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Research Article

Relationship Between Glucose-To-Lymphocyte, Albumin-To-Alkaline Phosphatase and Neutrophil-To-Lymphocyte Ratios and Prognosis in Young Patients with Pancreatic Cancer

Engin Kut

Medical Oncology Clinic of Manisa State Hospital, Manisa, Türkiye

Abstract

Objectives: Younger patients with cancer are usually diagnosed at a more advanced stage and have a more aggressive clinic; however, it tolerates chemotherapy better. Therefore, the prognosis of elder and young patients may be different. Glucose-to-lymphocyte (GLR), neutrophil-to-lymphocyte ratio (NLR), and albumin-to-alkaline phosphatase and neutrophil-to-lymphocyte ratio (AAPR) have been previously associated with prognosis in many cancers. There is no study evaluating the relationship between GLR, NLR, AAPR and prognosis in pancreatic cancer aged under 65 years. Therefore, we conducted this study to determine whether there is such a relationship.

Methods: A total of 101 patients between 2009 and 2020 were evaluated retrospectively.

Results: High GLR, NLR, and Low AAPR patients had a poor prognosis. The results of the multivariate analysis were as follows: GLR [hazard ratio(HR) for OS 1.97, p=0.041) and HR for PFS 1.90, p=0.043], NLR (HR for OS 1.535, p=0.049 and HR for PFS 1.62, p=0.045), and AAPR (1.597 for OS, p=0.046 and HR for PFS 1.99, p=0.39).

Conclusion: GLR, NLR, and AAPR were associated with the prognosis of pancreatic cancer in our study. They can be used as easy, cheap and practical biomarkers to determine the monitoring treatment and prognosis of patients with pancreatic cancer.

Keywords: Glucose-to-lymphocyte ratio, albumin-to-alkaline phosphatase ratio, neutrophil-to-lymphocyte ratio, pancreatic cancer, prognosis

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Pancreatic cancer is the 12th most common cancer according to the GLOBOCAN 2020 data and ranks seventh among the causes of cancer-related deaths.[1] Despite the developments in recent years, the increasing trend in the incidence of pancreatic cancer and associated mortality continues.[1,2] The five-year life expectancy is 2-10% in all stages of pancreatic cancer.[2] Stage is the most important factor in the prognosis of patients with this cancer.[2] There is no other standard marker to show prognosis in follow-up and treatment.

Pancreatic cancer is generally seen in advanced ages. The median age at which pancreatic cancer is seen is 70 years, and it occurs in one third of the patients after the age of 70 years. The incidence of pancreatic cancer under 50 years is less than 10%.[3] Young patients have a more aggressive course and are diagnosed at a more advanced stage; however, they also have better tolerance to chemotherapy and other aggressive treatments.[4,6] There is a complex relationship between cancer and the immune system, inflammation and nutritional status.[7,8] Neutrophil-to-lymphocyte ratio (NLR), glucose-to-lymphocyte ratio (GLR), and albumin-to-alkaline phosphatase ratio (AAPR), which show the nutritional, inflammatory and immune status of patients, have been pre-

Address for correspondence: Engin Kut, MD. Manisa Devlet Hastanesi Tıbbi Onkoloji Kliniği, Manisa, Türkiye
Phone: +90 541 188 70 74 **E-mail:** drenginkut@gmail.com

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viously associated with prognosis in many cancers.[9-11]

As in other diseases, elderly patients with pancreatic cancer may have differences in disease characteristics due to comorbidities, physiological changes, weakening of the immune system, and associated chronic inflammation. Therefore, in the current study, for the first time in the literature, we examined the relationship between prognosis and NLR, GLR and AAPR in patients with metastatic pancreatic cancer aged under 65 years.

Methods

Study Population

Patients over the age of 18 and under 65 years of age, followed up with metastatic pancreatic cancer in the Department of Medical Oncology of Manisa City Hospital between 2009 and 2020, and who received gemcitabine-cisplatin or FOLFIRINOX treatment regimens in any order and in the first two steps were evaluated retrospectively. The metastases of the patients were radiologically detected using positron emission computed tomography, magnetic resonance imaging, and/or computed tomography.

Data Collection

The patient demographic characteristics, such as age, sex, metastasis sites, Eastern Cooperative Oncology Group (ECOG) performance scores, white blood cell (WBC), neutrophil, platelet and lymphocyte counts, alkaline phosphatase (ALP), albumin, hemoglobin, GLR, NLR and AAPR values, OS and PFS were recorded and and the relationship of these factors with survival was examined. GLR by dividing the blood glucose value (mg/dL) by the lymphocyte count (10^3/μL), NLR was obtained by dividing the neutrophil count (10^3/μL) by the lymphocyte count (10^3/μL), and AAPR by the dividing albumin value (g/dL) by the alkaline phosphatase value (IU/L). The median values of the patients were 72.4 for GLR, 2.66 for NLR, and 0.016 for AAPR. The patients were divided into two groups as high and low according to NLR, GLR, and AAPR values [NLR (≤2.66 versus >2.66), GLR (≤72.14 versus >72.14), AAPR (≤0.016versus >0.016)], and below and above 2 according to ECOG perfromans score (>2 versus ≤2). Overall Survival was calculated as the time from the date of chemotherapy to mortality for the patients that died and the last follow-up for the survivors. Progression-free survival (PFS) was calculated for first-line therapy, as the time from initiation of first therapy to clinical or radiological progression or death from any cause.

Statistical Analysis

Descriptive statistics were presented as mean, standard deviation, median, minimum and maximum values for numerical variables and as numbers and percentages for categorical variables. Survival analyses were performed using the Kaplan-Meier method. Factors affecting survival were examined with the Cox regression. P<0.05 was considered significant in all statistical analyses.

Results

A total of 101 patients, 67 (66.3%) men and 34 (33.7%) women, with a median age of 55 (35-64) years were retrospectively evaluated. The ECOG performance score was 0-1 in 66 (65.3%) patients and 2-4 in 35 (34.7%). Bone metastasis was present in 12 (11.9%) patients, lung metastasis in 25 (24.8%), peritoneal metastasis in 31 (30.2%), liver metastasis in 46 (45.5%), and lymph node metastasis in 21 (20.8%) (Table 1 and 2). All patients had received at least two lines of chemotherapy.

Table 1. Demographic and clinical characteristics of all patients

	Number (n)	Percentage (%)
Sex		
Male	67	66.3
Female	34	33.7
ECOG performance score		
2<	66	65.3
2≤	35	34.7
Metastasis site		
Liver	46	45.5
Peritoneum	31	30.2
Lymph node	21	20.8.5
Lung	25	24.8
Bone	12	11.9
Comorbidities		
Diabetes mellitus	7	6.9
Hypertension	20	19.8
Coronary artery disease	20	19.8
Hypothyroidism	5	4.9
NLR		
<2.66	50	49.5
≥2.66	51	50.5
GLR		
<72.14	47	46.5
≥72.14	54	53.5
AAPR		
<0.016	48	47.5
≥0.016	53	52.5
Metastasis at the time of diagnosis		
Present	81	80.2
Absent	20	18.8

ECOG: Eastern Cooperative Oncology Group; GLR: Glucose-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; AAPR: Albumin-to-alkaline phosphatase ratio.

Table 2. Demographic and clinical characteristics of all patients

Parameter	Mean±SD Median (min-max)
Hemoglobin (g/dL)	12.03±2.13
Albumin (g/dL)	3.41±0.72
WBC (10^3/µL)	6.45 (3.50-15.00)
Neutrophil (10^3/µL)	3.50 (2.50-10.5)
Lymphocyte (10^3/µL)	1.65 (0.9-3.3)
Platelet (10^3/µL)	274 (133-589)
Ca 19-9 (U/mL)	5974 (1.84-265480)
Glucose (mg/dL)	108 (77-250)
ALP (IU/L)	178 (51-1151)

WBC: White blood cell; CA19-9: Carbonhydrate abtigen 19-9; ALP: Alkaline phosphatese.

The median OS time was 12 [95% confidence interval (CI): 9.71-14.29)] months and, The median progression-free survival was 7.04 (95% CI, 6.326-7.754) months for first-line chemotherapy. High GLR, NLR and Low AAPR had a poor prognosis. Median OS was 12.67 (95% CI, 9.54-15.80) months versus 8.77 (95% CI, 4.92-12.62) months for GLR low versus high patients, 12.6 (95% CI, 4.35-19.65) months versus 10.00 months (95% CI, 4.35–15.65) months were for NLR low versus high paitents, and 11.2 (95% CI, 8.44–13.92) months versus 7.6 (95% CI, 5.44–13.92) months for AAPR high versus low patients (Fig. 1). Median PFS was 5.27 (95% CI, 3.36-7.24) months versus 3.71 (95% CI, 3.99-5.07) months for GLR low versus high patients, 4.37 (95% CI, 3.15-5.16) months versus 3.35 (95% CI, 2.35–5.45) months for NLR low versus high patients, and 4.53 (95% CI, 3.04–6.02) months versus 3.91 (95% CI, 3.05–4.76) months for AAPR high versus low patients (Fig. 2). In the univariance analysis OS was associated with ECOG performance score (p=0.023), GLR (p=0.013), NLR (p=031), and AAPR (p=0.019) and and PFS was significant relationship with CA 19-9 (p=0.047), GLR (p=0.033), NLR (p=0.04), and AAPR (p=0.024) (Table 3 and 4). The results of the multivariate analysis were as follows: GLR [hazard ratio(HR) for OS 1.97, p=0.041) and HR for PFS 1.90, p=0.043], NLR (HR for OS 1.535, p=0.049 and HR for PFS 1.62, p=0.045), and AAPR (1.597 for OS, p=0.046 and HR for PFS 1.99, p=0.39) (Table 3 and 4).

Discussion

Pancreatic cancer is seen less frequently in young people than in the elderly, but it is diagnosed at a more advanced stage and have a more aggressive course in the former.[4-6] Therefore, our study included only patients under 65 years with metastatic pancreatic cancer. In the literature, a relationship has been reported between glucose levels and many cancers.[13-15] High glucose level causes hyperglycemia, hyperinsulinemia, cellular hypoxia, decreased antioxidant capacity, increased release of inflammatory cytokines (vasculer endothelial growth factor (VEGF), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α) etc.), and increased chronic inflammation.[16,17]

Cancer cells meet their energy requirement through anaerobic glycolysis.[18] Cancer cells prefer glycolysis independent of oxygen. In hypoxemia, there is an increase in glycolysis with hypoxia-inducible factor 1 (HIF-1).[19] Glycolysis provides not only energy but also metabolites that are necessary for the tumor microenvironment. Glucose uptake is higher in cancer cells with high cell growth, division rates and energy needs. Therefore, high-grade tumors have a higher glucose uptake. Positron emission tomography PET-

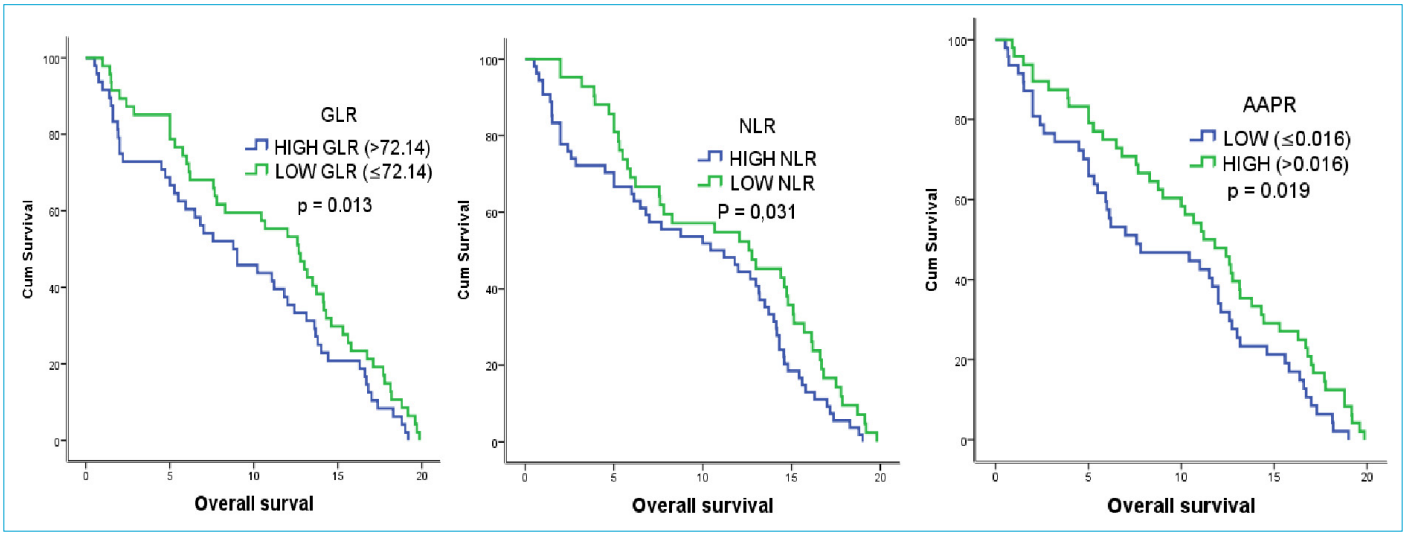

Figure 1. Kaplan-Meier curves showing overall survival glucose-to-lymphocyte ratio (GLR), Neutrophil-to-lymphocyte ratio (NLR), and albumin-to-alkaline phosphatase ratio (AAPR).

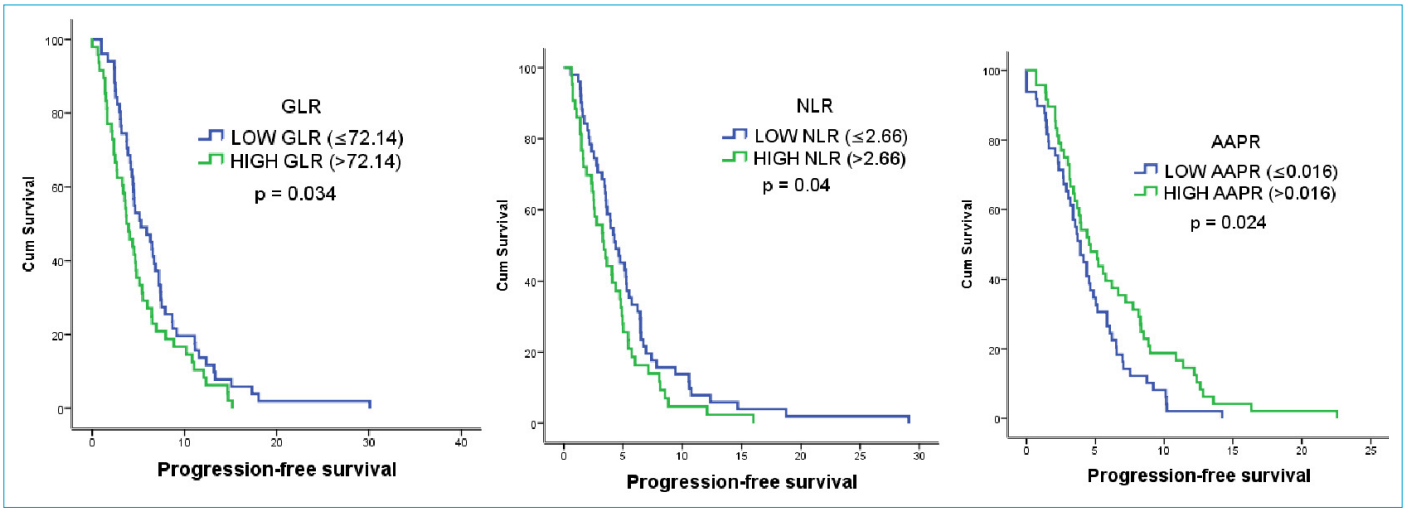

Figure 2. Kaplan-Meier curves showing progression-free survival glucose-to-lymphocyte ratio (GLR), Neutrophil-to-lymphocyte ratio (NLR), and albumin-to-alkaline phosphatase ratio (AAPR).

CT imaging is performed by utilizing the glucose uptake of cancer cells.

Lymphocytes are immune system elements that play an important role in host defense. They inhibit the proliferation and metastasis of tumor cells. In their deficiency, tumor cells escape immune elimination. A relationship has been found between lymphocytes and many cancers.[20-22]

GLR can reflects both the inflammatory and immune status of patients and provides information about the prognosis of the patients. In our study, a significant relationship was

Table 3. Correlation between overall survival and clinical factors

	Univariate analysis (HR, 95% CI)	p	Multivariate analysis (HR, 95% CI)	p
Age	1.012 (0.977-1.045)	0.49		
Gender	1.452 (0.948-2.223)	0.86		
ECOG score	1.624 (1.070-2.464)	0.023	1.557 (0.937-2.584)	0.084
Metastasis site				
Surrenal	1.334 (0.843-2.112)	0.21		
Bone	1.075 (0.584-1.997)	0.81		
Liver	1.223 (0.592-2.525)	0.58		
Peritoneum	1.222 (0.884-1.834)	0.33		
Lung	1.334 (0.843-2.112)	0.21		
Laboratory				
Hemoglobin (g/dL)	1.344 (0.880 -2.060)	0.27		
Albumin (g/dL)	0.992 (0.960-1.030)	0.67		
WBC (10^3/μL)	1.571 (0.710-3.490	0.67		
Neutrophil (10^3/μL)	1.120 (0.600-2.080)	0.71		
Lymphocyte (10^3/μL)	1.008 (0.980-1.040)	0.64		
Platelet (10^3/μL)	1.000 (0.098- 1.020)	0.53		
CA 19-9 (ng/mL)	0.860 (0.580-1.260)	0.44		
Glucose (mg/dL)	1.001(0.999-1.002)	0.23		
ALP (IU/L)	1.000 (1.000-1.001)	0.34		
GLR	1.836 (1.136-2.966)	0.013	1.97 (1.472-3.362)	0.041
NLR	1.513 (1.356-3.813)	0.031	1.535 (1.598-4.021)	0.049
AAPR	1.723 (1.132- 2.645)	0.019	1.597 (1.007-2.314)	0.046

HR: Hazard ratio; CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; WBC: White blood cell; CA19-9: Carbonhydrate antigen 19-9; GLR: Glucose-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; AAPR: Albumin-to- alkaline phosphatase ratio.

Table 4. Correlation between progression-free survival and clinical factors

	Univariate analysis (HR, 95% CI)	p	Multivariate analysis (HR, 95% CI)	p
Age	0.996 (0.964-1.1030)	0.82		
Gender	1.103 (0.719-1.692)	0.65		
ECOG score	1.192(0.778-1.826)	0.42		
Metastasis site				
Bone	1.163 (0.630-2.140)	0.627		
Liver	1.105 (0.699-1.746)	0.66		
Peritoneum	1.379 (0.912-2.085)	0.127		
Lung	1.527 (0.737-3.164)	0.254		
Laboratory				
Hemoglobin (g/dL)	1.071 (1.000-1.150)	0.61		
Albumin (g/dL)	1.870(1.140-2.750)	0.11		
WBC (/µL)	0.69 (0.45-1.06)	0.09		
Neutrophil (/µL)	1.06 (0.61-1.84)	0.82		
Lymphocyte (/µL)	1.08 (0.71-1.64)	0.71		
Platelet (/µL)	1.12 (0.65-1.95)	0.67		
CA19-9	1.46 (1.01-2.09)	0.047	0.99 (0.5-1.5)	0.7
Glucose (mg/dL)	1.00 (0.998-1.002)	0.97		
ALP (IU/L)	1.000 (1.00-1.001)	0.74		
GLR	1.495 (1.050- 2.184)	0.034	1.90 (1.19-2.98)	0.043
NLR	1.441 (1.92-2.850)	0.04	1.62 (1.14-3.20)	0.045
AAPR	1.563 (1.034-2.361)	0.024	1.99 (1.11-2.92)	0.039

HR: Hazard ratio; CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; WBC: White blood cell; CA 19-9: Carbonhydrate abtigen 19-9; GLR: Glucose-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; AAPR: Albumin-to-alkaline phosphatase ratio.

found between GLR and OS time in both the univariance and multivariance analyses. Similar to our study, Zhong et al. reported GLR as an independent prognostic factor in patients with inoperable pancreatic cancer, Zhang et al. suggested that GLR was an independent prognostic factor in patients with resected pancreatic cancer, and Navarro et al. determined GLR as an independent prognostic factor in patients with operated T2' gallbladder cancer in literature.[12,23-24] Our study is important because our study is the first in the literature to show this relationship in metastatic non-elderly patients with pancreatic cancer.

Neutrophils are cells play a role in host defense and immune modulation. They are involved a in both acute and chronic inflammation. It has been reported that neutrophils play a role in the formation of tumor microenvironment, angiogenesis, and tumor metastasis and progression by secreting mediators such as VEGF in the presence of inflammation. Therefore, neutrophils, together with lymphocytes, may be associated with prognosis as they reflect the inflammatory and immune status of patients.[25-26]

A relationship has been shown between NLR and prognosis in many cancers.[11,27-29] In our study, there was a significant correlation between NLR and survival time, similar to other age groups and cancers. In patients with cancer, pro-inflammatory mediators are secreted from cells to meet the increased glucose requirement due to increased glycolysis. These mediators cause immune reaction, inflammation, and gluconeogenesis in the host. Cachexia is common secondary to the catabolic process caused by secreted metabolites and increased gluconeogenesis.[30,31] In addition, in patients with pancreatic cancer, the mechanical effect of the tumor, dysfunction of the pancreas in digestion, and cytotoxic treatments may accelerate the development of malnutrition by causing changes in taste, pain, and oral intake deficiency.

Albumin is a negative acute phase protein. The level of albumin may vary due to proinflammatory mediators secreted in malnutrition and decreased synthesis.[32-34] Therefore, this parameter can provide information about both the nutritional and inflammation status of patients. Alkaline phosphatase is a member of hydrolase enzymes found in all tissues. However, it is most frequently elevated in liver, biliary tract, bone and kidney diseases. In cancer, alkaline phosphatase has been reported to play a role in tumor growth, metastasis and progression by regulating inflammatory signal transmission, immune response, and cell cy-

cle.[35-37] AAPR, which evaluates albumin and ALP together, was first reported in 2015 to be associated with prognosis in hepatocellular carcinoma and reflect the nutritional, immune and inflammatory status of patients.[10] Since then, it has been shown to be associated with prognosis in many cancers.[38-43] In previous studies, AAPR was reported to be independent prognostic factor by Pu et al. in a sample consisting of operated patients and Zhang et al., who evaluated patients with unresectable pancreatic cancer.[44-45] In our study, we found that among patients with metastatic pancreatic cancer aged under 65 years, survival was associated with AAPR in both univariance and multivariance analyses, which is consistent with the literature.

The limitations of our study include its retrospective and single-centered design and the small number of patients. However, our study is important since it is the first in the literature to show the relationship between survival time and NLR, GLR, and AAPR in young patients with pancreatic cancer.

Young patients differ from elderly patients due to comorbidities, physiological changes and different tumor biology of the latter. Therefore, this study is important because it is the first to demonstrate the presence of a relationship between GLR, NLR and AAPR and prognosis in patients under 65 years.

In conclusion, GLR, NLR, and AAPR were associated with the prognosis of pancreatic cancer in our study.They can be used as easy, cheap and practical biomarkers to determine the monitoring treatment and prognosis of patients with pancreatic cancer.

Disclosures

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki and reviewed and approved by the Health Sciences Ethics Committee of Manisa Celal Bayar University (decision no: 20.478.486, date: 05.02.2020).

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Conflict of Interest: None declared.

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