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ORIGINAL ARTICLE

The Predictivity Evaluation of Prognostic Nutritional Index, Neuthrophil to Lymphocyte Ratio and Platalet to Lymphocyte Ratio with Gustave- Roussy Immune Score in Patients Diagnosed with Pancreatic Carcinoma: Single Center Trial

Hatice BAŞARAN GÖKŞEN, Alaettin ARSLAN

Department of Radiation Oncology, Kayseri City Hospital, Kayseri-*Türkiye*

OBJECTIVE

Nowadays, Gustave-Roussy immunoscoring is used to predict treatment sensitivity and survival, especially in the patient group for which immunotherapy is planned for lung cancer. In this study, we aimed to compare the prognostic importance of systemic inflammatory parameters with the immune score in pancreatic cancer (PC), which is a type of cancer with an immunological and poor prognosis.

METHODS

101 patients diagnosed with PC who were diagnosed or treated in our center between 2014 and 2024 were included in the study. The values of prognostic nutritional index (PNI), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), Gustave Roussy immune score (GRIm-s), and eosinophil-to-monocyte ratio (EMR) were calculated according to laboratory parameters at the time of diagnosis. Survival and regression analyses were performed inter-groups for each variable.

RESULTS

Cut-off values were calculated for GRIm-s, PNI, NLR, PLR, hemoglobin, albumin, lactate dehydrogenase, and EMR. In terms of survival analyses, GRIm-s, PNI, hemoglobin, NLR, albumin, and PLR were statistically significant for OS (p=0.00, p=0.03, p=0.032, p=0.00, p=0.00, p=0.029). In the multivariate Cox regression analysis, GRIm-s was the most powerful variable affecting OS independently (HR: 2.538, 95% CI: 1.558-4.135, p:0.000).

CONCLUSION

GRIm-s is a reliable and prognostic value in terms of survival in PC. Besides, the predictive ability of that score is much better than other values.

Keywords: Gustave Roussy immune score; pancreatic carcinoma; prognostic nutritional index; systemic inflamatuary score.

INTRODUCTION

Although pancreatic cancer is a relatively rare type of cancer in terms of incidence, it is a lethal malignancy with a high mortality rate. Despite the improved survival of many types of cancer in oncology with early diagnosis and treatment, pancreatic cancer remains far behind this improvement. While 15%–20% of patients can be diagnosed at the resectable stage, the 5-year survival does not exceed 20% even in operated patients.[1]

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Dr. Hatice BAŞARAN GÖKŞEN
Kayseri Şehir Hastanesi,
Radyasyon Onkolojisi Kliniği,
Kayseri-Türkiye
E-mail: dr.htcbsrn@outlook.com

In this case, the factors that have an impact may be the tumor microenvironment and genetic and epigenetic changes that vary from person to person. The main cells found in the tumor microenvironment are fibroblasts, endothelial cells, and inflammatory cells. In parallel with this dominance situation, there is a desmoplastic-fixed extracellular matrix, impaired angiogenesis, and ineffective anti-cancer immunity around pancreatic cancer.[2] As a result, the availability of treatment agents becomes difficult due to the hard stromal component, the treatment response is limited due to hypoxia, and the tumor-killing mechanisms are interrupted due to antigen presentation caused by impaired immunity.

Due to limited treatment options and short survival in pancreatic cancer, cheaper, practical, non-invasive indirect methods with prognostic prediction are also being investigated. The oldest and proven parameter is CA19-9. Tumor burden in pancreatic cancer and biliary tract malignancies has predictive importance in disease follow-up and treatment response evaluation.[3] However, other laboratory-supported parameters with prognostic importance include indirect systemic inflammatory and nutritional status evaluations such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and prognostic nutritional index (PNI).[4–6] Considering the hypoxic nature of pancreatic cancer, devoid of vascularization, intense inflammation around the tumor, and aggressive tumor structure, the Gustave-Roussy Immune score (GRIm-s) can be accepted as an evaluation parameter that covers all of these. This index, which consists of the combined scoring of NLR, albumin, and lactate dehydrogenase, can provide relatively practical and comprehensive prediction.

Our hypothesis in this study is that the GRIm-s, one of the laboratory parameters evaluated for pancreatic cancer survival, will be more predictive than other parameters and can be used practically and cheaply in clinical practice.

MATERIALS AND METHODS

This study was approved by the local university ethics committee (Date: 30/07/2024, Decision no: 137).

Patient Selection

One hundred and one patients diagnosed with pancreatic cancer who received diagnosis and/or treatment at our center between January 2014 and January 2024 were included in the study. Criteria for inclusion in the study included being over 18 years of age, having a pathological diagnosis of pancreatic cancer (adenocarcinoma, neuroendocrine carcinoma), applying to our center during the diagnosis or treatment phase, having the pathology report accessible, having hemogram and biochemistry laboratory results available before the surgical procedure, knowing the initial stage of the disease, having the date of death or the last follow-up date available, having no additional malignancy at the time of diagnosis, having no known autoimmune disease at the time of diagnosis, and having no medication use that would affect laboratory parameters. Survival time was calculated from the date of initial pathology (determined by biopsy or surgery) to the date of death or last follow-up.

GRIm-s and PNI Calculation

GRIm-s was obtained by scoring NLR, LDH, and albumin values. Groups were created as 0–1 and 2–3 by giving a score for the value above (for NLR and LDH) or below (for albumin) the cut-off values of these calculated values.

PNI calculation: It was done as [10×serum albumin (g/dL)]+[0.005×lymphocyte count per microliter].

Statistical Analysis

In terms of factors affecting survival, variables such as age, gender, disease stage, tumor location, number of metastases, operation status, blood group, hemoglobin, albumin, LDH, EMR, NLR, PLR, PNI, and GRIm-s were analyzed. Receiver operating characteristic (ROC) analysis was performed for the cut-off values of numerical variables, and since there were statistically insignificant results, the average values were taken as the cut-off value.

Data are given as frequency, percentage, mean ± standard deviation, and median (min-max). The suitability of the data for normal distribution was evaluated with the Shapiro-Wilk test and histogram and q-q graphs. Chi-square tests were used for comparisons between groups. Kaplan-Meier survival analysis and Cox regression methods were used to determine and compare overall survival. Hazard rates were calculated with 95% confidence intervals. Data analysis was evaluated with IBM SPSS version 21 (SPSS Inc, Chicago, IL, USA). A level of $p<0.05$ was considered significant.

RESULTS

A total of 101 patients were included in the study. Of these, 34 (33.7%) were women, and 67 (66.3%) were men. The median age was 63 years (range: 21–90). According to their stages, 9 patients (8.9%) were stage 1, 19 patients (18.8%) were stage 2, 29 patients (28.7%) were stage 3, and 44 patients (43.6%) were stage 4. The most common tumor location was the pancreatic head (67.3%). There

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Table 1 Patient's clinical and laboratory characteristics

Variable	Number (n=101)		Variable	Number (n=101)	
	n	%		n	%
Gender			Hemoglobin count (g/dL), range	7.7–18.2	
Female	34	33.7	<13.18	49	48.5
Male	67	66.3	>13.18	52	51.5
Age, median (range)	63 (21–90)		Albumin count (g/L), range	24–49	
Stage			<38.78	47	46.5
Stage I	9	8.9	>38.78	54	53.5
Stage II	19	18.8	LDH count (units/L), range	112–876	
Stage III	29	28.7	<259.23	60	59.5
Stage IV	44	43.6	>259.53	41	40.6
Tumor location			EMR, range	0–1.67	
Uncinat	9	8.9	<0.258	62	61.4
Head	68	67.3	>0.258	39	38.6
Corpus	18	17.8	NLR, range	0.81–15.5	
Tail	6	5.9	<3.8	64	63.4
Metastasis condition			>3.8	37	36.6
Null	58	57.4	PLR, range	52.98–480.28	
Single	4	4	<166.99	55	54.5
Oligo	9	8.9	>166.99	46	45.5
Multipl	30	29.7	PNI, range	30.15–64.3	
Operation status			<47.93	55	54.5
Yes	33	32.7	>47.93	46	45.5
No	68	67.3	GRIm-s		
Blood group			0–1	64	63.4
0	24	23.8	2–3	37	36.6
A	57	56.4	Survival status		
B	13	12.9	Ex	78	77.2
AB	7	6.9	Survi	23	22.8

LDH: Lactate dehydrogenase; EMR: Eosinophil to monocyte ratio; NLR: Neuthrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; PNI: prognostic nutritional index; GRIm-s: Gustave Roussy Immune score

were no metastases at baseline in 58 patients (57.4%). Most patients were inoperable at diagnosis (67.3%). The most common blood group was A (56.4%).

The mean values for the numerical variables hemoglobin, albumin, LDH, EMR, NLR, PLR, and PNI were 13.18, 38.78, 259.23, 0.258, 3.8, 166.99, and 47.93, respectively. The GRIm-s of 64 of the patients (63.4%) was in the 0–1 group. Overall, 77.2% of all patients were deceased (Table 1). The median OS was 10 months (range: 1–90 months).

Survival analyses were performed in terms of NLR, PLR, PNI, and GRIm-s. While the median survival of the group with an NLR value <3.8 was 18 months, the median survival of the >3.8 group was 8 months (Fig. 1). While the median OS of patients with GRIm-s 0–1 was 23 months, that of patients with GRIm-s 2–3 was 6 months (Fig. 2). For PLR, the median survival of the <166.99 group was 14 months, and the >166.99 group was 11 months (Fig. 3). The median survival of the group with a PNI value of >47.93 was 22 months, while that of the group with a PNI value of <47.93 was 9 months (Fig. 4).

One of the remarkable survival results relates to blood type. OS for O, A, B, and AB blood groups was 14 months, 11 months, 5 months, and 70 months, respectively (p=0.004) (Fig. 5).

When the factors affecting survival were analyzed in univariate Cox regression analysis, stage, operation status, number of metastases, blood group, hemoglobin, albumin, NLR, PLR, PNI, and GRIm-s were found to be statistically significant (p values: 0.001, 0.002, 0.000, 0.011, 0.055, 0.000, 0.000, 0.029, 0.002, and 0.002, respectively). Among these, the number of metastases and GRIm-s were determined to be independent factors affecting survival in multivariate Cox regression analysis (HR: 1.389, 95% CI: 1.165–1.657, p=0.000; HR: 2.538, 95% CI: 1.558–4.135, p=0.000, respectively) (Table 2).

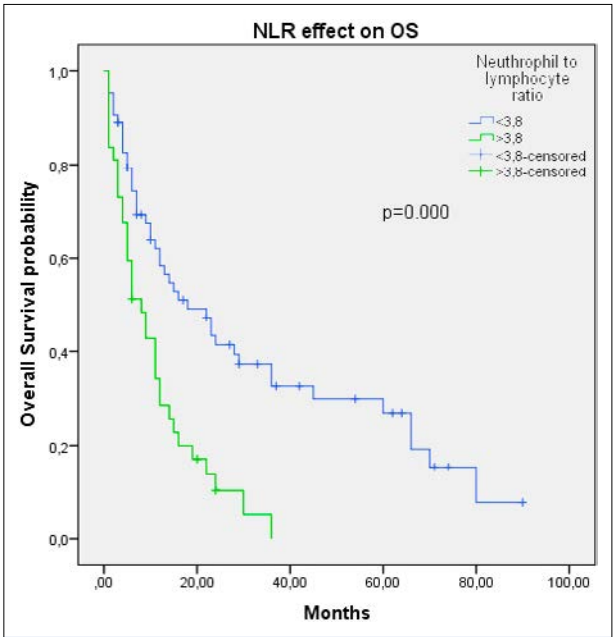

Fig. 1. Neuthrophil to lymphocyte ratio (NLR) effect on overall survival (OS).

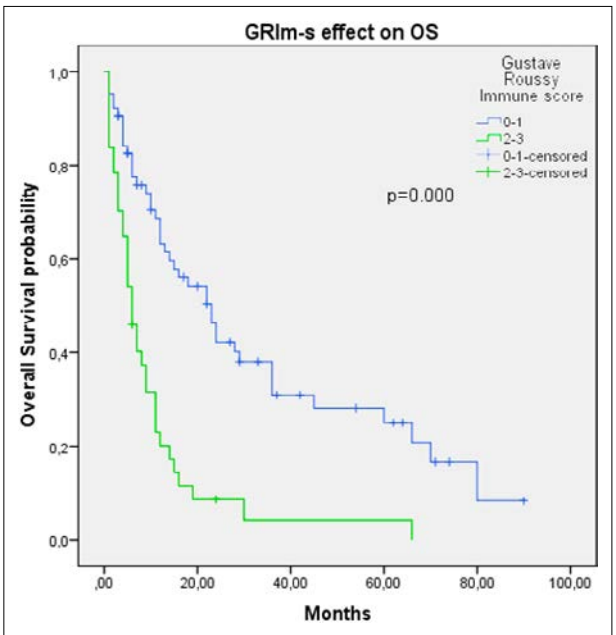

Fig. 2. Gustave-Roussy Immune score (GRIm-s) effect on overall survival (OS).

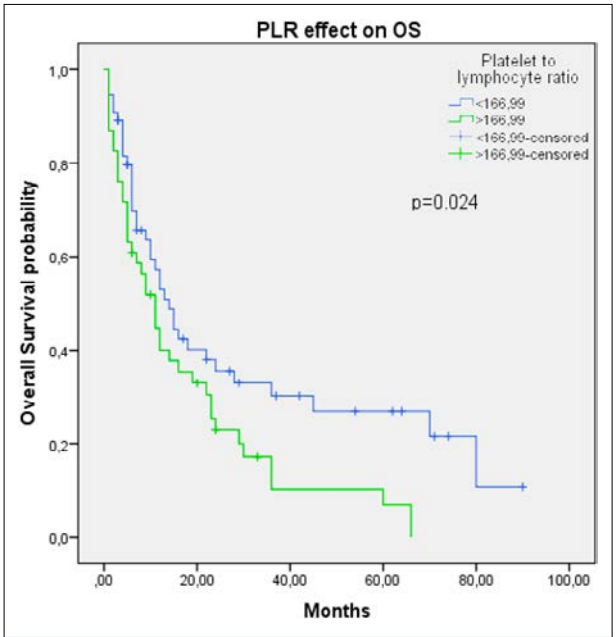

Fig. 3. Platelet to lymphocyte ratio (PLR) effect on overall survival (OS).

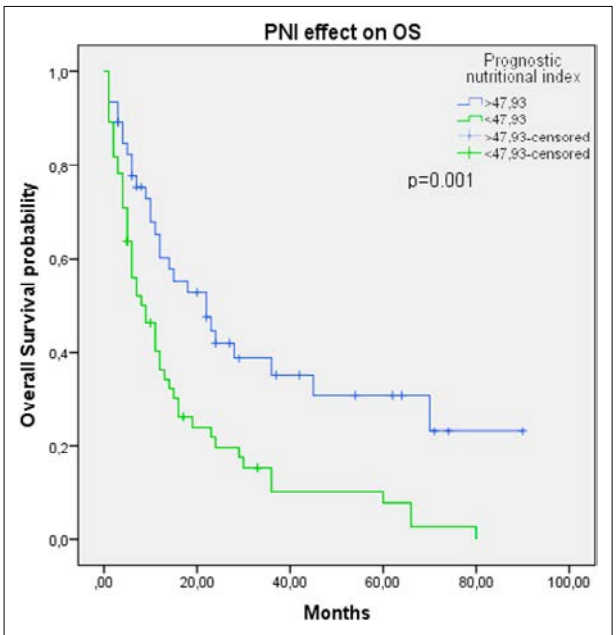

Fig. 4. Prognostic nutritional index (PNI) effect on overall survival (OS).

DISCUSSION

In the literature, studies on GRIm-s are concentrated especially on lung cancer and provide results on immunotherapy response prediction, disease prognosis, and chemotherapy sensitivity.[7–11] There is limited data beyond lung cancer. These can be listed as ovarian cancer, esophageal cancer, biliary tract cancer, hepatocellular cancer, and pancreatic cancer.[12–16] Two recent studies have evaluated pancreatic cancer.[17,18] While one of them focused on operable patients, the other evaluated advanced-stage patients.

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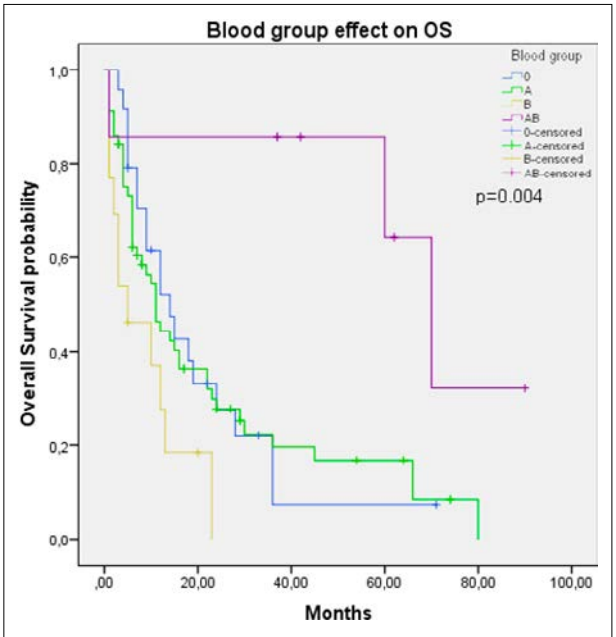

Fig. 5. Blood group effect on overall survival (OS).

In the study by Basoglu et al.,[17] only GRIm-s was evaluated, and it was specific to operated patients. Patients over a 12-year period were included retrospectively, and the patients' postoperative pathological features (perineural invasion, lymphovascular invasion, surgical margins) and body mass indexes were analyzed. Pre-surgical GRIm-s evaluation was found to be prognostic for survival. In this study, we examined patient groups from all stages, the majority of which consisted of stage 4 patients. Data were obtained based on laboratory parameters even before a biopsy was performed. The study included patients who applied to our center over a total of 10 years.

In another study conducted by Ma et al.[18] on patients with advanced pancreatic cancer, NLR, PLR, PNI, and Memorial Sloan Kettering Prognostic Score (MPS) were evaluated in addition to GRIm-s. MPS is obtained by scoring NLR and albumin values. NLR, GRIm-s, and MPS were found to be poor prognostic indicators in the high-risk group. The pathological correlation of these values was made with CD8+ tumor-infiltrating lymphocytes. As a result, lower median CD8+ tumor-infiltrating lymphocytes were detected in the high-risk patient group with GRIm-s and MPS. In another study on MPS, Lebenthal et al.[19] showed that MPS was prognostic in patients with metastatic pancreatic cancer.

MPS is an evaluation method very similar to GRIm-s and has almost the same variables. Although LDH evaluation within GRIm-s may make this scoring more powerful, it may show false elevations in patients with comorbidities and/or synchronous cancer. The pathological correlation conducted by Ma et al.[18] is the original aspect of their study, as there is no pathological correlation in our study. We also found the GRIm-s value to be prognostic in terms of survival and compared it with other laboratory parameters. Additionally, there is no data regarding blood groups in these studies, whereas our study offers a separate evaluation of this aspect.

In a different study, Imaoka et al.[20] evaluated the modified Glasgow Prognostic Score (mGPS) in

Table 2 Cox-regression analyzes in terms of overall survival

Parameters	HR	95% CI	p
Stage (stage I- reference)	6.192	2.155–17.786	**0.001**
Operation status	2.304	1.372–3.867	**0.002**
Metastasis number (null- reference)	3.104	1.838–5.239	**0.000**
Blood group (AB- reference)	2.125	1.001–4.508	**0.011**
Hemoglobin count (g/dL)	1.548	0.990–2.419	**0.055**
Albumin count (mg/dL)	2.361	1.498–3.721	**0.000**
LDH count (units/L)	1.177	0.747–1.854	0.481
NLR	2.447	1.520–3.941	**0.000**
PLR	1.654	1.051–2.603	0.029
PNI	2.126	1.333–3.391	0.002
GRIm-s	3.019	1.884–4.838	**0.000**
Multivariate cox-regression analyzes in terms of overall survival			
Metastasis number	1.389	1.165–1.657	**0.000**
GRIm-s	2.538	1.558–4.135	**0.000**

HR: Hazard ratio; CI: Confidence interval; LDH: Lactate dehydrogenase; NLR: Neuthrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; PNI: Prognostic nutritional index; GRIm-s: Gustave Roussy Immune score

pancreatic cancer. The mGPS evaluation is based on C-reactive protein and albumin values. As a result of this study, mGPS was found to be prognostic for survival in pancreatic cancer. In our study, CRP was included in the data. Pre-treatment CRP values for 15 patients could not be reached, but no effect on survival was detected in the evaluation of the CRP values of the remaining patients.

LDH, an indirect indicator of anaerobic glycolysis and hypoxia, was associated with treatment resistance in the study by Koukourakis et al.[21] and with poor survival in the study by Tas et al.[22] on patients with metastatic pancreatic cancer. Although LDH was associated with treatment resistance in one study and poor survival in the other, we did not find it to be prognostic in terms of survival in our study. This may be due to the mixed disease stages, as the patient group in the study by Koukourakis et al.[21] was exclusively metastatic.

In the meta-analysis conducted by Zhao et al.,[6] the contribution of PNI to prognosis in pancreatic cancer patients undergoing curative resection was proven. In the analysis, which included a total of 14 studies and 3,385 patients, it was shown that a low PNI value was associated with poor survival. In our study, we found PNI to be prognostically effective on survival. However, it lost this effect to GRIm-s in multivariate analysis.

When examining the relationship between blood groups and cancer, historical studies report disease distribution by blood group. In a study by Macafee, pancreatic cancer was less common in blood group A and more common in blood group B compared to the normal population.[23] In our study, most of the pancreatic cancer patients had blood type A. Additionally, when examined from a prognostic perspective, we found that the survival of the patient group with AB blood type was better. However, as blood group distribution shows racial differences, this distribution may vary between populations. No studies in the literature have examined survival differences by blood type in detail. This makes our study result original. This result must be supported by a larger-scale study.

Limitations of the Study

The limitations of our study include its retrospective nature, limited number of patients, single-center scope, and non-specificity to disease stage and treatment modality. Its strengths include random patient selection, comparison of laboratory parameters with one another, and the ability to provide predictions for clinical conditions such as blood type and the number of metastases, which are limited in the literature.

CONCLUSION

Pancreatic cancer, even in limited stages, continues to be a life-limiting malignancy. For this reason, it is an oncological condition in which supportive treatment is at the forefront, along with developments in oncological treatments. Treatment planning through practical and inexpensive nutritional and laboratory parameters is an acceptable option for disease prognosis prediction. As concluded in our study, using GRIm-s for this prediction is a noteworthy and acceptable method. Additionally, it provides a strong alternative as a prognostically superior option compared to other parameters.

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Ethics Committee Approval: The study was approved by the Kayseri City Hospital Non-interventional Clinical Research Ethics Committee (no: 137, date: 30/07/2024).

Authorship contributions: Concept – H.B.G.; Design – A.A.; Supervision – H.B.G.; Materials – A.A.; Data collection and/or processing – H.B.G.; Data analysis and/or interpretation – H.B.G.; Literature search – A.A.; Writing – H.B.G.; Critical review – A.A.

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