**Definitions and Reliability Assessment of Elementary Ultrasound Lesions in Giant Cell Arteritis: A Study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group**

**Supplementary material**

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1. **METHODS SYSTEMATIC LITERATURE REVIEW**
	1. **Literature review**

In order to retrieve all studies providing a definition for ultrasound (US) abnormalities suggestive of large vessel vasculitis (LVV), we systematically searched for studies on the role of US in diagnosis, outcome prediction and monitoring disease activity or damage of LVV as well as for cross-sectional studies addressing the involvement of cranial and extra-cranial large arteries in patients suffering from GCA and/or polymyalgia rheumatica (PMR). The key questions were framed in the PICO format (Population, Intervention, Comparator, Outcome) as detailed in Online Supplementary Tables S1a-c. The population of interest consisted of adult patients (≥18 years) with a suspected LVV (for diagnostic studies: giant cell arteritis (GCA), Takayasu arteritis (TAK) and idiopathic aortitis) and/or established primary LVV and/or PMR for cross-sectional studies and for studies on monitoring of disease activity or damage, or prognosis. Given the frequent involvement of extra-cranial large arteries in PMR patients and the high probability that US changes of LVV had been defined and reported in studies screening PMR patients for the presence of LVV, we also included US studies on patients with established PMR in our search. For diagnostic accuracy of US in GCA, physician’s clinical diagnosis (at first assessment, but also during follow-up) and temporal artery biopsy (TAB) were accepted as reference standards. For TAK, conventional angiography was accepted as reference standard in addition to physician´s clinical diagnosis. Full research reports (excluding research letters, abstracts) of cohort and case-control studies with prospective and retrospective design enrolling at least 20 patients were eligible, as well as cross-sectional and longitudinal studies with n≥20.

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

|  |
| --- |
| What is the value of **[ultrasound]** (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” was not defined by any specific criteria for this SLR. Statements such as LVV “was suspected”, or patients “were referred for assessment of possible LVV” were acceptable, as were combinations of various clinical symptoms with/without laboratory results to define the target population |
| Intervention | ultrasound |
| comparator  | temporal artery biopsy, physician’s diagnosis at baseline and diagnosis including follow-up analyses |
| outcome  | test performance reflected in sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios |

GCA, giant cell arteritis; SLR, systematic literature review; TAK, Takayasu arteritis; LVV, large vessel vasculitis

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

|  |
| --- |
| In primary LVV (Population), what is the value of positive **[ultrasound]** (Intervention) to predict outcome (Outcome) compared to negative [imaging] (Comparator)? |
| population | patients with primary LVV, particularly cranial and/or extra-cranial large vessel GCA, TAK and isolated aortitis, according to physicians’ final diagnosis |
| intervention | ultrasound |
| 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 the 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; ESR, erythrocyte sedimentation rate; GC, Glucocorticoid; GCA, giant cell arteritis; TAK, Takayasu arteritis; SLR, LVV, large vessel vasculitis

**Online Supplementary Table S1c.** Key questions of ultrasound on **monitoring**

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

GCA, giant cell arteritis; TAK, Takayasu arteritis; LVV, large vessel vasculitis

* 1. **Study selection, data extraction and assessment of risk of bias**

The systematic literature review (SLR) was conducted by two reviewers (CDu and CDe). The MEDLINE, EMBASE and the Cochrane library databases were searched for articles published in German or English (because of German mother language of both reviewers) from their inception dates (1946, 1974 and 1993, respectively) until November 23rd,2014. The search strategy was based on combinations of index terms (MeSH), text words/phrases and truncated words (Online Supplementary Text S1).

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

Exp, explode; \*, truncation; /, Mesh term; mp, keyword; ADJ, adjacent

**MEDLINE**

1. exp Giant Cell Arteritis/
2. (temporal ADJ2 arteritis).mp.
3. (giant ADJ2 cell ADJ2 arteritis).mp.
4. Horton.mp
5. GCA.mp
6. exp Aortitis/
7. exp Takayasu Arteritis/
8. (Takayasu ADJ2 arteritis).mp.
9. (large ADJ2 vessel ADJ2 vasculitis).mp.
10. (large ADJ2 vessel ADJ2 arteritis).mp.
11. LVV.mp.
12. (giant ADJ2 cell ADJ2 Aortitis).mp.
13. (aortitis adj2 syndrome).mp.
14. (Tak\* adj2 arteritis).mp.
15. OR/1-14
16. exp Ultrasonography/
17. ultrasound.mp
18. ultrasonograph\*.mp.
19. sonograp\*.mp.
20. (Colour ADJ2 Doppler).mp.
21. (Duplex adj2 ultrasound).mp.
22. Duplex.mp.
23. OR/16-22
24. 15 AND 23

**EMBASE**

1. exp Giant Cell Arteritis/
2. (temporal ADJ2 arteritis).mp.
3. (giant ADJ2 cell ADJ2 arteritis).mp.
4. Horton.mp
5. GCA.mp
6. exp Aortitis/
7. exp Takayasu Arteritis/
8. (Takayasu ADJ2 arteritis).mp.
9. (large ADJ2 vessel ADJ2 vasculitis).mp.
10. (large ADJ2 vessel ADJ2 arteritis).mp.
11. LVV.mp.
12. (giant ADJ2 cell ADJ2 Aortitis).mp.
13. (aortitis adj2 syndrome).mp.
14. (Tak\* adj2 arteritis).mp.
15. OR/1-14
16. exp Ultrasonography/
17. ultrasound.mp
18. ultrasonograph\*.mp.
19. sonograp\*.mp.
20. (Colour ADJ2 Doppler).mp.
21. (Duplex adj2 ultrasound).mp.
22. Duplex.mp.
23. OR/16-22
24. 15 AND 23

**THE COCHRANE LIBRARY**

1. Giant Cell Arteritis.mp.
2. Temporal Arteritis.mp.
3. Takayasu Arteritis.mp.
4. Aortic Syndromes.mp.
5. Aortitis.mp.
6. OR/1-5
7. Ultrasonography.mp.
8. Ultrasound.mp.
9. Colour Doppler.mp.
10. Duplex.mp.
11. OR/7-10
12. 6 AND 11

The reviewers independently screened all titles and abstracts to identify potentially eligible studies which were then reviewed in full-text. Papers fulfilling the inclusion criteria were proceeded to data extraction. Both reviewers independently retrieved the data using a pre-defined data extraction sheet. The following data were extracted in addition to the definition(s) of US key lesions of LVV: studies’ main characteristics [year of publication, setting, number of included patients, inclusion criteria, use of glucocorticoids (GC) before performance of US], patient characteristics [number (%) of females, patients’ age], disease characteristics [number (%) of patients fulfilling clinical criteria for GCA or TAK, number (%) of patients with positive TAB, number (%) of patients with the extra-cranial large vessel (LV)-GCA subset], technical aspects (US devices used, US elementary lesions with details on definitions and structures investigated, description of US settings), index test (lesions identified by the index test that are analysed), reference standard, diagnostic performance [raw data to calculate sensitivity, specificity, positive (LR+) and negative likelihood ratio (LR-)] and parameters required for the assessment of the risk of bias (RoB). For prognostic and monitoring studies the following items were retrieved: study´s aim, inclusion criteria, number of patients included, number (%) of patients with follow-up, period of follow-up, investigated structures, signs and time of change, prognostic factors and outcome, US related data (US devices used, US elementary lesions with details on definitions and structures investigated, description of US settings). For descriptive cross-sectional studies the study´s aim, inclusion criteria, number of patients included, investigated structures, US related data (US devices used, US elementary lesions with details on definitions and structures investigated, description of US settings) were retrieved.

The RoB of the diagnostic and prognostic studies was also appraised independently by the same two reviewers conducting the SLR. For studies on diagnostic accuracy, the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool was used comprising four domains: patient selection, index test, reference standard, as well as flow and timing. Each of these domains was evaluated as having a “low”, “high” or “unclear” RoB, whereas concerns about applicability were evaluated in the first three domains also as “low”, “high” or “unclear”.(1) The overall judgement of study quality as depicted in Online Supplementary Tables 1 and 3 was arbitrarily defined: low, if there were concerns in ≥5/10 RoB items and/or concerns of applicability in 3/3 items; moderate, if there were concerns in 4/10 RoB and/or concerns in ≥1/3 applicability items; and high, if there were concerns in ≤3/10 RoB items and in none of the applicability parameters.(2)

The Quality In Prognosis Studies (QUIPS) tool was applied for the assessment of prognostic studies evaluating the following aspects: study participation and attrition, prognostic factor measurement, outcome measurement, study confounding as well as statistical analysis/reporting. For each QUIPS domain, the RoB was rated as “high”, “moderate”, “low” or “unclear”.(3) For retrospective diagnostic accuracy studies or cross-sectional studies evaluating the LV-involvement in GCA and PMR patients, a RoB assessment was not possible, because the QUADAS-2 tool was developed for the evaluation of prospective studies; hence, the individual items of the QUADAS-2 are not applicable to retrospective and cross-sectionals studies. Besides, retrospective and cross-sectional studies were mainly descriptive as detailed below.

Discrepancies between reviewers regarding study selection, data extraction and RoB assessment were solved by discussion.

* 1. **Data analysis**

Descriptive statistics was used to report data. Frequencies and percentages were shown for categoricalvariables, individual results on the diagnostic performance were reported.

1. **RESULTS SYSTEMATIC LITERATURE REVIEW**

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

**2.1. STUDIES ASSESSING DIAGNOSTIC ACCURACY**

*2.1.1. Main characteristics and results*

**Online Supplementary Table S2.** Main characteristics of diagnostic studies on ultrasound (US) in giant cell arteritis (GCA).1 Retrospective and case-control studies are italicised.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **n**  | **n female****(%)** | **study design** | **inclusion criteria** | **reference****standard** | **n final diagn GCA (%)** | **n TAB+****(%)** | **n LV-GCA** | **investigated****structures** | **elementary lesions** | **quality assessment** |
| Schmidt WA 1997(4) | 112 | NR | prospectivecohort | suspected GCA + PMR | ACR criteriaor TAB | 30(27) | 21(78) | NR | TA | halostenosis/occlusionhalo/stenosis/occlusion | high |
| Venz S1998(5) | 20 | 12(60) | prospective cohort | suspected GCA | TAB | 6(30) | 6(30) | NR | TA | halostenosis | high |
| LeSar CJ2002(6) | 32 | 21(66) | prospectivecohort | suspected GCA | TAB | 7(22) | 7(100) | NR | TA | halostenosishalo/stenosis | high |
| Nesher G2002(7) | 69 | NR | prospectivecohort | suspected GCA | clinical diagn 6mor TAB | 14(20) | 9(64) | NR | TA | halo | high |
| Salvarani C 2002(8) | 86 | 55(64) | prospectivecohort | suspected GCA + PMR | ACR criteriaor TAB | 20(23) | 15(75) | NR | TA | halo | high |
| Schmid R2002(9) | 20 | 11(55) | prospectivecohort | headache, AION, temporal tenderness, TA abnormality, jaw claudication, lockjaw, PMR | ACR criteriaor TAB | 15(75) | 12(80) | NR | TA | halo | high |
| Murgatroyd H 2003(10) | 26 | NR | prospectivecohort | suspected GCA | TAB | 7(27) | 7(100) | NR | TA | halo | high |
| Pfadenhauer K 2003(11) | 67 | 51(76) | prospectivecohort | suspected GCA | ACR criteriaor TAB | 40(60) | 33(83) | NR | TA, occipital | halo/stenosis/occlusion | high |
| Reinhard M 2004(12) | 83 | 49(59) | prospectivecohort | NR | ACR criteriaor TAB | 43(52) | 33(77) | NR | TA | haloocclusionconspiciuous vessel wall pulsation | high |
| Romera-Villegas A 2004(13) | 68 | 48(71) | prospectivecohort | suspected GCA | TAB | 22(32) | 22(100) | NR | TA | halo/stenosis/occlusion | low |
| Karahaliou M 2006(14) | 55 | 30(55) | prospectivecohort | ESR >50 mm/h, headache, jaw claudication, fever, PMR, TA tenderness, visual impairment | clinical diagn 3mor TAB | 22(40) | 18(82) | NR | TA | halostenosis | low |
| *Bley T**2008*(15) | *59* | *32**(54)* | *retrospective**cohort* | *suspected GCA + US**+ MRI2* | *clinical diagn ≥6m**or TAB* | *36**(61)* | *24**(67)* | *NR* | *TA* | *halo* | *NA* |
| Ghinoi A2008(16) | 20 | 15(75) | prospectivecohort | suspected GCA | ACR criteriaor TAB | 11(55) | 9(82) | NR | TA | halo | low |
| *Perez-Lopez J**2009*(17) | *60* | *18**(38)* | *prospective**case-control* | *suspected GCA**+ PMR**+ controls*  | *ACR criteria* *or PMR class**criteria*(18)*or TAB* | *30**(64)* | *29**(97)* | *NR* | *TA, ophthalmic* | *halo**stenosis**halo/stenosis (TA)**halo/stenosis (TA+ophthalmic)* | *NA* |
| Aschwanden M 2010(19) | 72 | 45(63) | prospectivecohort | suspected GCA,suspected LV-GCA (PET+, ESR >50 mm/h, age>50y) | ACR criteria | 38(53) | 35(95) | 12 | TA, carotid, vertebral, subclavian, axillary, femoral, popliteal | halo/stenosis | mod |
| *Maldini C**2010*(20) | *77* | *49**(64)* | *retrospective**cohort* | *suspected GC* *+ US**+ TAB3* | *clinical diagn ≥6m**or TAB* | *19**(25)* | *13**(68)* | *NR* | *TA* | *halo**halo unilateral/**stenosis/occlusion**halo bilateral/**stenosis/occlusion* | *NA* |
| Habib HM 2012(21) | 32 | 19(59) | prospectivecohort | ESR >50 mm/h, headache, jaw claudication, fever, PMR, TA tenderness, visual impairment | clinical diagn 3mor TAB | 16(50) | 15(94) | NR | TA | halo | mod |
| *Hauenstein C 2012*(22) | *59* | *32**(54)* | *retrospective**cohort* | *suspected GCA + US**+ MRI4* | *clinical diagn ≥6m**or TAB* | *36**(61)* | *24**(67)* | *NR* | *TA* | *halo* | *NA* |
| *Pfenninger L 2012*(23) | *57* | *52**(91)* | *retrospective cohort* | *suspected GCA + US**+ TAB5* | *TAB* | *27**(47)* | *27**(47)* | *NR* | *TA* | *halo**halo/stenosis/occlusion* | *NA* |
| Aschwanden M 2013(24) | 80 | 55(69) | prospectivecohort | suspected GCA | ACR criteria | 43(54) | 20(53) | NR | TA | halostenosisocclussioncompression | low |
| *Black R**2013*(25) | *50* | *36**(72)* | *retrospective cohort* | *suspected GCA + US6* | *clinical diagn**or TAB* | *12**(24)* | *5**(42)* | *NR* | *TA* | *halo* | *NA* |
| *Muratore F**2013*(26) | *160* | *NR* | *retrospective**cohort* | *suspected GCA + US**+ TAB5* | *TAB* | *63**(39)* | *63**(39)* | *NR* | *TA* | *halo* | *NA* |
| Diamantopoulos A 2014(27) | 88 | 54(61) | prospectivecohort | CRP >5 mg/dl, headache, jaw claudication, fever, PMR, TA tenderness, visual impairment | clinical diagn 6mor TAB | 46(52) | 26(67) | 17 | TA, carotids, axillary | halo | low |
| Aschwanden M 2015(28) | 60 | 40(67) | prospectivecohort | suspected GCA | ACR criteria | 24(40) | 13(72) | NR | TA | compression | low |

1no study on diagnostic accuracy of ultrasound for Takayasu arteritis and idiopathic aortitis was identified by the systematic literature review

2suspected GCA + US + MRI, only patients with suspected disease, who underwent both imaging examinations (US and MRI) within 2 weeks and were on glucocorticoid treatment < 2 weeks were eligible for inclusion

3suspected GCA + US + TAB, only patients with suspected disease, who underwent both US and TAB within 30 days were included

4suspected GCA + US + MRI, only patients with suspected disease, who underwent both imaging examinations (US and MRI) within 10 days and were on glucocorticoid treatment < 2 weeks were included

5suspected GCA + US + TAB, only patients with suspected disease, an available ultrasound examination as well as TAB were included

6suspected GCA + US, only patients with suspected disease and an available ultrasound examination were included

ACR, American College of Rheumatology; AION, acute ischemic opticus neuropathy; APR, acute phase reactants; CRP, C-reactive protein; diagn, diagnosis; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; LV, large vessel; mod, moderate; m, months; MRI, magnetic resonance imaging; n, number of finally included patients in analysis; NA, not applicable; n female, number of females; n final diagn GCA, number of patients finally diagnosed with GCA; n LV-GCA, number of GCA patients with extra-cranial large vessel involvement; NR, not reported; n TAB+, number of positive temporal artery biopsy results in finally diagnosed GCA patients; PMR, Polymyalgia rheumatica; PET+, imaging signs suggestive for LV-GCA in positron emission tomography; quality assessment (arbitrarily defined): low, if there were concerns in ≥5/10 RoB items and/or concerns of applicability in 3/3 items; moderate, if there were concerns in 4/10 RoB and/or concerns in ≥1/3 applicability items; and high, if there were concerns in ≤3/10 RoB items and in none of the applicability parameters; TA, temporal artery/-ies; TAB+, patients with a positive histology suggesting vasculitis, US, ultrasound

**Online Supplementary Table S3.** Study characteristics and main findings on the diagnostic accuracy of ultrasound (US) in giant cell arteritis (GCA).1 Retrospective and case-control studies are italicised.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Techn** | **reference****standard** | **US key elementary lesions** | **Sens (%)** | **Spec (%)** | **Sens (%)** | **Spec (%)** | **quality assessment** | **definitions of US key elementary lesions**2 |
|  |  |  |  | **US *vs* clinical diagnosis** | **US *vs* TAB** |  |  |
| Schmidt WA1997(4) | 10 MHz | ACR criteriaor TAB | halostenosis/occlusionhalo/stenosis/occlusion | 738093 | 1009393 | 768695 | 928885 | high | **halo**: NR **(cut-off NR)****stenosis**: blood-flow velocity >2-fold before the stenosis, perhaps with wave forms of turbulence and reduced velocity behind the stenosis**occlusion**: NR |
| Venz S1998(5) | 12 MHz | TAB | halo | NA | NA | 99 | 83 | high | **halo**: hypoechoic, paravasal thickening **(cut-off NR)** |
| LeSar CJ2002(6) | 10 MHz | TAB | halostenosishalo/stenosis | NA | NA | 8643100 | 928480 | high | **halo**: hypo-/anechoic region surrounding the perfused lumen of TA or branches for a discrete region **(cut-off NR)****stenosis**: ≥2-fold ↑ peak systolic velocity accompanied by poststenotic turbulences |
| Nesher G2002(7) | 15 MHz | clinical diagn 6m or TAB | halo | 86 | 78 | 78 | 61 | high | **halo**: hypoechoic (dark) periluminal halo in 2 planes **(cut-off NR)** |
| Salvarani C2002(8) | 10 MHz | ACR criteriaOr TAB | halo | 35 | 79 | 40 | 79 | high | **halo**: NR (**cut-off: ≥1mm)** |
| Schmid R2002(9) | 8 MHz | ACR criteriaor TAB | halo | 41 | 99 | 50 | 99 | high | **halo**: hypoechoic, perivascular halo in 2 planes **(cut-off NR)** |
| Murgatroyd H 2003(10) | 10 MHz | TAB | halo | NA | NA | 86 | 68 | high | **halo**: hypoechoic area surrounding the affected artery in both longitudinal and axial sections **(cut-off NR)** |
| Pfadenhauer K 2003(11) | 9 MHz | ACR criteriaor TAB | halo/stenosis/occlusion | 83 | 89 | 91 | 82 | high | **halo:** periarterial hypoechogenic area **(cut-off NR)****stenosis**: segmental ↑ blood flow velocity with wave forms indicating turbulence not attributable to other abnormalities like kinking of the artery**occlusion**: absent flow |
| Reinhard M2004(12) | 10 MHz | ACR criteriaor TAB | haloocclusionbilateral haloconspiciuous vessel wall pulsation | 6016NA65 | 10098NA80 | 67214770 | 93938367 | high | **halo**: hypoechoic vessel wall thickening **(cut-off NR)****occlusion**: non-perfused vessel**pseudo-occlusion (stenosis):** massive halo with a filiform or only spot-like colour signal in combination with segments without a visible colour signal**conspiciuous vessel wall pulsation**: reduced or missing vessel wall pulsation by M-mode assessment |
| Romera-Villegas A 2004(13) | 10 MHz | TAB | halo/stenosis/occlusion | NA | NA | 95 | 91 | low | **halo**: hypoechoic halo around the TA with or without presence of segmental stenoses, occlusions, or both **(cut-off NR)****stenosis**: peak systolic velocity twice the rate registered in the previous area**occlusion**: NR |
| Karahaliou M 2006(14) | 11 MHz | clinical diagn 3m or TAB | halobilateral halostenosis | 824141 | 9110073 | NANANA | NANANA | low | **halo**: hypoechogenic ring areas, which appear around the lumen of the TA in one or more sites, unilaterally or bilaterally **(cut-off NR)****stenosis**: segmental ↑ blood-flow velocity perhaps with waveforms indicating turbulence not attributed to other abnormalities (i.e. kinking, arteriosclerosis), consideration of stenosis in an area 1. with blood-flow velocity ≥2x with the flow velocity recorded in the area right before, 2. there was local flow turbulence and 3. there were low blood-flow velocities at the arterial segment right after**occlusion**: absent flow |
| *Bley T**2008*(15) | *10 MHz* | *clinical diagn ≥6m or TAB* | *halo* | *67* | *91* | *79* | *59* | *NA* | ***halo:*** *dark concentric halo surrounding a residual colour flow signal in at least 1 vessel segment of the superficial TA or its branches* ***(cut-off NR)*** |
| Ghinoi A2008(16) | 12 MHz | ACR criteriaor TAB | halo | 82 | 100 | 78 | 100 | low | **halo**: hypoechoic region surrounding the perfused lumen of the TA or branches for a discrete region **(cut-off NR)** |
| *Perez-Lopez J 2009*(17) | *10 MHz* | *ACR criteria**or PMR class criteria*(18)*or TAB* | *halo**stenosis**halo/stenosis (TA)**halo/stenosis (TA + ophthalmic)* | *73**43**80**90* | *80**97**80**80* | *72**41**79**90* | *72**89**72**72* | *NA* | ***halo:*** *hypoechogenic rim surrounding the colour-coded flow in TA* ***(cut-off NR)******stenosis****: blood flow velocity ≥2x the rate recorded in the area before the stenosis, perhaps with wave forms demonstrating turbulence and reduced velocity behind the area of stenosis****occlusion:*** *NR* |
| Aschwanden M 2010(19) | 9 MHz17 MHz | ACR criteria | halo/stenosis | 55 | 100 | NA | NA | mod | **halo (TA)**: NR **(cut-off NR)****stenosis (TA)**: NR**halo (extra-cranial large arteries)**: circumferential, homogenous, hypoechoic wall thickening (with or without stenosis), well delineated towards the luminal side and absence of arteriosclerosis **(cut-off NR);** in lower limb arteries an echolucent stripe within the wall thickening was considered as an additional sign of vasculitis |
| *Maldini C**2010*(20) | *7.5 MHz* | *clinical diagn ≥6m or TAB* | *halo**halo unilateral/**stenosis/occlusion**halo bilateral/**stenosis/occlusion* | *10**20**10* | *100**62**95* | *17**50**17* | *100**72**96* | *NA* | ***halo:*** *anechoic ring ≥ 0.3mm thick, separating surrounding tissue from the colored arterial lumen, seen in both transverse and longitudinal planes****stenosis:*** *localized acceleration with a ≥2-fold* ↑ *peak systolic velocity or dampened velocity curve with a ≥2-fold peak systolic velocity decrease compared with either the upstream segment or contralateral artery****occlusion:*** *non-existent Doppler signal* |
| Habib HM2012(21) | 10 MHz | clinical diagn 3m or TAB | halobilateral halo | 8137 | 88100 | NANA | NANA | mod | **halo:** hypoechoic periluminal dark halo of >0.5mm in it`s sagittal diameter found around the perfused lumen of the common superficial TA or any of the frontal or parietal rami **(cut-off >0.5mm)****stenosis:** blood flow velocity more than twice the rate recorded in the area before the stenosis with wave forms demonstrating turbulence and reduced velocity behind the area of stenosis**occlusion:** absent flow |
| *Hauenstein C 2012*(22)*3* | *10 MHz* | *clinical diagn ≥6m or TAB* | *halo* | *88* | *92* | *92* | *57* | *NA* | ***halo****: dark, concentric halo surrounding a residual color flow signal appearing in at least one vessel segment (main stem, frontal or parietal branch)* ***(cut-off NR)*** |
| *Pfenninger L**2012*(23) | *NR* | *TAB* | *halo**halo/stenosis/occlusion* | *NA**NA* | *NA**NA* | *11**44* | *97**90* | *NA* | ***halo:*** *an area of missing signal around the TA in 2 planes (transverse and longitudinal)* ***(cut-off NR)******stenosis:*** *NR****occlusion:*** *NR* |
| Aschwanden M 2013(24) | 17 MHz | ACR criteria | halostenosisocclusioncompression | 7913879 | 100100100100 | NANANANA | NANANANA | low | **halo:** NR **(cut-off NR)****stenosis:** NR**occlussion:** NR**compression sign:** arterial wall remaining visible upon compression, i.e. echogenicity different than the surrounding tissue due to vessel wall inflammation |
| *Black R**2013*(25) | *NR* | *clinical diagn**or TAB* | *halo* | *42* | *94* | *40* | *81* | *NA* | ***halo:*** *NR* ***(cut-off NR)*** |
| *Muratore F**2013*(26) | *12 MHz* | *TAB* | *unilateral halo**bilateral halo* | *NA**NA* | *NA**NA* | *83**73* | *81**100* | *NA* | ***halo:*** *dark, hypoechoic circumferential wall thickening with a diameter >0.4mm (cut-off >0.4mm)* |
| Diamantopoulos A 2014(27) | 13 MHz | clinical diagn 6m or TAB | halo | 100 | 91 | NA | NA | low | **halo (TA, axillary, common carotid arteries):** hypoechoic ring (eccentric or circumferential) around the vessel wall in longitudinal and transverse scans (cut-off NR) |
| Aschwanden M 2015(28) | 17 MHz | ACR criteria | compression | 77 | 100 | NA | NA | low | **compression sign:** maintenance of a thickened contrasted vessel wall after application of slight pressure via the transducer in B-mode imaging |

1no study on diagnostic accuracy of ultrasound for Takayasu arteritis and idiopathic aortitis was identified by the systematic literature review

2only in Patients/Methods and Results` sections provided definitions of US key elementary lesions suggestive for large vessel vasculitis were retrieved

3only diagnostic performance of US for patients under GC treatment of 0-1 day are shown, in the original paper also results for 2-4 days and >4 days GC treatment were provided

↑ increased

ACR, American College of Rheumatology; diagn, diagnosis; GCA, giant cell arteritis; m, months; MHz, megahertz; NA, not applicable; NR, not reported; quality assessment (arbitrarily defined): low, if there were concerns in ≥5/10 RoB items and/or concerns of applicability in 3/3 items; moderate, if there were concerns in 4/10 RoB and/or concerns in ≥1/3 applicability items; and high, if there were concerns in ≤3/10 RoB items and in none of the applicability parameters; Sens, sensitivity; Spec, specificity; TA, temporal artery/-ies; TAB, temporal artery biopsy; Techn, technical aspects related to imaging methods; US, ultrasound; *vs*, versus

*2.1.2. Details of the risk of bias assessment*

For studies on diagnostic accuracy, the 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 RoB 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.(1)

**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 S4.** Risk of bias assessment of diagnostic accuracy studies on ultrasound (US)

|  |  |  |  |
| --- | --- | --- | --- |
| **STUDY** | **RISK OF BIAS** | **APPLICABILITY CONCERNS** | **QUALITY ASSESSMENT** |
|  | **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** |  |
| Schmidt WA 1997(4) | ☺ | ☹1 | ☺ | ☹2 | ☺ | ☺ | ?3 | ?3 | ☹4 | ☺ | ☹1 | ☺ | ☺ | high |
| Venz S 1998(5) | ☺ | ☺ | ?3 | ?3 | ?3 | ☺ | ?3 | ?3 | ☺ | ☺ | ?5 | ☺ | ☺ | high |
| LeSar CJ 2002(6) | ?6 | ☺ | ?3 | ?3 | ☺ | ☺ | ?3 | ?3 | ☹7 | ☺ | ?6 | ☺ | ☺ | high |
| Nesher G 2002(7) | ?3 | ☺ | ?3 | ?3 | ☺ | ☺ | ☹8 | ☺ | ☹4 | ☺ | ☺ | ☺ | ☺ | high |
| Salvarani C 2002(8) | ☺ | ☺ | ☺ | ☺ | ?9 | ☹10 | ☹8 | ☺ | ☺ | ☺ | ☹11 | ☹9 | ☹10 | high |
| Schmid R 2002(9) | ?3 | ☺ | ?3 | ?3 | ☺ | ☺ | ?3 | ?3 | ☺ | ☺ | ?12 | ☹13 | ☺ | high |
| Murgatroyd H 2003(10) | ?3 | ☺ | ?3 | ☹14 | ?3 | ☺ | ?3 | ?3 | ☺ | ☺ | ☹15 | ☹16 | ☺ | high |
| Pfadenhauer K 2003(11) | ☹17 | ☺ | ☺ | ?3 | ☺ | ☺ | ?3 | ☺ | ☹4 | ☹17 | ☹18 | ☺ | ☺ | high |
| Reinhard M 2004(12) | ?3 | ☺ | ?3 | ?3 | ☺ | ☺ | ☹8 | ☹19 | ☹4 | ☺ | ?20 | ☺ | ☺ | high |
| Romera-Villegas A 2004(13) | ☺ | ☺ | ☹21 | ☹14 | ☺ | ☺ | ☺ | ?3 | ☺ | ☺ | ☺ | ☺ | ☺ | low |
| Karahaliou M 2006(14) | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☹8 | ☺ | ☹4 | ☹22 | ☺ | ☺ | ☺ | low |
| Ghinoi A 2008(16) | ☺ | ☺ | ?3 | ☺ | ☺ | ☺ | ☹8 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | low |
| Aschwanden M 2010(19) | ☺ | ☺ | ☺ | ☹23 | ☺ | ☺ | ☹24 | ?3 | ☹4 | ☺ | ☺ | ☺ | ☺ | mod |
| Habib HM 2012(21) | ?3 | ☺ | ☺ | ☺ | ☺ | ☹25 | ☹8 | ☺ | ☺ | ☺ | ☺ | ☹26 | ☺ | mod |
| Aschwanden M 2013(24) | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☹27 | ☺ | ☹4 | ☺ | ☺ | ☺ | ☺ | low |
| Diamantopoulos A 2014(27) | ☺ | ☺ | ☺ | ☹14 | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | ☺ | low |
| Aschwanden M 2015(28) | ☺ | ☺ | ☺ | ?3 | ☺ | ☺ | ?3 | ☺ | ☹4 | ☺ | ☺ | ☺ | ☺ | low |

quality assessment (arbitrarily defined): low, if there were concerns in ≥5/10 RoB items and/or concerns of applicability in 3/3 items; moderate, if there were concerns in 4/10 RoB and/or concerns in ≥1/3 applicability items; and high, if there were concerns in ≤3/10 RoB items and in none of the applicability parameters;

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 an ophthalmologic unit with ophthalmologic signs (e.g. visual impairment) as key symptom for suspected cranial GCA, thus in this study possibly only a subgroup of the population of interest is included

6 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

7 bilateral temporal artery biopsies performed in 75% of patients

8 temporal artery biopsies were guided by ultrasound

9 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

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

11 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

12 performed in a neuro-angiologic laboratory, thus in this study possibly only a subgroup of the population of interest is included

13 patients were on glucocorticoid treatment for a mean of 17 days (range 0-96 days) with known reducing applicability of the index test, stenoses and/or occlusions not accepted as US elementary lesions suggesting large vessel vasculitis

14 investigator performing ultrasound was not blinded to clinical data

15 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

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

17 67 out of 115 patients with suspicion of GCA were included in the study, only some reasons for exclusions described

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

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

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

21 PMR patients excluded

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

23 ultrasound was blinded to clinical classification of study participants; however, ultrasound findings that were initially not clearly classifiable as vasculitis were recorded as "suspicious for vasculitis" and reclassified as "vasculitis” if at least one other segment was defined as "vasculitis"

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

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

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

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

**2.2. STUDIES ASSESSING OUTCOME PREDICTION**

*2.2.1. Main characteristics and results*

**Supplementary Table S5.** Summary of study characteristics and main findingsfor outcome prediction of ultrasound (US) in giant cell arteritis (GCA).1,2 Retrospective and case-control studies are italicised.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  **Study ID** | **inclusion criteria** | **n final diagn GCA\*** | **n pat** **follow-up****(%)** | **time period****follow-up** | **investigated structures** | **US key elementary lesions** | **definitions of US key elementary lesions**3 | **time to change** | **summary of main findings** |
| Schmidt WA 2008(29) | new diagnosis GCA | 106 | 60(57) | 50 ± 31 m¥ | TA, subclavian, axillary, brachial | non-stenotic wall swelling (“halo”)stenosisocclusion | **non-stenotic wall swelling (“halo”):** NR **(cut-off NR)****stenosis:** artery lumen >50% of the original lumen together with characteristic Doppler curves showing turbulences and ↑ systolic and diastolic blood flow velocities**occlusion:** inability to delineate colour in the former artery lumen which shows a hypoechoic or mid-echoic appearance | NR | trend ↑ risk for PAOD (P=0.07) in LV-GCA *vs* cranial GCA patientstrend ↑ risk for osteoporotic fractures (P=0.09) in LV-GCA *vs.* cranial GCA patients |
| DeMiguel E 2012(30) | new diagnosis cranial GCA + relapse | 30 | 28(93) | every 2 wk - 1st mevery 4 wk till halo disappearance | TA | halo | **halo:** homogenous dark wall surrounding a colour Doppler signal of ≥0.3mm in the longitudinal view at the time of peak systolic blood flow **(cut-off ≥0.3mm)** | 8 wk¥ (2-30 wk)‡ | halo disappearance after 12.6 vs. 6.5 wk¥ (P<0.01) when patients with >1 *vs.* 1 involved TA branch(es) were compared |
| *Czihal M 2013*(31) | *diagnosis of GCA + involvement proximal arm arteries* | *34* | *34**(100)* | *21.9 ± 17.1 m¥**(6-88 m)‡* | *subclavian, axillary, proximal brachial* | *“vasculitis”* | ***“vasculitis”:*** *circumferential,**homogeneous and hypoechogenic wall**thickening* ***(cut-off NR)*** | *NR* | *benign prognosis, no critical limb ischemia during follow-up**patients with persistent ischemic symptoms showed more frequently subclavian involvement vs patients with symptom relief (82% vs. 20%, P=0.04)* |

1no study on outcomeprediction of ultrasound for Takayasu arteritis and idiopathic aortitis was identified by the systematic literature review

2no discriminative descriptions for acute or chronic vasculitic US lesions were reported

3only in Patients/Methods and Results` sections provided definitions of US key elementary lesions suggestive for large vessel vasculitis were retrieved

¥ mean; ‡ range; ↑ increased;

GCA, giant cell arteritis; LV, large vessel; m, months; n final diagn GCA, number of patients finally diagnosed with GCA; NR, not reported; n pat follow-up, number of patients undergoing follow-up; P, p-value; PAOD, peripheral arterial occlusive disease; pat, patients, TA, temporal artery/-ies; *vs*, versus; wk, week, y, year

*2.2.2. Details of the risk of bias assessment*

For studies on outcome prediction, the RoB was appraised independently by the two reviewers (CDu, CDe) 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.(3)

**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 S6.** Risk of bias assessment of studies outcome prediction of ultrasound (US) in giant cell arteritis (GCA)

|  |  |
| --- | --- |
| **STUDY** | **RISK OF BIAS** |
|  | **STUDY PARTCIPATION** | **STUDY ATTRITION** | **PROGNOSTIC FACTOR MANAGEMENT** | **OUTCOME MEASUREMENT** | **STUDY CONFOUNDING** | **STATISTICAL ANALYSIS/ REPORTING** | **OVERALL RATING** |
| **Giant cell arteritis** |  |
| Schmidt WA 2008(29) | ?1 | ☹2 | ?3 | ☹4 | ?5 | ?6 | high |
| DeMiguel E 2012(30) | ☹7 | ☺ | ☺ | ☺ | ☹8 | ☹9 | mod |

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

**2.3. STUDIES ASSESSING MONITORING DISEASE ACTIVITY**

*2.3.1. Main characteristics and results*

**Supplementary Table S7.** Summary of study characteristics and main findingsfor studies on monitoring disease activity by ultrasound (US) in giant cell arteritis (GCA).1,2 Retrospective studies are italicised.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **inclusion criteria** | **n final diagnosis GCA** | **n pat follow-up****(%)** | **time period follow-up** | **investigated structures** | **US key elementary lesions** | **definitions of US key elementary lesions**3 | **summary of findings** |
| Schmidt WA 1997(4) | suspected GCA+PMR | 30 | 22(73) | every 3-4dtill halo disappearance | TA | halostenosis/occlusionhalo/stenosis/occlusion | **halo**: NR **(cut-off NR)****stenosis**: blood-flow velocity >2-fold before the stenosis, perhaps with wave forms of turbulence and reduced velocity behind the stenosis**occlusion**: NR | halo disappearance after16d\* (7-56d)¥# |
| Salvarani C 2002(8) | suspected GCA+PMR | 20 | 6(30) | at 1m | TA | halo | **halo**: NR **(cut-off NR)** | halo disappearance in 6/6 pat# |
| Schmid R 2002(9) | suspected GCA | 15 | 6(40) | at 3m | TA | halo | **halo**: hypoechoic, perivascular halo in 2 planes **(cut-off NR)** | halo disappearance in 5/6 pat# |
| Schmidt WA 2002(32) | new diagnosis GCA | 33 | 10(30) | 9-21d for c-GCA,at 6 + 24m for LV-GCA | NR | inflammatory artery wall pathologies w/wo stenosis, stenosis, occlusion, aneurysm, arteriosclerotic lesions | **inflammatory artery wall pathologies w/wo stenosis:** dark (hypoechoic), homogenous wall thickening **(cut-off NR)****stenosis:** NR**occlusions:** NR**aneurysm:** NR**arteriosclerotic lesions:** bright (mid- orhyperechoic) lesions with an irregular surface frequently presenting with coexisting calcifications | 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(11) | suspected GCA | 40 | 5(13) | NR | TA, occipital | halo/stenosis/occlusion | **halo:** periarterial hypoechogenic area **(cut-off NR)****stenosis**: segmental ↑ blood flow velocity with wave forms indicating turbulence not attributable to other abnormalities like kinking of the artery**occlusion**: absent flow | halo and stenoses disappearance in 3/5 pat, recanalisation of occlusions in 2/5 pat after 13-42d¥# |
| Karahaliou M 2006(14) | ESR >50 mm/h, headache, jaw claudication, fever, PMR, TA tenderness, visual impairment | 22 | 18(82) | every 2 wk for 3m | TA | halobilateral halostenosis | **halo**: hypoechogenic ring areas appearing around the TA lumen in one or more sites, unilaterally or bilaterally **(cut-off NR)****stenosis**: segmental ↑ blood-flow velocity perhaps with waveforms indicating turbulence not attributed to other abnormalities (kinking, arteriosclerosis), consideration of stenosis in an area 1.) with blood-flow velocity ≥2x with the flow velocity recorded in the area right before, 2.) presence of local flow turbulence and 3.) low blood-flow velocities at the arterial segment right after**occlusion**: absent flow | halo disappearance after 22d\*(9/18 pat at wk 2, 9/18 pat at wk 4)#  |
| Schmidt WA 2008(29) | new diagnosis GCA | 106 | 60(57) | 41m for c-GCA39m for LV-GCA | subclavian, axillary, brachial | non-stenotic wall swelling (“halo”)stenosisocclusion | **non-stenotic wall swelling (“halo”):** NR **(cut-off NR)****stenosis:** artery lumen >50% of the original lumen together with characteristic Doppler curves showing turbulences and ↑ systolic and diastolic blood flow velocities**occlusion:** unability of US to delineate colour in the former artery lumen showing a hypo- or mid-echoic appearance | US signs of vasculitis resolved in 30%, improved in 53%, remained unchanged in 8%, worsened in 10% of pat# |
| Perez-Lopez J 2009(17) | suspected GCA+PMR | 30 | 26(22 GCA/4 PMR)(87) | at wk 6 + 6m | TA, ophthalmic | halo (TA)stenosis (TA)stenosis/occlusion (ophthalmic) | **halo:** hypoechogenic rim surrounding the colour-coded flow in TA **(cut-off NR)****stenosis**: blood flow velocity ≥2x the rate recorded in the area before the stenosis, perhaps with wave forms demonstrating turbulence and ↓ velocity behind the area of stenosis**occlusion:** NR | halo disappearance in 50% of pat at wk 6, halo persistence in 10/18 (symptom free) pat at 6m# |
| Aschwanden M 2010(19) | suspected c-GCA + LV-GCA (PET, ESR >50 mm/h, age>50y) | 38 | 9 LV-GCA(75) | at 6m | carotid, vertebral, subclavian, axillary, femoral, popliteal | halo/stenosis | **halo (TA)**: NR **(cut-off NR)****halo (extra-cranial large arteries)**: circumferential, homogenous, hypoechoic wall thickening (w/wo stenosis), well delineated towards the luminal side and absence of arteriosclerosis **(Cut-off NR), i**n lower limb arteries an echolucent stripe within the wall thickening was considered as an additional sign of vasculitis**stenosis (TA)**: NR  | US signs of vasculitis resolved in 8/84 segments, persisted in 76/84 segments; new vasculitic lesions occurred in 1 pat at 2 segments# |
| DeMiguel E 2012(30) | new diagnosis GCA+ relapse | 30 | 30(100) | every 2 wk - 1st mevery 4 wk – till halo disappearance | TA | halo | **halo:** homogenous dark wall surrounding a colour Doppler signal of ≥0.3mm in the longitudinal view at the time of peak systolic blood flow **(cut-off ≥0.3mm)** | halo disappearance in 36/38 patafter 10 wk\* (2-30 wk)¥# |
| Habib HM 2012(21) | ESR >50 mm/h, headache, jaw claudication, fever, PMR, TA tenderness, visual impairment | 16 | 15(81) | at wk 2,4,8,12 | TA | halo | **halo:** hypoechoic periluminal dark halo of >0.5mm in it`s sagittal diameter found around the perfused lumen of the common superficial TA or any of the frontal or parietal rami **(cut-off >0.5mm)****stenosis:** blood flow velocity > twice the rate recorded in the area before the stenosis with wave forms demonstrating turbulence and ↓ velocity behind the area of stenosis**occlusion:** absent flow | halo disappearance in 13/13 pat after 21d‡:(9 pat at wk 2, 4 pat at wk 4)stenoses and occlusions persisted during FU# |
| *Hauenstein C 2012*(22) | *suspected GCA + US + MRI4* | *36* | *0-1d on GC: 16 (44)*5*2-4d on GC: 10 (28)*5*>4d on GC: 10 (28)*5 | *0-1d on GC**2-4d on GC**>4d on GC*  | *TA* | *halo* | ***halo:*** *dark, concentric halo surrounding a residual colour flow signal appearing in at least 1 vessel segment (main stem, frontal or parietal branch)* ***(cut-off NR)*** | *sensitivity of US compared to clinical diagnosis rapidly* ↓ *from 88% under GC treatment of 0-1d to 50% under GC treatment of >4d*5# |
| *Czihal M**2013*(31) | *diagnosis of GCA + involvement proximal arm arteries* | *34* | *34**(100)* | *21.9 ± 17.1m\***(6-88m)¥* | *subclavian, axillary, proximal brachial* | *“vasculitis”* | ***“vasculitis”:*** *circumferential,**homogeneous and hypoechogenic wall**thickening* ***(cut-off NR)*** | *vasculitic wall swelling disappearance in 11/34 pat*#*persistent signs of vasculitis (halo, stenosis, occlusion) in 68% of extremities*# |

1no study on monitoring of ultrasound for Takayasu arteritis and idiopathic aortitis was identified by the systematic literature review

2no discriminative descriptions for acute or chronic vasculitic US lesions were reported

3only in Patients/Methods and Results` sections provided definitions of US key elementary lesions suggestive for large vessel vasculitis were retrieved

4suspected GCA + US + MRI, only patients with suspected disease, who underwent both imaging examinations (US and MRI) within 10 days and were on glucocorticoid treatment < 2 weeks were included

5only results for the comparison US to clinical diagnosis are shown, in the original study also results for the comparison US to temporal artery biopsy are provided

\* mean; ¥ range; # only descriptive results, no interference reported, ‡ median; ↑ increased; ↓ decreased

c, cranial; CRP, C-reactive protein; d, day(s); ESR, erythrocyte sedimentation rate; FU, follow-up; GC, glucocorticoid; 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; US, ultrasound; w/wo, with or without; wk, week; y, year

*2.3.2. 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.

**2.4. CROSS-SECTIONAL DESCRIPTIVE STUDIES ASSESSING THE INOLVEMENT OF CRANIAL AND EXTRA-CRANIAL LARGE ARTERIES IN PATIENTS WITH DIAGNOSED CRANIAL GIANT CELL ARTERITIS, POLYMYALGIA RHEUMATICA AND TAKAYASU ARTERITIS**

*2.4.1. Main characteristics and results*

**Online Supplementary Table S8.** Main characteristics of cross-sectional descriptive studies on the assessment of involvement of vasculitis in extra-cranial large arteries in giant cell arteritis (GCA) or polymyalgia rheumatica (PMR) patients and in the assessment of the role of US in Takayasu arteritis (TAK) by ultrasound (US).1 Retrospective studies are italicised.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **n**  | **inclusion criteria** | **reference****standard** | **n final diagn GCA (%)** | **n LV-GCA** | **investigated****structures** | **key elementary lesions** | **provided definitions key elementary lesions**2 | **summary main findings** |
| **Giant cell arteritis or polymyalgia rheumatica** |
| Stammler F2000(33) | 22 | diagnosis PMR | Bird criteria | 5(23) | NR | TA, carotidin suspicious cases shoulder, arm and renal arteries | halostenosisocclusion | **halo:** hypoechoic, perivascular wall thickening **(cut-off >0.3mm)****stenosis:** circumscribed ↑ flow velocity (PVR >3)**occlusion:** absent flow in artery that can be visualized | 7/22 (32%) PMR pat revealed US signs of vasculitis, finally confirmed by TAB in 5 pat, LV involvement observed in 2/5 finally diagnosed GCA pat# |
| Schmidt WA 2002(34) | 127 | new diagnosis PMR | Bird criteria | 25(20) | 2 | TA | halostenosisocclusion | **halo:** dark area, usually circumferential around the perfused lumen, to be demonstrated in two planes **(cut-off NR)****stenosis:** turbulent flow combined with ↑ persistent flow during diastole, blood-flow velocity >2-fold the rate recorded by pulsed wave Doppler US in the area before the stenosis, perhaps with waveforms demonstrating turbulence**occlusion:** wall of the artery with a dark area in the centre in grey scale US, colour Doppler US fails to show a colour signal in this dark area, i.e. no blood flow can be demonstrated | 8% of ‘pure’ PMR pat had US findings arousing suspicion of concomitant active c-GCA, finally confirmed by TAB in 4%# |
| Schmidt WA 2002(32) | 33 | new diagnosis GCA | ACR criteria(c-GCA)clinical examination, US, angiography (LV-GCA) | 33(100) | 10 | occipital, facial, carotid, subclavian, axillary, brachial, radial, ulnar, femoral, posterior tibial, dorsal pedal arteries, abdominal aorta, supratrochlear  | inflammatory artery wall pathologies w/wo stenosis, stenosis, occlusion, aneurysm, arteriosclerotic lesions | **inflammatory artery wall pathologies w/wo stenosis:** dark (hypoechoic), homogenous wall thickening **(cut-off NR)****stenosis:** NR**occlusions:** NR**aneurysm:** NR**arteriosclerotic lesions:** bright (mid- or hyperechoic) lesions with an irregular surface frequently presenting with coexisting calcifications | 10/33 (30%) GCA pat revealed involvement of extra-cranial large arteries, 2/10 were symptomatic# |
| Pfadenhauer K 2003(11) | 67 | suspected GCA | ACR criteria orTAB | 40(60) | NR | TA, occipital | halo/stenosis/occlusion | **halo:** periarterial hypoechogenic area **(cut-off NR)****stenosis**: segmental increase of blood flow velocity with wave forms indicating turbulence not attributable to other abnormalities like kinking of the artery**occlusion**: absent flow | 17/26 (65%) of c-GCA pat showed US signs of vasculitis in occipital arteries# |
| Pfadenhauer K 2005(35) | 127 | diagnosis GCA + PMR | ACR or Bird criteria | 93(73) | 10 | vertebral | halostenosisocclusion | **halo:** concentric hypoechogenic mural thickening **(cut-off NR)****stenosis**: segmental ↑ blood flow velocity with wave forms showing turbulence if not attributable to other abnormalities like kinking of the artery; degree of stenosis was calculated according to hemodynamic principles used in the classification of occlusive carotid artery disease regarding typical pre-/intra- and poststenotic abnormalities. Distal vertebral artery occlusion of V3/V4 was assumed if the Doppler signal in a normal wide V1/V2 segment of the artery showed a typical high resistance pattern with an absent end-diastolic flow**occlusion:** absent flow  | 14/93 (15%) GCA pat and 2/34 (6%) PMR showed US signs of vasculitis in the vertebral arteries#stenoses >50% were the most frequently observed vasculitic US lesions in GCA pat (12/93, 13%)#in all cases the V0/V1 segment was involved#4/4 GCA pat with vertebrobasilar ischemia revealed proximal vertebral occlusive disease in US# |
| Schmidt WA 2008(36) | 176 | new diagnosisc-GCA and LV-GCA | clinical diagnosis 6m (ACR criteria + GC response) or TAB (c-GCA)NR (LV-GCA) | 176(100) | 53 | TA, subclavian, axillary, brachial  | halostenosisocclusion | **halo (extra-cranial arteries):** homogenous wall swelling of ≥1.5mm **(cut-off ≥1.5mm)****stenosis:** artery lumen <50% of the original lumen together with characteristic Doppler curves showing turbulences and ↑ systolic and diastolic blood flow velocities**occlusion:** unability of US to delineate colour in the former artery lumen that showed a hypo- or mid-echoic appearance**arteriosclerosis:** non-homogeneous, in part hyperechoic wall thickening | in LV-GCA pat axillary, subclavian and/orbrachial arteries were affected in 98%, 61% and 21%, respectively#bilateral findings were observed in 79% of LV-GCA pat#TA US and histology were positive in 62% and 67% of LV-GCA cases, respectively# |
| Stammler F2009(37) | 182 | diagnosis PMRpat with atypical cephalea (<3/6 criteria: new onset headache, TA tender or ↓pulse, ESR>50mm/h, age≥50y, jaw or tongue claudication)suspected GCA (>3/6 criteria) | TAB | NR | 4 | TA, carotidin suspicious cases shoulder, arm, renal arteries, mesenterica superior, Truncus coeliacus | halostenosisocclusion | **halo:** hypoechoic, perivascular wall thickening **(cut-off >0.3mm)****stenosis:** circumscribed ↑flow velocity (PVR >3)**occlusion:** absent flow in artery that can be visualized | out of US key elementary lesions assessed, the ´halo´ sign revealed the best correlation with the clinical pre-test probability#in cases with low clinical or very high clinical probability of GCA a negative or positive US test result allows the exclusion or confirmation of the disease, respectively# |
| Aschwanden M 2010(19) | 72 | suspected GCA,suspected LV-GCA (PET+, ESR >50 mm/h, age>50y) | ACR criteria | 38(53) | 12 | TA, carotid, vertebral, subclavian, axillary, femoral, popliteal | halo/stenosis | **halo (TA)**: NR **(cut-off NR)****halo (extra-cranial large arteries)**: circumferential,homoge-nous, hypoechoic wall thickening (w/wo stenosis) , well delineated towards the luminal side and absence of arteriosclerosis **(cut-off: NR),** In lower limb arteries an echolucent stripe within the wall thickeningwas considered as an additional sign of vasculitis**stenosis (TA)**: NR  | 12/38 (32%) GCA pat showedUS signs of LV involvement in ≥1 vessel region(s) of upper and lower limb vessels# |
| Förster S2011(38) | 24 | new diagnosis GCA + physical investigation + US + PET | clinical diagn or TAB | 24(100) | NR | TA, carotid, vertebral, subclavian, axillary, brachial, abdominal aorta, iliac, femoral popliteal | halostenosisocclusion | **halo (extra-cranial arteries):** long, smooth, concentric, hypoechogenic thickening of the arterial wall >2.0mm with perivascular halo without haemodynamically significant stenosis of the lumen **(cut-off >2.0mm)****stenosis**: long, concentric, hypoechogenic thickening of the arterial wall**occlusion:** hypoechogenic occlusion of the artery with concentric, hypoechogenic thickening of the arterial wall in the adjacent arterial segments | combination of thorough clinical examinationand US allows detection of symptomatic andasymptomatic LV involvement in a large proportion of pat with newly diagnosed GCA# |
| *Czihal M**2012(39)* | *60* | *diagnosis GCA + complete clinical investigation of lower extremity arteries* | *ACR criteria**(c-GCA)**typical US findings leg/arm arteries +* *↑ CRP/ESR + clinical/lab response to GC (LV-GCA)*  | *60**(100)* | *32* | *TA, carotid, subclavian, axillary, brachial, femoral, popliteal*  | *"vasculitis”**stenosis**occlusion* | ***"vasculitis":*** *circumferential, hypoechogenic, homogenous wall thickening w/wo hyperechogenic stripe lining the innermost wall layer (lower extremity arteries)****(cut-off NR)******stenosis:*** *>50% diameter reduction, PVR ≥2.0 (PSV in stenosis/PSV of adjacent proximal normal arterial segment) (lower extremity arteries)****occlusion:*** *NR****arteriosclerosis:*** *inhomogeneous, excentric, partly calcified arterial wall changes* | *32/60 (53%) GCA pat presented with US involvement of femoro-popliteal arteries#**30/32 (94%) GCA pat with femoro-popliteal involvement also exhibited typical US vasculitis signs in TA, carotid and/or proximal arm arteries#* |
| *Czihal M**2012(40)* | *110* | *diagnosis GCA + complete clinical investigation of upper extremity arteries* | *ACR criteria or halo of TA in US**(c-GCA)**typical US vasculitis signs arm arteries (LV-GCA)* | *110**(100)* | *59* | *TA, carotid subclavian, axillary, brachial*  | *"vasculitis”**stenosis**occlusion* | ***"vasculitis":*** *circumferential, homogenous, hypoechogenic thickening of the vessel wall with smooth delineation towards the vessel lumen* ***(cut-off: NR)******stenosis:*** *>50% diameter reduction, PVR ≥ 2.0 (PSV in stenosis/PSV of adjacent proximal normal arterial segment (arm, common + external carotid), >50% stenosis characterized by a PSV of >125cm/s (internal carotid)****occlusion:*** *NR****arteriosclerosis:*** *irregularly delineated, non-homogeneous, excentric and/or calcified wall alterations* | *58/110 (53%) pat revealed US involvement of TA#**59/110 (54%) pat showed sonographic changes indicating extra-cranial LV-GCA of carotid and/or arm arteries#**proximal arm arteries were affected in**58/110 (53%) pat with bilateral sonographic changes in 55/58 pat (95%)#**axillary arteries were**most frequently involved, followed by subclavian arteries#* |
| Ghinoi A2012(41) | 45 | new diagnosis GCA | ACR criteria or TAB | 45(100) | 15 | TA, carotid, subclavian, anonymous, axillary, humeral, aortic arch, abdominal aorta, renal, iliac, mesenterica superior, Truncus coeliacus  | halo | **halo (extra-cranial arteries)**: dark, hypoechoic, circumferential wall thickening with a diameter ≥1.3mm **(cut-off ≥1.3mm)****arteriosclerosis:** isoechoic wall thickening or hyperechoic wall thickening and halo associated with calcifications | 18/62 (29%) of newly diagnosed GCA patients revealed extra-cranial LV involvement#the commoncarotid, subclavian, axillary and humeral arteries (in decreasing order of frequency) were most commonly involved#  |
| **Takayasu arteritis** |
| Taniguchi N1997(42) | 22 | established TAK | conventional angiography | 22(100) | NA | carotid | stenosis (non-stenotic, mild, moderate)occlusion dilatation | **non-stenotic vessel wall thickening**: NR **(cut-off NR)****stenosis:** NR**occlusion:** NR**dilatation:** NR | typical US vasculitic lesions include concentric thickening of vessel wall,luminal stenosis or occlusion, decrease or lack of flow in colour Doppler#US was more useful in estimation of severity of stenosis than conventional angiography#arterial wall thickness correlated with severity of stenosis (P<0.005) |
| Cantu C2000(43) | 21 | established TAK | ACR criteria | 21(100) | NA | brachiocephalic trunk, carotid, vertebralintra-cranial arteries3 | thickened vessel wall (“macaroni sign”)stenosisocclusion | **thickened vessel wall/macaroni sign:** homogeneous thickening with iso- or hyperechogenicity of the intima media thickness, **(cut-off NR)****stenosis (carotid):** colour fading, PSV >120cm/s, poststenotic turbulence **stenosis (vertebral):** increased flow velocities, poststenotic tubulences and aliasing phenomena**occlusion (carotid):** vessel lumen without flow **occlusion (vertebral):** absence of colour flow signal w/wo evidence of cervical collateral blood flow | US assessment of cerebral circulation in TAK pat allowed the detection of diverse vascular abnormalities#good correlation with magnetic resonance angiography findings |

1no discriminative descriptions for acute or chronic vasculitic US lesions were reported

2only in Patients/Methods and Results` sections provided definitions of US key elementary lesions suggestive for large vessel vasculitis were retrieved

3only definitions for extra-cranial large arteries were retrieved

# only descriptive results, no interference reported; ↑ increased; ↓ decreased

ACR, American College of Rheumatology; c, cranial; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; GCA, giant cell arteritis; lab, laboratory; LV, large vessel; n, number; NA, not applicable; n LV-GCA, number of GCA patients with extra-cranial large vessel involvement; 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; PSV, peak systolic velocity; PVR, peak velocity ratio; TA, temporal artery/-ies; TAB, temporal artery biopsy; TAK, Takayasu arteritis; US, ultrasound; w/wo, with or without; y, year

*2.4.2. Details of the risk of bias assessment*

For cross-sectional descriptive studies on the assessment of involvement of vasculitis in extra-cranial large arteries in giant cell arteritis (GCA) or polymyalgia rheumatica (PMR) patients and in the assessment of the role of US in Takayasu arteritis (TAK), no quality assessment was performed, because identified studies were mainly descriptive, hence no adequate quality assessment could be performed.

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