**Imaging in Diagnosis, Outcome Prediction and Monitoring of Large Vessel Vasculitis: A Systematic Literature Review and Meta-analysis Informing the EULAR Recommendations**

**Supplementary material**

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1. **DETAILS ON SEARCH STRATEGY**

**Online Supplementary Table S1a.** Key questions of imaging techniques on **diagnostic accuracy**

|  |
| --- |
| What is the value of **[imaging technique]** (Intervention) for the diagnosis of primary LVV (Outcome) in patients with suspected primary LVV (Population), using the final diagnosis as a **[reference standard]** (Comparator)? |
| population | patients (age of ≥18 years) with “suspected primary LVV”, particularly suspected cranial and/or large vessel GCA, TAK or isolated aortitisThe “suspicion” is not defined by any specific criteria for this SLR. Statements such as LVV “was suspected”, or patients “were referred for assessment of possible LVV” are acceptable, as are combinations of various clinical symptoms with/without laboratory results to define the target population |
| intervention | ultrasound, MRI +/- angiography, CT +/- angiography and PET +/- CT |
| comparator  | temporal artery biopsy, physician’s diagnosis at baseline and diagnoses including follow-up analyses |
| outcome  | test performance reflected in sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios |

CT, computed tomography; GCA, giant cell arteritis; SLR, systematic literature review; TAK, Takayasu arteritis; LVV, large vessel vasculitis; MRI, magnetic resonance imaging; PET, 18F-FDG positron emission tomography

**Online Supplementary Table S1b.** Key questions of imaging techniques on **outcome prediction**

|  |
| --- |
| In primary LVV (Population), what is the value of positive **[imaging]** (Intervention) to predict outcome (Outcome) compared to negative [imaging] (Comparator)? |
| population | patients with primary LVV, particularly cranial and/or large vessel GCA, TAK and isolated aortitis, according to physicians’ final diagnosis |
| intervention | ultrasound, MRI +/- angiography, CT +/- angiography and PET +/- CT |
| comparator | negative imaging |
| outcome | loss of vision in one or both eyes, mortality, stroke, heart attack, disease remission, disease relapse, physician global assessment of disease activity, patient global assessment of disease activity, pain severity, inflammatory markers (e.g. ESR, CRP), quality of life, mobility, fatigue, feeling of being unwell, ability to do usual everyday activities, ability to self-care, muscle weakness, impact on patients’ social environment, healthcare resource use and other health economic data, cumulative GC dose, duration of GC treatment, having to increase GC dose, discontinuation of GC therapy, bleeding from stomach, infection requiring admission, infection needing antibiotics, fractures, high blood pressure, cataract, glaucoma, GC-related side effects, other therapy-related side effects, hospitalization (due to disease, its complications, co-morbidity and/or treatment related complications) |

CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; GC, Glucocorticoid; GCA, giant cell arteritis; TAK, Takayasu arteritis; SLR, systematic literature review; LVV, large vessel vasculitis; MRI, magnetic resonance imaging; PET, 18F-FDG positron emission tomography

**Online Supplementary Table S1c.** Key questions of imaging techniques on **monitoring**

|  |
| --- |
| In primary LVV (Population), what is the value of **[imaging]** (Intervention) for monitoring disease activity/damage (Outcome) compared to not performing [imaging] (Comparator)? |
| Population | patients with primary LVV, particularly cranial and/or large vessel GCA, TAK and isolated aortitis, according to physicians’ final diagnosis |
| Intervention | ultrasound, MRI +/- angiography, CT +/- angiography and PET +/- CT |
| Comparator | not performing imaging |
| Outcome | all possible outcome measures reflecting ‘disease activity’ are collected without formal definition. Damage will include (but is not limited to) any LVV related ischemic complication, vascular stenosis, vascular occlusion, death, aneurysm development with/without dissection |

CT, computed tomography; GCA, giant cell arteritis; SLR, systematic literature review; TAK, Takayasu arteritis; LVV, large vessel vasculitis; MRI, magnetic resonance imaging; PET, 18F-FDG positron emission tomography

**Online Supplementary Table S1d.** Key questions of imaging techniques on **technical requirements**

|  |
| --- |
| In suspected/established primary LVV (Population), what technical requirements, settings and operational procedures (Intervention) should be applied when using **[imaging technique]** to achieve optimal results (Outcome) compared to not applying these settings/procedures (Comparator)? |
| Population | patients with primary LVV, particularly suspected/established cranial and/or large vessel GCA, TAK and isolated aortitis, according to physicians’ final diagnosis |
| Intervention | ultrasound, MRI +/- angiography, CT +/- angiography and PET +/- CT |
| Comparator | not applying these settings/procedures |
| Outcome | “optimal results” were not defined |

CT, computed tomography; GCA, giant cell arteritis; SLR, systematic literature review; TAK, Takayasu arteritis; LVV, large vessel vasculitis; MRI, magnetic resonance imaging; PET, 18F-FDG positron emission tomography

**Online Supplementary Text S1.** Key words for the search in MEDLINE, EMBASE and Cochrane Library Databases

**MEDLINE**

|  |  |
| --- | --- |
| 1. Vasculitis/ |  |

|  |  |
| --- | --- |
| 2. Giant Cell Arteritis/ |  |

|  |  |
| --- | --- |
| 3. Takayasu Arteritis/ |  |

|  |  |
| --- | --- |
| 4. ((large vessel or giant cell or isolated or cranial or temporal or young female) adj2 (vasculitis or vasculitides or arteritis or aortitides or aortitis or arteritides)).tw. |  |

|  |  |
| --- | --- |
| 5. ((Horton$ or takayasu$ or aortitis or pulseless) adj (disease or syndrome or arteritis)).tw. |  |

|  |  |
| --- | --- |
| 6. (lvv or gca).tw. |  |

|  |  |
| --- | --- |
| 7. or/1-6 |  |

|  |  |
| --- | --- |
| 8. Diagnostic Imaging/ |  |

|  |  |
| --- | --- |
| 9. exp Magnetic Resonance Imaging/ |  |

|  |  |
| --- | --- |
| 10. magnetic resonance.tw. |  |

|  |  |
| --- | --- |
| 11. mri$.tw. |  |

|  |  |
| --- | --- |
| 12. exp Ultrasonography/ |  |

|  |  |
| --- | --- |
| 13. (ultrasonic adj (diagnos$ or tomography or imaging$)).tw. |  |

|  |  |
| --- | --- |
| 14. echotomograph$.tw. |  |

|  |  |
| --- | --- |
| 15. echograph$.tw. |  |

|  |  |
| --- | --- |
| 16. ultrasonograph$.tw. |  |

|  |  |
| --- | --- |
| 17. ultrasound.tw. |  |

|  |  |
| --- | --- |
| 18. sonograph$.tw. |  |

|  |  |
| --- | --- |
| 19. exp Tomography, X-Ray Computed/ |  |

|  |  |
| --- | --- |
| 20. exp Contrast Media/ |  |

|  |  |
| --- | --- |
| 21. (computed adj2 tomography).tw. |  |

|  |  |
| --- | --- |
| 22. cat scan$.tw. |  |

|  |  |
| --- | --- |
| 23. ct.tw. |  |

|  |  |
| --- | --- |
| 24. Positron-Emission Tomography/ |  |

|  |  |
| --- | --- |
| 25. Positron emission tomograp$.tw. |  |

|  |  |
| --- | --- |
| 26. pet scan$.tw. |  |

|  |  |
| --- | --- |
| 27. exp Angiography/ |  |

|  |  |
| --- | --- |
| 28. (angiograph$ or arteriograph$ or Aortograph$ or Cineangiograph$ or Phlebograph$ or Portograph$).tw. |  |

|  |  |
| --- | --- |
| 29. or/8-28 |  |

|  |  |
| --- | --- |
| 30. 7 and 29 |  |

|  |  |
| --- | --- |
| 31. exp animals/ not humans.sh. |  |

|  |  |
| --- | --- |
| 32. 30 not 31 |  |

|  |  |
| --- | --- |
| 33. sensitiv:.mp. |  |

|  |  |
| --- | --- |
| 34. diagnos:.mp. |  |

|  |  |
| --- | --- |
| 35. di.fs. |  |

|  |  |
| --- | --- |
| 36. or/33-35 |  |

|  |  |
| --- | --- |
| 37. 32 and 36 |  |

|  |  |
| --- | --- |
| 38. incidence.sh. |  |

|  |  |
| --- | --- |
| 39. exp mortality/ |  |

|  |  |
| --- | --- |
| 40. follow-up studies.sh. |  |

|  |  |
| --- | --- |
| 41. prognos:.tw. |  |

|  |  |
| --- | --- |
| 42. predict:.tw. |  |

|  |  |
| --- | --- |
| 43. course:.tw. |  |

|  |  |
| --- | --- |
| 44. or/38-43 |  |

|  |  |
| --- | --- |
| 45. 32 and 44 |  |

|  |
| --- |
| 46. 37 or 45 |

**The Cochrane Library**

#1 MeSH descriptor: [Vasculitis] this term only

#2 MeSH descriptor: [Giant Cell Arteritis] this term only

#3 MeSH descriptor: [Takayasu Arteritis] this term only

#4 (("large vessel" or “giant cell” or isolated or cranial or temporal or “young female”) near/2 (vasculitis or vasculitides or arteritis or aortitides or aortitis or arteritides)):ti,ab

#5 ((Horton\* or takayasu\* or aortitis or pulseless) next (disease or syndrome or arteritis)):ti,ab

#6 (lvv or gca):ti,ab

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 MeSH descriptor: [Diagnostic Imaging] explode all trees

#9 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees

#10 "magnetic resonance":ti,ab

#11 mri\*:ti,ab

#12 MeSH descriptor: [Ultrasonography] explode all trees

#13 (ultrasonic next (diagnos\* or tomography or imaging\*)):ti,ab

#14 echotomograph\*:ti,ab

#15 echograph\*:ti,ab

#16 ultrasonograph\*:ti,ab

#17 ultrasound:ti,ab

#18 sonograph\*:ti,ab

#19 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees

#20 MeSH descriptor: [Contrast Media] explode all trees

#21 (computed near/2 tomography):ti,ab

#22 "cat scan\*":ti,ab

#23 ct:ti,ab

#24 MeSH descriptor: [Positron-Emission Tomography] this term only

#25 "Positron emission tomograp\*":ti,ab

#26 "pet scan\*":ti,ab

#27 MeSH descriptor: [Angiography] explode all trees

#28 (angiograph\* or arteriograph\* or Aortograph\* or Cineangiograph\* or Phlebograph\* or Portograph\*):ti,ab

#29 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28

#30 #7 and #29

**EMBASE**

#44. #35 OR #43 AND [humans]/lim AND [embase]/lim AND ('article'/it OR 'article in press'/it)

#43. #30 AND #42

#42. #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41

#41. outcome:ab,ti

#40. 'epidemiology'/lnk

#39. 'follow up\*'

#38. diagnos\*

#37. risk\*

#36. 'disease course'/exp

#35. #30 AND #34

#34. #31 OR #32 OR #33

#33. specificity:ab,ti

#32. predict\*:ab,ti

#31. 'diagnosis'/lnk

#30. #7 AND #29

#29. #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28

#28. angiograph\*:ab,ti OR arteriograph\*:ab,ti OR aortograph\*:ab,ti OR cineangiograph\*:ab,ti OR

 phlebograph\*:ab,ti OR portograph\*:ab,ti

#27. 'angiography'/exp

#26. 'pet scan\*':ab,ti

#25. 'positron emission tomograp\*':ab,ti

#24. 'positron emission tomography'/de

#23. ct:ab,ti

#22. 'cat scan\*':ab,ti

#21. (computed NEAR/2 tomography):ab,ti

#20. 'contrast medium'/exp

#19. 'computer assisted tomography'/exp

#18. sonograph\*:ab,ti

#17. ultrasound:ab,ti

#16. ultrasonograph\*:ab,ti

#15. echograph\*:ab,ti

#14. echotomograph\*:ab,ti

#13. (ultrasonic NEAR/2 (diagnos\* OR tomography OR imaging\*)):ab,ti

#12. 'echography'/exp

#11. mri:ab,ti

#10. 'magnetic resonance':ab,ti

#9. 'nuclear magnetic resonance imaging'/exp

#8. 'diagnostic imaging'/exp

#7. #1 OR #2 OR #3 OR #4 OR #5 OR #6

#6. lvv:ab,ti OR gca:ab,ti

#5. ((horton\* OR takayasu\* OR aortitis OR pulseless) NEAR/2 (disease OR syndrome OR arteritis)):ab,ti

#4. (('large vessel' OR 'giant cell' OR isolated OR cranial OR temporal OR 'young female') NEAR/2

 (vasculitis OR vasculitides OR arteritis OR aortitides OR aortitis OR arteritides)):ab,ti

#3. 'aorta arch syndrome'/de

#2. 'giant cell arteritis'/de

#1. 'vasculitis'/de



**Online Supplementary Figure S1.** Flowchart of the systematic literature review with detailed results of the selection process by the two reviewers (R1, CDe; R2, CDu)

**2. STUDIES ASSESSING DIAGNOSTIC ACCURACY**

*2.1. Main characteristics and results*

**Online Supplementary Table S2.** Study characteristics and main findings on the diagnostic accuracy of ultrasound in giant cell arteritis (GCA)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **suspected diagnosis well-defined\*** | **longitudinal study**¥ | **reference standard blinded to index test** | **studies without GC**‡ | **Techn** | **reference****standard** | **index test** | **Sens (%)** | **Spec (%)** | **Sens (%)** | **Spec (%)** | **RoB** |
|  |  |  |  |  |  |  |  | **US *vs* clinical diagnosis** | **US *vs* TAB** |  |
| Schmidt WA 1997(1) | no | no | NR | no | 10 MHz | ACR criteria orTAB | halostenosis/occlusionhalo/stenosis/occlusion | 738093 | 1009393 | 768695 | 928885 | high |
| LeSar CJ 2002(2) | no | no | NR | yes | 10 MHz | TAB | halostenosishalo/stenosis | NA | NA | 8643100 | 928480 | high |
| Nesher G 2002(3) | no | yes | no | yes | 15 MHz† | clinical diagnosis 6m orTAB | halo | 86 | 78 | 78 | 61 | high |
| Salvarani C 2002(4) | no | no | no | yes | 10 MHz | ACR criteria orTAB | halo | 35 | 79 | 40 | 79 | high |
| Murgatroyd H 2003(5) | no | no | NR | NR | 10 MHz | TAB | halo | NA | NA | 86 | 68 | high |
| Pfadenhauer K 2003(6) | no | no | NR | no | 9 MHz | ACR criteria orTAB | halo/stenosis/occlusion | 83 | 89 | 91 | 82 | high |
| Reinhard M 2004(7) | no | no | no | no | 10 MHz | ACR criteria orTAB | haloocclusionbilateral halo | 6016NA | 10098NA | 672147 | 939383 | high |
| Romera-Villegas 2004(8) | no | no | yes | NR | 10 MHz | TAB | halo/stenosis/occlusion | NA | NA | 95 | 91 | low |
| Karahaliou M 2006(9) | yes | yes | no | yes | 11 MHz | clinical diagnosis 3m orTAB | halobilateral halostenosis | 824141 | 9110073 | NANANA | NANANA | low |
| Pfadenhauer K 2007(10) | no | no | NR | no | 9 MHz | clinical diagnosis(retrospectively confirmed) | halo/stenosis | 69 | 91 | NA | NA | mod |
| Zaragoza-Garcia JM 2007(11) | no | no | no | yes | 7.5 MHz | TAB | halohalo/stenosis | NA NA | NANA | 80100 | 9277 | high |
| Aschwanden M 2010(12) | yes | no | no | no | 9 MHz17 MHz† | ACR criteria | halo/stenosis | 55 | 100 | NA | NA | mod |
| Habib HM 2012(13) | yes | yes | no | yes | 10 MHz | clinical diagnosis 3m orTAB | halobilateral halo | 8137 | 88100 | NANA | NANA | mod |
| Aschwanden M 2013(14) | no | no | no | no | 17 MHz† | ACR criteria | halostenosisocclusioncompression | 7913879 | 100100100100 | NANANANA | NANANANA | low |
| Diamantopoulos A 2014(15) | yes | yes | yes | no | 13 MHz† | clinical diagnosis 6m orTAB | halo | 100 | 91 | NA | NA | low |
| Aschwanden M 2015(16) | no | no | NR | no | 17 MHz† | ACR criteria | compression | 77 | 100 | NA | NA | low |
| Luqmani R 2016(17) | no | yes | no | no | 10 MHz or > | clinical diagnosis 6m orTAB | halo/stenosis/occlusion | 54 | 81 | 73 | 69 | mod |

\*suspected diagnosis well-defined, studies with detailed definition of suspicion of giant cell arteritis; ¥longitudinal studies, studies with clinical diagnosis after follow-up as reference standard; ‡studies without GC, studies in which no glucocorticoid treatment was started before the performance of the ultrasound examination; †high resolution devices were defined as >12 MHz probes for ultrasound;

ACR, American College of Rheumatology; GCA, giant cell arteritis; m, months; MHz, megahertz; NA, not applicable; NR, not reported; RoB, overall appraisal of risk of bias and concerns about applicability (arbitrarily defined) (high, in the case of concern on ≥5/10 risk of bias items or concern on 3/3 applicability items out of the QUADAS-2 tool; moderate, in case of concern on 4/10 risk of bias items and/or concern on ≥1/3 applicability items out of the QUADAS-2 tool, low, in case of concern on ≤3/3 risk of bias items and no concern about applicability); Sens, sensitivity; Spec, Specificity; TAB, temporal artery biopsy; Techn, technical aspects related to imaging methods; US, ultrasound; *vs*, versus

**Online Supplementary Table S3.** Study characteristics and main findings on the diagnostic accuracy of magnetic resonance imaging in cranial giant cell arteritis (GCA) and Takayasu arteritis (TAK)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **suspected diagnosis well-defined\*** | **longitudinal study**¥ | **reference standard blinded to index test** | **studies without GC**‡ | **Techn** | **reference****standard** | **index test** | **Sens (%)** | **Spec (%)** | **Sens (%)** | **Spec (%)** | **RoB** |
|  |  |  |  |  |  |  |  |  | **MRI *vs* clinical diagnosis** | **MRI *vs* TAB** |  |
| **Giant cell arteritis** |
| Bley TA 2005(18) | yes | no | yes | no | 3T\* | ACR criteria orTAB | wall thickening + contrast enhancement score (1-4) | 89 | 92 | 100 | 80 | low |
| Bley TA 2007(19) | yes | yes | yes | no | 1.5T (29)3T (38) | clinical diagnosis 6m orTAB | wall thickening + contrast enhancement score (0-3) | 81 | 97 | 91 | 73 | low |
| Geiger J 2010(20) | no | no | NR | NR | 3T\* | ACR criteria orTAB | wall thickening + contrast enhancement score (0-3) | 68 | 73 | 91 | 50 | high |
| Franke P 2014(21) | no | no | NR | NR | 3T\* | TAB | wall thickening + contrast enhancement score (0-3) | NA | NA | 88 | 100 | high |
| Klink T 2014(22) | yes | yes | yes | no | 1.5T (30)3T (155) | clinical diagnosis 6m orTAB | wall thickening + contrast enhancement score (0-3) | 81 | 88 | 91 | 75 | mod |
| [Veldhoen S](http://www-1ncbi-1nlm-1nih-1gov-1pubmed.han.medunigraz.at/pubmed/?term=Veldhoen%20S%5BAuthor%5D&cauthor=true&cauthor_uid=24895039) 2014(23) | no | no | yes | no | 1.5T (40)3T (59) | TAB | wall thickening + contrast enhancement(artery wall/ temporal muscle) | NA | NA | 42 | 90 | high |
| Siemonsen S 2015(24) | no | no | yes | no | 3T\* | ACR criteria orTAB | TA, occipital,[wall thickening + contrast enhancement score (0-3)]intracranial (enhancement) | 8050 | 8080 | NANA | NANA | mod |
| Rhéaume M 2017(25) | no | yes | yes | no | 3T\* | ACR criteria orTAB orclinical diagnosis FU (NR) | wall thickening + contrast enhancement score (0-3) | 39 | 82 | 94 | 78 | mod |
| **Takayasu arteritis** |
| Yamada I 2000(26) | no | no | NR | NR | 1.5T | conventionalangiography | luminal changes (stenosis, occlusion, dilatation, aneurysms) | 73 | 78 |  |  | low |

\*suspected diagnosis well-defined, studies with detailed definition of suspicion of giant cell arteritis; ¥longitudinal studies, studies with clinical diagnosis after follow-up as reference standard; ‡studies without GC, studies in which no glucocorticoid treatment was started before the performance of the magnetic resonance imaging examination; †high resolution devices were defined as 3T magnetic resonance imaging machines;

ACR, American College of Rheumatology; FU, follow-up; GCA, giant cell arteritis; m, months; MRI, magnetic resonance imaging; NA, not applicable; NR, not reported; RoB, overall appraisal of risk of bias and concerns about applicability (arbitrarily defined) (high, in the case of concern on ≥5/10 risk of bias items or concern on 3/3 applicability items out of the QUADAS-2 tool; moderate, in case of concern on 4/10 risk of bias items and/or concern on ≥1/3 applicability items out of the QUADAS-2 tool, low, in case of concern on ≤3/3 risk of bias items and no concern about applicability); Sens, sensitivity; Spec, Specificity; T, Tesla; TA, temporal artery/-ies; TAB, temporal artery biopsy; Techn, technical aspects related to imaging methods; *vs*, versus

**Online Supplementary Table S4.** Study characteristics and main findings on the diagnostic accuracy of 18F-FDG-positron emission tomography in extra-cranial large vessel giant cell arteritis (GCA)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **suspected diagnosis well-defined\*** | **longitudinal study**¥ | **reference standard blinded to index test** | **studies without GC**‡ | **Techn** | **reference****standard** | **index test** | **Sens (%)** | **Spec (%)** | **Sens (%)** | **Spec (%)** | **RoB** |
|  |  |  |  |  |  |  |  |  | **PET *vs* clinical diagnosis** | **PET *vs* TAB** |  |
| Blockmans D 2000(27) | yes | no | NR | yes | CTI-Siemens | TAB | wall thickening + contrast enhancement score (1-4) | 56†◊ | 98†◊ | 77# | 66# | mod |
| Lariviere D 2016(28) | no | yes | NR | no | Discovery 690 (GE) | clinical diagnosis 6m | wall thickening + contrast enhancement score (0-3) | 67 | 100 | NA | NA | low |

\*suspected diagnosis well-defined, studies with detailed definition of suspicion of giant cell arteritis; ¥longitudinal studies, studies with clinical diagnosis after follow-up as reference standard; ‡studies without GC, studies in which no glucocorticoid treatment was started before the performance of the PET examination; †PET (thorax); #PET (thorax and legs), ◊GCA was diagnosed in TAB proven cases, but also in PMR cases with 18F-FDG uptake in large vessels suggestive for vasculitis, representing circular reasoning as the test of interest was part of the reference standard;

GCA, giant cell arteritis; m, months; NR, not reported; PET, 18F-FDG-prositron emission tomography; RoB, overall appraisal of risk of bias and concerns about applicability (arbitrarily defined) (high, in the case of concern on ≥5/10 risk of bias items or concern on 3/3 applicability items out of the QUADAS-2 tool; moderate, in case of concern on 4/10 risk of bias items and/or concern on ≥1/3 applicability items out of the QUADAS-2 tool, low, in case of concern on ≤3/3 risk of bias items and no concern about applicability); Sens, sensitivity; Spec, Specificity; TAB, temporal artery biopsy; Techn, technical aspects related to imaging methods; *vs*, versus

**Online Supplementary Table S5.** Study characteristics and main findings on the diagnostic accuracy of computed tomography angiography in extra-cranial large vessel giant cell arteritis (GCA) and Takayasu arteritis (TAK)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **suspected diagnosis well-defined\*** | **longitudinal study**¥ | **reference standard blinded to index test** | **studies without GC**‡ | **Techn** | **reference****standard** | **index test** | **Sens (%)** | **Spec (%)** | **Sens (%)** | **Spec (%)** | **RoB** |
|  |  |  |  |  |  |  |  |  | **CTA *vs* clinical diagnosis** | **CTA *vs* CA** |  |
| **Giant cell arteritis** |
| Lariviere D 2016(28) | no | yes | NR | no | Discovery 690 (GE) | clinical diagnosis 6m | wall thickening + contrast enhancement score (1-4) | 73 | 78 | NA | NA | low |
| **Takayasu arteritis** |
| Yamada I 1998(29) | no | no | NR | NR | Xvigor, Toshiba | CA | wall thickening + contrast enhancement score (0-3) | NA | NA | 67 | 100 | low |

\*suspected diagnosis well-defined, studies with detailed definition of suspicion of giant cell arteritis; ¥longitudinal studies, studies with clinical diagnosis after follow-up as reference standard; ‡studies without GC, studies in which no glucocorticoid treatment was started before the performance of the computed tomography angiography examination;

CA, conventional angiography; CTA, computed tomography angiography; GCA, giant cell arteritis; m, months; NR, not reported; RoB, overall appraisal of risk of bias and concerns about applicability (arbitrarily defined) (high, in the case of concern on ≥5/10 risk of bias items or concern on 3/3 applicability items out of the QUADAS-2 tool; moderate, in case of concern on 4/10 risk of bias items and/or concern on ≥1/3 applicability items out of the QUADAS-2 tool, low, in case of concern on ≤3/3 risk of bias items and no concern about applicability); Sens, sensitivity; Spec, Specificity; Techn, technical aspects related to imaging methods; *vs*, versus

*2.2. Details of the risk of bias assessment*

For studies on diagnostic accuracy, the risk of bias (RoB) was appraised independently by the two reviewers (CDe, CDu) using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, that comprises four domains: patient selection, index test, reference standard, as well as flow and timing. The risk of bias is appraised in each domain, whereas concerns about applicability are evaluated in the first three domains. Each domain is rated as high, low or unclear, with “high” designating either a high RoB or substantial concerns about applicability.(30)

**Risk of bias**

Domain 1 – patient selection:

Signalling question 1 (P1): Was a consecutive or random sample of patients enrolled?

Signalling question 2 (P2): Was a case-control design avoided?

Signalling question 3 (P3): Did the study avoid inappropriate exclusions?

Domain 2 – index test:

Signalling question 1 (IT1): Were the index test results interpreted without knowledge of the results of the reference standard?

Signalling question 2 (IT2): If a threshold was used, was it pre-specified?

Domain 3 – reference standard:

Signalling question 1 (R1): Is the reference standard likely to correctly classify the target condition?

Signalling question 2 (R2): Were the reference standard results interpreted without knowledge of the results of the index test?

Domain 4 – flow and timing:

Signalling question 1 (FT1): Was there an appropriate interval between index test and reference standard?

Signalling question 2 (FT2): Did all patients receive the same reference standard?

Signalling question 3 (FT3): Were all patients included in the analysis?

**Concerns on Applicability**

Signalling question 1 (APS): Are there concerns that the included patients and setting do not match the review question?

Signalling question 1 (AIT): Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Signalling question 1 (ARS): Are there concerns that the target condition as defined by the reference standard does not match the question?

Icons indicate a low (☺), high (☹) or unclear (?) risk of bias regarding the corresponding question of evaluation.

**Online Supplementary Table S6.** Risk of bias assessment of diagnostic accuracy studies on imaging techniques

|  |  |  |  |
| --- | --- | --- | --- |
| **STUDY** | **RISK OF BIAS** | **APPLICABILITY CONCERNS** | **RoB** |
|  | **PATIENT SELECTION** | **INDEX TEST** | **REFERENCE STANDARD** | **FLOW AND TIMING** | **PATIENT SELECTION** | **INDEX TEST** | **REFERENCE STANDARD** |  |
|  | **P1** | **P2** | **P3** | **IT1** | **IT2** | **R1** | **R2** | **FT1** | **FT2** | **FT3** | **APS** | **AIT** | **ARS** |  |
| **Ultrasound** |
| **Giant cell arteritis** |
| Schmidt WA 1997(1) | ☺ | ☹1 | ☺ | ☹2 | ☺ | ☺ | ?3 | ?3 | ☹4 | ☺ | ☹1 | ☺ | ☺ | high |
| LeSar CJ 2002(2) | ?5 | ☺ | ?3 | ?3 | ☺ | ☺ | ?3 | ?3 | ☹6 | ☺ | ?5 | ☺ | ☺ | high |
| Nesher G 2002(3) | ?3 | ☺ | ?3 | ?3 | ☺ | ☺ | ☹7 | ☺ | ☹4 | ☺ | ☺ | ☺ | ☺ | high |
| Salvarani C 2002(4) | ☺ | ☺ | ☺ | ☺ | ?8 | ☹9 | ☹7 | ☺ | ☺ | ☺ | ☹10 | ☹8 | ☹9 | high |
| Murgatroyd H 2003(5) | ?3 | ☺ | ?3 | ☹11 | ?3 | ☺ | ?3 | ?3 | ☺ | ☺ | ☹12 | ☹13 | ☺ | high |
| Pfadenhauer K 2003(6) | ☹14 | ☺ | ☺ | ?3 | ☺ | ☺ | ?3 | ☺ | ☹4 | ☹14 | ☹15 | ☺ | ☺ | high |
| Reinhard M 2004(7) | ?3 | ☺ | ?3 | ?3 | ☺ | ☺ | ☹7 | ☹16 | ☹4 | ☺ | ?17 | ☺ | ☺ | high |
| Romera-Villegas A 2004(8) | ☺ | ☺ | ☹18 | ☹11 | ☺ | ☺ | ☺ | ?3 | ☺ | ☺ | ☺ | ☺ | ☺ | low |
| Karahaliou M 2006(9) | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☹7 | ☺ | ☹4 | ☹19 | ☺ | ☺ | ☺ | low |
| Pfadenhauer K 2007(10) | ☺ | ☺ | ☹20 | ☺ | ☺ | ☺ | ?3 | ?3 | ☹4 | ☺ | ☹15 | ☺ | ☺ | mod |
| Zaragoza-Garcia HM(11) | ☺ | ☺ | ☹21 | ?3 | ☹22 | ☺ | ☹7 | ☹7 | ☺ | ☹21 | ☺ | ☺ | ☺ | high |
| Aschwanden M 2010(12) | ☺ | ☺ | ☺ | ☹25 | ☺ | ☺ | ☹26 | ?3 | ☹4 | ☺ | ☺ | ☺ | ☺ | mod |
| Habib HM(13) | ?3 | ☺ | ☺ | ☺ | ☺ | ☹23 | ☹7 | ☺ | ☺ | ☺ | ☺ | ☹24 | ☺ | mod |
| Aschwanden M 2013(14) | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☹27 | ☺ | ☹4 | ☺ | ☺ | ☺ | ☺ | low |
| Diamantopoulos A 2014(15) | ☺ | ☺ | ☺ | ☹11 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | low |
| Aschwanden M 2015(16) | ☺ | ☺ | ☺ | ?3 | ☺ | ☺ | ?3 | ☺ | ☹4 | ☺ | ☺ | ☺ | ☺ | low |
| Luqmani R 2016(17) | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☹28 | ☺ | ☺ | ☺ | ☺ | ☹29 | ☹30 | mod |
| **Magnetic resonance imaging** |  |
| **Giant cell arteritis** |  |
| Bley TA 2005(18) | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ?3 | ?3 | ☹4 | ☺ | ☺ | ☺ | ☺ | low |
| Bley TA 2007(19) | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ?3 | ?3 | ☹4 | ☺ | ☺ | ☹31 | ☺ | low |
| Geiger J 2010(20) | ☺ | ☺ | ?3 | ?3 | ☺ | ☺ | ?3 | ?3 | ☹4 | ☺ | ☺ | ☺ | ☺ | high |
| Franke P 2014(21) | ☺ | ☺ | ☹32 | ?3 | ?3 | ☺ | ?3 | ?3 | ☹4 | ☺ | ☺ | ☺ | ☺ | high |
| Klink T 2014(22) | ☺ | ☺ | ☹33 | ☺ | ☺ | ☺ | ☺ | ☺ | ☹4 | ☺ | ☺ | ☹31 | ☺ | mod |
| Veldhoen S 2014(23) | ☺ | ☺ | ☹34 | ?3 | ☺ | ☺ | ?3 | ?3 | ☺ | ☹35 | ☺ | ☹31 | ☺ | high |
| Siemonsen S 2014(24) | ☺ | ☺ | ☹36 | ☺ | ☺ | ☺ | ?3 | ?3 | ☹4 | ☺ | ☺ | ☺ | ☺ | mod |
| Rhéaume M 2017(25) | ☺ | ☺ | ☺ | ☺ | ☺ | ☺/?37 | ?3 | ☹38 | ☺/☹39 | ☺ | ?40 | ☺ | ☺ | mod |
| **Takayasu arteritis** |  |
| Yamada I 2000(26) | ☺ | ☺ | ☺ | ?41 | ☺ | ☺ | ?3 | ☹42 | ☺ | ☺ | ☺ | ☺ | ☺ | low |
| **18F-FDG-PET** |  |
| **Giant cell arteritis** |  |
| Blockmans D 2000(27) | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ?3 | ?3 | ☺ | ☺ | ☺ | ☺ | ☹43 | mod |
| Lariviere D 2016(28) | ☺ | ☺ | ?3 | ☺ | ☺ | ☺ | ?3 | ?3 | ☺ | ☺ | ☺ | ☺ | ☺ | low |
| **Computed tomography angiography** |  |
| **Giant cell arteritis** |  |
| Lariviere D 2016(28) | ☺ | ☺ | ?3 | ☺ | ☺ | ☺ | ?3 | ?3 | ☺ | ☺ | ☺ | ☺ | ☺ | low |
| **Takayasu arteritis** |  |
| Yamada I 1998(29) | ☺ | ☺ | ?3 | ☺ | ☺ | ☺ | ?3 | ☹42 | ☺ | ☺ | ☺ | ☺ | ☺ | low |

RoB, overall appraisal of risk of bias and concerns about applicability (arbitrarily defined) (high, in the case of concern on ≥5/10 risk of bias items or concern on 3/3 applicability items out of the QUADAS-2 tool; moderate, in case of concern on 4/10 risk of bias items and/or concern on ≥1/3 applicability items out of the QUADAS-2 tool, low, in case of concern on ≤3/3 risk of bias items and no concern about applicability);

1 patients undergoing temporal biopsy "to rule out the disease" were included

2 only 1 out of 2 investigators performing ultrasound was blinded to clinical data

3 no statement

4 temporal artery biopsy was not performed in all patients

5 performed in a centre for vascular surgery. Only patients referred to biopsy were investigated and therefore, the study might have included only a subgroup of the population of interest

6 bilateral temporal artery biopsies performed in 75% of patients

7 temporal artery biopsies were guided by ultrasound

8 no definition for vasculitis lesions in ultrasound given, different cut-off values (including a cut-off of ≥1mm) were used to define the “halo” sign

9 non-Giant Cell Arteritis (GCA) patients include 12 patients suffering from Polymyalgia rheumatica (PMR) with histologic and clinical evidence for GCA

10 only 26 patients with suspicion of GCA, but 60 patients with suspicion of PMR included; only 20 patients with final diagnosis of GCA, but 75 patients with final diagnosis of PMR, 12 PMR patients with histologic evidence for GCA

11 investigator performing ultrasound was not blinded to clinical data

12 no details about “suspicion” of GCA, no patient´s characteristics, no details about glucocorticoid treatment, performed in an ophthalmologic unit where presumably only a part of all GCA patients are followed

13 no detailed description of the performance of ultrasound, image examples are not characteristic and raise some concern

14 67 out of 115 patients with suspicion of GCA were included in the study, only some reasons for exclusions described

15 no definition for suspicion of GCA and patients´ characteristics given, patients in a department of neurology possibly represent only a subset of GCA patients

16 almost all (79/83) GCA patients were on glucocorticoid treatment for >6 days

17 no patients´ characteristics given, patients referred to ultrasound centre possibly represent only a subpopulation of the patients of interest

18 PMR patients excluded

19 GCA patients (n=5) not completing follow-up were excluded

20 patients (n=17) with atypical presentation (LV-GCA, silent GCA) were excluded

21 patients declining biopsy or those with inconclusive biopsy result were excluded (n=5)

22 no definition of the “halo” sign was given

23 two patients were classified as Takayasu arteritis, no details regarding these patients were given

24 image examples are not characteristic, and this raise some concern

25 ultrasound was blinded to clinical classification of study participants, unless findings were not clearly classifiable as vasculitis. These ultrasound lesions were initially recorded as "suspicious for vasculitis" and reclassified as "vasculitis” if at least one other segment was defined as "vasculitis"

26 in cases with LV-GCA, the result of ultrasound examination influenced the clinical diagnosis

27 final diagnosis of GCA was influenced by ultrasound result, biopsy was guided by ultrasound

28 result of ultrasound examination was communicated after 2 weeks to clinicians on request if glucocorticoid withdrawal was considered because of a working diagnosis other than GCA

29 only 4 out of 24 sonographers had experience with GCA, only part of examiners passed ultrasound test by first attempt

30 high variability of biopsy results, only a minority of biopsies were performed according to BSR recommendations

31 different field strengths (1.5T and 3T) were used for the study

32 only patients undergoing temporal artery biopsy were included, however, the indication for performing a biopsy was not described

33 patients with incomplete follow-up after MRI were excluded, no exact data on attrition were available

34 the study included only patients with an available MRI of deep temporal artery/muscle and a temporal artery biopsy

35 patients without temporal artery biopsy were excluded

36 patients with unclear diagnoses were excluded

37 only 23% of patients fulfilling the ACR criteria had a positive temporal artery biopsy result

38 mean time on glucocorticoids when MRI and temporal artery biopsy were performed: 8 days (up to 48) and 14 days (up to 60), respectively

39 171/171 underwent temporal artery biopsy, however there were only 23% positive biopsy results in patients fulfilling the ACR criteria (137/171). Rheumatologists’ final diagnosis was available for 162/171 patients and it was GCA in 48% of cases (78/162).

40 only patients with indication for a biopsy were included, it remains unclear whether patients with a clear-cut diagnosis were not recruited

41 description raised concerns on possible interpretation of magnetic resonance angiography and conventional angiography by both radiologists

42 within 3 months

43 GCA and PMR patients were not treated separately for the calculation of the diagnostic value of positron emission tomography

**3. STUDIES ASSESSING OUTCOME PREDICTION**

*3.1. Main characteristics and results*

**Supplementary Table S7.** Summary of study characteristics and main findingsfor outcome prediction of ultrasound, magnetic resonance imaging ± angiography, computed tomography ± angiography and 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) in giant cell arteritis (GCA)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **inclusion criteria** | **n final diagn GCA\*** | **n pat** **follow-up****(%)** | **time period****FU** | **investigated structures** | **time to change** | **investigated outcome** | **comparison performed** | **summary of findings** |
|  |  |  |  |  | **Ultrasound** |  |  |  |  |
| Schmidt WA 2008(31) | new diagnosis GCA | 106 | 60(57) | 50 ± 31m | TA, subclavian, axillary, brachial | NR | AIONamaurosis fugaxarterial hypertensiondiabetes mellitusPAODstrokemyocardial infarctionaortic aneurysmsmalignancyosteoporosisosteoporotic fracturesstop GC medicationGC dose¥◊#duration GC therapy (m)¥ | LV-GCA*vs*c-GCA | trend ↑ risk for PAOD (P=0.07) in LV-GCA patientstrend ↑ risk for osteoporotic fractures (P=0.09) in LV-GCA patients |
| DeMiguel E 2012(32) | new diagnosis. cranial GCA + relapse | 30 | 28(93) | every 2 wk - 1st mevery 4 wk till halo disappearance | TA | 8¥ (2-30)‡ wk | halo disappearance | >1*vs* 1 TA branch(es) involved | halo disappearance after 12.6 vs. 6.5 wk¥ (P<0.01) |
|  |  |  |  |  | **18F-FDG PET** |  |  |  |  |
| Blockmans D 2006(33) | suspected GCA | 35 | 22 (63) – 3m14 (40) – 6m | at 3m + 6m | aorta, subclavian, axillary, carotid, iliac, femoral | NR | semiquantitative vascular score (TVS,0-21) | remission*vs*relapse | at 3m: no difference of TVS¥ in patients with remission *vs* those with relapse (3.3 *vs* 1.8, NS)at 6m: no difference of TVS¥ in patients with remission *vs* those with relapse (4.8 *vs* 2.8, NS) |
| Blockmans D 2008(34) | TAB proven GCA + PET at diagnosis | 54 | 46(58) | 47 ± 30m | aorta(6 levels) | NR | dilatation | PET+*vs*PET-  | ↑ diameter¥ of ascending aorta in PET+ (40mm) *vs* PET- patients (37mm, P=0.025) ↑ diameter¥ of descending aorta in PET+ (34mm) *vs* PET- patients (31mm, P=0.044)↑ volume thoracic aorta¥ in PET+ (253cm3) *vs* PET- patients (301cm3, P=0.029)  |
|  | **Computed tomography angiography** |
| Garcia-Martinez A 2014(35) | TAB proven GCA | 54 | 54 – 1st screen (100)36 – 2nd screen (67)14 – 3rd screen (26) | 5.4y – 1st screen8.7y – 2nd screen12.3y – 3rd screen | aorta | NR | ASD | ASD*vs*no ASD | trend↑mortality (any cause) for ASD patients (P=0.08)† |

\*no study on outcome prediction for TAK was identified by the systematic literature review. ¥ mean; ‡ range; † no detailed data reported; ◊ patients on steroids (mg/day); # all patients (mg/day); ↑ increased;

AION; acute ischaemic opticus neuropathy; ASD, aortic structural damage (defined as dilatation or aneurysm); APR, acute phase reactants; compar, comparator; CT, computed tomography; GCA, giant cell arteritis; LV, large vessel; m, months; n final diagn GCA, number of patients finally diagnosed with GCA; NR, not reported; NS, not significant; Pat in FU, number of patients undergoing follow-up; PET, 18F-FDG positron emission tomography; PET+, GCA patients presenting with 18F-FDG uptake in positron emission tomography; PET-, GCA patients without 18F-FDG uptake in positron emission tomography; P, p-value; PAOD, peripheral arterial occlusive disease; pat, patients; PET, 18F-FDG positron emission tomography; TA, temporal artery/-ies; TAB, temporal artery biopsy; TVS, total vascular score; wk, week, y, year

*3.2. Details of the risk of bias assessment*

For studies on outcome prediction, the risk of bias (RoB) was appraised independently by the two reviewers (CDe, Cdu) using the Quality In Prognosis Studies (QUIPS) tool evaluating the following domains: study participation, attrition, prognostic factor management, outcome measurement, study confounding, and statistical analysis/reporting. Each domain is rated as high, low or unclear, with “high” designating a high RoB.(36)

**Risk of bias**

Domain 1 – study participation:

Signalling question 1 (source of target population): Is the source population or population of interest adequately described for key characteristics?

Signalling question 2 (method used to identify population): Are the sampling frame and recruitment adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)?

Signalling question 3 (recruitment period): Is the period of recruitment adequately described?

Signalling question 4 (place of recruitment): Are the place of recruitment (setting and geographic location) adequately described?

Signalling question 5 (inclusion and exclusion criteria): Are the inclusion and exclusion criteria adequately described (e.g., including explicit diagnostic criteria or “zero time” description)?

Signalling question 6 (adequate study participation): Is there adequate participation in the study by eligible individuals?

Signalling question 7 (baseline characteristics): Is the baseline study sample (i.e., individuals entering the study) adequately described for key characteristics?

Summary (study participation):The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between prognostic factor and outcome.

Domain 2 – study attrition:

Signalling question 1 (proportion of baseline sample available for analysis): Is the response rate (i.e., proportion of study sample completing the study and providing outcome data) adequate?

Signalling question 2 (attempts to collect information on participants who dropped out): Are reasons for loss to follow-up are provided? If a threshold was used, was it pre-specified?

Signalling questions 3 (outcome and prognostic factor information on those lost to follow-up): Are participants lost to follow-up adequately described for key characteristics? Are there no important differences between key characteristics and outcomes in participants who completed the study and those who did not?

Summary (study attrition): Loss to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.

Domain 3 – prognostic factor measurement:

Signalling question 1 (definition of the prognostic factor): Is a clear definition or description of the prognostic factor provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement)?

Signalling questions 2 (valid and reliable measurement of the prognostic factor): Is the method of the prognostic factor measurement adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall)? Are continuous variables reported or appropriate cut-points (i.e., not data-dependent) used?

Signalling question 3 (method and setting of prognostic factor measurement): Is the method and setting of measurement of the prognostic factor the same for all study participants.

Signalling question 4 (proportion of data on prognostic factor available for analysis): Has an adequate proportion of the study sample complete data for the prognostic factor variable?

Signalling question 5 (method used for missing data): Are appropriate methods of imputation used for missing prognostic factor data.

Summary (prognostic factor measurement): The prognostic factor is adequately measured in study participants to sufficiently limit potential bias.

Domain 4 – outcome measurement:

Signalling question 1 (definition of the outcome): Is a clear definition of outcome provided, including duration of follow-up and level and extent of the outcome construct?

Signalling question 2 (valid and reliable measurement of outcome): Is the method of outcome measurement used adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).

Signalling question 3 (Valid and Reliable Measurement of Confounders): Is the method and setting of outcome measurement the same for all study participants?

Summary (outcome measurement): Outcome of interest is adequately measured in study participants to sufficiently limit potential bias.

Domain 5 – study confounding:

Signalling question 1 (important confounders measured): Are all important confounders, including treatments (key variables in conceptual model), measured?

Signalling question 2 (definition of the confounding factor): Are clear definitions of the important confounders measured provided (e.g., including dose, level, and duration of exposures)?

Signalling question 3 (valid and reliable measurement of confounders): Is the measurement of all important confounders adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall)?

Signalling question 4 (method and setting of confounding measurement): Are the method and setting of confounding measurement the same for all study participants?

Signalling question 5 (method used for missing data): Are appropriate methods used if imputation is used for missing confounder data?

Signalling questions 6 (appropriate accounting for confounding): Are important potential confounders accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups)? Are important potential confounders accounted for in the analysis (i.e., appropriate adjustment)?

Summary (study confounding): Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between the prognostic factor and outcome.

Domain 6 – statistical analysis and reporting:

Signalling question 1 (presentation of analytical strategy): There is sufficient presentation of data to assess the adequacy of the analysis?

Signalling questions 2 (model development strategy): Is the strategy for model building (i.e., inclusion of variables in the statistical model) appropriate and based on a conceptual framework or model? Is the selected statistical model adequate for the design of the study?

Signalling question 3 (reporting of results): Is there no selective reporting of results?

Summary (statistical analysis and reporting): The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.

Icons indicate a low (☺), high (☹) or unclear (?) risk of bias depicting the summary rating to the corresponding questions of evaluation.

**Supplementary Table S8.** Risk of bias assessment of studies outcome prediction of imaging techniques

|  |  |
| --- | --- |
| **STUDY** | **RISK OF BIAS** |
|  | **STUDY PARTCIPATION** | **STUDY ATTRITION** | **PROGNOSTIC FACTOR MANAGEMENT** | **OUTCOME MEASUREMENT** | **STUDY CONFOUNDING** | **STATISTICAL ANALYSIS/ REPORTING** | **OVERALL RATING** |
| **Ultrasound** |  |
| **Giant cell arteritis** |  |
| Schmidt WA 2008(31) | ?1 | ☹2 | ?3 | ☹4 | ?5 | ?6 | high |
| DeMiguel E 2012(32) | ☹7 | ☺ | ☺ | ☺ | ☹8 | ☹9 | mod |
| **18F-FDG-PET** |  |
| **Giant cell arteritis** |  |
| Blockmans D 2006(33) | ☺/☹10 | ☺ | ?/☹10 | ☺ | ?11 | ?11 | mod |
| Blockmans D 2008(34) | ☹12 | ☹13 | ☺ | ? 14 | ☹15 | ? 16 | mod |
| **Computed tomography** |  |
| **Giant cell arteritis** |  |
| Garcia-Martinez A 2014(35) | ☹17 | ☹18 | ?19 | ☺/?20 | ☹8 | ☹9 | high |

1 selection of Giant Cell Arteritis (GCA) controls was unclear

2 different time periods of follow-up in Large Vessel (LV)-GCA (40 months) and GCA control (59 months) groups

3 different proportions of patients in both groups (LV-GCA 40/53, GCA control 20/40) underwent follow-up

4 inconsistent follow-up of outcome parameters and prognostic factors. Outcome parameters (e.g. eye involvement, length of glucocorticoid therapy) were sparsely or not described

5 only age, sex and symptom duration were accounted for in the analysis

6 the statistical model neither included sensitivity analyses nor was the possibility of negative confounding addressed

7 patients with new diagnosis and relapsing GCA were pooled resulting in a high risk of selection bias

8 lack of details on possible confounding factors and whether they were accounted for in statistical analysis

9 only basic statistical analyses performed, without using risk models. High risk of selective reporting of data

10 unclear risk of bias for baseline 18F-FDG-positron emission tomography (18F-FDG-PET) score mainly because no cut-off was provided. High risk for the reduction of FDG uptake as no definition for normal and abnormal findings was provided

11 confounding factors were either not addressed, or no adjustment for confounding factors was performed. However, as there was no association between prognostic factors and outcomes observed, there is only a small risk of negative confounding

12 GCA patients with 18F-FDG-PET at diagnosis were included, possibly not reflecting the whole spectrum of the disease, no details about patients` characteristics were reported

13 only 46/79 (58%) eligible patients were included in the final analysis

14 inconsistent follow-up of outcome parameter

15 not all relevant confounding factors were considered (e.g. baseline aortic diameter, smoking), incomplete data description

16 selective outcome bias is likely

17 only patients with follow-up were included in the analysis (54/125, 43%), details on patients’ selection was provided partially

imaging modalities [computed tomography (CT), ultrasound]

18 only a proportion of patients underwent follow-up, those patients were not described for key characteristics

19 only a proportion of patients underwent a CT scan (44/54, 82%)

20 low risk of bias for death, moderate risk of bias for aortic structural damage, because not all patients received the same imaging test for evaluating aortic damage

**4. STUDIES ASSESSING MONITORING DISEASE ACTIVITY**

*4.1. Main characteristics and results*

**Supplementary Table S9.** Summary of study characteristics and main findingsfor studies on monitoring disease activity on ultrasound, magnetic resonance imaging ± angiography, computed tomography ± angiography and 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) in giant cell arteritis (GCA) and Takayasu arteritis (TAK)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **inclusion criteria** | **n final diagnosis GCA/TAK** | **n Pat FU****(%)** | **time period FU** | **investigated structures** | **time to change** | **outcome** | **comparison performed** | **summary of findings** |
| **Ultrasound** |
| **Giant cell arteritis** |
| Schmidt WA 1997(1) | suspected GCA+PMR | 30 | 22(73) | every 3-4dtill halo disappearance | TA | 16d\*7-56d¥ | halo disappearance | none | halo disappearance after16d\* (7-56d)¥# |
| Salvarani C 2002(4) | suspected GCA+PMR | 20 | 6(30) | at 1m | TA | NR | halo disappearance | none | halo disappearance in 6/6 pat# |
| Schmidt WA 2002(37) | new diagnosis GCA | 33 | 10(30) | 9-21d for c-GCA,at 6 + 24m for LV-GCA | NR | 16d\* for c-GCA9-21d\* for LV-GCA | halo disappearancenew halo/occlusions | none | halo disappearance in 7/8 c-GCA pat after 16d\*, in LV-GCA pat halo disappearance was reported within 9-21d¥; occurrence of new halos/occlusions in 1/8 c-GCA and 2/2 LV-GCA pat# |
| Pfadenhauer K 2003(6) | suspected GCA | 40 | 5(13) | NR | TA, occipital | 13-42d¥ | halo + stenoses disappearancerecanalisation occlusions | none | halo and stenoses disappearance in 3/5 pat, recanalisation of occlusions in 2/5 patientsafter 13-42d¥# |
| Karahaliou M 2006(9) | ESR >50 mm/h, headache, jaw claudication, fever, PMR, TA tenderness, visual impairment | 22 | 18(82) | every 2 wk for 3m | TA | 22d\* | halo + stenoses disappearancerecanalisation occlusion | none | halo disappearance after 22d\*(9/18 pat at wk 2, 9/18 pat at wk 4)#  |
| Schmidt WA 2008(31) | new diagnosis GCA | 106 | 60(57) | 41m for c-GCA39m for LV-GCA | subclavian, axillary, brachial | NR | resolutionimprovementunchangedworse | none | US signs of vasculitis resolved in 30%, improved in 53%, remained unchanged in 8%, worsened in 10% of pat# |
| Perez-Lopez J 2009(38) | suspected GCA+PMR | 30 | 26(22 GCA/4 PMR)(87) | at wk 6 + 6m | TA | NR | halo disappearancehalo persistence | symptoms, laboratory findings† | halo disappearance in 50% of pat at wk 6, halo persistence in 10/18 (symptom free) pat at 6m# |
| Aschwanden M 2010(12) | suspected cGCA + LV-GCA (PET, ESR >50 mm/h, age>50y) | 38 | 9 LV-GCA(75) | at 6m | carotid, vertebral, subclavian, axillary, femoral, popliteal | NR | resolutionpersistencenew vasculitic lesions | none | US signs of vasculitis resolved in 8/84 segments, persisted in 76/84 segments; new vasculitic lesions occurred in 1 patient at 2 segments# |
| DeMiguel E 2012(32) | new diagnosis GCA+ relapse | 30 | 30(100) | every 2 wk - 1st mevery 4 wk – till halo disapp | TA | 10 wk\*2-30 wk¥ | halo disappearance | none | halo disappearance in 36/38 patafter 10 wk\* (2-30 wk)¥# |
| Habib HM 2012(13) | ESR >50 mm/h, headache, jaw claudication, fever, PMR, TA tenderness, visual impairment | 16 | 15(81) | at wk 2,4,8,12 | TA | 21d‡ | halo disappearancepersistence of stenoses/occlusions | clinical, laboratory findings†  | halo disappearance in 13/13 pat after 21d‡:(9 pat at wk 2, 4 patients at wk 4)stenoses and occlusions persisted during FU# |
| **Takayasu arteritis** |
| Fan W 2016(39) | TAK(ACR criteria) | 51 | 51(100) | NR | carotid | NR | wall thickness,outer vessel wall diameter | none | no correlation of US vasculitic lesions with remission or relapse# |
| **Magnetic resonance imaging** |
| **Giant cell arteritis** |
| Both M 2008(40) | GCA(ACR criteria)with complications | 25 | 11(36) | NR | aorta, supra-aortic arteries | NR | MRI score(0-12) | ESR, CRP, BVAS | no correlation of ΔTVS with ΔESR, ΔCRP, ΔBVAS changes during FU |
| **Takayasu arteritis** |
| Sun Y 2016(41) | TAK(ACR criteria) | 52 | 15(29) | at 6m | NR | NR | wall enhancement scoresluminal stenosisvessel wall thickening | none | at 6m wall enhancement scores\* decreased from 7 to4 (P=0.04)wall thickening and luminal stenoses remained unchanged |
| **18F-FDG PET** |
| **Giant cell arteritis** |
| Blockmans D 2006(33) | suspected GCA | 35 | 22 (63) – at 3m14 (40) – at 6m | at 3m + 6m | aorta, subclavian, axillary, carotid, iliac, femoral | NR | semiquantitative vascular score (TVS, 0-21) | none | at 3m TVS\* decreased from 9 to 2 (P<0.001)no further TVS decrease was reported at 6mno correlation of TVS with relapse |
| Both M 2008(40) | GCA (ACR criteria) with complications | 25 | 9(36) | NR | aorta, supra-aortic, lower extremity arteries | NR | semiquantitative vascular score (TVS, thoracic PET: 0-12, whole body PET: 0-18) | none | only thoracic PET score was associated with ∆ESR (r=0.68, P<0.05)no correlation of whole body PET activity score with ∆ESR, ∆CRP, ∆BVAS |
| **Computed tomography angiography** |
| **Giant cell arteritis** |
| Prieto-Gonzalez 2015(42) | TAB proven GCA | 40 | 35(88) | 13.5m | aorta, brachiocephalic trunk, carotid, subclavian, axillary, splanchnic renal, iliac, femoral | NR | wall thickness n involved vesselsenhancement | none | wall thickness\* decreased from 2.7 to 1.2mm at different aortic levels (all with P<0.05)n involved vessels decreased from 66 to 37†#contrast enhancement decreased in 15/16 patients†#overall vessel wall thickening persisted in 68% of patients during FU |

\* mean; ¥ range; # only descriptive results, no interference reported, ‡ median; † no detailed results/statistics reported, Δ change;

ACR, American College of Rheumatology; BVAS, Birmingham vasculitis activity score; c, cranial; CRP, C-reactive protein; d, days; ESR, erythrocyte sedimentation rate; FU, follow-up; GCA, giant cell arteritis; LV, large vessel; m, months; n, number; n pat FU, number of patients in follow-up; n pat final diagn GCA, number of patients finally diagnosed with GCA; NR, not reported; Pat, patients; PET, 18F-FDG positron emission tomography; PMR, Polymyalgia rheumatica; TA, temporal artery/-ies; TAB, temporal artery biopsy; TVS, total vascular score; US, ultrasound; wk, week; y, year

*4.2. Details of the risk of bias assessment*

For studies on monitoring, no quality assessment was performed, because identified studies were mainly descriptive, hence no adequate quality assessment could be performed.

**5. STUDIES ASSESSING TECHNICAL ASPECTS**

*5.1. Main characteristics and results*

**Supplementary Table S10.** Summary of study characteristics and main findingsfor studies on technical aspects on magnetic resonance imaging (w/wo angiography) and 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) in giant cell arteritis (GCA)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **n** | **inclusion criteria** | **n final diagn GCA** | **investigated structures** | **intervention** | **comparison performed** | **outcome** |
| **Magnetic resonance imaging** |
| Geiger J 2010(20) | 43 | suspected GCA | 28 | TA, occipital | T2 weighted imaging | contrast enhanced T1 weighted MRI | NR\*excellent interobserver agreement (=0.89) and correlation measurement wall thickness between T2 and CE T1 (r=0.82; P<0.001) |
| Franke P 2014(21) | 55 | suspected GCA | 14 | TA, occipital | 32-channel head coil | 12-channel head coil | Sens of 90% for 32-channel head coil, 83% for 12-channel head coil, Spec 100% for both channel head coilsexcellent interobserver agreement for 32- (=0.89) and 12-channel head coils (=0.96)increased SNR for 32- compared to 12-channel head coil (P<0.01) |
| **18F-FDG PET** |
| Hautzel H 2008(43) | 23 | suspected LV-GCA | 18 | aorta | TBR (SUV aorta/liver) in LV-GCA pat | TBR (SUV aorta/liver)in control group | TBR† 1.2 vs. 0.8 in LV-GCA patients *vs* controls I (P<0.01)TBR cut-off of 1 shows Sens 89% and Spec 95% for diagnosis of LV-GCAminor changes of hepatic metabolism did not influence results |
| Martinez-Rodriguez I 2013(44) | 23 | suspected GCA, assessment of disease activity in diagnosed LV-GCA | NR | supra-aortic truncs, aorta, iliac, femoral, tibioperoneal arteries | delayed acquisition (after 180min) | early acquisition (after 60min) | NR\* |
| Martinez-Rodriguez I 2014(45) | 43 | suspected LV-GCA | 25 | aorta | TBR (SUVmax aortic wall/lumen) in aortitis pat | TBR (SUVmax aortic wall/lumen) in non-aortitis pat | mean† TBR 1.7 *vs* 1.2 in aortitis *vs* non-aortitis patients (P<0.0001)TBR cut-off of 1.34 shows Sens 100% and Spec 94% for diagnosis of aortitis |

\*no direct comparison between two methods performed; † mean

GCA, giant cell arteritis; LV, large vessel; LVV, large vessel vasculitis; min, minutes; MRI, magnetic resonance imaging; NR, not reported; n, number of patients included in study; n final diagn GCA, number of patients finally diagnosed with GCA; Sens, sensitivity, SNR, signal to noise ratio; Spec, specificity; SUV, standardized uptake value; TA, temporal artery/-ies; TBR, target to background ratio

*5.2. Details of the risk of bias assessment*

For studies on technical aspects, no quality assessment was performed, because identified studies were mainly descriptive, hence no adequate quality assessment could be performed.

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