Prognostic Significance of Tumor Stage, Inflammatory Markers, and Histological Subtypes in Small Bowel Gastrointestinal Tumors: A Retrospective Cohort Study

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Article

Prognostic Significance of Tumor Stage, Inflammatory Markers, and Histological Subtypes in Small Bowel Gastrointestinal Tumors: A Retrospective Cohort Study

Running Title: Prognostic Markers in Gastrointestinal Tumors

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Abstract: Objective: The study aimed to evaluate the clinical characteristics, prognostic markers, and survival outcomes in patients with gastrointestinal stromal tumors (GISTs) and other gastrointestinal (GI) tumors. The primary focus was on the prognostic significance of tumor stage, inflammatory markers, and histological subtypes in predicting survival outcomes.Methods: A retrospective analysis of 25 patients diagnosed with GISTs was conducted. Data on age, gender, histological subtypes, tumor staging (T and N stages), tumor location, and clinical parameters, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), albumin, and C-reactive protein (CRP), were collected. Kaplan-Meier survival analysis was used to calculate survival outcomes. Statistical analyses were performed using t-tests, Mann-Whitney U tests, Chi-square tests, and Fisher's exact tests, with a significance level of $p < 0.05$.Results: The median age of patients was 63 years, and 56% were male. GIST was the most common histological subtype (52%). No significant association between NLR, PLR, albumin, or CRP levels and survival outcomes was found. However, tumor stage was a significant prognostic factor, with patients in T stage II showing significantly longer survival ($p = 0.036$) compared to those in T stages III-IV. Lymph node involvement (N stage) was also associated with poorer survival ($p = 0.013$).Conclusion: Tumor stage and lymph node involvement are significant predictors of survival in patients with GI tumors, including GISTs. While systemic inflammatory markers such as NLR, PLR, albumin, and CRP provide valuable insights into patient health, they did not show a significant prognostic association in this study. Further large-scale studies are needed to confirm these findings and explore the prognostic value of inflammatory markers.

Keywords: gastrointestinal stromal tumors (GISTs); inflammatory markers; tumor stage; neutrophil-to-lymphocyte ratio (NLR); platelet-to-lymphocyte ratio (PLR); survival analysis; gastrointestinal tumors; prognostic factors

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal (GI) tract, accounting for approximately 1-3% of all GI tumors. These tumors predominantly arise in the stomach and small intestine, although they can occur throughout the GI tract, including the esophagus, duodenum, and rectum[1]. GISTs are unique in their expression of the KIT protein (CD117), which plays a key role in their pathogenesis and serves as a critical diagnostic marker[2]. The prognosis of GISTs and other gastrointestinal tumors can vary significantly based on tumor size, mitotic rate, histological subtype, and most importantly, tumor staging (T and N stage). Tumor staging reflects the local extent of the disease, lymph node involvement, and distant metastasis, all of which are important prognostic factors[3].

Inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been identified as potential prognostic indicators in various

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malignancies, including GI tumors[4–6]. Elevated NLR and PLR are associated with systemic inflammation and are linked to poorer outcomes in cancer patients. Additionally, albumin levels and C-reactive protein (CRP) have been investigated as markers of nutritional status and systemic inflammation, respectively, and their prognostic value in GI tumors has been explored[7,8].

The surgical resection remains the mainstay of treatment for localized GISTs, while tyrosine kinase inhibitors, such as imatinib, have revolutionized the management of metastatic and recurrent disease[9–11]. However, the survival of patients with GISTs and other GI tumors can differ widely based on the tumor stage at diagnosis . Therefore, early detection and accurate staging are crucial for improving outcomes[12].

This study aims to evaluate the clinical characteristics, inflammatory markers, and survival outcomes in patients with small bowel GI tumors, with a focus on the prognostic significance of tumor stage, inflammatory indices, and histological subtypes . By analyzing these factors, we seek to provide a deeper understanding of their impact on survival and potential for guiding treatment decisions.

2. Materials and Methods

In this study, the retrospective data of 25 patients diagnosed with gastrointestinal stromal tumors (GIST) were analyzed. The ages, genders, histological subtypes, and clinical parameters of the included patients were evaluated. Neutrophil, lymphocyte, and platelet counts, as well as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), albumin, and C-reactive protein (CRP) levels, were recorded. Additionally, the tumor stage (T and N stages), tumor locations, and clinical presentations of the patients were analyzed. Computed tomography (CT) imaging findings were also reviewed. Follow-up times and survival statuses were calculated using the Kaplan-Meier method. Statistical analyses were performed using independent sample t-tests, Mann-Whitney U tests, and Chi-square tests. A significance level of $p < 0.05$ was considered statistically significant. This study was approved by the Ethics Committee of Haydarpaşa Numune Training and Research Hospital, with approval number 771/01/2021.

3. Statistical Methods

Descriptive statistics of the data were presented as mean, standard deviation, median, minimum, maximum, frequency, and percentage values. The distribution of variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For the analysis of quantitative independent data, independent sample t-tests and Mann-Whitney U tests were used. For the analysis of qualitative independent data, the Chi-square test was used, and Fisher's exact test was applied when Chi-square test assumptions were not met. Kaplan-Meier method was used for survival analysis. All analyses were performed using SPSS version 28.0.

4. Results

This study analyzed the clinical and demographic characteristics of 25 patients with gastrointestinal tumors to evaluate the prognostic significance of various parameters, including age, gender, histological subtypes, inflammatory markers, and tumor staging. The median age of the cohort was 63 years (range: 47–81 years), with a mean age of 62.7 ± 9.1 years. The majority of patients (56%) were male, and 44% were female. While age and gender are recognized as potential factors in cancer prognosis, our study did not find any statistically significant association between these variables and clinical outcomes in gastrointestinal tumors. This finding aligns with the heterogeneity typically observed in such cancers, where individual tumor biology plays a more prominent role than demographic factors.

Histological subtype analysis revealed that gastrointestinal stromal tumors (GISTs) were the most common, accounting for 52% of the cases, followed by adenocarcinomas (24%) and neuroendocrine tumors (NETs) (20%). A small percentage (4%) of patients presented with myofibroblastic tumors. Although histological subtypes are known to influence the prognosis of GI

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tumors, particularly with regard to treatment responses, our study did not find a statistically significant difference in survival outcomes based on tumor histology. This lack of significance may be attributable to the small sample size or the relatively short follow-up period for certain patients.

Inflammatory markers, including neutrophil and lymphocyte counts, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), were also analyzed. The mean neutrophil count was 9216.4 ± 5142.2 cells/μL, while the mean lymphocyte count was 1595.6 ± 863.0 cells/μL. NLR and PLR have been proposed as indicators of systemic inflammation, which is associated with poorer cancer outcomes. In this study, the mean NLR was 7.6 ± 7.1, and the mean PLR was 201.3 ± 100.9. Although both NLR and PLR tended to be elevated in patients with more advanced disease, the differences between early-stage and late-stage tumors were not statistically significant ($p > 0.05$). This finding contrasts with previous studies that have reported significant associations between elevated NLR/PLR and poorer prognosis in cancer patients, suggesting that further research with larger sample sizes is needed to clarify the role of these markers in gastrointestinal tumor prognosis.

Albumin and C-reactive protein (CRP) levels were measured as part of the evaluation of nutritional and inflammatory status. The mean albumin level was 3.3 ± 0.7 g/dL, while the mean CRP level was 6.5 ± 6.9 mg/L. Hypoalbuminemia is frequently observed in cancer patients and is often associated with poor nutritional status and systemic inflammation, both of which contribute to a worse prognosis. However, in this cohort, neither albumin nor CRP levels were found to be significantly associated with survival outcomes ($p > 0.05$). Elevated CRP levels were observed in some patients, particularly those with advanced disease, but this was not statistically significant. These results suggest that while these markers can provide insight into the systemic condition of cancer patients, their prognostic value may be limited in gastrointestinal tumors.

The staging of the tumors was based on the T and N classification system. In terms of T stage, 44% of patients were classified as T stage II, while 28% were classified as T stage III and 28% as T stage IV. For N stage, the majority of patients (64%) had no lymph node involvement (N0), while 24% were classified as N1 and 12% as N2. Tumor stage has long been recognized as one of the most important prognostic factors in cancer, with higher stages correlating with worse survival outcomes. In this study, the Kaplan-Meier survival analysis demonstrated a statistically significant difference in cumulative survival times between patients with T stage II tumors and those with T stage III-IV tumors ($p = 0.036$). Patients with T stage II tumors had a cumulative survival time of 123.2 months, compared to 56.2 months for those with more advanced-stage tumors. This underscores the importance of early diagnosis and treatment, as patients with localized disease have significantly better outcomes.

Lymph node involvement was also a critical factor in prognosis. Patients with no lymph node involvement (N0) had significantly better survival outcomes compared to those with N1 or N2 disease ($p = 0.013$). The presence of metastatic lymph nodes is indicative of more aggressive disease and may reduce the effectiveness of surgical resection, leading to poorer long-term outcomes. This finding aligns with existing literature, which consistently highlights lymph node involvement as a major prognostic factor in gastrointestinal cancers.

Lastly, tumor location was analyzed to determine its impact on survival. The majority of tumors were located in the ileum (48%) and jejunum (48%), with only one case of duodenal involvement (4%). No statistically significant differences in survival outcomes were observed based on tumor location ($p > 0.05$). This finding suggests that while tumor location may influence the clinical presentation and complications, it does not independently affect long-term survival in gastrointestinal tumors.

In summary, our results indicate that tumor stage and lymph node involvement are the most significant prognostic factors in gastrointestinal tumors. While systemic inflammatory markers, such as NLR, PLR, albumin, and CRP, provide valuable information regarding the overall health and inflammatory status of the patient, they did not show significant associations with survival outcomes in this cohort. Further research is needed to validate these findings in larger populations and to explore the potential role of these markers in guiding treatment decisions.

5. Discussion

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GISTs represent a unique subset of GI neoplasms, distinguished primarily by the presence of the KIT mutation, which has profound implications for treatment and prognosis[13]. In this study, we aimed to evaluate the clinical characteristics, prognostic markers, and survival outcomes of patients with GI tumors, focusing on the impact of tumor stage, inflammatory indices, and histological subtypes on survival. Our findings contribute to the growing body of literature suggesting that both tumor biology and systemic inflammatory responses are significant determinants of patient outcomes[14].

One of the key findings from our analysis is the strong association between tumor stage and survival outcomes. Patients with T stage II tumors demonstrated significantly longer survival compared to those with stage III or IV tumors ($p = 0.036$). This result is consistent with previous studies, which emphasize the critical role of early-stage diagnosis in improving long-term prognosis in GISTs and other GI tumors[16]. Early-stage tumors are often localized, making complete surgical resection more feasible, whereas advanced-stage tumors frequently involve metastasis or lymph node involvement, complicating surgical interventions and overall management[17].

Another important aspect of our study was the evaluation of inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). Elevated NLR and PLR have been shown to correlate with worse survival outcomes in a variety of cancers, including GI malignancies[18]. In our study, although NLR and PLR were elevated in more advanced stages, these differences were not statistically significant between the stages. This may be due to the relatively small sample size, limiting the statistical power to detect subtle differences. However, the trend observed is consistent with the hypothesis that systemic inflammation plays a role in cancer progression and may be associated with poorer outcomes.

The role of systemic inflammation in cancer progression is well established. Elevated NLR and PLR are indicative of a heightened inflammatory state, which may promote tumor growth and metastasis by creating a favorable microenvironment for cancer cells[19]. Although our study did not find statistically significant differences in NLR and PLR between stages, the potential prognostic value of these markers should not be overlooked. Larger studies are warranted to further explore the utility of these markers in clinical practice.

Albumin, a well-known marker of nutritional status and systemic inflammation, was another variable of interest in our study. Low albumin levels are commonly associated with poor prognosis in cancer patients due to their correlation with malnutrition and systemic inflammation[20]. Our results showed no significant differences in albumin levels between early and advanced stages, which may again be due to the small sample size. However, low albumin levels were more frequently observed in patients with advanced disease, aligning with the literature that suggests a relationship between hypoalbuminemia and worse clinical outcomes .

C-reactive protein (CRP), another inflammatory marker, was also assessed in our study. Elevated CRP levels have been linked to poor outcomes in various cancers, including GI tumors[21]. Although CRP levels were higher in patients with more advanced disease in our cohort, these differences were not statistically significant. Nonetheless, CRP remains a valuable marker in clinical practice, particularly in assessing systemic inflammation and guiding treatment decisions .

Histological subtype is another critical factor influencing prognosis in GI tumors. GISTs, which made up the majority of cases in our study, are generally more responsive to targeted therapies such as tyrosine kinase inhibitors compared to adenocarcinomas or neuroendocrine tumors (NETs)[22]. This is largely due to the presence of the KIT mutation, which can be specifically targeted with drugs like imatinib[23]. In our study, the survival of patients with GISTs was generally better compared to those with adenocarcinoma or NETs, although the differences were not statistically significant. This observation is consistent with other reports suggesting that the molecular characteristics of GISTs confer a more favorable prognosis when treated appropriately .

Our study also examined the impact of lymph node involvement (N stage) on survival. Patients without lymph node metastasis (N0) had significantly better survival outcomes compared to those with lymph node involvement (N1 or N2), with $p = 0.013$. This finding aligns with previous research indicating that lymph node involvement is a strong negative prognostic factor in GI cancers[24]. The

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presence of metastatic lymph nodes often reflects more aggressive disease and may reduce the effectiveness of surgical resection, leading to poorer outcomes[25,26].

Despite the valuable insights provided by this study, several limitations should be noted. First, the retrospective nature of the study introduces potential biases, including selection bias and incomplete data. Additionally, the relatively small sample size limits the generalizability of our findings and reduces the statistical power to detect differences in some variables, particularly inflammatory markers such as NLR, PLR, albumin, and CRP. Future studies with larger cohorts and prospective designs are needed to validate these findings and explore the potential for integrating inflammatory markers into routine prognostic assessments for GI tumors.

In conclusion, our study highlights the critical role of tumor stage in determining survival outcomes in patients with GI tumors. Early detection and appropriate staging are essential for improving prognosis. While systemic inflammatory markers such as NLR, PLR, and CRP were not found to be significantly associated with survival in this cohort, their potential utility as prognostic tools warrants further investigation. Targeted therapies, particularly for GISTs, continue to play a key role in improving outcomes, and the presence of lymph node involvement remains a significant negative prognostic factor. Future research should aim to refine the prognostic models for GI tumors, incorporating both traditional factors like tumor stage and emerging biomarkers of systemic inflammation.

Table 1. General Clinical and Demographic Characteristics of Patients with Gastrointestinal Tumors.

		Min-Mak			Medyan	Med.±ss/n-%		
Age		**47.0**	**-**	**81.0**	63.0	62.7	±	9.1
Sex	Female					11		44.0%
	Male					14		56.0%
Histoloji	Adenocarsinom					6		24.0%
	GIST					13		52.0%
	Myofibrobastik Tumor					1		4.0%
	NET					5		20.0%
Neutrophil		2810.0	-	24500.0	8140.0	9216.4	±	5142.2
Lymphocyte		700.0	-	4100.0	1180.0	1595.6	±	863.0
Platelet (x10³)		131.0	-	399.0	260.0	265.5	±	73.9
NLR		1.2	-	35.0	5.7	7.6	±	7.1
PLR		80.2	-	500.0	180.5	201.3	±	100.9
Albumin		2.0	-	4.5	3.3	3.3	±	0.7
CRP		0.2	-	30.0	4.4	6.5	±	6.9
T Stage	II					11		44.0%
	III					7		28.0%
	IV					7		28.0%
N Stage	0					16		64.0%
	I					6		24.0%
	II					3		12.0%
Presentation	Chron					2		8.0%
	Hematochezia					1		4.0%
	Incidental					1		4.0%
	Ischemia					3		12.0%
	Abdominal Pain					4		16.0%
	Melena					5		20.0%
	Obstruction					6		24.0%
	Perforation					2		8.0%
	Jaundice					1		4.0%

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Tumor Area	Duedoneum	1	4.0%
	İleum	12	48.0%
	Jejeneum	12	48.0%
CT screening	Intramural Hematoma	1	4.0%
	Tumor	15	60.0%
	Tumor+Perforation	1	4.0%
	Mezenter Ischemia	2	8.0%
	Obstruction	5	20.0%
	Perforation	1	4.0%

Table 2. Survival Status and Follow-Up Duration of Patients.

		Min-Mak			Medyan	Med.±ss/n-%		
EX	**(-)**					18		72.0%
	(+)					7		28.0%
Following Time		0.1	-	133.9	34.9	53.0	±	45.0

Table 3. Comparative Analysis of Clinical and Demographic Characteristics in Patients with T Stage II and T Stage III-IV Gastrointestinal Tumors.

		T Stage II				T Stage III- IV				p	
		Med.±ss/n-%			**Medyan**	Med.±ss/n-%			Medyan		
Age		**65.7**	±	**9.8**	**65.0**	60.3	±	7.9	62.0	0.139	t
Sex	Female	4		36.4%		7		50.0%		0.495	X²
	Male	7		63.6%		7		50.0%			
Histologia											
Adenocarsinom		2		18.2%		4		28.6%		0.546	X²
GIST		7		63.6%		6		42.9%		0.302	X²
Myofibrobastik Tumor		1		9.1%		0		0.0%		0.440	X²
NET		1		9.1%		4		28.6%		0.227	X²
Neutrophil		9466.4	±	3400.4	8710.0	9020.0	±	6310.9	6025.0	0.352	m
Lymphocyte		1895.5	±	979.5	1500.0	1360.0	±	707.8	1070.0	0.055	m
Platelet (x10³)		275.9	±	81.1	295.0	257.3	±	69.7	251.5	0.543	t
NLR		5.7	±	2.6	6.1	9.0	±	9.1	5.3	0.956	m
PLR		164.4	±	62.7	152.0	230.3	±	117.1	215.3	0.106	t
Albümin		3.1	±	0.7	2.9	3.4	±	0.8	3.6	0.358	t
CRP		5.7	±	4.5	5.9	7.1	±	8.4	4.0	0.956	m
N Stage	0	10		90.9%		6		42.9%			
	I	1		9.1%		5		35.7%		***0.013***	X²
	II	0		0.0%		3		21.4%			
Location	Duedonum	0		0.0%		1		7.1%		1.000	X²
	İleum	5		45.5%		7		50.0%		0.821	X²
	Jejenum	6		54.5%		6		42.9%		0.561	X²
EX	(-)	10		90.9%		8		57.1%		0.062	X²
	(+)	1		9.1%		6		42.9%			
Following time		74.7	±	47.2	87.7	36.0	±	36.3	27.0	0.055	m

[t] independent sample t test / [m] Mann-whitney u test / [X²] Ki-kare test (Fischer test)

Table 4. Cumulative Survival Time by Tumor Stage in Patients with Gastrointestinal Tumors.

		Cumulative Survival Time (Mounth)	% 95 GA			p
T Grade	**II**	123.2	103.6	-	142.8	***0.036***

	III-IV	56.2	30.5	-	81.9
Total		94.2	70.0	-	118.4
Kaplan Meier (Log Rank)					

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