# The giant cell arteritis (GCA) ultrasound score (OGUS) at diagnosis and after initial treatment predicts future relapses in GCA patients: results of a multicentre prospective study

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## Abstract

### Objectives
To test the prognostic role of ultrasonography at diagnosis of giant cell arteritis (GCA) and the change of ultrasound abnormalities during the initial weeks of follow-up for the prediction of relapse, vascular complications, or initiation of disease-modifying anti-rheumatic drugs (DMARDs).

### Methods
Prospective, multicentre study of patients with new-onset GCA undergoing serial ultrasound assessment at fixed time-points. The OMERACT GCA ultrasonography score (OGUS) was used to quantify vessel wall abnormalities. Relapse was defined as recurrence of GCA-related symptoms or rise of inflammatory markers requiring treatment. A multivariable Poisson model with robust variance estimator was applied, including age, sex, large-vessel GCA, glucocorticoid cumulative dose and baseline OGUS as covariates.

### Results
Ninety-seven patients were assessed in 849 visits. Thirty-five (36.1%) patients experienced a total of 66 relapses, with median time to relapse of 210 days (IQR 94.5-323.5). A higher OGUS at diagnosis was associated with an increased risk of relapse within 12 months [incidence rate ratio (IRR) for each 1 point-increase in OGUS: 1.85 (95%CI 1.05-3.32)].
At multivariable analysis, OGUS normalisation (scoring <1) over the first 3 weeks was negatively associated with subsequent relapses [IRR 0.44 (95% CI 0.22-0.88)], and predicted time to first relapse. OGUS reduction over the first 12 weeks was inversely associated with initiation of DMARDs. Ischaemic/aortic complications were rare.

### Conclusions
Ultrasonography has a prognostic role in GCA and can inform risk stratification. A higher OGUS at diagnosis is associated with relapse, while a higher degree and rapidity of improvement in the first weeks are linked with lower relapse rate.

**Keywords**: giant cell arteritis, ultrasound, relapse, prognosis, ultrasound score, OGUS

**What is already known on this topic**

- Ultrasonography of temporal and axillary arteries is a recommended tool for the diagnosis of giant cell arteritis (GCA) and is being increasingly used to monitor disease activity. The Outcome Measures in Rheumatology (OMERACT) ultrasonography large vessel vasculitis working group has recently developed a composite ultrasonography score for GCA (OGUS) to be used as a monitoring instrument.
- Reliable prognostic markers are lacking in GCA.

**What this study adds**

- This study demonstrates for the first time, in a prospective, multicentre cohort, that ultrasonography has a prognostic role in GCA.
- A higher OGUS at the diagnosis of GCA and the rapidity and degree of improvement of OGUS during the first 3-6 weeks of follow-up predict the risk of future relapses.

**How this study might affect research, practice, or policy**

- Based on the data of our study, ultrasonography offers the unprecedented opportunity to stratify the individual patient risk at the time of diagnosis of GCA or within the first weeks of follow-up.
- The severity and extension of disease activity measured with a feasible composite ultrasound score, and the early rapidity of ultrasonography response represent novel prognostic markers of GCA that can be addressed in future research studies to guide the best therapeutic strategy, determine the intensity of follow-up, and document early response to treatment.

## Introduction

Giant cell arteritis (GCA) is the most common systemic vasculitis in patients aged ≥ 50. GCA requires prompt treatment with high-dose glucocorticoids (GC). Adjunctive disease-modifying antirheumatic drugs (DMARDs) are frequently used to minimize GC exposure or to manage refractory/relapsing cases (1). Despite treatment, approximately half of patients experience a relapse (2). To date, there are no reliable biomarkers nor clinical predictors of relapse that could enable stratification of the individual risk and guide treatment decisions (1,3). Moreover, with the expanding use of IL-6 inhibitors, monitoring of GCA has become a challenge given that traditional acute phase reactants become unreliable (4). Imaging with ultrasonography of the temporal and axillary arteries is now recognized as a diagnostic modality for GCA (5). More recently, the measurement of quantitative ultrasound data, including the intima-media thickness (IMT) and the number of sites with halos, has expanded the information that can be routinely monitored (6). The Outcome Measures in Rheumatology (OMERACT) ultrasonography large vessel vasculitis (LVV) working group has recently published a novel ultrasonography score for GCA, the OMERACT Giant cell arteritis Ultrasonography Score (OGUS), that integrates information from the IMT of eight vessels into a single score. OGUS was demonstrated to be feasible and has construct validity and sensitivity to change (7–10).

To date, there is no robust data supporting a prognostic role of disease extent and severity as measured by ultrasonography in predicting clinical outcomes. Similarly, we do not know whether the rapidity of response to treatment influences the long-term clinical response. Identifying predictors of relapse is crucial in a treat-to-target strategy, particularly for the implementation of the concepts of disease stratification and personalized medicine in the management of LVV (11).

In the current study, we aim to prospectively evaluate the prognostic role of the baseline OGUS, along with its rapidity and degree of improvement in the initial weeks following the diagnosis of GCA, as predictors of future relapses (primary endpoint), the initiation of DMARD treatment, ischaemic events, and aortic aneurysms/dissections.

## Methods

### Patients and data collection

Patients with a new clinical diagnosis of GCA were recruited from the Rheumatology Departments of three referral centres in Italy, Portugal, and Germany into a prospective, observational cohort study between March 2017 and July 2020. Diagnosis was clinically confirmed during follow-up by expert rheumatologists. The study was approved by the Pavia Ethic, Lisbon Academic Medical Centre, and Bonn Ethical committees (references E 2016 0031606, 08/17 and 097/18, respectively). All patients provided written informed consent before inclusion in the study. Patients received treatment according to standard of care in line with international recommendations. The GC regimen was not pre-specified in the protocol but followed international recommendations (1,12). The methodology from the PROgnosis of Temporal Arteritis (PROTEA) study was applied as previously described (13). In brief, GCA patients were recruited if they presented with a positive ultrasonography result at diagnosis, defined as the presence of an inflammatory wall thickening (halo sign) assessed qualitatively (14) at ≥1 branch of the superficial temporal (TA) and/or axillary arteries (AX), and had not received high doses of GCs (≥ 30 mg/day of prednisolone or equivalent) for >15 days. The initial GCA diagnosis was made by expert rheumatologists specialized in LVV, who performed both the clinical and ultrasound evaluations, in accordance with the EULAR-recommended fast-track approach to this disease (1,5). Less than 10% of patients referred to the fast-track clinics with a final diagnosis of GCA and a negative ultrasound were not eligible for the study. LV-GCA was defined at diagnosis by the presence of positive ultrasound at the level of the AX. Patients were assessed clinically and by ultrasonography at baseline, weeks 1, 3, 6 and 12, and then every 3 months up to one year. Clinical follow-up continued thereafter with assessments every 3-4 months. At the discretion of the managing physician, computed tomography angiography, echocardiography, and chest x-ray, were used to screen for the presence of aortic aneurysms during follow-up. Extra visits were scheduled in case of relapse. Relapse was defined as the recurrence of GCA-related symptoms or increased levels of acute phase reactants not otherwise explained and requiring GC/treatment increase (4). Ultrasonographic findings were not part of the definition of relapse. We applied the EULAR definitions for major and minor relapse (1).

**Patient involvement**

Patients were not involved in defining the research question. Research methods and outcomes were discussed with participants who will be informed on the results of the study.

**Ultrasonography methodology and OGUS calculation**

Ultrasonography of the TA with the common, parietal, and frontal branches, and AX was performed bilaterally at each time-point. The whole length of the middle and distal segments of the AX were assessed with the patient abducting the arm. Ultrasonography was conducted by a single rheumatologist at each centre (SM, CP, VS). All of them had a similar background trainings and levels of experience (15). The sonographers were not blinded to the clinical data. The presence of a halo sign, the number of sites with halos, and the maximum value of IMT measured in longitudinal view on the wall distal to the probe on greyscale images were recorded (7,14). Colour Doppler was used to aid artery identification but was typically turned off during IMT measurement to ensure more precise values. An Esaote MyLab 7 ultrasound machine (L6-18 MHz linear probe) was used in Pavia, a GE Healthcare LOGIQ-E9 (8-18 MHz hockey stick probe) in Lisbon and a GE Healthcare Logic S10 (18-24 MHz hockey stick probe for TA, linear 6-15 MHz for AX) in Bonn. The following technical parameters were applied: greyscale frequency of 18 MHz for TA and 13-18 MHz for AX. Pulse repetition frequency of 2.5-3.5 kHz for TA and 3-4 kHz for AX, colour box adjusted to obtain an angle steer correction to avoid perpendicularity between sound waves and artery, and gain adjusted to fill only the lumen (5,16). The OGUS was calculated as previously described (7).

The OGUS score was calculated as follows: the sum of IMT measured in every segment of the temporal and axillary arteries divided by the rounded cut-off values of IMTs in each segment. The resulting value was then divided by the number of segments available (7).Reaching OGUS<1 was referred to as OGUS normalisation as this indicates that on average all segments are within the normal range (7). Importantly, OGUS <1 does not necessarily correspond to a normal (negative) ultrasound.

**Statistical analysis**

Patients' characteristics were reported as absolute and relative frequencies for categorical variables, mean ± standard deviations (SD) or median and inter-quartile range (IQR) for continuous ones, as appropriate.

When ascertained to be non-pathological, missing data on the IMT were imputed by values sampled from a Normal random variable, upward bounded by the IMT normal value. This

occurred only if halo was not present on ultrasound assessment. Missing visits' data were imputed by within-patients means between the previous and following values for quantitative variables or LOCF (last observation carried forward) in case of last available visit before censoring or categorical variables. A total of 5.4% of missing data were imputed.

A landmark definition of the exposure to the OGUS improvement or normalisation has been adopted at 1, 3, 6, and 12 weeks to evaluate the rapidity of response to an OGUS change while avoiding immortal time bias. In this framework, time at risk started after the exposure was ascertained at each time-point (17). Exposure has been coded as either the continuous 10% reduction in the OGUS (improvement) with respect to the baseline or as an OGUS <1. The continuous multiplicative effect of each 10% improvement of the OGUS on the risk ratio was calculated. We measured the percentage change in OGUS to differentiate the improvement effect from the starting baseline OGUS level; moreover, 10% units were set as the least numerically significant improvement that could be interpreted in relation to the starting OGUS. Univariable and multivariable Poisson regression models with robust variance estimators were used to evaluate the association between the rapidity and degree of OGUS improvement at different time-points. Multivariable model adjusted for potential clinically relevant confounders: age, sex, baseline OGUS, cumulative glucocorticoids, large-vessel GCA. Incidence Rate Ratios (IRR) provide relevant measures of the relative risk for count-type outcomes when Poisson models are applied. Time-to-event outcomes were investigated by means of Cox regression models and reported as Hazard Ratios (HR) whenever the proportional hazards assumption was respected. We checked the proportional hazards assumption through visualization of the Schoenfeld residuals and appropriate testing. Moreover, we inspected relations among covariates and modified model specification (for example by introducing time-varying effects) based on clinical considerations.

Cox models with time-varying clinically relevant covariates (age, GC pulses, cumulative GC dose, DMARDs, ischaemic events and OGUS improvement/normalization) (referred to as longitudinal analyses) were employed to assess the overall predictors' effects on the outcomes over time, i.e. the overall degree of response to an OGUS improvement during the entire follow-up period.

All analyses were made on software R version 4.2.2, R Core Team (2021), Foundation for Statistical Computing, Vienna, Austria.

## Results

### 1. Population characteristics at disease onset

We included 102 patients with GCA, five of whom were excluded due to incomplete ultrasonography data during the first weeks from diagnosis. The final population consisted of 97 patients with a confirmed diagnosis of GCA assessed in 849 visits, with a median follow-up of 388 (IQR 331-860) days, and with a median number of visits per patient of 9 (IQR 5-11). 62 (70%) patients had follow-up >12 months. The clinical presentation at disease diagnosis is shown in Table 1. Forty-two (43.3%) patients had LV-GCA. Thirty-one (31.9%) patients were on high-dose GC (>30 mg/day) when ultrasonography was conducted (for a mean of 2.1±3.7 days). Overall, 33 (34%) patients received GC pulse therapy. Temporal artery biopsy was performed prior to ultrasonography in 2 (1.9%) patients; one had a positive result, while the second had LV-GCA with a negative TAB. Visual symptoms (double vision, amaurosis fugax, visual loss) occurred in 36 (37.1%) patients, with permanent visual loss confirmed in 21 (21.6%).

**Table 1. Clinical presentation at disease diagnosis**

| | **Patients (n= 97#)** |
|---|---|
| Demographics | |
| Female sex; n (%) | 58 (59.8) |
| Age (years); mean±SD | 77.1 ± 8.3 |
| Symptoms at disease onset; n (%) | |
| Time between symptom onset and diagnosis (days); median (IQR) | 12 (3-40) |
| Constitutional symptoms (any) | 48 (49.5) |
| Fever (≥38ºC or 100.4F) | 13 (13.4) |
| Weight loss (≥2 kg) | 43 (44.3) |
| New persistent headache | 68 (70.1) |
| New onset of vision loss (unilateral or bilateral) | 21 (21.6)* |
| Stroke/TIA | 6 (6.2) |
| Jaw claudication | 57 (58.8) |
| Tongue claudication | 8 (8.2) |
| Scalp tenderness | 33 (34) |
| New onset of PMR | 55 (56.7) |
| Laboratory tests at disease diagnosis; median (IQR)/mean±SD | |
| ESR (mm/hour)§ | 91 (63-100) / 82±32 |
| CRP (mg/dL) | 5.1 (2.5-7.8) / 5.6±4 |
| Immunosuppressive treatment at the time of baseline ultrasound | |
| Number of patients on high doses of GCs**; n (%) | 31 (31.9) |

| | Patients (n= 97#) |
|---|---|
| Days on high dose of GCs**; mean ± SD | 2.1±3.7 |
| Starting GC dose (mg/day), median dose (IQR) / mean±SD | 60 (50-250) / 239±332 |
| Cumulative prednisolone (or equivalent) dose (mg); median (IQR) /mean±SD | 60 (0-487.5) / 290±415 |
| Treatment with intravenous methylprednisolone prior to baseline ultrasonography; n (%) | 7 (7.2) |

AX: axillary artery; CRP: C-reactive protein; DMARDs: disease-modifying antirheumatic drugs; ESR: erythrocyte sedimentation rate; GC: glucocorticoid; GCA: giant cell arteritis; IMT: intima-media thickness; LV: large vessel; PMR: polymyalgia rheumatica; SD: standard deviation; TA: temporal artery; TIA: transient ischaemic attack

#Italy (n=24 patients), Portugal (n=28 patients), Germany (n=45 patients)

* Relevant proportion of patients referred to fast-track clinic by ophthalmologists due to visual loss occurring as first symptom.

**≥30mg/day of prednisolone or equivalent already received at the time of baseline ultrasound. All patients were then treated with high-dose glucocorticoids (40-60 mg/day) according to current recommendations after the baseline ultrasound, upon confirmation of the diagnosis of GCA.

§ ESR at baseline was not performed in the German centre. There were no missing data on other parameters assessed.

## 2. Ultrasound findings at baseline

At baseline, all patients had at least one arterial segment displaying a halo with a median of 5 (IQR 3-6) segments per patient. Ultrasound findings at baseline are depicted in Table 2. TA was involved in 93 (95.8%) patients and AX in 42 (43.3%) patients. Thirty-eight (39%) patients had both TA and AX involvement, while 4 (4.1%) had exclusive AX ultrasound positivity. Higher C-reactive protein (CRP) values (> 5.1 mg/dl, median value for the population) were associated with increased OGUS at baseline.

**Table 2. Ultrasound findings at baseline**

| | Patients (n= 97) |
|---|---|
| Ultrasound characteristics at baseline | |
| Number of arterial segments with halo; n (%) | |
| One segment | 4 (4.1) |
| Two segments | 12 (12.4) |
| Three segments | 12 (12.4) |
| Four segments | 11 (11.3) |
| Five segments | 14 (14.4) |
| Six segments | 32 (33) |
| Seven segments | 7 (7.2) |
| Eight segments | 5 (5.2) |
| Temporal artery | |
| Common superficial TA halo; n (%) | 78 (80.4) |
| IMT superficial TA (mean±SD; mm) | 0.73±0.26 |
| Frontal branch halo; n (%) | 79 (81.4) |
| IMT frontal branch (mean±SD; mm) | 0.66±0.24 |
| Parietal branch halo; n (%) | 74 (76.3) |
| IMT parietal branch (mean±SD; mm) | 0.56±0.23 |

| | Patients (n= 97) |
|---|---|
| Axillary artery | |
| Axillary artery halo; n (%) | 42 (43.3) |
| IMT axillary artery (mean±SD; mm) | 1.42±0.31 |
| OGUS | |
| OGUS at baseline; median (IQR) / mean±SD | 1.35 (1.11-1.70) / 1.46±0.5 |
| OGUS at baseline <1; n (%) | 17 (17.5%) |

AX: axillary artery; IMT: intima-media thickness; n: number; OGUS: OMERACT Giant cell arteritis Ultrasonography Score; SD: standard deviation; TA: temporal artery

### 3. Clinical outcomes during follow-up

#### Relapses

During follow-up, 35 (36.1%) patients experiences ≥1 relapse, resulting in a total of 66 relapses, with a median time to relapse of 210 days (IQR 94.5-323.5) and an overall incidence rate of 42 (95%CI 32-53) per 100-person years. Sixteen (16.5%) patients relapsed once, 11 (11.3%) had two relapses, and 8 (8.2%) had ≥3 relapses (5 patients had 3 relapses, 2 patients had 4 relapses, 1 patient had 5 relapses). Thirty patients (30.9%) relapsed within one year of diagnosis. Relapse incidence rates were 29.1 (10.7-63.4) per 100-person years in the group with a follow-up < 12 months, and 43.9 (33.5-56.5) per 100-person years after 12 months of follow-up. Details on the clinical manifestations at the time of relapse are reported in the supplementary material. Forty-four patients (67%) had a positive ultrasound at the time of relapse. Of these, 38 (57%) had a positive ultrasound at the level of the TA, 11 (17%) at the AX, and 5 (7%) patients had both TA and AX involvement. Mean number of halos was 2±1.3.

An adjunctive DMARD during follow-up was added in 40 (41.2%) patients, with interleukin-6 inhibitor (tocilizumab) being the most frequent drug, prescribed in 26 (26.8%) cases, followed by methotrexate (MTX) in 14 (14.4%). Tocilizumab was prescribed at diagnosis in 20 patients, while 5 patients received it after a relapse. In one patient, tocilizumab was used during follow-up as part of a strategy to rapidly taper GC in the presence of severe osteoporosis. One patient was prescribed concomitant MTX in adjunction to tocilizumab to treat a second relapse. MTX was used to manage relapses in 11 patients; 3 patients received MTX during follow-up to spare GC given that they were affected by diabetes mellitus.
Thirty-seven (38%) patients were in GC-free remission at the end of follow-up.

#### Visual loss and aortic complications

There was one new case of permanent visual loss during a relapse occurring after 45 months of follow-up (in addition to 21 patients who had permanent visual loss at presentation). Seven (7.2%) patients developed aortic aneurysms detected by computed tomography angiography after a median of 48 months (IQR 8.5-85). One patient developed aortic dissection at 48 months of follow-up.

### 4. Ultrasound changes during follow-up

Ultrasonographic changes and information on OGUS during follow up are presented in Table 3. Differences between patients who eventually experienced a relapse during follow-up and non-relapsing patients are presented.

**Table 3. Ultrasonographic changes during follow-up**

| | **Overall** | **Relapsing patients (n=35)** | **Never relapsing patients (n=62)** |
|---|---|---|---|
| OGUS; median (IQR) | | | |
| Baseline | 1.35 (1.11-1.70)# | 1.47 (1.09-1.88) | 1.28 (1.12-1.54) |
| 1 week | 1.04 (0.76-1.47) | 1.34 (0.80-1.66) | 0.91 (0.75-1.28) |
| 3 weeks | 1.03 (0.76-1.31) | 1.16 (0.79-1.44) | 0.96 (0.76-1.23) |
| 6 weeks | 1.01 (0.82-1.21) | 0.94 (0.83-1.35) | 1.03 (0.83-1.15) |
| 12 weeks | 0.99 (0.82-1.15) | 0.98 (0.80-1.20) | 1.00 (0.83-1.09) |
| OGUS <1; n (%) | | | |
| Baseline | 17 (17.5) | 5 (14.3) | 12 (19.4) |
| 1 week | 46 (47.9) | 13 (37.1) | 33 (54.1) |
| 3 weeks | 44 (45.8) | 12 (34.3) | 32 (52.5) |
| 6 weeks | 46 (48.9) | 17 (50) | 41 (78.8) |
| 12 weeks | 45 (51.7) | 18 (51.4) | 27 (51.9) |
| Never reached OGUS <1 | 15 (15.5) | 4 (11.4) | 11 (17.7) |
| Number of sites with halo; median (IQR) | | | |
| Baseline | 5 (3-6) | 5 (3-6) | 6 (3-6) |
| 1 week | 2 (0-5.2) | 4 (0.5-5.5) | 1 (0-5) |
| 3 weeks | 3 (0-5.2) | 3 (0-5) | 1 (0-6) |
| 6 weeks | 2 (0-4) | 1 (0-3) | 3 (0-5) |
| 12 weeks | 2 (0-4) | 1 (0-3) | 2 (1-5) |

IQR: interquartile range; n: number; OGUS: OMERACT Giant cell arteritis Ultrasonography Score
Mean±SD values provided in supplementary material (Supplementary Table 1).
#Baseline mean OGUS according to site (Italy: 1.29±0.37; Portugal: 1.99±0.52; Germany: 1.23±0.24)
* Wilcoxon test or t-test for OGUS score, chi-square test for OGUS < 1 and Poisson tests for halo counts comparisons have been employed.

## 5. Association of OGUS with clinical outcomes

### 5.1 Relapse risk

Baseline OGUS was associated with the risk of relapse during the subsequent 12 months IRR for 1 point-increase in OGUS: 1.85 (95%CI 1.05-3.32)].

The same was demonstrated in the adjusted longitudinal analysis where the baseline OGUS was directly associated with the risk of relapse (HR 2.79; 95%CI 1.36-5.73 per 1 unit increase in baseline OGUS).

Moreover, OGUS was significantly higher in patients experiencing a relapse [OGUS in relapsing vs non-relapsing patients: test for the difference in trends, p-value = 0.004] (Supplementary Figure 1).

The rapidity and degree of reduction of OGUS during the first three-six weeks after diagnosis was associated with the risk of future relapse (Table 4, Table 5). At univariable analysis, the effect of a 10% reduction of OGUS at 6 weeks from diagnosis, compared to an earlier reduction, was significantly associated with the risk of relapse at 1 year [IRR 1.24 (95% CI 1.05-1.46)].

Reaching an OGUS <1 over the first 3 weeks from diagnosis, compared to a delayed improvement in OGUS, inversely correlated with the risk of relapse over a 3-year follow-up (Table 4, Supplementary Figure 2).

Cox model confirmed that OGUS <1 within 3 weeks of follow-up was significantly associated with the time to first relapse (Supplementary Table 2).

At multivariate analysis, adjusting for potential confounders, the inverse correlation between the OGUS normalisation at weeks 1 and 3 of follow-up and the risk of future relapse was confirmed [adjusted IRR at 3 weeks 0.44 (95% CI 0.22-0.88)] (Table 5).

Moreover, in the longitudinal analysis adjusted for confounders, both a 10% improvement in OGUS and the normalisation of OGUS were confirmed to be associated with a decrease in the risk of relapse (adjusted HR 0.67; 95%CI 0.53-0.86, and 0.37; 95%CI 0.17-0.81, respectively) (Table 6).

The longitudinal models for the percentage of OGUS improvement (Table 6) demonstrated that a 1-point increase in the baseline OGUS confers a 2.79-fold increase in the risk of relapse

during follow-up, while the 10% improvement of OGUS at any time-point compared to baseline is associated with a 33% reduction in the risk of relapse (Figure 1).

**Table 4. Univariable analysis of the factors associated with the clinical outcomes**

| | **IRR for future relapse at 1 year** | **IRR for future relapses over 3 years** | **IRR for adjunctive DMARD treatment** |
|---|---|---|---|
| **UNIVARIABLE** | | | |
| **Clinical and treatment characteristics** | | | |
| Age (one year older) | 0.98 (0.95-1.02) | 0.99 (0.95-1.02) | 0.99 (0.97-1.03) |
| Sex (male) | 0.69 (0.33-1.43) | 0.92 (0.47-1.81) | 1.34 (0.82-2.19) |
| LV-GCA | 0.59 (0.27-1.29) | 0.63 (0.29-1.32) | **1.96 (1.19-3.23)** |
| Ischaemic GCA subtype | 1.16 (0.59-2.25) | 0.91 (0.49-1.69) | na |
| PMR symptoms at onset of GCA | 1.08 (0.55-2.11) | 0.94 (0.51-1.72) | 0.94 (0.57-1.52) |
| CRP at diagnosis > 5.1 mg/dl* | 1.53 (0.79-2.98) | 1.14 (0.63-2.06) | 1.02 (0.6-1.74) |
| TCZ prescribed at diagnosis | 0.42 (0.13-1.34) | 0.54 (0.17-1.73) | 4.28 (2.86-6.41) |
| GC cumulative dose at baseline (effect of adjunctive 100 mg) | 0.98 (0.9-1.07) | 1.04 (0.96-1.13) | 0.95 (0.87-1.03) |
| GC cumulative dose at baseline adjusted for pulses (effect of adjunctive 100 mg) | 0.99 (0.89-1.1) | 1.03 (0.92-1.15) | 0.92 (0.84-1) |
| GC cumulative dose at 3 weeks (effect of adjunctive 100 mg) | 1 (0.99-1.02) | 1.01 (0.99-1.03) | 0.99 (0.98-1.01) |
| GC pulses | 0.8 (0.37-1.75) | 1.35 (0.66-2.76) | 1.13 (0.68-1.88) |
| **Ultrasound findings** | | | |
| OGUS reduction by 10% at 1 week | 0.92 (0.79-1.07) | 0.88 (0.76-1.01) | 1.14 (0.99-1.30) |
| OGUS reduction by 10% at 3 weeks | 0.98 (0.78-1.24) | 0.98 (0.78-1.24) | 0.96 (0.80-1.16) |
| OGUS reduction by 10% at 6 weeks | **1.24 (1.05-1.46)** | 1.18 (0.99-1.39) | 0.97 (0.83-1.14) |
| OGUS reduction by 10% at 12 weeks | 1.17 (0.95-1.45) | 1.15 (0.93-1.42) | 0.91 (0.79-1.05) |
| OGUS <1 at 1 week | 0.56 (0.28-1.12) | **0.49 (0.26-0.93)** | 1.55 (0.89-2.7) |
| OGUS <1 at 3 weeks | 0.49 (0.23-1.05) | **0.44 (0.22-0.88)** | 0.93 (0.54-1.61) |
| OGUS <1 at 6 weeks | 0.9 (0.47-1.72) | 0.68 (0.38-1.23) | 1.42 (0.81-2.48) |
| OGUS <1 at 12 weeks | 0.88 (0.45-1.72) | 0.88 (0.48-1.64) | **0.56 (0.31-0.99)** |

Univariable Poisson regression with relapse count and DMARD treatment introduction as dependent variables.
*median CRP value for the included population
CRP: C-reactive protein; DMARD: disease modifying anti-rheumatic drugs; GC: glucocorticoid; IRR: incidence rate ratio; LV-GCA: large-vessel giant cell arteritis; OGUS: OMERACT Giant cell arteritis Ultrasonography Score; PMR: polymyalgia rheumatica; TCZ: tocilizumab
In bold: statistically significant results

## Table 5. Multivariable analysis of the factors associated with the clinical outcomes

| | IRR for future relapse at 1 year | IRR for future relapse over 3 years | IRR for adjunctive DMARD treatment |
|---|---|---|---|
| OGUS reduction by 10% at 1 week | 0.85 (0.7-1.04) | 0.88 (0.76-1.01) | **1.16 (1.01-1.33)** |
| OGUS reduction by 10% at 3 weeks | 0.87 (0.67-1.13) | 0.96 (0.81-1.15) | 1.02 (0.86-1.2) |
| OGUS reduction by 10% at 6 weeks | 1.07 (0.87-1.31) | 1.18 (0.99-1.39) | 1.13 (0.96-1.34) |
| OGUS reduction by 10% at 12 weeks | 0.89 (0.67-1.18) | 1.15 (0.93-1.42) | 1.01 (0.83-1.24) |
| OGUS <1 at 1 week | 0.65 (0.28-1.51) | **0.49 (0.26-0.93)** | 1.39 (0.72-2.7) |
| OGUS <1 at 3 weeks | 0.49 (0.19-1.31) | **0.44 (0.22-0.88)** | 0.77 (0.42-1.42) |
| OGUS <1 at 6 weeks | 1.39 (0.61-3.14) | 0.68 (0.38-1.23) | 1.81 (0.99-3.29) |
| OGUS <1 at 12 weeks | 0.96 (0.42-2.22) | 0.88 (0.48-1.64) | 0.77 (0.38-1.59) |

Multivariable Poisson model with relapse count and DMARD treatment introduction as dependent variables.
DMARD: disease modifying anti-rheumatic drug; IRR: incidence rate ratios; OGUS: OMERACT Giant cell arteritis Ultrasonography Score. In bold: statistically significant results; Analysis adjusted for: age, sex, baseline OGUS, cumulative glucocorticoids, large-vessel giant cell arteritis

## Table 6. Adjusted longitudinal analysis of the factors associated with the risk of relapse

| **Longitudinal models – 10% improvement of OGUS** | | | **Longitudinal models – OGUS normalization < 1** | | |
|---|---|---|---|---|---|
| **Relapse** | | | **Relapse** | | |
| | HR | 95% CI | | HR | 95% CI |
| Age | 0.98 | 0.94-1.02 | Age | 0.98 | 0.94-1.02 |
| Sex (male) | 0.98 | 0.51-1.89 | Sex (male) | 0.95 | 0.49-1.84 |
| Baseline OGUS (effect of 1-point increase)** | **2.79** | **1.36-5.73** | Baseline OGUS (effect of 1-point increase) | 0.85 | 0.44-1.65 |
| 10% improvement of OGUS (continuous) | **0.67** | **0.53-0.86** | OGUS <1 | **0.37** | **0.17-0.81** |
| Ischaemic events | 0.53 | 0.26-1.05 | Ischaemic events | **0.45** | **0.22-0.92** |
| GC pulses previous visit | 1.73 | 0.59-5.07 | GC pulses previous visit | 2.27 | 0.80-6.47 |
| Cumulative GC (effect of adjunctive 1000 mg) | 0.59 | 0.02-18.08 | Cumulative GC (effect of adjunctive 1000 mg) | 0.22 | 0.01-4.68 |
| Cumulative GC (effect of adjunctive 1000 mg) (quadratic effect) | 0.56 | 0.02-12.64 | Cumulative GC (effect of adjunctive 1000 mg) (quadratic effect) | 1.38 | 0.08-24.57 |
| New DMARD previous visit | 0.81 | 0.34-1.88 | New DMARD previous visit | 0.81 | 0.36-1.80 |
| LV-GCA | 0.67 | 0.32-1.39 | * | | |

Adjusted time-varying Cox models assessing the longitudinal effect of 10% improvements in the OGUS (left panel) and OGUS normalization <1 (right panel) on the risk of relapse.
*LV-GCA not included in OGUS normalisation model because of high collinearity with new DMARD initiation
** Baseline OGUS (Effect of 0.5-point increase): HR 1.67 (95%CI: 1.17-2.39).
CI: confidence interval; OGUS: OMERACT Giant cell arteritis Ultrasonography Score; GC: glucocorticoid; DMARD: disease modifying anti-rheumatic drugs; LV-GCA: large-vessel giant cell arteritis.

### 5.2 Initiation of adjunctive immunosuppressive treatments

Initiation of DMARDs in the first 12 months of follow-up was more common in patients with LV-GCA at diagnosis (HR in multivariable analysis 3.38, 95%CI 2.26-5.05).

The association of the OGUS with the requirement of starting a DMARD was weak: OGUS at the time of diagnosis was not linked with the need for DMARDs, while the normalisation of OGUS over the first 12 weeks was inversely associated at univariable analysis [IRR at 12 weeks: 0.56 (0.31-0.99)] (Table 4). This was confirmed by Cox analysis [HR at 12 weeks: 0.79 (0.64-0.97)] (Supplementary Table 2) but not by multivariable regression analysis (Table 5).
At longitudinal multivariable analyses (adjusted for age, sex, baseline OGUS, 10% improvement of OGUS or OGUS normalisation, GC pulses, cumulative GC dose, relapse, and LV-GCA) the associations of OGUS improvement or normalisation with the initiation of DMARDs was not statistically significant.

### 5.3 Ischaemic events and aortic aneurysms/dissections

Ischaemic events and aortic complications did not correlate with baseline OGUS. During follow-up the number of ischaemic or aortic complications were too rare to allow for any statistical correlation with the ultrasonographic data.

### 5.5 Sensitivity analysis using single quantitative ultrasound data

We performed a sensitivity analysis to assess the effect of the single components of the OGUS and the effect of single quantitative ultrasound data (maximum IMT at the level of the TA, maximum IMT at the AX, number of halos) on the clinical outcomes of interest. This analysis confirmed the association between the degree and rapidity of IMT improvement, and the extension of disease measured by ultrasonography and the risk of relapse (Supplementary material and Supplementary Tables 3-4).

### 5.6 Sensitivity analysis of the impact of tocilizumab prescribed at diagnosis

Patients initiating TCZ indication at diagnosis (n=20) received the first dose after a mean of 9.5±3.4 days, therefore not affecting OGUS findings at baseline and at one week. The OGUS trend and rapidity of improvement from week 3 onwards did not significantly differ between patients receiving TCZ at diagnosis and patients treated with GC monotherapy (Supplementary Table 5).

## Discussion

This is the first study to demonstrate a prognostic role for ultrasound in GCA in a prospective international cohort of patients. We have shown that a higher OGUS at the time of diagnosis

and the rapidity and degree of ultrasound improvement during the first three to six weeks of follow-up significantly predict the risk of a future relapse and time to relapse.

For each one-point increase in the OGUS at diagnosis, the risk of relapse in the first year increases by 1.8-fold, and by 2.8-fold during longer follow-up. On the other hand, a 10% improvement at any time point in the first few weeks from diagnosis confers a 32% reduction in the risk of relapse. The percentage improvement follows a multiplicative trend meaning that a 30% improvement in OGUS would confer a 70% reduction in the risk of relapse. These results are especially relevant as they demonstrate for the first time that a non-invasive, cost-effective, repeatable imaging tool such as ultrasonography can be used for the risk stratification of patients at the time of diagnosis or shortly after.

Our findings suggest a biological plausibility where greater severity and extent of arterial involvement, indicated by a higher OGUS, likely reflects more severe disease activity, which in turn has subsequent prognostic implications. Histopathologic confirmation of such a hypothesis has been previously demonstrated, with the intensity of the transmural inflammation on TAB specimens being an independent predictor of relapse (18). Although a direct correlation between the degree of histologic inflammatory infiltrate and the IMT size has never been assessed, the halo sign has been reported to be more frequently detectable in patients with histological patterns showing transmural and media infiltration (19,20), and the grading of halo thickness to be higher in patients with intima hyperplasia (21). Studies on ultrasonography, including those on quantitative ultrasonography components, have demonstrated to effectively discriminate between disease states in GCA (active vs remission) (8,13,22). Our study confirmed that baseline OGUS was higher in patients subsequently affected by a relapse, suggesting that ultrasonography might be included as a parameter in the risk stratification of patients with GCA.

A higher OGUS may be due to larger IMT, or it may be computed in patients with a higher number of involved arterial segments displaying an IMT above the rounded normal cut-offs, and/or more extensive disease with the concomitant involvement of the AX. LV-GCA has been generally regarded as a prognostic factor increasing the risk of relapse based on a small number of retrospective studies (18,23–25). In our study, the presence of LV-GCA assessed by ultrasonography was not confirmed to correlate with the risk of relapse. Previous ultrasonographic studies had also questioned the role of AX positivity on ultrasonography as a predictor of the probability to attain clinical remission and had demonstrated a slower rate of improvement of AX ultrasonography findings in response to treatment (8,13,26). Further prospective studies will be needed to re-evaluate the value of LV-GCA as a risk factor for

relapse. Nonetheless, as we await more studies, we adjusted our analyses for the presence of LV-GCA and we can reasonably exclude that the prognostic role demonstrated for ultrasonography is dependent on the presence of LV-GCA. Moreover, the risk of overestimating the impact of AX involvement is counterbalanced by the design of the OGUS, scaling IMT measurements by normal cut-offs, offering the advantage of combining both TA and AX in a single score, while taking into account the magnitude of changes in different vessel sizes. Finally, the sensitivity analysis performed to address the impact of the single components of ultrasonography assessment (separated TA and AX IMT, and number of halos) confirmed the general results of our study and did not demonstrate a positive correlation between AX involvement and the risk of relapse, but rather, an association with an early improvement, also at the level of the AX, with a reduction of future disease exacerbations.

Our results suggest that rather than the involvement of extra-cranial large vessels itself, it is the extension and severity of disease detected by ultrasonography which influences the prognosis. This is in line with the findings from Czihal et al. showing that patients with extensive concomitant involvement of the TA and subclavian/AX arteries at diagnosis displayed a poorer response to treatment (24). On the other hand, previous studies trying to correlate quantitative ultrasonography findings or the improvement of vessel wall thickness with the risk of future relapse or treatment requirements had failed, however, these studies differed from the current one as the frequency of re-assessment of response was significantly less frequent or the follow-up shorter (6,27). A recent smaller retrospective study observed a potential association of lack of OGUS improvement at 3 and 6 months of follow-up and future risk of relapse (10). Our study shows that earlier assessment of the rapidity of improvement (first 3-6 weeks) combined with the degree (both percentage improvement and normalisation of OGUS) are key for the prognostic imaging stratification in GCA. Moreover, the identification of specific time-points for ultrasonography monitoring and the demonstration of a cut-off in the OGUS (<1) associated with better outcomes, improve the clinical applicability of our results and the possibility to validate the findings in future clinical trials. Future research exploring the baseline clinical factors associated with achieving an OGUS < 1 could provide insights into further prognostic markers and tailored approaches to GCA.

To rule out the prognostic effect on the risk of relapse demonstrated for the early improvement of OGUS being due to the intensity of initial treatment, we corrected our analyses for the use of GC pulses, the cumulative GC dose, and in longitudinal analyses, for the use of a new DMARDs. We also performed a sensitivity analysis which excluded a more rapid improvement

of OGUS in patients receiving TCZ early after diagnosis. A previous clinical trial assessing the role of TCZ monotherapy preceded by three GC pulses (the GUSTO trial) (22) demonstrated a significant effect of pulse GC therapy on the reduction of IMT and a transient increase and slower reduction of IMT in the TCZ group, in line with a possible trend observed in our cohort. The effect of the cumulative dose of GC, even more than the number of days on GC, in reducing TA halo IMT was also reported by Ponte et al. (13). To further reduce the confounding impact of prolonged GC treatment on ultrasonography findings, (28) we excluded patients that had received high-dose GCs for more than 15 days. The mean duration of GC treatment in our study was 2 days, hence, we expect a very limited impact of GC treatment on the results of our study.

Univariable analysis suggested a possible association between improvement of ultrasound findings and the requirement for DMARDs, however this association was not confirmed after adjusting for confounders and should therefore be interpreted with caution. Since the treatment protocol was not standardized, there might have been several factors that had influenced the decision to prescribe a DMARD, which were only partially captured in this study. Consequently, we cannot exclude a Type II error and another study with a standardized treatment algorithm would be needed to better investigate the predictive value of ultrasonography in regard to the use of DMARDs.

Our study failed to demonstrate an association between a higher OGUS at baseline and the risk of ischaemic events during follow-up. This is in line with previous studies with a similar research questions (6,28,29) and suggests that research should focus on alternative biomarkers that might predict tissue ischemia. Besides, we were unable to investigate a possible association between OGUS and the development of aneurysms and dissections because of the low number of events. Future prospective studies of large cohorts with standardized assessments for aortic dilatation are therefore required to investigate this issue.

This study has several strengths including the multicentre, international, prospective design with a pre-specified fixed protocol for ultrasonography assessments during follow-up, including very early monitoring at one, three, and six weeks which were often lacking in previous studies failing to demonstrate a prognostic role for ultrasonography (6). There was a high number of prospective visits (849 visits) on a high number of patients (in a rare disease) (30), allowing for a careful identification of ultrasonography changes and evaluation of clinical relapses. Ultrasonography was performed using high-end equipment by experienced operators who had received similar training. A score that has demonstrated good reliability, sensitivity

to change and convergent construct validity, also in comparison to other scoring systems, and allowing to combine information on both TA and AX, was applied (7,8). Moreover, the demonstration of the prognostic value for baseline ultrasonography and degree and rapidity of improvement was consistent across several different types of statistical analyses, corrected for the most relevant confounding factors, including detailed data on GC doses.

Despite the consistency across analyses and the biological plausibility that indicates a low risk of false positive results, we cannot exclude the possibility that a Type I error has been inflated, and we acknowledge this as a potential limitation.

The study has other potential limitations to consider including the fact that the sonographers were not blinded to the clinical/ultrasonographic information, including in cases of relapse. Although ultrasound findings were not considered in the relapse definition, we cannot entirely rule out their impact on the relapse rate due to the lack of blinding. However, this approach reflects current clinical practice in fast-track clinics for the diagnosis of GCA. Different ultrasound machines were used across the three centres, although the ultrasound machines were always the same for the monitoring of individual patients. A few patients did not attend all scheduled visits, even though we excluded patients with insufficient follow-up data in the first weeks of follow-up. In a minority of patients, follow-up was interrupted within 12 months from diagnosis due to the COVID pandemic or loss to follow-up. However, time-at risk and follow-up duration were accounted for in the analyses. Moreover, the prospective ultrasonography measurement was performed in the area with the thickest IMT, which might not have captured the same level of change compared to a fixed measurement location. Inter-rater reliability was not assessed, but this was confirmed to be good for OGUS in an international exercise (7,31). The results are generalizable only to patients with a positive ultrasound at diagnosis, while future studies should also investigate the value of OGUS among those who are considered to have a negative ultrasound result (but might nevertheless have minor variations of IMT during follow-up, the monitoring value of which is currently unknown). Since our study was conducted in a fast-track setting, we recruited a relatively high proportion of patients with predominant cranial disease and short symptom to diagnosis lag, while patients with isolated LV involvement were less numerous (4.1% with exclusive AX involvement). Patients were often referred by ophthalmology when presenting with visual symptoms, and this accounts for the relatively high frequency of visual loss in our cohort, despite the fast-track setting. Temporal artery branches were commonly involved in these patients and we know that IMT of TA is usually more sensitive to change to treatment than AX (13). The prognostic value of OGUS might have been different in a population with predominant or isolated LVV, longer

disease duration and extracranial symptoms as it might occur in regular out-patient clinics outside the fast-track setting. Future studies are therefore needed to confirm the prognostic value of OGUS in different populations and settings. Moreover, the non-standardized assessment of aneurysms during follow-up in this study may have limited the number of detected cases; however, there are currently no recommendations regarding the optimal frequency of screening or the preferred imaging method (5). Finally, while we excluded an influence of TCZ prescribed at diagnosis on the rapidity of improvement of OGUS in the first weeks of follow-up, in line with the literature (22), we cannot fully exclude that the use of TCZ might have had an influence on the prognostic value of OGUS because of the lack of power for this analysis, however, our study is of observational nature reflecting current clinical practice and a head to head comparison between GC and TCZ would be needed to clarify this issue and explore the dynamics of imaging changes in patients receiving early treatment with TCZ.

In conclusion, we demonstrated for the first time that ultrasonography can be used as a prognostic tool in the management of GCA. The extent and severity of disease measured at the time of diagnosis with a simple composite ultrasonography score predicts the risk of early relapse in the subsequent year, while the rapidity and degree of ultrasonographic improvement can be used to predict long-term relapses. These findings have relevant clinical implications. Being able to address the individual patient prognosis through a non-invasive, repeatable imaging tool directly at the time of diagnosis or within the very first few weeks of follow-up would offer in the future unprecedented chances of individualizing the patient treatment and intensity of monitoring based on the risk stratification during the early phases of the disease.

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Data sharing: Study protocol and raw data are accessible upon reasonable request.

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Competing interest: NK: AstraZeneca, GSK, Novartis (honoraria), Abbvie, AstraZeneca, GSK, Lilly, Pfizer (meetings attendance). WAS: Abbvie, GlaxoSmithKline, Novartis, Sanofi (grants contracts, consulting fees, honoraria); Fresenius Kabi (consulting fees), Amgen, Bristol Myers Squibb, Chugai, Johnson & Johnson, Medac, Roche, UCB (honoraria), University of Bonn (data safety monitoring board). CD: Abbvie, Sparrow, Novartis, Sanofi, Boehringer, Pfizer, Galapago, Lilly, Janssen, Roche (consulting fees, honoraria), UCB (honoraria); RL: EPSRC, NIHR, CSL Vifor (grants or contracts), Abbvie (consulting fees), CSL Vifor, SANA, Novartis, GSK (honoraria), CSL Vifor (data safety monitoring board/advisory board).

**Figure 1**. Relapse risk ratio according to each 0.5-point increase in baseline OGUS (Panel A), and each 10% improvement in OGUS (Panel B).