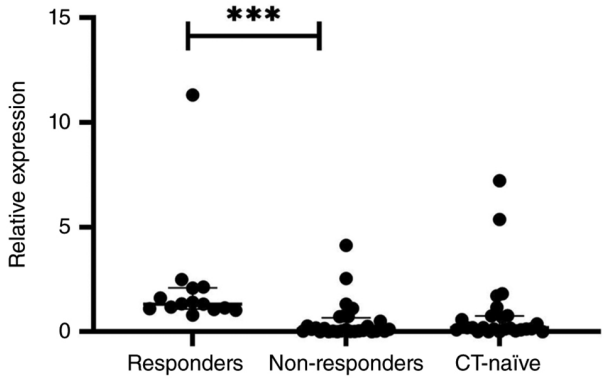

Figure 1. Circulating miRNA-30a expression according to treatment outcome. Relative expression levels of circulating miRNA-30a in responders (n=14), non-responders (n=28) and CT-naive patients (n=25). Each dot represents an individual patient. Horizontal lines indicate median values. ***P<0.001. miRNA, microRNA.

Association of circulating miRNA-30a with therapeutic outcome. In univariate logistic regression analysis, higher miRNA-30a expression was associated with therapeutic outcome, with increased miRNA-30a corresponding to a reduced probability of non-response (OR=0.239, 95% CI: 0.084-0.685, P=0.008).

In multivariable models adjusting for T-stage and N-stage, miRNA-30a remained associated with therapeutic outcome (adjusted OR=0.174, 95% CI: 0.030-0.995, P=0.049 and OR=0.302, 95% CI: 0.107-0.849, P=0.023, respectively), whereas pathological parameters were not significant predictors. (Table SIII).

Discriminative performance of circulating miRNA-30a for therapeutic outcome. ROC curve analysis demonstrated that circulating miRNA-30a levels were able to distinguish Responders from Non-responders. The area under the curve (AUC) was 0.91 (95% CI: 0.81-1.00, P<0.001), indicating good discriminatory performance. The optimal cut-off value was calculated using the Youden index (0.914) and was used to stratify patients into high and low expression groups for exploratory survival analysis (Fig. 3).

Association of circulating miRNA-30a expression with overall and disease-free survival. Kaplan-Meier analysis using the ROC-derived cut-off showed that patients with higher circulating miRNA-30a expression had longer overall survival compared to those with lower expression (P=0.033) (Fig. 4). No difference in disease-free survival was observed between the two groups (P=0.200) (Fig. S2). Cox regression analysis revealed similar findings, with higher miRNA-30a levels associated with a reduced risk of death (HR=0.283, 95% CI: 0.081-0.985, P=0.047).

Discussion

In the NAC setting, variability in therapeutic outcome remains a major clinical challenge in GC, highlighting the need for improved post-operative patient stratification. While response to therapy provides important information, it may not fully reflect disease behavior after treatment. Accordingly, therapeutic effect is a multifactorial process that extends beyond tumor-intrinsic characteristics, including systemic factors such as circulating mediators and inflammatory and signaling pathways that may influence both tumor progression and response to therapy (15). Emerging evidence further suggests that tumors actively interact with and modulate systemic homeostasis through neuroendocrine and immune signaling networks, thereby influencing host physiology in ways that may support tumor adaptation and progression (16).

MiRNAs have been implicated in the regulation of these processes and may contribute to the dynamic interplay between tumor biology and systemic circulation. In this setting, expression patterns of circulating miRNAs are closely linked to therapeutic intervention. Patterns observed in untreated disease primarily reflect intrinsic tumor biology, whereas profiles evaluated following therapeutic exposure may provide insight into disease characteristics that persist or emerge after treatment. Such expression signatures may capture therapy-associated differences that are not fully represented by imaging or pathological assessment alone (17-19), thereby offering additional information relevant to post-treatment stratification and patient management. In this framework, differences in circulating miRNA-30a expression between responders and non-responders observed in the present study, indicate an association with therapeutic outcome reflecting post-treatment, response-associated expression patterns rather than predictive capacity.

Across malignancies, miRNA-30a is generally described as a tumor-suppressive regulator, although its molecular mechanisms are not yet fully understood. Studies indicate that reduced miRNA-30a expression is associated with enhanced proliferation (20-22), invasion (23-28), and epithelial-mesenchymal transition (EMT) (29-31), while restoration of expression suppresses oncogenic signaling pathways and limits tumor progression. In GC, miRNA-30a has been shown to inhibit proliferation and cell-cycle progression through targets such as MAD2L1 (32) and FAPα (33), supporting its role in maintaining a less aggressive tumor phenotype.

Consistent with this background, our findings indicate that higher circulating miRNA-30a levels are linked to improved therapeutic outcome. Patients with increased miRNA-30a were more likely to derive clinical benefit from treatment and exhibited reduced disease burden, including lower pathological T stage and absence of nodal involvement. In parallel, higher miRNA-30a levels were also observed among patients with longer overall survival following NAC, suggesting an improved outcome. A notable difference in expression patterns was detected between responders and non-responders, with patients who benefited from therapy exhibiting a distinct profile, whereas those who did not, showed expression levels comparable to CT-naive patients, suggesting that, in the absence of therapeutic effect, post-treatment expression patterns may resemble those observed in untreated disease. These observations are consistent with previous reports linking miRNA-30a downregulation to tumor progression and metastatic potential (34), as well as with studies in other malignancies where reduced miRNA-30a expression has been associated with poorer pathological response and less favorable outcomes, including triple-negative breast cancer treated with neoadjuvant anthracycline- and taxane-based

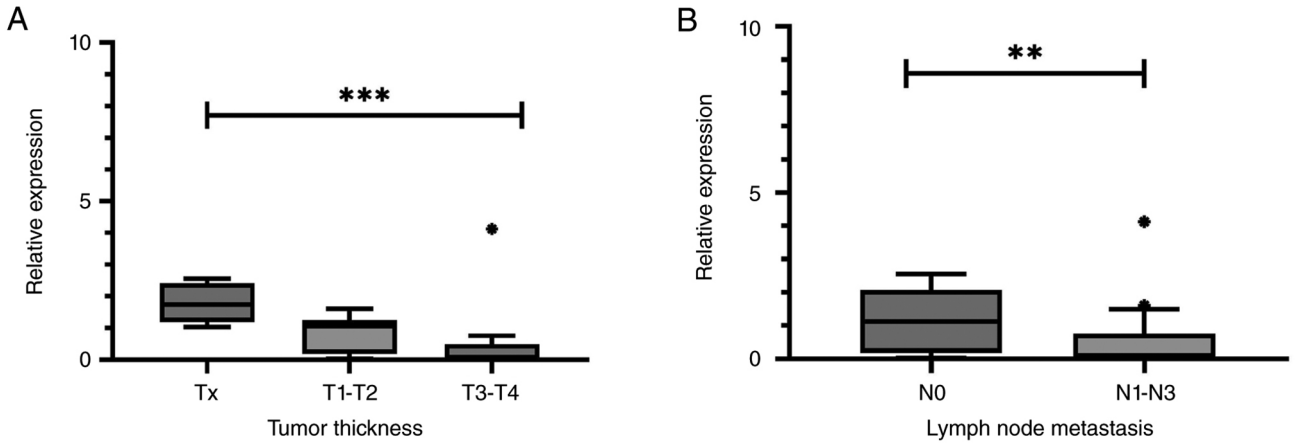

Figure 2. Association of circulating miRNA-30a expression with disease status. (A) Relative expression of circulating miRNA-30a according to pathological T stage. Statistical comparisons were performed between Tx (n=8), T1-T2 (n=13) and T3-T4 (n=21). (B) Relative expression of circulating miRNA-30a according to lymph node status. Statistical comparison was performed between N0 (n=19) and N1-N3 (n=23). Boxes represent the interquartile range, horizontal lines indicate median values, whiskers denote data dispersion and points represent outliers. **P=0.004; ***P=0.0003. miRNA, microRNA.

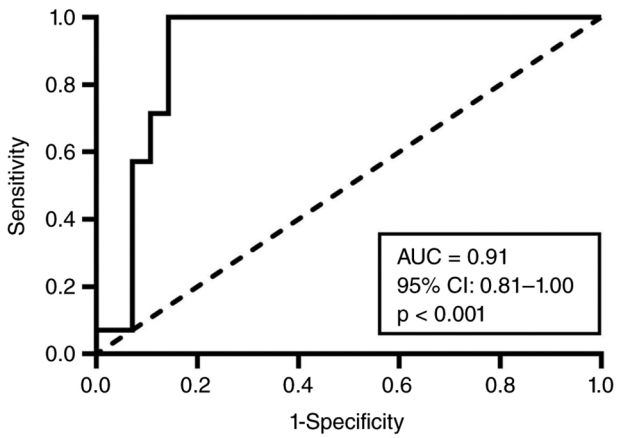

Figure 3. ROC curve analysis of circulating miRNA-30a for discrimination of treatment response. ROC curve illustrating the ability of circulating miRNA-30a expression to discriminate between responders (n=14) and non-responders (n=28). The solid line represents the performance of miRNA-30a, while the dashed diagonal line indicates the line of no discrimination (AUC=0.5). The AUC was 0.91 (95% CI, 0.81-1.00; P<0.001). AUC, area under the curve; CI, confidence interval; ROC, Receiver operating characteristic; miRNA, microRNA.

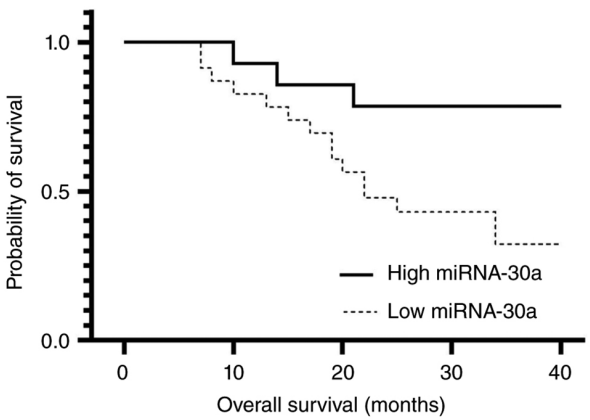

Figure 4. Kaplan-Meier overall survival analysis according to circulating miRNA-30a expression. Kaplan-Meier curves showing overall survival stratified by circulating miRNA-30a expression (high vs. low; n=42). The solid line represents patients with high miRNA-30a expression, while the dashed line represents patients with low expression. Statistical significance was P=0.033. miRNA, microRNA.

regimens (35-37). Evidence also suggests that restoration of miRNA-30a enhances sensitivity to platinum-based agents through suppression of epithelial-mesenchymal transition (EMT) and modulation of autophagy-related pathways, both implicated in chemoresistance (38,39). In addition, preclinical studies demonstrating reduced proliferation and invasive capacity following miRNA-30a upregulation further support the association between elevated levels and less aggressive disease features observed in our cohort (25,34).

Recent epidemiological evidence indicates that survival outcomes in GC have improved over time, particularly in patients with earlier-stage disease, largely reflecting advances in multimodal treatment approaches, including NAC. Population-based data indicate marked stage-dependent differences in survival, with reported 5-year relative survival rates of 77.7% for localized disease, 37.4% for regional disease, and 10.2% for distant-stage GC. Nevertheless, variability in clinical outcomes persists, especially among patients with more advanced disease stages, highlighting the significant variability in disease behavior even within stage-defined groups (40-42). In this context, circulating miRNA-30a, considered alongside survival outcomes and treatment efficacy, may provide additional insight into post-treatment disease behavior and support a more comprehensive assessment beyond conventional methods. Rather than directly reflecting population-level survival trends, it may capture inter-individual differences in treatment-associated disease dynamics that are not fully accounted for by standard clinicopathological parameters.

An important limitation of this observational study is that no causal or mechanistic conclusions can be drawn, and the observed associations should be interpreted in the context of complex tumor-host systemic interactions that require further functional investigation (16). In addition, the relatively small cohort size may restrict the detection of more subtle expression differences, and some of the observed findings may be influenced by the imbalance in subgroup sizes. Therefore,

the findings of multivariable and survival analyses should be considered exploratory and interpreted with caution, particularly given the limited number of events and subgroup sizes. Larger prospective studies including all treatment phases and extended follow-up are needed to clarify expression changes of miRNA-30a and determine whether monitoring may improve clinical evaluation and relapse prediction. The clinical relevance of such approaches is underscored by ongoing efforts such as the ENLIGHT trial (NCT07243015), which aims to develop and validate miRNA-based liquid biopsy signatures for minimal residual disease detection in GC (43).

Overall, several key findings with biological relevance and clinical potential were identified. Circulating miRNA-30a expression is linked to therapeutic outcome and appears to reflect treatment benefit in patients with GC treated with NAC. Its application alongside conventional assessment strategies may contribute to improved post-treatment disease monitoring and patient stratification, subject to further validation in larger prospective studies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

VKD and MMK were involved in the conception and design of the study. VKD, AM and AT provided administrative support, were responsible for sample and data collection, and performed experiments. VKD, MMK and PTA were involved in the provision of study materials and patient enrollment. VKD, AV and PTA performed data analysis and interpretation. All authors contributed to manuscript writing. All authors critically revised the manuscript, commented on previous versions, and read and approved the final manuscript. VKD, MMK and PTA confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study was approved by the Research and Ethics Committee of Aretaieio Hospital, National and Kapodistrian University of Athens (approval no. 415/21-02-2022). Written informed consent was obtained from all participants prior to inclusion in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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