Development of a diagnostic prediction model for giant cell arteritis by sequential application of Southend Giant Cell Arteritis Probability Score and ultrasonography: a prospective multicentre study

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Summary

Background Giant cell arteritis is a critically ischaemic disease with protean manifestations that require urgent diagnosis and treatment. European Alliance of Associations for Rheumatology (EULAR) recommendations advocate ultrasonography as the first investigation for suspected giant cell arteritis. We developed a prediction tool that sequentially combines clinical assessment, as determined by the Southend Giant Cell Arteritis Probability Score (SGCAPS), with results of quantitative ultrasonography.

Methods This prospective, multicentre, inception cohort study included consecutive patients with suspected new onset giant cell arteritis referred to fast-track clinics (seven centres in Italy, the Netherlands, Spain, and UK). Final clinical diagnosis was established at 6 months. SGCAPS and quantitative ultrasonography of temporal and axillary arteries with three scores (ie, halo count, halo score, and OMERACT GCA Score [OGUS]) were performed at diagnosis. We developed prediction models for diagnosis of giant cell arteritis by multivariable logistic regression analysis with SGCAPS and each of the three ultrasonographic scores as predicting variables. We obtained intraclass correlation coefficient for inter-rater and intra-rater reliability in a separate patient-based reliability exercise with five patients and five observers.

Findings Between Oct 1, 2019, and June 30, 2022, we recruited and followed up 229 patients (150 [66%] women and 79 [34%] men; mean age 71 years [SD 10]), of whom 84 were diagnosed with giant cell arteritis and 145 with giant cell arteritis mimics (controls) at 6 months. SGCAPS and all three ultrasonographic scores discriminated well between patients with and without giant cell arteritis. A reliability exercise showed that the inter-rater and intra-rater reliability was high for all three ultrasonographic scores. The prediction model combining SGCAPS with the halo count, which was termed HAS-GCA score, was the most accurate model, with an optimism-adjusted C statistic of 0·969 (95% CI 0·952 to 0·990). The HAS-GCA score could classify 169 (74%) of 229 patients into either the low or high probability groups, with misclassification observed in two (2%) of 105 patients in the low probability group and two (3%) of 64 of patients in the high probability group. A nomogram for easy application of the score in daily practice was created.

Interpretation A prediction tool for giant cell arteritis (the HAS-GCA score), combining SGCAPS and the halo count, reliably confirms and excludes giant cell arteritis from giant cell arteritis mimics in fast-track clinics. These findings require confirmation in an independent, multicentre study.

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Introduction

Giant cell arteritis is a critically ischaemic, organ-threatening disease,[1,2] for which it is vital to make a diagnosis quickly, not only to confirm the disorder but also to exclude conditions mimicking it. Several mimics of giant cell arteritis, such as infection, cancer, head and neck pathology, and systemic rheumatological diseases, are equally serious conditions when it comes to early diagnosis and management.[3] For less serious conditions, it is important to avoid inappropriate empirical glucocorticoid treatment while offering symptom alleviation and correct management advice.

Clinical manifestations of giant cell arteritis are protean and often characterised by a mix of constitutional, cranial, ischaemic, and polymyalgic symptoms with raised inflammatory markers. These scenarios are often difficult to distinguish from conditions mimicking giant cell arteritis.[4] A fast-track algorithmic process based on probability scores to drive investigations with ultrasound and appropriate additional tests is needed. The Southend Giant Cell Arteritis Probability Score (SGCAPS) stratifies patients into low-risk, intermediate-risk, and high-risk categories based on demographics, symptoms, physical signs, and C-reactive protein concentration in blood.[5,6] The

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Research in context

Evidence before this study

Untreated giant cell arteritis is a critically ischaemic disease with protean manifestations such as sight loss, which can be reduced by fast-track clinics. There is an urgent need for a point-of-care objective, prediction tool integrating clinical and ultrasonography findings in suspected giant cell arteritis referrals in order to avoid underdiagnosis (increasing risk of ischaemic complications) and over-diagnosis (glucocorticoid toxicity). We performed a search on PubMed using the terms "giant cell arteritis AND (prediction model OR probability score)" to identify relevant studies in any language from inception to Nov 11, 2023. The search revealed the existence of various prediction tools to assess the probability of giant cell arteritis based on clinical findings, with the Southend Giant Cell Arteritis Probability Score (SGCAPS) being the most extensively validated tool. However, none of the identified prediction tools incorporated ultrasonography findings.

Added value of this study

We developed a simple point-of-care prediction tool for giant cell arteritis using data obtained by sequential application of the SGAPS and quantitative ultrasonography. It should improve accuracy of giant cell arteritis diagnosis in clinical practice by encouraging interpretation of ultrasonographic findings in the light of previous standardised clinical probability scoring. This post-test probability assessment is aided by use of a simple nomogram.

Implications of the available evidence

This prediction tool (termed HAS-GCA score) may allow rapid assessment of the post-test probability of giant cell arteritis enabling correct and rapid confirmation of giant cell arteritis and exclusion of giant cell arteritis mimics in fast-track clinics. It needs further prospective validation through international networks in multicentre independent datasets. This effort would simultaneously expand the provision of fast-track giant cell arteritis clinics offering expertise in giant cell arteritis ultrasonography.

SGCAPS is publicly available and easy to calculate.[5] It has been externally validated by independent, retrospective studies from many centres.[7–10] Recently, the SGCAPS was compared with other prediction tools for giant cell arteritis in a prospective study.[11] In that study, SGCAPS was identified as the most accurate clinical prediction tool.[11] Such a probability-based approach integrates vascular ultrasonography as a clinically adjunct key test to predict the post-test likelihood of giant cell arteritis as likely, unlikely, or uncertain. Uncertainty requires additional tests or clinical evaluation. This principle of point-of-care rheumatology ultrasound is gaining in popularity.

Ultrasonographic examination of temporal and axillary arteries, enabling visualisation of arterial wall inflammation in giant cell arteritis as a hypoechoic non-compressive halo sign, has become standard in the diagnostic work-up of giant cell arteritis.[12,13] The halo sign is a dichotomous finding, with cutoff values for arterial wall thickness reported for the three temporal artery segments and axillary arteries.[14] In addition, three ultrasonographic scores have been developed to quantify the extent and severity of vascular inflammation in giant cell arteritis. This includes the halo count,[15] halo score,[15] and OMERACT GCA Ultrasound Score (OGUS).[16] The halo count represents the number of arterial segments with the halo sign, as determined by bilateral examination of the three temporal artery segments and axillary arteries (range 0–8). The halo score and OGUS reflect wall swelling; the intima-media thickness (IMT) of the arterial wall in the same eight arterial segments, scored in a semi-quantitative (halo score) or quantitative (OGUS) manner. These scores, adding a measure of extent and severity to the dichotomous halo sign, can improve diagnosis, since high values of any of the three ultrasonographic scores can add greater specificity associated with high probability of giant cell arteritis.

Integration of clinical and ultrasound features currently remains a subjective process dependent on the expertise of individual physicians. To standardise the assessment of the probability of giant cell arteritis, we aimed to develop a prediction model that incorporates the full SGCAPS and each of the three ultrasonographic scores (without categorisation, as this might lead to loss of valuable information within categories) to accurately identify patients with or without giant cell arteritis, as well as diagnostic uncertainty in which patients would benefit from additional diagnostic testing. We developed this prediction model from patients recruited in the HAS-GCA study (halo score as a diagnostic, prognostic, and disease monitoring tool for giant cell arteritis), a multicentre, prospective, longitudinal inception cohort study of patients with newly diagnosed giant cell arteritis and relevant controls recruited from individuals with suspected giant cell arteritis referred to fast-track clinics.[17] Secondary aims of the study were the validation of the SGCAPS and the comparison of the diagnostic performance of the three ultrasonographic scores for giant cell arteritis in this cohort.

Methods

Study design and participants

The HAS-GCA study was a prospective study including consecutive patients evaluated by rheumatologists and internists at giant cell arteritis fast-track clinics for suspected, new onset giant cell arteritis. Patients were referred by general practitioners and other medical

specialists as part of standard care. The study was done at seven centres in Europe (Southend and Poole, UK; Reggio Emilia, Milan, and Siena, Italy; Santander, Spain; Groningen, the Netherlands) from Oct 1, 2019, to June 30, 2022. Exclusion criteria were a previous temporal artery biopsy, which would not allow comprehensive ultrasonographic evaluation, or use of prednisolone of more than 7·5 mg daily for more than 14 days. The final diagnosis, confirmed at 6 months, was used as a reference standard in the current study. The diagnosis incorporated symptoms, laboratory tests, and ultrasonographic findings. Additional tests such as temporal artery biopsy, ^{18}F-fluorodeoxyglucose-positron emission tomography ([^{18}F]FDG-PET–CT), or CT angiography (CTA) were performed at the discretion of the treating clinician. All participants provided written informed consent. The study was approved by the research ethics committee London Stanmore (REC number 19/LO/1375) and local ethics committees of all participating centres in Spain, Italy, and the Netherlands. This study is reported in accordance with the TRIPOD statement for studies reporting a multivariate prediction model.[18]

Procedures

All data necessary for calculation of the SGCAPS were collected at baseline as reported previously (appendix 1 p 23).[5,6] Items of the SGCAPS include symptoms, physical signs, and laboratory test results. SGCAPS values can range from –2 to 32, with higher scores reflecting higher probability of giant cell arteritis. Three risk groups, as defined by SGCAPS, have been reported: low risk (SGCAPS <9), intermediate risk (SGCAPS 9–12), and high risk (SGCAPS >12).[6]

A full description of ultrasonography is provided in the appendix 1 (pp 1–2). Standardised ultrasound scans were done at baseline by experienced sonographers in accordance with European Alliance of Associations for Rheumatology (EULAR) imaging recommendations for large-vessel vasculitis.[12] Sonographers were not masked to clinical data. The halo sign was defined by previously reported IMT cutoff points.[14] The following ultrasound scores were determined: halo count (sum of halo positive arterial segments, range 0–8),[15] the halo score based on the sum of temporal artery halo score and axillary artery halo score,[15,19] and OGUS.[16] The axillary artery grading of the halo score was updated according to current definitions (appendix 1 pp 1–2).[14,20]

Five experienced sonographers participated in the reliability exercise (held after the 8th International Ultrasound workshop at Southend, UK, in September 2021). The exercise included five volunteers (four patients with a diagnosis of giant cell arteritis and one control) randomly selected by an independent assessor (BD) who was not a rater for this exercise. Sonographers were masked to the clinical information. Two rounds of scans were performed during which all raters examined all patients. IMT was measured bilaterally in all temporal artery segments and axillary arteries to calculate the three ultrasonographic scores. Each rater was allowed 20 min to scan each patient.

Statistical analysis

We used the Mann-Whitney U test to compare continuous variables of two independent groups. We

	All patients (n=229)	Patients with giant cell arteritis* (n=84)	Patients without giant cell arteritis (n=145)
Sex			
Men	79 (34%)	34 (40%)	45 (31%)
Women	150 (66%)	50 (60%)	100 (69%)
Mean age, years	71 (10)	75 (8)	69 (10)
Glucocorticoids used at baseline	92 (40%)	39 (46%)	53 (37%)
Median number of days steroids already used at baseline†	2·5 (1–5)	2 (1–4)	3 (1–5)
Median prednisolone equivalent dose at baseline (mg/day)†	40 (40–60)	40 (40–60)	40 (18–60)
Temporal artery biopsy positive‡	12 (5%)	12 (14%)	0
[^{18}F]FDG-PET–CT positive§	13 (6%)	13 (15%)	0
General headache	63 (28%)	16 (19%)	47 (32%)
Temporal headache	164 (72%)	62 (74%)	102 (70%)
Scalp tenderness	88 (38%)	42 (50%)	46 (32%)
Jaw claudication	55 (24%)	45 (54%)	10 (7%)
Tongue pain	8 (3%)	8 (10%)	0
Polymyalgic symptoms	75 (33%)	37 (44%)	38 (26%)
Previous diagnosis of polymyalgia rheumatica	26 (11%)	10 (12%)	16 (11%)
Fever	22 (10%)	16 (19%)	6 (4%)
Night sweats	44 (19%)	25 (30%)	19 (13%)
Weight loss	46 (20%)	30 (36%)	16 (11%)
Limb claudication	0	0	0
Blurred vision	66 (29%)	25 (30%)	41 (28%)
Diplopia	29 (13%)	13 (15%)	16 (11%)
Amaurosis fugax	25 (11%)	15 (18%)	10 (7%)
Anterior ischaemic optic neuropathy	18 (8%)	15 (18%)	3 (2%)
Central retinal artery occlusion	8 (3%)	4 (5%)	4 (3%)
Temporal artery thickening	25 (11%)	23 (27%)	2 (1%)
Temporal artery tenderness	45 (20%)	24 (29%)	21 (14%)
Temporal artery reduced pulse	21 (9%)	14 (17%)	7 (5%)
Median ESR, mm/h¶	40 (17–62)	59 (41–77)	28 (14–49)
Median CRP, mgl/L‖	19 (8–60)	60 (20–100)	11 (5–30)

Data are n (%), mean (SD), or median (IQR). CRP=C-reactive protein. ESR=erythrocyte sedimentation rate. [^{18}F]FDG-PET–CT=^{18}F-fluorodeoxyglucose-positron emission tomography. *Diagnosis confirmed at 6 months. †Data shown for patients on treatment. ‡Temporal artery biopsy done in 35 of 229 patients. §[^{18}F]FDG-PET–CT done in 35 of 229 patients. ¶ESR measured in 199 of 229 subjects. ‖CRP measured in 228 of 229 patients.

Table 1: **Patient characteristics**

See Online for appendix 1

performed a receiver operating characteristic (ROC) analysis with area under the curve (AUC). Optimal cutoff points were determined according to the Youden Index. We established the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio at the optimal cutoff points.

Inter-rater and intra-rater reliability were determined by intra-class correlation coefficient (ICC; two-way mixed effects model, single measures, absolute agreement), indicating excellent (ICC >0·9), good (ICC >0·75–0·9), moderate (0·5–0·75), or poor (<0·5) reliability. Bland–Altman plots were created by plotting the mean of the observations for each patient on the x-axis, and the difference between the observed values and the mean on the y-axis. The 95% limits of agreement were calculated as the mean difference plus or minus 1·96 times the standard deviation.

We established multivariable prediction models (full description in the appendix 1 pp 3–4), as obtained by binary logistic regression (the enter method), with SGCAPS and each of the three ultrasonographic scores (ie, halo count, halo score, and OGUS) as predicting variables and the final clinical diagnosis as the outcome (giant cell arteritis=1, no giant cell arteritis=0). SGCAPS and each of the three ultrasonographic scores were applied as continuous variables. Next, we did an internal validation of the models by bootstrapping 2000 samples of the original data set. We determined optimism-corrected C statistics and bootstrap shrinkage factors and used these to correct coefficients in the models to establish the final prediction models. Internal validation of the model was performed by subanalysis of patients from the largest centre versus the other centres. We created a nomogram of the logistic regression model with the online version of simple Nomo.[21] p values lower than 0·05 were considered significant. Data were analysed with IBM SPSS Statistics 27, MetaDiSc 1.4, STATA 15.1, STATA 18.0 and Graphpad Prism 9.

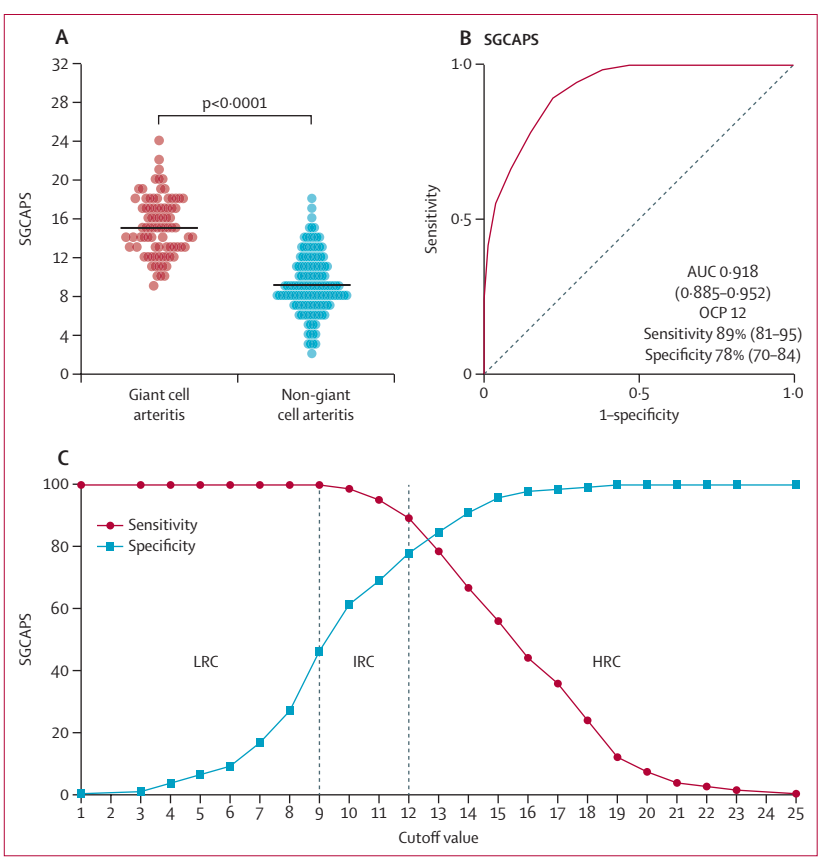

Figure 1: **Use of SGCAPS for the diagnosis of giant cell arteritis**
(A) SGCAPS in patients with (n=84) and without (n=145) giant cell arteritis. (B) Receiver operating characteristic analysis of SGCAPS for diagnosis of giant cell arteritis. The 95% CIs are provided for the diagnostic parameters. (C) Sensitivity and specificity of SGCAPS at different cutoff values of the SGCAPS. Significance tested by Mann Whitney U test. AUC=area under the curve. HRC=high risk category. IRC=intermediate risk category. LRC=low risk category. OCP=optimal cutoff point by Youden index. SGCAPS=Southend Giant Cell Arteritis Probability Score.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

229 patients with suspected giant cell arteritis were recruited to the study from Oct 1, 2019, with follow-up assessments completed by June 30, 2022 (appendix 1 p 16). The first patient was recruited on Oct 24, 2019, and the last was recruited on Dec 28, 2021 (control). A diagnosis of giant cell arteritis was confirmed in 84 (37%) patients at 6 months follow-up (all fulfilled the 2022 EULAR–American college of Rheumatology [ACR] criteria for giant cell arteritis).[22] Alternative diagnoses in patients without giant cell arteritis included other rheumatic or eye diseases, cancer, and infections (appendix 1 p 5). The mean age was 75 years (SD 8) among patients with giant cell arteritis and 69 years (10) in those without giant cell arteritis. Female participants were predominant, with a proportion of 60% among patients with giant cell arteritis and 69% among those without. Ethnic origin of the participants was not collected. 92 (40%) participants had already received glucocorticoid treatment for suspected giant cell arteritis at the time of inclusion in the study (table 1).

SGCAPS, as measured at baseline, was higher in patients with giant cell arteritis than in those without the disease (figure 1). The ROC analysis indicated that SGCAPS could discriminate well between patients with and without giant cell arteritis (figure 1), with an AUC of 0·918 (95% CI 0·885–0·952; appendix 1 p 6). SGCAPS classification was low-risk in 67 (29%) of 229 patients, intermediate-risk in 72 (31%) patients, and high-risk in 90 (39%) patients. The number of patients with confirmed giant cell arteritis at 6 months was 0 in low-risk patients, 17 (24%) in intermediate-risk patients, and 67 (74%) in high-risk patients (appendix 1 p 7).

The halo count was higher in patients with giant cell arteritis than in those without, and it showed good diagnostic accuracy for giant cell arteritis (figure 2), with

an AUC of 0·936 (95% CI 0·899–0·974). The same was true for the updated halo score and OGUS (appendix 1 p 17). Axillary artery grading for the halo score was updated based on the 20%, 40%, 60%, and 80% percentiles of abnormal IMT measured in this artery (appendix 1 pp 8–9). The revised axillary artery halo score primarily provided specificity for giant cell arteritis, whereas the temporal artery halo score showed high sensitivity and specificity for giant cell arteritis (appendix 1 pp 10, 18).

The reliability of the three main ultrasonographic scores was determined. The intraclass correlation coefficient for inter-rater and intra-rater reliability was high (ie, >0·9) for all three scores (appendix 1 p 11). Bland-Altman plots suggested relatively stable variation for halo count and OGUS across the range of scores (appendix 1 p 19). For the halo score, the variation in measurements tended to be larger in patients with higher halo scores.

Combining SGCAPS risk categories with the traditional classification of ultrasonographic findings in giant cell arteritis (ie, halo sign present or absent) allowed us to identify 117 patients with low post-test probability of giant cell arteritis and 73 patients with high post-test probability (figure 3A). Based on these results, the observed diagnostic accuracy of halo sign presence showed a sensitivity of 93% (95% CI 85–97), a specificity of 81% (74–87), a positive likelihood ratio (LR+) of 4·99 (3·53–7·04), and a negative likelihood ratio (LR–) of 0·09 (0·04–0·19; appendix 1 p 10). The number of patients misclassified by this stepwise approach was three (3%) patients among those with low post-test probability (ie, diagnosis was actually giant cell arteritis), and nine (12%) patients among those with high post-test probability (ie, diagnosis was not giant cell arteritis, including four patients with polymyalgia rheumatica). Two misclassified patients in the high probability group were eventually diagnosed with cancer mimicking giant cell arteritis.

Logistic regression analysis showed that SGCAPS and the respective ultrasonographic parameters were independent predictors for a diagnosis of giant cell arteritis (table 2). The relatively high coefficient estimate for OGUS was related to the relatively small values and range of this variable (median 0·65, IQR 0·54–0·97). Nagelkerke R^2 and the C statistic were high for all three models. Hosmer and Lemeshow test suggested the best goodness of fit for the SGCAPS–halo score model and the poorest fit for the SGCAPS–OGUS model ($p<0·05$). Models were then corrected for overfitting by bootstrapping. Optimism-corrected models were established (appendix 1 p 21). The SGCAPS–halo count prediction model is represented by the following equation:

$$\text{Probability of giant cell arteritis} = \frac{1}{1+e^{-(-7·107193+0·4175033\times\text{SGCAPS}+0·9940937\times\text{halo count})}}$$

The optimism-corrected models retained high C statistic values (optimism-adjusted C statistic 0·969, 95% CI 0·952 to 0·990, for the SGCAPS–halo count model; appendix 1 p 12), with good calibration (appendix 1 p 20). Easy calculation of the probability of giant cell arteritis according to these models can be done with the calculation file in appendix 2.

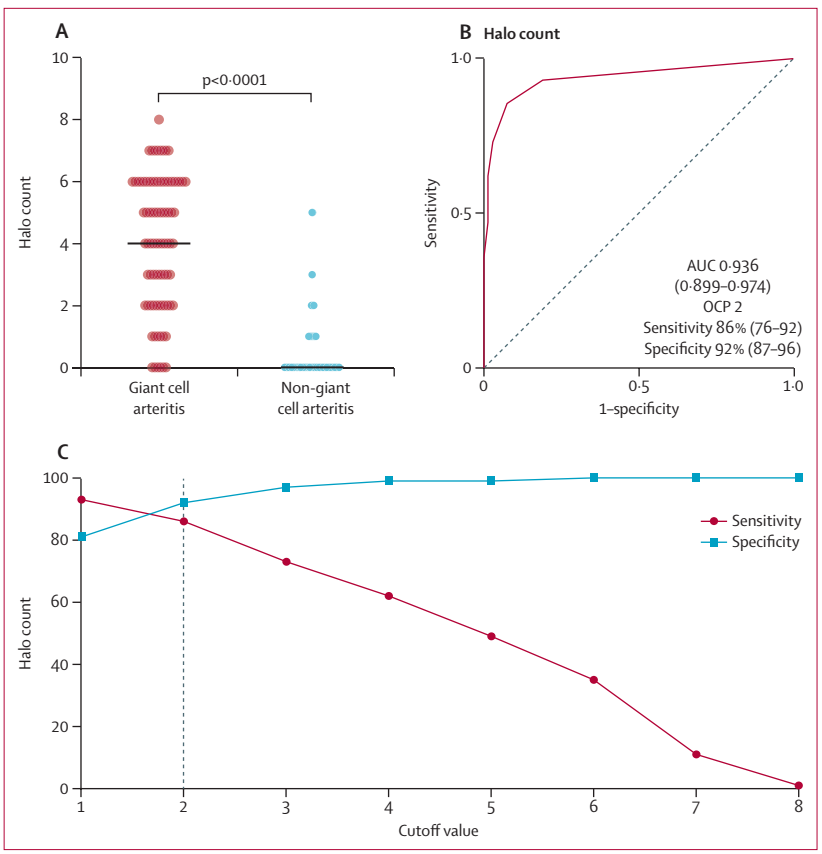

Figure 2: **Halo count for diagnosis of giant cell arteritis**
(A) Halo count in patients with (n=84) and without (n=145) giant cell arteritis. (B) Receiver operating characteristic analysis of halo count for diagnosis of giant cell arteritis. The 95% CIs are provided for the diagnostic parameters. The halo count is the number of arterial segments with a halo sign in eight regions (score range 0–8), as examined bilaterally in the three temporal artery segments and axillary arteries. (C) Sensitivity and specificity of halo count for diagnosis of giant cell arteritis. Significance tested by Mann–Whitney *U* test. AUC=area under the curve. OCP=optimal cutoff point by Youden index.

Optimal cutoff values defining low, intermediate, and high probability groups were established for the corrected models (appendix 1 p 13). The SGCAPS–halo count model showed the lowest rate of misclassification in the low and high probability groups, which together contained 169 (74%) of all patients (figure 3B). Misclassification rates were slightly higher in the SGCAPS–halo score and SGCAPS–OGUS models (appendix 1 p 21), which grouped 185 (81%) patients (SGCAPS–halo score model) and 187 (82%) patients (SGCAPS–OGUS model) into the low or high probability groups for giant cell arteritis. Details on misclassified patients are shown in the appendix 1 (pp 14–15). We did a geographical validation of the models with a subanalysis of misclassification rates in patients from the largest study centre (n=126) versus those from the other study centres (n=103). The performance of

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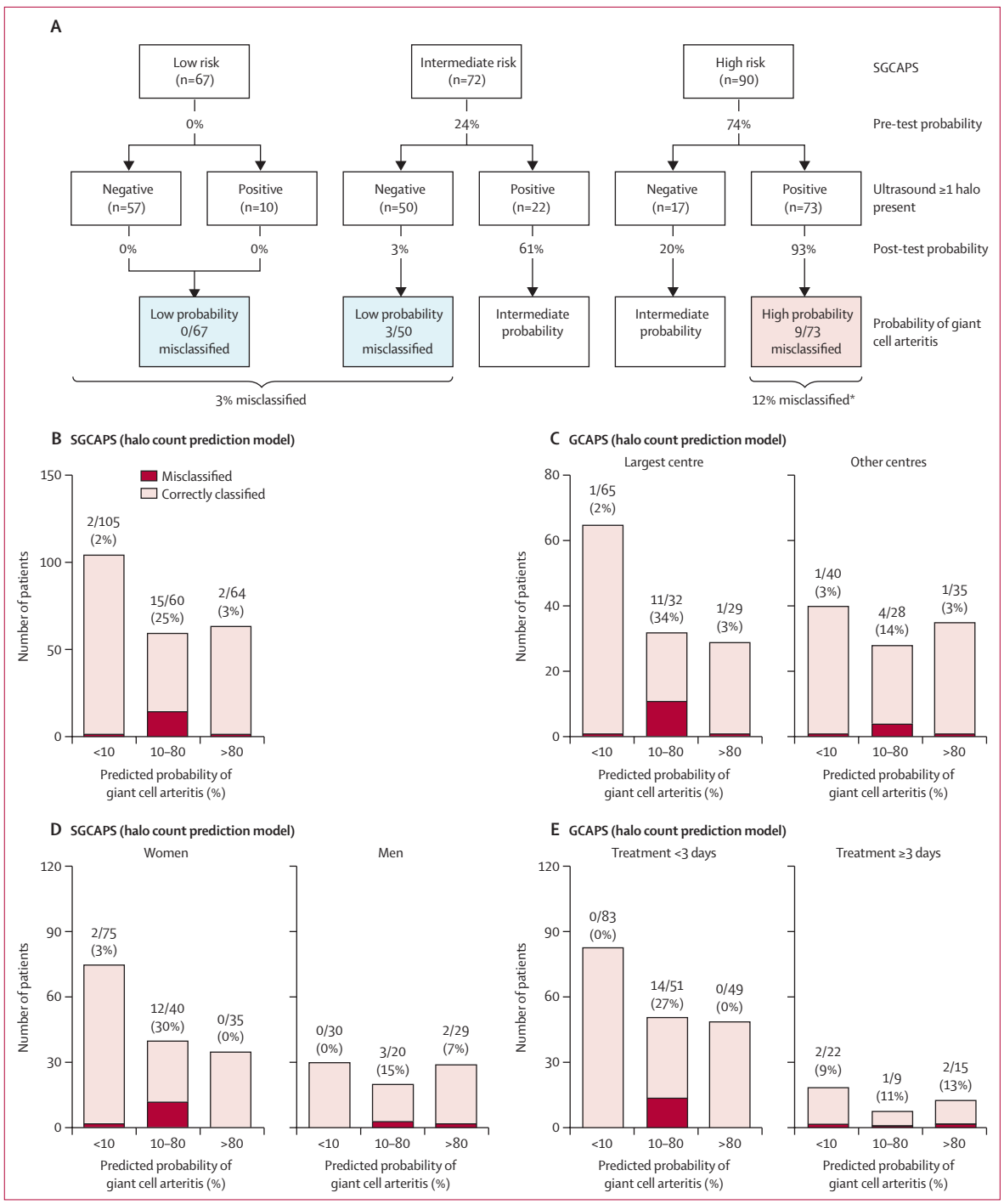

Figure 3: **Integrating SGCAPS and ultrasonography**

(A) Diagnostic performance of SGCAPS together with traditional interpretation of ultrasonography (ie, halo sign present [=positive test] or absent [=negative test]). Rates of misclassification are shown for the low and high probability groups identified by SGCAPS and halo sign presence. Post-test probability was established by using the pre-test probability according to SGCAPS risk categories and likelihood ratios for presence of halo sign (LR+ 4·987) or absence of halo sign (LR– 0·088). *Four patients had polymyalgia rheumatica. (B) Percentage of misclassified patients in the low probability, intermediate probability, and high probability groups as defined by the prediction model. Data are shown for all 229 patients. (C) Geographical validation of the prediction model by separate analysis of patients from the largest centre (n=126) and patients from the other centres (n=103). (D) Misclassification by HAS-GCA score in men (n=79) and women (n=150). (E) Misclassification by HAS-GCA score in patients on treatment for less than 3 days (n=183) and for 3 days or more (n=46). Applied cutoff of for predicted giant cell arteritis classification in the intermediate probability group: probability ≥0·5. LR+=likelihood ratio for presence of halo sign. LR–=likelihood ratio for absence of halo sign. SGCAPS=Southend Giant Cell Arteritis Probability Score.

	Coefficient (95% CI)	p value	Nagelkerke R^2	Likelihood χ^2 test		Hosmer and Lemeshow test p value	C statistic (95% CI)
				χ^2 (2)	p value		
SGCAPS–halo count model							
Constant	−7·390 (−9·845 to −4·934)	..	0·797	200·123	<0·0001	0·058	0·970 (0·951 to 0·990)
SGCAPS	0·436 (0·244 to 0·629)	<0·0001	..	..	..	..	..
Halo count	1·039 (0·649 to 1·428)	<0·0001	..	..	..	..	..
SGCAPS–halo score model							
Constant	−8·203 (−10·765 to −5·641)	..	0·805	203·596	<0·0001	0·369	0·969 (0·950 to 0·989)
SGCAPS	0·441 (0·248 to 0·634)	<0·0001	..	..	..	..	..
Halo score	0·375 (0·239 to 0·511)	<0·0001	..	..	..	..	..
SGCAPS–OGUS model							
Constant	−11·373 (−14·415 to −8·332)	..	0·792	198·448	<0·0001	0·026	0·968 (0·949 to 0·988)
SGCAPS	0·429 (0·236 to 0·621)	<0·0001	..	..	..	..	..
OGUS	7·208 (4·607 to 9·810)	<0·0001	..	..	..	..	..

Logistic regression analysis evaluating SGCAPS and halo count, halo score, or OGUS as predictors for a clinical diagnosis of giant cell arteritis. For all three models, the dependent variable was final diagnosis. OGUS=OMERACT Giant Cell Arteritis Ultrasound Score. SGCAPS=Southend Giant Cell Arteritis Probability Score.

Table 2: **Logistic regression analysis, by predicting variable**

the SGCAPS–halo count model was similar in the two groups (figure 3C). Overall, the SGCAPS–halo count model consistently showed lower misclassification rates than the other two models (appendix 1 p 22). Thus, the SGCAPS–halo count model was selected as the most accurate for the assessment of giant cell arteritis probability and termed HAS-GCA score. A nomogram for easy application of the HAS-GCA score in daily practice was created (appendix 1 p 24).

Finally, we did two subanalyses to better understand the performance of the HAS-GCA score. Sex-stratified analysis indicated that misclassification in the low probability group was restricted to women (n=2), whereas misclassification in the high probability group was only observed in men (n=2; figure 3D). In addition, misclassification in the low and high probability groups was only seen in patients treated with glucocorticoids for 3 days or more at the time of evaluation. In contrast, no misclassification occurred in these probability groups when patients had been treated for less than 3 days (figure 3E).

Discussion

We have developed a prediction model combining clinical and quantitative ultrasound features in order to obtain a standardised prediction of post-test probability of giant cell arteritis. The simplest model, based on SGCAPS and halo count, termed HAS-GCA score, showed good discrimination and could assign 74% of patients into either low or high probability groups. Only a small group required additional testing after sequential clinical and ultrasound assessment. Low rates of misclassification were observed in the low and high probability groups. Geographical validation of the HAS-GCA score demonstrated excellent performance of this model in very different circumstances.

An important advantage of the HAS-GCA score is that it effectively uses all clinical and ultrasonographic data obtained in patients with suspected giant cell arteritis. Categorisation of SGCAPS (ie, low, intermediate, and high risk) and ultrasonography findings (halo present or absent) might lead to loss of predictive information and introduce subjectivity dependent on the clinician's expertise.[18] Our findings standardise the assessment of the probability of giant cell arteritis by incorporating the full range of SGCAPS and each of the three ultrasonographic scores to accurately identify patients with or without giant cell arteritis, as well as areas of uncertainty in which patients would benefit from additional diagnostic testing. Importantly, the HAS-GCA score and the nomogram are easy to use without the need for a computer or calculator.

The SGCAPS was previously developed to aid clinicians in establishing the clinical probability of giant cell arteritis before additional testing by ultrasonography.[5] The diagnostic interpretation of single symptoms, signs, and laboratory tests might have little value in a protean disease such as giant cell arteritis.[4] The strength of SGCAPS lies in the standardised integration of multiple key clinical assessments such as demographics, mode of onset, signs, symptoms, C-reactive protein, and presence or absence of alternative diagnoses. It was developed and has been validated previously in retrospective cohorts.[7–10] Recently, Sargi and colleagues validated the SGCAPS in a prospective study.[11] They also demonstrated that the SGCAPS has higher accuracy for a clinical diagnosis of giant cell arteritis than other clinical prediction tools. Our study represents the second validation of SGCAPS in a prospective study, and the first to do so with a multicentre study design.

The three existing ultrasonographic scores, originally described for assessment of disease extent and severity in

temporal and axillary arteries of patients with giant cell arteritis, performed equally well for diagnosis. This includes the halo count, which is the simplest score, the halo score, and the OGUS.[15,16] The halo score was updated in the current study to reflect changes to axillary artery reference values. Since the collection of the original measurements underlying the axillary artery score,[23] the definitions of abnormal findings and machine performance have changed considerably,[14,20] leading to updated EULAR imaging recommendations.[12] Nevertheless, temporal artery grading still performed well, despite the halo score being developed with data obtained over 10 years ago in the TABUL study.[23] The OGUS, which is the most complex score, has been provisionally selected as the score for therapy monitoring on the basis of its performance in an online reliability exercise.[16] Our patient-based reliability exercise showed equally good reliability for all three scores. Nevertheless, inter-observer variability does exist even among ultrasonography experts, although this also applies to other diagnostic tests for giant cell arteritis such as temporal artery biopsy.[23] Our finding that the SGCAPS–halo count model performs well could expand generalisability since the halo count is the simplest of the three ultrasonographic scores to assess.

Although the HAS-GCA score aids data-driven decision-making in patients with suspected giant cell arteritis, it needs to be used with clinical circumspection. An important aspect of any prediction model is its ability to classify patients correctly.[18] The HAS-GCA score showed low misclassification rates in the low and high probability groups, similar to that reported for widely used prediction models, including Well's criteria for risk assessment of pulmonary embolism and deep vein thrombosis.[24] Misclassification in the low probability group (n=2) occurred in patients with isolated vertebral arteritis, while the few misclassified patients (n=2) in the high probability group were eventually diagnosed with cancer mimicking giant cell arteritis. An influencing factor in this context could be sex. Misclassified patients in the low probability group were all women, whereas misclassified patients in the high probability group were all men. This was associated with perceived absence of halo signs in the respective women and high halo counts in the men. Previous studies have already indicated that men might have more pronounced findings on ultrasonography than women, probably because of differences in arterial calibre and wall thickness.[15,25] Future studies should address whether IMT dimensions can be corrected for age and sex (manuscript in preparation). Overall, we recommend additional testing in situations of disease uncertainty, discordance between clinical assessment and ultrasound imaging, unexplained systemic symptoms and inflammation, and poor response to treatment. The HAS-GCA score should be considered as an adjunct to clinical reasoning of clinicians; improving the safety of giant cell arteritis diagnosis, when applied correctly in clinical practice.

Our study emphasises the value of fast-track clinics for suspected giant cell arteritis. Fast-track clinics provide rapid access to clinical and vascular ultrasonography evaluation and treatment, in order to reduce the occurrence of irreversible visual loss.[2,26] Recent EULAR recommendations emphasise the need to perform imaging within 3 days after start of therapy.[12] Our findings support this recommendation. The HAS-GCA score showed no misclassification in the low and high probability groups when patients had received treatment for less than 3 days at the time of the ultrasonographic evaluation. All misclassified patients in the low and high probability groups had been treated for 3 or more days. We are aware that expertise in vascular ultrasonography for giant cell arteritis is not yet available everywhere. We hope that the current study will encourage the use of SGCAPS and help in disseminating interest and skill in the application of vascular ultrasonography in clinics and populations that currently do not have this facility.

A strength of our study is its prospective design, including sequential clinical and ultrasonographic evaluation reflecting standard practice in fast-track clinics for giant cell arteritis. The study was performed in different centres and countries, allowing to test the HAS-GCA score performance under very distinct conditions.

Our study also has limitations. A limitation of any diagnostic study in giant cell arteritis is the inherent circularity in the decision-making since the predicting variables of the HAS-GCA score (ie, SGCAPS, each of the three ultrasonographic scores) affect the eventual clinician's diagnosis. However, no other gold standard for giant cell arteritis is currently available, and the only way to establish the diagnosis is by integrating all data obtained by extensive clinical, laboratory, imaging or biopsy assessment.[27] Leaving out part of the information will inherently compromise the validity of the diagnosis. Importantly, we confirmed the diagnoses after 6 months of follow-up, which is now common practice in diagnostic studies of giant cell arteritis.[23] As our study was focused on the development of a prediction model, the HAS-GCA score requires further external validation before its application in daily practice. We refrained from splitting our patient cohort into a separate development and validation cohort, as we preferred to develop our model based on all data available. Although efforts were made to mask the sonographers to the clinical data, unfortunately, due to the circumstances (COVID-19 pandemic), it was not easy to fully comply because of local restrictions. It is worth considering this in future studies. Another limitation might be that fast-track clinics for giant cell arteritis with expertise in vascular ultrasonography are not uniformly available. This emphasises the need for training courses offering vascular ultrasonography skills integrated into a point-of-care rheumatology ultrasound approach.

In conclusion, we have shown that a prediction tool for giant cell arteritis (the HAS-GCA score), combining SGCAPS and the halo count, reliably confirms or

excludes giant cell arteritis from giant cell arteritis mimics in fast-track clinics. The score is conveniently obtained with a nomogram using a standardised clinical assessment and the easily ascertained halo count. The applicability and safety of our findings require validation in independent, multicentre studies.

Contributors

All authors had full access to all the data in the study. AS and BD directly accessed and verified the underlying data reported in the manuscript. KSMvdG and BD take full responsibility for the accuracy of the data analysis. BD, KSMvdG, AS contributed to the conception and design of the work and drafting of the paper. AS contributed to overall data collection and management. KSMvdG did the data analysis. All authors contributed to source Data Collection (clinical and ultrasound assessment at sites) and reviewed the work critically for important intellectual content. All authors had final responsibility for the decision to submit for publication and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

KSMvdG reports having received a speaker fee from Roche and research support from AbbVie, paid to the University Medical Center Groningen (UMCG). EC reports honoraria from GlaxoSmithKline and Chiesi. DP-P received a research contract from the Carlos III Health Institute of Spain (Rio Hortega program, reference CM20/00006), in 2021–2022; honoraria from Lilly, Novartis, AbbVie, Amgen, Merck Sharp & Dohme, S&H Medical Service Science; and support for attending meetings from Lilly, AbbVie, Pfizer. EB is an employee of the UMCG, received grants from the Dutch Arthritis Society DAS and the EU/EFPIA/Innovative Medicines Initiative 2 Joint Undertaking Immune-Image (grant number 831514) and received a speaker fee for a talk on giant cell arteritis at a post EULAR symposium organised by Mark Two Academy in the Netherlands in 2023, all were paid to the UMCG. EB is a board member of non-profit organisation ARCH (Auto-immune Research Hub) in the Netherlands. BD reports consultancy fees from Novartis, AbbVie, Sanofi. All other authors declare no competing interests.

Data sharing

Data are available upon reasonable request.

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