ORIGINAL RESEARCH

GLR in Colorectal Cancers: An Easily Accessible Prognostic Marker

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Background and Objectives: Colorectal cancer remains a significant health concern, necessitating reliable prognostic indicators for effective management. This study explores the preoperative prognostic significance of the Glucose/Lymphocyte Ratio (GLR) in colorectal cancers.

Methods: The study retrospectively analyzed records of patients who underwent surgery for elective colorectal cancers between January 1, 2013, and December 31, 2021, at the Koşuyolu Training and Research Hospital Gastroenterologic Surgery Department. Demographic, clinicopathological, and follow-up data were comprehensively assessed. A cutoff was established from GLR ratios and patients were divided into two groups for prognosis analysis.

Results: The study enrolled 222 eligible patients, examining variables such as age, sex, ASA score, neoadjuvant treatment, lymphovascular and perineural invasion, tumor grade, TNM stage, and GLR. The groups consisted of 128 patients with low GLR and 94 patients with high GLR. Statistical analyses revealed relations between GLR levels ($p \leq 0.001$) and various prognostic factors such as age ($p = 0.034$), Perineural Invasion (PNI) ($p = 0.002$), tumor grade ($p = 0.017$), TNM stage ($p = 0.003$), and surgery time ($p = 0.029$), individuals with GLR ≥ 3.04 were observed to show higher mortality rates ($p = 0.001$). Above GLR cutoff point of 3.04 patients showed better overall survival rates. All survival related parameters were related with prognosis in univariant Cox regression tests. In multivariant cox regression tests GLR ≥ 3.04 significantly increased mortality by 2.9 times. ($p = 0.003$).

Conclusion: This study demonstrates that GLR, calculated from preoperative glucose and lymphocyte values serves as an independent prognostic factor in colorectal cancers. The findings suggest potential applications for GLR in survival analyses, with significant associations identified in age, PNI, tumor grade, TNM stage, and surgery time. Further investigations are warranted in homogeneous patient populations.

Keywords: colorectal cancer, prognostic factor, survival, Glucose-to-lymphocyte Ratio, cancer-specific survival

Introduction

Colorectal cancers rank as the fourth most prevalent cancer globally, yet advancements in screening methods and surgical techniques enable early diagnosis.[1] Not only screening methods but also clinical presentations such as colorectal cancer of unidentified origin (CUP) contribute to the increased incidence of colorectal cancers, despite being considered as favorable variants of colorectal cancer in these clinical contexts.[2] Postoperative follow-up protocols primarily rely on patients' pathological results, with an increasing tendency toward the use of serum biomarkers in contemporary practices. CEA and CA19.9 values, commonly used in post-diagnosis recurrence monitoring, can also be utilized for diagnosis, unlike in the metastatic disease presence where they are found to be high together with K-Ras mutation. Tissue K-ras activity is used in assessing tumor aggressiveness and chemotherapy sensitivity, while miRNAs are markers that can be found in tissue or blood, showing a spectrum of effects whose diversity is still under research. The miR-19a oncogene associated with FOLFOX resistance in advanced stage CRCs, while upregulation of miR-126 is correlated with bevacizumab resistance in terms of treatment response to anti-VEGF or anti-EGFR inhibitors effective in metastatic colon cancers; conversely, overexpression of miR-31, miR-100, miR-125b, and downregulation of miR-7 are respectively associated with cetuximab resistance.[3]

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Easily accessible prognostic markers are not only significant in cancer patients but also hold importance in various clinical aspects. Studies have indicated the potential utility of easily accessible tests such as Neutrophil/Lymphocyte Ratio (NLR), Platelet/Lymphocyte Ratio (PLR), Lymphocyte/Monocyte Ratio (LMR), and the "Hematocrite, Albumin, Leukocyte, and Platelet" (HALP) score in assessing the prognosis of colon cancers.[4–8]

The prognostic value of a novel marker, the preoperative Glucose/Lymphocyte Ratio (GLR), has been demonstrated in assessing survival rates in patients with acute pancreatitis.[9] In a separate study, GLR was identified as an independent indicator of mortality in patients undergoing cardiac surgery who developed acute kidney failure during the postoperative period.[10] In contemporary evaluations of cancer patients, two studies have demonstrated that Glucose/Lymphocyte Ratio (GLR) levels serve as an independent risk factor for survival in pancreatic and gallbladder cancers.[11,12]

While its role has been investigated in several malignancies, its specific impact on colorectal cancer remains an area of ongoing research. Previous studies have shown that GLR is a ratio where the increased glucose consumption in neoplastic cells, together with the hyperglycemia resulting from the hypoxic microenvironment in perineoplastic tissues, is combined with the inflammatory processes developing in neoplastic cells.[11,12] It is considered that not only hepato-biliary pathologies but also neoplastic pathologies associated with glucose intolerance or triggered by inflammation that can be evaluated in relation to it. This study aims to explore the role of these biomarkers in the prognosis of colorectal cancer, providing a foundation for more effective guidance in patient treatment planning and surveillance analysis.

Methods

Ethical Approval and Study Design

Before data collection, ethical approval for the study was obtained with decision number 2024/1/765 from the Ethics Committee of the same institution. The patient consent for the review of their medical records was not required in retrospective studies for committee. The study was conducted in accordance with ethical standards and patient confidentiality and privacy were strictly maintained.

This retrospective cohort study focused on the examination of records of patients who underwent surgery for colorectal malignancies at the Gastroenterologic Surgery Department of Koşuyolu Training and Research Hospital between January 1, 2013, and December 31, 2021. Ethical approval was obtained before commencing data collection, ensuring adherence to the principles outlined in the Declaration of Helsinki and relevant ethical guidelines.

Inclusion Criteria

Patients were included in the study based on specific criteria to ensure homogeneity and relevance to the research objectives. The inclusion criteria comprised the following: Patients who underwent elective surgery for histologically confirmed colon and rectum adenocarcinoma were considered, required blood samples taken within the period ranging from a maximum of 1 month to a minimum of 1 week before the scheduled surgery, for patients who received neoadjuvant therapy; blood samples collected at least 1 month after completing the treatment, having comprehensive clinical and pathological data available for analysis and only patients aged 18 years or older were considered.

Exclusion Criteria

To ensure the integrity and specificity of the study, the following exclusion criteria were applied: Patients who underwent palliative or emergency surgery, patients who did not undergo R0 resection. Cases with inadequate dissection, positive surgical margins, or R2 resection were excluded to maintain the study's focus on complete and oncologically appropriate surgical resections, ensuring the findings' reliability and validity. Other criterias were patients not operated on according to oncological principles; patients with postoperative follow-up durations less than 30 days, patients with the presence of acute or chronic inflammatory diseases during the study period or evidence of infections in the diagnostic process and patients with the presence of hemolysis in the collected blood samples, those with insufficient data or those with inadequate clinical and pathological information and patients with a history of diabetes history were excluded. Patients with secondary diabetes resulting from conditions such as Cushing's disease, Glucagonoma, Pheochromocytoma, Hyperthyroidism, Somatostatinoma, Hepatogenic diabetes, or drug-induced diabetes were also excluded from the study.

Data Collection

Preoperative blood tests provided essential parameters for the calculation of Glucose/Lymphocyte Ratio (GLR). Values for Glucose and Lymphocyte were extracted from blood tests conducted on patients within intervals ranging from 2 months to 1 week prior to surgeries. Fasting blood glucose values, which were originally in g/dL, have been converted to mmol/L as previously described.[11,12]

For patients who underwent neoadjuvant therapy, blood test results taken at least 1 month after the completion of the treatment were included in the study. All data were obtained from the electronic database, ensuring accuracy and reliability in the analysis.

The utilization of these specific ratios and the inclusion of data from distinct time intervals contribute to a comprehensive understanding of the preoperative hematological profile and its potential implications on the outcomes of colorectal cancer surgeries.

Demographic information, preoperative tumor markers, prior operation records, history of neoadjuvant therapy, pathology data, operation durations, postoperative follow-up complications, length of hospital stays, and survival data were retrospectively reviewed for all patients. Serum carcinoembryonic antigen (CEA) [0–5 ng/mL], cancer antigens 19.9 [0–37 U/mL] normal ranges utilized from previous studies.[13,14] Glucose levels were measured in millimoles per liter (mmol/L), while lymphocyte levels were measured in milligrams per deciliter (mg/dL). GLR levels were calculated by dividing the glucose values by the lymphocyte values. After calculating GLR, a ROC curve was determined to calculate the GLR cutoff value. Lymphovascular Invasion (LVI), Perineural Invasion (PNI), Tumor Grade, TNM stage status records demonstrated from pathology records. American Society of Anaesthesiologists (ASA) and operation duration records obtained from anesthesia records.[15]

Surgery and Follow-up

The study was initiated by collecting data from 354 individuals who underwent surgery at our center between 2011 and 2021. Of this group, 126 were excluded for reasons such as missing pathology or diagnostic data (15 cases), incomplete postoperative data (5 cases), a history of diabetes (92 cases), emergency or palliative surgery (12 cases), autoimmune diseases (2 cases), and inflammatory conditions (3 cases). An additional 6 subjects were excluded due to a postoperative follow-up period less than 3 months. Ultimately, 222 participants met the inclusion criteria (Figure 1).

Among these, tumor localizations were distributed as follows: cecum (27), ascending colon (39), transverse colon (7), descending colon (16), sigmoid colon (59), and rectum (69). Two patients exhibited synchronous lesions in the
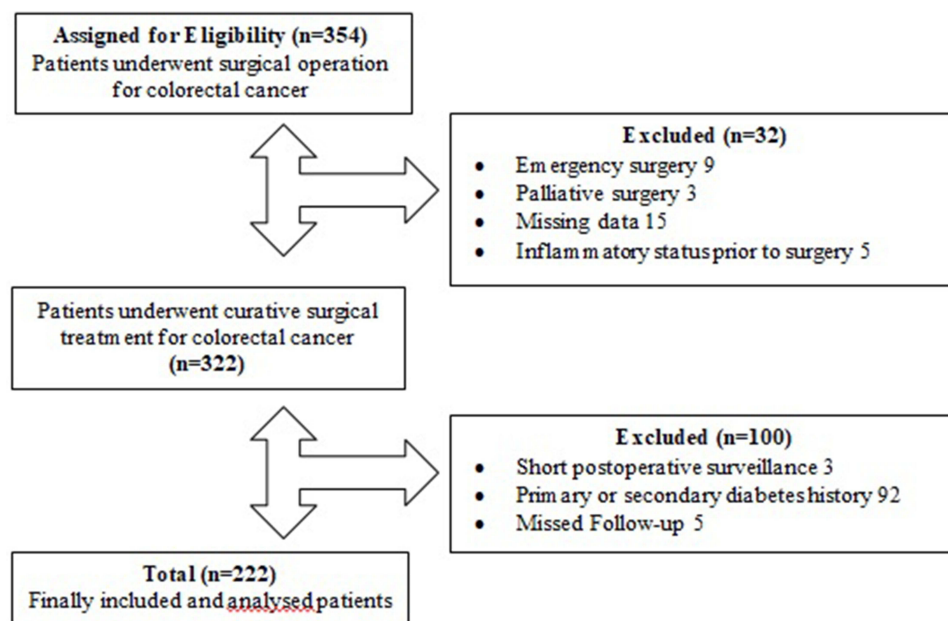

Figure 1 Flowchart of the study design and patient data enrolment.

descending and ascending colon. Neoadjuvant chemoradiotherapy was routinely administered to patients with mid and low rectal cancer before surgery.

Statistical Analysis

The software IBM® SPSS® (Statistical Package for the Social Sciences) version 25 (IBM Corp. Armonk, NY, USA) was used for statistical analysis. The distribution of numerical data was performed using the Kolmogorov–Smirnov test with the non-normal distribution results. Qualitative data were presented as frequency and percentage. Continuous measurements were presented as median (IQR). The chi-square test was utilized for comparisons involving categorical variables. The relationship between continuous parameters and mortality through the application of the Mann–Whitney U-test. Additionally, the Receiver Operating Characteristic (ROC) curve was examined to determine the cut-off value of GLR. For the analysis of factors influencing mortality multivariate Cox regression tests were conducted. A significance level of 0.05 was considered for all tests.

Results

Demographic and clinicopathological data were analyzed for 354 patients with colon cancer in our study. The patients were divided into two groups, with 128 having high GLR and 94 having low GLR. When patients were compared by age, those aged 65 and older exhibited higher survival rates (p = 0.034). Examination of pathological factors revealed lower survival rates in patients with PNI presence compared to those without (p=0.002). Grouping patients based on tumor grade and TNM stage showed lower survival rates associated with higher grade and stage (p = 0.017 and p = 0.003, respectively) (Table 1).

Table 1 Demographic and Clinicopathologic Characteristics of Patients

Variables		Not Alive	Alive	$p^{\dagger}$
		n=48 (%21.6)	n=174 (%78.4)	
Age, years	≥65	24 (17.1%)	116 (82.9%)	0.034
	<65	24 (29.3%)	58 (70.7%)	
Sex	Male	26 (19.1%)	110 (80.9%)	0.254
	Female	22 (25.6%)	64 (74.4%)	
ASA score	<3	19 (26.4%)	53 (73.6%)	0.232
	≥3	29 (19.3%)	121 (80.7%)	
Neoadjuvant	No	32 (18.7%)	139 (81.3%)	0.054
	Yes	16 (31.4%)	35 (68.6%)	
LVI	No	31 (20.5%)	120 (79.5%)	0.564
	Yes	17 (23.9%)	54 (76.1%)	
PNI	No	27 (16.6%)	136 (83.4%)	0.002
	Yes	21 (35.6%)	38 (64.4%)	
Tumor grade	Well	2 (5.1%)	37 (94.9%)	0.017
	Moderately	37 (24.2%)	116 (75.8%)	
	Poorly	9 (30%)	21 (70%)	
TNM stage	I–II	19 (14.6%)	111 (85.4%)	0.003
	III–IV	29 (31.5%)	63 (68.5%)	
		Median (IQR)		$p^{\ddagger}$
BMI, kg/m²		28.0 (23.9–32.2)	26.1 (24.0–30.1)	0.195
CEA, ng/mL		2.0 (1.2–5.9)	2.4 (1.4–5.4)	0.559
CA 19.9 ng/mL		7.6 (3.1–16.2)	9.5 (4.9–20.1)	0.071
Surgery time, min.		235 (170–263)	240 (195–310)	0.029

Notes: †Chi-Square, ‡Mann Whitney U.
Abbreviations: LVI, Lymphovascular Invasion; PNI, Perineural Invasion; BMI, Body Mass Index; LOS, Length of Hospital Stay; IQR, Inter Quartile Range.

The ROC curve analysis revealed that GLR values below the cutoff of 3.04 demonstrated moderate sensitivity (62.5%) and specificity (63.2%) with 0.716 of AUC-value for overall survival rates, providing better results ($p < 0.001$). On the other hand, ROC curve analyses revealed both glucose and lymphocyte counts were not related with prognosis. Glucose values below the cutoff of 98.5 g/dl showed a low sensitivity (%50) and specificity (%51.1) for better prognosis with 0.509 of AUC-value ($p = 0.849$). Lymphocyte counts below the cutoff of 1.81 showed a low sensitivity (%52.9) and specificity (%56.3) for better prognosis with 0.563 of AUC-value ($p = 0.179$) (Table 1) (Figure 2).

Survival analysis using Kaplan–Meier test was conducted based on the GLR cutoff, and the results are presented in Figure 3. Accordingly, individuals with GLR ≥ 3.04 were observed to show higher mortality rates ($p = 0.001$). Other variables were recorded similar (Table 2).

The analysis was categorized based on the GLR cutoff point; higher mortality rate was found in patients with high GLR values ($p = 0.001$). Similar results were observed between the groups in the other parameters; (Table 3). Survival analysis using Kaplan–Meier test was conducted based on the GLR cutoff, and the results are presented in Figure 3. Accordingly, individuals with GLR ≥ 3.04 were observed to experience significantly higher mortality ($p = 0.001$).

All factors associated with mortality in Table 1 and GLR included in univariate regression analysis. All parameters found associated with mortality. Then a multivariate Cox regression analysis is proceeded for identifying prognostic factors for mortality in patients with colon cancer. The presence of PNI significantly increased the risk of mortality, with an OR of 2.173 and a statistically significant p-value of 0.045. Patients in TNM stage III–IV had a significantly higher risk of mortality, with an OR of 2.245 and a statistically significant p-value of 0.030. Additionally, it was observed that GLR ≥ 3.04 significantly increased mortality by 2.9 times. ($p = 0.003$). It was observed that other risk factors were not significant for mortality. ($p > 0.05$) (Table 4).

Discussion

This study was conducted to evaluate the use of preoperative GLR as an easily accessible prognostic marker in overall survival monitoring for colorectal cancer patients with curative procedures reached. Our study demonstrated that PNI presence and advanced stage acts as an independent mortality factor besides GLR.

There are various factors which may lead to poor impact on prognosis of cancer patients, such as older age, tumor stage, histological differentiation, tumor site, etc. While older age is thought to potentially affect prognosis, particularly through increased susceptibility to complications, consensus on its impact on survival has not yet been reached.[16] One of
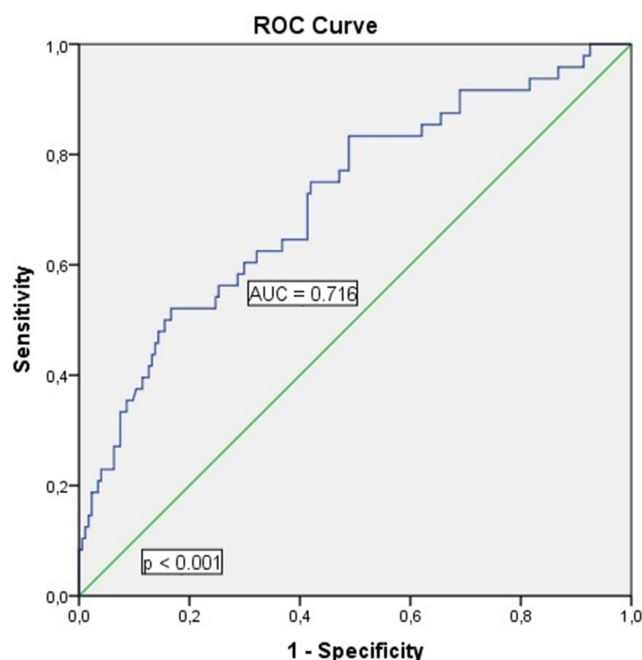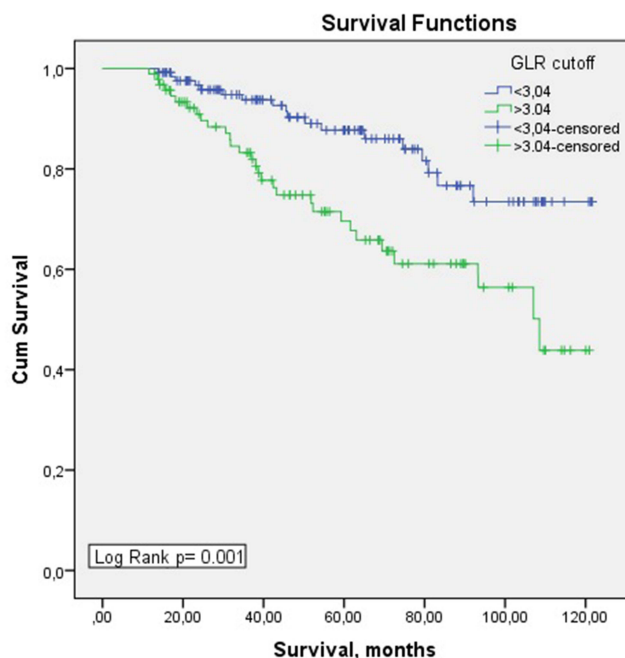

Figure 2 ROC analysis of GLR.

Figure 3 Survival analysis based on GLR groups.

these factors is manifested in the form of hyperglycemia due to insulin resistance. Neoplastic cells demonstrating rapid progression require intense energy and substrates at this stage, with glucose providing a significant portion of the required nutrients. Furthermore, the metabolism of the host organism, to balance the energy equilibrium in favor of its own needs, influences the development of hyperglycemia.[17] Additionally, hyperglycemia has been shown to play a role in cancer pathogenesis through the Epithelial–Mesenchymal Transition and microenvironment hypoxia pathways.[18,19] Regarding this, a literature review from 2018, analyzing seven studies, indicates that elevated glucose levels, even in non-diabetic cases, are associated with cancer mortality due to similar mechanisms.[20]

Cancer patients' survival and pathogenesis evaluations emphasize the importance of immunity, a concept increasingly highlighted in studies. When evaluating the relationship between inflammation and cancer, it has been demonstrated that direct cytotoxic mechanisms on tumor cells lead to the elimination of tumor cells directly, and the release of mediators by elements of the humoral system accompanies this process Lymphocytes are a fundamental component of the immune system, regardless of whether they are involved in humoral or cellular pathways.[21] In a systematic review conducted in 2018, examining 46 studies, it was shown that preoperative low lymphocyte levels could be an adverse prognostic indicator in patient groups with solid tumors.[22] Additionally PD-1 and CTLA-4 are immune checkpoint molecules that regulate immune responses and are found on immune cell surfaces. In colorectal cancer with MMR deficiency, PD-L1 expression on immune cells is notably higher compared to MMR-proficient tumors. Screening for DNA mismatch repair defects involves immunohistochemistry (IHC) and/or MSI testing. However, there are challenges in simplifying the

Table 2 ROC Analysis of Glucose, Lymphocyte and GLR

	AUC	95% CI	Cutoff	Sensitivity%	Specificity%	p
Glucose	0.509	0.417–0.601	98.5	51.1	50	0.849
Lymphocyte	0.563	0.466–0.661	1.81	52.9	56.3	0.179
GLR	0.716	0.631–0.800	3.04	62.5	63.2	<0.001

Abbreviations: AUC, Area Under Curve; CI, Confidential Interval.

Table 3 Demographic and Clinicopathologic Characteristics of Patients Scaled by GLR Cutoff Point

Variables		GLR<3.04	GLR≥3.04	$p^{\dagger}$
		n=128 (%57.7)	n=94 (%42.3)	
Age, years	≥65	83 (59.3%)	57 (40.7%)	0.521
	<65	45 (54.9%)	37 (45.1%)	
Sex	Male	82 (60.3%)	54 (39.7%)	0.317
	Female	46 (53.5%)	40 (46.5%)	
ASA score	<3	36 (50.0%)	36 (50.0%)	0.110
	≥3	92 (61.3%)	58 (38.7%)	
Neoadjuvant	No	99 (57.9%)	72 (42.1%)	0.896
	Yes	29 (56.9%)	22 (43.1%)	
LVI	No	87 (57.6%)	64 (42.4%)	0.985
	Yes	41 (57.7%)	30 (42.3%)	
PNI	No	96 (58.9%)	67 (41.1%)	0.535
	Yes	32 (54.2%)	27 (45.8%)	
Tumor grade	Well	26 (66.7%)	13 (33.3%)	0.399
	Moderately	84 (54.9%)	69 (45.1%)	
	Poorly	18 (60.0%)	12 (40.0%)	
TNM stage	I–II	74 (56.9%)	56 (43.1%)	0.792
	III–IV	54 (58.7%)	38 (41.3%)	
Mortality	No	110 (63.2%)	64 (36.8%)	0.001
	Yes	18 (37.5%)	30 (62.5%)	
		Median (IQR)		$p^{\ddagger}$
BMI, kg/m²		27.0 (24.4–31.5)	26.0 (23.3–29.8)	0.096
CEA, ng/mL		2.4 (1.4–5.1)	2.2 (1.4–7.2)	0.562
CA 19.9 ng/mL		8.8 (4.3–18.7)	10.1 (5.0–18.8)	0.344
Surgery time, min.		240 (190–305)	240 (185–300)	0.682

Notes: †Chi-Square, ‡Mann Whitney U.
Abbreviations: LVI, Lymphovascular Invasion; PNI, Perineural Invasion; BMI, Body Mass Index; IQR, Inter Quartile Range; GLR, Glucose/Lymphocyte Ratio.

Table 4 Prognostic Factors for Mortality, Identified by Multivariate Cox Regression Analysis

Prognostic Factors	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Age, ≥65 years	2.000	1.047–3.822	0.036	1.483	0.708–3.105	0.296
PNI, yes	2.784	1.418–5.463	0.003	2.173	1.018–4.642	0.045
Grade						
Well	1			1		
Moderately	7.929	1.564–40.186	0.012	1.301	0.496–3.412	0.112
Poorly	1.344	0.566–3.188	0.503	4.042	0.721–22.668	0.592
TNM stage, III–IV	2.689	1.396–5.182	0.003	2.245	1.084–4.652	0.030
GLR, ≥3.04	2.865	1.480–5.546	0.002	2.909	1.426–5.932	0.003
Surgery time, min.	1.005	1.001–1.009	0.018	1.005	1.000–1.009	0.051

Abbreviations: CI, Confidence Interval; OR, Odds Ratio; PNI, Perineural Invasion; GLR, Glucose/Lymphocyte Ratio.

biological and technical diversity of MSI testing into usable data. Literature suggests that IHC testing for mismatch repair machinery may produce varying results for a specific germline mutation, potentially due to somatic mutations.[23]

Rather than a single-parameter assessment, the validity of employing ratios of two parametric variables has been proven in many studies, making it a reliable method. Glucose and lymphocyte level alterations were thought to impact cancer patients through various pathways, leading to the formation and evaluation of GLR. In a study conducted by Zhong et al,[11] it was demonstrated that GLR independently indicates mortality in pancreatic cancer patients. Similarly, in our study, GLR was shown to be an independent predictor of survival. In parallel studies, diabetic patients were excluded with a similar sensitivity (66.4%) and specificity (77.6%) values, a comparable AUC (0.768), but higher cutoff (4.452) values were achieved.[9] In another study evaluating the prognostic impact of GLR in pancreatic cancers, increased GLR ratios were demonstrated to be an independent prognostic factor too. The GLR cutoff value in the study was 3.47, and the AUC value was 0.693, parallel to our study. However, diabetic patients were included in the study. Although the authors claim that the inclusion of diabetic patients would not make a difference, this situation may lead to a selection bias in the study.[24] In a study by Navarro et al, involving 197 patients with gallbladder cancer, and GLR was reported as an independent risk factor for mortality with sensitivity of 70.7% and specificity of 71.8%. Glucose values were calculated in the study as g/dl, with a cutoff value of 69.3, equivalent to 3.81 in mmol/L, aligning with our study. Diabetic patients were included in this study as well, but a distinction was made between diabetic and non-diabetic patients, yielding similar results in multivariate analyses.[12]

In a recent study involving 1448 colorectal cancer patients, the impact of GLR on overall survival was investigated. GLR was shown to be a significant prognostic marker alongside age, BMI, and tumor stage. Authors found GLR as a more sensitive mortality indicator than other parameters. The study included 134 diabetic patients. The GLR cutoff analysis showed higher values in diabetic patients. This value was also higher than the one in our study. There was a difference between diabetic and nondiabetic patient groups in the evaluation based on GLR cutoff. When multivariate analysis was applied in the study, it was stated that diabetic patients did not constitute an independent risk factor for mortality.[25]

Besides GLR; similar to many colon cancer studies in the literature, our study identified advanced TNM stage and the presence of PNI as independent risk factors for mortality.[11,12,22]

One of the primary limitations of the study is its retrospective design. Furthermore, the number of patients remaining after meeting the inclusion criteria led to a limited sample size. Additionally, the inclusion of rectal cancer patients who received neoadjuvant therapy has introduced heterogeneity into the study population. However, we found that neoadjuvant chemotherapy showed similar mortality rates, when patients were examined according to GLR values. We can highlight the strength of our study as the first to exclude diabetic patients from colorectal cancer research, thereby avoiding selection bias.

Conclusion

Our study has demonstrated that the Glucose-to-Lymphocyte Ratio (GLR) can be utilized in the survival analysis of colorectal cancers. In selected patient populations, such as isolated colon or rectal cancer with large sample size may present better outcomes for validation.

Disclosure

The authors report no conflicts of interest in this work.

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