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Preoperative Aspartate Aminotransferase-to-Lymphocyte Ratio as an Independent Prognostic Biomarker in Patients Undergoing Curative Resection for Gastric Cancer

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ABSTRACT

Background

Systemic inflammation is increasingly recognized as a key determinant of tumor progression and survival in gastric cancer. The aspartate aminotransferase-to-lymphocyte ratio (AALR) has recently emerged as a novel inflammation-based biomarker. This study aimed to investigate the association between preoperative AALR and clinicopathological characteristics and to evaluate its prognostic significance in patients with gastric cancer undergoing curative resection.

Methods

In this retrospective cohort study, 126 patients with stage I–III gastric adenocarcinoma who underwent curative surgery were included. Preoperative AALR was calculated using routine laboratory parameters. Patients were stratified into low and high AALR groups according to an optimal cut-off value of 9.09. Associations between AALR and clinicopathological variables were analyzed using the chi-square test and Student's t-test, as appropriate. Overall survival (OS) was assessed using the Kaplan–Meier method and compared with the log-rank test. Prognostic factors were evaluated using univariate and multivariate Cox proportional hazards regression analyses.

Results

Elevated AALR was significantly associated with unfavorable clinicopathological characteristics. Kaplan–Meier survival analysis demonstrated that patients with AALR ≥ 9.09 had significantly poorer overall survival compared to those with AALR < 9.09 (median OS: 15 vs. 42 months, respectively). The survival difference between the groups was statistically significant (log-rank $\chi^2=8.14$, $p=0.004$). In univariate Cox analysis, AALR was significantly

associated with overall survival. Multivariate analysis identified high AALR (HR: 1.08; 95% CI: 1.01–1.15; $p=0.033$) and perineural invasion as independent poor prognostic factors.

Conclusions

AALR is an inexpensive, readily available, and independent prognostic biomarker in gastric cancer. Elevated AALR is associated with aggressive tumor characteristics and significantly worse survival outcomes. Incorporating AALR into routine clinical assessment may improve risk stratification and prognostic evaluation in patients with gastric cancer.

Keywords: Gastric cancer; Aspartate aminotransferase-to-lymphocyte ratio; Systemic inflammation; Prognosis; Overall survival

HIGHLIGHTS

- Elevated AALR is significantly associated with worse overall survival in gastric cancer.
- High AALR correlates with adverse clinicopathological characteristics.
- AALR is an independent prognostic factor in multivariable Cox regression analysis.
- AALR is an inexpensive and readily available biomarker derived from routine laboratory tests.
- Incorporating AALR may improve risk stratification in patients with gastric cancer.

INTRODUCTION

Gastric cancer remains one of the leading causes of cancer-related mortality worldwide despite substantial advances in diagnostic modalities, perioperative chemotherapy, and multimodal treatment strategies [1]. Although tumor stage represents the cornerstone of prognostic assessment, marked heterogeneity in survival outcomes persists among patients with comparable clinicopathological characteristics. This variability highlights the biological complexity of gastric cancer and underscores the need for reliable, easily accessible prognostic biomarkers that can complement conventional staging systems [2].

Growing evidence indicates that chronic systemic inflammation is a critical driver of carcinogenesis, tumor progression, and metastatic dissemination. The tumor microenvironment is shaped by a complex interplay between cancer cells, stromal components, immune cells, and inflammatory mediators. Pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and other signaling molecules activate pathways including STAT3 and NF- κ B, which promote tumor proliferation, angiogenesis, epithelial–mesenchymal transition, and resistance to apoptosis. Moreover, sustained inflammatory signaling contributes to immune evasion by suppressing cytotoxic T-cell activity and facilitating the expansion of regulatory immune subsets [3].

Given this biological background, systemic inflammatory markers derived from routine laboratory tests have attracted considerable interest as surrogate indicators of tumor-related inflammation and host immune status. Indices such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have demonstrated prognostic value in gastric cancer and are increasingly recognized as inexpensive and reproducible tools for risk stratification [4,5]. However, no single biomarker has yet achieved universal acceptance, and further refinement of inflammation-based prognostic indices remains warranted.

Lymphocytes constitute a central component of antitumor immunity. Tumor-infiltrating lymphocytes, particularly CD8⁺ cytotoxic T cells, play a pivotal role in tumor control and are associated with improved oncologic outcomes. Peripheral lymphopenia, however, reflects impaired host immune competence and has consistently been linked to poor survival across multiple malignancies [6].

Aspartate aminotransferase (AST) is a widely available biochemical enzyme that reflects hepatocellular injury, systemic metabolic stress, and inflammatory burden. Beyond its traditional role as a liver function marker, elevated AST levels may indicate increased tumor-associated metabolic activity and systemic catabolic status. Cancer-related cachexia, tissue hypoxia, and micro-metastatic liver involvement may contribute to increased AST levels, even in the absence of overt hepatic disease[7].

The aspartate aminotransferase-to-lymphocyte ratio (AALR) integrates these two biologically meaningful parameters into a composite index that may simultaneously capture systemic inflammation, metabolic stress, and compromised immune surveillance. By combining a marker of systemic tissue injury with an indicator of immune capacity, AALR may provide a

more comprehensive representation of tumor–host interaction than isolated laboratory parameters[8].

Recent studies have suggested that elevated AALR is associated with adverse outcomes in various malignancies. A meta-analysis demonstrated that high AALR predicts poorer survival in patients with hepatocellular carcinoma (HCC) and is strongly correlated with aggressive tumor characteristics such as vascular invasion and advanced stage [7,8]. Similarly, Chen et al. [8] reported that preoperative AALR is a simple, noninvasive, and effective prognostic indicator in HCC. Nevertheless, data regarding the prognostic significance of AALR in gastric cancer remain limited, and existing studies have yielded inconsistent results [9,10].

Importantly, the potential association between AALR and adverse histopathological features—such as tumor aggressiveness, perineural invasion, lymphovascular invasion, and nodal involvement—has not been comprehensively investigated in gastric cancer. Clarifying whether AALR correlates with unfavorable pathological characteristics and whether it provides independent prognostic information beyond established clinicopathological factors is essential before its incorporation into routine clinical practice.

Given the biological plausibility linking systemic inflammation and impaired immunity to tumor progression, and considering the limited evidence in gastric cancer, we hypothesized that elevated preoperative AALR would be associated with more aggressive clinicopathological features and poorer overall survival in patients undergoing curative resection for stage I–III gastric adenocarcinoma.

Accordingly, the present study aimed to (1) evaluate the relationship between preoperative AALR and clinicopathological characteristics, (2) assess its impact on overall survival, and (3) determine whether AALR serves as an independent prognostic factor in multivariable analysis.

MATERIALS AND METHODS

Ethical Approval

Ethical approval was obtained from the Tekirdağ Namık Kemal University Ethics Committee (Protocol No: 2025.23.02.01). Due to the retrospective nature of the study, individual informed consent was not required for participation. However, written informed consent was obtained from all patients for the use of anonymized surgical images and video recordings.

Study Design and Patient Selection

In this retrospective study, patients who underwent curative surgery for stage I–III gastric cancer between January 2019 and December 2024 at Tekirdağ Namık Kemal University Faculty of Medicine were reviewed. A total of 186 medical records were screened.

Patients with histopathologically confirmed stage I–III gastric adenocarcinoma and available preoperative laboratory and clinicopathological data were included in the study. Patients with stage IV disease, active infection, chronic inflammatory disease, hematological disorders, liver cirrhosis, or incomplete clinical and pathological data were excluded from the analysis.

A total of 126 patients who met the inclusion criteria were enrolled. Clinical, pathological, and biochemical data—including age, sex, tumor stage, lymph node status, histological grade, perineural invasion, lymphovascular invasion, and tumor type—were obtained from medical records and pathology reports and recorded for analysis.

Patients were subsequently divided into two groups according to high and low AALR values and compared in terms of the aforementioned parameters (Figure 1).

Laboratory Parameters and Calculation of AALR

Blood samples were obtained within one week prior to surgery. AST levels and lymphocyte counts were derived from routine laboratory tests. The aspartate aminotransferase-to-lymphocyte ratio (AALR) was calculated by dividing the AST value by the absolute lymphocyte count.

Since most laboratory and inflammatory parameters showed normal distribution and no established cut-off value for AALR exists, patients were initially evaluated according to the mean AST/LYM value. The optimal cut-off value for AALR was determined as 9.09, and patients were categorized into low (<9.09) and high (≥ 9.09) AALR groups accordingly. The

mean AALR value was used as the cut-off for group classification, while ROC analysis was conducted as a complementary method to assess predictive performance.

Follow-up

Postoperative follow-up included physical examination, blood tests including tumor markers, and imaging studies (chest, abdominal, and pelvic CT or MRI). These assessments were performed every 3 months during the first two years after surgery and every 6 months thereafter up to 5 years. Upper gastrointestinal endoscopy was performed annually. The mean follow-up duration was 34.2 months.

The primary endpoint of this study was overall survival (OS). OS was defined as the time from the date of surgery to death from any cause. Progression-free survival (PFS) was not included due to the limited number of patients with recurrence.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation (SD), as appropriate. Categorical variables were presented as numbers and percentages. Comparisons between AALR groups were performed using Student's t-test or the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables.

Overall survival was defined as the time from surgery to death or last follow-up. Survival curves were generated using the Kaplan–Meier method and compared using the log-rank (Mantel–Cox) test. Prognostic factors associated with survival were evaluated using univariate and multivariate Cox proportional hazards regression analyses. Variables with $p < 0.10$ in the univariate analysis were included in the multivariate model. Results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). A p -value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 18.0 for Windows (IBM SPSS Inc., USA).

RESULTS

Patient Characteristics

A total of 126 patients who met the inclusion criteria were analyzed. The baseline clinicopathological characteristics of the study population are summarized in Table 1. Patients were divided into low and high AALR groups based on the cut-off value of 9.09.

Among the 126 patients included in the study, 79 (62.7%) were male and 47 (37.3%) were female. There were 15 (11.9%) patients with stage I disease, 41 (32.5%) with stage II, and 70 (55.6%) with stage III. The mean age was 62.7 years (± 11.9). The mean tumor size was 5.91 ± 2.65 cm.

Perineural invasion was present in 70 patients (55.6%), and lymphovascular invasion was observed in 94 patients (74.6%). There were 62 patients (49.2%) in the high AALR group (≥ 9.09) and 64 patients (50.8%) in the low AALR group (< 9.09).

During the follow-up period, 83 patients died. Patients with high AALR had a higher mortality rate compared to those with low AALR (39.6% vs. 26.1%, $p < 0.001$) (Table 1).

Survival Analysis

Kaplan–Meier survival analysis demonstrated a significant difference in overall survival between the two groups. Patients with AALR ≥ 9.09 had significantly poorer overall survival compared to those with AALR < 9.09 (median survival: 15 vs. 42 months, respectively).

The mean survival time was 38.6 months in the high AALR group and 28.3 months in the low AALR group. The difference between survival curves was statistically significant according to the log-rank test ($\chi^2 = 8.14$, $p = 0.004$) (Figure 2).

Univariate and Multivariate Cox Regression Analyses

Univariate Cox regression analysis identified AALR, tumor stage, lymph node status, TNM stage, and perineural invasion as factors significantly associated with overall survival. Variables with $p < 0.10$ in the univariate analysis were included in the multivariate Cox regression model.

In multivariate analysis, high AALR remained an independent prognostic factor associated with increased risk of death (HR: 1.08, 95% CI: 1.01–1.15, $p = 0.033$). Perineural invasion was also identified as an independent adverse prognostic factor. Other clinicopathological variables did not retain statistical significance in the multivariate model (Figure 3), (Table 2).

ROC Curve Analysis

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive performance of AALR for overall mortality. The area under the curve (AUC) was 0.677 (95% CI: 0.582–0.772, $p=0.001$), indicating a moderate discriminative ability of AALR for predicting mortality in patients with gastric cancer (Figure 4).

DISCUSSION

In the present study, we demonstrated that the aspartate aminotransferase-to-lymphocyte ratio (AALR) is a significant prognostic biomarker in patients with gastric cancer. Elevated AALR may reflect increased systemic inflammation and impaired immune response.

The role of systemic inflammation in tumor progression and adverse oncological outcomes is increasingly recognized [6,11,12]. Inflammatory mediators enhance angiogenesis, promote tumor cell proliferation, and suppress antitumor immune responses[13,14]. In this context, inflammation-based biomarkers derived from routine laboratory tests have gained considerable attention in recent years due to their simplicity and clinical applicability. Although indices such as the neutrophil-to-lymphocyte ratio have been extensively investigated in gastric cancer, data regarding AALR remain limited[15,16,17].

Aspartate aminotransferase is not only a marker of hepatocellular injury but also reflects systemic metabolic stress and inflammatory burden[17,18]. Lymphocytes constitute a fundamental component of antitumor immunity, and lymphopenia has been associated with impaired immune surveillance and poor survival outcomes. By integrating these two biologically meaningful parameters, AALR provides a composite index that reflects both systemic inflammation and immune dysfunction. The findings of this study support the hypothesis that elevated AALR represents an unfavorable biological tumor microenvironment.[18,19]

In our cohort, high AALR was significantly associated with adverse clinicopathological features. Furthermore, Kaplan–Meier survival analysis revealed a clear separation between

survival curves of low and high AALR groups, with significantly shorter median survival observed in patients with elevated AALR. The difference demonstrated by the log-rank test was further confirmed by Cox regression analyses. Importantly, the persistence of AALR as an independent prognostic factor in multivariate analysis indicates that its prognostic value is not merely a reflection of tumor stage or other pathological variables. Similar associations between inflammation-based indices and poor survival have been reported in gastric cancer [15,20]

Perineural invasion was also identified as an independent adverse prognostic factor in this study, consistent with previous reports demonstrating its association with aggressive tumor behavior and poor survival in gastric cancer[21,22]. The coexistence of elevated AALR and perineural invasion may define a subgroup of patients with particularly aggressive tumor biology. Such patients may benefit from closer surveillance strategies or more intensive adjuvant treatment approaches.

From a clinical perspective, AALR offers several practical advantages. It can be easily obtained from routine preoperative blood tests, is cost-effective, and is simple to calculate. Therefore, it can be readily integrated into daily clinical practice without additional costs or advanced diagnostic procedures[23,24,25,28]. The contribution of AALR to survival-based risk stratification makes it a complementary tool to conventional staging systems. Furthermore, given the increasing importance of tumor-immune interactions in therapeutic decision-making, inflammation-related biomarkers may contribute to more individualized treatment approaches [26,27,29,30].

However, this study has certain limitations. The retrospective and single-center design may introduce selection bias. Dynamic changes in AALR during the treatment course were not evaluated. Therefore, prospective and multicenter studies are warranted to validate these findings and to explore treatment strategies guided by AALR-based risk stratification. The optimal cut-off value for AALR was determined based on the distribution characteristics of our cohort, as no universally accepted threshold has been established in the literature. Although different studies have used varying cut-off values, the absence of a standardized definition reflects the emerging nature of this biomarker. Future large-scale prospective studies using time-dependent ROC analysis may help establish an evidence-based universal threshold for clinical use.

In conclusion, this study demonstrates that elevated AALR is independently associated with poorer survival in gastric cancer. AALR may serve as a simple, inexpensive, and clinically applicable biomarker for risk stratification and prognostic assessment in patients with gastric cancer.

DECLARATIONS

Previous Communications

This manuscript has not been previously presented at any local or international scientific meeting and has not been submitted elsewhere for publication.

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Availability of Data and Materials

The corresponding author will provide additional information regarding the data presented in this study upon reasonable request.

Financial Support and Sponsorship

None.

Conflicts of Interest

The authors declare no conflicts of interest.

Clinical trial number: not applicable.

Authors' Contributions

Conceptualization: Suat Benek, Kasım Caglayan

Data Curation: Suat Benek, Birol Topçu, Hadi Sasani

Investigation: Suat Benek, Kasım Caglayan, Hadi Sasani, Birol Topçu

Methodology: Suat Benek, Kasım Caglayan

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Table 1. Relationship between AALR and clinicopathological characteristics

Variable	Category	Overall (n=126)	Low AALR n (%)	High AALR n (%)	p value
Gender	Male	79 (62.7)	41 (32.5)	38 (30.1)	p = 0.581
Age	<70	85 (67.39)	48 (38.09)	37 (29.3)	p = 0.036
	≥70	41 (32.61)	15 (11.9)	26 (20.6)	
Lauren type	Intestinal	60 (47.6)	27 (21.42)	33 (26.19)	p = 0.247
	Diffuse	66 (52.4)	37 (29.36)	29 (23.01)	
T stage	T1	12 (9.5)	6 (4.5)	6 (4.5)	p = 0.286
	T2	17 (13.5)	8 (6.3)	9 (7.1)	
	T3	52 (41.3)	31 (24.6)	21 (16.6)	
	T4	45 (35.7)	18 (14.2)	27 (21.4)	
N stage	N0	30 (23.8)	19 (15.07)	11 (11.9)	p = 0.063
	N1	22 (17.5)	14 (11.1)	8 (6.3)	
	N2	27 (21.4)	9 (7.1)	18 (14.2)	
	N3	47 (37.3)	21 (16.6)	26 (20.6)	
Histopathological grade	Grade 1	11 (8.7)	4 (3.1)	7 (5.5)	p = 0.588
	Grade 2	37 (29.4)	20 (15.8)	17 (13.4)	
	Grade 3	78 (61.9)	39 (30.9)	39 (30.9)	
Perineural invasion (P)	Yes	70 (55.6)	35 (27.7)	35 (27.7)	p = 1.000
Lymphovascular invasion	Yes	94 (74.6)	44 (34.9)	50 (39.6)	p = 0.219
Recurrence	Yes	11 (8.73)	3 (2.30)	8 (6.30)	p = 0.115
Death	Yes	83 (65.9)	33 (26.1)	50 (39.6)	p < 0.001
Tumor location	Esophagogastric	25 (19.8)	14 (11.1)	11 (11.9)	p = 0.617
	Corpus	54 (42.9)	28 (22.2)	26 (20.6)	
	Antrum	47 (37.3)	21 (16.6)	26 (20.6)	
Blood group	Type A	67 (53.1)	31 (24.6)	36 (28.5)	p = 0.245
	Type B	21 (16.6)	14 (11.1)	7 (5.5)	
	Type O	38 (30.1)	18 (14.2)	20 (15.8)	
TNM stage	Stage I	15 (11.9)	10 (7.9)	5 (3.9)	p = 0.247
	Stage II	41 (32.5)	22 (17.4)	19 (15.07)	
	Stage III	70 (55.6)	31 (24.6)	39 (30.9)	
Neoadjuvant CRT	Yes	28 (22.2)	12 (9.5)	16 (12.6)	p = 0.391
Continuous variables					
Variable	Overall	Low AALR	High AALR	p value	
Age (years)	62.7 ± 11.9	61.3 ± 11.2	64.1 ± 12.4	p = 0.192	
Overall survival (months)	34.2 ± 28.5	38.5 ± 30.9	28.3 ± 26.6	p = 0.048	
Tumor size (cm)	5.91 ± 2.65	5.37 ± 2.46	6.10 ± 2.84	p = 0.438	

Table 2. Univariate and multivariate Cox regression analysis for overall survival

Variable	Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value
Age	1.018 (0.998–1.038)	p = 0.077	1.009 (0.978–1.040)	p = 0.593
T2 vs T1	0.468 (0.207–1.060)	p = 0.069	0.296 (0.028–3.104)	p = 0.310
T3 vs T1	0.338 (0.149–0.769)	p = 0.010	0.523 (0.085–3.211)	p = 0.484
T4 vs T1	0.617 (0.383–0.996)	p = 0.048	0.826 (0.369–1.846)	p = 0.641
N1 vs N0	0.325 (0.173–0.614)	p = 0.001	0.072 (0.006–0.864)	p = 0.038
N2 vs N0	0.429 (0.224–0.822)	p = 0.011	0.214 (0.052–0.872)	p = 0.031
N3 vs N0	0.568 (0.321–1.005)	p = 0.052	0.325 (0.127–0.834)	p = 0.019
Histopathological grade	0.718 (0.309–1.670)	p = 0.443	0.393 (0.083–1.866)	p = 0.198
Histopathological grade	0.695 (0.423–1.142)	p = 0.151	0.469 (0.187–1.177)	p = 0.363
Lymphovascular invasion	0.740 (0.438–1.049)	p = 0.260	3.084 (0.947–10.037)	p = 0.061
Perineural invasion (PN)	0.34 (0.209–0.553)	p < 0.001	0.20 (0.08–0.47)	p < 0.001
Lauren type (intestinal)	0.34 (0.05–2.51)	p = 0.291	0.42 (0.03–6.58)	p = 0.533
Lauren type (diffuse)	0.36 (0.05–2.65)	p = 0.317	0.31 (0.02–6.05)	p = 0.438
AALR	1.05 (1.02–1.07)	p = 0.001	1.08 (1.01–1.15)	p = 0.033

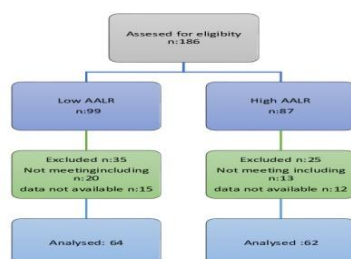
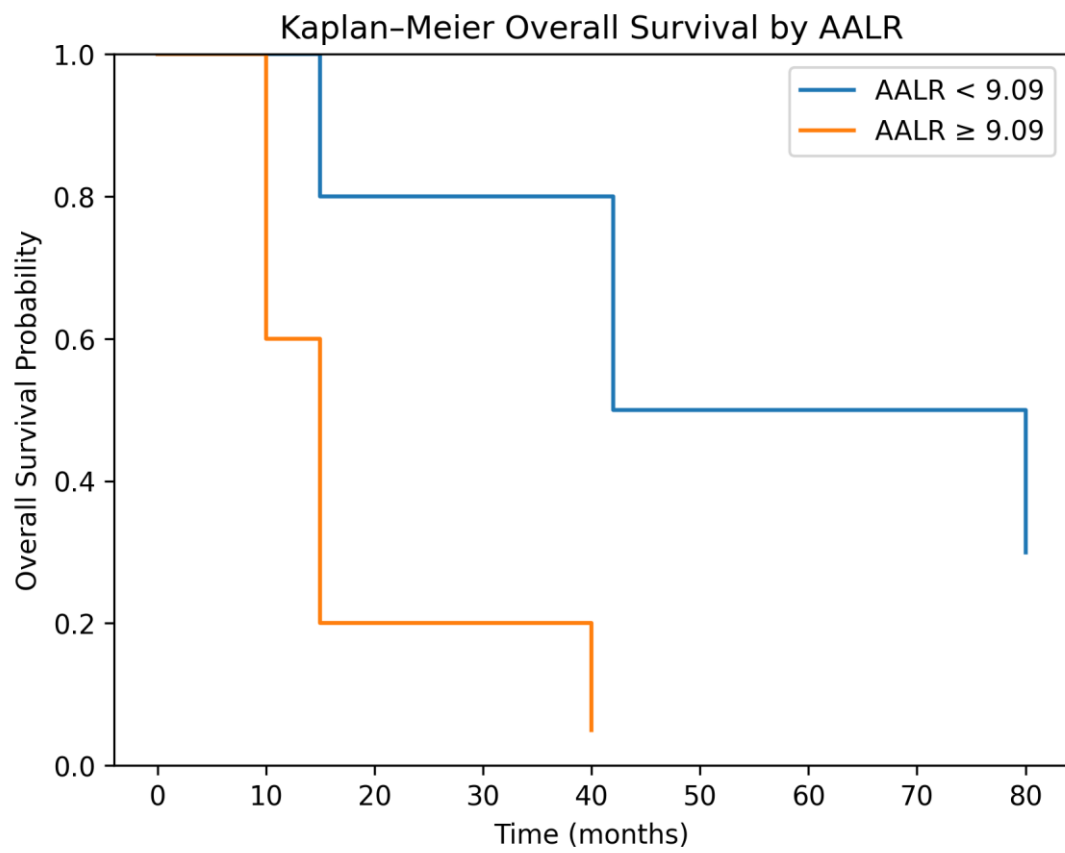


Figure 1: Consort flowcharts how patients' recruitment process

Figure 1. CONSORT flowchart illustrating the patient recruitment process.



Figure

2. Kaplan-Meier curves for overall survival according to AALR levels.

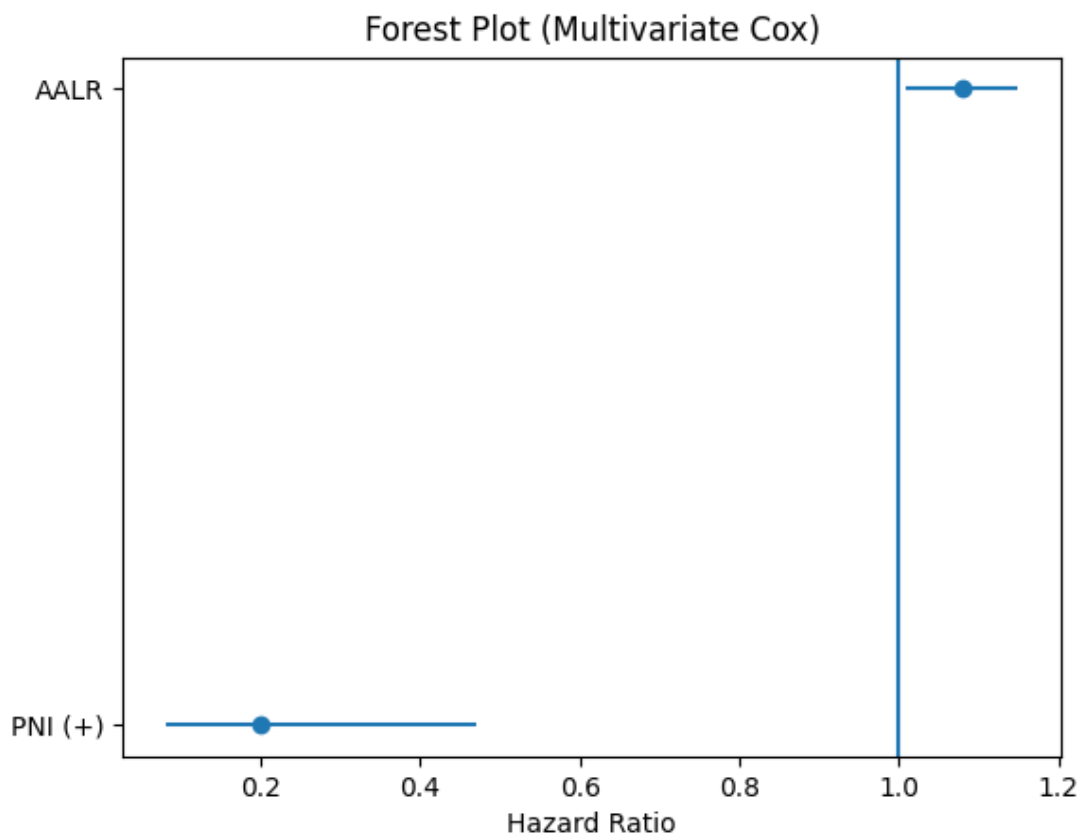


Figure 3. Forest plot of multivariate Cox regression analysis for overall survival.

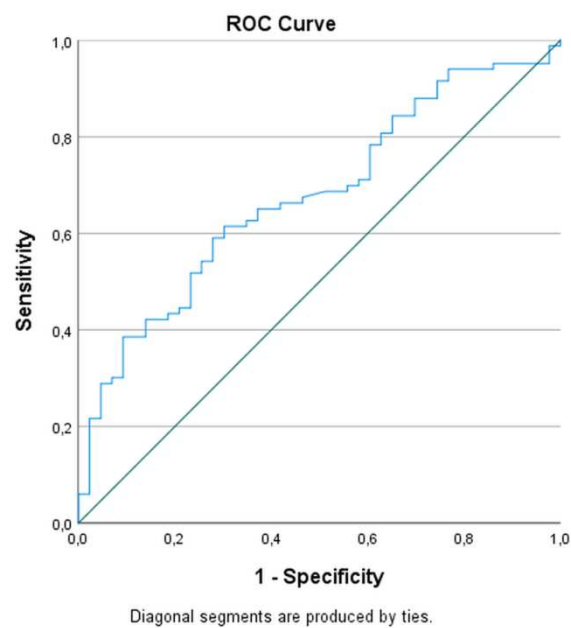


Figure 4. Receiver operating characteristic (ROC) curve demonstrating the predictive performance of AALR for overall mortality in patients with gastric cancer. The area under the curve (AUC) was 0.677.

