J Surg Med. 2021;5(9):889-893.
DOI: 10.28982/josam.991055

Research article

Journal of Surgery and Medicine
e-ISSN=2602-2079

Prognostic value of preoperative glucose to lymphocytes ratio in patients with resected gastric cancer

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Ethics Committee Approval
Ethics committee approval was obtained from Hitit University Clinical Research Ethics Committee (Date: 2021 Issue: 107).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 September 20

Abstract

Background/Aim: There are no definitive tests that determine postoperative survival in gastric cancer. Simple and cheap laboratory markers are needed for clinicians to guide them preoperatively. The aims of our study were to analyze the importance of preoperative glucose-lymphocyte ratio (GLR) in the prognosis of patients with gastric cancer (GC), and to compare the success of GLR in predicting prognosis with the success of neutrophil-lymphocyte ratio (NLR) and C-reactive protein-albumin ratio (CAR).

Methods: We carried out a cross-sectional study on 196 GC patients. CAR, NLR and GLR values were calculated from the blood samples taken 24 hours before the surgery. Lymphovascular invasion, serosal invasion, and the number of metastatic lymph nodes were determined, and the prediction ability of glucose to lymphocyte ratio (GLR), neutrophil to lymphocyte ratio (NLR), and C-reactive protein to albumin ratio (CAR) were evaluated. In addition, the effect of GLR and NLR on the ability to predict overall survival was assessed. The mean follow-up period was 37 (6-69) months.

Results: A moderate and weak positive correlation was found between GLR, NLR and the number of metastatic lymph nodes (r=0.415, $P<0.001$; r=0.193, $P=0.007$, respectively). GLR and NLR were significant for predicting lymphovascular and serosal invasion ($P<0.001$). CAR was insufficient in lymphovascular invasion differentiation (AUC (95% CI): 0.582 (0.501-0.662)) ($P=0.529$) and serosal invasion differentiation ($P=0.529$). GLR significantly predicted overall survival ($P=0.002$). Patients with a GLR value of <4.12 had a significantly longer overall survival than those with GLR>4.12. NLR was insignificant for overall survival ($P=0.233$).

Conclusion: GLR value may contribute to the planning of the therapy process by predicting both the prognosis of the disease and the overall survival before surgery.

Keywords: Overall survival, Gastric cancer, Predict, Glucose-Lymphocyte ratio

How to cite: Yıldırım MB, Özkan MB. Prognostic value of preoperative glucose to lymphocytes ratio in patients with resected gastric cancer. J Surg Med. 2021;5(9):889-893.

Introduction

Gastric cancer is the fifth most common cancer and ranks second among gastrointestinal tract cancers. It ranks fourth among cancer-related deaths in the world. More than one million new diagnoses were made in 2020, and it caused approximately 760,000 deaths [1]. The high mortality of gastric cancer is because most cases are end-stage at the time of diagnosis. The five-year survival rate of even stage II-III gastric cancers that have a chance of surgery is around 35-50% [2]. Although there are many subtypes of gastric cancers, adenocarcinoma is the most common, with a rate of 95% [3]. Currently, the only curative treatment for gastric cancer is post-surgical chemoradiotherapy [4]. An average of twenty-five thousand gastrectomies are performed each year in the United States because of gastric cancer [5].

Knowing whether the operation will affect the patient's survival or whether it will be curative is especially important for the physician and the patient in terms of treatment decisions in the preoperative period. For this reason, the stage of the disease should be evaluated in detail before the operation with imaging methods and clinical examination. There are many prognostic evaluation methods such as histological grade, lymph node involvement, distant metastasis, and vascular invasion. Distant metastasis revealed by the imaging methods are unresectable. However, even if the patients are diagnosed at an operable stage, the 5-year survival rate after surgery is below 20%, especially in stage 3 cancers [6]. Currently, there are no definitive tests that determine postoperative survival; however, some markers, such as those of the inflammatory process, may help determine the prognosis [7, 8]. The neutrophil-lymphocyte ratio (NLR), C-reactive protein albumin ratio (CAR), platelet-lymphocyte ratio (PLR), and mean platelet volume were frequently researched [8, 9]. The glucose requirement increases secondary to the rapid growth around the tumor cells. Oxidative phosphorylation increases both to increase local immune suppression and meet the glucose requirement of these cells, thereby increasing the number of immature neutrophils in the blood [10]. It is also known that diabetes and increased blood sugar increase the risk of multiple neoplasms in the gastrointestinal tract, and elevated blood glucose values may affect clinical overcome and overall survival in cancer patients [11]. An increase in the rate of glucose-lymphocyte ratio (GLR) due to hyperglycemia and immunosuppression is expected in cancer patients. The ratio of preoperative blood glucose level and lymphocyte counts significantly predicts prognosis in pancreatic cancers [12]. There is still a need for a more accurate and comprehensive assessment system with improved sensitivity and specificity for the assessment of prognosis. Based on this preliminary information, the power of GLR to predict prognosis, lymphovascular invasion, serosal invasion, and survival of patients with gastric cancer were compared with NLR and CAR.

Materials and methods

The data of the patients who underwent gastrectomy with the diagnosis of gastric cancer at Hitit University Erol Olcok Training and Research Hospital between 01/01/2016 and 08/01/2021 were retrospectively analyzed after obtaining the approval of Hitit University Clinical Research Ethics Committee (Date: 2021 Issue: 107). Patients over the age of 18 years who were diagnosed with gastric adenocarcinoma and who underwent total or subtotal gastrectomy and lymph node dissection were included in the study. Patients with unavailable data, patients with acute inflammatory disease, diabetes patients, patients with comorbidities (Cushing's syndrome, glucagonoma, hyperthyroidism, etc.), patients using drugs that increase blood sugar glucose, individuals under the age of 18 years who underwent gastrectomy for pathological diagnoses other than adenocarcinoma, patients with early-stage gastric cancer, patients who received neoadjuvant chemotherapy and patients with end-stage disease who underwent surgery for gastric cancer but could not undergo gastrectomy were excluded. The reason for the exclusion of patients with early-stage gastric cancer is that serosal invasion is not detected because the tumor does not extend beyond the submucosa. The study was conducted per the Declaration of Helsinki after obtaining written consent from all patients.

Study protocol and definitions

The data of the patients, namely, age, gender, operation time, laboratory results, hospital stay, and pathological diagnoses were obtained from the hospital registry. Lymphovascular invasion, serosal invasion, the lymph node number of the patients were found, and the prediction ability of glucose lymphocyte ratio (GLR), neutrophil lymphocyte ratio (NLR), and C-reactive protein albumin ratio (CAR) were compared. In addition, the effect of GLR and NLR on the ability to predict overall survival was evaluated.

Follow-up

Overall survival (OS) was defined as the interval between the date of pathologically confirmed diagnosis and the date of death or last follow-up. All patients in this study were followed up regularly by an independent researcher by a telephone call or medical record review.

Statistical analysis

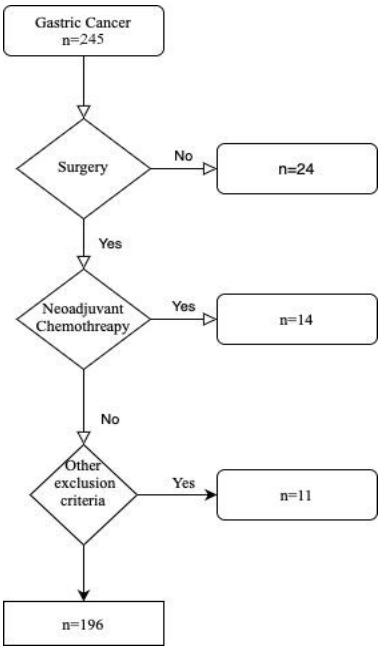
Statistical analysis was carried out using SPSS (Version 22,0, SPSS Inc., Chicago, IL, USA) software. Normally and non-normally distributed numerical data were presented as mean (standard deviation) and median (min-max), respectively. Categorical data were given as frequency and percentage (%). The Shapiro-Wilk test was used to determine whether the data were normally distributed. In the comparison of numerical variables between two independent groups, Student's t-test or Mann-Whitney U test was used depending on whether the data were normally distributed. Correlation analysis between numerical variables was conducted with the Spearman correlation coefficient per the data distribution. ROC (Recipient Operating Characteristic) analysis was used to decide whether GLR and NLR values were significant in predicting lymphovascular and serous invasion. The interpretation of the area under the curve (AUC) calculated by ROC analysis was as follows: 0.9-1: Excellent, 0.8-0.9: Good, 0.7-0.8: Fair, 0.6-0.7: Poor and 0.5-0.6: Unsuccessful. Youden index (maximum sensitivity and specificity) was used to calculate the best cut-off point in ROC analysis. Sensitivity, specificity, positive-negative predictive values (PPV-NPV), and likelihood ratio (L+) values were calculated to assess the discriminating power of cut-off

points calculated after ROC analysis in predicting lymphovascular and serosal invasion. Proportion comparisons between categorical variables were carried out using the Chi-square test. The Kaplan-Meier test was used to figure out the survival times of the groups formed according to the cut-off points determined for GLR and NLR, and the Log Rank (Mantel-Cox) test was used to compare the survival times. $P<0.05$ was considered statistically significant.

Results

After implementing the exclusion criteria, 196 patients were included in the study (Figure 1), who were divided into two groups according to the presence of lymphovascular invasion (Group I, n=91) and serosal invasion (Group II, n=57).

Figure 1: Flowchart



The gender distribution of the patients in groups I and II ($P=0.889$, $P=0.835$, respectively), their mean ages ($P=0.188$, $P=0.424$, respectively), and the hospital stay ($P=0.077$, $P=0.499$, respectively) were similar. Lymphovascular invasion and serosal invasion were significant in terms of mortality ($P<0.001$) (Table 1).

Table 1: Demographic data

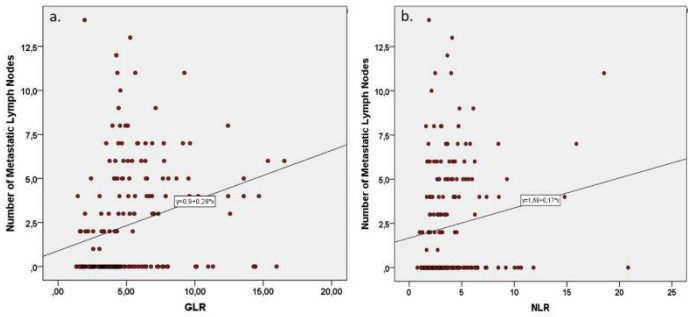
		Lymphovascular Invasion		*P*-value	Serosal Invasion		*P*-value
		No (n=105)	Yes (n=91)		No (n=139)	Yes (n=57)	
Gender	Female	28 (26.7%)	25 (27.5%)	0.899[a]	37 (26.6%)	16 (28.1%)	0.835[a]
	Male	77 (73.3%)	66 (72.5%)		102 (73.4%)	41 (71.9%)	
Mortality	Alive	70 (66.7%)	16 (17.6%)	<0.001[a]	74 (53.2%)	12 (21.1%)	<0.001[a]
	Dead	35 (33.3%)	75 (82.4%)		65 (46.8%)	45 (78.9%)	
Age		68.44(12.05)	70.7(12.5)	0.188[b]	69.06(11.77)	70.61(13.51)	0.424[b]
Duration of hospitalization (day)		15 (2-85) 17.13 (9.54)	16 (4-69) 19.35 (10.94)	0.077[c]	15 (2-85) 17.65 (9.39)	16 (8-69) 19.40 (12.08)	0.499[c]

[a] Chi-square test, [b] Student's t-test with mean (standard deviation), [c] Mann-Whitney U test with median (min-max)

The operation time was 183 (62) minutes in patients with lymphovascular invasion and 177 (64) minutes in patients without, 185 (68) minutes in those with serosal invasion and 178 (61) minutes in those without. No significant difference was found between groups in the duration of surgery.

There was a moderate and weak positive correlation between GLR, NLR and the number of metastatic lymph nodes (r=0.415, $P<0.001$, r=0.193, $P=0.007$, respectively). CAR and the number of metastatic lymph nodes were not correlated ($P=0.094$) (Figure 2).

Figure 2: Correlation between GLR and NLR and metastatic lymph node



GLR and NLR were significant for predicting lymphovascular and serosal invasion ($P<0.001$) (Table 2). CAR was insufficient in differentiating lymphovascular invasion (AUC (95% CI): 0.582 (0.501-0.662)) ($P=0.529$) and serosal invasion ($P=0.529$).

Table 2: Predictive power of GLR, NLR, and CAR to predict lymphovascular and serosal invasion

	Lymphovascular Invasion		*P*-values	Serosal Invasion		*P*-values
	No (n=105)	Yes (n=91)		No (n=139)	Yes (n=57)	
GLR	3.27 (1.3-15.9) (4.03(2.67))	5.23 (1.3-16.5) (6.13(3.16))	<0.001	3.82 (1.3-15.9) (4.56(2.93))	5.21 (1.3-16.5) (6.08(3.21))	<0.001
NLR	2.83 (0.7-11.8) (3.26(2.05))	3.56 (1.5-20.8) (4.47(3.37))	<0.001	2.91 (0.7-20.8) (3.62(2.79))	3.65 (1.5-15.9) (4.32(2.79))	0.012
CAR	4.13 (0.5-40.5) (5.98(6.85))	4.56 (0.6-82.8) (8.48(11.65))	0.049	4.31 (0.5-82.8) (7.31(10.2))	4.52 (0.7-44.1) (6.72(7.09))	0.529

Mann-Whitney U test with median (min-max) (mean, standard deviation)

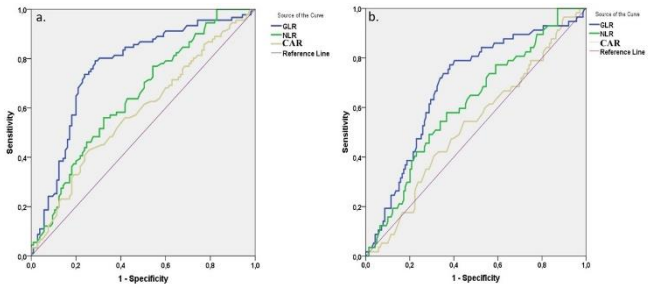
ROC (Receiver Operating Characteristic) analysis results and sensitivity, selectivity, positive-negative predictive values, and likelihood ratio (+) values of GLR and NLR values are presented in Table 3. The ROC curves are shown in Figure 3. ROC analysis showed that the GLR parameter was significant in lymphovascular invasion differentiation at a reasonable level (0.7<AUC<0.8, Table 3), and in terms of serosal invasion, it was at an acceptable level (0.6<AUC<0.7, Table 3). NLR parameter was significant at an acceptable level in the differentiation of both lymphovascular invasion (0.6<AUC<0.7, Table 3) and serosal invasion (0.6<AUC<0.7, Table 3).

Table 3: ROC (Receiver Operating Characteristic) analysis results for GLR and NLR values with sensitivity, specificity, positive-negative predictive values, and likelihood ratio (+) values

	Lymphovascular Invasion		Serosal Invasion	
	GLR	NLR	GLR	NLR
AUC (95%CI)	0.762 (0.692-0.831)	0.646 (0.569-0.722)	0.689 (0.608-0.770)	0.615 (0.530-0.700)
Cut-off	4.12	3.335	4.21	3.375
Sensitivity	79.1% (69.1-86.6)	56% (45.2-66.3)	77.2% (63.8-86.8)	57.9% (44.1-70.5)
Specificity	71.4% (61.6-79.6)	67.6% (57.6-76.2)	61.9% (53.2-69.8)	63.3% (54.6-71.1)
PPV	70.5% (60.6-78.9)	60% (48.7-70.3)	45.3% (35.3-55.7)	39.2% (28.9-50.5)
NPV	79.7 (69.9–87)	63.9 (54.2–72.7)	86.8% (78.2-92.5)	78.5% (69.6-85.5)
LR +	2.76 (2.01-3.81)	1.73 (1.24-2.41)	2.02 (1.56-2.61)	1.57 (1.15-2.15)

GLR: Glucose to lymphocyte ratio, NLR: Neutrophil to lymphocyte ratio, AUC: Area Under the ROC Curve, CI: Confidence Interval, PPV: Positive Predictive Values, NPV: Negative Predictive Values, LR: Likelihood Ratio

Figure 3: ROC curves



The cut-off points of GLR for predicting lymphovascular and serosal invasion were 4.12 and 4.21, respectively. The classification success rates of these values were 56% (45.2-66.3), and 57.9% (44.1-70.5), respectively, and selectivity were 71.4% (61.6-79.6) and 61.9% (53.2-69.8), respectively (Table 3).

The cut-off points of NLR were 3.33 and 3.37, respectively. The classification success rates of these values were 79.1% (69.1-86.6), and 77.2% (63.8-86.8), respectively, and selectivity were 67.6% (57.6-76.2), and 63.3% (54.6-71.1), respectively (Table 3).

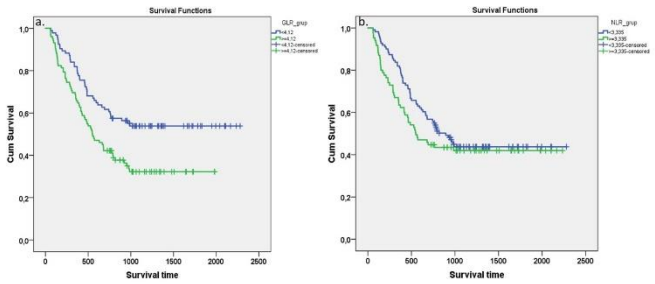
Survival times significantly differed between the GLR groups (P=0.002). Patients with a GLR value below 4.12 had a significantly longer life expectancy than patients with a GLR value above 4.12 (Table 4). There was no statistically significant difference in survival times between the NLR groups (Figure 4).

Table 4: Kaplan Meier survival analysis results: means and medians for survival time

	Groups	Mean				Median				*P*-values
		Estimate	Std. Error	95% Confidence Interval Lower Bound	Upper Bound	Estimate	Std. Error	95% Confidence Interval Lower Bound	Upper Bound	
GLR	<4.12	1430.1	96.65	1240.6	1619.5	1075	101.4	896.1	1201.1	0.002[a]
	>=4.12	913.6	77.74	761.2	1066	549	82.9	386.5	711.4	
NLR	<3.335	1272.6	87.58	1101	1444.3	894	102.6	692.9	1095.1	0.233[a]
	>=3.335	1123.7	104.3	919.1	1328.2	549	116.7	320.1	777.8	

[a] Log Rank (Mantel-Cox) test

Figure 4: Survival Time



Discussion

This study analyzed the relationship between gastric cancer and the ability of GLR, NLR, and CAR to determine the prognosis. CAR and NLR are inflammatory response markers that effectively predict the prognosis in various cancers [13-15]. Zhong et al. stated that GLR has an essential role in determining the prognosis in pancreatic cancer patients, and that GLR alone is more effective in determining the average overall survival than NLR and CAR [12]. In another study, CAR and NLR were shown to have strong prognostic predictive values for gastric cancer [16]. No study investigated the value of GLR in gastric cancer. In our study, GLR and NLR were effective both in demonstrating lymphovascular and serosal invasion. However, CAR could not significantly differentiate lymphovascular invasion or serosal invasion (Table 2). A GLR cut-off value of 4.12 was significant in showing lymphovascular invasion, with 79.1% sensitivity and 71.4% specificity. Although NLR successfully predicts lymphovascular invasion with a cut-off value of 3.33, it has lower specificity and sensitivity than GLR. In predicting serosal invasion, the GLR and NLR cut-off values were 4.21 and 3.37, respectively. GLR is better in predicting serosal invasion than NLR. In particular, the 86.8% negative predictive value of GLR for serosal invasion plays a critical role in deciding neoadjuvant therapy before surgery. Lymphovascular and serosal invasion are the most critical factors in determining the prognosis and aggressiveness of gastric cancer [17-19]. Our results showed that mortality was significantly higher in the patient group with lymphovascular or serosal invasion. Previous studies have shown that gastric cancer patients with serosal invasion have a higher rate of peritoneal involvement and need neoadjuvant chemoradiotherapy [20–22].

One of the important factors determining the overall survival of gastric cancer is the number of metastatic lymph nodes [23–26]. In this study, while NLR and GLR were significantly related to the number of metastatic lymph nodes, CAR was not. Since D1 and D2 lymph node dissection for gastric cancers is still controversial, it may be useful to decide on D2 lymph node dissection by considering the preoperative NLR and GLR values. There are many survival analyses with NLR and CAR values in terms of gastric cancer. A meta-analysis conducted in 2015 revealed that increased NLR value was inversely proportional to survival [27]. However, we observed that the NLR value was not effective enough to predict the overall survival, while GLR value was (P=0.002). Kaplan Meier survival analysis revealed that the overall survival was 1430 days in patients with a GLR value below 4.12, and 913.6 days in patients with a GLR value above 4.12. Since there is no study on GLR in predicting survival among gastric cancer patients, this article may guide the future studies.

Limitations

This study inevitably has limitations as it was planned retrospectively, including small sample size, its single-center design, and not including gastric cancer subtypes other than adenocarcinoma. However, we believe that we obtained important findings, considering the absence of any other studies examining GLR values in gastric cancer. We aim to provide clinicians with a new and helpful tool that can be easily accessed and calculated, in addition to traditional methods and staging systems, while planning individualized treatment for gastric cancer.

Conclusion

GLR value is a successful immunological indicator in predicting lymphovascular and serosal invasion without added cost before surgery. The correlation between the number of metastatic lymph nodes and GLR can guide the surgeon for the width of the lymph node dissection. Furthermore, GLR value contributes to the planning of the therapy process by predicting both the prognosis of the disease and overall survival before surgery. Prospective randomized controlled studies are needed for predictivity success of GLR value on overall survival in gastric cancer patients.

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