Marvisi Chiara (Orcid ID: 0000-0001-7027-1410)
Bolek Ertugrul Cagri (Orcid ID: 0000-0003-3886-2813)
Alibaz-Oner Fatma (Orcid ID: 0000-0002-6653-1758)
Salvarani Carlo (Orcid ID: 0000-0003-3708-3148)
Quinn Kaitlin A (Orcid ID: 0000-0002-5794-194X)
Grayson Peter C (Orcid ID: 0000-0002-8269-9438)

Development of the Takayasu's Arteritis Integrated Disease Activity Index

Chiara Marvisi, M.D. [1,2], Ertugrul Cagri Bolek, M.D.[3], Mark A. Ahlman, M.D.[4], Hugh Alessi, B.A.[5], Christopher Redmond, M.D.[5], Francesco Muratore, M.D.[1,2], Elena Galli, M.D.[1,2], Caterina Ricordi, M.D.[2], Sema Kaymaz-Tahra, M.D.[6], Salih Ozguven, M.D.[7], Fatma Alibaz-Oner, M.D.[6], Haner Direskeneli, M.D.[6], Carlo Salvarani, M.D.[1,2], Kaitlin A. Quinn, M.D.[5]*, Peter C. Grayson, M.D.[5]*

Affiliations

1. Rheumatology Unit, Azienda USL-IRCCS di Reggio Emilia, Italy
2. University of Modena and Reggio Emilia, Modena, Italy
3. Hacettepe University Vasculitis Research Centre, Ankara, Turkey
   Division of Rheumatology, Department of Internal Medicine, Hacettepe University, Ankara, Turkey
4. Nuclear Medicine Department, Medical College of Georgia, Augusta, GA, USA
5. Systemic Autoimmunity Branch, National Institutes of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, USA
6. Department of Internal Medicine, Division of Rheumatology, Marmara University, School of Medicine, Istanbul, Turkey
7. Department of Nuclear Medicine, Marmara University, School of Medicine, İstanbul, Turkey

*Kaitlin A. Quinn, MD and *Peter C. Grayson, MD: equal contribution as last author.

Corresponding Author
Peter C. Grayson, MD, MSc
National Institutes of Health
10 Center Drive, Rm 13103D
Bethesda, MD 20892

Key Words: Takayasu's arteritis, large vessel vasculitis, disease assessment, disease activity, outcome measure, imaging, PET-CT
Running title: Disease activity assessment in Takayasu's Arteritis

Funding: This study was supported by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH)

Word count: 4081

ABSTRACT

Background: Accurate clinical assessment of disease activity in Takayasu's arteritis (TAK) can be challenging. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) can directly measure vascular inflammation. This study details the development of a new type of disease activity index called the Takayasu's Arteritis Integrated Disease Activity Index (TAIDAI).

Methods: Clinical symptoms for TAIDAI were identified from a literature review. Each symptom was paired to FDG-PET findings in corresponding arterial territories. Constitutional symptoms were paired with acute phase reactant levels. One point was given for each clinical symptom paired with supporting FDG-PET or laboratory abnormalities and summed into the TAIDAI score. A TAIDAI of ≥1 defined active disease. To assess performance of TAIDAI, face validity, content validity and sensitivity to change were evaluated within a prospective observational cohort of patients with TAK.

Results: Seventeen clinical symptoms were paired to imaging or laboratory abnormalities. In a cohort of 96 patients contributing 204 study visits, TAIDAI showed excellent sensitivity (96.3%) and good specificity (79.2%) compared to physician's clinical assessment. TAIDAI significantly correlated with physician global assessment, PET Vascular Activity Score (PETVAS), patient global assessment, and acute phase reactant levels. In patients treated with either TNF inhibitors or tocilizumab, a TAIDAI of 0 was achieved in 21 of 23 (91%) patients who met a pre-defined definition of clinical response.

Conclusion: TAIDAI is new type of disease activity index in TAK whereby clinical symptoms are integrated with specific laboratory and imaging findings. TAIDAI should be validated in future randomized controlled trials in TAK.

SIGNIFICANCE AND INNOVATION

- There is no consensus how to define disease activity and measure treatment response in Takayasu's arteritis.
- We propose a novel type of disease activity index called the Takayasu's arteritis integrated disease activity index (TAIDAI).
- Clinical, imaging, and laboratory assessments are evaluated in a hierarchical manner in TAIDAI and scored only when present in specific combinations.
- TAIDAI is the first disease activity assessment to incorporate ^{18}F-FDG-PET as a measure of vascular inflammation.

INTRODUCTION

Clinical assessment of patients with Takayasu's arteritis (TAK) is challenging because disease activity in this form of vasculitis is both difficult to define and to measure. Historically, the medical history and vascular physical examination have been the foundation to evaluate disease activity in TAK (1). However, accurately differentiating active disease from damage can be difficult at the bedside. The same clinical symptom (e.g., limb claudication) may reflect ongoing arterial inflammation that requires therapeutic intervention or may represent chronic damage that is not further modifiable by additional medical treatment. Moreover, patients with TAK can present with non-specific constitutional symptoms, such as fatigue and malaise, which can represent active disease, yet these same symptoms are often prevalent at later phases of disease despite treatment. Thus, clinical assessment of TAK may often be subjective and variable between different raters.

Laboratory values, such as acute phase reactants, can be useful to supplement clinical assessment; however, up to 50% of patients with TAK do not have elevated levels of the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), even during periods of clinically active disease (2,3). Similarly, CRP levels may not fully reflect disease activity in patients under tocilizumab treatment. Further, ESR and CRP can remain persistently elevated in a sizeable proportion (up to 40%) of patients with TAK (2,4).

Vascular imaging has been used to complement clinical and laboratory assessments. Non-invasive angiography [such as magnetic resonance (MRA) or CTA] is recommended to establish a diagnosis of TAK, and a significant proportion of vascular

abnormalities may only be detected by non-invasive angiography rather than by the physical examination (5). While non-invasive angiography is useful to define luminal arterial damage, assessment of wall morphology by specific imaging sequences is technically challenging and interpreting active vasculitis based off non-invasive angiography is often not reliable across different readers (6). ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) can be used to evaluate and quantitate vascular inflammation with good reliability and corresponds more closely with clinical assessment compared to non-invasive angiography (7,8). However, there are concerns about the specificity of FDG uptake in the arterial wall to define active vasculitis, as other factors such as vascular remodeling and atherosclerosis may contribute to this signal. Increased arterial FDG uptake has been observed in patients with TAK during periods of otherwise apparent clinical remission (7–9).

Currently, there is no consensus how to define disease activity in TAK, especially in situations of isolated laboratory or imaging abnormalities in absence of corresponding clinical symptoms. Several indices have been proposed to measure disease activity in TAK and most rely on direct clinical assessment without consideration of concomitant imaging-based findings (10,11). No index has incorporated FDG-PET with clinical and laboratory assessments. Two recent randomized controlled trials in TAK independently developed different definitions of disease activity, making comparison between the trials difficult (12,13).

Given the complexity of disease activity assessment in TAK, defining the direct relationships between specific symptoms and corresponding imaging abnormalities at the arterial level may help objectively differentiate active disease from damage. The

aim of this study was to develop a novel disease activity index that can be used to define and measure disease activity in TAK. An ideal disease activity index would objectively reflect the complex relationships between clinical, imaging, and laboratory-based assessments of disease activity and could be used to measure treatment response and define disease states (i.e., active disease and remission).

PATIENTS AND METHODS

Development of the Takayasu's Arteritis Integrated Disease Activity Index (TAIDAI)

A literature review was conducted to identify clinical symptoms associated with TAK as potential criterion items. Consideration was given to large cohort studies involving at least 100 patients, items from prior disease activity indices, items from prior outcome measures in randomized controlled trials, and items identified in the OMERACT Delphi Consensus for TAK (3,10–17).

To be included as a criterion item in the index, a clinical symptom must be identified in the literature review and must be physiologically associated with vascular disease in a specific arterial territory or territories. For example, right carotidynia can be physiologically associated with disease in the right carotid artery, and leg claudication can be associated with disease in the abdominal aorta or iliofemoral arteries. Although not directly linked to a specific vascular territory, constitutional symptoms were included because they represent a potentially important component of disease activity and have been incorporated into outcome definitions in prior randomized controlled trials in TAK (12,13). Two reviewers (CM and PG) reviewed clinical symptoms specifically related to TAK and designed the final list.

Physical examination findings (e.g., pulse inequalities, bruits, or blood pressure abnormalities) were not considered because it is difficult to time precisely when these abnormalities occur, changes in these features are difficult to monitor accurately over time, and vascular examination findings are typically related to vascular damage rather than active disease. Extra-vascular symptoms (e.g., arthritis, rash, and features of

luminal gastrointestinal disease) were not considered because, while these symptoms may be associated with TAK, they often occur independent of vascular inflammation (18).

The fundamental assumption of TAIDAI is that the relationships between clinical symptoms, vascular imaging findings, and laboratory values are more important than additive assessment of these individual measures of disease activity. Recognizing the perceived importance of clinical disease activity and the uncertainty of abnormal vascular imaging findings or laboratory values in absence of clinical symptoms, TAIDAI integrates clinical symptoms, FDG-PET findings, and laboratory values in a hierarchical manner, with the highest importance placed on clinical symptoms supported by vascular imaging and laboratory studies.

TAIDAI is scored using a stepwise approach. In the first step, the rater records all clinical symptoms present within seven days of assessment without subjectively determining whether the symptom may be related to active disease or damage. In step two, the rater records the acute phase reactant levels and the presence of PET activity within specific arterial territories. In step three, the TAIDAI items are scored by giving one point to each clinical symptom present in step one that is correctly paired with PET activity in a corresponding arterial territory in step two. Constitutional symptoms are only scored when paired with increased levels of CRP ≥ 10 mg/L or ESR ≥ 40 mm/hour, and these thresholds were selected to be consistent with definitions used in prior treatment trials in TAK (12). For each clinical symptom paired with a corresponding PET or laboratory abnormality in step three, one point is assigned. The total points are summed from step three to calculate the TAIDAI score. Clinical

symptoms without corresponding FDG-PET activity are not scored to increase reliability of the instrument by minimizing the role of the clinician to subjectively interpret whether a symptom represents active disease or damage. FDG-PET activity or elevated acute phase reactants without corresponding clinical symptoms are also not scored because the clinical significance of these abnormalities in isolation is unclear in TAK.

Although TAIDAI exists on a continuous scale of 0-17, a TAIDAI score of 0 defines clinical remission, and a TAIDAI >0 defines active disease. This dichotomous outcome was chosen to create a standardized definition of disease activity states in TAK and to facilitate the conduct of therapeutic trials where the primary endpoint is the achievement of clinical remission.

Assessment of TAIDAI in an Observational Cohort

Study Population and Clinical Assessment:

To test the performance characteristics of TAIDAI, data were collected from patients with TAK recruited in an ongoing prospective, observational cohort at the National Institutes of Health (NIH) in Bethesda, MD, USA. All patients fulfilled the 2022 ACR/EULAR criteria for TAK (19). Patients could be enrolled at various stages during the disease course. Per protocol, all patients underwent clinical evaluation and laboratory testing at the NIH Clinical Center within 24 hours prior to FDG-PET imaging.

Clinical disease activity was recorded as active or remission at each visit by the clinician who was blinded to all imaging studies. *Active disease* was defined as the presence of any clinical disease features directly attributed to vasculitis at the time of assessment. Elevated acute phase reactant levels alone were not sufficient evidence of clinical active disease. *Remission* was defined as the absence of any clinical symptoms directly attributable to vasculitis, regardless of acute phase reactants. For every assessment, the confidence of the clinical evaluation was also recorded. Physician global assessment and patient global assessment of disease activity at the time of the study visit were independently scored on a scale of 0-10, with higher scores indicating more severe disease.

When possible, patients underwent follow-up clinical and imaging assessments at a minimum interval of six months. Changes in clinical disease activity, CRP and ESR levels, physician and patient global assessment, and treatment over the follow-up interval were assessed. Increased treatment was defined as adding a new biologic or conventional disease-modifying anti-rheumatic drug (DMARD) or an increase in the daily glucocorticoid dose by ≥50% at any point during the follow-up period. Patients in whom treatment with either a tumor necrosis factor (TNF) inhibitor or tocilizumab was initiated after the initial study visit were selected, and clinical responsiveness to treatment was evaluated. *Complete response* was defined as the resolution of any clinical symptoms directly attributable to vasculitis by the study investigator and a prednisone dose not exceeding 50% of the dose of the pre-treatment visit.

FDG-PET Protocol and Interpretation:

All patients underwent whole-body FDG-PET studies within 24 hours after clinical evaluation per a standardized imaging protocol, as previously described (7). Briefly, patients ≥ 18 years of age underwent FDG-PET-CT. Image acquisition commenced at a 2-hour uptake time with a Siemens Biograph mCT (Siemens Medical Solutions, Erlangen, Germany). Image reconstruction employed CT attenuation correction and iterative reconstruction (24 iterations, 3 subsets, 256 matrix, 1.2 zoom, 1.5mm slice thickness, time-of-flight, point spread function correction, no post reconstruction filtering). To minimize radiation exposure, patients <18 years of age underwent whole body FDG-PET-magnetic resonance (MR) with a Siemens Biograph mMR (Siemens Medical Solutions, Erlangen, Germany). PET-MR reconstruction employed MR-based attenuation correction and iterative reconstruction (172 matrix, 1.2 zoom, 2.03mm slice thickness, point spread function correction, 4.0 Gaussian post-reconstruction filtering). Adult patients received a fixed dose of FDG (10mCi) and pediatric patients received a weight-based dose (0.1mCi/kg).

A single reader reviewed all FDG-PET scans, blinded to clinical status. Qualitative assessment of FDG uptake was evaluated in four aortic segments (ascending, arch, descending, and abdominal aorta) and 15 branch arteries (brachiocephalic, pulmonary, carotids, subclavian, axillaries, vertebral, iliac and femoral arteries). Active vasculitis in an arterial territory was defined as greater FDG uptake in the arterial wall compared to the liver. The PET Vascular Activity Score (PETVAS) was calculated for nine arterial territories (ascending aorta, aortic arch, descending thoracic aorta, abdominal aorta, brachiocephalic, left and right carotid, and left and right subclavian arteries), as previously described (7). For each FDG-PET scan, the reader's global

impression of disease activity was recorded based on visual assessment of all arterial territories.

This study was approved by the NIH ethics (ID# 14-AR-0200).

Statistical Analysis

In accordance with ACR guidelines for the development of response criteria, face validity, content validity, and discriminant validity were evaluated (20,21). To assess face validity, the sensitivity and specificity of TAIDAI versus clinical disease activity assessment was evaluated. Because clinical assessment is an imperfect gold standard for disease activity assessment in TAK, performance testing of TAIDAI was restricted only to visits where there was confidence of clinical assessment by the evaluating physician. Logistic regression models were used to identify clinical features associated with discordance or concordance between TAIDAI and clinical assessment using the following predictor variables: each clinical symptom included in TAIDAI, daily prednisone dose, ESR and CRP. Only variables with $p < 0.10$ in univariable analyses were included in the multivariable model, and backwards selection was used to identify the final list of variables that optimized the Akaike Information Criteria. To determine content validity, Spearman's correlation coefficients were calculated among different measures of disease activity in TAK, including TAIDAI, physician global assessment, patient global assessment, PETVAS, CRP and ESR. To assess discriminant validity, patients treated with a TNF inhibitor or tocilizumab with at least one follow-up visit were studied. Comparison in the median change of TAIDAI scores between responders and non-responders was analyzed using the Mann-Whitney test, and the frequency of patients who achieved a TAIDAI=0 was compared using Fisher's exact test. To

calculate inter-rater reliability, two independent raters (CM, PCG) scored whether a clinical symptom was present in a randomly selected subset of 20 study visits and agreement was calculated using Cohen's kappa. Continuous variables are presented as median or mean and interquartile range (IQR) or standard deviation (SD), and categorical variables as numbers and percentages, as appropriate. All analyses were performed using JMP version 14 or GraphPad Prism version 8.

RESULTS

Development and assessment of the score

Seventeen clinical symptoms were included in TAIDAI and paired with PET activity in at least one of 19 arterial territories or acute phase reactant levels. The three step approach to score each TAIDAI item and to summarize the final score is shown in **Figure 1**.

Study Population and clinical assessment

Ninety-six patients with TAK contributed data from 204 study visits. PET-MR was performed in 25 patients younger than 18 years over 61 study visits. Baseline demographic characteristics are reported in **Table 1.** Median disease duration at the time of baseline assessment was 25 months (IQR 9-91). Median time between study visits was 6 (IQR 6-8) months. Inter-rater agreement for clinical symptom assessment was excellent (Cohen's kappa = 0.85). Clinically active disease was present in 61/204 (30%) visits overall, and in 35/96 (36.5%) visits at baseline. However, clinical assessment was certain in only 123/204 (60.2%) visits where 96 (78%) visits were considered not clinically active and active disease was present in 27 (22%) visits. The median TAIDAI score was 0 (range 0-9) and did not differ between patients who underwent PET-CT versus PET-MR imaging (p=0.88). The absolute values of the clinical symptoms and of the paired FDG-PET activity in corresponding arterial territories are reported in **Figure 2**.

Performance characteristics of TAIDAI

In the 123 study visits where the clinician was certain about disease activity assessment, TAIDAI showed excellent sensitivity of 96.2% (95% CI 0.82-0.99) and good specificity of 79.3% (95% CI 0.70-0.86). As expected, if cases were not restricted to situations where the clinician was clinically certain about disease activity status, the performance characteristics of TAIDAI were lower with a sensitivity 80.3% (95%CI 0.70-0.90) and specificity 72% (95%CI 0.65-0.79).

A TAIDAI score of 0 to define remission and >0 to define active disease was concordant with clinical assessment of disease activity in 152/204 (74.5%) visits. TAIDAI was discordant with clinical assessment in 52/204 (25.5%) visits. In 12/204 (5.9%) visits, TAIDAI was 0 despite the clinician rating disease as clinically active. This type of discordance was associated with use of higher doses of daily prednisone at the time of assessment. Compared to concordant visits, the mean dose of prednisone at discordant visits was 13.12 mg/day (SD ±18.44) versus 5.89 mg/day (SD ±10.89) ($p<0.0001$). In the other type of discordance, TAIDAI was > 0 despite the clinician rating disease as clinical remission during 40/204 (19.6%) visits. On univariable analyses, the presence of leg and arm claudication [Odds Ratio 4.48 (95%CI 9.55-2.1); $p<0.01$; Odds ratio 2.2 (95%CI 4.45-1.08); $p=0.03$, respectively] and constitutional symptoms [Odds Ratio 5.85 (95% CI 2.22-15.37); $p<0.01$] were independent predictors of this type of discordance. In contrast, presence of carotidynia [Odds Ratio 5.91 (95% CI 1.15-0.91); $p=0.04$] was associated with concordance between TAIDAI and clinical assessment. On multivariable analyses (**figure 3)**, carotidynia was associated with concordance [Odds ratio 9.15 (95% CI 1.70-49.12)], whereas constitutional symptoms and arm claudication were associated with discordance [Odds ratio 0.18 (95% CI 0.07-0.45); Odds ratio 0.38 (95% CI 0.16-0.89),

respectively]. CRP or ESR values were not associated with agreement between clinical assessment and TAIDAI.

Correlations with other assessments

Multivariate analysis was conducted to assess the relationship between different outcome measures used to assess disease activity and TAIDAI (**Table 2**). Physician global assessment, patient global assessment, PETVAS, ESR, and CRP correlated most strongly with TAIDAI than each other. The strongest correlations were observed between TAIDAI and physician global assessment (ρ=0.55, p<0.0001) and TAIDAI and PETVAS (ρ=0.47, p<0.0001). Patient global assessment correlated more strongly with TAIDAI (ρ=0.30, p=0.0002) than with physician global assessment (ρ=0.21, p=0.01). The correlations between TAIDAI and ESR or CRP were moderate but significant (ρ=0.20, p=0.04; ρ=0.31, p<0.0001, respectively).

Responsiveness to change

Thirty-one patients were treated with either a TNF inhibitor or tocilizumab (20 and 11 patients, respectively) and had at least one follow-up visit at a 6-month interval after the initiation of treatment. Before treatment 19/31 (61.3%) had a TAIDAI >0. The median dose of prednisone at the baseline visit was 10 mg daily (IQR 7.5-15 mg daily). After six months 23/31 (74.2%) met the definition of complete response to treatment. The median of TAIDAI went from 2 (IQR 0-5.5) to 1 (IQR 0-4) in eight patients who failed TNF inhibitor or Tocilizumab (p=0.06) and went from 1 (IQR 0-1) to 0 in 23 patients who responded to treatment (either TNF inhibitors or Tocilizumab), p<0.01. A TAIDAI of 0 was achieved in 21/23 (91%) patients who met the definition of complete

response ($p<0.01$) (see **figure 4** for an explicative clinical case). A TAIDAI of 0 was also achieved in 3/8 (37.5%) patients who did not meet the definition of complete response based on continued glucocorticoid treatment >50% the dose of the initial visit.

DISCUSSION

Identifying a standardized method to define and monitor disease activity is an unmet need in TAK. In this study, we propose a novel type of disease activity index intended for use as an outcome measure in future therapeutic trials. In many rheumatologic diseases, a *composite disease activity index* is often used to measure disease activity, whereby different aspects of a disease are scored and combined into a single numerical value. In contrast, we propose an *integrated disease activity index* for use in TAK whereby different aspects of disease activity are scored only when present in specific combinations. In an observational cohort of patients with TAK, TAIDAI is feasible to implement, objective, and has appropriate face, content, and discriminant validity to assess disease activity and to define remission. A TAIDAI-based definition of active disease may not always correspond with the clinician's assessment of disease activity. Given the lack of a perfect gold standard for disease activity, it is possible in these situations that TAIDAI may overestimate disease activity based on PET scan abnormalities or the treating physician may underestimate disease activity.

Compared to prior disease activity indices proposed for TAK, TAIDAI is uniquely different. In the Indian Takayasu Activity Score (ITAS2010), which was derived from a list of disease manifestations scored in the Disease Extent Index (DEI.Tak), the rater is tasked with only scoring symptoms that are deemed to represent active vasculitis (10,11). In clinical practice, this distinction is often difficult and can lead to poor reliability between different assessors. Furthermore, unlike the ITAS2010, TAIDAI does not score vascular examination findings (e.g., bruits and pulse abnormalities). While the vascular examination is a critical component of disease assessment for patients with TAK, accurately determining when a new vascular examination finding

occurred, whether it represents active disease or damage, or whether it has indeed changed over time can be challenging.

Unlike the ITAS2010, clinical items in TAIDAI are not weighted based on perceived clinical importance. Each of the items present in TAIDAI represents an important aspect of disease activity that could impact a patient's quality of life to a variable degree. Prior disease activity indices in TAK weight items based on physician-based assessment of disease severity, which may not always correlate with patient perception. Importantly, patient assessment of disease activity correlated more strongly with TAIDAI than with physician, imaging, or laboratory-based assessments in this study, suggesting that TAIDAI uniquely and simultaneously represents different perspectives of disease activity in TAK.

TAIDAI is the first disease activity score that incorporates FDG-PET as a marker of vascular inflammation. In the "NIH criteria," also known as the Kerr criteria, new or worsening "typical angiographic features" are considered a component of disease activity in TAK (1). However, these criteria lack clear definitions as to what constitutes typical angiographic features and were never intended to be used as a marker of disease activity. In contrast to non-invasive angiography, which is typically used to measure vascular damage, FDG-PET is a direct marker of vascular inflammation (22,23). When physicians are given information about FDG-PET findings along with clinical symptoms, inter-rater reliability regarding disease activity status significantly improves and physicians report more confidence in clinical assessment (24). While FDG-PET is considered within standard of care for the diagnostic assessment of large-vessel vasculitis, there is controversy regarding the role of serial vascular imaging to

monitor disease activity due to concerns about the specificity of increased arterial FDG uptake to represent clinically meaningful inflammation. Studies report abnormal arterial FDG uptake in 20-58% of patients with large-vessel vasculitis who are otherwise in apparent clinical remission, and the significance of subclinical FDG-PET activity remains unclear (7–9). In line with these uncertainties, TAIDAI does not score FDG-PET activity in absence of corresponding disease-associated clinical symptoms. Similarly, elevated acute phase reactants in absence of clinical symptoms are not considered.

Since TAIDAI is based on the integration of clinical and imaging assessment, FDG-PET must be performed as close to the time of clinical assessment as possible. In this study, all patients underwent FDG-PET within 24 hours of the clinical visit per protocol, limiting the possibility of confounders such as changes in treatment and disease activity between assessments. Defining the maximum acceptable time interval between clinical and imaging-based assessment remains an unmet need, and future studies that use TAIDAI must carefully consider this time interval in study design. The impact of glucocorticoids on TAIDAI score must also be considered when designing a clinical trial that uses TAIDAI as an outcome measure. Glucocorticoids can reduce vascular inflammation on FDG-PET in a dose dependent manner (25), and in this study, increased daily prednisone dose was associated with discordance between clinical assessment and TAIDAI score.

This study has several noteworthy strengths. TAIDAI represents a novel disease activity index in TAK that uniquely integrates clinical and imaging assessment to define active versus remission in a reliable and objective way. Performance characteristics

of TAIDAI have been assessed using data from a cohort where clinical and imaging assessments were performed blinded to each other by disease experts. FDG-PET scans were performed per a standardized protocol and all images were interpreted by a central reader to minimize confounding due to technical issues and to reduce misclassification bias.

Nevertheless, several potential limitations should be outlined. TAIDAI was developed using data collected within an ongoing single-center, prospective observational cohort. Issues related to selection bias and generalizability of findings are potential concerns. Whether TAIDAI would be useful in other observational cohorts where data are collected in the context of routine clinical practice needs to be studied. There are potential drawbacks to a disease activity index that is dependent on advanced molecular imaging. TAIDAI is intended for use in therapeutic trials and is likely not feasible, cost effective, or advisable to implement in routine clinical practice. While obtaining vascular imaging studies is not necessary at every clinic visit, the fundamental concept of TAIDAI that vascular imaging findings should be considered in the context of specific associated clinical symptoms should instruct clinicians about these important relationships whenever imaging studies are obtained in routine practice. Radiation exposure represents another potential limitation of TAIDAI and attempts to minimize radiation through use of PET-MR or low dose CT protocols are advisable to reduce risk.

Given the limitations in our current understanding of the pathophysiology of TAK, there are opportunities to improve how disease activity is defined and measured. Accordingly, TAIDAI may further refined and optimized by incorporating novel

circulating biomarkers or PET radiotracers, if these measures have improved performance characteristics to monitor disease activity compared to acute phase reactants or FDG. Prospective data that better defines the relationships between isolated laboratory or vascular imaging abnormalities and clinical outcomes in TAK may influence specific circumstances in which these items could be scored independent of clinical symptoms. Testing the performance of TAIDAI on a continuous scale to define gradations of change in disease activity or as a prognostic biomarker may also help to define the clinical utility of this index.

A randomized controlled trial that demonstrates convincing therapeutic efficacy remains an unmet need in TAK. This study demonstrates that TAIDAI has the necessary face validity, content validity, and responsiveness to change to be considered as an outcome measure in future treatment trials in TAK.

References

1. Kerr GS. Takayasu Arteritis. *Ann Intern Med* 1994;120:919. Available at: http://annals.org/article.aspx?doi=10.7326/0003-4819-120-11-199406010-00004. Accessed July 1, 2019.
2. Salvarani C, Cantini F, Boiardi L, Hunder GG. Laboratory investigations useful in giant cell arteritis and Takayasu's arteritis. *Clin Exp Rheumatol* 2003;21. Available at: https://pubmed.ncbi.nlm.nih.gov/14740424/. Accessed March 11, 2023.
3. Quinn KA, Gribbons KB, Carette S, Cuthbertson D, Khalidi NA, Koening CL, et al. Patterns of clinical presentation in Takayasu's arteritis. *Semin Arthritis Rheum* 2020;50:576–581.
4. Maksimowicz-Mckinnon K, Clark TM, Hoffman GS. Limitations of Therapy and a Guarded Prognosis in an American Cohort of Takayasu Arteritis Patients. *Arthritis Rheum* 2007;56:1000–1009. Available at: https://onlinelibrary.wiley.com/doi/10.1002/art.22404. Accessed March 11, 2023.
5. Grayson PC, Tomasson G, Cuthbertson D, Carette S, Hoffman GS, Khalidi NA, et al. Association of vascular physical examination findings and arteriographic lesions in large vessel vasculitis. *J Rheumatol* 2012;39:303–309. Available at: https://pubmed.ncbi.nlm.nih.gov/22174204/. Accessed November 24, 2022.
6. Prieto-González S, García-Martínez A, Tavera-Bahillo I, Hernández-Rodríguez J, Gutiérrez-Chacoff J, Alba MA, et al. Effect of Glucocorticoid Treatment on Computed Tomography Angiography Detected Large-Vessel Inflammation in Giant-Cell Arteritis. A Prospective, Longitudinal Study. *Medicine* 2015;94:e486. Available at: /pmc/articles/PMC4602705/. Accessed November 24, 2022.
7. Grayson PC, Alehashemi S, Bagheri AA, Civelek AC, Cupps TR, Kaplan MJ, et al. 18 F-Fluorodeoxyglucose-Positron Emission Tomography As an Imaging Biomarker in a Prospective, Longitudinal Cohort of Patients With Large Vessel Vasculitis. *Arthritis Rheumatol* 2018;70:439–449. Available at: https://pubmed.ncbi.nlm.nih.gov/29145713/. Accessed November 24, 2022.
8. Galli E, Muratore F, Mancuso P, Boiardi L, Marvisi C, Besutti G, et al. The role of PET/CT in disease activity assessment in patients with large vessel vasculitis. *Rheumatology (Oxford)* 2022. Available at: https://pubmed.ncbi.nlm.nih.gov/35258570/. Accessed November 24, 2022.
9. TAHRA SK, ÖZGÜVEN S, ÜNAL AU, ÖNER FA, ÖNEŞ T, ERDİL TY, et al. Assessment of Takayasu arteritis in routine practice with PETVAS, an 18F-FDG PET quantitative scoring tool. *Turk J Med Sci* 2022;52:313–322. Available at: https://pubmed.ncbi.nlm.nih.gov/36161613/. Accessed November 24, 2022.
10. Sivakumar MR, group for the I, Misra RN, group for the I, Bacon PA, group for the I. OP14. THE INDIAN PERSPECTIVE OF TAKAYASU ARTERITIS AND DEVELOPMENT OF A DISEASE EXTENT INDEX (DEI.TAK) TO ASSESS TAKAYASU ARTERITIS. *Rheumatology* 2005;44:iii6–iii7. Available at: https://academic.oup.com/rheumatology/article/44/suppl_3/iii6/1773500. Accessed November 24, 2022.
11. Misra R, Danda D, Rajappa SM, Ghosh A, Gupta R, Mahendranath KM, et al. Development and initial validation of the Indian Takayasu Clinical Activity Score (ITAS2010). *Rheumatology (Oxford)* 2013;52:1795–1801. Available at: https://pubmed.ncbi.nlm.nih.gov/23594468/. Accessed November 24, 2022.
12. Langford CA, Cuthbertson D, Ytterberg SR, Khalidi N, Monach PA, Carette S, et al. A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of

Takayasu Arteritis. *Arthritis Rheumatol* 2017;69:846–853. Available at: https://pubmed.ncbi.nlm.nih.gov/28133931/. Accessed November 24, 2022.
13. Nakaoka Y, Isobe M, Takei S, Tanaka Y, Ishii T, Yokota S, et al. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). *Ann Rheum Dis* 2018;77:348–354. Available at: https://pubmed.ncbi.nlm.nih.gov/29191819/. Accessed November 24, 2022.
14. Vanoli M, Daina E, Salvarani C, Sabbadini MG, Rossi C, Bacchiani G, et al. Takayasu's arteritis: A study of 104 Italian patients. *Arthritis Care Res (Hoboken)* 2005;53:100–107. Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/art.20922. Accessed November 24, 2022.
15. Soto ME, Espinola N, Flores-Suarez LF, Reyes PA. Takayasu arteritis: clinical features in 110 Mexican Mestizo patients and cardiovascular impact on survival and prognosis. *Clin Exp Rheumatol* 2008;26:S9-15. Available at: https://europepmc.org/article/med/18799047. Accessed November 24, 2022.
16. Schmidt J, Kermani TA, Bacani AK, Crowson CS, Cooper LT, Matteson EL, et al. Diagnostic features, treatment, and outcomes of Takayasu arteritis in a US cohort of 126 patients. *Mayo Clin Proc* 2013;88:822–830. Available at: https://pubmed.ncbi.nlm.nih.gov/23849994/. Accessed November 24, 2022.
17. Aydin SZ, Direskeneli H, Merkel PA, Toloza S, Blockmans D, Sato EI, et al. Assessment of Disease Activity in Large-vessel Vasculitis: Results of an International Delphi Exercise. *J Rheumatol* 2017;44:1928–1932. Available at: https://www.jrheum.org/content/44/12/1928. Accessed November 24, 2022.
18. Kwon OC, Lee S-W, Park Y-B, Oh JS, Lee SH, Hong S, et al. Extravascular manifestations of Takayasu arteritis: focusing on the features shared with spondyloarthritis. Available at: https://doi.org/10.1186/s13075-018-1643-7. Accessed March 12, 2023.
19. Grayson PC, Ponte C, Suppiah R, Robson JC, Gribbons KB, Judge A, et al. 2022 American College of Rheumatology/EULAR classification criteria for Takayasu arteritis. *Ann Rheum Dis* 2022;81:ard-2022-223482. Available at: https://pubmed.ncbi.nlm.nih.gov/36351705/. Accessed November 24, 2022.
20. Felson DT, Anderson JJ. Methodological and statistical approaches to criteria development in rheumatic diseases. *Baillieres Clin Rheumatol* 1995;9:253–266.
21. Singh JA, Solomon DH, Dougados M, Felson D, Hawker G, Katz P, et al. Development of classification and response criteria for rheumatic diseases. *Arthritis Care Res (Hoboken)* 2006;55:348–352.
22. Quinn KA, Ahlman MA, Malayeri AA, Marko J, Civelek AC, Rosenblum JS, et al. Comparison of Magnetic Resonance Angiography and 18F-fluorodeoxyglucose Positron Emission Tomography in Large-Vessel Vasculitis. *Ann Rheum Dis* 2018;77:1165. Available at: /pmc/articles/PMC6045453/. Accessed November 24, 2022.
23. Besutti G, Muratore F, Mancuso P, Ferrari M, Galli E, Spaggiari L, et al. Vessel inflammation and morphological changes in patients with large vessel vasculitis: a retrospective study. *RMD Open* 2022;8:e001977–e001977. Available at: https://europepmc.org/articles/PMC8734042. Accessed November 24, 2022.
24. Quinn KA, Alessi HD, Ponte C, Rose E, Ahlman MA, Redmond C, et al. Use of 18F-fluorodeoxyglucose positron emission tomography to standardize clinical trial recruitment in Takayasu's arteritis. *Rheumatology (Oxford)* 2022;61:4047–4055.

Available at: https://europepmc.org/articles/PMC9536789. Accessed November 24, 2022.
25. Schönau V, Roth J, Tascilar K, Corte G, Manger B, Rech J, et al. Resolution of vascular inflammation in patients with new-onset giant cell arteritis: data from the RIGA study. *Rheumatology* 2021;60:3851–3861. Available at: https://academic.oup.com/rheumatology. Accessed March 11, 2023.

FIGURE LEGENDS

Figure 1. TAIDAI score sheet. Each row represents a symptom paired with specific arterial territories. In step one, all the clinical symptoms considered are listed. Each symptom must be scored only if present within seven days of clinical evaluation. In step two, only the arterial territories with an active FDG-PET must be scored. Step three is for the total TAIDAI calculation: each clinical symptom correctly paired with a corresponding FDG-PET abnormality contributes one point to the total TAIDAI score.

Figure 2. Bar graph showing the number of clinical symptoms (blue bars) and the absolute number of corresponding arterial territories with FDG-PET activity (red bars). Of note, constitutional symptoms are paired with elevated acute phase reactants rather than FDG-PET findings. TAIDAI items (green bars) are only scored when a clinical symptom and corresponding PET or laboratory abnormality occurs within the same patient at the same study visit. For example, while the prevalence of constitutional symptoms and elevated acute phase reactants is high across the cohort, these two items occurred less frequently within the same patient, resulting in fewer TAIDAI points.

Figure 3. Forest Plot showing the results of the multivariate analysis to assess the predictors for concordance or discordance between clinical assessment and TAIDAI. Concordance between TAIDAI and clinical assessment was defined by clinical assessment active and TAIDAI active or the opposite. Discordance was defined by a clinical assessment active and TADAI not active, or the opposite.

Figure 4. Representative images of a clinical case. The patient presented with abdominal ischemic pain and bilateral carotidynia. **Figure A and B** show ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) magnetic resonance (FDG-PET MR) findings at baseline detecting active vasculitis at the abdominal aorta (**Figure A,** red arrow) and around the carotid arteries (**Figure B**, white arrows). In this case, the total TAIDAI score of the patient was 3. **Figures C and D** show the FDG-PET MR findings six months later. The patient was started on a TNF inhibitor with resolution of carotidynia but still complained of mild, intermittent abdominal pain. There was no active vasculitis on FDG-PET imaging (**Figures C and D**, red and white arrows, respectively). Since there was no correspondence between clinical symptoms and activity of FDG-PET, the TAIDAI was 0.

Table 1. Characteristics of the cohort at enrollment

Baseline characteristics	N=96
Age	33.4 (±14.4)
Female	79 (82%)
Disease duration (months)	25 (9-91)
Prednisone dose (mg/day)	0 (0-10)
Any DMARD at enrollment	71 (74%)
Specific DMARD at enrollment Methotrexate TNF inhibitor Tocilizumab Azathioprine Mycophenolate mofetil	 32 (33%) 16 (17%) 16 (17%) 6 (6%) 5 (5%)
CRP (mg/L)	3 (0.9-17)
ESR (mm/1sthour)	10 (4-23)
PhGA	1.5 (±2.1)
Clinically Active Disease	35 (36.5%)
Active PET	61 (63.5%)
PETVAS	14 (10-19)
TAIDAI	1.2 (±1.8)

Data are presented as mean (SD), median (IQR) or n (%).

Abbreviations used in the table: CRP (C-reactive protein), DMARD (disease modifying antirheumatic drug), ESR (erythrocyte sedimentation rate), PhGA (physician global assessment), PET (positron emission tomography), PETVAS (PET Vascular Activity Score), TAIDAI (Takayasu Arteritis Integrated Disease Activity Index).

Table 2. Spearman's Correlations between different assessments of disease activity in Takayasu's Arteritis

	By Variable	p value	Spearman ρ
TAIDAI	PhGA	<.0001*	0.5523
TAIDAI	PETVAS	<.0001*	0.4742
PETVAS	PhGA	<.0001*	0.3686
TAIDAI	CRP	<.0001*	0.3128
TAIDAI	PtGA	0.0002*	0.3026
ESR	PhGA	0.0003*	0.2535
ESR	PtGA	0.0076*	0.2158
PtGA	PhGA	0.0110*	0.2058
TAIDAI	ESR	0.0043*	0.1991
CRP	PhGA	0.0489*	0.1384
ESR	CRP	0.0819	0.1221
CRP	PETVAS	0.1223	0.1085
ESR	PETVAS	0.2475	0.0813
CRP	PtGA	0.7259	-0.0287
PETVAS	PtGA	0.3454	-0.0771

Abbreviations used in the table: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PETVAS = PET vascular activity score; PhGA = physician global assessment; PtGA = patient global assessment; TAIDAI = Takayasu's arteritis integrative disease activity assessment.

TAIDAI (Takayasu's Arteritis Integrated Disease Activity Index) Scoring Sheet

Only score Step Two, if an Item in the same row is present in Step One. Only score Step Three, if Items are present in the same row in both Steps One and Two.

	Step One: Check if clinical symptom present within 7 days of evaluation →	**Step Two: Check if active vasculitis by imaging or labs** (FDG uptake in arterial territory > liver by inspection) →	**Step Three:** 1 pt each
1.	☐ Left carotidynia	☐ Left Carotid	☐
2.	☐ Right carotidynia	☐ Right Carotid	☐
3.	☐ Left arm claudication	☐ Left Subclavian or Left Axillary	☐
4.	☐ Right arm claudication	☐ Right Subclavian or Right Axillary	☐
5.	☐ Left leg claudication	☐ Left Iliofemoral or Abdominal Aorta	☐
6.	☐ Right leg claudication	☐ Right Iliofemoral or Abdominal Aorta	☐
7.	☐ Left frontotemporal headache	☐ Left Carotid	☐
8.	☐ Right frontotemporal headache	☐ Right Carotid	☐
9.	☐ Left posterior headache / neck pain	☐ Left Vertebral	☐
10.	☐ Right posterior headache / neck pain	☐ Right Vertebral	☐
11.	☐ Vertigo or lightheadedness	☐ Left or Right Vertebral or Left or Right Carotid	☐
12.	☐ Visual disturbance	☐ Left Carotid or Right Carotid	☐
13.	☐ Jaw claudication	☐ Left Carotid or Right Carotid	☐
14.	☐ Back pain	☐ Thoracic or Abdominal Aorta	☐
15.	☐ Ischemic chest pain	☐ Thoracic Aorta	☐
16.	☐ Ischemic abdominal pain	☐ Abdominal Aorta or Mesenteric	☐
17.	☐ Constitutional symptoms	☐ CRP ≥ 10mg/L or ESR ≥ 40 mm/hr	☐
		Total TAIDAI Score *sum all Items from Step Three*	☐

figure_1.tif

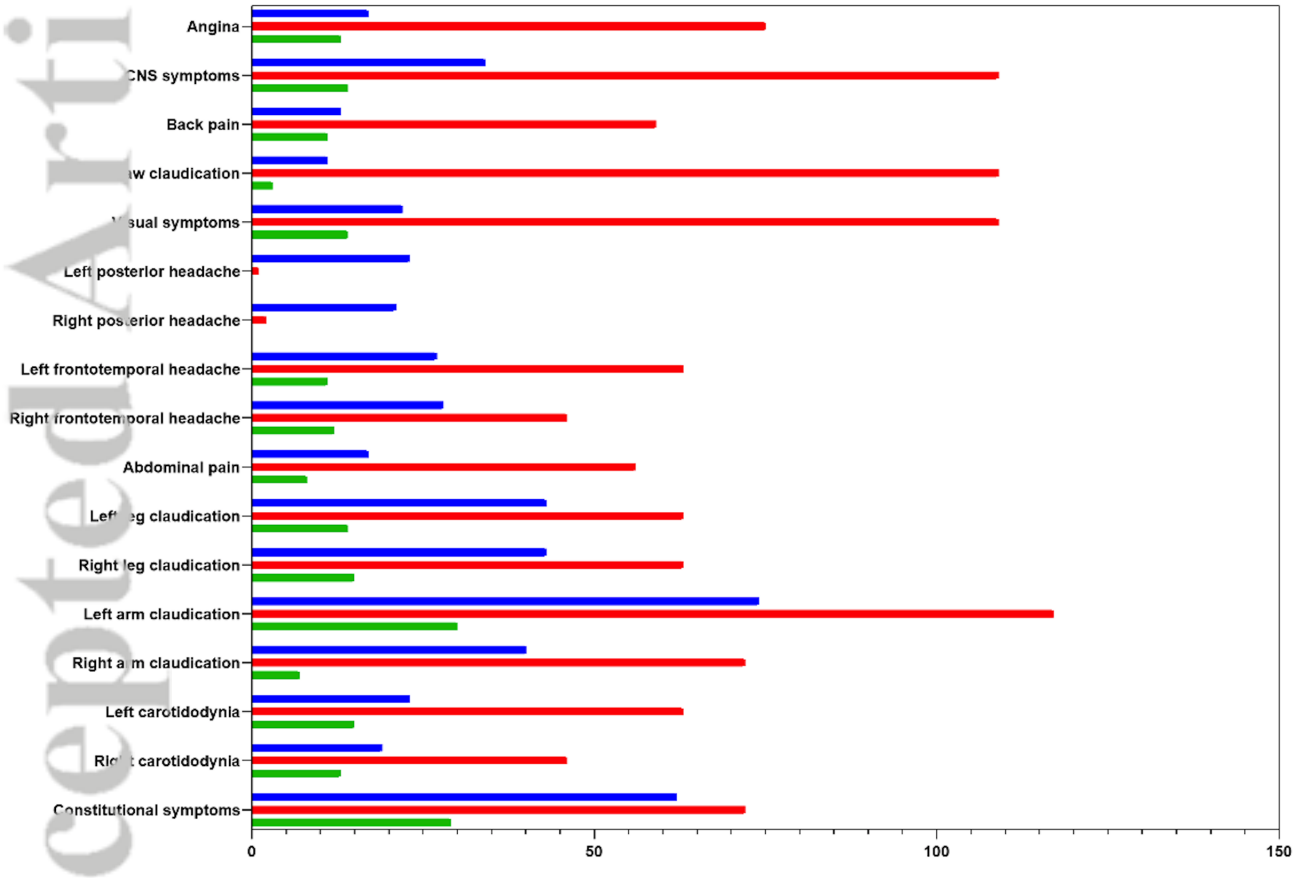

Figure2_.tiff

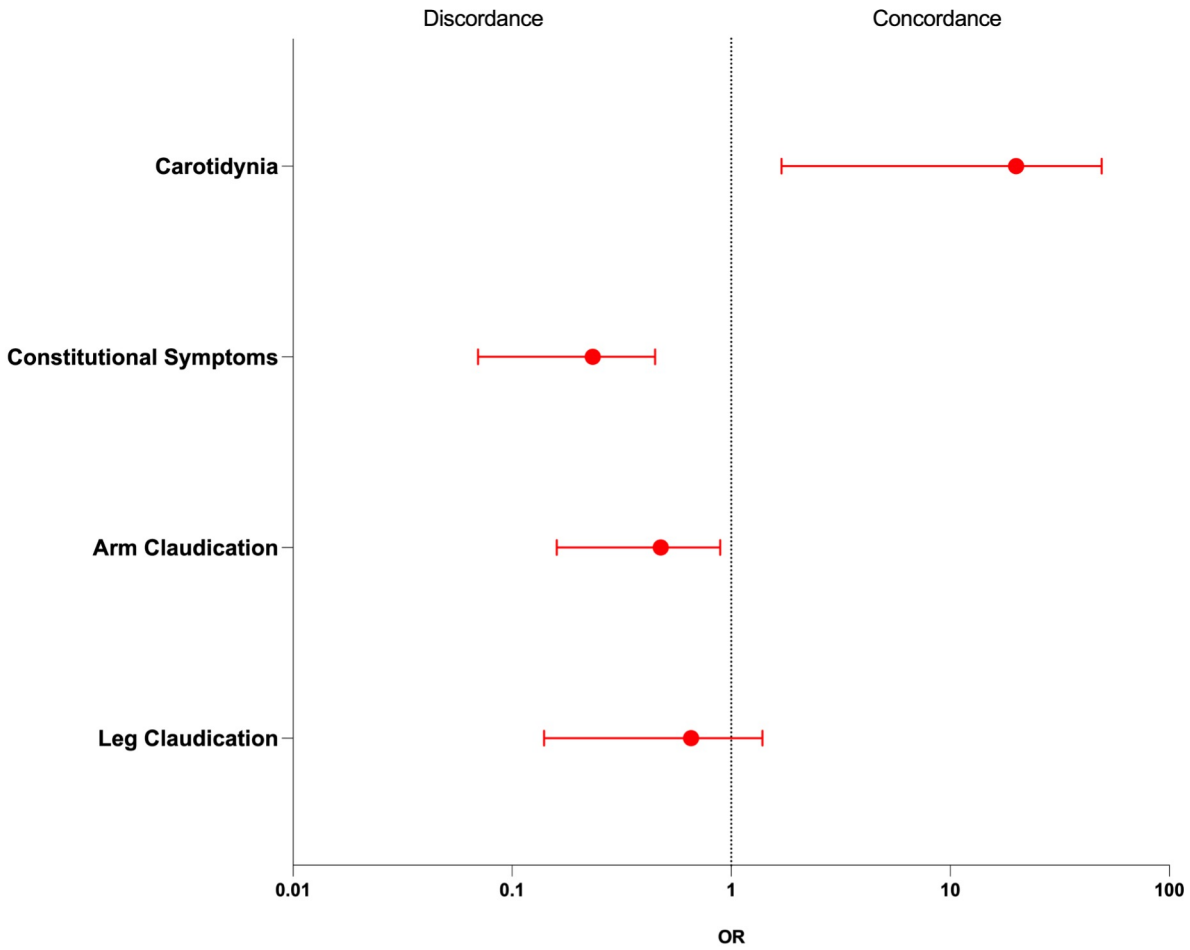

Figure_3.tiff

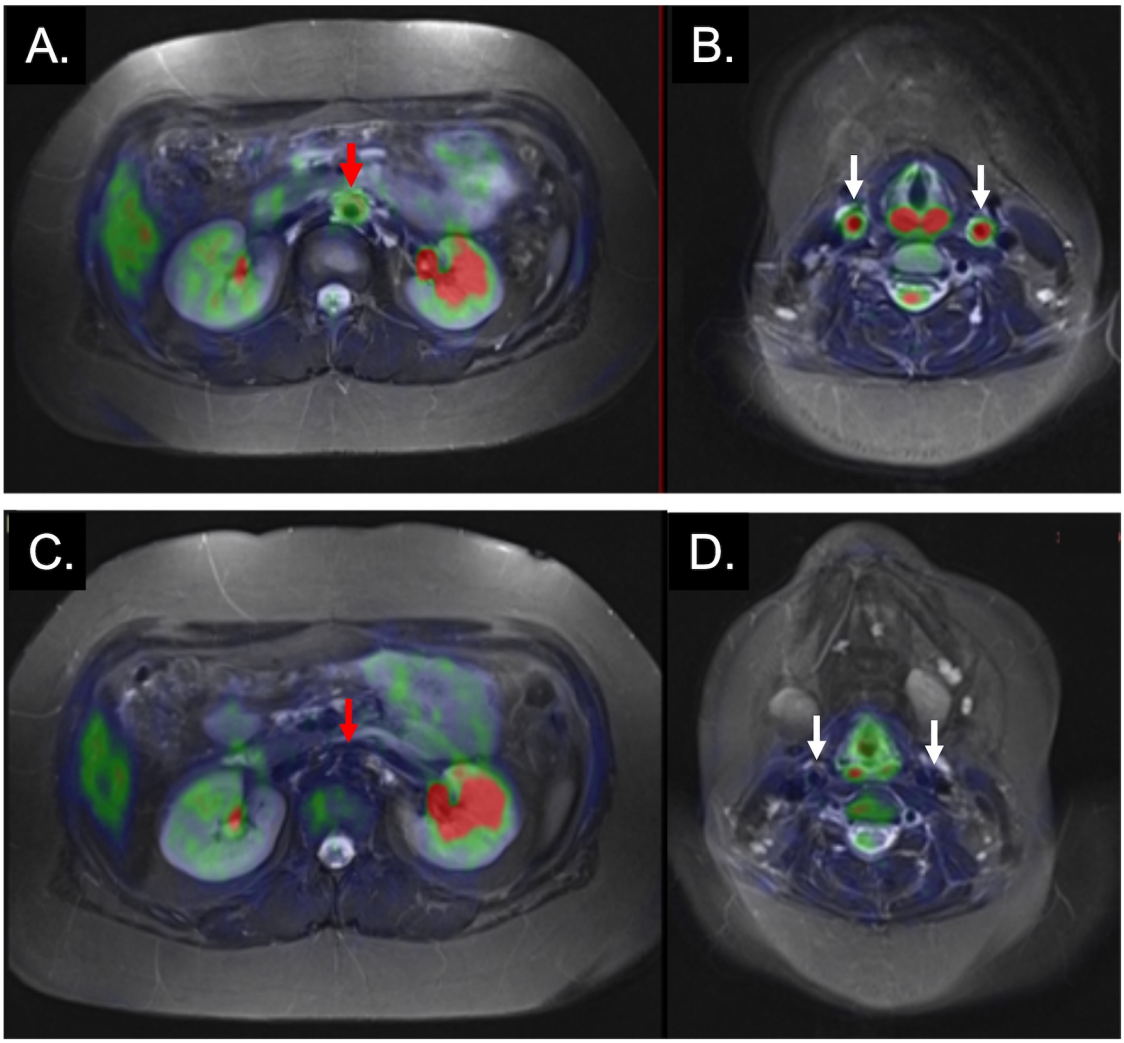

Figure 4.tiff