

1 **Original Research Article**

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3 **Assessment of Takayasu arteritis in routine practice with PETVAS, an 18F-FDG**
4 **PET quantitative scoring tool**

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8 **Competing interest:** All authors declare that they have no conflicts of interest.

9 **Acknowledgements:** None

10 **Informed Consent:** This study was approved by Marmara University Local Ethical
11 Committee (protocol number: 09.2019.605) and written informed consent was obtained
12 from each participant.

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1 Assessment of **Takayasu** arteritis in routine practice with PETVAS, an **18F-FDG**
2 **PET** quantitative scoring tool

3

4 **ABSTRACT**

5 **Background/aim:** The aim of this study was to evaluate the value of PET Vascular
6 Activity Score (PETVAS) during the follow-up of patients with **Takayasu** arteritis.

7 **Materials and methods:** **Takayasu** arteritis patients who underwent 18F-
8 Fluorodeoxyglucose (FDG) PET imaging were evaluated retrospectively. In 8 patients
9 both 1 and 2-hour imagings were also performed prospectively. For PETVAS, 9 arterial
10 areas were scored between 0-3 according to the FDG uptake.

11 **Results:** Forty-six images of 34 patients were evaluated. PETVAS was higher in patients
12 with clinically active disease ($p=0.03$) and in C-reactive protein (CRP) elevated group
13 among clinically inactive patients ($p=0.0015$). PETVAS correlated with CRP ($p=0.003$,
14 $r=0.53$) and erythrocyte sedimentation rate ($p=0.005$, $r=0.41$), whereas age, disease
15 duration, immunosuppressive and **glucocorticoid (GC)** treatments were not associated
16 with PETVAS. First vs 2nd-hour **PETVAS was** similar in patients who had both 1st and
17 2nd hour PET scans ($p=0.67$).

18 **Conclusion:** We observed higher **PETVAS** in patients with active disease and elevated
19 acute phase reactants. Although scores in our study (performed at one-hour) were lower
20 compared to the original PETVAS study performed at two hours, PETVAS seems to be
21 a reliable tool to quantify FDG PET scores in routine practice.

1 **Key words:** Large-vessel vasculitis, imaging, positron emission tomography,
2 fluorodeoxyglucose, Takayasu arteritis

3

4 **1.Introduction**

5 Takayasu arteritis (TAK) is a primary large-vessel vasculitis affecting aorta and its main
6 branches [1]. Conventional digital subtraction angiography (DSA) which provides
7 information about luminal changes used to be the gold standard imaging method for the
8 diagnosis of TAK. However, as an invasive method which cannot delineate information
9 about vessel-wall inflammation, DSA is mostly replaced by Magnetic Resonance
10 Angiography (MRA), Computed Tomography Angiography (CTA), Doppler Ultrasound
11 (US) or Positron Emission Tomography (PET) in recent years [2].

12 FDG PET/CT is a non-invasive, verified imaging modality to detect the regional
13 distribution of ¹⁸F-FDG in oncological diseases and also has a promising value for large-
14 vessel vasculitis (LVV). Interpretation of FDG uptake is based on the principle of
15 determining metabolically active cells such as immune/inflammatory cells invading the
16 vessel wall in LVV [3]. It can reflect the localization and degree of inflammation [4].
17 Previous studies have shown that FDG PET/CT is useful in the diagnosis of LVV with a
18 specificity of up to 90% [5]. FDG PET/CT also has a role in detecting disease activity
19 with a sensitivity of 70-87% and specificity of 73-87% [6-7]. Therefore, FDG PET/CT is
20 recommended as one of the major imaging modalities for the diagnosis and monitoring
21 of primary LVVs, such as Takayasu arteritis (TAK) and giant-cell arteritis.

22 However, interpretation of FDG PET/CT has some challenges. The main controversies in
23 LVV are the lack of standardization in the definition of vascular inflammation and the

1 time interval between the FDG administration and acquisition [8]. In recent ‘EULAR
2 recommendations for the use of imaging in LVV in clinical practice’ a minimum of 60
3 minutes between intravenous FDG administration and acquisition is advised, but a
4 delayed acquisition may be chosen to increase the sensitivity of detecting FDG uptake in
5 LVV [2]. However, most studies with FDG PET/CT in the literature is performed at one-
6 hour and the data from studies comparing the first hour and delayed acquisition is
7 controversial [8-11].

8 Recently PETVAS (PET Vascular Activity Score), a quantitative score assessed at 2-
9 hours of FDG uptake, is introduced for a standardized assessment of FDG PET/CT in
10 LVV [12]. In this study, we aimed to evaluate the value of PETVAS (performed at one-
11 hour) during the initial diagnosis and follow-up of patients with TAK in routine practice.

12

13 **2. Materials and methods**

14 **2.1. Patients**

15 In this single centre study 34 patients who were diagnosed with Takayasu arteritis and
16 underwent FDG PET/CT imaging during their routine follow-up were evaluated
17 retrospectively. All patients fulfilled American College of Rheumatology (ACR) 1990
18 classification criteria for Takayasu arteritis [13]. Demographic and clinical characteristics
19 of the patients were recorded from patients’ charts. The study was approved by the local
20 Ethics Committee (No: 09.2019.605). All patients provided written informed consent.
21 The study was performed in accordance with the Declaration of Helsinki.

22 Physician’s Global Assessment (PGA) was used to determine clinical activity according
23 to Kerr (NIH) criteria. Patients were accepted as active according to the Kerr's criteria if

1 two of the following four items were positive: systemic features with no other cause,
2 elevated CRP, features of vascular ischemia or inflammation or typical angiographic
3 features [14]. The IS and/or GC use and the doses of the treatments were recorded. GC
4 doses were given in prednisolone equivalent doses.

5 **2.2 FDG-PET/CT Imaging Technique**

6 All patients had fasted for at least 6 hours before FDG PET/CT imaging was performed
7 and only oral hydration with glucose-free water was allowed. FDG PET/CT scans were
8 performed consistent with European League Against Rheumatism (EULAR) and the
9 European Association of Nuclear Medicine (EANM), the Cardiovascular Council of the
10 Society of Nuclear Medicine and Molecular Imaging (SNMMI), and the PET Interest
11 Group (PIG), and endorsed by American Society of Nuclear Cardiology
12 recommendations (ASNC) [2, 8]. The blood glucose level of the patients that were
13 checked before the FDG administration is required to be below 126 mg/dl. All patients
14 rested in a quiet and temperature-balanced room (20-22 C) for 60 minutes after
15 intravenous injection of 3.7 MBq (0.1 mCi)/kg of FDG. Only oral contrast, not an
16 intravenous agent, was administered according to our local departmental protocols. Image
17 acquisition was performed using an integrated PET/CT system (Discovery-16LS, GE
18 Healthcare). PET images were obtained from mid-skull to below the knees in 3D mode
19 and reconstructed in transverse, coronal and sagittal planes. For attenuation correction
20 and anatomic orientation, a low-dose CT scan was performed. After the image
21 acquisition, data were transferred to a workstation (Advantage Windows Workstation 4.5,
22 GE Healthcare) for processing and interpretation.

1 Image acquisition was performed one hour after FDG administration. In 8 patients both
2 1 and 2-hour imagings were acquired prospectively to compare the characteristics of
3 images in early and delayed time intervals.

4 **2.3. Image Interpretation**

5 Two independent nuclear physicians who were blinded to the clinical data, interpreted
6 the images. A total of 15 arterial areas (ascending aorta, aortic arch, descending thoracic
7 aorta, abdominal aorta, innominate, carotid arteries, subclavian arteries, axillary arteries,
8 iliac arteries, and femoral arteries) were evaluated. In the PETVAS scoring, performed at
9 one hour of the FDG uptake, 9 arterial areas (ascending aorta, aortic arch, descending
10 thoracic aorta, abdominal aorta, right carotid artery, left carotid artery, innominate artery,
11 right subclavian artery and left subclavian artery) were scored between 0 and 3 according
12 to the FDG uptake separately, as originally suggested (scale 0-27) [12]. The FDG uptake
13 is graded as grade 0= no uptake, grade 1=less than liver involvement, grade 2=equal
14 involvement to the liver, grade 3=greater than liver involvement (representative PET/CT
15 images showing maximum and minimum PETVAS are presented in Figures 1a and 1b).
16 The 'visual analysis' (VA) using the liver FDG uptake as the reference was also assessed
17 and compared with PETVAS. If the uptake of an arterial area is equal to or greater than
18 liver uptake (\geq grade 2) that arterial area is considered as 'active' or 'positive'. 'Active
19 PET-CT' is defined as the presence of at least one active arterial area.

20 **2.4. Statistical analysis**

21 For continuous normally-distributed variables, results are expressed as mean \pm SD. In the
22 case of non-normally distribution median (min-max) values are presented. Chi-square test
23 and Fischer's exact test were used to compare the categorical data. Independent

1 continuous variables were compared with the Mann-Whitney U test. Wilcoxon signed
2 rank test was used to compare the first and second-hour **PETVAS** of the prospective
3 group. A p value of <0.05 was considered statistically significant. Correlation analyses
4 were performed with Spearman's rank method. Logistic regression analysis was used to
5 assess variables associated with positive PET results. **Logistic regression analysis was**
6 **performed for two different dependent variables. In the first analysis, active PET**
7 **according to visual analysis (VA) was used as the dependent variable. Female gender,**
8 **age, glucocorticoid dose, disease duration, BMI, active disease, immunosuppressive use,**
9 **ESR and CRP were evaluated as covariates. In the second logistic regression analysis**
10 **PETVAS 5.5 which had 76% specificity and 70.6% sensitivity for active disease was used**
11 **as a threshold. The predictive factors for PETVAS ≥ 5.5 were evaluated.** Statistical
12 Package for the Social Sciences 20.0 (SPSS, Chicago, IL, USA) was used to perform the
13 analysis.

14

15 **3.Results**

16 Forty-six imagings of 34 patients (F/M: 28/6) were evaluated. Mean disease duration
17 was 9.3 ± 6.5 years and the mean age was 40.5 ± 15.1 years. Median CRP level was 16.3
18 (2-126) mg/L. Patients characteristics at the time of imaging are given in Table 1. In the
19 majority of patients, aortic arch (87%) was involved followed by ascending aorta (78%)
20 and brachiocephalic artery (50%) (Figure 2). Median 3.5 (0-15) arterial regions were
21 involved.

22 Twenty-five (54%) imagings were evaluated to be PET-positive according to visual
23 analysis and median **PETVAS** was 4.5 (0-27). Patients who had a positive PET assessed

1 with visual analysis (VA) had higher **PETVAS** than patients who were VA inactive
2 (median score 8.0 vs 2.0, $p < 0.001$) (Figure 3). Twelve (70%) clinically active patients
3 had positive PET. Interestingly PET was also positive in 45% (13/29) of the patients who
4 had inactive disease. Active PET-CT according to visual analysis had a sensitivity of
5 70.6% and specificity of 55.2% in the distinction of clinically active patients from inactive
6 patients. **PETVAS** were also significantly higher in patients who were considered to have
7 active disease (median **PETVAS** 7 (0-27) vs 4 (0-17), $p=0.03$). When we used a cut-off
8 value of 5.5 for PETVAS the specificity was 75.9% (area under curve=0.69).

9 **PETVAS** of the patients who experienced at least one relapse after imaging and who
10 remained in remission were similar in the whole group (median score 5 (0-27) vs 4 (0-
11 26), $p=0.11$). PETVAS were also similar between relapsing and non-relapsing patients
12 (PETVAS 4 (0-17) vs 3 (0-4), $p=0.12$) among the clinically inactive group. No difference
13 in **PETVAS** was present between patients who were taking GC vs non-GC use (median
14 PETVAS: GC+: 4 (0-17) vs GC-: 5 (1-27), $p=0.90$) or according to immunosuppressive
15 (ISs) use (ISs+: 4 (0-17) vs ISs-: 5 (2-27), $p=0.55$). PETVAS also was not correlated with
16 age ($p=0.66$, $r=0.07$) and disease duration ($p=0.67$, $r=-0.06$).

17 Eleven of 13 (85%) inactive patients with VA PET positivity were in the elevated CRP
18 subgroup. Median PETVAS values were also significantly higher in the CRP elevated
19 inactive group ($p=0.0015$) (Table 2). A positive correlation was observed between
20 **PETVAS** and both CRP ($p=0.003$, $r=0.53$) and ESR ($p=0.005$, $r=0.41$) levels.

21 In **univariable** logistic regression analysis, only CRP (**OR (95% CI): 1.05 (1.01-1.11),**
22 **$p=0.02$**) was associated with active PET according to visual analysis, but ESR (**OR (95%**
23 **CI): 1.01 (0.99-1.04), $p=0.10$**) and active disease (**OR (95% CI): 2.95 (0.82-10.5), $p=0.09$**)

1 had a trend towards an association. In **multivariable** analysis none of the variables showed
2 an association with only CRP having a trend for association (**OR (95% CI): 1.05 (0.99-**
3 **1.11), p=0.06**). When we evaluated variables associated with higher **PETVAS** with a
4 threshold of 5.5, although ESR and CRP levels were associated with $PETVAS > 5.5$ in
5 **univariable** analyses, only CRP was found to be a predictive factor for higher PETVAS
6 values in **multivariable** analysis (Table 3).

7 In 43 (94%) imagings **PETVAS** was > 0 and the treatment was changed in 25 (58%)
8 patients. Among patients with a **PETVAS** > 0 , nine patients were clinically inactive but
9 had high CRP levels. FDG PET/CT was performed during diagnostic period for 5
10 patients. In 20 (49%) of the remaining 41 images PET-CT was positive and treatment was
11 changed in 18 (90%) of the PET positive patients. Nine out of 11 (82%) clinically inactive
12 patients with elevated CRP and positive PET underwent a treatment change which was
13 defined as GC dose increase and/or ISs change.

14 Twelve patients had follow-up PET scans with a mean 29.5 ± 14.5 months interval
15 between baseline and follow-up imaging. At baseline imaging 10 of 12 (83%) patients
16 with follow-up imaging had positive PET/CT according to VA. Among this group,
17 median **GC** dose was 5 mg (0-7.5) in VA active PET/CT group and 1.25 mg (0-2.5) in
18 VA inactive group. Immunosuppressive (IS) treatment was increased in 8 (8/10, 80%)
19 patients with active PET at baseline. Among these 8 patients with treatment change,
20 treatment was switched to another csDMARD in 4 patients with a conventional disease-
21 modifying antirheumatic drug (csDMARD) therapy. IS treatment and **GC** therapy were
22 added to 2 patients who were not on IS treatment during the first imaging whereas
23 treatment was increased to TNF inhibitors for 2 patients with active PET at initial
24 imaging. Median PETVAS at follow-up visit significantly decreased after treatment

1 change compared to baseline imaging (PETVAS 1st vs 2nd imaging : 9 (5-17) vs 5.5 (2-
2 17), p=.0.04). PETVAS was similar in baseline and follow-up images in 4 patients
3 without treatment change (Median PETVAS1st vs PETVAS 2nd 3.5(2-5) vs 2.5 (2-14),
4 p=0.52).

5 In 8 patients PET-CT was performed both in the first and second hours of the FDG uptake.
6 Median PETVAS was similar in 1st and 2nd hours (3.5 (2-6) vs 3.0 (0-9), p=0.67). In the
7 2nd hour scans, PETVAS increased in 3, decreased in 3 and was stable in 2 patients
8 compared to the 1st-hour uptake (Figure 4). According to VA one imaging was considered
9 active in 1st hour and 2 imagings were active in the 2nd hour of FDG uptake (p=0.25). In
10 28% of the imagings which had a PETVAS >0 (12/43), a PET involvement of an artery
11 other than the arteries used for assessing PETVAS were observed.

12

13 **4.Discussion**

14 In our study, FDG PET/CT assessment with PETVAS (assessed at one hour)
15 demonstrated higher scores in patients with Takayasu arteritis who were considered
16 clinically active or had increased CRP levels. However, the scores were lower compared
17 to the original PETVAS performed at two hours and the uptakes in 1st and 2nd hour after
18 FDG administration were not different in our study.

19 Disease activity assessment is challenging in TAK. Imaging modalities are not routinely
20 recommended for patients in clinical remission in recent EULAR guidelines [2].
21 However, if the clinical and laboratory findings are not adequately conclusive, imaging
22 methods can be required before the final clinical judgement. FDG PET/CT is a non-
23 invasive, functional imaging method which has promising results in the assessment of

1 TAK and recommended in the diagnosis and follow-up of TAK patients [2]. In our routine
2 clinical practice, we choose to use FDG PET/CT imaging mostly for patients who have
3 persistent APR response without clear clinical signs and symptoms of ischemia or patients
4 with typical clinical findings in the early disease phase, mostly in the diagnostic period.

5 There are no precise criteria for the assessment of FDG uptake for PET-CT in LVV.
6 However, a number of FDG PET/CT interpretation methods have been developed. Visual
7 analysis is a commonly used semiquantitative method, comparing the interested arterial
8 area uptake with the background uptake of liver. An uptake equal to or higher than liver
9 uptake corresponds to active vascular involvement [15-19]. Highest standard uptake
10 value (SUV) of the arterial territories (SUVmax), the ratio of SUVmax to SUV liver
11 (SUVratio) and mean SUV of the arterial areas (SUVmean) are also used for quantitative
12 analysis of the FDG uptake [20-21]. Finally, PETVAS, which is a total quantitative score
13 of most commonly involved 9 arteries in LVV, is developed recently to increase the
14 discriminative value of PET assessment and standardize clinical and therapeutic studies
15 [12].

16 In the study in which PETVAS was originally described, Grayson et al. observed that
17 active FDG PET/CT differentiated clinically active LVV patients from comparators with
18 a sensitivity and specificity of over 80%. However, more than half of the patients (58%)
19 who were in remission clinically according to NIH criteria were also interpreted to have
20 active FDG PET/CT and the specificity of FDG PET/CT in distinguishing clinically
21 active patients from inactives was only 42%. In the comparator group who did not have
22 an LVV diagnosis, 17% of patients were found to have active vasculitic lesions. When
23 **PETVAS** was used with a cut-off value of >20 the sensitivity increased to 68% and
24 specificity to 71% [12]. PETVAS was also used in a study in which the relationship

1 between different disease activity measures, such as patient reported outcomes, physician
2 reported outcomes, laboratory outcomes and imaging outcomes in LVV was assessed.
3 PETVAS, which was considered as the imaging outcome, had the strongest association
4 in distinguishing the active disease defined by PGA [22].

5 In another study, Zhang et al. showed that SUV max, SUV mean and SUV ratios were
6 significantly higher in clinically active group compared to the inactives and with a 2.1
7 SUV max cut-off they reported 86.2% sensitivity and 90% specificity [21]. Schramm et
8 al. also described 68.4% sensitivity and 91.3% specificity according to VA for active
9 disease [23]. In contrast to these studies, Arnoud et al. reported no correlation between
10 clinical activity and FDG uptake [17]. Kang et al. compared the performance of PETVAS
11 and SUVmax for disease activity assessment in TAK patients. They found that PETVAS,
12 which provides a global PET activity assessment, was superior for distinguishing active
13 disease compared to regional assessment with SUVmax [24]. In the current study, we also
14 observed that PETVAS were significantly higher in clinically active patients. A positive
15 FDG PET/CT according to VA is observed in clinically active patients with a sensitivity
16 of 70.6% and specificity of 55.2%. With a PETVAS threshold score of 5.5, the specificity
17 increased to 76% with a sensitivity of 70.6%.

18 Although most of the studies in the literature suggest that clinical activity is associated
19 with FDG PET/CT positivity, the implications of an active FDG PET/CT assessment in
20 clinically inactive patients are not well described. It may be a sign of ongoing subclinical
21 inflammation which was previously shown in some surgical specimens [14, 25]. Lee et
22 al. reported that in clinically inactive patients with an active vasculitic FDG uptake at
23 baseline, follow-up scans showed a decrease in FDG uptake with less vasculitic extension
24 after immunosuppressive treatments [15]. Grayson et al. found active PET in nearly 60%

1 of patients who were clinically inactive. The most likely cause was suggested as
2 subclinical vasculitis rather than vascular remodelling and atherosclerosis [12]. Similar
3 to these results 45% of our clinically inactive patients had active FDG PET/CT and most
4 of these patients had elevated CRP levels (85%) despite lack of clinical findings.

5 CRP is a commonly used biomarker for disease activity assessment in TAK. However,
6 its association with FDG PET/CT findings is variable in the literature. In a recent
7 systematic review, when CRP effect on PET positivity was evaluated [26], five out of
8 nine studies [16, 18-19, 27-28] reported an association between CRP and FDG PET/CT
9 while other four studies [15, 17, 20, 29] found no association. Therefore, the authors
10 concluded the effect of CRP on FDG PET/CT positivity only as 'moderate'. We also
11 observed a correlation between CRP and visual analysis in clinically inactive patients
12 which led to treatment changes in our patient group. When a **PETVAS** of > 5.5 was used
13 as a cut-off, logistic regression analysis also demonstrated a weak but significant
14 association with CRP. In 82% of the clinically inactive patients with elevated CRP and
15 positive PET, treatment was changed **in our patients**. Therefore, isolated increased acute
16 phase response with active PET findings seem to have an impact on treatment decisions.
17 **In such patients in whom the clinical and laboratory findings are not sufficient, the**
18 **recommended imaging methods (MR angiography (MRA), CT angiography (CTA) and**
19 **PET CT) could be chosen to determine the clinical activity. MRA can detect luminal**
20 **changes and pre-stenotic lesions such as contrast enhancement, vessel wall thickening**
21 **and periarterial lesions without radiation exposure[2]. CTA is useful in assessment of**
22 **active disease by demonstrating wall thickening and low attenuation ring which is**
23 **assessed in the late contrast phase and have a high specificity for active disease [30]. PET**
24 **CT is also a good option for detecting subclinical inflammation and may identify the focus**

1 of vascular inflammation earlier which may be an advantage for PET over other imaging
2 modalities [2]. In summary, these patients should be followed closely and when needed
3 the most suitable and available imaging method should be chosen by the clinician in
4 individual basis.

5 PETVAS has also been assessed in terms of being a predictor of clinical relapses. Grayson
6 et al. reported that higher PETVAS were associated with higher relapse rates during
7 follow-up in LVV patients [12]. In a retrospective study including 17 LVV patients, the
8 intensity of FDG uptake in baseline FDG PET/CT and extension of active vasculitic
9 involvement were significantly higher in patients with relapsing disease [31]. In contrast,
10 Blockmans et al observed no association of relapses with FDG PET/CT activity in biopsy-
11 proven Giant Cell Arteritis (GCA) patients [32]. Consistent with these results, PETVAS
12 was similar between patients who had a future relapse vs non-relapsing disease in our
13 study.

14 Data from previous studies suggest that GC treatment reduces the FDG uptake [12, 32-
15 34] and the uptake decreases with duration of GC treatment [33, 35]. However GC use
16 also causes increase in liver FDG uptake which may cause underestimation of vascular
17 uptake [36]. Less is known about the effect of immunosuppressives on vascular FDG
18 PET/CT assessments, but some studies reported improvement in FDG uptake with
19 glucocorticoid-sparing agents [34, 37-38]. In a recent study, a decrease in PETVAS was
20 observed after GC and/or ISs treatments [34]. However, there was no difference in
21 PETVAS between patients according to GC or IS use in our study, which might be
22 explained by our low median GC doses.

23 Standardization of optimal timing in FDG PET/CT in LVV is still lacking. Delayed
24 acquisitions of FDG PET/CT imagings may increase the sensitivity of detecting vasculitis

1 as a result of an increase in vessel-wall uptake and a decrease in the blood pool uptake by
2 longer timing [9, 12]. In a prospective study with 43 patients who were being evaluated
3 with the suspicion of LVV, FDG PET/CT was performed 180 minutes after FDG injection
4 and semiquantitative SUV values and target to background ratio (TBR) were better in
5 differentiating LVV patients from the controls [11]. However in another study evaluating
6 PET activity in both 60 minute and 180 minutes of FDG uptake, although SUV max, SUV
7 mean and TBR increased with time, after correction for partial volume effects with
8 contrast-enhanced CT (CECT) assistance, the SUV values and TBR were similar in both
9 time intervals [10]. Quinn et al evaluated one-hour time-point PET-MR and two hour
10 time-point PET-CT scans of 69 LVV patients. The percentage of positive PET scans
11 increased from 56% to 77% and clinically active disease, which was defined as presence
12 of clinical features directly assigned to vasculitis, was more common in the only delayed-
13 time-point PET positive patients. As there was a strong correlation in SUV sum values
14 between one and two-hour uptake, they reported that the same arterial territories were
15 involved with greater SUV values at two-hour time point [39].

16 PET studies in LVV patients were mostly performed at 60 minutes of acquisition in the
17 literature. Our results showed no difference in 1st and 2nd-hour images. In 1st hour
18 evaluation, one out of eight FDG PET/CT scans was active according to VA. Two patients
19 had active FDG PET/CT according to VA in 2nd-hour evaluation which was not
20 statistically significant compared to the 1st hour. Therefore, there is not strong enough
21 evidence about delayed PET-CT imaging for detecting vasculitis in our study. Delayed
22 imaging requires prolonged waiting times, which makes PET-CT imaging less convenient
23 in routine clinical practice.

1 PETVAS values in our study were lower than reported by Grayson et al. Also, Kang et
2 al, who reported a mean PETVAS value of 9.2, found lower numerical PETVAS values
3 [24] than National Institutes of Health (NIH) study. Different patient characteristics may
4 be a possible explanation for these variable results. Our TAK patient group who were
5 mostly under ISs treatment for a long time had a younger mean age and a longer disease
6 duration with a similar percentage of glucocorticoid use compared to NIH study cohort.
7 Some technical reasons such as PET-CT machine properties and variability between
8 readers among institutions may also explain lower PETVAS values in our study. We,
9 therefore, think that a standardization study of FDG PET/CT quantitative assessment
10 among nuclear medicine specialists is necessary before any quantitative PET/CT tool is
11 widely accepted.

12 The main strength of our study was that we have reported our real-life experience in our
13 TAK patients without any interventions in contrast to clinical trials. **However**, our study
14 had some limitations. Retrospective design and use of PETVAS in routine practice limit
15 our conclusions. A control group to detect sensitivity and specificity of the one-hour
16 **PETVAS** distinguishing TAK patients from comparators is also lacking. Finally, all
17 patients did not have a concomitant angio-CT or MRA imaging showing vascular luminal
18 changes at the time of disease activity assessment which is included in NIH criteria. This
19 may have resulted in underestimating the number of patients with active disease.

20 In conclusion, the current study reflects the application of PETVAS to routine daily
21 practice as a quantitative FDG PET/CT imaging tool in **Takayasu** arteritis. We observed
22 higher **PETVAS** in patients with active clinical features or with elevated CRP levels in
23 remission. Although our scores were lower compared to the original study, PETVAS
24 seems a promising tool for the quantitative analysis of PET scans. Further studies are

1 required with PETVAS, especially in therapeutic trials, to demonstrate its role better for
2 the management of LVV.

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1 **FIGURE LEGENDS**

2 **Figure 1. Representative PET/CT images showing maximum (PETVAS=27) (a) and**
3 **minimum (PETVAS=0) (b) scores**

4 **Figure 2. Distribution of vascular FDG uptake in Takayasu arteritis patients**

5 **Figure 3. PETVAS values of patients according to clinical disease activity and PET**
6 **positivity determined with visual analysis. PETVAS was** significantly higher in
7 patients who were clinically active ($p=0.03$) (a) and who had active PET according to
8 visual analysis ($p<0.01$) (b).

9 **Figure 4. Comparison of 1st and 2nd-hour PETVAS.**

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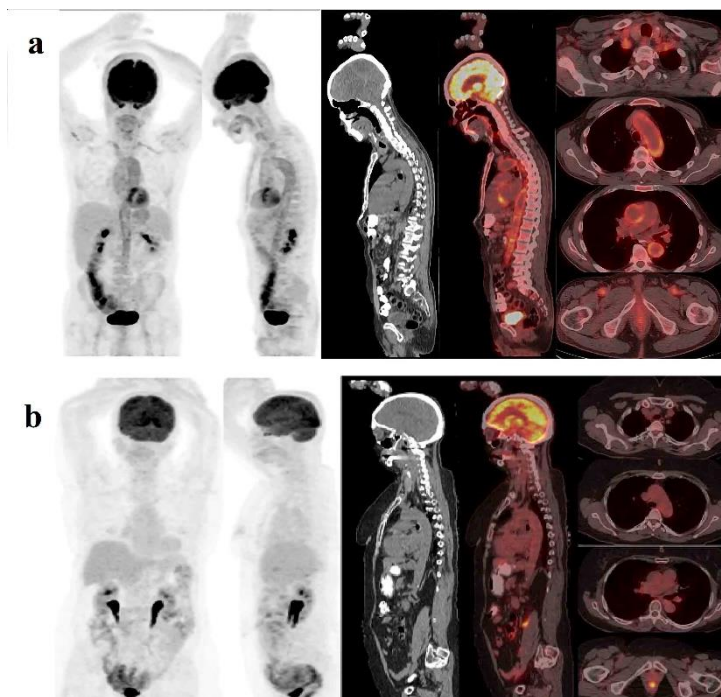
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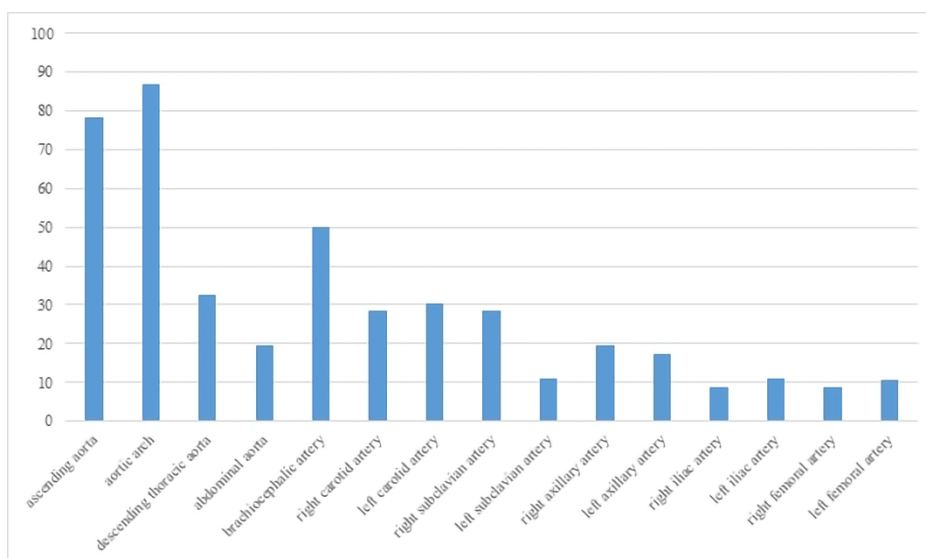


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2 **Figure 1. Representative PET/CT images showing maximum (PETVAS=27) (a) and**
 3 **minimum (PETVAS=0) (b) scores**

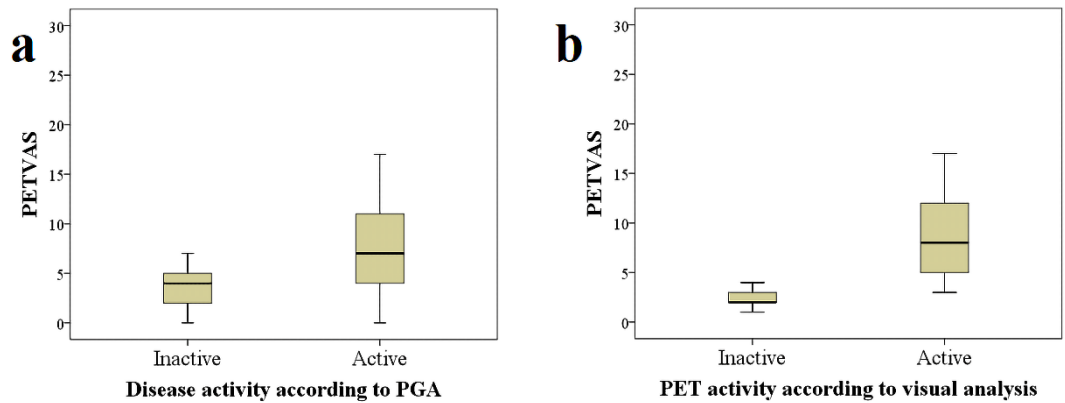
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7 **Figure 2. Distribution of vascular FDG uptake in Takayasu arteritis patients**

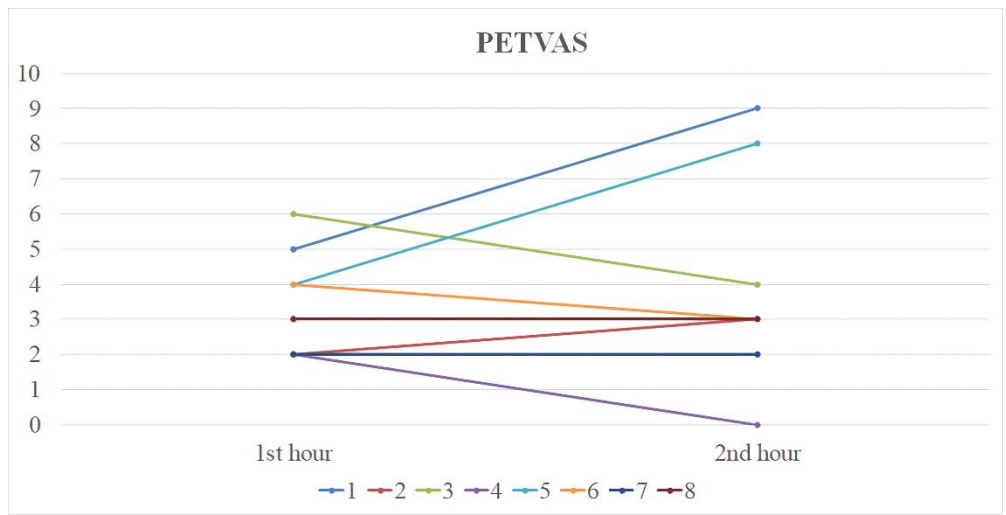


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2 **Figure 3. PETVAS values of patients according to clinical disease activity and PET**
 3 **positivity determined with visual analysis. PETVAS was** significantly higher in
 4 patients who were clinically active ($p=0.03$) **(a)** and who had active PET according to
 5 visual analysis ($p<0.01$) **(b)**.

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9 **Figure 4. Comparison of 1st and 2nd-hour PETVAS**

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1 **Table 1. The demographic and clinical features of Takayasu arteritis patients during**
 2 **the time of imaging.**

Gender, (Female/Male)	28/6
Age, years, mean±SD	40.5± 15.1
Disease duration, years, mean±SD	9.3 ±6.5
Cardiovascular risk factors	
Diabetes, n (%)	2(6)
Hypertension, n (%)	15(46)
Hyperlipidemia, n (%)	9(27)
Smoking-ever, n (%)	11(33)
BMI, kg/m ² , mean±SD	23.0±3.6
Immunosuppressives n (%)	35 (76)
Azathioprine	18(39)
Methotrexate	6(13)
Leflunomide	9(20)
TNF-α inhibitors	4(9)
Glucocorticoid use present, n (%)	29(63)
Glucocorticoid dose, mg [†] , median(range)	5 (2.5-80)

Acute phase reactants	
ESR, mm/h, mean±SD	49.1±28.0
CRP, mg/L, median(range)	16.3(2-126)

1 †Prednisolone equivalent dose

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- 1 **Table 2. The disease activity and PET-CT interpretation according to visual**
- 2 **analysis.**

		Disease activity according to NIH criteria		p
		Active (n=17)	Inactive (n=29)	
Median PETVAS		7(0-27)	4(0-17)	0.03
Visual analyse	Active PET, n (%)	12 (48)	13 (52)	0.09
	Inactive PET, n (%)	5 (24)	16 (76)	
Inactive Group (According to NIH criteria)				
		Elevated CRP (n=16)	Negative CRP (n=13)	p
Median PETVAS		5(2-17)	3(0-5)	0.0015
Visual analysis	Active PET, n (%)	11 (85)	2 (15)	0.008
	Inactive PET, n (%)	5 (31)	11 (69)	

3

1 **Table 3. Variables associated with PETVAS > 5.5 scores in logistic regression**
 2 **analysis.**

	Univariable analysis		Multivariable analysis†	
	OR (95% CI)	p	OR (95% CI)	p
Female sex	0.28 (0.04-1.79)	0.20	-	
Age, years	1.01 (0.96-1.06)	0.63	-	
Glucocorticoid dose, mg/d	0.97 (0.90-1.04)	0.40	-	
Disease duration, months	0.99 (0.98-1.00)	0.29	-	
BMI, kg/m ²	0.96 (0.78-1.18)	0.72	-	
ISs present	0.84 (0.21-3.30)	0.80	-	
ESR, mm/h	1.02 (1.01-1.04)	0.04	0.99 (0.95-1.02)	0.61
CRP, mg/L	1.08 (1.02-1.14)	0.007	1.07 (1.01-1.14)	0.02

3 †Only variables with a p-value of <0.2 in univariable analysis were involved in
 4 multivariable analysis

5 ESR: Erythrocyte Sedimentation Rate, CRP: C reactive protein, OR: Odds ratio, CI:

6 Confidence interval