# Associations of volumetric whole-body $^{18}$F-FDG PET/CT parameters with the CA 19-9 level and haemogram parameters in pancreatic adenocarcinoma

**Eşref Araç**[1] **MD,**
**Canan Can**[2] **MD,**
**Halil Kömek**[2] **MD**

*1. Department of Internal Medicine, Saglik Bilimleri University Diyarbakir Gazi Yasargil Training and Research Hospital, Diyarbakir, Turkey*
*2. Department of Nuclear Medicine, Saglik Bilimleri University Diyarbakir Gazi Yasargil Training and Research Hospital, Diyarbakir, Turkey.*

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***Corresponding author:***
Eşref Araç, MD
Gazi Yasargil Egitim Ve Arasturma Hastanesi İç hastaluklaru.
Diyarbakir, Turkey
Telephone: +904122580101
Fax: +90- (412) 2580060
esrefarac@gmail.com

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## Abstract

**Objective:** The present study compared metabolic and volumetric fluorine-18-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography/computed tomography (PET/CT) parameters [metabolic tumour volume (MTV), total lesion glycolysis (TLG), and maximum standardized uptake value (SUVmax)] with carbohydrate antigen (CA) 19-9 tumour marker levels and haemogram parameters [(neutrophil-lymphocyte ratio, mean platelet volume (MPV), and platelet-lymphocyte ratio] as prognostic and diagnostic markers of pancreatic cancer. **Materials and Methods:** A total of 66 patients who underwent $^{18}$F-FDG PET/CT in our nuclear medicine clinic between February 2017 and March 2019, and had a diagnosis of pancreatic adenocarcinoma, were included in this retrospective study. The enrolled patients had not been administered steroids or operated on. Among these patients, whose haemogram parameters and tumour markers could not be assessed by PET/CT within the same week were excluded. The MTV, TLG, and SUVmax values were calculated from primary tumours and metastases in all patients. **Results:** Spearman's rho correlation, used to examine the relationship between the CA 19-9 level and PET parameters, revealed a statistically significant positive correlation of CA 19-9 with the whole-body MTV ($MTV_{WB}$) ($P<0.001$) and whole-body TLG ($TLG_{WB}$) ($P<0.001$). Although no significant relationship was found between the neutrophil count and $TLG_{WB}$ according to Spearman's rho correlation, in an artificial neural network using the hidden layer activation function, the neutrophil count showed the strongest association with $MTV_{WB}$ among all included variables. The primary pancreatic tumour MTV and TLG values showed statistically significant positive correlations with the metastases MTV, metastases TLG, $MTV_{WB}$, and $TLG_{WB}$ values. **Conclusion:** The CA 19-9 level is considered an important marker of tumour load; it shows a statistically significant positive correlation with parameters such as $MTV_{WB}$ and $TLG_{WB}$, which provide a measure of the whole-body tumour load. It appears that the MTV and TLG values of the primary pancreatic tumour could also be used as markers of the whole-body tumour load, given their associations with $MTV_{WB}$ and $TLG_{WB}$.

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## Introduction

Adenocarcinoma is the most common and deadliest form of pancreatic cancer and is the 11$^{th}$ most common cancer type worldwide with 338,000 new diagnoses and 334,000 deaths reported annually and is the 7$^{th}$ most common cause of cancer-related mortality [1]. Pancreatic adenocarcinomas have a poor prognosis even with diagnosis in the early stages, and the outcome is generally not curative, despite intensive treatments. The incidence of adenocarcinoma in Turkey in 2015 was 5.6 and 3.3 per 100,000 population for males and females, respectively [2]. Furthermore, there are 3,633 new cases every year [3]. At the time of diagnosis, 52% of patients have widespread disease, 26% have regional spread, and only 15%-20% are debulkable. The 1- and 5-year overall survival (OS) rates for pancreatic cancer are 20% and 9%, respectively [4].

Carbohydrate antigen (CA) 19-9 is a serum tumour marker expressed in the glycolipid structure as sialyl lacto-N-fucopentaose II ganglioside [5]. The CA 19-9 tumour marker is widely used in pancreatic cancer management, including for early diagnosis [6] and to predict the prognosis, monitor treatment, and assess potential curative treatments [7]. In previous studies, increased levels of CA 19-9 were found in approximately 60%-80% of patients with locally advanced or metastatic pancreatic carcinoma [7].

In the context of pancreatic adenocarcinoma, fluorine-18-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography (PET) has become an important tool for diagnosing

hypermetabolic cancer, disease staging, assessing treatment effectiveness, and detecting recurrence [8, 9]. In addition, the maximum standardized uptake value (SUVmax), metabolic tumour volume (MTV), and total lesion glycolysis (TLG), which are volumetric PET parameters, are prognostic factors [10]. In the present study, we evaluated the associations of metabolic and volumetric $^{18}$F-FDG PET/computed tomography (CT) parameters (MTV, TLG, and SUVmax) with CA 19-9 tumour marker levels and haemogram parameters [neutrophil-lymphocyte ratio (NLR), mean platelet volume (MPV), and platelet-lymphocyte ratio (PLR)], as prognostic and diagnostic markers of pancreatic cancer.

## Materials and Methods

Patients diagnosed with pancreatic adenocarcinoma who underwent $^{18}$F-FDG PET/CT for diagnosis and staging at our nuclear medicine clinic between February 2017 and March 2019 were included in this retrospective study. Recurrence and restaged patients were excluded from the study. We enrolled patients who had not been administered steroids or operated on. Patients whose haemogram parameters and tumour markers could not be assessed by PET/CT within the same week were excluded. A total of 66 patients who met the study criteria were included. The study was approved by the Hospital Ethics Committee under Approval No. 350, dated 25.09.2019. All patients signed a written informed consent form for anonymised evaluation and publication of their data.

### $^{18}$F-FDG PET/CT scanning protocol

All patients were asked to refrain from eating for at least 6 hours before their scan. Cessation of intravenous (i.v.) glucose was requested. The blood glucose level was confirmed to be ≤140mg/dL before the $^{18}$F-FDG injection in all patients. One hour after the $^{18}$F-FDG injection (3.5-5.5MBq/kg), CT images [120kV, 80mAs/slice, 700mm transaxial field of view (FOV), no gap, 64×0.625 mm collimation, pitch of 1.4, 0.5 s rotation time, 3.3mm slice thickness, and 512×512 matrix] from the vertex to the middle of the thigh were obtained in the supine position, using the 4-ring, 20cm axial FOV Discovery IQ PET/CT device (GE Healthcare, Milwaukee, WI, USA) Bedside PET [20cm 3D FOV, ordered subset expectation-maximization algorithm (OSEM), 5 iterations/12 subsets, full width at half maximum (FWHM) 3mm] images were obtained from 2.5 minutes onwards. All patients without contraindications were given IV contrast at a dose of 1.5mL/kg before the CT imaging. Attenuation corrected emission images were obtained using contrast or non-contrast CT data.

### Evaluation of images

All $^{18}$F-FDG PET/CT images were evaluated by a nuclear medicine specialist, with 10 years of experience, using PET Volume Computerized Assisted Reporting (PET-VCAR; GE Healthcare) and the Advantage Workstation software (version 4.7; GE Healthcare). Volumes of interest (VOI) were drawn manually in three planes to include the primary pancreatic lesion, regional lymph nodes, and distant metastases (liver, lung, bone, etc). The MTV and TLG (MTV×SUVmean) values were obtained for each lesion using a SUV threshold value of 40%. Whole body MTV ($MTW_{WB}$) and whole body TLG ($TLG_{WB}$) values were calculated by adding MTV and TLG values from all lesions (Figure 1).

### Statistical analysis

SPSS software (version 25.0; IBM Corporation, Armonk, NY, USA) was used to analyse the data. The Shapiro-Wilk test was used to evaluate the normality of the data. Spearman's rho was used to analyse correlations between variables. Multilayer perceptron neural network analysis was performed to determine the variables most strongly associated with $TLG_{WB}$ and $MTV_{WB}$. The gradient descent method was used to optimise the neural network algorithm, with hyperbolic tangent neural network approximation as the hidden layer activation function, and identity as the output layer activation function. The mini-batch method was used to select the training data; 70% of the data were used for the training set and 30% for the testing set. Quantitative data are shown as means± standard deviation (SD) or median (minimum/maximum) values, and the categorical data are provided in tables as numbers (%). A P-value of <0.05 was considered significant.

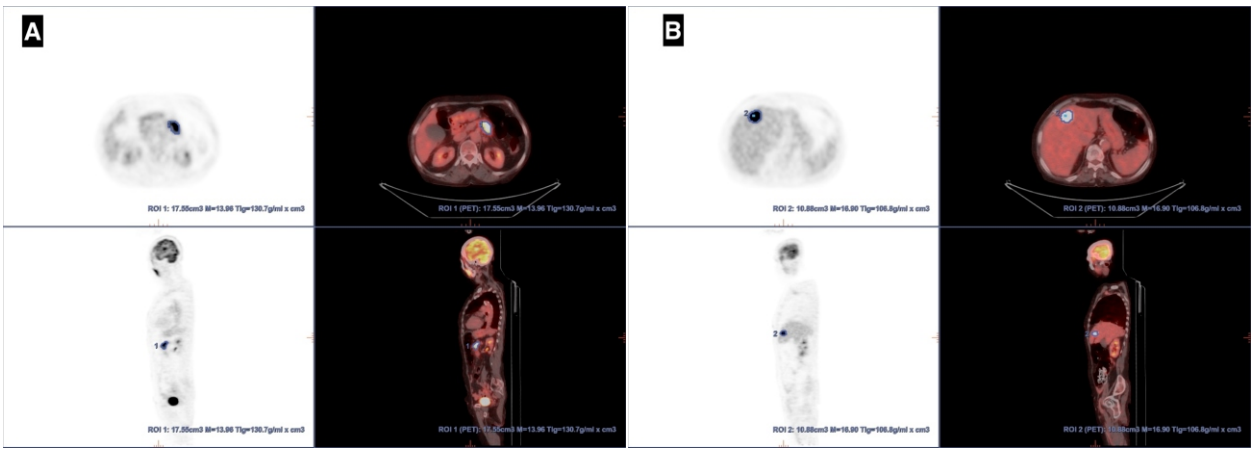


**Figure 1.** Female aged 73 years; CA 19-9:4073U/mL, $MTV_{WB}$: 28,38cm$^3$, $TLG_{WB}$: 237,5g/mL.cm$^3$, a) pancreas MTV: 17,55cm$^3$, pancreas TLG: 130,7g/mL.cm$^3$, b) liver metastasis MTV: 10,8cm$^3$, liver metastasis TLG: 106,8g/mL.cm$^3$

## Results

Of the 66 patients included in the study, 36 (55%) were male, and the mean age was 60.83±13.15 years. The primary tumour was localised at the head of the pancreas in 40 (61%) patients, in the pancreatic body in 19 (29%) and in the pancreatic tail in 7 (10%); 33 (50%) patients had metastasis (Table 1).

***Table 1.*** *Patient characteristics.*

| Characteristic | Number of patients [constituent ratio (%)] |
|---|---|
| **Total number of patients** | 66 |
| **Age at diagnosis (years)** | |
| Mean | 60.83 |
| Range | 22-85 |
| **Sex** | |
| Male | 36 |
| Female | 30 |
| **Primary localization** | |
| Pancreas head | 40 (61%) |
| Pancreas body | 19 (29%) |
| Pancreas tail | 7 (10%) |
| **Sites of metastasis** | |
| Peritoneum | 2 |
| Lung | 9 |
| Liver | 19 |
| Bone | 5 |
| Regional Lymph nodes | 28 |

Evaluation of organ and tissue invasion revealed that 15 patients had omental and mesenteric invasion, and 6 had organ invasion. Gastric invasion was the most common form of organ invasion.

Splenic vein and artery invasion was observed in seven patients, superior mesenteric artery and vein invasion in four patients, and portal vein invasion in one patient.

The mean, median, and minimum/maximum values of the PET/CT and hematologic parameters are shown in Table 2.

Spearman's rho was used to analyse the haematological and PET/CT parameters; a statistically significant relationship was seen between pancreatic tumour size and platelet count (r:-0.319, P=0.009). However, there was no significant relationship between the other haematological parameters and PET/CT parameters (Table 3).

Although no statistically significant relationship was found between neutrophil count and $TLG_{WB}$ by Spearman's rho, neutrophil count showed the strongest association with TLGWB among the variables included in the artificial neural network with hidden layer activation function (Figure 2).

Spearman's rho revealed statistically significant positive correlations of CA 19-9 level with $MTV_{WB}$ (r:0.435, P<0.001) and $TLG_{WB}$ (r:0.409, P:0.001), and a positive correlation between CA 19-9 level and regional lymph node size (r:0.407, P=0.048), liver TLG (r:0.4071, P=0.042), and liver SUVmax (r:0.497, P=0.030). No significant relationship was found between the CA 19-9 level and pancreatic primary tumour MTV, TLG, or SUVmax (Table 3).

In the artificial neural network analysis with hidden layer activation function, the variable showing the strongest association with $MTV_{WB}$ was the CA 19-9 level (Figure 3).

Spearman's rho revealed statistically significant positive correlations of the pancreas MTV with metastasis MTV, metastasis TLG, $TLG_{WB}$, and $MTV_{WB}$ (P=0.018, P=0.030, P<0.001, and P<0.001, respectively). Pancreas TLG showed statistically significant positive correlations with metastasis MTV, metastasis TLG, $MTV_{WB}$, $TLG_{WB}$, liver MTV, and liver TLG (P= 0.024, P=0.023, P<0.001, P<0.001, P=0.0044, and P=0.026, respectively; Table 4).

## Discussion

In this study, patient age and gender, and the location of the pancreatic cancer, were similar to those in recent studies conducted both in Turkey and elsewhere [11, 12].

Previous studies have shown that haematological parameters, especially the NLR and PLR, have prognostic value in terms of OS and progression-free survival (PFS) in pancreatic cancer [13-15].

Mirili et al. (2019) reported a positive correlation between neutrophil count and primary tumour MTV, $MTV_{WB}$ and $TLG_{WB}$ in their study of small-cell lung cancer patients [16]. Previous studies have examined the relationships between hematologic and PET parameters in colon, oesophageal, and breast cancers [17-19], but no studies until now have examined the relationships between haematological and PET parameters in pancreatic cancers. Thus, the present study makes an important contribution to the literature.

Although Spearman's rho revealed no significant relationship between the neutrophil count and $TLG_{WB}$, neutrophil count showed the strongest association with $TLG_{WB}$ in neural network analysis.

***Table 2.*** *Mean and median PET and haematological parameter values.*

| | N | Mean | Standard Deviation | Median | Minimum | Maximum |
|---|---|---|---|---|---|---|
| **Pancreas SUVmax** | 66 | 7,58 | 4,27 | 6,54 | 2,7 | 27,5 |
| **Pancreas size on CT mm** | 66 | 36,46 | 17,59 | 32,5 | 9 | 116 |
| **Pancreas MTV** | 66 | 32,13 | 51,06 | 17,25 | 0,37 | 295 |
| **Pancreas TLG** | 66 | 167,13 | 494 | 71,13 | 1,1 | 4002 |
| **Regional LN SUVmax** | 28 | 3.83 | 1.78 | 3.55 | 1.50 | 8.56 |
| **Regional LN size** | 24 | 11.92 | 6.55 | 10.00 | 6.00 | 38.00 |
| **Liver MTV** | 19 | 189.43 | 267.86 | 35.86 | 0.91 | 1003.00 |
| **Liver TLG** | 19 | 786.64 | 1112.44 | 145.90 | 5.50 | 3735.00 |
| **Liver SUVmax** | 19 | 7.87 | 3.78 | 7.04 | 3.87 | 17.92 |
| **MTVWB** | 66 | 93.53 | 175.56 | 24.09 | 0.37 | 1034.15 |
| **TLGWB** | 66 | 418.65 | 846.22 | 96.86 | 1.10 | 4002.00 |
| **Metastasis MTV** | 33 | 122.79 | 225.38 | 16.02 | 0.91 | 1003.00 |
| **Metastasis TLG** | 33 | 503.04 | 937.62 | 57.00 | 5.30 | 3735.00 |
| **Neutrophil** | 66 | 4.98 | 1.92 | 4.87 | 1.59 | 11.37 |
| **Lymphocyte** | 66 | 1.71 | 0.65 | 1.66 | 0.43 | 3.52 |
| **NLR** | 66 | 3.29 | 1.67 | 3.16 | 0.86 | 9.46 |
| **Plt** | 66 | 242.71 | 99.70 | 223.40 | 109.00 | 663.00 |
| **PLR** | 66 | 165.60 | 118.71 | 133.32 | 50.28 | 918.60 |
| **MPV** | 66 | 9.78 | 1.10 | 9.80 | 5.79 | 12.50 |
| **CA 19-9** | 66 | 2251.60 | 3719.56 | 521.45 | 0.60 | 18966.00 |

***Table 3.*** *Relationships of PET and haematological parameters.*

| | $MTV_{WB}$ | $TLG_{WB}$ | Regional LN SUVmax | Regional LN Size | Pancreas MTV | Pancreas TLG | Pancreas SUVmax | Pancreatic tumour size on CT (mm) | Liver TLG | Liver SUVmax |
|---|---|---|---|---|---|---|---|---|---|---|
| | r | r | r | r | r | r | r | r | r | r |
| | P | P | P | P | P | P | P | P | P | P |
| **Neutrophils** | 0.016 | 0.047 | 0.203 | 0.309 | -0.012 | 0.008 | -0.025 | -0.118 | 0.195 | -0.104 |
| | 0.898 | 0.707 | 0.300 | 0.142 | 0.926 | 0.951 | 0.844 | 0.345 | 0.424 | 0.673 |
| **Lymphocytes** | 0.087 | 0.062 | 0.032 | 0.351 | 0.063 | 0.020 | -0.071 | -0.170 | -0.058 | -0.361 |
| | 0.488 | 0.619 | 0.870 | 0.093 | 0.618 | 0.872 | 0.572 | 0.172 | 0.814 | 0.128 |
| **NLR** | -0.058 | -0.027 | 0.218 | -0.236 | -0.074 | -0.049 | -0.002 | -0.023 | 0.325 | 0.358 |
| | 0.646 | 0.831 | 0.265 | 0.267 | 0.555 | 0.695 | 0.985 | 0.856 | 0.175 | 0.132 |
| **Plt** | -0.133 | -0.098 | 0.344 | 0.368 | -0.114 | -0.102 | -0.045 | -0.319 | 0.223 | -0.123 |
| | 0.286 | 0.434 | 0.073 | 0.077 | 0.363 | 0.413 | 0.721 | **0.009** | 0.359 | 0.616 |
| **PLR** | -0.235 | -0.178 | 0.219 | -0.013 | -0.174 | -0.123 | 0.004 | -0.125 | 0.121 | 0.109 |
| | 0.057 | 0.152 | 0.263 | 0.953 | 0.161 | 0.324 | 0.972 | 0.319 | 0.622 | 0.658 |
| **MPV** | 0.039 | 0.034 | -0.049 | 0.005 | -0.061 | -0.040 | -0.056 | -0.046 | 0.069 | 0.075 |
| | 0.756 | 0.787 | 0.804 | 0.980 | 0.625 | 0.753 | 0.653 | 0.713 | 0.780 | 0.761 |
| **CA 19-9** | 0.435 | 0.409 | 0.071 | 0.407 | 0.219 | 0.164 | 0.123 | 0.204 | 0.471 | 0.497 |
| | **<0.001** | **0.001** | 0.718 | **0.048** | 0.077 | 0.189 | 0.323 | 0.100 | **0.042** | **0.030** |

*r, Spearman's rho test correlation coefficient*

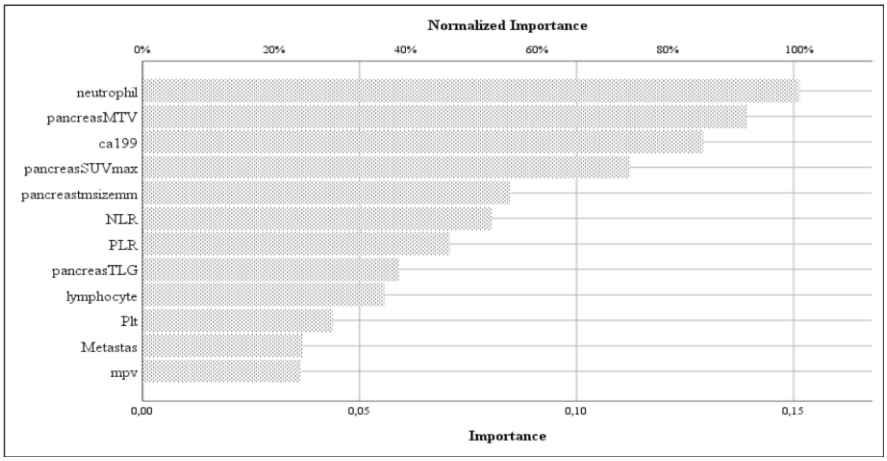


**Figure 2.** Relationship between $TLG_{WB}$ and variables included in the artificial neural network with hidden layer activation function.

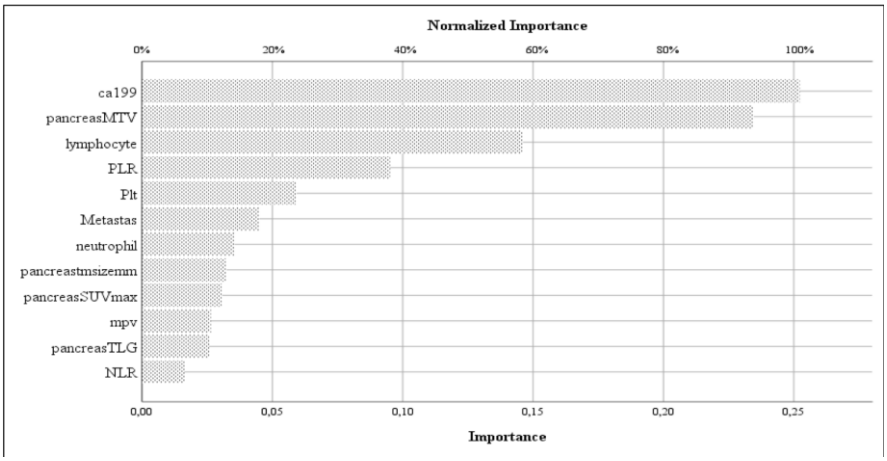


**Figure 3.** Relationship between $MTV_{WB}$ and variables included in the artificial neural network with hidden layer activation function.

***Table 4.*** *Relationships of PET parameters for pancreatic primary mass, metastasis parameters and liver PET parameters.*

| | Pancreas MTV | Pancreas TLG | Pancreas SUVmax | Pancreatic tumour size on CT (mm) |
|---|---|---|---|---|
| | r | r | r | r |
| | P | P | P | P |
| **Metastasis MTV** | 0.410 | 0.391 | 0.042 | 0.321 |
| | 0.018 | 0.024 | 0.818 | 0.069 |
| **Metastasis TLG** | 0.377 | 0.394 | 0.101 | 0.334 |
| | 0.030 | 0.023 | 0.576 | 0.057 |
| **$MTV_{WB}$** | 0.781 | 0.727 | 0.276 | 0.455 |
| | <0.001 | <0.001 | 0.025 | <0.001 |
| **$TLG_{WB}$** | 0.718 | 0.801 | 0.517 | 0.498 |
| | <0.001 | <0.001 | <0.001 | <0.001 |
| **Regional LN SUVmax** | 0.130 | 0.204 | 0.144 | 0.082 |
| | 0.511 | 0.297 | 0.464 | 0.679 |
| **Regional LN Size** | 0.169 | -0.027 | 0.022 | 0.142 |
| | 0.430 | 0.901 | 0.918 | 0.508 |

*(continued)*

| | | | | |
|---|---|---|---|---|
| **Liver MTV** | 0.361 | 0.466 | 0.167 | 0.003 |
| | 0.128 | 0.044 | 0.495 | 0.991 |
| **Liver TLG** | 0.368 | 0.509 | 0.300 | 0.117 |
| | 0.121 | 0.026 | 0.212 | 0.634 |
| **Liver SUVmax** | -0.070 | 0.106 | 0.333 | 0.132 |
| | 0.775 | 0.665 | 0.163 | 0.591 |

*Spearman's rho test. r: Correlation coefficient*

In the literature, the loss of intracellular high mobility group box 1 (HMGB1) [20, 21], which is a newly discovered pancreatic tumour suppressant, is associated with chromosomal instability; moreover, it increases oncogenic K-Ras signal activation in pancreatic lesions by promoting interleukin 6 (IL-6) secretion, with extracellular nucleosomes leaking into the neutrophils [20]. The relationship between neutrophil count and TLGWB in the present study is thought to be a product of this physiopathology.

We identified a significant relationship between pancreatic tumour size and platelet count, as well as among platelet count, the PLR, and metastasis. Similar to neutrophils, platelets are responsible for the secretion of various growth factors such as platelet-derived growth factor (PDGF), platelet factor 4 (PF4), transforming growth factor-beta (TGF)-B, vascular endothelial growth factor (VEGF), and thrombospondin. These factors are involved in mitogen activation, the proliferation of tumour cells, and the growth and metastasis of the tumour mass. Studies have revealed that platelets play a role in tumour angiogenesis and invasion [22-24].

Examination of the relationship of the CA 19-9 level with the PET/CT results and volumetric PET parameters revealed statistically significant positive correlations of CA 19-9 with $MTV_{WB}$ and $TLG_{WB}$, P<0.001 and P=0.001, respectively), and weak positive correlations of CA 19-9 with lymph node size, the presence of metastatic tumour, and liver TLG (P=0.048, P=0.030, and P=0.042, respectively).

Considering that the $MTV_{WB}$ and $TLG_{WB}$ values, which significantly correlate with CA 19-9, represent the whole-body tumour load, the whole-body tumour load can, by extension, be predicted accurately based on the CA 19-9 level.

In pancreatic cancer patients, volumetric and metabolic PET parameters show a strong correlation with tumour biology, pathologic grade, recurrence, PFS, and OS [25-28]. Few studies have analysed the associations of metabolic PET parameters with tumour markers. Shi et al. (2015) included 60 operable pancreatic adenocarcinoma patients in their study and found a strong positive correlation among the MTV and TLG values of the pancreas, and CA 19-9 and CA 125 levels. However, only patients with lesions confined to the pancreas were included in their study; metastatic patients were excluded, so correlations with the whole-body tumour load could not be assessed [29].

Carbohydrate antigen 19-9 has higher sensitivity for the diagnosis of pancreatic cancer compared to other tumour markers [30]. Studies have shown that the CA 19-9 level can be used as a resectability criterion, and that liver metastasis, peritoneal metastasis, and vascular invasion, which cannot be detected using conventional imaging methods, may be seen in cases with high CA 19-9 levels (> 215U/mL) during surgical operations [31, 32].

In addition to reports indicating that preoperative CA 19-9 levels may be a prognostic factor for survival, other studies have reported that a decrease in the level of CA 19-9 noted on evaluation of the chemotherapy response may not correspond to the CT findings; moreover, there is no relationship between this decrease and survival [33, 34]. However, it is generally thought that the CA 19-9 level should be used to evaluate the response to chemotherapy [35].

The present study showed that, as the MTV and TLG values of the primary pancreatic tumour increased, the MTV, TLG, $MTV_{WB}$, and $TLG_{WB}$ values of the metastases increased. Based on these results, the primary tumour load in the pancreas may be an indicator of the total tumour load. In their study capturing volumetric $^{18}$F-FDG PET/CT parameters for pancreatic neuroendocrine tumours, Satoh et al. reported that metastasis increased with primary pancreatic tumour MTV [36]. Another recent study reported that primary tumour MTV in the pancreas was associated with lymph node metastasis [37].

Limitations of the study: Being a retrospective study is the first limitation of the present study. However, most studies in the literature are designed retrospectively. The second limitation of the study is the low sample size. Another limitation of the study is that the T staging and correlation studies could not be performed due to the small size of the sample and patients with different organ metastases were collected in a single group.

*In conclusion*, the present study showed that the CA 19-9 level was positively correlated with metabolic and volumetric PET/CT parameters in pancreatic adenocarcinoma. CA 19-9 is considered to be a strong prognostic marker of pancreatic adenocarcinoma and shows statistically significant positive correlations with $MTV_{WB}$ and $TLG_{WB}$ (total tumour load). It is also thought that the MTV and TLG values of the primary pancreatic tumour may have prognostic value for predicting metastasis and estimating the whole-body tumour load ($MTV_{WB}$ and $TLG_{WB}$).

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