Subclavian arteries involvement in patients with giant cell arteritis: do we need a modified Halo Score?

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Abstract

Objective: To assess whether adding the subclavian arteries examination into the ultrasound (US) Southend Halo Score, as proposed in the modified Halo Score, improves the diagnostic accuracy of giant cell arteritis (GCA) and its relationship with systemic inflammation.

Methods: Retrospective observational study of patients referred to a GCA fast track pathway (FTP) over a 1-year period. Patients underwent US exam of temporal and large vessel (LV) (carotid, subclavian and axillary) arteries. The extent of inflammation was measured by the halo count, the Southend Halo Score and the modified Halo Score. The gold standard for GCA diagnosis was clinical confirmation after 6 months follow-up.

Results: 64 patients were evaluated in the FTP, 17(26.5%) had GCA. Subclavian arteries involvement was present only in patients with GCA (29.4% versus 0%,$p<0.001$). Overall, the three scores showed excellent diagnostic accuracy for GCA (ROC AUC 0.906, 0.930 and 0.928, respectively) and moderate correlations with acute phase reactants (0.35-0.51, $p<0.01$). Only the modified Halo Score correlated with markers of inflammation in patients with LV involvement.

Conclusions: The inclusion of subclavian arteries examination in the modified Halo Score does not improve the diagnostic accuracy of GCA. Nevertheless, it correlates better with markers of systemic inflammation in LV-GCA

Introduction

Giant cell arteritis (GCA) is the most common form of large vessel (LV) vasculitis(1). Currently, the gold standard for its diagnosis is a temporal artery (TA) biopsy; however, EULAR recommendations propose temporal and axillary arteries ultrasound (US) as first-line investigation when predominantly cranial GCA is suspected(2). Recently, two novel US scoring systems, the halo count and the Southend Halo Score, have been developed to quantify the extent of inflammation by US in GCA. These scores include the assessment of the three TA segments and axillary arteries(3). According to their findings, a high degree of vascular inflammation on US might strongly support GCA diagnosis and it correlates with markers of systemic inflammation and higher risk for ocular ischaemia. On the other hand, a modified Halo Score, which adds evaluation of subclavian arteries, has been recently proposed by Chattopadhyay et al(4). According to the authors, their addition to the Southend Halo Score may correct its tendency to underestimate the burden of inflammation in LV-GCA and Takayasu arteritis. However, this hypothesis needs to be supported by further evidence.

The objective of this study was to assess whether performing a modified Halo Score that includes the evaluation of subclavian arteries, improves the diagnostic accuracy and to evaluate its correlation with markers of inflammation in CGA in comparison with the original halo count and Southend Halo Score.

Methods

Patients

This is a retrospective observational study including patients referred to a US fast track pathway (FTP)(5) for evaluation of possible GCA over a one-year period. All patients referred to the FTP underwent US examination within 24 hours per protocol. The study was performed in routine daily practice conditions including consecutive unselected patients.

Data collection

The following variables were collected: demographics; clinical manifestations (headache, scalp tenderness, jaw claudication, visual symptoms and ocular ischaemia diagnosis, fever, polymyalgia and constitutional symptoms), use of glucocorticoids before the US evaluation and laboratory parameters including C- reactive protein (CRP), erythrocyte sedimentation rate (ESR), haemoglobin and platelets. TA biopsy and 18F-FDG-PET/CT were performed according to the treating clinician criteria. The gold standard for GCA diagnosis was clinical confirmation after 6 months follow-up.

Ultrasound assessment

All patients underwent bilateral US examination of the three TA segments (common superficial TA, its parietal and frontal branches) and extracranial (carotid, subclavian and axillary) arteries. The exam was performed by the same evaluator using an EsaoteMyLab8 (Esaote, Genoa) with a high frequency (12–18 MHz) transducer. The extent of vascular inflammation was quantified according to: 1)the halo count(3), number of TA segments and axillary arteries with a halo ranging from 0 to 8, 2)the Southend Halo Score(3), a composite index that incorporates both the number of halos and the maximum halo thickness in each region ranging from 0 to 48, and 3)the modified Halo Score (4): a composite index which includes three vascular territories: TA, subclavian and axillary arteries ranging from 0 to 32(Fig. 1).

Statistical analysis

Chi-square test or Fisher's exact test were used to analyze differences between proportions; Student's t test was used for comparison between means. Criterion validity was evaluated using receiver operating characteristic (ROC) curves with GCA clinical diagnosis as external criterion and construct validity was determined by Spearman's rank correlation coefficient (rho). All tests were two-sided; p values < 0.05 were considered statistically significant.

Ethical approval

This study was performed in accordance with the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration of 1975, as revised in 1983. Research ethics committee approval for the protocol was obtained prior to commencing the study (JMC03-REUMA0620).

Results

Patient characteristics

We analyzed data from sixty-four patients referred to the FTP, of whom 65% were female and mean age was 75.3 years. A deeper description of this population is presented in Table 1. A clinical diagnosis of GCA was established in 17 (26.5%) patients after 6 months follow-up. GCA patients tend to have higher acute phase reactants (APR) and presented more frequently with headache and jaw claudication. Only 2 (4.3%) patients without GCA versus 15 (88.2%) with GCA had positive US findings according to the ultrasonographer criteria. Among patients with GCA, 12 (70.6%) had cranial (TA) involvement, 8 (47.15%) had axillary involvement and 5 (29.4%) had subclavian arteries involvement. We found a mixed pattern with involvement of both TA and LV arteries in 5 (29.4%) patients(Table 1).

Diagnostic accuracy of the ultrasound scores for giant cell arteritis

Halo counts, Southend Halo Scores and modified Halo Scores were higher in patients with final diagnosis of GCA than patients without GCA ($p<0.001$)(Table 1). The area under the ROC curve (AUC) of the three proposed scores showed similar diagnostic accuracy for a clinical diagnosis of GCA (AUC 0.906, 0.930 and 0.928, respectively) and their optimal cut-off points yielded similar sensitivity, specificity and likelihood ratios for all the scores(Table 2).

Correlation of ultrasound with markers for systemic inflammation

All US scores correlated positively with variables measuring systemic inflammation as ESR and CRP. The correlation between the US scores and platelets was low and negative ($p<0.05$), except for the modified Halo Score ($p=0.053$)(Table 3). Haemoglobin levels showed no correlation with any of the scores. However, in the subgroup of patients presenting LV involvement, moderate correlations were found between the modified Halo Score and ESR (rho 0.712, $p<0.05$), haemoglobin (rho 0.703, $p<0.05$) and platelets (rho 0.734, $p<0.05$), but not with the other two US scores(Figure 2).

Discussion

Our study shows that adding subclavian arteries examination into the Southend Halo Score(3), as proposed in the modified Halo Score(4), does not improve the diagnostic accuracy of the former version for the US scores. However, the modified Halo Score shows better correlation with markers of inflammation in LV-GCA patients.

US has shown high sensitivity and specificity for diagnosing GCA(6–9) and therefore recent EULAR recommendations identified TA and axillary arteries US as the first-line investigation in patients with predominantly cranial GCA(2). In addition, the halo count and Southend Halo Score have recently been proposed to quantify the extent of vascular inflammation by US and correlate with systemic markers of inflammation and risk for ocular ischaemia(3). These novel score systems have also been validated in routine care and showed an excellent diagnostic accuracy for GCA diagnosis(10,11).

Wall swelling at subclavian arteries can be seen by US in LV-GCA patients(12–14), but involvement of subclavian arteries in the absence of vasculitic changes in the axillary arteries is rare and most clinical

guidelines include only axillary arteries on the LV examination(2,15). In this context, a novel modified Halo Score has been proposed including the assessment of three vascular territories (TA, axillary and subclavian arteries) instead of two, as the Southend Halo Score may underestimate the burden of inflammation in LV-GCA and Takayasu arteritis(4,16).

To our knowledge, this is the first study specifically designed to compare the diagnostic value of the three published quantitative scores for GCA diagnosis(3,4). According to our findings, the modified Halo Score does not improve the diagnostic accuracy when compared to halo count and Southend Halo Score(Table 2). All scores showed excellent ability to discriminate between patients with and without GCA, as indicated by high AUC in the ROC curve. Thus, the inclusion of the subclavian arteries into the Southend Halo Score increases the burden on the US examination as requires extra time, without improving its diagnostic accuracy.

Overall, all scores showed moderate correlations with markers of inflammation, except for haemoglobin levels(Table 3). However, in the LV-GCA subgroup the modified Halo Score seems to have some advantages, as it showed moderate positive correlations with ESR and platelets and moderate negative correlation with haemoglobin levels(Figure 2). Halo count and Southend Halo Score showed no correlation with laboratory findings in patients with LV involvement. Although grades of the axillary arteries included in the Southend Halo Score are multiplied by 3 in order to equate the inflammation of the TA and LV arteries, the fact that the modified Halo Score is based on the sum of the two higher scores of the 3 scanned regions (TA, axillary or subclavian arteries), seems to be related to a better detection capability of the general burden of inflammation. These findings may be relevant for monitoring purposes. Since the use of Tocilizumab challenged the assessment of activity in GCA due to suppression of the APR, the use of imaging may have a key role in monitoring treatment response(17). According to our data, the modified Halo Score is linked to markers of inflammation at baseline in LV-GCA patients.

Some limitations should be noted. First, our sample size warrants further validation in larger and additional populations. Second, the retrospective design is a prominent limitation, thus TA biopsy was only performed according to clinician criteria. Third, the ultrasonographer was not blinded to clinical data.

In summary, the inclusion of subclavian arteries examination by the modified Halo Score does not improve the diagnostic accuracy of GCA diagnosis over the halo count and Southend Halo Score. However, it correlates better with markers of systemic inflammation in LV-GCA and could be of additional value in monitoring response to therapy. Further studies are necessary to confirm these findings.

Declarations

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Contributors

All authors made substantial contributions to the conception and design of this study. Study design, subject recruitment and US examination were performed by JMC. JMC and LCM collected the epidemiological and clinical data. JMC and IC performed the statistical analysis. JMC, JMB, BSB, IC, LCM, LTF and JAG drafted the manuscript. All co-authors revised the final manuscript.

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Competing interests

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Patient consent for publication

not required.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research

Data availability

All data generated or analysed during this study are included in this published article

Ethics approval

The research protocol have been approved by the Research ethical Committee of Hospital General Universitario Gregorio Marañón, and all patients gave informed written consent for their participation in the study.

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. enero de 2013;65(1):1–11.
2. Dejaco C, Ramiro S, Duftner C, Besson FL, Bley TA, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis. 2018;77(5):636–43.
3. van der Geest KSM, Borg F, Kayani A, Paap D, Gondo P, Schmidt W, et al. Novel ultrasonographic Halo Score for giant cell arteritis: assessment of diagnostic accuracy and association with ocular ischaemia. Ann Rheum Dis. 2020;79(3):393–9.
4. Chattopadhyay A, Ghosh A. «Halo Score»: missing large-vessel giant cell arteritis- do we need a «modified Halo Score»? Ann Rheum Dis. 2020.

5. Diamantopoulos AP, Haugeberg G, Lindland A, Myklebust G. The fast-track ultrasound clinic for early diagnosis of giant cell arteritis significantly reduces permanent visual impairment: towards a more effective strategy to improve clinical outcome in giant cell arteritis? Rheumatology (Oxford). enero de. 2016;55(1):66–70.
6. Ball EL, Walsh SR, Tang TY, Gohil R, Clarke JMF. Role of ultrasonography in the diagnosis of temporal arteritis. Br J Surg. 2010;97(12):1765–71.
7. Arida A, Kyprianou M, Kanakis M, Sfikakis PP. The diagnostic value of ultrasonography-derived edema of the temporal artery wall in giant cell arteritis: a second meta-analysis. BMC Musculoskelet Disord. 2010;11:44.
8. Karassa FB, Matsagas MI, Schmidt WA, Ioannidis JPA. Meta-analysis: test performance of ultrasonography for giant-cell arteritis. Ann Intern Med. 1 de marzo de 2005;142(5):359 – 69.
9. Rinagel M, Chatelus E, Jousse-Joulin S, Sibilia J, Gottenberg J-E, Chasset F, et al. Diagnostic performance of temporal artery ultrasound for the diagnosis of giant cell arteritis: a systematic review and meta-analysis of the literature. Autoimmun Rev. 2019;18(1):56–61.
10. Molina Collada J, Martínez-Barrio J, Serrano-Benavente B, Castrejón I, Caballero Motta LR, Trives Folguera L, et al. Diagnostic value of ultrasound halo count and Halo Score in giant cell arteritis: a retrospective study from routine care. Ann Rheum Dis. 2020.
11. van der Geest KS, Dasgupta B. Response to: «Diagnostic value of ultrasound halo count and Halo Score in giant cell arteritis: a retrospective study from routine care» by Molina Collada et al. Ann Rheum Dis. 5 de agosto de 2020;.
12. Löffler C, Hoffend J, Benck U, Krämer BK, Bergner R. The value of ultrasound in diagnosing extracranial large-vessel vasculitis compared to FDG-PET/CT: A retrospective study. Clin Rheumatol. 2017;36(9):2079–86.
13. Ghinoi A, Pipitone N, Nicolini A, Boiardi L, Silingardi M, Germanò G, et al. Large-vessel involvement in recent-onset giant cell arteritis: a case-control colour-Doppler sonography study. Rheumatology. 2012;51(4):730–4.
14. Schmidt WA, Seifert A, Gromnica-Ihle E, Krause A, Natusch A. Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis. Rheumatology. 2008;47(1):96–101.
15. Mackie SL, Dejaco C, Appenzeller S, Camellino D, Duftner C, Gonzalez-Chiappe S, et al. British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis. Rheumatology. 2020;59(3):e1–23.
16. van der Geest KSM, Dasgupta B. Response to: «“Halo Score”: missing large vessel giant cell arteritis-do we need a modified “Halo Score?”» by Chattopadhyay and Ghosh. Ann Rheum Dis. 2020.
17. Coath F, Gillbert K, Griffiths B, Hall F, Kay L, Lanyon P, et al. Giant cell arteritis: new concepts, treatments and the unmet need that remains. Rheumatology. 2019;58(7):1123–5.

Tables

Table 1
Clinical, laboratory and ultrasound findings of patients included in the fast track pathway with or without GCA clinical confirmation. GCA: giant cell arteritis; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; US: ultrasound; SD: standard deviation

	Total n = 64	Patients with GCA n = 17	Patients without GCA n = 47	p
Age, mean (SD)	75.3 (10.7)	76.5 (9.6)	74.8 (11.1)	0.5
Female, n (%)	42 (65.6%)	10 (58.8%)	32 (68.1%)	0.491
Baseline use of steroids, n (%)	30 (47.6%)	7 (41.2%)	23 (50%)	0.534
Temporal artery biopsy positive n = 13, no. of patients	5 (38.5%)	5 (50%)	0 (0%)	0.231
Temporal artery biopsy length (mm) n = 13, mean (SD)	5.8 (2.9)	6.2 (3.2)	4.7 (1.5)	0.450
^{18}F-FDG-PET/CT positive n = 14, no. of patients	7 (50%)	5 (62.5%)	2 (33.3%)	0.592
Fulfilling 1990 GCA criteria, no. of patients	16 (25%)	8 (47.1%)	8 (17%)	0.022
Headache, no. of patients	31 (48.4%)	12 (70.6%)	19 (40.4%)	0.033
Scalp tenderness, no. of patients	4 (6.3%)	2 (11.8%)	2 (4.3%)	0.285
Jaw claudication, no. of patients	12 (18.8%)	9 (52.9%)	3 (6.4%)	< 0.001
Visual symptoms, no. of patients	12 (18.8%)	6 (35.3%)	6 (12.8%)	0.051
Fever, no. of patients	8 (12.5%)	2 (11.8%)	6 (12.8%)	1
Polymyalgia, no. of patients	29 (45.3%)	10 (58.8%)	19 (40.4%)	0.192
Ocular ischaemia, no. of patients	4 (6.3%)	2 (11.8%)	2 (4.3%)	0.285
Abnormal TA clinical examination, no. of patients	5 (7.8%)	3 (17.6%)	2 (4.3%)	0.112
CRP (mg/dL), mean (SD)	4.7(6.5)	9.1 (8.5)	3 (4.7)	0.001
ESR (mm/h), mean (SD)	52.8 (34.6)	68.3 (33.3)	46.8 (33.3)	0.044
Haemoglobin (g/dL), mean (SD)	12.5 (1.7)	11.8 (1.6)	12.7 (1.7)	0.059

	Total n = 64	Patients with GCA n = 17	Patients without GCA n = 47	p
Platelets 10^9/L, mean (SD)	276.1 (105.8)	323.4 (116.3)	258.7 (97.3)	0.52
Positive US findings, no. of patients	17 (26.6%)	15 (88.2%)	2 (4.3%)	< 0.001
Temporal artery positive US findings, no. of patients	13 (20.3%)	12 (70.6%)	1 (2.1%)	< 0.001
Axillary positive US findings, no. of patients	9 (14.1%)	8 (47.1%)	1 (2.1%)	< 0.001
Subclavian positive US findings, no. of patients	5 (7.8%)	5 (29.4%)	0 (0%)	< 0.001
Temporal artery + axillary or subclavian positive US findings, no. of patients	5 (7.9%)	5 (29.4%)	0 (0%)	0.003
Halo sign positive, no. of patients	17 (26.6%)	15 (88.2%)	2 (4.3%)	< 0.001
Compression sign positive, no. of patients	10 (15.6%)	9 (52.9%)	1 (2.1%)	< 0.001
Halo Count, mean (SD)	0.7 (1.5)	2.6 (1.9)	0.04 (0.2)	< 0.001
Halo Score, mean (SD)	4.6 (8.7)	15.9 (9.7)	0.5 (2.6)	< 0.001
Modified Halo Score, mean (SD)	2.5 (4.8)	8.5 (5.8)	0.3 (1.2)	< 0.001

Table 2
Diagnostic accuracy of halo count, Halo Score and modified Halo Score for a clinical diagnosis of GCA after 6 months follow-up. Youden index was used to determine the optimal cut-off points. AUC, area under the curve; LR+, positive likelihood ratio; LR−, negative likelihood ratio; Sens, sensitivity; Spec, specificity

	AUC	Optimal cut-off	Sens	Spec	LR+	LR-
Halo count	0.906	≥ 1	82%	96%	20.5	0.19
Halo Score	0.930	≥ 2	88%	96%	22	0.13
Modified Halo Score	0.928	≥ 1	88%	96%	22	0.13

Table 3
Correlations between halo count, Halo Score and modified Halo Score with markers of systemic inflammation (CRP, ESR, haemoglobin and platelets). rho: Spearman's rank correlation coefficient; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate

		ESR		CRP		Haemoglobin		Platelets	
		rho	p	rho	p	rho	p	rho	p
Halo count	rho	0.39	0.003	0.5	< 0.001	-0.08	0.536	0.34	0.008
Halo Score	rho	0.35	0.01	0.49	< 0.001	-0.08	0.524	0.28	0.031
Modified Halo Score	rho	0.36	0.008	0.51	< 0.001	-0.08	0.538	0.247	0.053

Figures

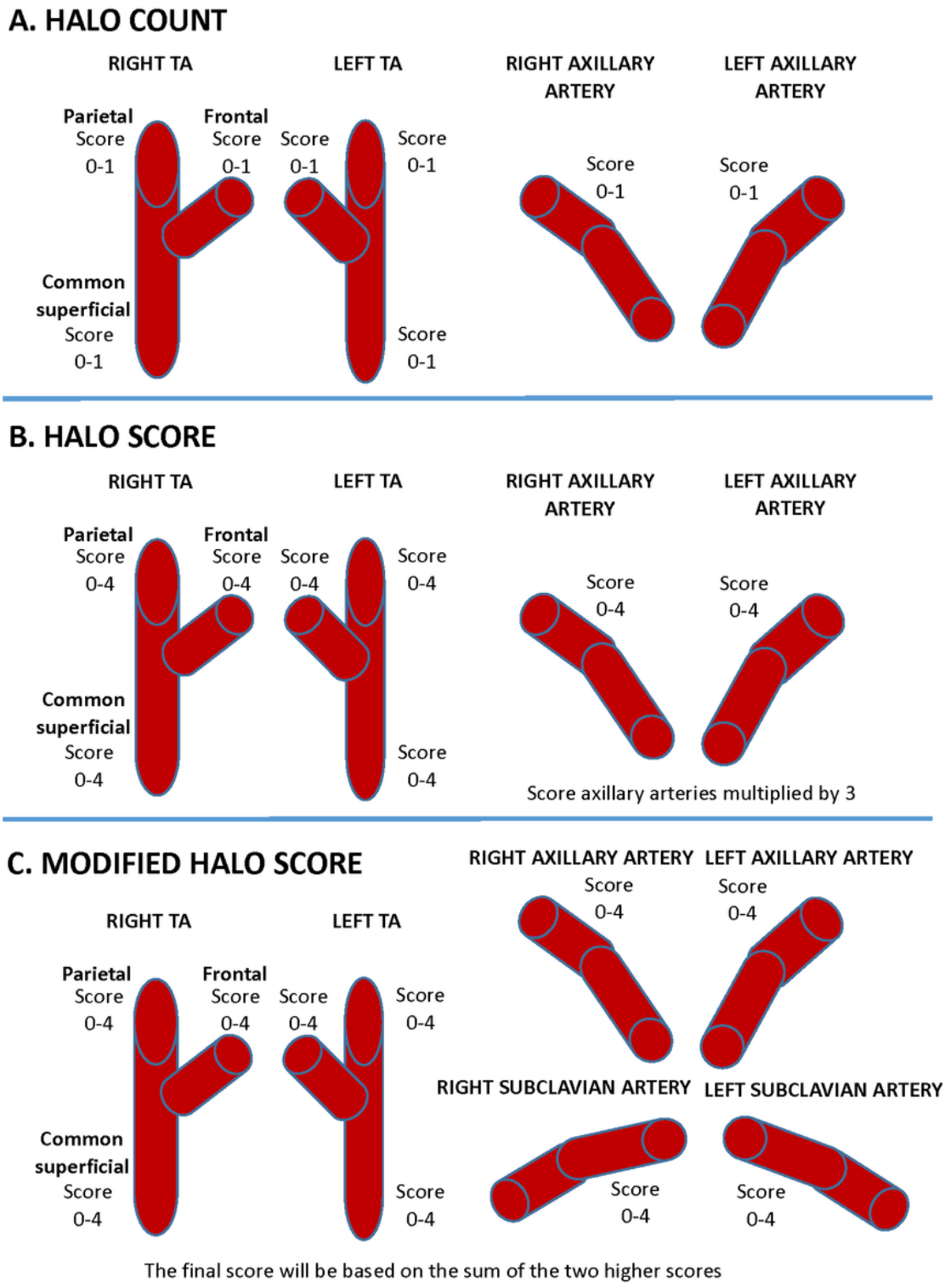

Figure 1

Proposed scores to quantify the extent of vascular inflammation by ultrasound in giant cell arteritis. A. Halo count(3): number of the three TA segments and axillary arteries with a halo sign ranging from 0 to 8. B. Halo Score(3): a composite index that incorporated the thickness of each halo, ranging from 0 to 48. Axillary artery scores are multiplied by 3 to give equal weight to the TA and axillary arteries. C: Modified

Halo Score(4): Adding the assessment of subclavian arteries to the previous index. The final score will be based on the sum of the two higher scores of the three vascular territories, ranging from 0 to 32.

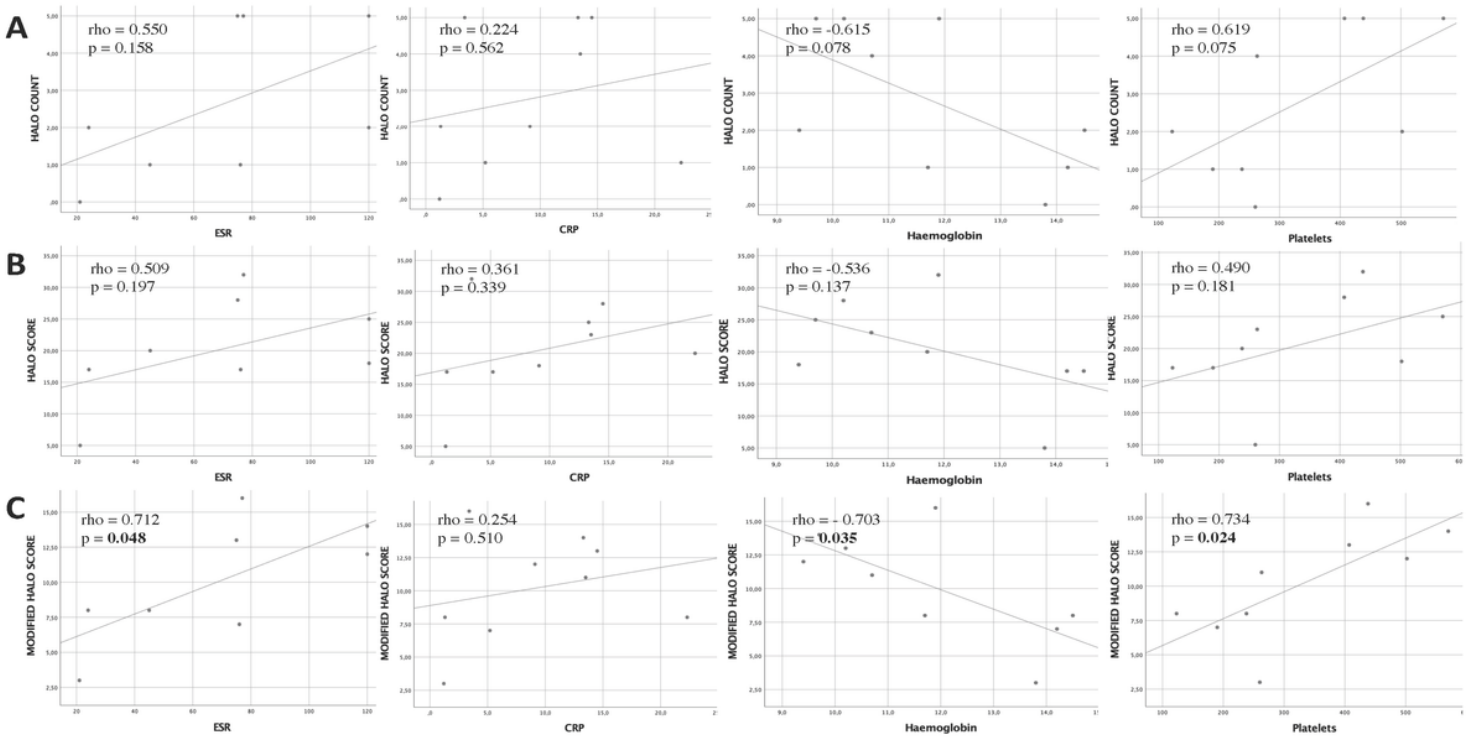

Figure 2

Correlations between halo count (A), Halo Score (B) and (C) modified Halo Score with markers of systemic inflammation (CRP, ESR, haemoglobin and platelets) in patients with large vessel involvement. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate