Does 18F-Fluodordeoxyglucose Positron Emission Tomography (PET) Correlate with Disease Activity in Patients who are Receiving Treatment for Giant Cell Arteritis (GCA): a Systematic Review and Meta-Analysis.

by

Alison H. Clifford

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

in

Translational Medicine

Department of Medicine

University of Alberta

ABSTRACT

Introduction: The utility of obtaining follow up 18-F fluorodeoxyglucose positron emission tomography (FDG PET) imaging in patients with giant cell arteritis (GCA) is unclear. We performed a systematic review and meta-analysis to determine how often vascular FDG PET uptake improves or normalizes in GCA patients after starting immunosuppressive treatment.

Methods: An electronic literature search of MEDLINE (Ovid), EMBASE, CINAHL, Scopus, and Cochrane Library from inception through November 4 2020 was performed. Longitudinal studies assessing the correlation of follow-up 18F-FDG PET and clinical or biochemical disease activity in GCA patients receiving treatment were included. Screening, full text review and data extraction was performed by 2 independent reviewers. Meta-analysis of the pooled sensitivity of improved PET for those with clinical or biochemical improvement, and normalized PET for those in clinical remission was performed. Subgroup analyses were performed to examine the tocilizumab-treated patients (TCZ subgroup), studies using international consensus criteria for PET interpretation (CC subgroup), as well as use of hybrid PET/CT (PET/CT subgroup) imaging, and effects of size (Pt Number subgroup).

Results: Of 18 included studies, most described improvement of FDG uptake in GCA patients after starting immunosuppressive treatment, but normalization of PET occurred less commonly among patients in remission. The pooled sensitivity of improved PET uptake for those with clinical improvement was 0.85 (95% CI 0.76-0.93, I^2=0), the pooled sensitivity of improved PET uptake for those with biochemical improvement was 0.84, (95% CI 0.74-0.93, I^2=0), and the pooled sensitivity for normalized PET in those in clinical remission was 0.43 (95% CI 0.34-0.53,

I^2=9.2). Results were similar in the CC , PET/CT and Pt Number subgroups (pooled sensitivity for PET normalization was 0. 41, 95% CI 0.28, 0.55; 0.43, 95% CI 0.32, 0.55; and 0.41, 95% CI 0.33, 0.51), however more heterogeneity was observed (I^2=50.3%, 92.5%, and 95.3% respectively.) The pooled sensitivity for PET normalization improved to 0.80 (95% CI 0.65-0.93, I^2=0) in the TCZ subgroup.

Conclusion: Vascular FDG uptake improved in the majority (85%) of GCA patients who experienced clinical improvement on treatment and normalized in 43%. Limited data suggested follow up PET scans normalized more often in TCZ-treated patients. Additional prospective longitudinal studies of FDG PET are needed.

PREFACE

This thesis is an original work by Dr. Alison Clifford, and required the effort of many valuable colleagues. Ms. Janice Kung, medical librarian, performed the literature search for the systematic review. Dr. Joanne Homik, MD, MSc, performed second review of titles/abstracts, full text screening, and manuscript editing. Dr. Ashley Yip, MD, performed second review for full text review and data collection. Mr. Ben Vandermeer performed statistical analysis and manuscript editing. Dr Jan Willem Cohen Tervaert, MD, PhD, assisted with concept formation, and manuscript editing. I was responsible for study concept and design, data collection, analysis, and writing. No part of this thesis has been previously published.

ACKNOWLEDGEMENTS

I would like to extend my sincere thanks to my supervisor, Dr. Jan Willem Cohen Tervaert, as well as Drs. Paolo Raggi, Stephanie Keeling, and Joanne Homik, the members of my supervisory committee, for their collective patience, sage advice, and continued support over the years. I also wish to acknowledge the Anthony Russell Scholarship Fund, University of Alberta, Edmonton, Canada, for providing financial support.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

GCA= giant cell arteritis

FDG= 18F-fluorodeoxyglucose

PET= positron emission tomography

CT= computerized tomography

TCZ= tocilizumab

ESR= erythrocyte sedimentation rate

CRP= C-reactive protein

NIH= National Institute of Health

BVAS= Birmingham vasculitis activity score

TP=true positive

TN=true negative

FP=false positive

FN=false negative

SUV= standardized uptake value

LVV=large vessel vasculitis

Chapter 1: Introduction

Giant cell arteritis (GCA) is the most common primary systemic vasculitis of older persons.[1–3] Although often considered a disease of the temporal arteries, inflammation of the aorta and major arteries is present in most patients[4,5] and is often under-recognized. Patients with GCA are treated with high dose prednisone, and increasingly frequently, tocilizumab (TCZ), however, relapses occur in 25-75% of patients over time,[6] resulting in a high lifetime cumulative exposure to glucocorticoids, with frequent adverse events.[7]

There is currently no gold standard test for determining disease activity in GCA—in clinical practice, this is typically determined by a physician global assessment, incorporating symptoms, physical signs, and laboratory markers. ESR and CRP, although commonly used in decision-making, are neither sensitive nor specific for GCA, and are silenced by tocilizumab, making them of little value in patients receiving this medication.[6] Indeed, in a subsequent analysis of a large prospective study in GCA, ESR or CRP were falsely normal in one third of GCA patients experiencing clinical flare, and falsely elevated in over half of patients in remission.[6] Diagnostic imaging studies that can visually depict active large vessel inflammation are therefore of high interest for assessing disease activity. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) is a functional imaging modality that depicts glucose metabolism within blood vessel walls.[8] It reliably identifies active large vessel inflammation in GCA patients before glucocorticoids are initiated, with a high pooled sensitivity of 90% and specificity of 98% for the diagnosis.[9] The utility of FDG PET in assessing disease activity over time in patients receiving treatment, however, is still debated.[4,10–12] While some studies describe persistent vascular FDG

uptake despite achievement of clinical remission in treated GCA patients,[4] others have reported complete normalization of FDG uptake within 2 weeks of therapy.[13] These discrepancies may arise due to differences in the criteria for what constitutes an "active" scan, as well as differences in doses and duration of treatments received and timing of follow up scans. From a mechanistic perspective, it is postulated that glucocorticoids may interfere with an accurate FDG PET scan interpretation by directly inhibiting uptake of FDG into vascular cells (via inhibition of glut transporters), and/or by increasing hepatic uptake of tracer (the most commonly used organ for determining "background" FDG uptake), resulting in falsely normal PET in treated patients.[14] In addition, PET scans in treated patients may also be falsely positive if persistent vascular FDG uptake may occur due to processes other than active vasculitis, such as vascular wall remodelling, or concomitant atherosclerosis in an elderly patient.[14,15]

In 2018, a systematic review to inform the EULAR recommendations for imaging in large vessel vasculitis found insufficient data to determine the utility of PET for follow-up.[16] It was recommended that follow-up PET imaging not be pursued in patients in clinical remission, but consideration be given to re-imaging those who subsequently flare.[17] While objective, this approach may result in difficulty interpreting "flare" scans in clinical practice, if we acknowledge that FDG uptake may improve but not completely resolve in some or perhaps many patients. Another more recent systematic review and meta-analysis evaluating the role of PET during treatment of patients with different types of large vessel vasculitis, found that FDG PET had a moderate sensitivity (77%) and specificity (71%) for determining disease flare during treatment using cross sectional studies, however, how often PET normalizes in those patients who subsequently enter clinical remission could not be determined.[18]

Due to the significant risks associated with both under- and over-treatment of GCA, understanding which biomarkers accurately reflect disease activity in patients treated with glucocorticoids and TCZ is a high priority. We performed a systematic review and meta-analysis to assess the longitudinal value of repeat FDG PET scans over time in GCA patients starting treatment, to determine how often follow up PET improves in patients who clinically improve on treatment. Our review addressed 3 questions: 1) how often does vascular FDG uptake improve on follow up PET in GCA patients who clinically improve after starting or escalating immunosuppressive treatment, 2) how often does vascular FDG uptake improve on follow up PET in GCA patients who biochemically improve after starting or escalating immunosuppressive treatment, and 3) how often does vascular FDG uptake normalize in treated GCA patients who enter clinical remission.

Chapter 2: Methods

The systematic review and meta-analysis is reported in accordance with PRISMA 2020 statement. The protocol for this systematic review and meta-analysis was registered in PROSPERO (CRD42020219141), available at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=219141&VersionID=14223 98.

Data sources and search strategy:

An electronic literature search of MEDLINE (via Ovid), EMBASE, CINAHL, Scopus, and Cochrane Library (Wiley) from date of inception through November 4 2020 was performed by a University of Alberta medical librarian (JK.) No language or date limits were applied. Please refer to supplemental data for full-text search strategies (see Appendix 1.) Reference lists from included studies were hand searched for additional relevant papers. The search was performed using terms: "PET", or "positron emission tomography" or "positron emission tomography/computerized tomography", or "PET/CT", or "FDG-PET" or "F-fluorodeoxyglucose positron emission tomography", or "FDG-PET/MR" or "F-fluorodeoxyglucose positron emission tomography/magnetic resonance imaging" with "giant cell arteritis", or "GCA", or "temporal arteritis", or "large vessel vasculitis", or "aortitis", or "Horton's disease." For full texts that were not retrieved automatically using EndNote, a full text request was submitted via University of Alberta interlibrary loan. Full texts not received within 3 months of the request submission were excluded (mean time to recovery of full texts was 5.3 days, +/- 4.34.) All unique references were imported into Covidence,[19] a web-based program to facilitate the screening process for systematic reviews.

Study Selection:

Studies that addressed the correlation between follow-up 18-F FDG PET or hybrid imaging (FDG PET/CT, FDG PET/CTA, FDG PET/MR) and disease activity in GCA patients receiving treatment for ≥ 3 months were included. Inclusion criteria were the following: full published manuscripts, including a minimum of 2 GCA patients starting/escalating treatment with ≥3 month follow-up. For inclusion, "treatment" may have included prednisone (or other glucocorticoid), methotrexate, tocilizumab, anti-TNF therapy, abatacept, or any other biologic or conventional immunosuppressive medication. Patients must have had a positive baseline PET documenting large vessel vasculitis, and at least 1 follow-up scan over time (≥3 months after treatment start or escalation), with PET results classified as either positive or negative (using either a set visual cut-off score, semi-quantitative cut-off score, or nuclear medicine physician's opinion), or as improved/worsened/unchanged (based on pre-determined score, including PETVAS, total vascular score, or SUVmax or target blood:pool ratios, or nuclear medicine physician opinion). Studies must have also documented an assessment of disease activity, considered in this review as the gold standard for disease activity, using either: physician opinion (or decision to escalate treatment as a surrogate of this), a disease activity score [for ex: NIH criteria or Birmingham vasculitis activity score (BVAS)] or an arterial biopsy result, or CRP/ESR (contributing data to review question #2 only.) Individual patient data must have been available to permit calculation of the pooled sensitivity and specificity of PET improvement or normalization [documented as yes/no], for clinical or biochemical improvement or clinical remission [yes/no] in treated patients.

Exclusion criteria: Studies using only other forms of disease activity assessment (for ex: other imaging modality results) as the gold standard for disease activity were excluded, as were studies that did not document a baseline positive PET for large vessel vasculitis. Studies using PET for diagnosis of GCA only, those with insufficient data to determine the absolute numbers of true-positive (TP), true-negative (TN), false-positive (FP) and false-negative (FN) PET scans, as well as abstracts, single case reports, editorials and review articles were excluded.

Study eligibility, data collection and extraction:

Two reviewers independently reviewed all the retrieved abstracts and titles to determine initial study eligibility, then full manuscripts for study inclusion (AC, JH.) Discrepancies were resolved by consensus.

Data was extracted independently by 2 reviewers (AC, AY) and recorded using standardized forms. Disagreements were resolved by consensus. Baseline study data recorded included: lead author, year of publication, country of study, study type (cross-sectional, prospective or retrospective cohort, randomized control trial, etc), number GCA patients described, mean/median age of patients, % female, type of treatments received between baseline and follow-up PET scan (prednisone, tocilizumab, methotrexate, other [list]), time between baseline and follow-up PET scan (months), type of imaging scan (PET, PET/CT, PET/CTA, PET/MR), number of scans performed per patient, methods of PET interpretation (visual score cut-off, semi-quantitative score cut-off, expert opinion), and methods of disease activity assessment (physician opinion/decision to treat, NIH criteria or BVAS, biopsy). The results of follow up PET scans (positive, negative, or improved/unchanged/worsened), and patients' clinical disease

activity status (active, remission) at time of scans was recorded. For each included study, we extracted data regarding the number of TP, TN, FP, FN PET scans for GCA disease activity (using clinical disease activity assessment as gold standard for questions 1 and 3, and ESR and/or CRP for question 2.)

A quality assessment of the studies was performed independently by 2 reviewers (AC, AY) using the Quality Assessment of Diagnostic Studies-2 (QUADAS-2).[20] Disagreements were resolved by consensus, and final results were reported in tabular form.

Statistics

Studies were grouped according to ability to contribute data to each of the 3 review questions. Subgroup analyses were also performed to assess the frequency of PET improvement or normalization over time in GCA patients who received tocilizumab specifically (TCZ subgroup), and to assess the frequency of PET normalization during follow up using internationally recommended consensus criteria to define an "active" versus normal FDG PET (Consensus Criteria, or CC subgroup).[8] The latter subgroup consisted of only those studies that defined "active vasculitis" on FDG PET using visual scores from 0-3 in comparison to the liver, with grade 0 or 1 vascular uptake signifying a normal PET, and grade 2 or 3 vascular uptake signifying active vasculitis. Additional subgroup analyses were also performed to examine the effect of improvements in imaging technology over time by limiting analysis to those studies that used PET/CT hybrid imaging (PET/CT subgroup) and the effect of study size by evaluating only those studies with a minimum of 5 patients with serial scans (Pt Number subgroup.)

Descriptive statistics (mean +/-standard deviation, or median and range, as appropriate) were used to summarize the features of individual studies. A meta-analysis of the pooled sensitivity and specificity of 1) improved FDG PET for clinical improvement in treated GCA patients, 2) improved FDG PET for biochemical improvement in treated GCA patients, and 3) normalized FDG PET for clinical remission in treated GCA patients, was planned using a bivariate model. In the case of insufficient data (ie: a required minimum of four studies containing joint estimates of both sensitivity and specificity), a pooled sensitivity analysis using the Freeman-Tukey double arc sine method for pooling proportions was performed. [21] Pooled data with 95% confidence intervals (CI) was presented using forest plots, with an assessment for study heterogeneity using I^2. P-values of <0.05 were considered significant.

Chapter 3: Results

Literature search

The search strategy identified 1932 unique studies, of which 1764 were excluded after title/abstract screening. The remaining 168 studies underwent full-text review of which 150 were excluded. See Figure 1 for flow diagram of screened studies. The most common reasons for study exclusion were publication available in abstract form only, or insufficient detail provided to extract individual patient data.[22–26] Ultimately, 18 studies were included in the systematic review and meta-analysis,[4,27–43] as they either contained sufficient data to assess for the sensitivity/specificity of PET improvement for clinical improvement (15 studies),[28–41,43] biochemical improvement (15 studies),[27–32,34–40,42,43] or PET normalization for clinical remission in treated GCA patients (16 studies.)[4,27–29,31–41,43]

Qualitative analysis (systematic review)

Table 1 describes the baseline data of the 18 included studies.[4,27–43] Studies were published between 2002 and 2020. Of these, the majority (16 studies) were conducted in Europe, with 1 each from U.S.A. and Japan. Five prospective cohort studies were included,[4,27,29,41,43] and the remaining studies were retrospective cohort. Included GCA patients were of older age (in all studies, average age>50 years), and predominantly female. In accordance with study inclusion criteria, after baseline positive scan, all GCA patients were treated with new or escalating doses of immunosuppressive therapy, most commonly prednisone (used in 17/18 studies), methotrexate (7 studies, 33 patients) and tocilizumab (6 studies, 27 patients).[27–29,38–40] Other immunosuppressants, including azathioprine (3 patients), mycophenolate mofetil (1 patient), cyclophosphamide (7 patients), anti-TNF (3 patients), anakinra (2 patients), chloroquine and

cyclosporine (not specified) were rarely used. In one study, all patients received treatment, but the type of immunosuppression was not described.[43] The clinical assessment of disease activity (gold standard) was determined by the clinician's opinion in nearly all of the studies (16 of 18) , typically informed by the presence of symptoms, signs and inflammatory markers. Two studies used a formal clinical disease activity score (the BVAS in 1 study,[37] and the NIH/Kerr index in another.[29])

Performance, image acquisition and interpretation of PET

In most studies, 18F-FDG PET/CT imaging was performed, while 5 studies used 18F-FDG PET only. No studies describing PET-MR were included. All studies contained longitudinal PET data, with a median of 2 to 4 PET scans per patient described in each, and some studies including up to 5 follow up scans per patient, over a median of 3-19 months (range 3-54 months). Variability was seen in the acquisition of PET imaging. Twelve studies reported the time between injection of FDG and image acquisition, with 60 mins being the most common uptake time (10 studies)[4,29,31,32,35,37–39,42,43], while 1 study waited 90 mins[36] and another waited 120 mins.[27] PET scans were described using the Nuclear Medicine physician's opinion in all 18 studies, while visual scores were also reported in 12 studies.[4,27,29,32,35–37,39–43] Visual scores typically described vessel uptake in comparison to liver uptake, however in 3 studies no comparator organ was used or specified, and in 1 pulmonary uptake was used for comparison. Semi-quantitative scoring methods were performed in 8 studies, including vessel standardized uptake values (SUVmean or max),[29,35,38–40,42] or summed visual scores, such as PETVAS,[27,39] or Total Vascular Scores (TVS).[4,35] The definition of "active vasculitis" by PET differed between studies, most often relying on the Nuclear Medicine physician's opinion[27,30,31,34,38] or the

presence of vascular FDG uptake greater than or equal to that of the liver.[32,37,39,40,42] See Table 2 for full details of imaging characteristics of included studies.

Assessment of Study Quality

Variability in the performance and interpretation of the index test, as well the reference standard were the main sources of bias in the 18 included studies (see Figures 2a and 2b, and QUADAS results for individual studies in Appendix 2.) In many studies, it was unclear whether PET or clinical assessment were interpreted blinded with respect to one another, and in some, it was explicitly stated that they were not.

Main Findings

A summary of the main PET findings in each study can be found in Table 3. In most studies, FDG uptake improved on follow up PET scans (by either Nuclear Medicine opinion, visual scores, or semi-quantitative measures) in the treated patients who clinically improved. In 11 of the 15 studies, repeat PET scan improved in all of the 56 cases in which a repeat scan was performed during period of clinical improvement.[28–31,35–41] However, in the remaining 4 studies describing 54 cases, improved FDG uptake occurred in only 27 (between 40% to 66.7% cases in individual studies.)[32–34,43] Some of these studies suggested that ongoing improvement in vascular FDG uptake may occur with longer follow up. For example, in one retrospective study by de Boysson et al, among 34 follow up scans conducted in patients in ongoing clinical remission, 12 of 25 (48%) PET scans improved at median 11 months follow up, however, 5 of 7 (71%) scans improved when repeated at 15 months. No further improvement was seen in the remaining 2 scans repeated 20 and 25 months, however.[32] Similarly, in a smaller study by

Daumas et al, among 5 patients evaluated at baseline, 6 and 12 months with PET/CT, although only 1 of the 5 follow up scans improved at 6 months, 3 of 5 scans improved by 12 months.[33]

Similarly, most studies found that FDG uptake improved in follow up PET scans performed in those with biochemical improvement. In 10 of the 15 studies, improvement in FDG uptake occurred in all of the 40 cases in which biochemical improvement occurred.[28–31,34–36,38–40] In the remaining 5 studies, however, improved FDG uptake occurred in only 44 of 72 cases.[27,32,37,42,43] In addition, 2 cases were described in which follow up PET improved in patients who had a rise in CRP but no clinical symptoms of active disease---in one of these cases, additional work-up led to an alternative diagnosis of urinary tract infection to explain the elevated inflammation marker.[36]

Repeat PET scans were less likely to normalize in treated patients who achieved clinical remission, however. In 5 of the 16 studies describing this outcome, all of the 28 repeat scans done in patients in clinical remission normalized.[28,31,38,40,41] However, in the other 11 studies describing 124 follow up scans done in patients in clinical remission, normalization of FDG uptake occurred in only 37 cases.[4,27,29,32–37,39,43] Among the 5 prospectively conducted studies, 1 found that repeat PET normalized in 3 of 3 (100%) patients in clinical remission,[41] while the other 4 studies found that follow up PET normalized in 0/6 (0%),[43] 3/14 (21.4%),[27] 10/30 (33.3%),[4] and 1 of 2 (50%)[29] patients in remission, respectively. As was seen for improvement in FDG uptake, some studies suggested repeat PET scans were more likely to fully normalize with increased duration of treatment/time since active disease. For example, in de Boysson et al, only 4 of the 25 scans (16%) done at 11 months follow up normalized, however, by 15 months, 2 of 7

(28.6%) repeat scans had done so.[32] Similarly, in Blockmans et al, although no statistically significant improvement in total vascular FDG scores was seen beyond 3 months follow up, at 6 months follow up, complete resolution of FDG uptake occurred in 2 of the 8 patients who still had uptake at 3 months.[4]

Four studies described the results of repeat PET over time in patients who had clinically active disease despite treatment.[4,34,37,42] In 3 of these studies, all follow up scans done in patients with clinically active disease were still positive.[34,37,42] In one study, however, PET remained positive in 11 of the 14 (78.6%) prospectively conducted follow up PET scans, but normalized in the other 3 (21.4%) despite ongoing clinical activity.[4]

Tocilizumab (TCZ) subgroup

Differences in immunosuppressive treatment were hypothesized to introduce heterogeneity into this review. In particular, the effect of tocilizumab on follow up PET was of interest, as use of this medication results in rapid normalization of systemic inflammatory markers. Six studies, 4 retrospective and 2 prospective, described the results of repeat PET in a total 44 GCA patients starting TCZ. Among retrospective studies, follow up PET scans improved in all 28 cases described and normalized in all but 1.[28,38–40] In the first prospectively conducted study, of 2 patients started on tocilizumab, repeat PET/CT at 6 months normalized in 1, and improved but remained technically active in the other.[29] In a larger prospective study, serial PET/CT scans were conducted regularly every 6 months in patients with GCA or TAK, and clinical disease activity and PET scans were interpreted blinded to one another. Of 14 GCA patients who

entered clinical remission after starting TCZ for active disease, follow up PET/CT scan normalized in only 3 (21.4%) at 6 months, according to Nuclear Medicine physician's opinion.[27]

Other subgroups: Consensus criteria (CC), PET/CT, Pt Number

Due to variability in the way in which "active vasculitis" on FDG PET was defined, studies reporting PET activity using the proposed standardized FDG PET/CT interpretation criteria for large vessel vasculitis, as per a recent international consensus paper[8] were assessed separately. Five studies used these criteria, of whom 3 studies used grade 3 vascular uptake to define "active vasculitis",[32,39,40] and 2 studies[37,42] considered either grade 2 or 3 uptake as positive for "active vasculitis." Among these studies, PET scans performed between 6.5 to 12 months (3-54 months) follow up normalized in 6/34 (17.6%),[32] 6/13 (46.2%),[37] 5/6 (83.3%),[39] and 8/8 (100%)[40] cases when clinical remission was achieved, respectively. In one study, repeat scans were only performed in 6 patients with ongoing clinically active disease, and remained positive in all (100%).[42]

Twelve of the 18 studies utilized PET/CT hybrid technology, rather than PET alone.[27–29,32–35,37–39,41,42] Generally, these studies were performed more recently, all between the years of 2011 and 2020. In 7 of the 10 studies with available data, follow up imaging improved in all of the patients who experienced clinical improvement.[28,29,35,37–39,41] Normalization of all scans performed in remission was less common, and occurred in only 3 studies.[28,38,41]

Ten studies performed serial PET evaluations in at least 5 patients over time (Pt Number subgroup.)[4,27,32,33,37–40,42,43] These studies described a median of 11 combined clinical and PET

imaging assessments over time (range 6-44 assessments per study.) Repeat PET improved in all patients in 4 of the 7 studies in which these data were available, [37–40] but normalization of all scans in those in remission occurred in only 2 of 10 studies.[38,40]

Quantitative analyses (meta-analyses)

The results of sensitivities and specificities of individual studies can be found in Appendix 3. As few studies reported the results of follow up PET scans in patients with ongoing clinically active disease, there was insufficient data to calculate both sensitivity and specificity in most studies. Fewer than 4 studies with both measures were available, therefore we were unable to use a bivariate model or calculate hierarchical summary receiver operator characteristics (HSROC) plots to identify optimal cut-points for sensitivity and specificity of PET. In lieu, pooled sensitivities, using the Freeman-Tukey double arc sine method for pooling proportions was performed.

Fifteen studies (n=119 follow up scans) contributed data to determine how often repeat PET improved in treated GCA patients with clinical improvement. The pooled sensitivity of improved follow up PET for clinical improvement in treated patients was 0.85 (95% CI 0.76-0.93), with low heterogeneity, I^2=0%. Similarly, 15 studies (n=119 follow up scans) contributed data to determine how often repeat PET improved in treated GCA patients with biochemical remission. The pooled sensitivity of improved follow up PET for biochemical remission was 0.84, (95% CI 0.74-0.93), with I^2=0, indicating low heterogeneity. Sixteen studies (n=175 follow up scans) contributed data to determine how often repeat PET normalized in treated GCA patients in clinical remission. The pooled sensitivity of normalized follow up PET for treated

patients in clinical remission was 0.43, (95% CI 0.34-0.53), with I^2=9.2, indicating low heterogeneity. See Figures 3 a, b, c for forest plots of pooled sensitivities.

When the meta-analysis was limited to the CC subgroup, the pooled sensitivity of normalized follow up PET for those in clinical remission was not substantially different at 0.41 (95% CI 0.28, 0.55), however heterogeneity was moderate, with an I^2=50.3%. Similarly, the pooled sensitivity of normalized follow up PET for those in the Pt Number and PET/CT subgroups were similar to that of the overall group, at 0.41 (95% CI 0.33, 0.51), and 0.43 (95% CI 0.32, 0.55), respectively, but heterogeneity was high, with I^2 =95.3% and I^2 =92.5%, respectively. However, when the analysis was limited to the TCZ subgroup, the pooled sensitivity of PET normalization for patients in clinical remission improved to 0.80 (95%CI 0.65, 0.93), with an I^2=0%. The results of the subgroup pooled sensitivities can be found in Figure 4 a, b, c, d.

Figure 1. Flow diagram of included studies.

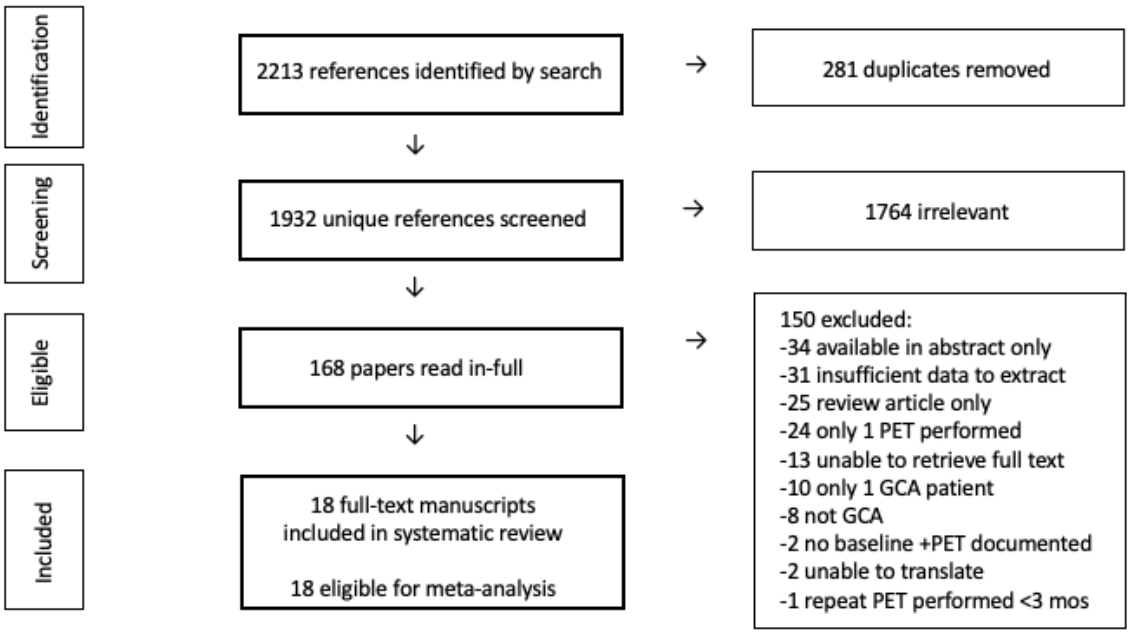


Table 1. Baseline clinical characteristics of included studies.

Author, year (ref #)	Country	Study design	# GCA	Age (yrs)	Female (%)	Prednisone Use	TCZ Use	Other treatment	Mos b/w PET scans, median, (range)	# PET scans per patient, median (range)
Banerjee, 2020 (27)	USA	Prospective	31	72	74	Yes, 21	Yes, 17	3 anti-TNF, 13 MTX	6 (5-12)	3 (2-6)
Regola, 2020 (39)	Italy	Retrospective	24	74	79.2	Yes, all	Yes, all (IV, sc)	6 MTX, 1 AZA	12 (12)	NS (1-3)
Conticini, 2020 (40)	Italy	Retrospective	8	67.9	62.5	Yes, all	Yes, all	1 MTX 1 CYC	12 (3-12)	2 (2)
Vitiello, 2018 (38)	Italy	Retrospective	12	68.6	67	Yes, all	Yes, all	7 MTX	11.6 (+/-8.8)*	2 (2)
deBoysson, 2017 (32)	France	Retrospective	25	69	68	Yes, all	No	No	11 (9-25)	2 (2-4)
Dellavedova, 2016 (42)	Italy	Retrospective	15	65.6	80	Yes, all	No	Some MTX, AZA, chloroquine, CsA	6.5 (4-54)	2 (2-3)
Bruls, 2016 (41)	Belgium	Prospective	3	74	100	Yes, all	No	MTX, AZA	NS (5-54)	2 (2)
Muto, 2014 (35)	Japan	Retrospective	3	81.3	66.7	Yes, all	No	No	4.6 (+/-3.1)*	2 (2)
Daumas, 2014 (33)	France	Retrospective	26	66.8	76.9	Yes, all	No	3 MTX	NS (6-26)	2 (2)
Ly, 2014 (34)	France	Retrospective	2	79	100	Yes, all	No	2 Anakinra 1 disulone	17 (11-30)	3.5 (2-5)
Salvarani, 2012 (29)	Italy	Prospective	2	59	0	Yes, all	Yes, all (IV)	No	6 (6)	2 (2)
Beyer, 2011 (28)	Germany	Retrospective	2	75.5	50	Yes, all	Yes, all	AZA, MMF	6 (6)	2 (2)
Henes, 2011 (37)	Germany	Retrospective	6	63.2	NS	Yes, all	No	CYC	6.75 (3-24)	4 (2-5)
Blockmans, 2006 (4)	Belgium	Prospective	35	72.7	71.4	Yes, all	No	No	3 (3-16)	2 (2-4)
deLeeuw, 2004 (36)	Netherlands	Retrospective	2	72	100	Yes, all	No	No	10 (2-24)	2 (2)
Meller, 2003 (43)	Germany	Prospective	14	62	60	NS	NS	NS	19 (4-30)	2 (2)
Brodmann, 2003 (30)	Austria	Retrospective	7	71.9	85.7	Yes	No	No	3 (3)	2 (2)
Belhocine, 2002 (31)	Belgium	Retrospective	3	62.7	66.7	Yes, all	No	No	5.5 (3-6)	2 (2)

Table 1 Legend: yrs (years), mos (months), sc (subcutaneous), TCZ (tocilizumab), USA (United States of America), anti-TNF (anti-tumour necrosis factor), MTX (methotrexate), AZA (azathioprine), NS (not specified), CYC (cyclophosphamide), CsA (cyclospoprine A), MMF (mycophenolate mofetil). Results represent means unless otherwise specified. * only data for mean +/- standard deviation available.

Table 2. Baseline imaging characteristics of included studies.

Author, year	Type of Imaging	PET interpretation : Visual Analysis	PET interpretation : Semi - quantitative analysis	PET interpretation : Nuclear Medicine physician opinion (y/n), # readers	PET read blinded	Definition of "Active Vasculitis "on PET	Method of clinical disease activity assessment (gold standard)
Banerjee, 2020	PET/CT	Vessel uptake relative to liver (graded 0-3)	PETVAS (0-27) Not done	Yes, 2	Yes	Nuclear Medicine physician opinion	Physician global (any symptoms=active, no symptoms=remission), blind to PET
Regola, 2020	PET/CT	Vessel uptake relative to liver (graded 0-3)	PETVAS (0-27) SUVmax vessel/liver ratio for each vessel	Yes, 1	NS	Visual vessel uptake > liver (grade 3)	Clinician opinion
Conticini, 2020	PET +/- CTA	Vessel uptake relative to liver (graded 0-3)	SUVmax vessels	Yes, NS	NS	Visual vessel uptake > liver (grade 3)	Clinician opinion
Vitiello, 2018	PET/CT	Not done	SUV max and mean of vessels	Yes, 1	NS	Nuclear Medicine physician opinion	Clinician opinion
deBoysson , 2017	PET/CT	Vessel uptake relative to liver (graded 0-3)	Not done	Yes, 1	No	Visual vessel uptake > liver (grade 3)	Clinician opinion, blind to PET
Dellavedova, 2016	PET/CT	Vessel uptake relative to liver (graded 0-3)	SUVmax vessel/liver ratio	Yes, 2	Yes	Visual vessel uptake ≥ liver (grade 2 or 3)	Clinician opinion, blind to PET
Bruls, 2016	PET/CT	Vessel uptake relative to background*	Not done	Yes, NS	NS	Any increased focal vessel uptake compared with the background	Clinician opinion
Muto, 2014	PET/CT	Vessel uptake graded as 0=none, 1=minimal uptake, 2= clearly increased uptake 3= marked uptake	TVS based on summed visual score of 7 vessels (0-21) SUVmax vessels	Yes, 4	Yes	Visual vessel uptake ≥ grade 1	Clinician opinion, blind to PET
Daumas, 2014	PET/CT	Not done	Not done	Yes, 1	NS	NS	Clinician opinion
Ly, 2014	PET/CT	Not done	Not done	Yes	No	Nuclear Medicine	Symptoms, inflammatory

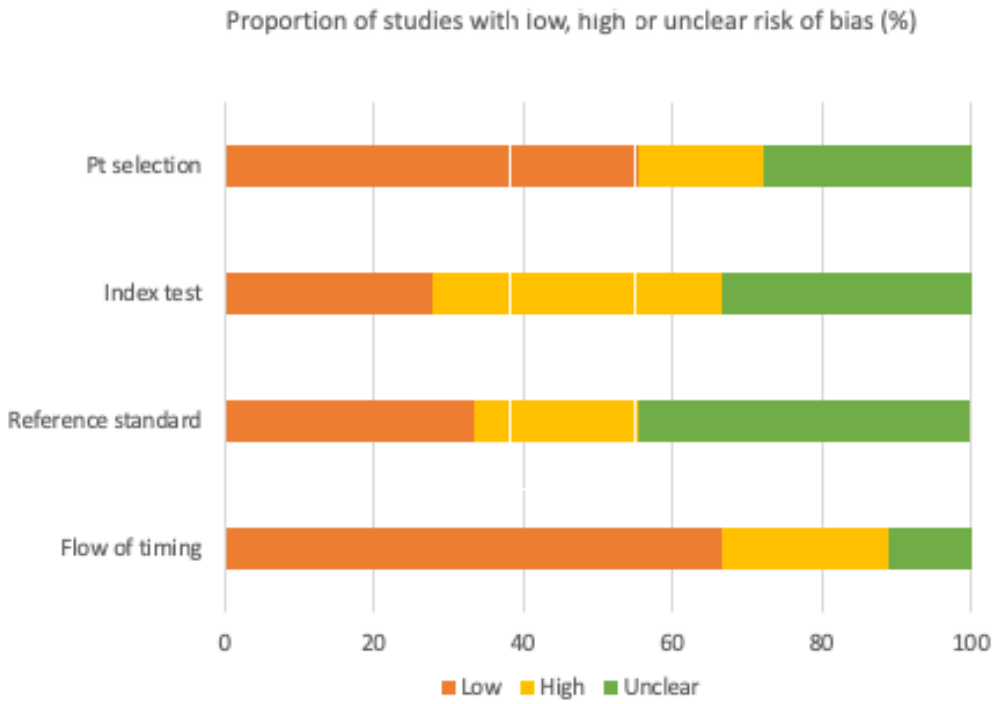
						physician opinion	markers, biopsy in 1 patient
Salvarani, 2012	PET/CT	Vessel uptake relative to liver (graded 0-3)	SUVmax vessel/liver	Yes, NS	NS	2 or more vessels with ≥ grade 2 FDG uptake	Kerr index
Beyer, 2011	PET/CT	Not done	Not done	Yes, NS	NS	NS	Clinician opinion
Henes, 2011	PET/CT	Vessel uptake relative to liver (graded 0-3)	Not done	Yes, NS	NS	Visual vessel uptake ≥ liver (grade ≥ 2)	BVAS ESR, CRP
Blockmans, 2006	PET	Vessel uptake (0=negative, 1=minimal vessel uptake, 2=clearly increased vessel uptake, 3=very marked vessel uptake)	TVS based on summed visual score of 7 vessels (0-21)	Yes, 2	Yes	Visual vessel uptake ≥ 1	Clinician opinion, blind to PET
deLeeuw, 2004	PET	Vessel uptake grade relative to pulmonary background (0=less than pulmonary background, 1=similar to pulmonary background, 2=greater than pulmonary background, 3=uptake clearly greater than pulmonary background)	Not done	Yes, 1	Yes	Visual vessel uptake ≥ 1	Clinical symptoms, blind to PET
Meller, 2003	PET	Vessel uptake relative to liver (graded 0-3)	Not done	Yes, 2	Yes	hPET: ≥ grade 1 in aorta, or ≥ grade 2 in branch vessels; dPET: ≥ grade 2 in aorta, ≥ or grade 3 in branch vessels	Clinical/lab improvement, blind to PET
Brodmann, 2003	PET	Not done	Not done	Yes, NS	NS	Nuclear Medicine physician opinion	Clinician opinion

Belhocine, 2002	PET	Not done	Not done	Yes, NS	NS	Nuclear Medicine physician opinion	Clinician opinion

Legend: * background not specified. Vessel uptake relative to liver grading scheme 0=no uptake, 1< liver, 2=liver, 3>liver. Clinician opinion refers to assessment of patients' symptoms and inflammatory markers, unless otherwise specified. SUV (standardized uptake value), PETVAS (validated summed visual score)[11], NS (not specified), TVS (total vascular score, summed visual score), BVAS (Birmingham Vasculitis Activity Score), hPET (hybrid PET), dPET (dedicated PET).

Figure 2. Summary of QUADAS-2 results, A) assessment of risk of bias in 18 included studies, and B) assessment of applicability concerns in 18 included studies.

A.



B.

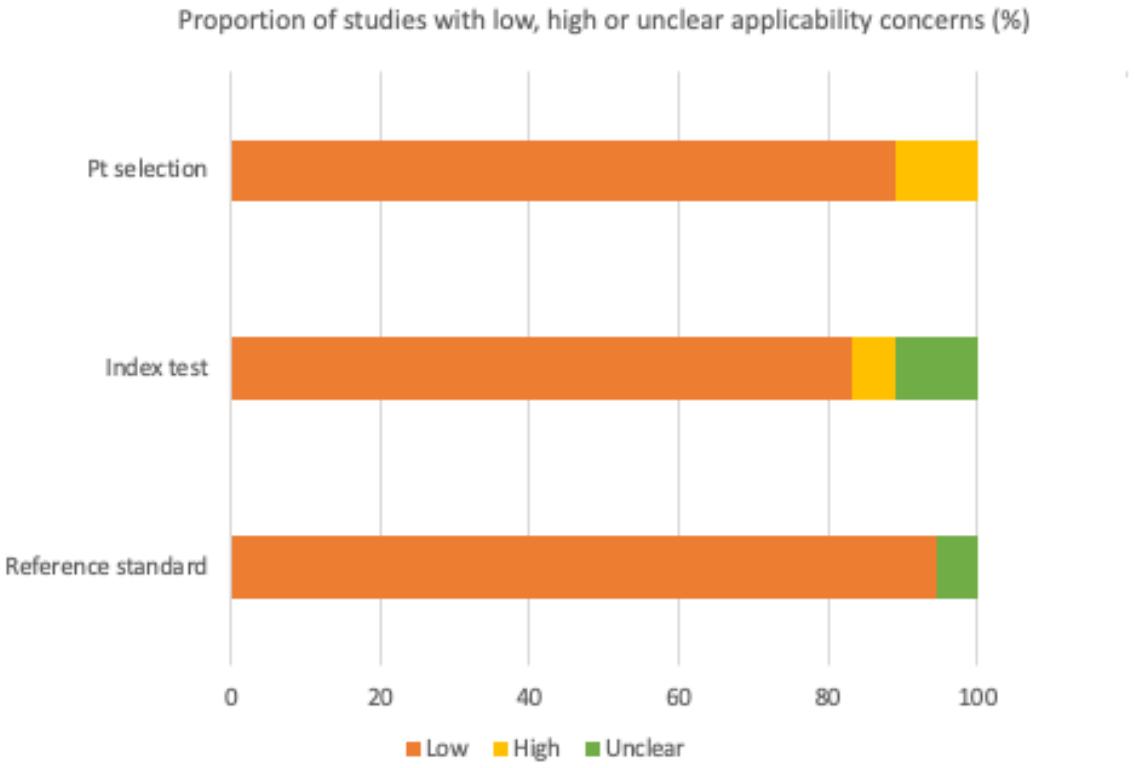

Proportion of studies with low, high or unclear applicability concerns (%)
Pt selection
Index test
Reference standard
0
20
40
60
80
100
Low
High
Unclear

Table 3. Summary of main findings of repeat PET scans in GCA patients receiving treatment.

Author	Treatment (# pts)	Results of F/U PET scans in patients with clinical improvement/clinical remission	Results of F/U PET scans in patients with biochemical (ESR,CRP) improvement	Results of F/U PET scans in patients with clinically active disease
Banerjee, 2020	Pred (21) TCZ (17) MTX (13) Anti-TNF (3)	Only sufficient data available to determine PET outcome in those treated with TCZ -Of 17 GCA patients starting TCZ, 14 (82.4%) clinically improved. -in 3/14 (21.4%) F/U PET/CT normalized	-Of 17 GCA patients starting TCZ, ESR/CRP improved in all 17 -in 14/17 (82.4) F/U PET/CT improved	Unable to determine
Regola, 2020	Pred (24) TCZ (24)	Only sufficient data to determine PET outcomes in 6 of 24 GCA patients with LVV who started TCZ and were followed to 12 months with repeat PET/CT -at 12 mos, all 6 (100%) were in clinical remission -in 6/6 (100%) F/U PET/CT at 12 mos improved -in 5/6 (83.3) F/U PET/CT at 12 mos normalized	-at 12 mos, ESR and CRP improved in all 6 (100%) -in 6/6 (100%) F/U PET/CT at 12 mos improved	No F/U scans during active disease reported
Conticini, 2020	Pred (8) TCZ (8) MTX (1) CYC (1)	Of 8 GCA with LVV on baseline PET, all were treated with pred & TCZ, and all 8 (100%) entered clinical remission. -in 8/8 (100%) cases, F/U PET/CT between 3-12 mos improved -in 8/8 (100%) cases, F/U PET/CT between 3-12 mos normalized	Of 8 GCA treated patients, ESR/CRP improved in 8 (100%). -in 8/8 (100%) F/U PET/CT between 3-12 mos improved	No F/U scans during active disease reported
Vitiello, 2018	Pred (12) TCZ (12) MTX (7)	Of 12 GCA patients starting pred & TCZ, 12 (100%) entered clinical remission. -in 12/12 (100%) cases, F/U PET/CT at mean 11.6 mos improved -in 12/12 (100%) cases, F/U PET/CT at mean 11.6 mos normalized	Of 12 GCA treated patients, ESR/CRP improved in all 12 (100%). -in 12/12 (100%) F/U PET/CT at mean 11.6 mos improved	No F/U scans during active disease reported
deBoysson, 2017	Pred (34)	Of 25 GCA patients starting pred, 25 had 2nd scan at median 11 mos, 7 had 3rd scan an additional 6 mos later, and 2 pts had 4th scan at additional 11 more months (total= 34	Among treated patients who had repeat PET/CT scans, ESR/CRP were improved in all cases (100%)	No F/U scans during active disease reported

		F/U scans performed.) All patients were in clinically remission at time of F/U scans (100%.) -17/34 (50%) F/U PET/CT scans done during clinical remission improved. -6/34 (17.6%) F/U PET/CT scans done during clinical remission normalized	-17/34 (50%) F/U PET/CT scans improved	
Dellavedova,2016	Pred (15) MTX (3) AZA (NS) Chlqn (NS) CsA (NS)	No F/U scans done in patients with clinical improvement.	No F/U scans done in patients with biochemical improvement.	Among 15 GCA, 6 had 8 repeat PET/CT performed between 4-12 mos F/U while disease was clinically active despite treatment -F/U PET remained active in 8/8 follow up scans (100%)
Bruls, 2016	Pred (3) MTX (NS)	Of 3 GCA patients starting pred, 3 (100%) clinically improved. -in 3/3 (100%) cases, F/U PET/CT improved* -in 3/3 (100%) cases, F/U PET/CT normalized*	Not enough information to answer	No F/U scans during active disease reported
Muto, 2014	Pred (3)	Of 3 GCA patients starting pred, 3 (100%) clinically improved. -in 3/3 (100%) cases F/U PET/CT at mean 4.6 mos improved -in 0/3 (0%) cases F/U PET/CT at mean 4.6 mos normalized	Of 3 GCA patients treated, ESR/CRP were improved in all 3 (100%) -in 3/3 (100%), F/U PET/CT at mean 4.6 mos improved	No F/U scans during active disease reported
Daumas, 2014	Pred (26) MTX (3)	Of 26 GCA patients, 5 had repeat PET/CT at 6 mos and again 12 mos F/U (total=10 follow up scans performed). All patients were in clinical remission at time of F/U scan. -at 6 mos F/U: 1/5 (20%) PET/CT scans normalized -at 12 mos F/U: 3/5 (60%) PET/CT scans normalized.	Not enough information to answer	No F/U scans during active disease reported
Ly, 2014	Pred (2) Anakinra (2) Disulone (1)	2 GCA patients had 5 F/U PET/CT scans (at 11, 14, 16, 22, 28 mos) after starting treatment. -in 4/5 cases, patients were in clinical remission at time of F/U PET/CT	Only 1 patient had repeat inflammatory markers reported at time of F/U PET/CT. ESR/CRP improved in 1/1 (100%.)	Among 2 GCA, 1 had repeat PET/CT while disease was clinically active.

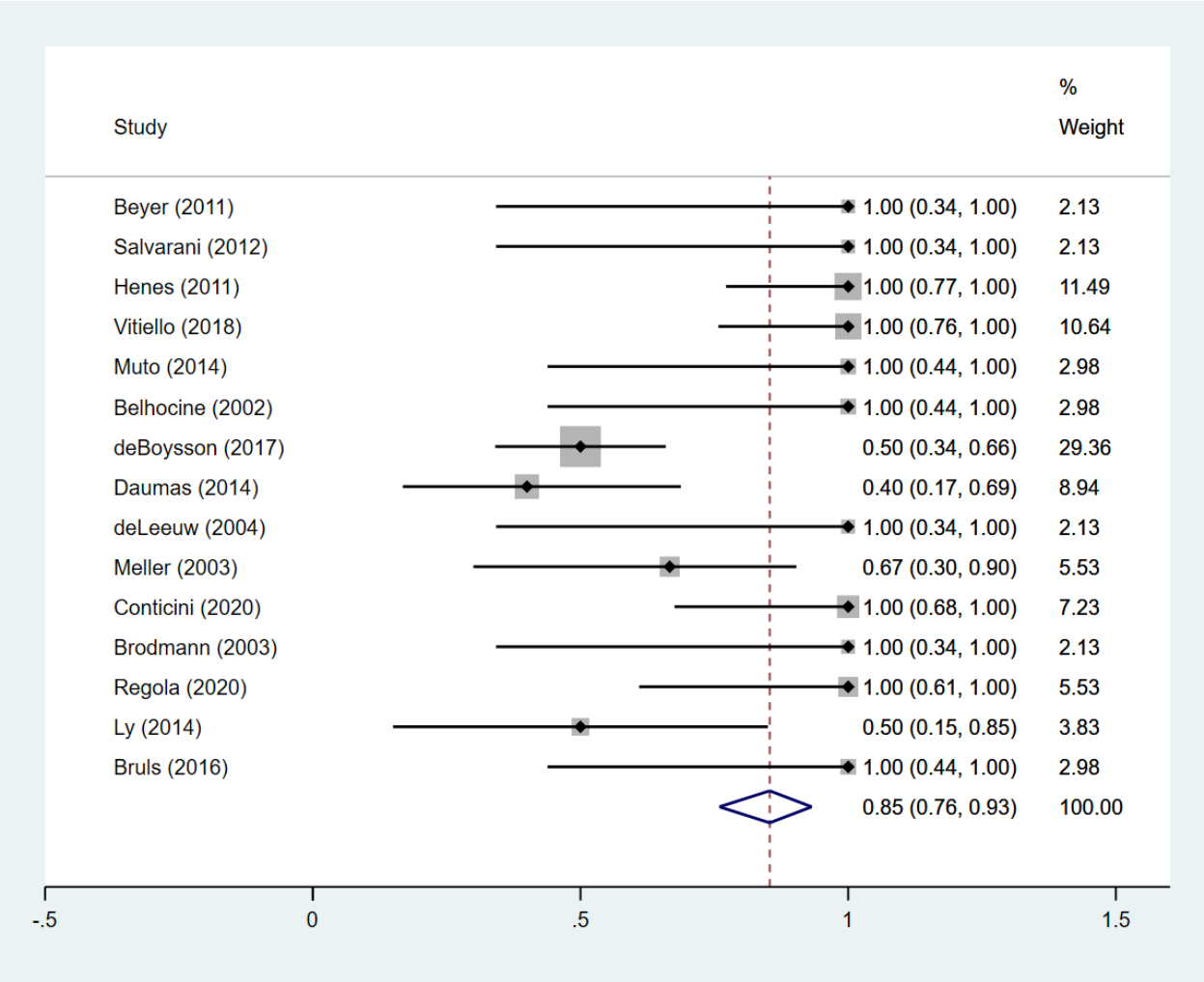
		-in 2/4 (50%) cases in clinical remission, PET/CT improved/ normalized.	-in 1/1 (100%) F/U PET/CT improved	F/U PET/CT scan did not improve in the patient with persistently clinically active disease.
Salvarani, 2012	Pred (2) TCZ (2)	Of 2 GCA patients starting treatment, 2 (100%) clinically improved. -in 2/2 (100%) cases, F/U PET/CT at 6 mos improved. -in 1/2 (50%) cases, F/U PET/CT at 6 mos normalized.	Inflammatory markers improved over time in 2/2 (100%.) -in 2/2 (100%) F/U PET/CT at 6 mos improved	No F/U scans during active disease reported
Beyer, 2011	Pred (2) TCZ (2)	Of 2 GCA patients starting treatment, 2 (100%) clinically improved. -in 2/2 (100%), F/U PET/CT at 6 mos improved -in 2/2 (100%), F/U PET/CT at 6 mos normalized.	Inflammatory markers improved over time in 2/2 (100%.) -in 2/2 (100%) F/U PET/CT at 6 mos improved	No F/U scans during active disease reported
Henes, 2011	Pred (6) CYC (6)	6 GCA patients had 15 F/U PET/CT scans, done 3-24 mos after starting pred & CYC treatment for severe disease. At time of 13/15 F/U scans, patients were in clinical remission. -in 13/13 (100%) cases, F/U PET/CT scan improved in clinical remission - in 6/13 (46.2%) cases, scans normalized in clinical remission	Inflammatory markers were improved at time of 13/15 (87%) repeat PETs. -F/U PET/CT scan improved in 9/13 (69.2%) cases when inflammatory markers improved.	2/15 (13.3%) F/U PET/CT scans were done when patients had clinically active disease -F/U PET/CT did not show improvement in 2/2 (100%) patients with active clinical disease
Blockmans, 2006	Pred (35)	29/35 GCA pts had baseline + PET/CT scan. These 29 patients underwent 30 follow up PET/CT scans after starting treatment and while in clinical remission (22 at 3 mos fu, 8 at 6 mos F/U) -Follow up PET scans normalized in 10/30 (33.3%) scans done during clinical remission	Not enough information to answer	Among 14 scans done during clinical relapse: -F/U PET was still abnormal in 11/14 (78.6%) -F/U PET was normal in 3/14 (21.4%)
deLeeuw, 2004	Pred (2)	Of 2 GCA patients starting treatment, 2 (100%) clinically improved. F/U PET/CT performed between 2-24 mos. -in 2/2 (100%) cases, F/U PET/CT improved. -in 0/2 (0%) cases, F/U PET/CT normalized.	Inflammatory markers improved over time in 1 of 2 patients (50%). -F/U PET/CT scan improved in 1/1 (100%) patients with improved inflammatory markers	No F/U scans during active disease reported

Meller, 2003	Not specified (14)	Of 14 GCA patients, 6 patients underwent 6 F/U PET scans while in clinical remission at median 19 mos. - in 4/6 (66.7%), F/U PET scan improved - in 0/6 (0%), F/U PET scan normalized	Of 6 GCA patients, inflammatory markers improved over time in all 6 (100%). - in 4/6 (66.7%), F/U PET improved	No F/U scans during active disease reported
Brodmann, 2003	Pred (7)	Of 7 GCA pts, 2 had F/U PET at 3 mos after starting pred, and while in clinical remission. -in 2/2 (100%) F/U PET/CT at 3 mos improved	Of 2 GCA patients, ESR/CRP improved in both (100%) -in 2/2 (100%), F/U PET/CT improved	No F/U scans during active disease reported
Belhocine, 2002	Pred (3)	Of 3 GCA patients starting pred, 3 (100%) clinically improved. F/U PET/CT was done between 3-6 mos. -in 3/3 (100%) F/U PET/CT improved -in 3/3 (100%) F/U PET/CT normalized	Of 3 GCA patients, ESR/CRP were improved in both (100%) -in 3/3 (100%), F/U PET/CT improved	No F/U scans during active disease reported

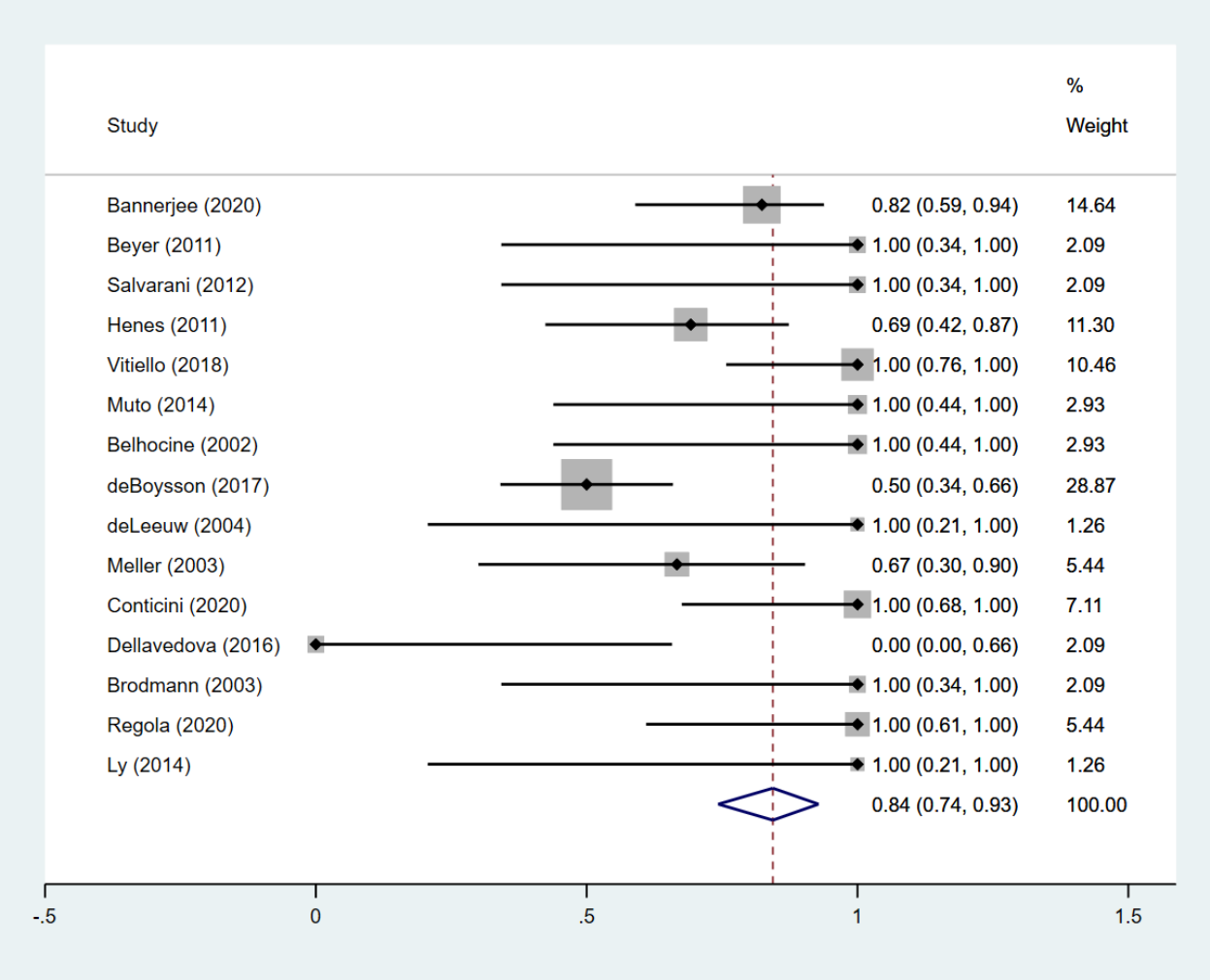
Abbreviations: F/U (follow-up), pred (prednisone),TCZ (tocilizumab), anti-TNF (anti-tumour necrosis factor), MTX (methotrexate), AZA (azathioprine), CYC (cyclophosphamide), CsA (cyclosporine A), Chlqn (chloroquine), mos (months). *timing of follow up PET scan not specified

Figure 3. Pooled sensitivities of follow up PET in treated GCA patients, A) pooled sensitivity of improved FDG PET for clinical improvement in treated GCA patients, I^2=0, B) Pooled sensitivity of improved FDG PET for biochemical improvement in treated GCA patients, I^2=0, C) Pooled sensitivity of normalized FDG PET for clinical remission in treated GCA patients, I^2=9.2%.

A.



B.


Study
% Weight
Bannerjee (2020) 0.82 (0.59, 0.94) 14.64
Beyer (2011) 1.00 (0.34, 1.00) 2.09
Salvarani (2012) 1.00 (0.34, 1.00) 2.09
Henes (2011) 0.69 (0.42, 0.87) 11.30
Vitiello (2018) 1.00 (0.76, 1.00) 10.46
Muto (2014) 1.00 (0.44, 1.00) 2.93
Belhocine (2002) 1.00 (0.44, 1.00) 2.93
deBoysson (2017) 0.50 (0.34, 0.66) 28.87
deLeeuw (2004) 1.00 (0.21, 1.00) 1.26
Meller (2003) 0.67 (0.30, 0.90) 5.44
Conticini (2020) 1.00 (0.68, 1.00) 7.11
Dellavedova (2016) 0.00 (0.00, 0.66) 2.09
Brodmann (2003) 1.00 (0.34, 1.00) 2.09
Regola (2020) 1.00 (0.61, 1.00) 5.44
Ly (2014) 1.00 (0.21, 1.00) 1.26
0.84 (0.74, 0.93) 100.00
-.5
0
.5
1
1.5

C.

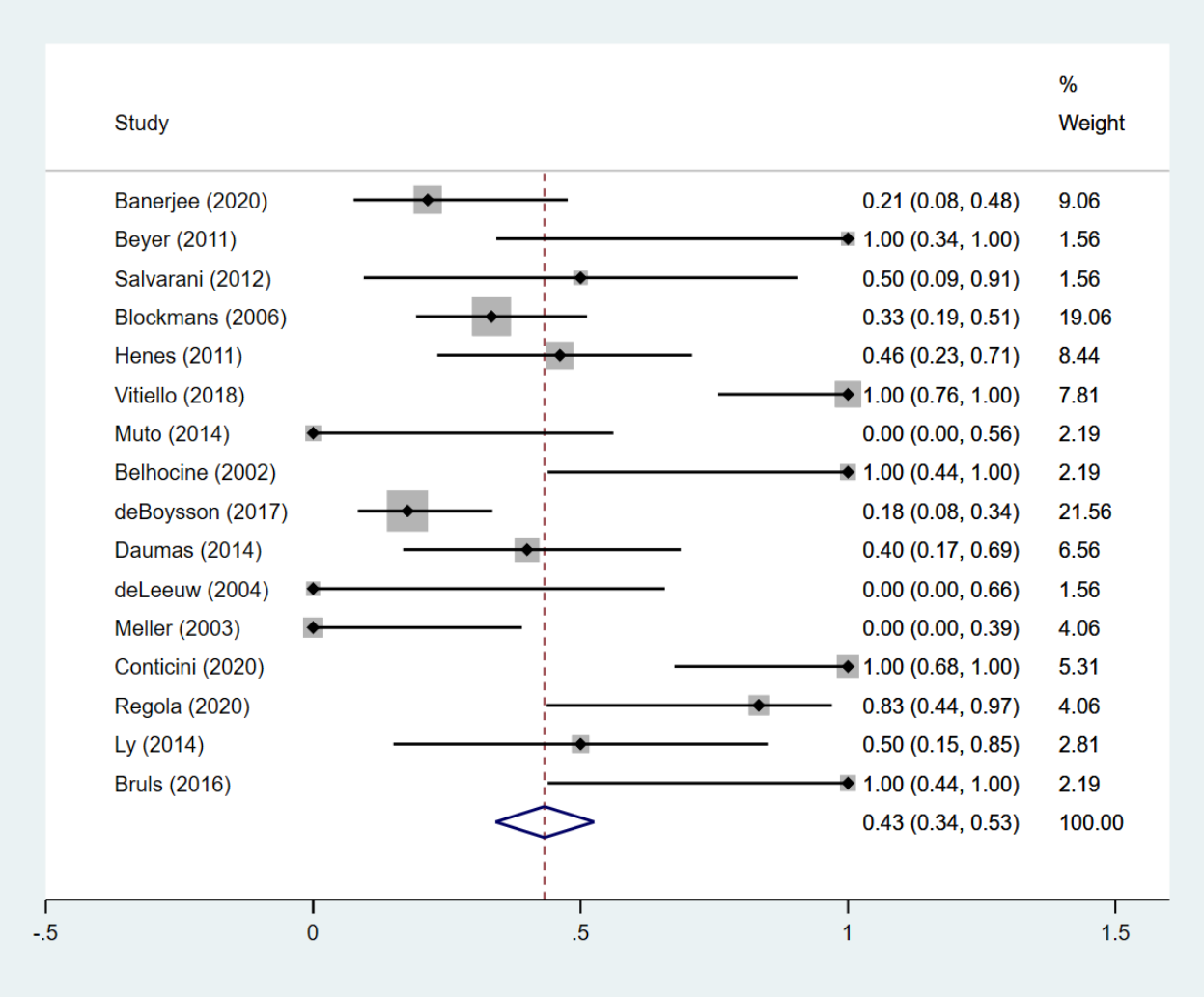
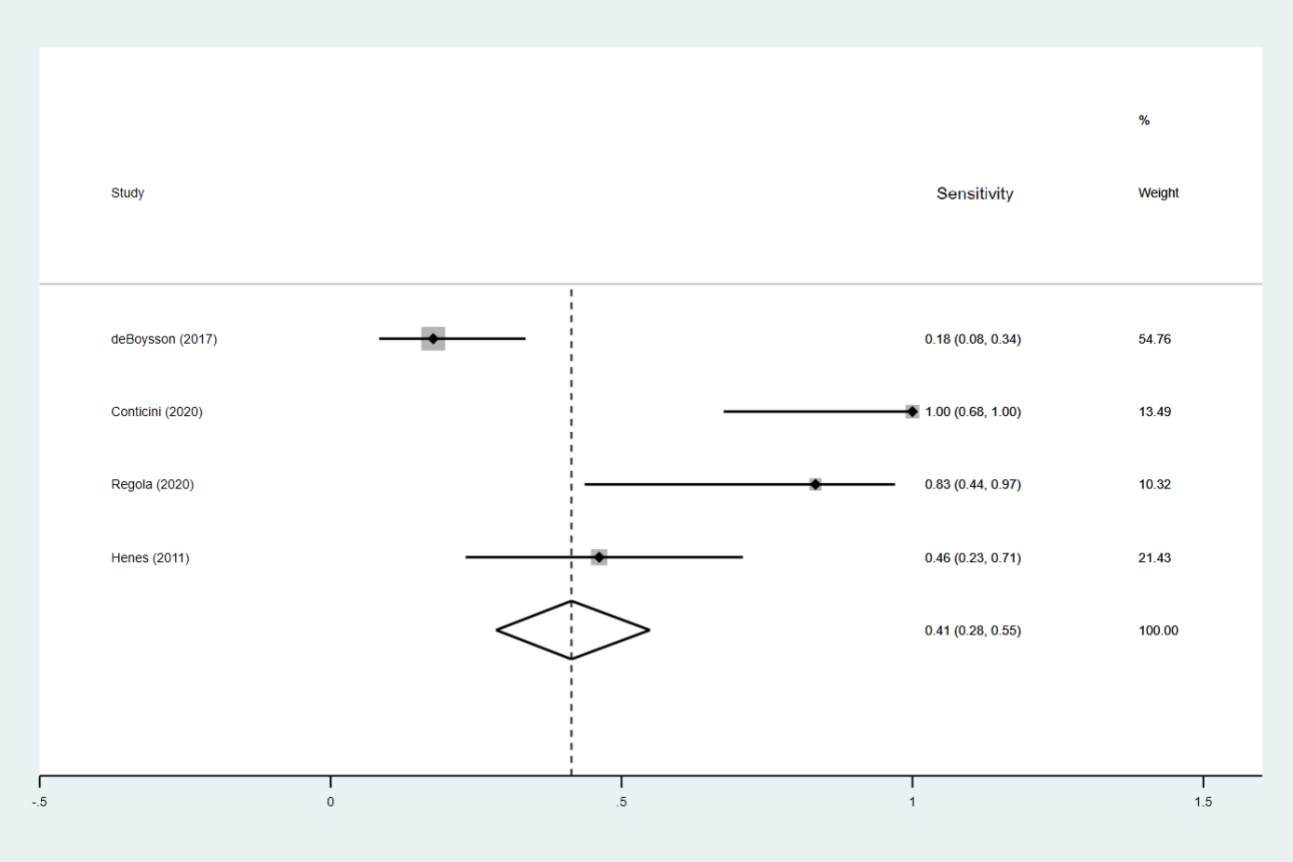
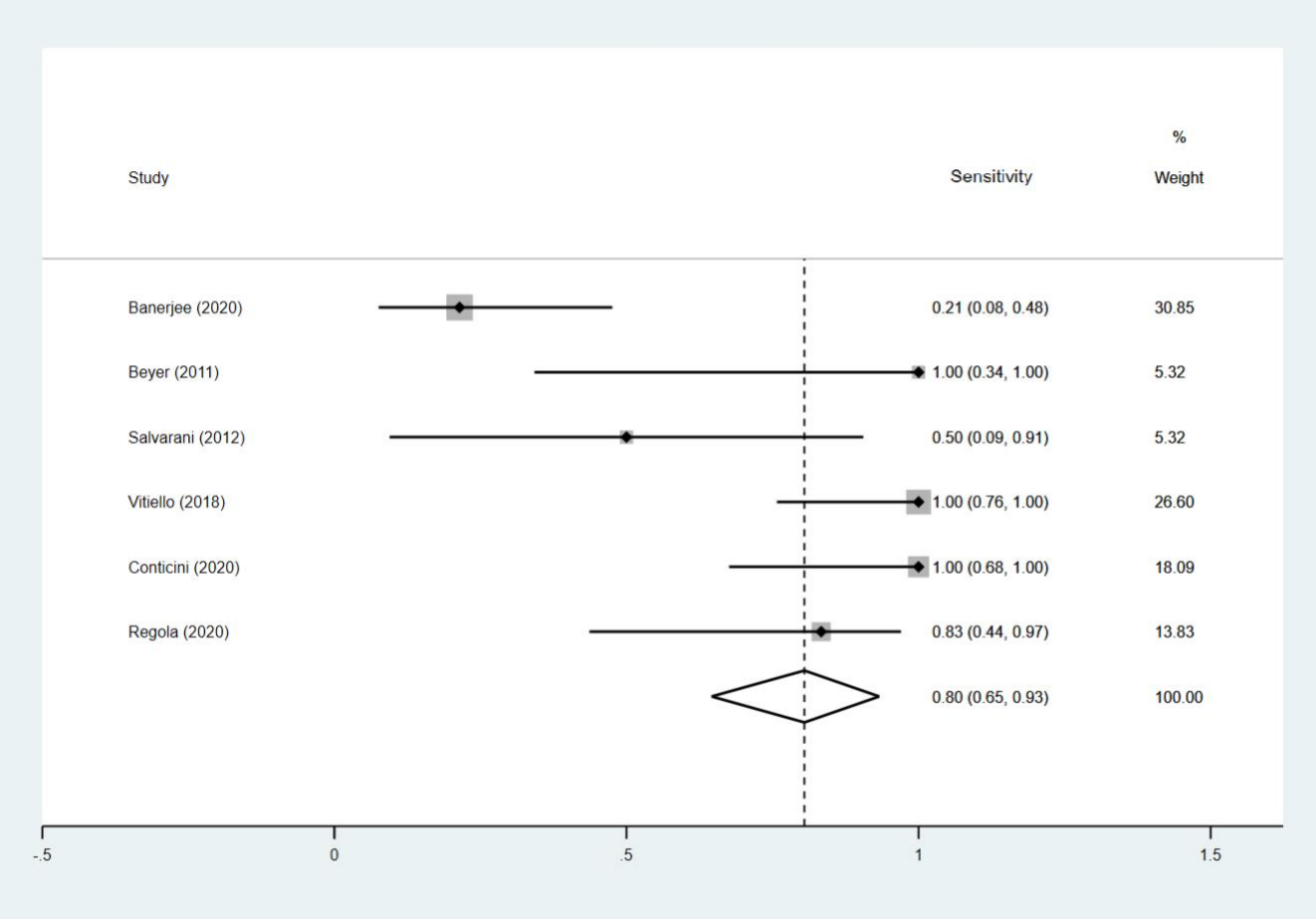

Study
% Weight
Banerjee (2020) 0.21 (0.08, 0.48) 9.06
Beyer (2011) 1.00 (0.34, 1.00) 1.56
Salvarani (2012) 0.50 (0.09, 0.91) 1.56
Blockmans (2006) 0.33 (0.19, 0.51) 19.06
Henes (2011) 0.46 (0.23, 0.71) 8.44
Vitiello (2018) 1.00 (0.76, 1.00) 7.81
Muto (2014) 0.00 (0.00, 0.56) 2.19
Belhocine (2002) 1.00 (0.44, 1.00) 2.19
deBoysson (2017) 0.18 (0.08, 0.34) 21.56
Daumas (2014) 0.40 (0.17, 0.69) 6.56
deLeeuw (2004) 0.00 (0.00, 0.66) 1.56
Meller (2003) 0.00 (0.00, 0.39) 4.06
Conticini (2020) 1.00 (0.68, 1.00) 5.31
Regola (2020) 0.83 (0.44, 0.97) 4.06
Ly (2014) 0.50 (0.15, 0.85) 2.81
Bruls (2016) 1.00 (0.44, 1.00) 2.19
0.43 (0.34, 0.53) 100.00
-.5
0
.5
1
1.5

Figure 4. Pooled sensitivities of subgroup analyses, A) normalized PET for clinical remission in Consensus Criteria subgroup, I^2= 50.3%, B) normalized PET for clinical remission in TCZ subgroup, I^2=0%, C) normalized PET for clinical remission in Pt Number subgroup, I^2=95.3%, D) normalized PET for clinical remission in PET/CT subgroup, I^2=92.5%.

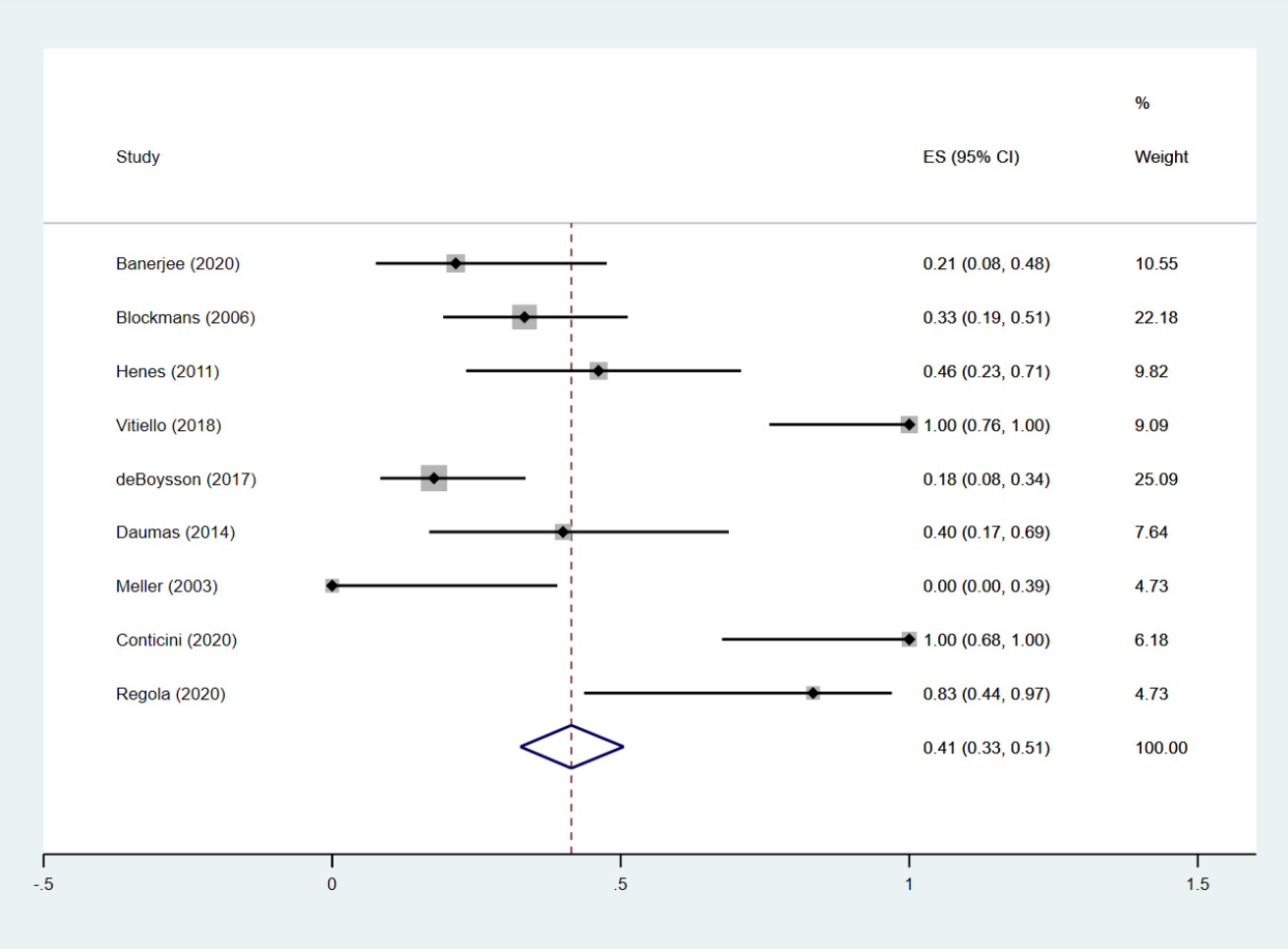
A.



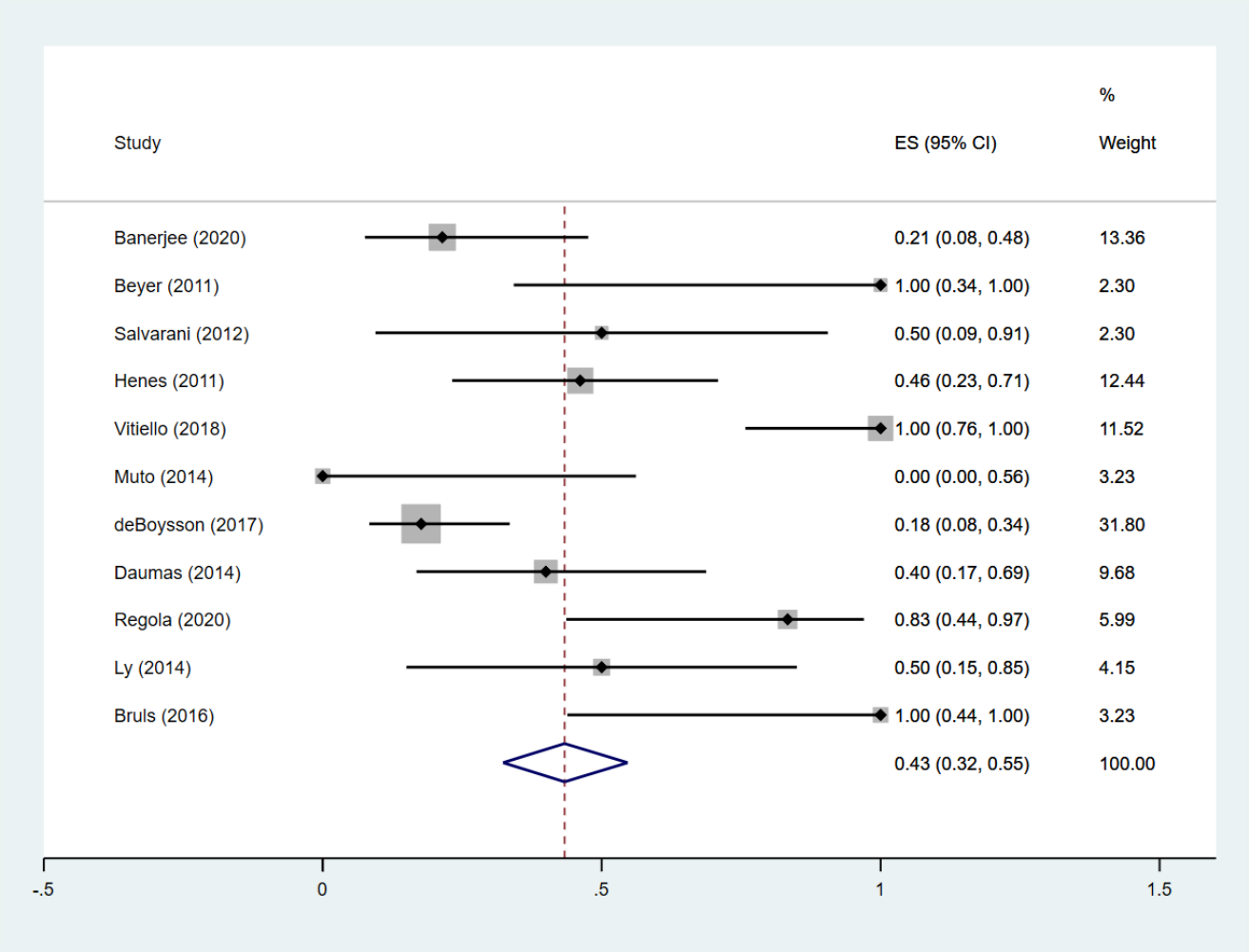
B.


Study
Sensitivity
%
Weight
Banerjee (2020)
0.21 (0.08, 0.48)
30.85
Beyer (2011)
1.00 (0.34, 1.00)
5.32
Salvarani (2012)
0.50 (0.09, 0.91)
5.32
Vitiello (2018)
1.00 (0.76, 1.00)
26.60
Conticini (2020)
1.00 (0.68, 1.00)
18.09
Regola (2020)
0.83 (0.44, 0.97)
13.83
0.80 (0.65, 0.93)
100.00
-.5
0
.5
1
1.5

C.


Study
ES (95% CI)
%
Weight
Banerjee (2020)
0.21 (0.08, 0.48)
10.55
Blockmans (2006)
0.33 (0.19, 0.51)
22.18
Henes (2011)
0.46 (0.23, 0.71)
9.82
Vitiello (2018)
1.00 (0.76, 1.00)
9.09
deBoysson (2017)
0.18 (0.08, 0.34)
25.09
Daumas (2014)
0.40 (0.17, 0.69)
7.64
Meller (2003)
0.00 (0.00, 0.39)
4.73
Conticini (2020)
1.00 (0.68, 1.00)
6.18
Regola (2020)
0.83 (0.44, 0.97)
4.73
0.41 (0.33, 0.51)
100.00
-.5
0
.5
1
1.5

D.


Study
ES (95% CI)
%
Weight
Banerjee (2020)
0.21 (0.08, 0.48)
13.36
Beyer (2011)
1.00 (0.34, 1.00)
2.30
Salvarani (2012)
0.50 (0.09, 0.91)
2.30
Henes (2011)
0.46 (0.23, 0.71)
12.44
Vitiello (2018)
1.00 (0.76, 1.00)
11.52
Muto (2014)
0.00 (0.00, 0.56)
3.23
deBoysson (2017)
0.18 (0.08, 0.34)
31.80
Daumas (2014)
0.40 (0.17, 0.69)
9.68
Regola (2020)
0.83 (0.44, 0.97)
5.99
Ly (2014)
0.50 (0.15, 0.85)
4.15
Bruls (2016)
1.00 (0.44, 1.00)
3.23
0.43 (0.32, 0.55)
100.00
-.5
0
.5
1
1.5

Chapter 4: Discussion

Our systematic review found that follow up vascular FDG uptake on PET improves in most (85%) GCA patients over time who clinically improve on immunosuppressive treatment but normalizes in only 43% of those achieving clinical remission. For clinicians, these findings underscore the importance of always interpreting follow up PET scans in the context of the clinical activity of the patient and also in the context of prior PET imaging. Knowing that vascular FDG uptake does not remit entirely in a substantial proportion of patients in clinical remission emphasizes that persistent uptake in a patient should not be assumed to be a sign of treatment failure. Rather, in these patients, the finding of new vascular FDG uptake (in a previously unaffected territory), is a clear sign of disease progression that should warrant consideration of treatment. These data suggest that follow up PET(CT) may be used as an adjunct to help assess a patient's disease activity over time, when used in combination with clinical symptoms, signs, and inflammatory markers and that PET(CT) can be used , as part of the shared decision-making process with GCA patients. Given that FDG uptake usually improves but often does not resolve, if using PET for follow up, it may be prudent to plan a repeat a one-time scan at the time of clinical remission (for example around 6 month mark of treatment) to document the patients' "best" radiographic response. This may facilitate recognition of a worsened scan in case of future flare, and allow identification of those patients who have achieved a radiographic (as well as clinical) remission.

Our findings are in keeping with those of a recent systematic review and meta-analysis by van der Geest et al, in which improvement in the majority of FDG PET/CT scans repeated over time in patients with all types of large vessel vasculitis was also observed. In their analysis, FDG

PET-CT was found to have a moderate sensitivity (77%) and specificity (71%) for detecting relapsing/refractory LVV over time. In contrast to their study, in which high heterogeneity precluded an assessment of how often PET normalized with treatment over time, we broadly included all studies with longitudinal assessment of PET in GCA patients over time, and identified additional studies that could contribute data to answer this question. We found that normalization of follow FDG PET scans was documented in just under half of GCA patients who entered remission over time, with low heterogeneity. Of course, due to the small total number of included patients/scans in our analysis, it is important to recognize that this pooled sensitivity truly only summarizes the observed values of studies that were included/have been published thus far.

Whether persistent vascular FDG uptake in GCA patients otherwise in clinical remission occurs due to a separate process such as atherosclerosis, or due to natural remodelling of a previously damaged vessel wall, or represents ongoing subclinical vasculitis remains to be determined. In support of the first possibility, it is now well-documented that there is a substantial inflammatory component to atherosclerosis, and that vulnerable plaques, in particular, can actively take up FDG.[44] As GCA patients are by definition elderly, concomitant atherosclerosis is a possibility, however, the radiographic features of FDG uptake in atherosclerosis are typically distinct from those of vasculitis (focal and patchy).[8] Similar to our results, previous work in Takayasu's arteritis, a closely-related large vessel vasculitis, found that vessel wall edema on magnetic resonance angiogram (initially thought to represent active vascular inflammation) was identified in >50% of patients in clinical remission. The presence of vessel wall edema did not correlate well with the development of new vascular lesions over time, suggesting that this imaging

abnormality may represent vascular remodelling rather than active inflammation in at least some patients.[45] With respect to FDG imaging, specifically, it has been previously established that a number of cells types, in addition to acute inflammatory cells, such as fibroblasts and endothelial cells, also rely on glucose for metabolism, and that increased cellular consumption of glucose may be induced by states of hypoxia, as well as by pro-inflammatory cytokines.[46,47] It follows that persistent vascular FDG uptake seen in GCA patients could equally likely occur as a result of vessel wall healing, as by active vasculitis.

There is also accumulating data to support the concept that subclinical vasculitis persists in a proportion of patients with GCA. In one study by Unizony et al, for example, autopsy data from a GCA patient on TCZ confirmed widespread histopathological evidence of active vasculitis in multiple medium to large arteries despite the perception of clinical and biochemical remission.[48] Additionally, a retrospective review of aortic surgical biopsies from the Cleveland Clinic found that only 10 of 42 (24%) GCA patients with proof of active aortitis on histopathology had any symptoms of active vasculitis at the time of surgery.[49] In a recent study by Grayson et al, an increased risk of subsequent clinical relapse (55% vs 11%, p=0.03) was detected among large vessel vasculitis patients whose PET/CT remained "active" despite clinical remission, suggesting that ongoing vascular uptake may indeed reflect smoldering disease.[11] Interestingly, the overall frequency of "normalized" PET observed in our study (43%) correlates very well with the frequency of long term clinical remission previously published from a large prospectively conducted trial in GCA. In this study, subsequent analysis found that 42% of GCA patients previously treated with tocilizumab and prednisone remained in long-term remission for 2 years after stopping immunosuppression, while the other 58% relapsed over time.[50] It is possible that

normalization of FDG PET may identify a subset of GCA patients that have achieved a "deep remission" and be less likely to relapse in time. Further studies directly assessing the relationship between persistent FDG uptake during clinical disease remission and risk of future relapse are needed.

Several sources of heterogeneity were identified across the included studies. We hypothesized that one important source of heterogeneity was the use of varied criteria (physician opinion, visual scores, or semi-quantitative scores) to define an active versus normal PET scan for large vessel vasculitis. To further assess this, we performed a subgroup analysis of the studies that used visual grade 2 or 3 vascular uptake (in comparison to the liver) to define active large vessel uptake, in accordance with a prior study[9] and the joint procedural recommendations of the European Association of Nuclear Medicine, Society of Nuclear Medicine and Molecular Imaging, PET-interest group, and endorsed by ASNC.[8] When looking at the 4 studies that used this standardized definition, and could contribute data for calculating the pooled sensitivity of normalized PET scan among treated patients in clinical remission, the results were not substantially different (41%) from that observed for all studies, however, heterogeneity was moderate at 50.3%, suggesting this result may be unreliable. It is possible that the heterogeneity and overall lack of difference observed is due to the overall small number of patients and follow up scans (63 total) in this subgroup. Additionally. as most studies relied on the Nuclear Medicine physician's opinion to determine PET activity, it is also possible that no difference was observed as most reading physicians were using a similar visual uptake score to gauge vascular activity, even if not explicitly stated.

Additional sources of heterogeneity are possible. We included studies that took place over 2 decades (2002-2020) and during this time, substantial advances in the quality and performance of PET imaging occurred. In particular, in 6 of the 18 studies, PET imaging was performed without the use of concomitant CT and therefore localization and image quality may have been reduced in these papers. When we examined only those studies who utilized PET/CT hybrid imaging, however, the pooled sensitivity for PET normalization in those in clinical remission was the same (43%) as the overall group, however, heterogeneity was high (92.5%) making this result unreliable. Similarly, in order to maximize yield, we opted to include all identified manuscripts describing the results of serial PET in GCA patients over time, however, a number of these papers had very small numbers of patients, possibly increasingly the likelihood of bias. When we limited our analysis to only those studies that described the outcomes of at least 5 patients serially over time, we again found that the result was the same (pooled sensitivity of 41% for PET normalization), but with high heterogeneity (95.3%.)

Another possible source of heterogeneity within our data was the type of immunosuppressive treatment received by GCA patients over time. Given the possible inhibitory effects of glucocorticoids on glucose transport receptors, there was concern that prednisone use may result in false normalization of large vessel FDG uptake, however, in this study focusing on long-term follow up (>= 3 months) we did not observe this. Prednisone was given to nearly all patients included in this study, and although large vessel uptake improved in the majority (85%) of those in clinical remission, it normalized in only 43%. On the other hand, tocilizumab is an IL-6 inhibitor that is increasingly frequently used in GCA patients, with either new or relapsing disease.[51] When our analysis was limited to the TCZ-treated subgroup, interestingly, PET

response over time was improved, with an estimated 80% of repeat scans normalizing in patients in clinical remission on this therapy. This finding correlates with the reduced risk of clinical flares observed in GCA patients treated with TCZ,[6] and may indicate that TCZ is more effective than prednisone at controlling inflammation at the vascular level. It is important to note, however, that studies in the TCZ subgroup were generally small in number, and blinding of PET interpretation was not always specified. In the single study in which it was specified that both PET and clinical disease activity were interpretated blinded to one another, follow up PET/CT scans normalized in only 21.4% of GCA patients.[27] Additional prospective studies assessing the radiographic response in GCA patients treated specifically with tocilizumab are needed.

Our study has several limitations. Overall, there was a small number of patients and follow up PET scans. In the included studies, repeat scans were predominantly done in patients who clinically improved, with few scans reported in those with ongoing disease activity, which rendered us unable to calculate a specificity in most studies. For our meta-analysis, we pooled the sensitivities across studies, however this assumed that specificities were likely similar across studies, which may not be the case. Several possible sources of heterogeneity between studies were observed, including differences in the acquisition and interpretation of PET scans, duration of time between follow up scans, and differences in immunosuppressive treatment. Because most studies were conducted retrospectively, it was unclear in many whether PET results and clinical assessments were interpreted blinded to one another, introducing another potential source of bias.

Study strengths include the use of broad search criteria which yielded a very high number of studies for screening, and the inclusion of only studies in which a positive baseline PET scan was documented, and with longitudinal data available, in order to address the question of how often PET improves or normalizes over time. Another study strength is the focus on a single population (GCA) rather than including all patients with large vessel vasculitis, as some confounders (ie: atherosclerosis) may be more likely to affect FDG uptake in the elderly population. We also performed several subgroup analyses, in particular to specifically address the sensitivity of PET when interpreted according to consensus recommendations, and in patients treated specifically with tocilizumab.

Future research should focus on the performance of prospectively-conducted FDG PET/CT scans in a larger number of GCA patients to confirm these results. In particular, a future study where serial scans are performed longitudinally starting in newly-diagnosed treatment-naïve GCA patients randomized to different therapeutic strategies (prednisone monotherapy, tocilizumab, methotrexate, vs newly-emerging therapies) and interpreted blinded to clinical assessment of disease activity would be of great interest. Follow up scans repeated every 6 months over longer periods of time (>24+ months) would help inform whether ongoing improvement in vascular FDG uptake occurs over time in patients in persistent remission, and to confirm whether those patients who achieve radiographic remission will be less likely to clinically relapse in time.

Chapter 5: Conclusions

In conclusion, vascular FDG uptake improves over time along with clinical improvement in the majority (85%) of treated GCA patients, and normalization of uptake occurs in fewer than half of patients (43%). Limited data suggests normalization of PET uptake may occur more often (80% of time) in GCA patients receiving TCZ. FDG PET may provide useful information to aid in the assessment of disease activity and help guide clinical decision-making, but it is imperative that results are always interpreted in comparison to prior/baseline imaging and in the clinical context of the patient.

Bibliography

1. Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis. *N Engl J Med*. 2003;349(2):160-169. doi:10.1056/NEJMra022694

2. Gonzalez-Gay MA, Miranda-Filloy JA, Lopez-Diaz MJ, et al. Giant cell arteritis in northwestern Spain: a 25-year epidemiologic study. *Medicine (Baltimore)*. 2007;86(2):61-68. doi:10.1097/md.0b013e31803d1764

3. Crowson CS, Matteson EL. Contemporary prevalence estimates for giant cell arteritis and polymyalgia rheumatica, 2015. *Semin Arthritis Rheum*. 2017;47(2):253-256. doi:10.1016/j.semarthrit.2017.04.001

4. Blockmans D, de Ceuninck L, Vanderschueren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. *Arthritis Rheum*. 2006;55(1):131-137. doi:10.1002/art.21699

5. Ostberg G. Morphological changes in the large arteries in polymyalgia arteritica. *Acta Med Scand Suppl*. 1972;533:135-159.

6. Stone JH, Tuckwell K, Dimonaco S, et al. Glucocorticoid Dosages and Acute-Phase Reactant Levels at Giant Cell Arteritis Flare in a Randomized Trial of Tocilizumab. *Arthritis Rheumatol*. 2019;71(8):1329-1338. doi:10.1002/art.40876

7. Proven A, Gabriel SE, Orces C, O'Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. *Arthritis Rheum*. 2003;49(5):703-708. doi:10.1002/art.11388

8. Slart RHJA, Writing group, Reviewer group, et al. FDG-PET/CT(A) imaging in large vessel vasculitis and polymyalgia rheumatica: joint procedural recommendation of the EANM, SNMMI, and the PET Interest Group (PIG), and endorsed by the ASNC. *Eur J Nucl Med Mol Imaging*. 2018;45(7):1250-1269. doi:10.1007/s00259-018-3973-8

9. Soussan M, Nicolas P, Schramm C, et al. Management of large-vessel vasculitis with FDG-PET: a systematic literature review and meta-analysis. *Medicine (Baltimore)*. 2015;94(14):e622. doi:10.1097/MD.0000000000000622

10. Quinn KA, Ahlman MA, Malayeri AA, et al. Comparison of magnetic resonance angiography and 18F-fluorodeoxyglucose positron emission tomography in large-vessel vasculitis. *Ann Rheum Dis*. 2018;77(8):1165-1171. doi:10.1136/annrheumdis-2018-213102

11. Grayson PC, Alehashemi S, Bagheri AA, 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(3):439-449. doi:10.1002/art.40379

12. Salvarani C, Soriano A, Muratore F, Shoenfeld Y, Blockmans D. Is PET/CT essential in the diagnosis and follow-up of temporal arteritis? *Autoimmun Rev*. 2017;16(11):1125-1130. doi:10.1016/j.autrev.2017.09.007

13. Nielsen BD, Gormsen LC, Hansen IT, Keller KK, Therkildsen P, Hauge EM. Three days of high-dose glucocorticoid treatment attenuates large-vessel 18F-FDG uptake in large-vessel giant cell arteritis but with a limited impact on diagnostic accuracy. *Eur J Nucl Med Mol Imaging*. 2018;45(7):1119-1128. doi:10.1007/s00259-018-4021-4

14. Stellingwerff MD, Brouwer E, Lensen KJDF, et al. Different Scoring Methods of FDG PET/CT in Giant Cell Arteritis: Need for Standardization. *Medicine (Baltimore)*. 2015;94(37):e1542. doi:10.1097/MD.0000000000001542

15. Rominger A, Saam T, Wolpers S, et al. 18F-FDG PET/CT identifies patients at risk for future vascular events in an otherwise asymptomatic cohort with neoplastic disease. *J Nucl Med*. 2009;50(10):1611-1620. doi:10.2967/jnumed.109.065151

16. Duftner C, Dejaco C, Sepriano A, Falzon L, Schmidt WA, Ramiro S. Imaging in diagnosis, outcome prediction and monitoring of large vessel vasculitis: a systematic literature review and meta-analysis informing the EULAR recommendations. *RMD Open*. 2018;4(1):e000612. doi:10.1136/rmdopen-2017-000612

17. Dejaco C, Ramiro S, Duftner C, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis*. 2018;77(5):636-643. doi:10.1136/annrheumdis-2017-212649

18. van der Geest KSM, Treglia G, Glaudemans AWJM, et al. Diagnostic value of [18F]FDG-PET/CT for treatment monitoring in large vessel vasculitis: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging*. 2021;48(12):3886-3902. doi:10.1007/s00259-021-05362-8

19. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.

20. Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-536. doi:10.7326/0003-4819-155-8-201110180-00009

21. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. *J Epidemiol Community Health*. 2013;67(11):974-978. doi:10.1136/jech-2013-203104

22. Walter MA, Melzer RA, Schindler C, Müller-Brand J, Tyndall A, Nitzsche EU. The value of [18F]FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and

extent of disease. *Eur J Nucl Med Mol Imaging*. 2005;32(6):674-681. doi:10.1007/s00259-004-1757-9

23. Rimland CA, Quinn KA, Rosenblum JS, et al. Outcome Measures in Large Vessel Vasculitis: Relationship Between Patient-, Physician-, Imaging-, and Laboratory-Based Assessments. *Arthritis Care Res (Hoboken)*. 2020;72(9):1296-1304. doi:10.1002/acr.24117

24. Sammel AM, Hsiao E, Schembri G, et al. Cranial and large vessel activity on positron emission tomography scan at diagnosis and 6 months in giant cell arteritis. *Int J Rheum Dis*. 2020;23(4):582-588. doi:10.1111/1756-185X.13805

25. Nannini C, Niccoli L, Sestini S, Laghai I, Coppola A, Cantini F. Remission maintenance after tocilizumab dose-tapering and interruption in patients with giant cell arteritis: an open-label, 18-month, prospective, pilot study. *Ann Rheum Dis*. 2019;78(10):1444-1446. doi:10.1136/annrheumdis-2019-215585

26. Scheel AK, Meller J, Vosshenrich R, et al. Diagnosis and follow up of aortitis in the elderly. *Ann Rheum Dis*. 2004;63(11):1507-1510. doi:10.1136/ard.2003.015651

27. Banerjee S, Quinn KA, Gribbons KB, et al. Effect of Treatment on Imaging, Clinical, and Serologic Assessments of Disease Activity in Large-vessel Vasculitis. *J Rheumatol*. 2020;47(1):99-107. doi:10.3899/jrheum.181222

28. Beyer C, Axmann R, Sahinbegovic E, et al. Anti-interleukin 6 receptor therapy as rescue treatment for giant cell arteritis. *Ann Rheum Dis*. 2011;70(10):1874-1875. doi:10.1136/ard.2010.149351

29. Salvarani C, Magnani L, Catanoso M, et al. Tocilizumab: a novel therapy for patients with large-vessel vasculitis. *Rheumatology (Oxford)*. 2012;51(1):151-156. doi:10.1093/rheumatology/ker296

30. Brodmann M, Passath A, Aigner R, Seinost G, Stark G, Pilger E. F18-FDG-PET as a helpful tool in the diagnosis of giant cell arteritis. *Rheumatology (Oxford)*. 2003;42(10):1264-1266. doi:10.1093/rheumatology/keg317

31. Belhocine T, Kaye O, Delanaye P, et al. [Horton's disease and extra-temporal vessel locations: role of 18FDG PET scan. Report of 3 cases and review of the literature]. *Rev Med Interne*. 2002;23(7):584-591. doi:10.1016/s0248-8663(02)00620-3

32. de Boysson H, Aide N, Liozon E, et al. Repetitive 18F-FDG-PET/CT in patients with large-vessel giant-cell arteritis and controlled disease. *Eur J Intern Med*. 2017;46:66-70. doi:10.1016/j.ejim.2017.08.013

33. Daumas A, Rossi P, Bernard-Guervilly F, et al. [Clinical, laboratory, radiological features, and outcome in 26 patients with aortic involvement amongst a case series of 63 patients with giant cell arteritis]. *Rev Med Interne*. 2014;35(1):4-15. doi:10.1016/j.revmed.2013.06.007

34. Ly KH, Stirnemann J, Liozon E, Michel M, Fain O, Fauchais AL. Interleukin-1 blockade in refractory giant cell arteritis. *Joint Bone Spine*. 2014;81(1):76-78. doi:10.1016/j.jbspin.2013.06.004

35. Muto G, Yamashita H, Takahashi Y, et al. Large vessel vasculitis in elderly patients: early diagnosis and steroid-response evaluation with FDG-PET/CT and contrast-enhanced CT. *Rheumatol Int*. 2014;34(11):1545-1554. doi:10.1007/s00296-014-2985-3

36. de Leeuw K, Bijl M, Jager PL. Additional value of positron emission tomography in diagnosis and follow-up of patients with large vessel vasculitides. *Clin Exp Rheumatol*. 2004;22(6 Suppl 36):S21-26.

37. Henes JC, Mueller M, Pfannenberg C, Kanz L, Kötter I. Cyclophosphamide for large vessel vasculitis: assessment of response by PET/CT. *Clin Exp Rheumatol*. 2011;29(1 Suppl 64):S43-48.

38. Vitiello G, Orsi Battaglini C, Carli G, et al. Tocilizumab in Giant Cell Arteritis: A Real-Life Retrospective Study. *Angiology*. 2018;69(9):763-769. doi:10.1177/0003319717753223

39. Regola F, Cerudelli E, Bosio G, et al. Long-term treatment with tocilizumab in giant cell arteritis: efficacy and safety in a monocentric cohort of patients. *Rheumatol Adv Pract*. 2020;4(2):rkaa017. doi:10.1093/rap/rkaa017

40. Conticini E, Sota J, Falsetti P, et al. The Role of Multimodality Imaging in Monitoring Disease Activity and Therapeutic Response to Tocilizumab in Giant Cell Arteritis. *Mediators Inflamm*. 2020;2020:3203241. doi:10.1155/2020/3203241

41. Bruls S, Courtois A, Nusgens B, et al. 18F-FDG PET/CT in the Management of Aortitis. *Clin Nucl Med*. 2016;41(1):28-33. doi:10.1097/RLU.0000000000001016

42. Dellavedova L, Carletto M, Faggioli P, et al. The prognostic value of baseline (18)F-FDG PET/CT in steroid-naïve large-vessel vasculitis: introduction of volume-based parameters. *Eur J Nucl Med Mol Imaging*. 2016;43(2):340-348. doi:10.1007/s00259-015-3148-9

43. Meller J, Strutz F, Siefker U, et al. Early diagnosis and follow-up of aortitis with [(18)F]FDG PET and MRI. *Eur J Nucl Med Mol Imaging*. 2003;30(5):730-736. doi:10.1007/s00259-003-1144-y

44. Sriranjan RS, Tarkin JM, Evans NR, Le EPV, Chowdhury MM, Rudd JHF. Atherosclerosis imaging using PET: Insights and applications. *British Journal of Pharmacology*. 2021;178(11):2186-2203. doi:10.1111/bph.14868

45. Tso E, Flamm SD, White RD, Schvartzman PR, Mascha E, Hoffman GS. Takayasu arteritis: utility and limitations of magnetic resonance imaging in diagnosis and treatment. *Arthritis Rheum*. 2002;46(6):1634-1642. doi:10.1002/art.10251

46. Folco EJ, Sheikine Y, Rocha VZ, et al. Hypoxia but not inflammation augments glucose uptake in human macrophages: Implications for imaging atherosclerosis with 18fluorine-labeled 2-deoxy-D-glucose positron emission tomography. *J Am Coll Cardiol*. 2011;58(6):603-614. doi:10.1016/j.jacc.2011.03.044

47. Wu JC, Nguyen PK. Imaging Atherosclerosis With F18-Fluorodeoxyglucose Positron Emission Tomography: What Are We Actually Seeing?**Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology. *Journal of the American College of Cardiology*. 2011;58(6):615-617. doi:10.1016/j.jacc.2011.04.021

48. Unizony S, Arias-Urdaneta L, Miloslavsky E, et al. Tocilizumab for the treatment of large-vessel vasculitis (giant cell arteritis, Takayasu arteritis) and polymyalgia rheumatica. *Arthritis Care Res (Hoboken)*. 2012;64(11):1720-1729. doi:10.1002/acr.21750

49. Clifford AH, Arafat A, Idrees JJ, et al. Outcomes Among 196 Patients With Noninfectious Proximal Aortitis. *Arthritis Rheumatol*. 2019;71(12):2112-2120. doi:10.1002/art.40855

50. Stone JH, Han J, Aringer M, et al. Long-term effect of tocilizumab in patients with giant cell arteritis: open-label extension phase of the Giant Cell Arteritis Actemra (GiACTA) trial. *The Lancet Rheumatology*. 2021;3(5):e328-e336. doi:10.1016/S2665-9913(21)00038-2

51. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of Tocilizumab in Giant-Cell Arteritis. *N Engl J Med*. 2017;377(4):317-328. doi:10.1056/NEJMoa1613849

APPENDICES

Appendix 1. Full search strategy.

Database	Search Strategy
MEDLINE **Ovid MEDLINE(R) ALL** 1946 to November 03, 2020	1. (positron emission tomograph* or PET).mp. 2. exp Positron-Emission Tomography/ 3. (PET-CT* or PETCT*).mp. 4. exp Fluorodeoxyglucose F18/ 5. (FDG-PET or 18FDG PET).mp. 6. ((18F or 18-F or F18 or F-18 or "18") adj2 FDG).mp. 7. FDG-PET-MR.mp. 8. ((18F or 18-F or F18 or F-18 or "18" or fluorine) adj2 fluorodeoxyglucose).mp. 9. ((18F or 18-F or F18 or F-18 or "18" or fluorine) adj2 fluoro-deoxyglucose).mp. 10. 18-F-fluor-2-deoxy-D-glucose.mp. 11. or/1-10 12. exp Giant Cell Arteritis/ 13. giant cell arteriti*.mp. 14. giant cell aortic arteriti*.mp. 15. GCA.ti,ab. 16. temporal arteriti*.mp. 17. large vessel vasculiti*.mp. 18. aortitis.mp. 19. Horton* disease.mp. 20. cranial arteriti*.mp. 21. senile arteriti*.mp. 22. granulomatous arteriti*.mp. 23. or/12-22 24. 11 and 23
Embase **Ovid Embase** 1974 to 2020 November 03	1. (positron emission tomograph* or PET).mp. 2. exp positron emission tomography/ 3. (PET-CT* or PETCT*).mp. 4. exp fluorodeoxyglucose f 18/ 5. (FDG-PET or 18FDG PET).mp. 6. ((18F or 18-F or F18 or F-18 or "18") adj2 FDG).mp. 7. FDG-PET-MR.mp. 8. ((18F or 18-F or F18 or F-18 or "18" or fluorine) adj2 fluorodeoxyglucose).mp. 9. ((18F or 18-F or F18 or F-18 or "18" or fluorine) adj2 fluoro-deoxyglucose).mp. 10. 18-F-fluor-2-deoxy-D-glucose.mp. 11. or/1-10 12. exp giant cell arteritis/

	13. giant cell arteriti*.mp. 14. giant cell aortic arteriti*.mp. 15. GCA.ti,ab. 16. temporal arteriti*.mp. 17. large vessel vasculiti*.mp. 18. aortitis.mp. 19. Horton* disease.mp. 20. cranial arteriti*.mp. 21. senile arteriti*.mp. 22. granulomatous arteriti*.mp. 23. or/12-22 24. 11 and 23
CINAHL	S1 "positron emission tomograph*" or PET S2 (MH "Tomography, Emission-Computed+") S3 PET-CT* or PETCT* S4 (MH "Fludeoxyglucose F 18") S5 FDG-PET or 18FDG PET S6 ((18F or 18-F or F18 or F-18 or "18") N2 FDG) S7 FDG-PET-MR S8 ((18F or 18-F or F18 or F-18 or "18" or fluorine) N2 fluorodeoxyglucose) S9 ((18F or 18-F or F18 or F-18 or "18" or fluorine) N2 fluoro-deoxyglucose) S10 18-F-fluor-2-deoxy-D-glucose S11 18-F-fluor-2-deoxy-D-glucose *[SmartText Searching]* S12 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 S13 (MH "Giant Cell Arteritis") S14 "giant cell arteriti*" S15 TI GCA OR AB GCA S16 "giant cell aortic arteriti*" S17 "giant cell aortic arteriti*" *[SmartText Searching]* S18 "temporal arteriti*" S19 "large vessel vasculiti*" S20 aortitis S21 "Horton* disease" S22 "cranial arteriti*" S23 "senile arteriti*" S24 "senile arteriti*" *[SmartText Searching]* S25 "granulomatous arteriti*" S26 S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 S27 S12 AND S26
Scopus	TITLE-ABS-KEY ("positron emission tomograph*" OR pet OR pet-ct* OR petct* OR "FDG-PET-MR" OR ((18f OR f18 OR "18"

	) W/2 fdg) OR ((18f OR f18 OR "18" OR fluorine) W/2 fluorodeoxyglucose) OR ((18f OR f18 OR "18" OR fluorine) W/2 fluoro-deoxyglucose) OR "18 F fluor 2 deoxy D glucose") AND TITLE-ABS-KEY ("giant cell arteriti*" OR "temporal arteriti*" OR "large vessel vasculiti*" OR aortitis OR "Horton* disease" OR "cranial arteriti*" OR "senile arteriti*" OR "granulomatous arteriti*")
Cochrane Library via Wiley	#1 positron emission tomograph* or PET #2 [mh "Positron-Emission Tomography"] #3 PET-CT* or PETCT* #4 [mh "Fluorodeoxyglucose F18"] #5 FDG-PET or 18FDG PET #6 ((18F or 18 F or F18 or F 18 or "18") NEAR/2 FDG) #7 FDG-PET-MR #8 ((18F or 18 F or F18 or F 18 or "18" or fluorine) NEAR/2 fluorodeoxyglucose) #9 ((18F or 18 F or F18 or F 18 or "18" or fluorine) NEAR/2 fluoro-deoxyglucose) #10 18 F fluor 2 deoxy D glucose #11 {OR #1-#10} #12 [mh "Giant Cell Arteritis"] #13 giant cell arteriti* #14 giant cell aortic arteriti* #15 GCA:ti,ab #16 temporal arteriti* #17 large vessel vasculiti* #18 aortitis #19 Horton* disease #20 cranial arteriti* #21 senile arteriti* #22 granulomatous arteriti* #23 {OR #12-#22} #24 #11 AND #23
Google Scholar	(positron emission tomography OR FDG PET OR Fluorodeoxyglucose F18) AND ("giant cell arteritis" OR "large vessel vasculitis" OR "Horton disease" OR "temporal arteritis")

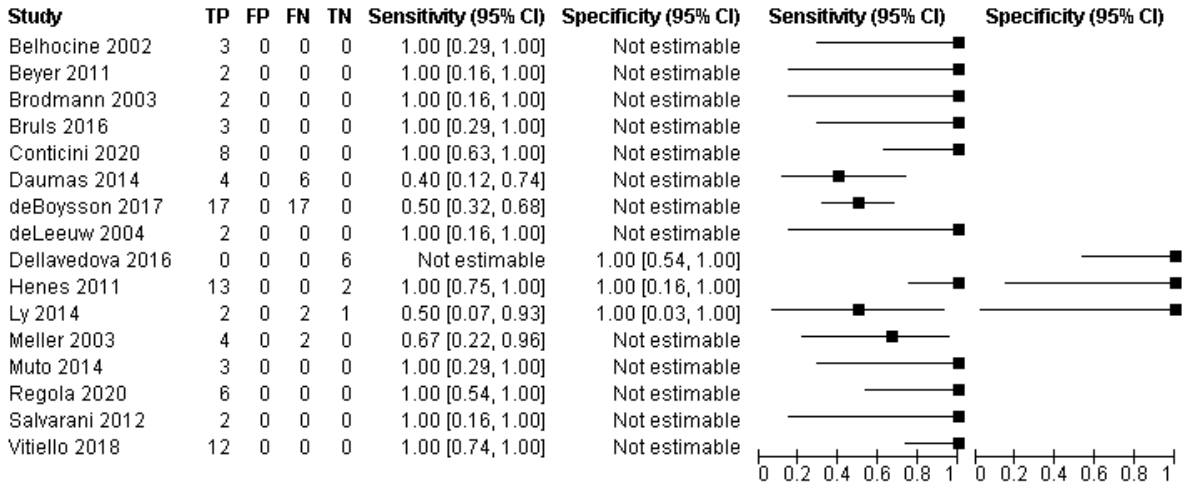
Appendix 2. QUADAS-2 results of individual studies.

	Patient selection (RoB)	Index test (RoB)	Reference standard (RoB)	Flow and Timing (RoB)	Patient selection (Applicability)	Index test (Applicability)	Reference standard (Applicability)
Banerjee, 2020	☺	☺	☺	☹	☺	☺	☺
Regola, 2020	☺	?	?	☹	☺	☺	☺
Contincini, 2020	?	☹	?	☺	☺	☺	☺
Vitiello, 2018	?	☹	?	☺	☺	☹	☺
deBoysson, 2017	☹	?	☺	☺	☺	☺	☺
Dellavedova, 2016	☺	☺	☺	☹	☺	☺	☺
Bruls, 2016	☺	?	?	?	☺	☺	?
Muto, 2014	☺	☺	☺	☺	☹	☺	☺
Daumas, 2014	☺	☹	☹	☹	☺	☺	☺
Ly, 2014	☹	?	?	☺	☹	?	☺
Salvarani, 2012	☺	?	☹	☺	☺	☺	☺
Beyer, 2011	☹	☹	☹	☺	☺	☺	☺
Henes, 2011	?	☹	?	☺	☺	☺	☺
Blockmans, 2006	☺	☺	☺	☺	☺	☺	☺
deLeeuw, 2004	☺	☺	☺	☺	☺	☺	☺
Meller, 2003	☺	?	?	?	☺	☺	☺
Brodmann, 2003	?	☹	☹	☺	☺	?	☺
Belhocine, 2002	?	☹	?	☺	☺	☺	☺

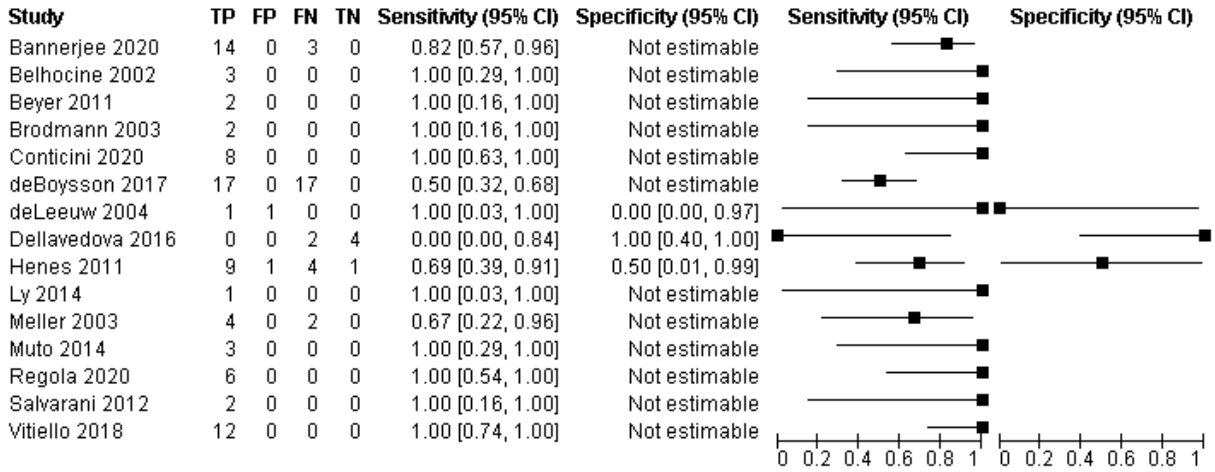
Legend: ☺= low, ☹=high, ?=unclear, RoB=risk of bias.

Appendix 3. Sensitivity and specificity plots of included studies.

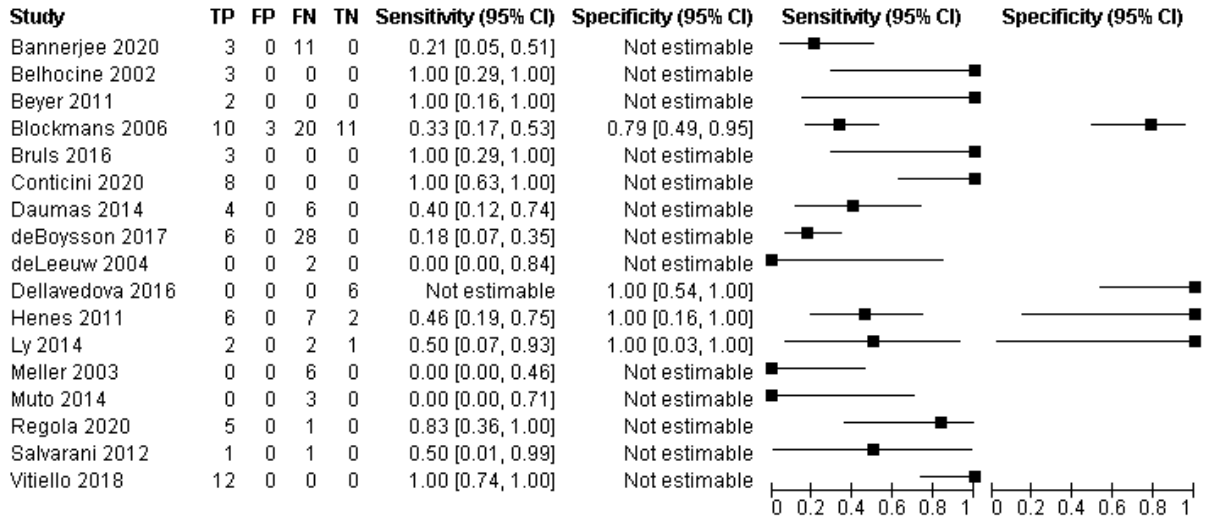
Supplemental Figure 1a: Sensitivity and specificity of improved FDG PET for clinical improvement in treated GCA patients, per individual studies



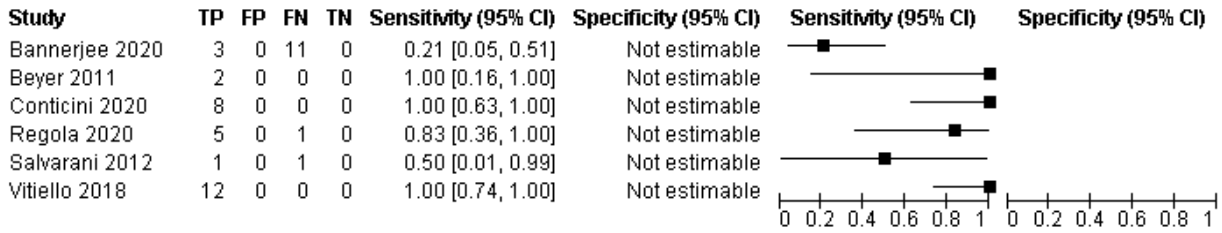
Supplemental Figure 1b: Sensitivity and specificity of improved FDG PET for biochemical improvement in treated GCA patients, per individual studies.



Supplemental Figure 1c: Sensitivity and specificity of normalized FDG PET for clinical remission in treated GCA patients, per individual studies.



Supplemental Figure 1d: Sensitivity and specificity of normalized FDG PET for clinical remission in GCA patients treated with tocilizumab, per individual studies (TCZ subgroup.)



Supplemental Figure 1e: Sensitivity and specificity of normalized FDG PET according to international consensus criteria for clinical remission in treated GCA patients, per individual studies (Consensus criteria subgroup.)