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ORIGINAL ARTICLE

Gustave Roussy Immune Score in Operable Pancreatic Ductal Adenocarcinoma: Its Association with Quantitative 18F-FDG PET/CT Parameters and Histopathological Features, and Prognostic Significance

Kerim ŞEKER,[1] Süleyman KOÇ,[2] Hatice ÖZER,[3] Zekiye HASBEK[1]

[1]Department of Nuclear Medicine, Sivas Cumhuriyet University, Faculty of Medicine, Sivas-*Türkiye*
[2]Department of General Surgery, Sivas Cumhuriyet University Faculty of Medicine, Sivas-*Türkiye*
[3]Department of Medical Pathology, Sivas Cumhuriyet University Faculty of Medicine, Sivas-*Türkiye*

OBJECTIVE

This study aimed to investigate the relationship and prognostic value of the Gustave Roussy Immune Score (GRIm Score), quantitative 18F-FDG PET/CT parameters, and histopathological features in operable pancreatic ductal adenocarcinoma (PDAC) patients.

METHODS

We retrospectively analysed 18F-FDG PET/CT data, routine pre-operative blood tests (for GRIm Score), and post-surgical pathology (LVI, PNI, etc.) from 41 operable PDAC patients (2016-2024). The GRIm Score (0-3) was determined using LDH, Albumin, and NLR. Patients were categorized into low (0-1) and high (2-3) GRIm groups for statistical evaluation.

RESULTS

No significant correlation was found between the GRIm score and PET/CT or pathology features. Mean overall survival was 12.97 months. Patients with high GRIm scores showed significantly shorter survival (6.2 months vs. 16.7 months, $p<0.001$). Multivariate survival analysis confirmed that both the GRIm score (HR=10.258, $p<0.001$) and the presence of LVI (HR=14.899, $p=0.019$) were independent prognostic factors. Other parameters did not show a significant association with survival.

CONCLUSION

The GRIm score, easily and cost-effectively calculated from routine blood tests, holds significant and independent prognostic value in operable PDAC patients. Its independence from conventional tumor features suggests promising potential for assessing prognosis.

Keywords: 18F-FDG PET/CT; GRIm score; histopathology; pancreatic ductal adenocarcinoma; survival.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is among the most aggressive and lethal cancers. Globally, it ranks as the 12th most common type of cancer and is the 6th leading cause of cancer-related deaths, accounting for approximately 467,000 fatalities.[1] PDAC's aggressive biological behaviour, its tendency

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Dr. Kerim ŞEKER
Sivas Cumhuriyet Üniversitesi Tıp Fakültesi,
Nükleer Tıp Anabilim Dalı,
Sivas-Türkiye
E-mail: kerimseker@cumhuriyet.edu.tr

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for early spread to regional or distant sites, and its late-appearing, non-specific symptoms are the primary reasons for its poor prognosis.[2]

The five-year survival rate is approximately 12%, and radical surgical procedures remain the only treatment option that can potentially offer a cure for the patient.[2,3] Only 10–20% of patients are suitable for surgical resection at the time of diagnosis. Even for those undergoing radical surgical resection, the 5-year overall survival rate remains low, between 10–29%.[4]

Positron emission tomography/computed tomography (PET/CT) using 18-Fluorodeoxyglucose (18F-FDG) is currently noted in guidelines as being under development for PDAC, unlike for other solid tumours. However, studies over the past decade have demonstrated the potential utility of 18F-FDG PET/CT imaging in the diagnosis and staging of pancreatic cancer. Beyond staging, 18F-FDG PET/CT images also provide valuable insights into tumour behaviour and aggressiveness through quantitative metabolic parameters derived from the primary tumour. These include the standardized uptake value (SUV), metabolic tumour volume (MTV), and total lesion glycolysis (TLG). Primary tumours exhibiting high maximum SUV (SUV_{max}), MTV, and TLG values are associated with a higher tumour grade and poorer survival outcomes.[4–7]

Traditional determinants of patient survival following pancreaticoduodenectomy include tumour margin, tumour type, tumour size, tumour differentiation, and regional lymph node status. Two other frequently reported, but less thoroughly analysed, parameters are perineural invasion (PNI) and lymphovascular invasion (LVI). PNI has been concluded to be highly significant in patient prognosis after pancreatic tumour resection. Furthermore, the presence of LVI has been reported to decrease survival in neuroendocrine tumours of the pancreas. It's hypothesized that PNI may be responsible for local failure due to tumour growth along the nerves that innervate the pancreas and ultimately form the periarterial neural plexus. Similarly, the presence of LVI may be responsible for regional or distant metastasis in lymph nodes or other organs like the lungs and liver. Pathological tumour size is also associated with poor overall survival.[8,9]

The Gustave Roussy Immune Score (GRIm score) was recently developed to improve participant selection for Phase I trials involving non-small cell lung cancer patients treated with immune checkpoint inhibitors. The GRIm score is a composite measure derived from serum lactate dehydrogenase (LDH) levels, serum albumin concentration (Alb), and the neutrophil-lymphocyte ratio (NLR). These parameters can provide insights not only into immunogenicity but also into components of the tumour microenvironment. Notably, elevated NLR and low albumin levels are indicative of high inflammation.[10] The other component of the GRIm score, lactate dehydrogenase (LDH), is associated with intracellular hypoxic reactions that contribute to the formation of a hypovascular microenvironment. A high GRIm score may help identify patients with aggressive disease and a poor survival prognosis in both localized and PDAC.[11,12]

This study aims to assess the relationship between the GRIm score, derived from pre-operative blood samples, and metabolic data from primary tumours on 18F-FDG PET/CT images, as well as histopathological findings from post-operative tumour specimens, in PDAC patients eligible for surgery. Furthermore, it seeks to determine the prognostic significance of these combined parameters.

MATERIALS AND METHODS

In this study, following approval from the Sivas Cumhuriyet University Faculty of Medicine Ethics Committee (Decision No: 2025-04/88), quantitative 18F-FDG PET/CT data, histopathological data, and blood samples from patients diagnosed with PDAC between January 1, 2016, and June 15, 2024, were retrospectively evaluated. These data were acquired using the PET/CT scanner (Discovery600 PET/CT GE Medical Systems, USA) at Cumhuriyet University Faculty of Medicine Hospital and analysed with the "IBM Statistics Package for the Social Sciences version 26.0 (SPSS ver. 26.0)" statistical software. The study was conducted according to the Helsinki Declaration.

Patient Selection Criteria

Patients included in this study met the following criteria: They were considered suitable for curative surgical resection due to a pancreatic mass and underwent either a Whipple operation or distal pancreatectomy with curative intent. Prior to surgery, specifically within 14 days, they had undergone 18F-FDG PET/CT imaging for primary staging without any did not receive any preceding neoadjuvant treatment prior to surgery. Following successful surgical resection, all patients were routinely referred to the Medical Oncology department for standard adjuvant treatment protocols. Within 7 days before surgery, routine blood tests performed for surgical preparation provided accessible

neutrophil and lymphocyte counts, as well as albumin and LDH levels. Furthermore, complete post-operative histopathological data and at least one year of follow-up data were available for these patients.

Patients were excluded from the study if they had a second malignancy other than PDAC, did not undergo 18F-FDG PET/CT imaging for pre-curative surgical staging, or if there was a gap of more than 14 days between imaging and operation. Additionally, patients were excluded if pre-operative routine blood test results were unavailable, or if more than 7 days elapsed between the blood tests and the operation date, or if there was missing data for at least one of the neutrophil or lymphocyte counts, albumin, or LDH levels. Patients with inaccessible post-operative histopathological data or a follow-up period of less than 1 year were also excluded.

18F-FDG PET/CT Imaging Protocol

Before 18F-FDG PET/CT imaging, patients fasted for at least 6 hours. Their blood glucose levels were confirmed to be below 180 mg/dL before 18F-FDG injection. For eligible patients, 18F-FDG was injected intravenously at a dose of 0.1 mCi/kg, and images were acquired approximately 60 minutes post-injection. PET images underwent attenuation correction using CT images. First, a CT scan was performed. Immediately following the CT scan, a standard PET imaging protocol was applied in 3D mode, with an acquisition time of 2 minutes per bed position, extending from the vertex to the mid-thigh. All PET images were acquired in 3D mode. CT images were obtained without intravenous contrast administration, at 70 mA, 120 kV, and an axial slice thickness of 2.5 mm. The spatial resolution of the PET camera system was 5 mm. BT and PET images were coregistered and fused into transaxial, coronal, and sagittal views. For each patient, axial PET slices containing the primary pancreas tumour were processed into DICOM (Digital Imaging and Communications in Medicine) format with a 128×128 matrix. The data were then transferred to a processing workstation (AW Volume Share5 GE Medical Systems S.C.S, France) via the DICOM protocol.

18F-FDG PET/CT Image Analysis

18F-FDG PET/CT images were visually and quantitatively assessed by two experienced nuclear medicine specialists. For the PET images, an adaptive threshold of 42% of the maximum lesional metabolic activity was applied, and a volume of interest (VOI) was positioned to encompass the primary tumour. This relative threshold method was selected to ensure reproducible and accurate calculation of the MTV for the primary tumour, which helps in minimizing the partial volume effect inherent PET quantification.[13] The SUV_{max}, SUV_{mean}, and MTV values for the primary tumour were automatically calculated from the PET images using the PET REV software on the workstation. Total Lesion Glycolysis (TLG) was then computed by multiplying MTV by SUV_{mean}.

Histopathological Evaluation

Postoperative histopathological examinations of the patients were retrospectively reviewed and re-evaluated according to the 8th edition of the American Joint Committee on Cancer.[14] From existing histopathology results, the maximum pathological dimension of the primary tumour (Dpat), tumour grade (G), pathological tumour stage (pT), pathological nodal stage (pN), and the presence of lymphovascular invasion (LVI) and perineural invasion (PNI) were recorded. For patients with identified pT and pN stages, the TNM stages were also defined.

GRIm Score Evaluation

For each patient, routine blood tests were retrospectively evaluated from the hospital information system, specifically examining hemogram and biochemistry panels conducted within 7 days prior to surgery. From the hemogram panel, neutrophil count (NS) and lymphocyte count (LS) were recorded. Albumin (Alb) and LDH levels were recorded from the biochemistry panel. Each patient was then scored as follows: LDH>upper limit of normal received 1 point, Alb<35 grams/liter received 1 point, and NS/LS (NLR)>6 received 1 point. The sum of these points defined the patient's total GRIm score, which could range from 0 to 3. Patients were subsequently categorized into two groups based on their GRIm scores, as originally defined by Bigot et al.:[10] A low-score group (GRIm score: 0 and 1) and a high-score group (GRIm score: 2 and 3).

Statistical Analysis

Data obtained from our study were analysed using SPSS 26.0. The Shapiro-Wilk test was employed to assess the normality of data distribution. For normally distributed data, Student's t-test was used for group comparisons. If data did not follow a normal distribution, the Mann-Whitney U test was applied for comparisons between two independent groups, while the Kruskal-Wallis test was utilized for comparisons involving more than two independent groups. When using ANOVA for comparisons with more than two groups, Tukey's HSD test was applied to identify dif-

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fering groups when the assumption of homogeneity was met, and Tamhane's T2 test was used when this assumption was violated. The Chi-square test was employed for evaluating count data. The effects of parameters on survival were examined using the log-rank test. Survival rates were calculated using Kaplan-Meier survival analysis. Additionally, to identify independent prognostic factors, multivariate analysis was performed using the Cox proportional hazard regression model, including variables found to be significant in the univariate analysis and other clinically relevant factors. A significance level of 0.05 was set.

RESULTS

Patient Characteristics

Our study included 41 operable PDAC patients. Of these, 56.1% were male (n=23) and 43.9% were female (n=18). The average age of the included patients was 65 years (ranging from 49 to 84 years). At the end of at least one year of follow-up from diagnosis, it was observed that 85.4% (n=35) of the patients had died, while 14.6% (n=6) were still alive. The mean overall survival for these patients was 12.97 months (ranging from 0.2 months to 37.4 months).

The mean (± standard deviation (s.d.)) values for the quantitative metabolic parameters of the primary tumour were calculated as follows: SUV_{max} was 5.85 (±1.84), SUV_{mean} was 3.36 (±1.03), MTV was 19.59 (±12.95), and TLG was 62.51 (±41.84).

The mean (± s.d.) maximum histopathological dimension of the primary tumour was calculated as 36.77 mm (±14.36 mm). Histopathologically, primary tumours were reported as 7.3% (n=3) Grade 1, 87.8% (n=36) Grade 2, and 4.9% (n=2) Grade 3. PNI was observed in 95.1% (n=39) of cases, with only 4.9% (n=2) showing no PNI. LVI was positive in 80.5% (n=33) of cases, while it was not detected in 19.5% (n=8). Regarding pathological T stages, 4.9% (n=2) of cases had T1 tumours, 65.9% (n=27) had T2, 22% (n=9) had T3, and 7.2% (n=3) had T4 tumours. The pathological N stages of the patients were determined as N0 in 17.1% (n=7), N1 in 31.7% (n=13), and N2 in 51.2% (n=21). All patients were non-metastatic. When examining the TNM stages, 4.9% (n=2) were classified as Stage 1A, 9.8% (n=4) as Stage 1B, 2.4% (n=1) as Stage 2A, 29.3% (n=12) as Stage 2B, and 53.6% (n=22) as Stage 3.

The GRIm score was calculated as low (GRIm score: 0 and 1) in 65.9% (n=27) of patients, while it was high (GRIm score: 2 and 3) in 34.1% (n=14).

Table 1 Relationship between quantitative 18F-FDG PET/CT and quantitative histopathological parameters with GRIm score

	Low GRIm score (score 0–1, n=27)	High GRIm score (score 2–3, n=14)	p
SUV_{max}	5.8 (±1.92)	5.94 (±1.75)	0.891
SUV_{mean}	3.35 (±1.08)	3.37 (±0.96)	0.967
MTV	20.54 (±14.97)	17.74 (±7.88)	0.912
TLG	64.63 (±47.2)	58.43 (±30.09)	0.978
Dpat	36.19 (±15.21)	37.86 (±13.05)	0.284

Values in this context are expressed as the mean (± standard deviation). 18F-FDG PET/CT: 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography; GRIm: Gustave roussy immune; SUV_{max}: Maximum standardized uptake value; SUV_{mean}: Mean standardized uptake value; MTV: Metabolic tumour volume; TLG: Total lesion glycolysis, Dpat: Maximum pathological dimension

Relationship Between GRIm Score, Quantitative 18F-FDG PET/CT Data, and Histopathological Features

No significant relationship was observed between the low and high GRIm score patient groups concerning either the quantitative 18F-FDG PET/CT parameters or the histopathological features (p>0.05). The quantitative data pertaining to these findings are summarized in Table 1 and Table 2.

Survival Analysis of Variables

Before performing survival analysis, continuous numerical variables were characterized by their median (min – max) values. The median values for SUV_{max}, SUV_{mean}, MTV, TLG, and Dpat were determined to be 5.4 (3.37 –11.0), 3.06 (2.0–6.32), 18.02 (3.5–54.84), 52.67 (11.94–195.23), and 30 (6.0–85.0), respectively. These variables were then categorized into two groups: Those equal to or below the median value, and those above the median value. Survival analysis was conducted after all data were organized as categorical variables.

For the entire cohort, the mean overall survival was calculated as 12.97 months (95% CI: 9.5–16.3 months), and the median overall survival was 10.6 months (95% CI: 6.2–14.9 months).

When all variables were evaluated, a significant relationship was found between GRIm score, LVI status, and survival. The low GRIm score group comprised 27 patients; 21 of them died during the follow-up period, while 6 were still alive. In contrast, the high GRIm score group consisted of 14 patients, all of whom died within the follow-up period. The estimated mean overall sur-

Table 2 Relationship between categorical histopathological features and GRIm score (n=41)

Histopathological feature	GRIm score	Frequency	p	Histopathological feature	GRIm score	Frequency	p
Perineural invasion			0.296	pT3	Low (0–1)	5	
Negative	Low (0–1)	2			High (2–3)	4	
	High (2–3)	0		pT4	Low (0–1)	2	
Positive	Low (0–1)	24			High (2–3)	1	
	High (2–3)	15		pN stage			0.857
Lymphovascular invasion			0.15	pN0	Low (0–1)	4	
Negative	Low (0–1)	7			High (2–3)	3	
	High (2–3)	1		pN1	Low (0–1)	9	
Positive	Low (0–1)	20			High (2–3)	4	
	High (2–3)	13		pN2	Low (0–1)	14	
Tumour grade			0.228		High (2–3)	7	
Grade 1	Low (0–1)	3		TNM stage			0.726
	High (2–3)	0		1A	Low (0–1)	1	
Grade 2	Low (0–1)	22			High (2–3)	1	
	High (2–3)	14		1B	Low (0–1)	3	
Grade 3	Low (0–1)	2			High (2–3)	1	
	High (2–3)	0		2A	Low (0–1)	0	
pT stage			0.827		High (2–3)	1	
pT1	Low (0–1)	1		2B	Low (0–1)	8	
	High (2–3)	1			High (2–3)	4	
pT2	Low (0–1)	19		3	Low (0–1)	15	
	High (2–3)	8			High (2–3)	7	

(pT: Pathological T stage pN: Pathological N stage TNM: Tumour-Node-Metastasis stage)

vival for the low GRIm score group was 16.7 months (95% CI: 12.3–21.2 months), with a median survival of 16.0 months (95% CI: 10.3–21.7 months). Conversely, the high GRIm score group had an estimated mean overall survival of 6.2 months (95% CI: 2.9–9.4 months), and a median survival of 3.3 months (95% CI: 0–12.1 months). The Log-Rank (Mantel-Cox) test, which assesses the equality of survival distributions between groups, revealed a statistically significant difference (Chi-square=13.020, df=1, p<0.001). This finding indicates that the GRIm score creates a statistically significant difference in survival duration, demonstrating that patients with a low GRIm score have significantly longer survival times compared to those with a high GRIm score (Table 3, Fig. 1).

There were 8 patients in the group without LVI; 6 of these died during the follow-up period, while 2 remained alive. Conversely, the LVI-positive group consisted of 33 patients, with 29 dying during the follow-up and 4 surviving. The estimated mean overall survival for the LVI-negative group was 22.6 months (95% CI: 13.5–31.7 months), and the median survival was 17.6 months (95% CI: 13.5–21.6 months). In contrast, the LVI-positive group had an estimated mean overall survival of 10.6 months (95% CI: 7.4–13.8 months), and a median survival of 9.400 months (95% CI: 6.0–12.7 months). The Log-Rank (Mantel-Cox) test, used to compare survival distributions between groups, revealed a statistically significant difference (Chi-square=5.659, df=1, p=0.017). This finding indicates that the presence of LVI significantly impacts survival duration, showing that patients without lymphovascular invasion have considerably longer survival times than those with it (Table 3, Fig. 1).

No significant relationship was observed between other parameters and survival, and these findings are summarized in Table 3.

Multivariate Survival Analysis

Multivariate Cox Proportional Hazard Regression analysis was performed including variables with prognostic significance in the univariate analysis (GRIm Score and LVI) and other clinically relevant factors (Grade, pT/pN stages, SUV_{max} categories).

The analysis demonstrated that a High GRIm Score (HR=10.258, 95% CI: 2.935–35.852, p<0.001) and the presence of LVI (HR=14.899, 95% CI: 1.555–142.720,

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Table 3 Relationship of quantitative 18F-FDG PET/CT parameters, histopathological features, and GRIm score with overall survival

Group	Mean (month)	95% CI (mean)	Median (month)	95% CI (median)	Chi-square value	df	p
SUV_{max}					0.951	1	0.329
≤5.4	14.719	9.786–19.652	13.400	5.962–20.838			
>5.4	11.084	6.479–15.689	9.400	6.172–12.628			
SUV_{mean}					1.238	1	0.266
≤3.06	15.077	9.583–20.571	12.500	4.625–20.375			
>3.06	10.725	9.566–16.37	10.600	7.974–1.226			
MTV					0.130	1	0.718
≤18.02	12.499	8.525–14.474	13.400	0.688–26.112			
>18.02	13.648	8.146–19.150	10.100	7.470–12.730			
TLG					0.000	1	0.992
≤52.67	12.948	8.817–17.080	13.400	4.974–21.826			
>52.67	12.803	7.646–17.959	9.400	5.236–13.564			
Dpat					0.012	1	0.914
≤30 mm	13.304	8.508–18.099	13.400	7.409–19.391			
>30 mm	12.682	7.938–17.426	9.400	5.845–12.955			
Tumour grade					1.090	2	0.580
Grade 1	21.333	0.000–44.343	31.500	N/A			
Grade 2	12.619	9.115–16.123	10.600	7.943–13.257			
Grade 3	9.450	0.000–25.620	1.200	N/A			
Perineural invasion					0.001	1	0.981
Negative	14.150	7.388–20.912	10.700	N/A			
Positive	12.965	9.365–16.564	10.100	4.850–15.350			
Lymphovascular invasion					5.659	1	0.017*
Negative	22.609	13.504–31.715	17.600	13.559–21.641			
Positive	10.666	7.491–13.841	9.400	6.041–12.759			
pT stage					2.016	3	0.569
pT1	20.500	12.877–28.123	15.000	N/A			
pT2	12.545	8.268–16.822	12.500	4.688–20.312			
pT3	14.661	7.094–22.228	10.600	7.326–13.874			
pT4	7.400	0.000–17.564	3.300	0.000–6.661			
pN stage					0.272	2	0.873
pN0	12.329	6.319–18.338	15.000	0.000–36.813			
pN1	12.005	7.058–16.953	10.700	4.183–17.217			
pN2	13.782	8.025–19.539	9.400	6.576–12.224			
TNM stage					3.518	4	0.621
1A	20.500	12.877–28.123	15.000	N/A			
1B	9.700	1.601–17.799	3.600	0.000–17.712			
2A	6.500	6.500–6.500	6.500	N/A			
2B	11.528	6.204–16.851	10.600	4.478–16.722			
3	14.094	8.440–19.748	10.100	1.176–19.024			
GRIm score					13.020	1	<0.001*
Low (0–1)	16.757	12.312–21.201	16.000	10.299–21.701			
High (2–3)	6.200	2.998–9.402	3.300	0.000–12.100			
Overall	12.968	9.566–16.370	10.600	6.246–14.954			

*: In statistical analyses, a p-value less than 0.05 ($p<0.05$) indicates statistical significance. 18F-FDG PET/CT: 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography; GRIm: Gustave roussy immune; CI: Confidence interval; df: Degrees of freedom; SUV_{max}: Maximum standardized uptake value; SUV_{mean}: Mean standardized uptake value; MTV: Metabolic tumour volume; TLG: Total lesion glycolysis; Dpat: Maximum histopathological dimension; pT: Pathological T stage; pN: Pathological N stage; TNM: Tumour-node-metastasis stage; N/A: Not applicable

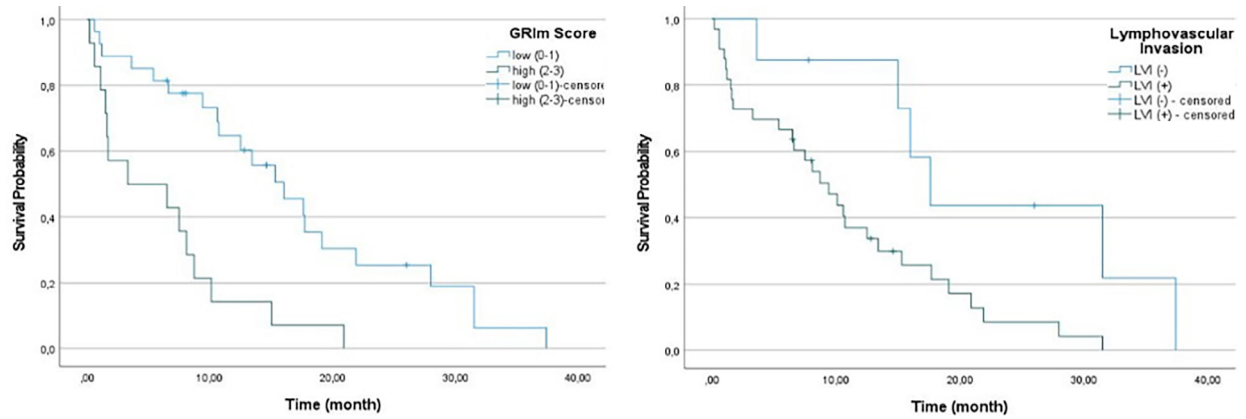

Fig. 1. Overall survival (OS) analysis by Kaplan-Meier method, confirming the significant prognostic value of the gustave roussy immune score (GRIm score) and lymphovascular invasion (LVI) status. Both variables were further validated as independent poor prognostic factors in multivariate Cox regression analysis (Log-rank p<0.001 for GRIm score, p=0.017 for LVI).

Table 4 Multivariate cox proportional hazard regression analysis for overall survival

Variable	HR	95% CI (lower–upper)	p
Independent prognostic factors			
GRIm score	10.258	2.935–25.852	**<0.001**
Lymphovascular invasion	14.899	1.555–142.720	**0.019**
Other factors			
SUV_{max}	0.934	0.089–9.854	0.955
SUV_{mean}	1.475	0.180–12.083	0.717
MTV	0.321	0.079–1.296	0.111
TLG	2.010	0.366–11.056	0.422
Dpat	0.245	0.062–0.971	0.145
Tumour grade	0.962	0.152–6.103	0.967
Perineural invasion	1.026	0.136–7.712	0.980
pT stage	1.687	0.677–4.204	0.261
pN stage	0.304	0.022–4.154	0.372
TNM Stage	1.573	0.235–10.520	0.640

In statistical analyses, a p-value less than 0.05 (p<0.05) indicates statistical significance. HR: Hazard ratio; CI: Confidence interval; GRIm: Gustave roussy immune; SUV_{max}: Maximum standardized uptake value; SUV_{mean}: Mean standardized uptake value; MTV: Metabolic tumour volume; TLG: Total lesion glycolysis; Dpat: Maximum histopathological dimension; pT: Pathological T stage; pN: Pathological N stage; TNM: Tumour-node-metastasis stage

p=0.019) were independent poor prognostic factors for overall survival. Other parameters included in the multivariate model were not found to have significant independent prognostic value (Table 4).

DISCUSSION

In this study, we assessed the relationship between the GRIm score, calculated from pre-operative routine blood tests, and quantitative metabolic parameters derived from primary tumour 18F-FDG PET/CT images, as well as histopathological features of the primary tumour, in operable PDAC patients. We also evaluated the prognostic value of these parameters. While existing literature explores the association of 18F-FDG PET/CT imaging and histopathological features with survival in PDAC patients, there are limited studies evaluating the prognostic value of the GRIm score. Furthermore, we couldn't find any studies that specifically assessed the relationship between the GRIm score and quantitative parameters from 18F-FDG PET/CT images or histopathological features.

In our study, a significant relationship was observed between the GRIm score and the overall sur-

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vival durations of operable PDAC patients. Patients with a high GRIm score were found to have significantly shorter mean survival times compared to those with a low GRIm score (6.2 months vs. 16.7 months). A study by Ma et al.,[12] which compared different immune scoring systems in advanced pancreatic cancer patients, also demonstrated that the GRIm score had higher predictive value and that patients with a high GRIm score had shorter overall survival times. In a study conducted by Basoglu et al.[11] on operable PDAC patients, it was also shown that patients with a high GRIm score had shorter survival. Our study's results align with existing literature, indicating that an elevated GRIm score is a poor prognostic factor for patient outcomes.

Albumin, a key component of the GRIm score, reflects a patient's nutritional status and the inflammatory process. Decreased nutrition and increased inflammation, often associated with disease severity, progression, and prognosis, reduce albumin synthesis. LDH, another component, is a marker of tumour hypoxia. Elevated LDH levels indicate increased tumour hypoxia and heightened macrophage-mediated angiogenesis and invasion. NLR (neutrophil-lymphocyte ratio), the third marker, signifies a rise in neutrophil count alongside a decrease in lymphocyte count. Neutrophils, through the mediators they secrete, can suppress lymphocyte proliferation and lead to a reduction in lymphocyte numbers, particularly CD8+ tumour-infiltrating lymphocytes. This imbalance disrupts immune system homeostasis and weakens the anti-tumoural effect on tumour tissue.[11,12,15–17] The GRIm score has the potential to offer a more holistic approach to prognosis by integrating these individual biomarkers.

Furthermore, our study found no correlation between the GRIm score and quantitative 18F-FDG PET/CT parameters or histopathological features. This suggests that the GRIm score provides a distinct prognostic insight for operable PDAC patients, separate from the tumour's metabolic and morphological characteristics. This finding was strongly validated by our Multivariate Cox Regression Analysis, which demonstrated that the GRIm score is an independent poor prognostic factor for overall survival (HR=10.258, p<0.001). This result reinforces the potential of the GRIm score as a simple and cost-effective tool that complements complex imaging and pathology data in predicting prognosis.

In our study, we concluded that patients with histopathological LVI had a shorter mean overall survival duration compared to those without LVI (22.6 months vs. 10.6 months). Furthermore, the Multivariate Cox Regression Analysis confirmed LVI as a second independent poor prognostic factor (HR=14.899, p=0.019). Many studies in the literature have shown that the presence of LVI is associated with shorter overall survival in resected PDAC patients, and our study reached similar conclusions. A study by Takahashi et al.[18] reported that the median overall survival for patients with LVI was 17 months, while it was 22.5 months for those without LVI. Similarly, a study by Chatterjee et al.[19] demonstrated that patients with muscular venous invasion, a specific histological subtype of LVI, had shorter overall survival compared to those without LVI or those with invasion confined to non-muscular lymphovascular spaces. A recently published meta-analysis by Javed et al.[20] also identified LVI as being associated with long-term survival in resected PDAC patients, demonstrating shorter long-term survival in those with LVI.

In our study, no significant relationship was found between quantitative 18F-FDG PET/CT parameters and overall survival duration. However, literature reviews indicate that tumours with higher SUV_{max}, MTV, and TLG values are associated with shorter overall survival.[6,21,22] Our results, however, contradict findings in the existing literature. Possible reasons for this discrepancy might include the relatively smaller patient cohort in our study. Furthermore, our study specifically included patients with a clear indication for surgical resection who had not received any prior treatment, while excluding those with borderline surgical indications or those who underwent neoadjuvant therapy before surgery. This selection criterion likely resulted in a more homogeneous patient cohort. Variations in the 18F-FDG PET/CT imaging protocols used across studies could also account for these differences.

In our study, we found no significant association between overall survival and other histopathological features, aside from LVI. However, existing literature consistently reports that advanced pT, pN, and TNM stages, higher tumour grade, and the presence of PNI are all poor prognostic indicators, with numerous studies demonstrating significantly shorter overall survival in tumours exhibiting these characteristics.[23–28] We believe the primary reasons we couldn't replicate these findings in our study are the relatively small patient cohort and the homogeneous distribution of most patient characteristics. For instance, 87.2% of patients had Grade 2 tumours, and PNI was

present in 95% of patients. While a large proportion of patients (65.9%) had T2 tumours, T1 (4.9%) and T4 (7.3%) tumours were less common. This distribution of histopathological features was relatively homogeneous, which we believe was insufficient to yield statistical significance. Despite a more heterogeneous distribution for the pN stage, we hypothesize that the small patient number still prevented us from achieving statistically significant results.

Limitations of Our Study

Our study has several limitations, primarily due to its retrospective nature and the relatively small patient cohort. Regarding the clinical management, we only included patients eligible for upfront surgery who did not receive neoadjuvant therapy. While this selection created a homogeneous cohort, the exact details of received adjuvant chemotherapy (e.g., specific regimen, duration, tolerance) were not standardized or prospectively collected. However, we state in the Methods that all patients were routinely referred for standard adjuvant protocols. The most critical missing clinical data is the information regarding patient comorbidities. This absence is a limitation because underlying systemic conditions, independent of the tumour, can significantly influence the GRIm score components, particularly albumin and NLR, potentially confounding the survival analysis. Future prospective studies must be conducted to validate the GRIm score's prognostic value while prospectively collecting and controlling for these vital clinical variables.

CONCLUSION

Incorporating the GRIm score into the routine assessment of patients with resectable pancreatic ductal adenocarcinoma (PDAC) may facilitate more accurate prognostic predictions. The significant advantages of the GRIm score include its easy calculation from routine blood tests, its cost-effectiveness, and its non-invasive application. Our Multivariate Cox Regression Analysis demonstrated that the GRIm score, along with LVI, is an independent factor with significant prognostic value in this patient population. Furthermore, its lack of correlation with quantitative 18F-FDG PET/CT data and histopathological features makes it a promising tool for evaluating patient prognosis. Further research with larger patient populations is needed to validate the prognostic value of the GRIm score and to investigate its promising characteristics in more detail.

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Informed Consent: Informed consent was obtained from all participants.

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