# UNIVERSIDAD COMPLUTENSE DE MADRID

FACULTAD DE MEDICINA


# TESIS DOCTORAL

Nuevas perspectivas en el uso de la imagen en la evaluación de pacientes con arteritis de células gigantes

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

Juan Molina Collada

DIRECTORES

Eugenio de Miguel Mendieta
Isabel Castrejón Fernández

# UNIVERSIDAD COMPLUTENSE DE MADRID
# FACULTAD DE MEDICINA


TESIS DOCTORAL

**Nuevas perspectivas en el uso de la imagen en la evaluación de pacientes con arteritis de células gigantes**

Memoria para optar al grado de doctor presentada por

**Juan Molina Collada**

Directores

**Eugenio de Miguel Mendieta**

**Isabel Castrejón Fernández**

Madrid, 2025

# UNIVERSIDAD COMPLUTENSE DE MADRID
# FACULTAD DE MEDICINA

**Programa de doctorado en ciencias médico quirúrgicas**


TESIS DOCTORAL

**Nuevas perspectivas en el uso de la imagen en la evaluación de pacientes con arteritis de células gigantes**

Memoria para optar al grado de doctor presentada por

**Juan Molina Collada**

Directores

**Eugenio de Miguel Mendieta**

**Isabel Castrejón Fernández**

Madrid, 2025

# AGRADECIMIENTOS

## AGRADECIMIENTOS

“Has hecho todo lo que tenías que hacer. Lo único que puedes hacer ahora es esperar la carrera” — **Haruki Murakami** (2008) *De qué hablo cuando hablo de correr*

Embarcarse en un programa de doctorado es una carrera de fondo, en el que cada pequeño esfuerzo y cada pequeño paso cuentan para llegar a la meta. No hay ninguna duda de que un corredor no experimentado jamás terminaría un maratón sin que alguien le guíe, le marque el ritmo y le haga saber cuánto queda hasta el final. Durante estos años, he tenido la gran suerte de rodearme de personas que han hecho que la carrera discurra siempre cuesta abajo.

Quiero agradecer en primer lugar a mis directores de tesis, Eugenio e Isabel, los mejores entrenadores que todo corredor pueda imaginar. Ambos me han corregido, aportado ideas, me han frenado cuando era necesario y empujado cuando no sabía hacia dónde ir. En definitiva, me han enseñado a ver la investigación con otros ojos y este trabajo también es suyo.

A todos los reumatólogos que me han visto recorrer las calles de esta carrera, a mis compañeros del Hospital La Paz y a mis compañeros del Hospital Gregorio Marañón, que siempre han creído y apoyado los proyectos que traía entre manos.

A mis amigos, Luis y Rodri, porque son mis amigos.

A mi familia melillense y colombiana, porque siempre me han acogido con los brazos abiertos.

A mi familia, mi abuelo y mi abuela, mis tíos, mis primos, que han sido testigos de esta carrera, aun cuando ni siquiera sabía caminar.

A mis padres, porque para ellos todos mis logros son gigantes, pero no saben que todos son suyos.

A mi hermana Pau, Sergio y Sergito, por ser mi ejemplo a seguir desde siempre.

A Luisa, porque a veces me espera y me felicita al final de las carreras, pero siempre corre conmigo.

A Yoko, que nos hace reaprender todo cada día.

A Dobby, que pasó de vivir con nosotros a vivir en nosotros.

Y a Noel, que aún no has llegado, pero lo vas a revolucionar todo.

# ÍNDICE

# ABREVIATURAS

## AREVIATURAS

ACG: arteritis de células gigantes

ACG-GV: arteritis de células gigantes con afectación de grandes vasos

PCR: proteína C reactiva

VSG: velocidad de sedimentación globular

ACR: Colegio Americano de Reumatología

EULAR: Liga Europea de Enfermedades Reumáticas

RM: resonancia magnética

TEP: tomografía por emisión de positrones

TC: tomografía computarizada

GIM: grosor íntima media

OGUS: OMERACT GCA ultrasonography score

# RESUMEN

## RESUMEN

El uso de las técnicas de imagen ha ganado especial importancia en el diagnóstico y monitorización de la arteritis de células gigantes (ACG) en las últimas décadas. En concreto, se recomienda el uso de la ecografía como la primera prueba de imagen a realizar en pacientes con sospecha de ACG y, dada su importancia en el diagnóstico, ha sido recientemente incluida en los nuevos criterios de clasificación de ACG del Colegio Americano de Reumatología (ACR) y la Liga Europea de Enfermedades Reumáticas (EULAR) del 2022. Su uso se ha extendido en práctica clínica, siendo fundamental en las consultas de diagnóstico rápido de ACG. Dada su relevancia y uso creciente, ha desplazado a la biopsia de la arteria temporal en el diagnóstico, una técnica invasiva y con elevada tasa de falsos negativos. A pesar de la expansión de las técnicas de imagen, en el manejo del paciente con ACG, todavía quedan muchos interrogantes para optimizar su uso en práctica clínica, tanto en el diagnóstico como en la monitorización y predicción de medidas de desenlace de la enfermedad a largo plazo.

El presente proyecto de investigación tiene como objetivo principal evaluar el valor de las técnicas de imagen en la mejora del diagnóstico y la monitorización de pacientes con ACG. Desde el punto de vista diagnóstico se pretende: a) evaluar puntos de corte del índice íntima media ecográfico, para diferenciar pacientes con y sin ACG; b) evaluar el impacto del riesgo cardiovascular en la interpretación de los hallazgos ecográficos; c) comparar la utilidad diagnóstica de la ecografía respecto a otras técnicas diagnósticas en pacientes con ACG con afectación de vaso grande; d) evaluar las limitaciones de la ecografía en este contexto; e) determinar el impacto de la inclusión de las técnicas de imagen en los nuevos criterios de clasificación de la ACG. Además, como objetivos adicionales, se plantea analizar el valor de la ecografía en la predicción de complicaciones isquémicas, así como su utilidad pronóstica en la predicción de recidivas durante el seguimiento.

Para responder a estos objetivos, se han llevado a cabo distintos estudios de carácter retrospectivo mediante el análisis de datos de pacientes evaluados en consultas de diagnóstico rápido por ecografía, en varios centros participantes durante los últimos cinco años. Esta red colaborativa de consultas de diagnóstico rápido de ACG comparte un protocolo estandarizado de evaluación, que incluye la realización de ecografía en un plazo inferior a 48 horas desde la sospecha clínica. En función del resultado de la ecografía y de la probabilidad clínica de ACG, se estable un tratamiento específico o se continúa el estudio con pruebas adicionales.

Entre los resultados principales obtenidos en este proyecto de investigación destacan los siguientes:

- Discriminación diagnóstica: El uso de puntos de corte del índice íntima media ecográfico permite discriminar entre pacientes con y sin ACG, especialmente en los casos en los que los signos ecográficos tradicionales no son concluyentes.

- Riesgo cardiovascular: El riesgo cardiovascular influye en la valoración de la ecografía. En pacientes con alto riesgo cardiovascular, la precisión diagnóstica de los índices ecográficos disminuye.
- Afectación de vaso grande: Tanto la ecografía como la tomografía por emisión de positrones - tomografía computarizada (TEP-TC) son técnicas válidas para el diagnóstico de ACG con afectación de vaso grande, mostrando hallazgos consistentes entre sí. No obstante, una ecografía negativa no excluye completamente la posibilidad de afectación de vaso grande.
- Detección de aortitis: La mayoría de pacientes sin afectación de vaso grande en ecografía tampoco presentan aortitis en TEP/TC. Por tanto, el impacto clínico de la limitación ecográfica en la detección de aortitis es bajo.
- Criterios de clasificación: La inclusión de técnicas de imagen en los nuevos criterios de clasificación ACR/EULAR 2022 de ACG mejora su aplicabilidad diagnóstica frente a criterios previos. Sin embargo, su especificidad limitada impide su uso en práctica clínica con este fin.
- Fenotipos ecográficos y riesgo de complicaciones isquémicas: Diferentes fenotipos ecográficos se asocian con distintas manifestaciones isquémicas. En particular, los pacientes con ACG de vaso grande presentan mayor riesgo de complicaciones isquémicas como accidentes cerebrovasculares.
- Valor pronóstico: La cuantificación del grosor de la pared vascular mediante ecografía podría ser útil para predecir recidivas durante el seguimiento.

Nuestros resultados aportan nuevos avances en el uso de las técnicas de imagen en el manejo de los pacientes con ACG. Estos hallazgos pueden ayudar a la aplicación de estas técnicas en práctica clínica, guiar recomendaciones, así como sentar las bases de futuras preguntas de investigación.

# SUMMARY

## SUMMARY

The use of imaging techniques has gained special importance in the diagnosis and monitoring of giant cell arteritis (GCA) in recent decades. Specifically, ultrasound is recommended as the first imaging test to be performed in patients with suspected GCA. Given its importance in diagnosis, it has recently been included in the new 2022 American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) GCA classification criteria. Its use has become widespread in clinical practice and is essential in fast-track clinics for GCA diagnosis. Due to its growing relevance, ultrasound has replaced temporal artery biopsy for diagnosis, a more invasive technique with a high false-negative rate. Despite the expanding use of imaging techniques in GCA management, many questions remain regarding how to optimize their use in clinical practice, both for diagnosis and for monitoring and predicting long-term disease outcomes.

The main objective of this research project is to evaluate the value of imaging techniques in improving the diagnosis and monitoring of patients with GCA. From a diagnostic perspective, the aims are to: a) assess cut-off values for the ultrasound intima-media thickness to differentiate between patients with and without GCA; b) evaluate the impact of cardiovascular risk on the interpretation of ultrasound findings; c) compare the diagnostic utility of ultrasound with other diagnostic techniques in patients with large-vessel GCA; d) assess the limitations of ultrasound in this context; e) determine the impact of including imaging techniques in the new 2022 GCA classification criteria. Additionally, secondary objectives include analyzing the value of ultrasound in predicting ischemic complications and its prognostic value for predicting relapses during follow-up.

To address these objectives, several retrospective studies have been conducted by analyzing data from patients assessed in fast-track ultrasound clinics at several participating centers over the past five years. This collaborative network of fast-track GCA clinics follows a standardized evaluation protocol, which includes performing an ultrasound within 48 hours of clinical suspicion. Based on the ultrasound results and the clinical probability of GCA, a specific treatment is initiated or further testing is performed.

Key results from this research project include:

- Diagnostic discrimination: The use of intima-media thickness cut-off values enables discrimination between patients with and without GCA, especially in cases where traditional ultrasound signs are inconclusive.
- Cardiovascular risk: Cardiovascular risk affects ultrasound interpretation. In patients with high cardiovascular risk, the diagnostic accuracy of ultrasound indices decreases.
- Large-vessel involvement: Both ultrasound and positron emission tomography-computed tomography (PET-CT) are valid techniques for diagnosing large-vessel GCA, showing consistent findings. However, a negative ultrasound does not fully exclude the possibility of large-vessel involvement.

- Detection of aortitis: Most patients without large-vessel involvement on ultrasound also show no signs of aortitis on PET/CT. Therefore, the clinical impact of ultrasound's limitation in detecting aortitis is low.
- Classification criteria: The inclusion of imaging techniques in the 2022 ACR/EULAR GCA classification criteria improves diagnostic value compared to previous criteria. However, their limited specificity prevents their use in clinical practice for this purpose.
- Ultrasound phenotypes and risk of ischemic complications: Different ultrasound phenotypes are associated with different ischemic manifestations. In particular, patients with large-vessel GCA have a higher risk of ischemic complications such as strokes.
- Prognostic value: Measuring vascular wall thickness with ultrasound may be useful in predicting relapses during follow-up.

Our findings provide new insights into the use of imaging techniques in the management of patients with GCA. These results may support the implementation of these techniques in clinical practice, guide future recommendations, and lay the background for future research questions.

# INTRODUCCIÓN

# INTRODUCCIÓN

## Arteritis de células gigantes: aspectos epidemiológicos y clínicos

La arteritis de células gigantes (ACG) es una vasculitis sistémica caracterizada por inflamación de arterias de mediano y gran calibre, con predilección por la aorta y sus ramas principales (1). Afecta predominantemente a personas caucásicas, con una incidencia anual general de 15-25 casos por cada 100.000 individuos mayores de 50 años (2). La incidencia aumenta progresivamente con la edad, alcanzando su punto máximo entre los 70-80 años, y presenta mayor frecuencia en mujeres, con una proporción de 2-4:1 respecto a hombres (3).

Los síntomas y signos más frecuentes de la ACG son consecuencia de la afectación de las arterias craneales, sobre todo las arterias temporales, lo que se denomina ACG craneal. La aparición de cefalea de nueva aparición, predominantemente en la región temporal, es uno de los síntomas más frecuentes de la enfermedad y la claudicación mandibular uno de los más específicos (4).

La afectación de arterias extracraneales en ACG, como la aorta y sus principales ramas, se denomina ACG de grandes vasos (ACG-GV) y puede ocurrir en el 20-80% de los pacientes, dependiendo de la modalidad de imagen utilizada para su diagnóstico (5–7). Los pacientes con este tipo de afectación pueden presentar síntomas y signos atípicos entre los que destacan claudicación de miembros, soplos y ausencia o disminución de pulsos. También pueden presentar síntomas sistémicos o bien ser asintomáticos (8). Entre las posibles complicaciones tardías de la ACG-GV se incluyen la valvulopatía cardíaca y aneurismas y/o disección aórtica (9).

Los síntomas sistémicos como astenia, fiebre y pérdida de peso, aunque inespecíficos, suelen estar presentes al diagnóstico. La polimialgia reumática y la ACG son enfermedades íntimamente ligadas. Aproximadamente el 40-60% de los pacientes con ACG presentan síntomas compatibles con polimialgia reumática, y entre el 16% y el 23% de los pacientes con diagnóstico de polimialgia reumática tienen vasculitis subclínica evidenciada mediante técnicas de imagen (10). Actualmente, se promueve el uso del término enfermedad del espectro relacionado con ACG-polimialgia reumática para definir y englobar dos entidades clínicas que comparten etiopatogenia, manifestaciones clínicas y estrategias terapéuticas (11).

Los pacientes con ACG pueden presentar manifestaciones isquémicas, especialmente la neuropatía óptica isquémica anterior (NOIA) (12), los accidentes cerebrovasculares(13) y el infarto de miocardio. Tradicionalmente, las complicaciones isquémicas, sobre todo la afectación visual, se han vinculador al fenotipo craneal de la enfermedad. Sin embargo, el territorio vertebrobasilar se afecta en más del 50% de los pacientes que presentan accidente cerebrovascular. La relación entre los distintos fenotipos de ACG identificados por ecografía y el riesgo de complicaciones isquémicas no ha sido bien caracterizada todavía y no se ha establecido si ciertos fenotipos predisponen a distintas complicaciones isquémicas. Es relevante destacar que estas complicaciones suelen aparecer al diagnóstico o en los primeros días o semanas de la enfermedad, en contraste con las

complicaciones aórticas (dilatación, aneurisma o disección) que suelen ocurrir tras meses o años desde el diagnóstico.

Hasta ahora no hay suficiente evidencia para afirmar que la mortalidad asociada a la ACG o a las comorbilidades que sus tratamientos implican en un perfil de pacientes de edad avanzada sea mayor que la de la población general y constituye uno de los interrogantes en la actualidad (14,15).

En la mayoría de pacientes con ACG encontramos elevación de reactantes de fase aguda al diagnóstico, como proteína C reactiva (PCR) y velocidad de sedimentación globular (VSG). Sin embargo, en casos de enfermedad localizada, sin predominio de síntomas constitucionales, los valores de PCR y/o VSG pueden ser bajos o normales, y este subgrupo de pacientes tiene mayor riesgo de desarrollo de complicaciones isquémicas craneales, sobre todo NOIA (12,16).

Respecto al tratamiento, se recomienda iniciar glucocorticoides a dosis altas tan pronto como sea posible para conseguir un adecuado control de la actividad de la enfermedad y prevenir complicaciones (17). No obstante, la terapia con glucocorticoides conlleva efectos adversos en hasta el 80% de los pacientes, sobre todo al inicio del tratamiento (18). Por ello, es esencial un diagnóstico preciso y rápido del paciente con sospecha de ACG, para evitar efectos adversos derivados de glucocorticoides. Como terapia ahorradora de glucocorticoides, el único tratamiento biológico aprobado en ACG es el tocilizumab (19). Su indicación de uso varía según las distintas recomendaciones, desde pacientes con eventos adversos relacionados con glucocorticoides, a pacientes con recidiva (20) o en todos los pacientes al inicio de la enfermedad (21). Otros inmunosupresores como metotrexato pueden ser efectivos (22), generalmente como alternativa a tocilizumab.

## Criterios diagnósticos y de clasificación en ACG

Dado que no existen criterios de diagnóstico para ACG, el patrón oro de referencia para evaluar la validez de las distintas pruebas diagnósticas es el diagnóstico clínico, generalmente apoyado por pruebas objetivas como biopsia o imagen. Hasta la aparición de las pruebas de imagen, la biopsia de arteria temporal la base del diagnóstico de los pacientes con ACG. Sin embargo, la heterogeneidad en los hallazgos histológicos, así como su posible afectación parcheada pueden dificultar su interpretación y reducir su sensibilidad. Según un metaanálisis reciente, la sensibilidad de la biopsia de arteria temporal es de hasta el 77% (23). Sin embargo, su naturaleza invasiva y la presencia de falsos negativos ha llevado a la búsqueda de pruebas complementarias alternativas, especialmente pruebas de imagen.

Los criterios de clasificación fueron desarrollados en 1990 por el Colegio Americano de Reumatología (ACR) y permitieron la inclusión de una población más homogénea en ensayos clínicos. Se clasificaba al paciente con ACG si cumplían al menos 3 de los siguientes criterios: edad >50 años, cefalea, exploración patológica de la arteria temporal, VSG elevada y positividad de la biopsia de arteria temporal (24). Sin embargo, estos criterios se desarrollaron para diferenciar la ACG de otras vasculitis, no de otras entidades

no vasculíticas y, por tanto, no son adecuados para el diagnóstico (25). Además, los criterios ACR se establecieron antes del uso generalizado de las técnicas de imagen y solo tenían en cuenta las manifestaciones craneales de la enfermedad.

En 2022, se han propuesto unos nuevos criterios de clasificación para ACG en un esfuerzo colaborativo del ACR y la Liga Europea de Enfermedades Reumáticas (EULAR), establecidos en una cohorte de desarrollo y una cohorte de validación. La sensibilidad y especificidad de los nuevos criterios frente al diagnóstico clínico de ACG es del 87% y 94.8%, respectivamente (26). Estos criterios incluyen los hallazgos de imagen reflejando su creciente uso en la práctica clínica y otorgando el mismo peso a la ecografía de arterias temporales, u otras pruebas de imagen, y a la biopsia de arteria temporal. Aunque estos criterios se han desarrollado con el fin de clasificar a los pacientes para su inclusión en ensayos clínicos, dado que incluyen nuevas variables respecto a los criterios ACR 1990, podrían ser también de utilidad en el diagnóstico de la enfermedad. Para ello, son necesarios estudios que determinen el valor diagnóstico de los nuevos criterios en práctica clínica.

## Validez de la imagen en el diagnóstico de ACG

La imagen ha cobrado gran relevancia en el diagnóstico en las últimas décadas, desplazando a la biopsia de arteria temporal como la primera prueba a realizar en pacientes con sospecha de ACG (27). Las pruebas de imagen de mayor relevancia en el diagnóstico son la ecografía, la resonancia magnética (RM) y la tomografía por emisión de positrones (TEP) combinada con tomografía computarizada (TC).

### Ecografía

La utilidad de la ecografía en ACG se describió por primera vez en 1995 (28) y desde entonces su uso no ha dejado de expandirse. El cambio de paradigma en el uso de la ecografía fue la publicación de las primeras recomendaciones EULAR para el uso de la imagen en vasculitis de vaso grande (27). Según estas recomendaciones, una prueba de imagen positiva y probabilidad pretest alta de ACG es suficiente para el diagnóstico. Además, este abordaje diagnóstico a través de la ecografía en las llamadas consultas de diagnóstico rápido de ACG, ha demostrado reducir el número de complicaciones visuales (29,30).

El signo del halo, base del diagnóstico ecográfico, se caracteriza por un engrosamiento homogéneo e hipoecoico de la pared arterial (31). La imposibilidad de comprimir completamente la arteria al aplicar presión con la sonda de ecografía se conoce como signo de la compresión (31). La sensibilidad y la especificidad de la ecografía para el diagnóstico de ACG, tomando como estándar de referencia el criterio clínico, es de 88% y 96%, respectivamente(32). Además de los signos clásicos ecográficos, con equipos de ecografía de alta resolución, se puede determinar el grosor íntima media (GIM) de la pared arterial. Se han publicado distintos puntos de corte del GIM en distintos territorios arteriales para distinguir pacientes con y sin ACG, así como para fines de monitorización (0.42-0.44 mm para el tronco común superficial de la arteria temporal, 0.29-0.36 para la rama parietal, 0.34 para la rama frontal y 1 mm para la arteria axilar) (33–35). Sin

embargo, aunque puede ser de utilidad en práctica clínica, el diagnóstico ecográfico de ACG en la actualidad todavía se basa en los signos clásicos cualitativos. Por tanto, son necesarios más estudios, que evalúen el valor diagnóstico de los puntos de corte del GIM en distintas poblaciones, incluyendo pacientes con alto riesgo cardiovascular (36,37), así como la técnica correcta al medir el GIM en función del ciclo cardiaco (38).

Mediante ecografía es posible evaluar la mayoría de vasos de mediano y gran tamaño que se afectan en ACG-GV, con la excepción de la aorta torácica. Al igual que en las arterias temporales se puede determinar el GIM de las arterias extracraneales. Las recomendaciones EULAR del 2018 recomiendan la evaluación con ecografía de las arterias axilares en el caso de que la ecografía de arterias temporales sea negativa (27). Esta estrategia se basa en estudios recientes que demuestran un aumento de la sensibilidad de la ecografía cuando se incluyen las arterias axilares, sin disminuir significativamente la especificidad (39–41).

### Resonancia magnética

Mediante RM se puede detectar el engrosamiento de la pared arterial y el realce de contraste en las arterias temporales (42). Al contrario que con la ecografía, se pueden evaluar los vasos intracraneales, así como la patología orbitaria, incluyendo la afectación de la arteria ciliar posterior que constituye la causa más frecuente de pérdida de visión permanente en ACG (43). Con RM también se puede evaluar los cambios en arterias extracraneales, incluyendo daño estructural como estenosis, oclusión y aneurismas. Respecto al criterio clínico, la RM tiene una sensibilidad y especificad para el diagnóstico de ACG del 81% y 98%, respectivamente (32).

La RM tiene la ventaja de no usar radiación ionizante, al contrario que la TC y TEP. Sin embargo, entre sus limitaciones se incluyen la baja tolerabilidad en pacientes con claustrofobia, los posibles artefactos en pacientes con implantes metálicos, las reacciones adversas a los contrastes, y su baja disponibilidad.

### Tomografía por emisión de positrones/tomografía computarizada

La TEP/TC ha sido considerada tradicionalmente de poca utilidad para el diagnóstico de ACG craneal, debido a la baja resolución y a la proximidad de las arterias temporales al parénquima cerebral. Las recomendaciones EULAR del 2018 no recomendaban el uso de la TEP/TC, ni tampoco de la TC, para la evaluación de las arterias craneales. Sin embargo, con equipos de TEP/TC de última generación se consiguen reconstrucciones de imágenes con 1 mm de resolución, que han permitido obtener una alta sensibilidad y especificidad, en comparación con la biopsia de arteria temporal (44,45). Además, al contrario que con la ecografía, se puede evaluar la aorta en su totalidad. Las recomendaciones EULAR del 2018 situaban al mismo nivel todas las pruebas de imagen disponibles para la evaluación de la ACG-GV. Teniendo en cuenta la limitación de la ecografía para evaluar correctamente la aorta, son necesarios estudios comparativos que evalúen la validez diagnóstica de ecografía y la TEP/TC para el diagnóstico de ACG-GV. Globalmente, la sensibilidad y especificidad de la TEP/TC respecto al criterio clínico es del 76% y 95%, respectivamente (32).

La principal ventaja de la TEP/TC respecto a otras pruebas de imagen es la capacidad de excluir otros diagnósticos diferenciales, principalmente cáncer e infección, en pacientes con sospecha de ACG-GV. En los casos de fiebre de origen desconocido o síndrome constitucional (presentaciones clínicas habituales en pacientes con ACG-GV), la TEP/TC parece ser una opción coste-efectiva como parte del proceso diagnóstico (46).

## Validez de la imagen en la monitorización de ACG

Hasta el momento, no disponemos de herramientas fiables para evaluar la actividad de la enfermedad en pacientes con ACG. Las recidivas durante el descenso de glucocorticoides son frecuentes. Tocilizumab en combinación con una pauta más rápida de descenso de glucocorticoides ha demostrado reducir el riesgo de recidiva respecto al tratamiento convencional (19), pero menos de un cuarto de los pacientes en el estudio de extensión a 2 años consiguen remisión sostenida sin tratamiento (47). Aunque con menos frecuencia que al debut de la enfermedad, existe riesgo de complicaciones isquémicas con ceguera o accidente cerebrovascular durante las recidivas. Además, los aneurismas y la disección arterial se desarrollan con mayor frecuencia en territorios con inflamación activa y en pacientes con un mayor número de recidivas (48,49).

Las recomendaciones EULAR del 2018 establecieron que no había suficiente evidencia para el uso de la imagen en pacientes con ACG en remisión clínica y bioquímica (sin síntomas ni signos de enfermedad activa y normalización de PCR y VSG) (27). Esto se debe a que los hallazgos detectados al diagnóstico mediante pruebas de imagen no siempre se resuelven durante el tratamiento. El significado clínico de estos hallazgos residuales no se ha determinado en ciertas situaciones, por ejemplo, la relación entre recidivas a largo plazo en pacientes con captación persistente de ACG-GV en TEP/TC (5). Por tanto, la investigación en este campo se centra en la actualidad en establecer la resolución de los hallazgos de las distintas pruebas de imagen con el tratamiento, así como la correlación entre persistencia o empeoramiento de actividad por imagen y signos o síntomas de actividad clínica.

### Ecografía

Una vez iniciado el tratamiento, se ha descrito que las arterias temporales se normalizan más rápido que las arterias extracraneales. En los primeros estudios de ecografía en ACG, el signo del halo persistía durante una media de 16 días (50). No obstante, las sondas utilizadas eran mucho menos sensibles que las que se usan en la actualidad. Otros estudios han demostrado que la sensibilidad de la ecografía para detectar alteraciones se reduce desde el segundo día tras el tratamiento (51,52). En general, se puede observar la resolución de las alteraciones en arterias temporales tras 2 a 4 semanas tras el inicio de la terapia. La afectación en arterias axilares puede permanecer más tiempo, con mejorías a partir de las 6 semanas de tratamiento (53). En un estudio se detectaron cambios sugestivos de vasculitis en el 70% de los pacientes tras un periodo de seguimiento de 50 meses de seguimiento (54), y en otro el incremento del GIM persistió hasta 4 años (55).

Hay pocos estudios publicados que hayan investigado la correlación entre hallazgos ecográficos y variables de desenlace en ACG. De Miguel et al. demostraron correlación de la desaparición del signo del halo en arterias temporales y reducción de PCR y VSG. Los pacientes que presentaron recidiva tenían menos segmentos arteriales afectados, menor PCR y VSG y una desaparición del halo más rápida en comparación con los hallazgos al diagnóstico de la enfermedad (56). Ponte et al. estudiaron la sensibilidad al cambio del signo del halo y del GIM durante el seguimiento y demostraron correlación entre GIM en arterias temporales y marcadores de actividad de la enfermedad como PCR, VSG y Birmingham Vasculitis Activity Score. Curiosamente, no se encontró la misma correlación con los hallazgos en arterias axilares.

En los últimos años, se ha intentado cuantificar el grado de inflamación por ecografía con fines de monitorización. En este contexto, se han publicado distintos índices ecográficos compuestos incluyendo distintos segmentos arteriales (57–59). El Halo Score incluye 6 segmentos de la arteria temporal y ambas axilares, asignando distintos grados en función del GIM de cada segmento. Este índice ha demostrado ser útil en el diagnóstico en práctica clínica (60,61) y para monitorizar la respuesta al tratamiento (62). Más recientemente, el grupo OMERACT de ecografía ha publicado el índice OGUS (OMERACT giant cell arteritis ultrasonography score, por sus siglas en inglés) en un esfuerzo conjunto para unificar la cuantificación de inflamación vascular por ecografía con fines de monitorización (63). OGUS ha demostrado fiabilidad intra e interobservador y sensibilidad al cambio (63). Un estudio danés, que comparaba varios índices ecográficos cuantitativos, demostró que OGUS era el índice con mayor magnitud de cambio (64). Sin embargo, queda por determinar si los hallazgos ecográficos y la cuantificación de la inflamación vascular realizada al diagnóstico o durante el seguimiento, predicen recidivas futuras que puedan ayudar al clínico a tomar decisiones y prevenir complicaciones en los pacientes con ACG.

### Tomografía por emisión de positrones/tomografía computarizada y resonancia magnética

La TEP/TC es la segunda prueba de imagen más utilizada, tras la ecografía, para la monitorización de ACG, aunque en la mayoría de estudio su uso se limita a la evaluación extracraneal. El uso de radiación ionizante (hasta 32 mSv para un estudio del cuerpo entero) y su disponibilidad restringida a hospitales terciarios son sus limitaciones más importantes para evaluar la actividad de la enfermedad de forma rutinaria. Por otra parte, la RM no usa radiación, es más barata, tiene mayor disponibilidad que la TEP/TC y potencialmente podría monitorizar tanto la afectación craneal como extracraneal. No obstante, la evidencia del uso de la RM en monitorización se ha centrado hasta la fecha exclusivamente en la afectación extracraneal.

El grupo de Blockmans et al. demostraron una reducción en el número e intensidad de segmentos arteriales en TEP/TC tras 3 meses de tratamiento, pero no se observaron mejoría a los 6 meses (5). Al comparar los hallazgos en pacientes que recidivaron durante el seguimiento no se identificaron diferencias entre los hallazgos en PET basales, a los 3 y 6 meses. Grayson et al. estudiaron longitudinalmente los hallazgos en TEP/TC a intervalos

de 6 meses en pacientes con ACG. Sus resultados muestran gran discordancia entre remisión clínica y captación anormal en TEP/TC en hasta el 57.7% de los pacientes. La especificidad del TEP/TC para diferenciar vasculitis y remisión por imagen fue del 42%. Sin embargo, la correlación entre vasculitis clínicamente activa y hallazgos en TEP/TC fue mejor, con una sensibilidad del 85% y especificidad del 83%.

Probablemente la combinación de TEP y RM (TEP/RM) constituya una opción a considerar para la monitorización de ACG en el futuro, ya que evita el uso de radiación asociado a la TEP/TC. Un estudio reciente de comparación entre TEP/TC y TEP/RM ha demostrado buena correlación entre ambas pruebas tanto en la valoración cualitativa como semicuantitativa de vasculitis activa (65).

# OBJETIVOS

# OBJETIVOS

## Objetivo general

El objetivo general del presente proyecto de investigación es evaluar el valor de las técnicas de imagen en la mejora del diagnóstico y la monitorización de pacientes con ACG.

## Objetivos específicos

Entre los objetivos específicos se incluyen:

1. Definir puntos de corte óptimos del GIM para el diagnóstico por ecografía de pacientes con ACG.

2. Analizar el impacto del riesgo cardiovascular en la precisión diagnóstica de la ecografía en pacientes con ACG.

3. Evaluar el rendimiento diagnóstico de la ecografía y otras técnicas de imagen en pacientes con ACG-GV.

4. Comparar las limitaciones de la ecografía respecto a otras técnicas de imagen en el diagnóstico de pacientes con ACG.

5. Determinar la utilidad de los criterios de clasificación que incluyen imagen para el diagnóstico de ACG

6. Explorar la relación entre los fenotipos ecográficos y el tipo de complicaciones isquémicas asociadas en pacientes con ACG

7. Evaluar el valor pronóstico de la ecografía en la predicción de recidiva en pacientes con ACG durante el seguimiento

# PUBLICACIONES

## PUBLICACIONES

### 1. Ultrasound intima media thickness cut-off values for cranial and extracranial arteries in patients with suspected giant cell arteritis

López-Gloria K, Castrejón I, Nieto-González JC, Rodríguez-Merlos P, Serrano-Benavente B, González CM, Monteagudo Sáez I, González T, Álvaro-Gracia JM, Molina-Collada J. Ultrasound intima media thickness cut-off values for cranial and extracranial arteries in patients with suspected giant cell arteritis. Front Med (Lausanne). 2022 Aug 26;9:981804. doi: 10.3389/fmed.2022.981804.

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 26 August 2022
DOI 10.3389/fmed.2022.981804



OPEN ACCESS

EDITED BY
Andrea Di Matteo,
Marche Polytechnic University, Italy

REVIEWED BY
Diogo Jesus,
Universidade da Beira Interior, Portugal
Zunaid Karim,
Mid Yorkshire Hospitals NHS Trust, United Kingdom
Kate Smith,
Leeds Biomedical Research Centre (NIHR), United Kingdom

*CORRESPONDENCE
Juan Molina-Collada
molinacolladajuan@gmail.com

SPECIALTY SECTION
This article was submitted to Rheumatology, a section of the journal Frontiers in Medicine

RECEIVED 29 June 2022
ACCEPTED 11 August 2022
PUBLISHED 26 August 2022



# Ultrasound intima media thickness cut-off values for cranial and extracranial arteries in patients with suspected giant cell arteritis

Katerine López-Gloria [1,2], Isabel Castrejón [1,2], Juan Carlos Nieto-González [1,2], Pablo Rodríguez-Merlos [1,2], Belén Serrano-Benavente [1,2], Carlos Manuel González [1,2], Indalecio Monteagudo Sáez[1,2], Teresa González [1,2], José María Álvaro-Gracia [1,2] and Juan Molina-Collada [1,2]*

[1]Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [2]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain

**Objective:** To determine the optimal ultrasound (US) cut-off values for cranial and extracranial arteries intima media thickness (IMT) to discriminate between patients with and without giant cell arteritis (GCA).

**Methods:** Retrospective observational study including patients referred to an US fast-track clinic. All patients underwent bilateral US examination of the cranial and extracranial arteries including the IMT measurement. Clinical confirmation of GCA after 6 months was considered the gold standard for diagnosis. A receiver operating characteristic (ROC) analysis was performed to select the cut-off values on the basis of the best tradeoff values between sensitivity and specificity.

**Results:** A total of 157 patients were included, 47 (29.9%) with clinical confirmation of GCA after 6 months. 41 (87.2%) of patients with GCA had positive US findings (61.7% had cranial and 44.7% extracranial involvement). The best threshold IMT values were 0.44 mm for the common temporal artery; 0.34 mm for the frontal branch; 0.36 mm for the parietal branch; 1.1 mm for the carotid artery and 1 mm for the subclavian and axillary arteries. The areas under the ROC curves were greater for axillary arteries 0.996 (95% CI 0.991–1), for parietal branch 0.991 (95% CI 0.980–1), for subclavian 0.990 (95% CI 0.979–1), for frontal branch 0.989 (95% CI 0.976–1), for common temporal artery 0.984 (95% CI 0.959–1) and for common carotid arteries 0.977 (95% CI 0.961–0.993).

10.3389/fmed.2022.981804

**Conclusion:** IMT cut-off values have been identified for each artery. These proposed IMT cut-off values may help to improve the diagnostic accuracy of US in clinical practice.

KEYWORDS

**ultrasound, giant cell (temporal) arteritis, vasculitis, imaging, arteries**

## Introduction

Giant cell arteritis (GCA) is the most frequent systemic vasculitis in elderly patients. An early diagnosis and prompt treatment is crucial to prevent serious complications (1–3). Ultrasound (US) is a valid and reliable tool to detect inflammation in patients with GCA, the non-compressible halo sign being the most relevant US finding. It has been defined by the US Outcome Measures in Rheumatology (OMERACT) large vessel vasculitis working group as a "homogenous, hypoechoic wall thickening that is well delineated toward the luminal side that is visible both in longitudinal and transverse planes, most commonly concentric in transverse scans" (4). According to recent EULAR recommendations, patients with high clinical suspicion of GCA and a positive imaging test do not need additional tests, such as biopsy or other imaging methods, for GCA diagnosis (5). However, false-positive halos may be present in other forms of vasculitis (e.g., in ANCA-associated vasculitis), amyloidosis (6), infectious diseases or even in patients with atherosclerosis (7, 8). Thus, a positive halo needs to be interpreted in the clinical context with an evaluation of the pretest probability (9).

Although the halo sign has been considered the most useful sign to support GCA diagnosis, it can be highly influenced by the sonographer skills and the quality of the US equipment for Doppler settings and artifacts. Sensitivity is highly variable between studies, showing a pooled sensitivity of 77% and a pooled specificity of 96% compared to the clinical diagnosis of GCA (10). Nowadays, thanks to the availability of high resolution transducers, intima media thickness (IMT) of cranial and extracranial arteries can be accurately measured as homogeneous, hypoechoic or anechoic structure delineated by two parallel hyperechoic margins (11). An increased IMT suggestive of GCA may be easily assessed by US, giving the classical appearance of a halo sign using color Doppler mode. However, few data are published regarding the optimal cut-off values for IMT to differentiate patients and controls in clinical practice (12, 13), and only one group studied the subclavian and common carotid arteries, which should require replication.

Our primary objective is to define cut-off values for cranial and extracranial arteries to discriminate patients with and without GCA.

## Materials and methods

### Patients

This is a retrospective observational study including patients referred to a US fast-track pathway (14) for screening of possible GCA from 2019 to 2021. In our academic center, patients with suspected GCA are referred for US examination within 24 h per protocol. A bilateral US exam of the cranial (superficial temporal arteries and its frontal and parietal branches) and extracranial (carotid, subclavian, and axillary arteries) arteries is performed as part of the diagnostic work-up. The following inclusion criteria were applied: patients age > 18 years with GCA suspicion according to clinician criteria (history of ESR > 20 mm/h or CRP > 5 mg/l, or cranial/extracranial symptoms of GCA or PMR symptoms). Patients with a previous diagnosis or clinical history of GCA were excluded. All exams were performed in routine daily practice conditions including consecutive patients.

### Data collection

The following variables were collected: demographics, presenting symptoms, previous use of glucocorticoids or polymyalgia diagnosis, and laboratory variables as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin and platelets. GCA clinical diagnosis after 6 months follow-up by the referring rheumatologist was the gold standard for diagnosis.

### Ultrasound assessment

All patients underwent bilateral US examination of the three temporal artery (TA) segments (common superficial TA, it parietal and frontal branches) and extracranial (common carotid, subclavian and axillary) arteries within 24 h per protocol (excluding weekends with delays up to 48 h). The exam was performed in a supine position, by the same evaluator (JMC) using an EsaoteMyLab8 (Esaote, Genoa). For superficial TA at it parietal and frontal branches we used a 12–18 MHz

10.3389/fmed.2022.981804

frequency transducer [B-mode frequency, 18 MHz; depth, 15 mm; focus point at approximately 3–5 mm below the skin surface, depending on the depth of the segment; color Doppler frequency, 11 MHz, pulse repetition frequency (PRF), 2.0 KHz]. An 8–14 frequency transducer was used for extracranial arteries (B-mode frequency, 14 MHz; depth, 3 cm; focus at 2 cm below the skin surface depending on the depth of the segment; color Doppler frequency, 9 MHz; PRF, 3.0 kHz). The subclavian arteries were scanned at the infraclavicular fossa and axillary arteries at the axillary fossa. The IMT was measured in gray scale mode and the presence of a non-compressible halo sign was checked in all arteries. We checked the presence of a halo defined according to the recent OMERACT Large Vessel Vasculitis Ultrasound Working Group definition (4). The measurement of the IMT of each artery was made from the luminal–intimal interface to the medial–adventitial interfaces on the arterial wall distal to the probe on longitudinal planes. The measurement of the IMT was obtained on B mode in all arteries (not only those showing a halo). For the frontal and parietal branches, the IMT was measured approximately 1 cm distal to the bifurcation of the superficial TA, and for axillary arteries at the level of the humeral head. Color Doppler signal was used to confirm the correct measurement of the IMT in doubtful cases. The presence of a halo and/or compression sign in temporal arteries and the presence of a halo in extracranial arteries was considered a positive US finding for GCA.

## Statistical analysis

Quantitative data were described as mean (S.D.) and qualitative variables as absolute frequency and/or corresponding percentages. Mean IMT values of each artery were compared between patients according to GCA clinical diagnosis by independent samples *T*-test. Receiver operating characteristics (ROC) analysis was performed and the Youden index was used to determine the optimal cut-off value for IMT of each artery. SPSS software (version 23.0; IBM, Armonk, NY, United States) was used for statistical analysis.

## 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 (RHEUM0322) and written informed consent was determined to be not mandatory.

# Results

## Patients' characteristics

A total of 157 patients evaluated in the US fast-track pathway were included for analysis, of whom 67.5% were female and mean (*SD*) age was 73.7 (10.8) years, median (interquartile range 25th–75th) 74 (66–82). Polymyalgia rheumatica diagnosis before US examination was present in 43 (27.4%) patients and 78 (50%) patients were on steroids before US examination, mean (*SD*) corticosteroid dose was 48.4 (146.5) mg/day (min 2.5, max 1,000). After 6-months of follow-up, 47 (29.9%) patients had GCA clinical confirmation according to clinician diagnosis. TA biopsy was performed per clinician criteria in 31 patients, 10 (43.5%) with positive results. Clinical, laboratory and main US findings of patients with and without GCA are shown in **Table 1**. GCA patients had higher acute phase reactants: CRP [mg/dL) 10.7 (18.2) vs. 3.8 (5), $p = 0.001$ and ESR (mm/h) (68.2 (34) vs. 45 (31.8), $p = 0.001$].

## Ultrasound findings

US findings are presented in detail in **Tables 1**, **2**. In total, 41 (87.2%) patients with GCA and only 5 (4.5%) patients without GCA had positive US findings (overall sensitivity 87.2%, specificity 95.5%, positive predictive value 89.1%, negative predictive value 94.6%). Among patients with GCA, the most frequent finding was temporal artery involvement in 29 (61.7%) patients, followed by extracranial involvement in 21 (44.7%) patients and 9 (19.1%) patients with a mixed pattern of cranial and extracranial arteries involvement (**Figure 1**).

## Intima media thickness cut-off values

Values of IMT of cranial and extracranial arteries in patients with and without GCA are shown in **Table 2**. The IMT cut-off values showing the highest diagnostic accuracy to discriminate between patients with and without GCA were for the cranial arteries (0.44 mm for the common superficial temporal artery; 0.34 mm for the frontal branch and 0.36 mm for the parietal branch) and for the extracranial arteries (1.1 mm for the carotid artery and 1 mm for the subclavian and axillary arteries) (**Table 2**). The area under the ROC curve of the IMT for a clinical diagnosis of GCA was 0.984 (95% CI 0.959–1) for common superficial temporal artery, 0.989 (95% CI 0.976–1) for frontal branch, 0.991 (95% CI 0.980–1) for parietal branch, 0.977 (95% CI 0.961–0.993) for carotid, 0.99 (95% CI 0.979–1) for subclavian and 0.996 (95% CI 0.991–1) for axillary arteries. Sensitivities and specificities of each IMT cut-off value are shown in **Table 2**.

TABLE 1 Clinical, laboratory and US findings of patients with and without GCA.

| | Total $n = 157$ | Patients with GCA $n = 47$ (29.9) | Patients without GCA $n = 110$ (70.1) | *P* |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age, mean (*SD*) | 73.7 (10.8) | 75.3 (11.3) | 73 (10.6) | 0.245 |
| Female, *n* (%) | 106 (67.5) | 31 (66) | 75 (68.2) | 0.785 |
| Arterial hypertension, *n* (%) | 96 (61.5) | 30 (65.2) | 66 (60) | 0.541 |
| Mellitus diabetes, *n* (%) | 37 (23.7) | 13 (28.3) | 24 (21.8) | 0.388 |
| Smoker, *n* (%) | 16 (10.3) | 6 (13) | 10 (9.1) | 0.458 |
| Former smoker, *n* (%) | 26 (16.7) | 10 (21.7) | 16 (14.5) | 0.272 |
| **Clinical variables** | | | | |
| Baseline use of steroids, *n* (%) | 78 (50) | 21 (45.7) | 57 (51.8) | 0.482 |
| PMR diagnosis before US examination, *n* (%) | 43 (27.4) | 8 (17) | 35 (31,8) | 0.121 |
| **Laboratory findings** | | | | |
| CRP (mg/dL), mean (*SD*) | 5.9 (11.3) | 10.7 (18.2) | 3.8 (5) | 0.001 |
| ESR (mm/h), mean (*SD*) | 52.8 (34.2) | 68.2 (34) | 45 (31.8) | 0.001 |
| Hemoglobin (g/dL), mean (*SD*) | 13.7 (17.6) | 11.7 (1.6) | 14.5 (21) | 0.185 |
| Platelets $10^9$/L, mean (*SD*) | 293 (124.7) | 335.4 (143.3) | 274.7 (111.6) | 0.014 |
| **US variables** | | | | |
| Positive US findings*, *n* (%) | 46 (29.3) | 41 (87.2) | 5 (4.5) | <0.001 |
| Temporal artery positive US findings, *n* (%) | 32 (20.4) | 29 (61.7) | 3 (2.7) | <0.001 |
| Extracranial arteries positive US findings, *n* (%) | 23 (14.6) | 21 (44.7) | 2 (1.8) | <0.001 |
| Temporal + extracranial arteries positive US findings, *n* (%) | 9 (5.7) | 9 (19.1) | 0 (0) | <0.001 |

PMR, polymyalgia rheumatica; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; US, ultrasound; SD, standard deviation; *Presence of a halo and/or compression sign in temporal arteries and/or presence of a halo in extracranial arteries.

## Discussion

Few studies have defined IMT cut-off values for GCA diagnosis after adequate evaluation. In this observational cross-sectional study, we provide the optimal cut-off values for IMT of cranial and extracranial arteries.

Several studies have shown the usefulness and good performance of US for the diagnosis of GCA (15–19) and this has led to the recent EULAR recommendations (5) identifying US as the test of initial imaging in patients with suspected GCA presenting with predominantly cranial symptoms. Although the halo sign is considered the most characteristic US finding of GCA, the measurement of IMT provides a more accurate diagnosis, probably because it is not influenced by potential Doppler artifacts. However, when analyzing a quantitative measure as a diagnostic test it is important to provide the optimal cut-off values to differentiate between patients and controls.

In our sample, 87.2% of patients with GCA had positive US results with a positive predictive value of 89.1%. The most frequent finding was the involvement of the temporal arteries (61.7% of patients), followed by extracranial involvement (44.7%). The area under the ROC curve of each explored artery were high with excellent sensitivities and specificities and proposed IMT cut-off values showed the highest diagnostic accuracy to discriminate between patients and controls. These values are high enough to justify the use of these cut-off values with high diagnostic precision. Previous studies have suggested variables cut-off values for temporal arteries: 0.3 mm (20), 0.4 mm (21), 0.5 mm (22), 0.7 mm (23), and 1 mm (24). Moreover, cut-off values for extracranial arteries of 1.3 mm (25) and 2 mm (26), and 1.5 mm (27) for the axillary artery exclusively, have been suggested. All of them based on the criteria and clinical experience of each author, respectively. Our results are in line with a recent study by Ješe et al. (12), in which they determined potential cut-off values for IMT in seven preselected arteries (temporal, facial, occipital, carotid, vertebral, subclavian, and axillary) comparing them between patients with and without GCA. They found positive US findings in 98.4% of patients with GCA with involvement of the temporal artery in 77.4%, and involvement of extracranial arteries in 35.1%. In relation to the cut-off values, they reached high levels of diagnostic precision with an IMT of 0.4 mm for the temporal arteries and an IMT of 1 mm for the carotid, subclavian and axillary arteries. Our findings were also compared with a recent study investigating IMT cut-off values by Schäfer et al. (13) who compared the IMT of 40 newly diagnosed GCA patients and 40 healthy controls. In this study the control group consisted in patients with other rheumatic and non-rheumatic diseases, but not suspected GCA. They established cut-off values of 0.42 mm for the common superficial temporal artery, 0.34 mm for the frontal branch, 0.29 mm for the parietal branch, and 1 mm for the axillary artery. Our cut-off values for IMT of 0.44 mm for the common superficial temporal artery and 0.36 mm for the parietal branch differ from those proposed by Schäfer et al. (0.42 for the common superficial temporal artery and 0.29 for the parietal branch). Although we used a 18 MHz probe, these

10.3389/fmed.2022.981804

TABLE 2 Optimal IMT cut-off values for cranial and extracranial arteries.

| Artery | Side | Patients without GCA | Patients with GCA | Cut-off (mm) | AUC (CI 95%) | Sensitivity (%) | Specificity (%) | Geometric mean |
|---|---|---|---|---|---|---|---|---|
| Common superficial temporal artery mm, mean (*SD*) | Right | 0.33 (0.06) | 0.68 (0.28) | 0.43 | 0.997 (0.988–1) | 100 | 97.1 | 0.985 |
| | Left | 0.35 (0.11) | 0.57 (0.21) | 0.45 | 0.966 (0.905–1) | 100 | 92.3 | 0.961 |
| | Both | 0.34 (0.08) | 0.63 (0.25) | 0.44 | 0.984 (0.959–1) | 94.7 | 95.1 | 0.949 |
| Frontal branch mm, mean (*SD*) | Right | 0.26 (0.05) | 0.4 (0.18) | 0.34 | 0.994 (0.983–1) | 100 | 97.1 | 0.985 |
| | Left | 0.27 (0.05) | 0.4 (0.18) | 0.34 | 0.985 (0.962–1) | 100 | 96.1 | 0.980 |
| | Both | 0.26 (0.05) | 0.4 (0.18) | 0.34 | 0.989 (0.976–1) | 100 | 96.6 | 0.983 |
| Parietal branch mm, mean (*SD*) | Right | 0.27 (0.05) | 0.43 (0.18) | 0.36 | 0.994 (0.981–1) | 100 | 98.9 | 0.994 |
| | Left | 0.27 (0.05) | 0.41 (0.16) | 0.36 | 0.987 (0.967–1) | 100 | 97.6 | 0.988 |
| | Both | 0.27 (0.05) | 0.42 (0.17) | 0.36 | 0.991 (0.980–1) | 100 | 98.3 | 0.991 |
| Carotid mm, mean (*SD*) | Right | 0.8 (0.17) | 0.88 (0.29) | 1 | 0.974 (0.949–0.999) | 100 | 92.6 | 0.962 |
| | Left | 0.82 (0.15) | 1 (0.42) | 1.2 | 0.982 (0.961–1) | 90.9 | 96.2 | 0.935 |
| | Both | 0.81 (0.16) | 0.96 (0.36) | 1.1 | 0.977 (0.961–0.993) | 90 | 94 | 0.920 |
| Subclavian mm, mean (*SD*) | Right | 0.74 (0.18) | 0.99 (0.44) | 1 | 0.987 (0.97–1) | 100 | 93.4 | 0.966 |
| | Left | 0.67 (0.17) | 0.9 (0.35) | 1.1 | 0.991 (0.975–1) | 100 | 98.3 | 0.991 |
| | Both | 0.7 (0.18) | 0.94 (0.4) | 1 | 0.99 (0.979–1) | 100 | 96 | 0.980 |
| Axillary mm, mean (*SD*) | Right | 0.69 (0.16) | 0.99 (0.5) | 1 | 0.992 (0.982–1) | 100 | 96 | 0.980 |
| | Left | 0.67 (0.17) | 0.99 (0.49) | 1 | 0.998 (0.995–1) | 100 | 98.3 | 0.991 |
| | Both | 0.68 (0.17) | 0.99 (0.49) | 1 | 0.996 (0.991–1) | 100 | 97.1 | 0.985 |

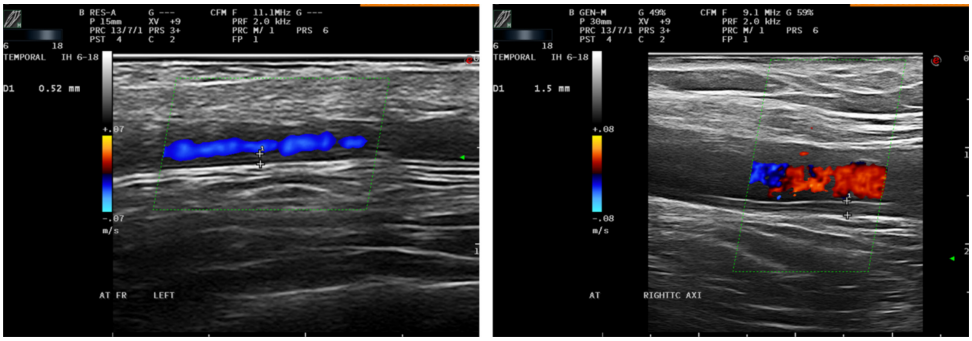


FIGURE 1
Longitudinal US scan (left) of the frontal branch of the left temporal artery in a patient with newly GCA diagnosis. Longitudinal US scan (right) of the right axillary artery in patient with large vessel GCA. Both arteries show increase IMT above the proposed cut-off values.

slight differences should be addressed in further studies. The proposed IMT cut-off of 1 mm for the axillary artery coincides with previous studies (13, 28). Our group previously presented preliminary data on the diagnostic value of IMT cut-off values studying the same population included in this work, with similar results (29).

Examination of the axillary arteries in patients with suspected GCA is most useful when US of the temporal arteries is negative or inconclusive and there is a high clinical suspicion of large vessel GCA (5). Although in this scenario it is not clear which extracranial arteries should be examined (30). Skoog et al. (31) recently evaluated the diagnostic performance of an extended US protocol (which in addition to temporal and axillary arteries, also includes subclavian, brachiocephalic, and carotid arteries) in patients with suspected GCA. According to their results, they found that 86% had involvement of the temporal arteries and 28% of patients showed inflammatory changes in both the temporal and extracranial arteries with a sensitivity of 95% and specificity of 98%. In our population, the sensitivity and specificity were slightly lower with values of 87.2 and 95.5%, respectively.

In 2018, De Miguel et al. (8) evaluated 40 patients with high cardiovascular risk and found an association between atherosclerotic disease and an increase of IMT values of the temporal arteries. Taking into account that atherosclerosis is prevalent in this group of patients presenting with clinical symptoms of GCA, they proposed a cut-off value for IMT of 0.34 mm in at least two temporal artery branches. In our study, the cut-off value for IMT of the temporal artery and its branches are in accordance with that proposed by De Miguel although the cardiovascular risk in our population was not specifically investigated. Despite the availability of excellent IMT cut-off values for the cranial and extracranial arteries, it is always important to take into account the clinical context of the patient, since findings above the proposed IMT cut-off values may be present in patients with atherosclerosis.

The main strength of our study is the systematically assessment of IMT in patients with suspected GCA in a well-established fast-track clinic. Our study has limitations including the retrospective design and being conducted in a single center. The initial use of steroids was relatively high, in almost half of the patients, that may affect the sensitivity of the US examination. However, polymyalgia rheumatica before US was present in 27.4% of the study population, finding comparable to previous studies (1, 32, 33). Ultrasonographer was not blinded to clinical data and clinician's making the diagnosis were not blinded to US findings, that may lead to bias in the diagnostic accuracy of US, although this bias is common in all studies aiming at validate a diagnostic tool in GCA. On the other hand, since no gold standard is valid for GCA diagnosis, we selected the clinical diagnosis at 6-month as the reference standard. However, as the majority of patients may continue with corticosteroid treatment at this time, other potential diseases may be masked. In addition, inter-observer reliability was not be investigated.

In summary, US of cranial and extracranial arteries has shown great diagnostic performance as an initial diagnostic test in patients with suspected GCA. These proposed cut-off values for IMT may help to improve the diagnostic accuracy of US in clinical practice. Finally, further validation of the cut-off values in different cohorts will be needed.

## Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving human participants were reviewed and approved by Research Ethical Committee of Hospital General Universitario Gregorio Marañón (RHEUM0322). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## Author contributions

KL-G and JM-C performed the study design, statistical analysis, subject recruitment, US examinations, and collection of the epidemiological and clinical data. KL-G, IC, JN-G, PR-M, BS-B, CG, IM, TG, JÁ-G, and JM-C drafted the manuscript. All authors revised the final manuscript and made substantial contributions to the conception and design of this study.

## Acknowledgments

We thank all the patients who participated in this study.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## References


1. Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia rheumatica and giant cell arteritis: A systematic review. *JAMA*. (2016) 315:2442–58. doi: 10.1001/jama.2016.5444

2. Soriano A, Muratore F, Pipitone N, Boiardi L, Cimino L, Salvarani C. Visual loss and other cranial ischaemic complications in giant cell arteritis. *Nat Rev Rheumatol.* (2017) 13:476–84. doi: 10.1038/nrrheum.2017.98

3. Koster MJ, Matteson EL, Warrington KJ. Large-vessel giant cell arteritis: Diagnosis, monitoring and management. *Rheumatology*. (2018) 57:ii32–42. doi: 10.1093/rheumatology/kex424

4. Chrysidis S, Duftner C, Dejaco C, Schäfer VS, Ramiro S, Carrara G, et al. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: A study from the OMERACT large vessel vasculitis ultrasound working group. *RMD Open.* (2018) 4:e000598. doi: 10.1136/rmdopen-2017-000598

5. 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) 77:636–43. doi: 10.1136/annrheumdis-2017-212649

6. Molina Collada J, Ruíz Bravo-Burguillos E, Monjo I, Bonilla G, Fernández E, Balsa A, et al. Positive ultrasound halo sign of temporal arteries due to amyloidosis. *Rheumatology.* (2019) 58:2067–9. doi: 10.1093/rheumatology/kez182

7. Fernández-Fernández E, Monjo-Henry I, Bonilla G, Plasencia C, Miranda-Carús ME, Balsa A, et al. False positives in the ultrasound diagnosis of giant cell arteritis: Some diseases can also show the halo sign. *Rheumatology*. (2020) 59:2443–7. doi: 10.1093/rheumatology/kez641

8. De Miguel E, Beltran LM, Monjo I, Deodati F, Schmidt WA, Garcia-Puig J. Atherosclerosis as a potential pitfall in the diagnosis of giant cell arteritis. *Rheumatology.* (2018) 57:318–21. doi: 10.1093/rheumatology/kex381

9. Thalhammer C, Husmann M, Glanzmann C, Studer G, Amann-Vesti BR. Carotid artery disease after head and neck radiotherapy. *Vasa.* (2015) 44:23–30. doi: 10.1024/0301-1526/a000403

10. Duftner C, Dejaco C, Sepriano A, Falzon L, Schmidt WA, Ramiro S. Imaging in diagnosis, outcome prediction and monitoring of large vessel vasculitis: A systematic literature review and meta-analysis informing the EULAR recommendations. *RMD Open*. (2018) 4:e000612. doi: 10.1136/rmdopen-2017-000612

11. Schmidt WA. Ultrasound in the diagnosis and management of giant cell arteritis. *Rheumatology.* (2018) 57:ii22–31. doi: 10.1093/rheumatology/kex461

12. Ješe R, Rotar Ž, Tomšiè M, Hoèevar A. The cut-off values for the intima-media complex thickness assessed by colour Doppler sonography in seven cranial and aortic arch arteries. *Rheumatology*. (2021) 60:1346–52. doi: 10.1093/rheumatology/keaa578

13. Schäfer VS, Juche A, Ramiro S, Krause A, Schmidt WA. Ultrasound cut-off values for intima-media thickness of temporal, facial and axillary arteries in giant cell arteritis. *Rheumatology.* (2017) 56:1479–83. doi: 10.1093/rheumatology/kex143

14. 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.* (2016) 55:66–70. doi: 10.1093/rheumatology/kev289

15. Schmidt WA, Kraft HE, Vorpahl K, Völker L, Gromnica-Ihle EJ. Color duplex ultrasonography in the diagnosis of temporal arteritis. *N Engl J Med.* (1997) 337:1336–42. doi: 10.1056/NEJM199711063371902

16. Ball EL, Walsh SR, Tang TY, Gohil R, Clarke JMF. Role of ultrasonography in the diagnosis of temporal arteritis. *Br J Surg.* (2010) 97:1765–71. doi: 10.1002/bjs.7252

17. 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. doi: 10.1186/1471-2474-11-44

18. Karassa FB, Matsagas MI, Schmidt WA, Ioannidis JPA. Meta-analysis: Test performance of ultrasonography for giant-cell arteritis. *Ann Intern Med.* (2005) 142:359–69. doi: 10.7326/0003-4819-142-5-200503010-00011

19. Rinagel M, Chatelus E, Jousse-Joulin S, Sibilia J, Gottenberg JE, 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) 18:56–61. doi: 10.1016/j.autrev.2018.07.012

20. De Miguel E, Roxo A, Castillo C, Peiteado D, Villalba A, Martín-Mola E. The utility and sensitivity of colour Doppler ultrasound in monitoring changes in giant cell arteritis. *Clin Exp Rheumatol.* (2012) 30:S34–8.

21. Muratore F, Boiardi L, Restuccia G, Macchioni P, Pazzola G, Nicolini A, et al. Comparison between colour duplex sonography findings and different histological patterns of temporal artery. *Rheumatology.* (2013) 52:2268–74. doi: 10.1093/rheumatology/ket258

22. Habib HM, Essa AA, Hassan AA. Color duplex ultrasonography of temporal arteries: Role in diagnosis and follow-up of suspected cases of temporal arteritis. *Clin Rheumatol.* (2012) 31:231–7. doi: 10.1007/s10067-011-1808-0

23. Karahaliou M, Vaiopoulos G, Papaspyrou S, Kanakis MA, Revenas K, Sfikakis PP. Colour duplex sonography of temporal arteries before decision for biopsy: A prospective study in 55 patients with suspected giant cell arteritis. *Arthritis Res Ther.* (2006) 8:R116. doi: 10.1186/ar2003

24. Salvarani C, Silingardi M, Ghirarduzzi A, Lo Scocco G, Macchioni P, Bajocchi G, et al. Is duplex ultrasonography useful for the diagnosis of giant-cell arteritis? *Ann Intern Med.* (2002) 137:232–8. doi: 10.7326/0003-4819-137-4-200208200-00006

25. 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) 51:730–4. doi: 10.1093/rheumatology/ker329

26. Förster S, Tato F, Weiss M, Czihal M, Rominger A, Bartenstein P, et al. Patterns of extracranial involvement in newly diagnosed giant cell arteritis assessed by physical examination, colour coded duplex sonography and FDG-PET. *Vasa.* (2011) 40:219–27. doi: 10.1024/0301-1526/a000096

27. 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) 47:96–101. doi: 10.1093/rheumatology/kem322

28. Lensen KDF, Voskuyl AE, Comans EFI, van der Laken CJ, Smulders YM. Extracranial giant cell arteritis: A narrative review. *Neth J Med.* (2016) 74:182–92.

29. Gloria KL, Rodríguez-Merlos P, Serrano-Benavente B, González JCN, Gonzalez C, Sáez IM, et al. Ab0594 ultrasound intima media thickness cut-off values for cranial and extracranial arteries in patients with giant cell arteritis. *Ann Rheum Dis.* (2022) 81:1423–4. doi: 10.1136/annrheumdis-2022-eular.3353

30. Molina Collada J, Martínez-Barrio J, Serrano-Benavente B, Castrejón I, Nieto-González JC, Caballero Motta LR, et al. Subclavian artery involvement in patients with giant cell arteritis: Do we need a modified Halo Score? *Clin Rheumatol.* (2021) 40:2821–7. doi: 10.1007/s10067-020-05577-4

31. Skoog J, Svensson C, Eriksson P, Sjöwall C, Zachrisson H. The diagnostic performance of an extended ultrasound protocol in patients with clinically suspected giant cell arteritis. *Front Med.* (2022) 8:807996. doi: 10.3389/fmed.2021.807996

32. Gonzalez-Gay MA. Giant cell arteritis and polymyalgia rheumatica: Two different but often overlapping conditions. *Semin Arthritis Rheum.* (2004) 33:289–93. doi: 10.1016/j.semarthrit.2003.09.007

33. González-Gay MA, Matteson EL, Castañeda S. Polymyalgia rheumatica. *Lancet.* (2017) 390:1700–12. doi: 10.1016/S0140-6736(17)31825-1


CITATION

López-Gloria K, Castrejón I, Nieto-González JC, Rodríguez-Merlos P, Serrano-Benavente B, González CM, Monteagudo Sáez I, González T, Álvaro-Gracia JM and Molina-Collada J (2022) Ultrasound intima media thickness cut-off values for cranial and extracranial arteries in patients with suspected giant cell arteritis. *Front. Med.* 9:981804. doi: 10.3389/fmed.2022.981804

## 2. Impact of cardiovascular risk on the diagnostic accuracy of the ultrasound Halo Score for giant cell arteritis.

Molina-Collada J, López Gloria K, Castrejón I, Nieto-González JC, Martínez-Barrio J, Anzola Alfaro AM, Rivera J, Álvaro-Gracia JM. Impact of cardiovascular risk on the diagnostic accuracy of the ultrasound Halo Score for giant cell arteritis. Arthritis Res Ther. 2022 Oct 13;24(1):232. doi: 10.1186/s13075-022-02920-9.

Molina-Collada *et al.*
*Arthritis Research & Therapy* (2022) 24:232
https://doi.org/10.1186/s13075-022-02920-9

Arthritis Research & Therapy

RESEARCH Open Access

# Impact of cardiovascular risk on the diagnostic accuracy of the ultrasound Halo Score for giant cell arteritis

Juan Molina-Collada[1,2*], Katerine López Gloria[1,2], Isabel Castrejón[1,2], Juan Carlos Nieto-González[1,2], Julia Martínez-Barrio[1,2], Ana M. Anzola Alfaro[1,2], Javier Rivera[1,2] and José María Álvaro-Gracia[1,2]

## Abstract

**Objective:** To evaluate the impact of cardiovascular risk (CVR) on the diagnostic accuracy of the ultrasonographic (US) Halo Score in patients with suspected giant cell arteritis (GCA).

**Methods:** Retrospective observational study of patients referred to our US fast track clinic with suspected GCA for a 2-year period. The intima-media thickness (IMT) of cranial and extra-cranial arteries and the Halo Score was determined to assess the extent of vascular inflammation. The European Society of Cardiology Guidelines on CV Disease Prevention were used to define different categories of CVR and patients were classified according to the Systemic Coronary Risk Evaluation (SCORE). The gold standard for GCA diagnosis was clinical confirmation after a 6-month follow-up.

**Results:** Of the 157 patients included, 47 (29.9%) had GCA after a 6-month follow-up. Extra-cranial artery IMT was significantly higher in patients with high/very high CVR than in those with low/moderate CVR, but only among patients without GCA. Non-GCA patients with high/very high CVR had also a significantly higher Halo Score in contrast with low/moderate CVR [9.38 (5.93) vs 6.16 (5.22); $p = 0.007$]. The area under the ROC curve of the Halo Score to identify GCA was 0.835 (95% CI 0.756–0.914), slightly greater in patients with low/moderate CVR (0.965 [95% CI 0.911–1]) versus patients with high/very high CVR (0.798 [95% CI 0.702–0.895]). A statistically weak positive correlation was found between the Halo Score and the SCORE ($r$ 0.245; $c = 0.002$).

**Conclusions:** Elevated CVR may influence the diagnostic accuracy of the US Halo Score for GCA. Thus, CVR should be taken into consideration in the US screening for GCA.

**Keywords:** Ultrasound, Halo Score, Giant cell arteritis, Cardiovascular risk, Vasculitis

## Introduction

Giant cell arteritis (GCA) is the most common form of large vessel vasculitis [1] and a potentially life-threatening inflammatory condition. When suspected, GCA requires prompt clinical evaluation and fast diagnostic imaging tests for an early and accurate diagnosis [2]. Due to its high specificity, the gold standard for its diagnosis has traditionally been considered a temporal artery (TA) biopsy. However, ultrasound (US) has emerged as a rapid and non-invasive imaging tool to detect signs of GCA. After more than 25 years since it was first described by Schmidt et al. [3], US has displaced TA biopsy being nowadays the preferred method to detect GCA. Moreover, the recently published European League Against Rheumatism (EULAR) guidelines recommends TA and axillary arteries (AA)

*Correspondence: molinacolladajuan@gmail.com

[2] Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain
Full list of author information is available at the end of the article

US exam as the first-line imaging test in centers with expertise when patients are presenting with cranial symptoms of GCA [4]. The diagnosis of GCA can be confirmed with US positive finding not requiring additional complementary exams. The halo sign is the most important US finding in GCA and it is defined as a homogeneous, hypoechoic wall thickening, well delineated towards the luminal side, visible in two perpendicular planes, most commonly concentric in transverse scan [5]. A recent meta-analysis by EULAR showed a pooled sensitivity of 77% and specificity of 96% for the halo sign [6]. Furthermore, the compression sign, which is defined as a thickened arterial wall that remains visible upon compression, is also useful for GCA screening [5].

In recent years, very high-resolution transducers have been available for the US exam providing new tools to assess GCA patients as the measurement of the intima-media thickness (IMT) by B-Mode without Doppler. In this context, cut-off values for TA and AA have been published, with excellent sensitivities and specificities (> 97%) for the diagnosis of GCA in subjects with a high pre-test probability [7–9]. More recently, the Halo Score has been proposed as a quantitative measure to determine the extent of vascular inflammation by US, incorporating the IMT of each halo [10]. According to these findings, the Halo Score correlates with systemic markers of inflammation and risk for ocular ischemia, and a high Halo Score (≥ 10) may help to confirm GCA diagnosis with high specificity (> 95%). This novel scoring system has also been validated in routine care showing good diagnostic accuracy [11, 12].

However, IMTs above the cut-off values that mimic a positive halo and compression sign have been also described in patients not having GCA [13] leading to false positives in patients with atherosclerosis [14], intimal hyperplasia on biopsy [15], or in several disorders as amyloidosis [16], vasculitis mimics, or lymphoma [17]. Thus, the trend towards the utilization of IMT cut-off values to diagnose GCA needs to be evaluated in the clinical context of patients with elevated cardiovascular risk (CVR). It has been described how a positive compression sign or IMTs above the traditional cut-off values may be present in patients without GCA in the presence of atherosclerosis or elevated CVR [15]. Besides, quantitative US tools like the Halo Score, relying on the measurement of each artery IMT, may be influenced by the CVR, so an accurate interpretation of the score needs to be taken into account in this context.

The primary objective of this study was to evaluate the impact of CVR on the diagnostic accuracy of the US Halo Score in patients with suspected GCA.

## Methods

### Patients

This was a retrospective cross-sectional study including patients referred to a US fast track clinic (FTC) [2] at our Academic Center for screening of possible GCA over a 2-year period (from June 2019 to June 2021). Patients with suspected GCA are referred to this US clinic for examination within 24 h per protocol. For the purposes of this study, only consecutive patients with GCA suspicion were included. The study was performed in routine clinical practice conditions.

### Data collection

The following variables were collected from the electronic health records: demographics, presenting symptoms (headache, scalp tenderness, jaw claudication, visual symptoms and ocular ischemia diagnosis by an ophthalmologist, fever, polymyalgia rheumatica, and constitutional symptoms), previous use of glucocorticoids, and laboratory variables as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin, and platelets. TA biopsy data were also included if available. The gold standard for GCA diagnosis was the clinical confirmation by the treating clinician after a 6 months follow-up. The clinical GCA diagnosis could be dismissed according to the clinician criteria, even in patients fulfilling ACR 1990 criteria or with positive imaging tests, if another more reasonable diagnosis was established.

### Cardiovascular risk stratification

To assess the CVR, the following variables were collected: body weight, height and body mass index, history of acute myocardial infarction, acute coronary syndromes, transient ischemic attack, stroke, aortic aneurism, peripheral artery disease, diabetes mellitus with or without organ damage, estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, cholesterol level (total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol), systolic and diastolic blood pressure, and smoking habit (current or previous smoker). The European Society of Cardiology (ESC) Guidelines on CV Disease Prevention in clinical practice were applied to define four different categories of CVR [18]. We calculated the risk score of each patient using the available ESC CVD Risk Calculator app for mobile devices (https://www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/esc-cvd-risk-calculation-app), and subjects were classified as very high, high, moderate, or low CVR. Patients with high or very high CVR were

compared with patients with low or moderate CVR to determine differences in the diagnostic accuracy of the Halo Score.

### Ultrasound assessment

The three TA segments (common superficial TA, its parietal and frontal branches) and extracranial (carotid, subclavian and distal axillary) arteries were bilaterally evaluated by US in all patients within 24 h per protocol (excluding weekends with delays up to 48 h). The exam was performed in a supine position, by a single experienced ultrasonographer (JMC) using an EsaoteMyLab8 (Esaote, Genoa) with a hockey stick 12–18 MHz high frequency transducer for the temporal arteries and an 8–14 frequency transducer for extracranial arteries. The distal axillary arteries were scanned from the axillary fossa. The focus was positioned at 5 mm below the skin for the TA and 2–3 cm for the axillary arteries. The pulse repetition frequency was 2–3 kHz. The color box was set at an angle between sound waves and artery < 60°. The presence or absence of a halo, compression, stenosis, or occlusion for cranial arteries and the presence of a halo for extracranial arteries were evaluated. The IMT was measured in gray scale mode in all the arteries included in the protocol if technically possible due to the maximum frequency probe (18 MHz). Doppler color mode was only used to better delineate the lumen of the vessel to improve the visibility of the IMT in unclear cases. The extent of vascular inflammation was quantified according to the Halo Score, identifying the maximum IMT in each artery and calculating the composite score according to predefined cut-off values. The halo grade scores of the axillary arteries were multiplied by a factor of 3. The Halo score values could range from 0 to 48 [10]. The presence of a halo and/or compression sign in temporal arteries or the presence of a halo in extracranial arteries in the absence of atherosclerosis was considered sufficient for a positive US examination. The ultrasonographer was not blinded to the clinical information of the patient.

### Statistical analysis

Quantitative data were described as mean (standard deviation, SD) and qualitative variables as absolute frequency (percentages). 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. The SPSS software (version 23.0; IBM, USA) was used for statistical analysis.

### 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 (RHEUM0322). The committee determined that written informed consent was not mandatory.

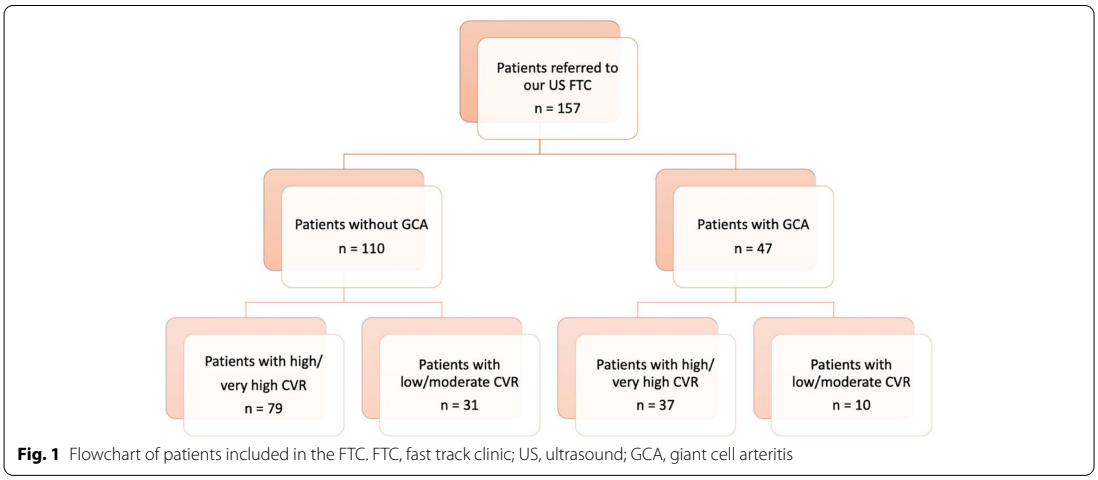


**Fig. 1** Flowchart of patients included in the FTC. FTC, fast track clinic; US, ultrasound; GCA, giant cell arteritis

## Results

### Patient characteristics

A total of 157 patients referred to the FTC were included for analysis; 106 (67.5%) were female with a mean age of 73.7 years. Figure 1 shows the patient flow diagram. After 6 months of follow-up, 47 (29.9%) patients were clinically diagnosed of GCA by the treating clinician. Polymyalgia rheumatica diagnosis before US examination was present

**Table 1** Clinical, laboratory variables, and US findings in patients with or without GCA

| | Total *n* = 157 | Patients with GCA *n* = 47 (29.9) | Patients without GCA *n* = 110 (70.1) | *p* |
|---|---|---|---|---|
| **Demographics** | | | | |
| **Age, mean (SD)** | 73.7 (10.8) | 75.3 (11.3) | 73 (10.6) | 0.245 |
| **Female, *n* (%)** | 106 (67.5) | 31 (66) | 75 (68.2) | 0.785 |
| **Clinical variables** | | | | |
| **Baseline use of steroids, *n* (%)** | 78 (50) | 21 (45.7) | 57 (51.8) | 0.482 |
| **PMR diagnosis before US examination, *n* (%)** | 43 (27.4) | 8 (17) | 35 (31,8) | 0.121 |
| **Body mass index, mean (SD)** | 27.2 (4.5) | 26.8 (2.8) | 27.4 (5.1) | 0.415 |
| **Systolic blood pressure, mean (SD)** | 128.3 (16.8) | 127.7 (19) | 128.6 (15.9) | 0.777 |
| **Diastolic blood pressure, mean (SD)** | 72.9 (10.6) | 69.4 (8.6) | 74.4 (11) | 0.003 |
| **Hypertension, *n* (%)** | 96 (61.5) | 30 (65.2) | 66 (60) | 0.541 |
| **Acute myocardial infarction, *n* (%)** | 6 (3.8) | 1 (2.2) | 5 (4.5) | 0.482 |
| **Arterial revascularization, *n* (%)** | 10 (6.4) | 4 (8.7) | 6 (5.5) | 0.451 |
| **Transient ischemic attack, *n* (%)** | 4 (2.6) | 0 (0) | 4 (3.7) | 0.188 |
| **Acute ischemic stroke, *n* (%)** | 12 (7.7) | 3 (6.5) | 9 (8.2) | 0.723 |
| **Peripheral artery disease, *n* (%)** | 2 (1.3) | 1 (2.2) | 1 (0.9) | 0.522 |
| **Diabetes mellitus type 2, *n* (%)** | 37 (23.7) | 13 (28.3) | 24 (21.8) | 0.388 |
| **Diabetes mellitus with target organ damage, *n* (%)** | 4 (2.6) | 1 (2.2) | 3 (2.7) | 0.842 |
| **Chronic kidney disease, *n* (%)** | 28 (17.9) | 6 (13) | 22 (20) | 0.302 |
| **Glomerular filtration rate (MDRD), mean (SD)** | 84.4 (23.4) | 84.1 (22.5) | 84.5 (23.8) | 0.931 |
| **Current or previous smokers, *n* (%)** | 41 (26.3) | 16 (34.8) | 25 (22.7) | 0.119 |
| **Very high CVR** | 70 (44.6) | 23 (48.9) | 47 (42.7) | 0.473 |
| **High CVR** | 46 (29.3) | 14 (29.8) | 32 (29.1) | 0.93 |
| **Moderate CVR** | 21 (13.4) | 6 (12.8) | 15 (13.6) | 0.883 |
| **Low CVR** | 20 (12.7) | 4 (8.5) | 16 (14.5) | 0.299 |
| **SCORE Score, mean (SD)** | 19.2 (21.2) | 20.6 (21.6) | 18.7 (21) | 0.601 |
| **Laboratory findings** | | | | |
| **CRP (mg/dL), mean (SD)** | 5.9 (11.3) | 10.7 (18.2) | 3.8 (5) | 0.001 |
| **ESR (mm/h), mean (SD)** | 52.8 (34.2) | 68.2 (34) | 45 (31.8) | 0.001 |
| **Hemoglobin (g/dL), mean (SD)** | 13.7 (17.6) | 11.7 (1.6) | 14.5 (21) | 0.185 |
| **Platelets $10^9$/L, mean (SD)** | 293 (124.7) | 335.4 (143.3) | 274.7 (111.6) | 0.014 |
| **Total cholesterol mg/dL, mean (SD)** | 181.9 (153.3) | 161.3 (42.6) | 190.6 (180.1) | 0.111 |
| **HDL cholesterol mg/dL, mean (SD)** | 54 (18.7) | 53.1 (20.7) | 54.3 (17.8) | 0.723 |
| **LDL cholesterol mg/dL, mean (SD)** | 97.4 (35.9) | 90.8 (30.9) | 100.1 (37.6) | 0.142 |
| **Histology** | | | | |
| **Positive temporal artery biopsy (*n* = 31), *n* (%)** | 10 (32.3) | 10 (43.5) | 0 (0%) | 0.023 |
| **US variables** | | | | |
| **Positive US findings, *n* (%)** | 46 (29.3%) | 41 (87.2%) | 5 (4.5%) | < 0.001 |
| **Temporal artery positive US findings, *n* (%)** | 32 (20.4%) | 29 (61.7%) | 3 (2.7%) | < 0.001 |
| **Extracranial arteries positive US findings, *n* (%)** | 23 (14.6%) | 21 (44.7%) | 2 (1.8%) | < 0.001 |
| **Temporal + extracranial arteries positive US findings, *n* (%)** | 9 (5.7%) | 9 (19.1%) | 0 (0%) | < 0.001 |
| **Halo Score, mean (SD)** | 11.4 (8.3) | 18.2 (9.2) | 8.5 (5.9) | < 0.001 |

*Abbreviations: GCA*, giant cell arteritis; *PMR*, polymyalgia rheumatica; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *US*, ultrasound; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *SD*, standard deviation

in 43 (27.4%) patients. Table 1 summarizes the baseline characteristics, clinical, laboratory and imaging findings of patients with and without GCA. Patients with GCA presented higher values of CRP, ESR, and platelets. TA biopsy was performed per clinician criteria in 31 patients with positive results in 10 (43.5%) GCA patients.

### Cardiovascular risk assessment

According to the ESC Guidelines on CV Disease Prevention, 70 (44.6%) patients were classified as very high CVR, 46 (29.3%) as high CVR, 21 (13.4%) as moderate CVR, and 20 (12.7%) as low CVR. Overall, mean score SCORE was 19.2 (21.2). There were no differences in CVR between patients with and without GCA (mean SCORE 20.6 [21.6] vs 18.7 [21]; $p = 0.601$) (Table 1).

### Ultrasound findings

Patients with GCA presented positive US findings more frequently than subjects without GCA (41 [87.2%] vs 5 [4.5%]; $p < 0.001$). Sensitivity and specificity of US vs GCA clinical confirmation was 87.2% and 95.5%, respectively, and positive and negative likelihood ratio was 19.38 and 0.13, respectively. Among patients with GCA, 29 (61.7%) had TA involvement and 21 (44.7%) had extra-cranial arteries inflammation according to US examination. A mixed pattern with involvement of both TA and extracranial arteries was found in 9 (19.1%) patients. Twenty (42.6%) patients had exclusive cranial involvement, while 12 (25.5%) had exclusive extracranial involvement. Mean Halo Score was significantly higher in patients with GCA (18.2 (9.2) vs 8.5 (5.9); $p < 0.001$) (Table 1).

### Impact of cardiovascular risk on the intima-media thickness of cranial and extracranial arteries

Among patients without GCA, extra-cranial artery IMT was significantly higher in patients with high/very high CVR than in those with low/moderate CVR (carotid IMT 0.83 (0.16) vs 0.74 (0.13); $p < 0.001$, subclavian IMT 0.74

**Table 2** Measurements of IMT in cranial and extracranial arteries and Halo Score values according to CVR

| | Total *n* = 157 | Patients with GCA *n* = 47 | | | Patients without GCA *n* = 110 | | |
|---|---|---|---|---|---|---|---|
| | | Patients with high/very high CVR *n* = 37 (78.7%) | Patients with low/moderate CVR *n* = 10 (21.3%) | *p* | Patients with high/very high CVR *n* = 79 (71.8%) | Patients with low/moderate CVR *n* = 31 (28.2%) | *p* |
| **Superficial temporal artery (right) mm, mean (SD)** | 0.43 (0.21) | 0.74 (0.26) | 0.39 (0.02) | 0.094 | 0.34 (0.06) | 0.31 (0.07) | 0.320 |
| **Superficial temporal artery (left) mm, mean (SD)** | 0.44 (0.19) | 0.58 (0.23) | 0.52 (0.15) | 0.695 | 0.35 (0.12) | 0.35 (0.07) | 0.994 |
| **Superficial temporal artery (both) mm, mean (SD)** | 0.43 (0.2) | 0.66 (0.25) | 0.45 (0.11) | 0.025 | 0.35 (0.09) | 0.32 (0.07) | 0.354 |
| **Frontal branch (right) mm, mean (SD)** | 0.3 (0.12) | 0.41 (0.18) | 0.34 (0.17) | 0.37 | 0.25 (0.04) | 0.26 (0.07) | 0.401 |
| **Frontal branch (left) mm, mean (SD)** | 0.3 (0.12) | 0.42 (0.18) | 0.28 (0.14) | 0.096 | 0.27 (0.05) | 0.26 (0.04) | 0.832 |
| **Frontal branch (both) mm, mean (SD** | 0.3 (0.12) | 0.42 (0.18) | 0.31 (0.15) | 0.056 | 0.26 (0.05) | 0.26 (0.06) | 0.577 |
| **Parietal branch (right) mm, mean (SD)** | 0.32 (0.13) | 0.45 (0.19) | 0.33 (0.1) | 0.125 | 0.27 (0.04) | 0.28 (0.07) | 0.504 |
| **Parietal branch (left) mm, mean (SD)** | 0.31 (0.12) | 0.41 (0.16) | 0.39 (0.16) | 0.006 | 0.27 (0.06) | 0.28 (0.09) | 0.288 |
| **Parietal branch (both) mm, mean (SD)** | 0.32 (0.12) | 0.43 (0.17) | 0.35 (0.12) | 0.102 | 0.27 (0.04) | 0.28 (0.08) | 0.173 |
| **Carotid artery (right) mm, mean (SD)** | 0.82 (0.21) | 0.85 (0.17) | 1 (0.54) | 0.112 | 0.83 (0.17) | 0.72 (0.14) | 0.002 |
| **Carotid artery (left) mm, mean (SD)** | 0.88 (0.28) | 0.92 (0.25) | 1.2 (0.6) | 0.310 | 0.84 (0.15) | 0.76 (0.12) | 0.006 |
| **Carotid artery (both) mm, mean (SD)** | 0.85 (0.25) | 0.88 (0.21) | 1.2 (0.6) | < 0.001 | 0.83 (0.16) | 0.74 (0.13) | < 0.001 |
| **Subclavian artery (right) mm, mean (SD)** | 0.81 (0.3) | 0.9 (0.34) | 1.2 (0.6) | 0.845 | 0.78 (0.17) | 0.62 (0.14) | < 0.001 |
| **Subclavian artery (left) mm, mean (SD)** | 0.73 (0.26) | 0.81 (0.26) | 1.1 (0.45) | 0.901 | 0.71 (0.18) | 0.58 (0.13) | < 0.001 |
| **Subclavian artery (both) mm, mean (SD)** | 0.77 (0.28) | 0.86 (0.31) | 1.2 (0.5) | 0.001 | 0.74 (0.18) | 0.6 (0.13) | < 0.001 |
| **Axillary artery (right) mm, mean (SD)** | 0.78 (0.34) | 0.93 (0.41) | 1.2 (0.72) | 0.268 | 0.72 (0.16) | 0.6 (0.15) | 0.001 |
| **Axillary artery (left) mm, mean (SD)** | 0.77 (0.34) | 0.92 (0.36) | 1.23 (0.78) | 0.0.92 | 0.71 (0.16) | 0.57 (0.15) | < 0.001 |
| **Axillary artery (both) mm, mean (SD)** | 0.77 (0.34) | 0.92 (0.38) | 1.22 (0.73) | 0.021 | 0.72 (0.16) | 0.59 (0.15) | < 0.001 |
| **Halo Score, mean (SD)** | 11.39 (8.3) | 18.5 (8.8) | 17.2 (10.6) | 0.69 | 9.38 (5.93) | 6.16 (5.22) | 0.007 |

*SD*, standard deviation

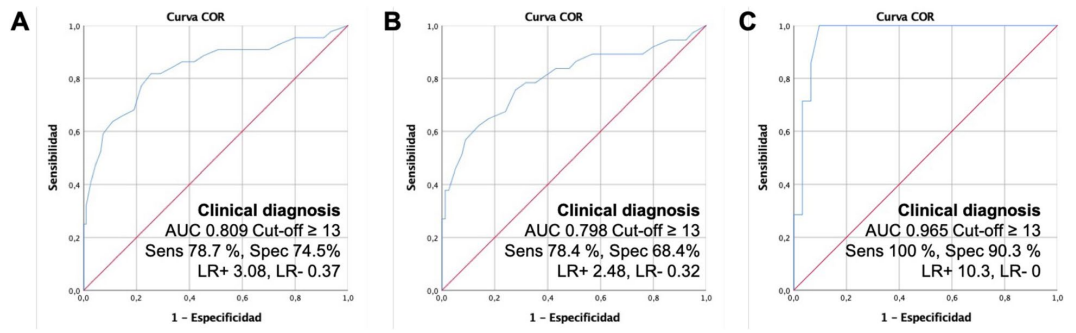


**Fig. 2** Diagnostic accuracy of the Halo Score for a clinical diagnosis of GCA after 6 months follow-up in **A** all LVV suspected patients, **B** patients with high to very high CVR, and **C** patients with low to moderate CVR. Youden index was used to determine the optimal cut-off points. AUC, area under the curve, LR+, positive likelihood ratio; LR−, negative likelihood ratio; ROC, receiver operating characteristic; Sens, sensitivity; Spec, specificity

(0.18) vs 0.6 (0.13); $p < 0.001$ and axillary IMT 0.71 (0.16) vs 0.57 (0.15); $p < 0.001$) (Table 2). Similarly, numerically higher IMT values were found in TA in patients with high/very high CVR vs low/moderate CVR in patients without GCA but without statistical significance.

Regarding the GCA group, patients with high/very high CVR had significantly higher IMT measurements in superficial TA (0.66 [0.25] vs 0.45 [0.11]; $p = 0.025$) and numerically higher IMT values in frontal and parietal branches (0.42 (0.18) vs 0.31 (0.15); $p = 0.056$ and 0.43 (0.17) vs 0.35 (0.12); $p = 0.102$, respectively). GCA patients showed significantly higher IMT values in patients with low/moderate CVR than in those with high/very high CVR (carotid IMT 0.88 (0.21) vs 1.2 (0.6); $p < 0.001$, subclavian IMT 0.86 (0.31) vs 1.2 (0.5); $p = 0.001$ and axillary IMT 0.92 (0.38) vs 1.22 (0.73); $p = 0.021$). However, patients with GCA and low/moderate CVR were significantly younger (58.4 vs 79.9; $p < 0.001$) and had extracranial artery involvement more frequently (70% vs 37.8%; $p = 0.07$) compared with those with GCA and high/very high CVR.

### Impact of cardiovascular risk on the diagnostic accuracy of the Halo Score

The Halo Score values were significantly higher in non-GCA patients with high/very high CVR vs low/moderate CVR (9.38 (5.93) vs 6.16 (5.22); $p = 0.007$) (Table 2). The area under the ROC curve of the Halo Score to identify GCA was 0.835 (95% CI 0.756–0.914), slightly greater in patients with low/moderate CVR (0.965 [95% CI 0.911–1]) versus patients with high/very high CVR (0.798 [95% CI 0.702–0.895]) (Fig. 2). A statistically weak positive correlation was found between the Halo Score and the SCORE ($r$ 0.245; $p = 0.002$) (Fig. 3).

## Discussion

In this observational cross-sectional study, we evaluated for the first time the impact of the CVR evaluation on the diagnostic accuracy of the most used US quantitative index, the Halo Score. Our main finding is that patients with high and very high CVR show higher US Halo Score affecting the diagnostic accuracy of this US index.

IMT cut-off values for GCA diagnosis have been previously described [7–9, 19], but the impact of the individually CVR on the diagnostic accuracy of US has not been well determined. Similar to our results, De Miguel et al evaluated the IMT of carotid and TA in 40 patients with high CVR [14]. They found that atherosclerotic disease with a carotid IMT > 0.9 mm increases the IMT of TA and might mimic the halo sign. They proposed a cut-off of TA IMT > 0.34 mm in at least two branches to minimize false positives in a GCA diagnosis, achieving high specificity (> 95%). In this study, the authors did not evaluate the impact of atherosclerosis or CVR in the extracranial (p.e axillary) artery IMT. More recently, Martire et al. [20] investigated the performance of previously proposed IMT cut-off values [7], scanning the temporal and axillary arteries in a cohort of non-GCA. They found that CVR was associated with higher IMT values, especially at superficial temporal artery level, showing IMT values higher than the proposed cut-off values in 21% of healthy subjects with high/very high CVR, and in only 3.2% of subjects with low/moderate CVR.

To our knowledge, this is the first study specifically design to evaluate the diagnostic performance of the US Halo Score for GCA in different CVR subgroups of patients. According to our findings, the diagnostic accuracy of the US Halo Score is reduced in patients with high/very high CVR in comparison with patients with low/moderate CVR. A possible explanation is that the

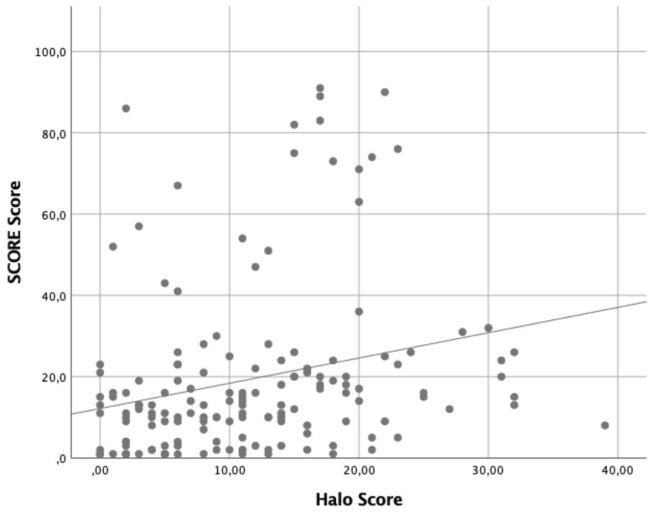


**Fig. 3** Correlation between the Halo Score and the SCORE score ($r$ 0.245; $p = 0.002$)

Halo Score is based on the measurement of the halo (or increased IMT), which would be influenced by the CVR of each individual patient. Our results are in line with other previously published by Martire et al. [20], although they studied a slightly different population (healthy subject without GCA or PMR), in contrast with a suspected GCA population in our cohort. In agreement with de Miguel et al. results [14], a numerically higher IMT of TA were found in patients with high/very high CVR, although we did not specifically include atherosclerosis in our analysis. Subjects without GCA with high/very high CVR had numerically higher IMT of TA and significantly higher IMT of extracranial arteries than those with low/moderate CVR (Table 2). Similarly, GCA patients with high/very high CVR had higher IMT of TA. Surprisingly, among patients with GCA, IMT of extracranial arteries was higher in those with low/moderate CVR. However, these results are explained by the fact that patients with GCA and extracranial involvement are significantly younger than those with TA involvement and, therefore, they had lower CVR. Our results highlight the importance of appropriate interpretation of IMT values when assessing patients with suspected GCA. The ultrasonographer should be cautious when assessing patients for GCA screening and be able to discard the disease even with IMT values above the diagnostic cut-offs if patients have a low pre-test probability and elevated CVR.

The main strength of the present study is that it is the first to evaluate the impact of CVR on the diagnostic accuracy of the Halo Score for GCA diagnosis, in a relatively large cohort of patients with suspected GCA evaluated in a well stablished FTC. This study has several limitations including the retrospective design and the limited data for some ancillary studies as TAB which was only performed per clinician criteria, consistent with real-world clinical practice. Second, the ultrasonographer was not blinded to clinical data. Third, intra and inter-observer reliability was not investigated.

In summary, high and very high CVR may influence the diagnostic accuracy of the US Halo Score leading to false-positive findings in these patients. Higher IMT values may be found in cranial and extracranial arteries in subjects with high/very high CVR without GCA. Thus, CVR should be taken into consideration in the US vascular assessment of patients with suspected GCA. These results need to be confirmed in additional cohorts to determine the need of a modified US Halo Score in patients with high and very high CVR.

**Acknowledgements**
The authors thank all the patients who participated in this study.

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

**Authors' contributions**
All authors made substantial contributions to the conception and design of this study. Study design, subject recruitment, US examinations, and collection of the epidemiological and clinical data were performed by JMC. JMC performed the statistical analysis. JMC, KL, IC, JCNG, JMB, AMAA, JR, and JAG drafted the manuscript. All co-authors revised the final manuscript. The author(s) read and approved the final manuscript.

**Funding**
The authors received no specific funding for this work.

**Availability of data and materials**
The data underlying this article are available in the article and in its online supplementary material.

## Declarations

**Ethics approval and consent to participate**
The research protocol have been approved by the Research ethical Committee of Hospital General Universitario Gregorio Marañón (RHEUM0322), and informed written consent was not mandatory for their participation in the study.

**Consent for publication**
Not required.

**Competing interests**
The authors declare that they have no competing interests.

**Author details**
[1]Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Calle del Dr. Esquerdo, 46, 28007 Madrid, Spain. [2]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain.

Received: 16 August 2022 Accepted: 30 September 2022
Published online: 13 October 2022

**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. 2013;65(1):1–11.
2. 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). 2016;55(1):66–70.
3. Schmidt WA, Kraft HE, Vorpahl K, Völker L, Gromnica-Ihle EJ. Color duplex ultrasonography in the diagnosis of temporal arteritis. N Engl J Med. 1997;337(19):1336–42.
4. 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.
5. Chrysidis S, Duftner C, Dejaco C, Schäfer VS, Ramiro S, Carrara G, et al. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group. RMD Open. 2018;4(1):e000598.
6. Duftner C, Dejaco C, Sepriano A, Falzon L, Schmidt WA, Ramiro S. Imaging in diagnosis, outcome prediction and monitoring of large vessel vasculitis: a systematic literature review and meta-analysis informing the EULAR recommendations. RMD Open. 2018;4(1):e000612.
7. Schäfer VS, Juche A, Ramiro S, Krause A, Schmidt WA. Ultrasound cut-off values for intima-media thickness of temporal, facial and axillary arteries in giant cell arteritis. Rheumatology (Oxford). 2017;56(9):1479–83.
8. Ješe R, Rotar Ž, Tomšič M, Hočevar A. The cut-off values for the intima-media complex thickness assessed by colour Doppler sonography in seven cranial and aortic arch arteries. Rheumatology (Oxford). 2021;60(3):1346–52.
9. Czihal M, Schröttle A, Baustel K, Lottspeich C, Dechant C, Treitl KM, et al. B-mode sonography wall thickness assessment of the temporal and axillary arteries for the diagnosis of giant cell arteritis: a cohort study. Clin Exp Rheumatol. 2017;35 Suppl 103(1):128–33.
10. 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.
11. Molina Collada J, Martínez-Barrio J, Serrano-Benavente B, et al. Diagnostic value of ultrasound halo count and Halo Score in giant cell arteritis: a retrospective study from routine care. Ann Rheum Dis. 2022;81:e175.
12. 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. 2022;81:e176.
13. Schmidt WA. The ultrasound halo sign of temporal arteries: is it always giant cell arteritis? Rheumatology (Oxford). 2019;58(11):1898–9.
14. De Miguel E, Beltran LM, Monjo I, Deodati F, Schmidt WA, Garcia-Puig J. Atherosclerosis as a potential pitfall in the diagnosis of giant cell arteritis. Rheumatology (Oxford). 2018;57(2):318–21.
15. Seitz L, Lötscher F. The intima-media thickness in suspected giant cell arteritis-sometimes it is worth taking a closer look. Rheumatology (Oxford). 2021;60(7):3039–41.
16. Molina Collada J, Ruíz Bravo-Burguillos E, Monjo I, Bonilla G, Fernández E, Balsa A, et al. Positive ultrasound halo sign of temporal arteries due to amyloidosis. Rheumatology (Oxford). 2019;58(11):2067–9.
17. Fernández-Fernández E, Monjo-Henry I, Bonilla G, Plasencia C, Miranda-Carús ME, Balsa A, et al. False positives in the ultrasound diagnosis of giant cell arteritis: some diseases can also show the halo sign. Rheumatology (Oxford). 2020;59(9):2443–7.
18. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur J Prev Cardiol. 2021;2021:zwab154.
19. López-Gloria K, Castrejón I, Nieto-González JC, Rodríguez-Merlos P, Serrano-Benavente B, González CM, et al. Ultrasound intima media thickness cut-off values for cranial and extracranial arteries in patients with suspected giant cell arteritis. Front Med (Lausanne). 2022;9:981804.
20. Martire MV, Cipolletta E, Di Matteo A, Di Carlo M, Jesus D, Grassi W, et al. Is the intima-media thickness of temporal and axillary arteries influenced by cardiovascular risk? Rheumatology (Oxford). 2021;60(11):5362–8.

## Publisher's Note

## 3. The role of ultrasound and FDG-PET/CT to detect extracranial artery involvement in patients with suspected large vessel vasculitis

Molina-Collada J, Castrejón I, Rivera J, Martínez-Barrio J, Nieto-González JC, López K, Montero F, Trives L, González C, Álvaro-Gracia JM. The role of ultrasound and FDG-PET/CT to detect extracranial artery involvement in patients with suspected large vessel vasculitis. Mod Rheumatol. 2023 Apr 13;33(3):549-556. doi: 10.1093/mr/roac058.

*Modern Rheumatology*, **00**, 2022, 1–8
DOI: https://doi.org/10.1093/mr/roac058
Advance Access Publication Date: 4 June 2022
**Original Article**

# The role of ultrasound and FDG-PET/CT to detect extracranial artery involvement in patients with suspected large vessel vasculitis

**Juan Molina-Collada*, Isabel Castrejón, Javier Rivera, Julia Martínez-Barrio, Juan Carlos Nieto-González, Katerine López, Fernando Montero, Laura Trives, Carlos González and José María Álvaro-Gracia**

Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain

*Correspondence: Juan Molina-Collada; molinacolladajuan@gmail.com; Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Calle del Dr. Esquerdo, 46, Madrid 28007, Spain.

## ABSTRACT

**Objective:** To assess the accuracy of ultrasound (US) versus fluorodeoxyglucose—positron emission tomography/computed tomography (FDG-PET/CT) to identify extracranial involvement in large vessel vasculitis (LVV).

**Methods:** A retrospective observational study of patients with suspected LVV. All patients underwent US exam within 24 h per protocol. FDG-PET/CT was performed according to clinician criteria. The gold standard for LVV diagnosis was clinical confirmation after 6 months.

**Results:** Of the 113 patients included (74.3% female, mean age 74 years), 37 (32.7%) were diagnosed with LVV after 6 months. The sensitivity and specificity of US were 86.5% and 96.1%, respectively. Only 12 (42.9%) of 28 patients undergoing a FDG-PET/CT per clinician criteria showed positive findings. The sensitivity and specificity of FDG-PET/CT for LVV were 61.1% and 90%, respectively. Taking FDG-PET/CT as the reference, US showed extracranial inflammation in 10/12 (83.3%) and detected 2 (12.5%) additional cases of extracranial involvement with negative FDG-PET/CT. Conversely, FDG-PET/CT was positive in two patients with negative US (one isolated aortitis and one aortoiliac involvement).

**Conclusions:** US and FDG-PET/CT are both valid tools to detect extracranial involvement. The presence of US extracranial artery inflammation is consistent with FDG-PET/CT examination, although a negative US scan does not rule out extracranial involvement.

**KEYWORDS:** Ultrasound; FDG-PET/CT; vasculitis; giant cell arteritis

## Introduction

Giant cell arteritis (GCA) is the most common form of large vessel vasculitis (LVV) [1]. Although the classic presentation of GCA involves the cranial arteries, the aorta and its branches (extracranial arteries) can be also affected in certain proportion of patients [2]. LVV with extracranial involvement may be more challenging to diagnose as the clinical manifestations are less specific including fever or weight loss [3] and present less frequently cranial manifestations [4].

Overall, LVV presentation is a potentially life-threatening inflammatory condition, in which feasible and fast diagnostic imaging testing is strongly recommended for an early and accurate diagnosis [5]. Traditionally, the gold standard for its diagnosis was a temporal artery (TA) biopsy. Although highly specific, a TA biopsy exhibits low sensitivity. The American College of Rheumatology (ACR) criteria [1] are meant useful to classify patients for their inclusion in clinical trials, while its use for diagnostic purposes lacks specificity to support clinical diagnosis [6]. In recently published European League Against Rheumatism (EULAR) recommendations, a TA and axillary arteries ultrasound (US) exam has been proposed as a first-line imaging test in centres with expertise in patients presenting with predominantly cranial symptoms of GCA [7]. US may potentially be used for the assessment of extracranial artery inflammation [2]. However, the value of this technique in assessing extracranial GCA is still unclear [8, 9]. To this respect, 18 F-fluorodeoxyglucose—positron emission tomography/computed tomography (FDG-PET/CT) has been considered the reference standard for detecting extracranial involvement. Moreover, EULAR recommendations give no priority to which imaging modality should be performed preferably in large vessel GCA [7], and studies comparing the diagnostic value of both imaging modalities are limited [10–12].

The primary objective of this study is to evaluate the clinical value of US versus FDG-PET/CT to detect extracranial artery involvement in patients with LVV. Our secondary objective includes the evaluation of both imaging techniques to detect cranial involvement.

Received 7 April 2022; Accepted 2 June 2022

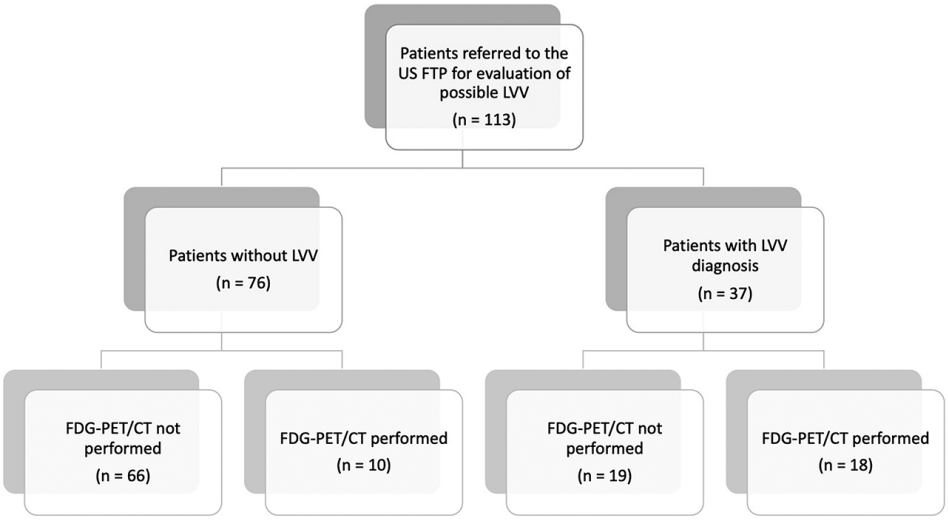


**Figure 1.** Flowchart of patients included in the FTP. FDG: fluorodeoxyglucose.

## Methods

### Patients

This is a retrospective observational study including patients referred to a US fast-track pathway (FTP) [5] for screening of possible LVV over a 2-year period. At our institution, patients with suspected LVV are referred for US examination within 24 h per protocol. An US exam is performed on both cranial and extracranial arteries (carotid, subclavian, and axillary arteries) as part of the diagnostic workup since 2019. FDG-PET/CT is performed according to the treating clinician. For the purposes of this study, only patients with GCA suspicion without a previous diagnosis who were referred to this unit were consecutively included (Figure 1). The study was performed in routine daily practice conditions including consecutive unselected patients.

### Data collection

The following variables were collected from the electronic health records: demographics; presenting symptoms (headache, scalp tenderness, jaw claudication, visual symptoms and ocular ischaemia diagnosis by an ophthalmologist, fever, polymyalgia, and constitutional symptoms), previous use of glucocorticoids, and laboratory variables such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), haemoglobin, and platelets. Additional ancillary tests including TA biopsy and FDG-PET/CT were reviewed and collected if available. The gold standard for LVV diagnosis was the clinical confirmation by the referring rheumatologist after a 6-month follow-up. In our centre, diagnosis of LVV is usually made taking into account clinical symptoms, elevated CRP and/or ESR, positive imaging findings with uptake in FDG-PET/CT in at least one large artery consistent with vasculitis and/or positive US findings, and if response to immunosuppressive treatment is present. Patients > 50 years of age are usually classified as GCA in accordance with the revised 2012 Chapel Hill consensus criteria whereas Takayasu arteritis may be supported by the application of ACR criteria from 1990. The clinical GCA diagnosis could be dismissed according to the clinician criteria, even in patients fulfilling ACR criteria or with positive imaging tests, if another more reasonable diagnosis was established.

### 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 within 24 h per protocol. The exam was performed in a supine position, by the same evaluator (JMC) at the same centre using an EsaoteMyLab8 (Esaote, Genoa) with a high frequency (12–18 MHz) transducer. The subclavian arteries were scanned from the infraclavicular fossa and axillary arteries from the axillary fossa. For each artery, the presence or absence of a halo sign was evaluated. A halo was defined as a homogenous, hypoechoic wall thickening, well-delineated towards the luminal side, visible both in longitudinal and transverse planes, most commonly concentric in transverse scans, according to the recent OMERACT Large Vessel Vasculitis Ultrasound Working Group definitions [13]. The presence of a halo and/or compression sign in temporal arteries and the presence of a halo and/or an intima-media thickness >1 mm in large vessel (LV) arteries was considered a positive US finding,

### FDG-PET/CT assessment

FDG-PET/CT was performed according to clinician criteria if considered necessary for diagnosis, usually in patients with high extracranial involvement suspicion (fever, constitutional symptoms, bruits, or arm claudication) or patients with negative US scan but high pretest probability of LVV. All FDG-PET/CT scans were performed at the same centre using a Siemens Biograph 6–4 R TruePoint PET/CT Scanner (Siemens Medical Systems, Knoxville, TN, USA). All PET images were assessed by expert nuclear medicine physicians, but not blinded to clinical data or US findings. An artery

FDG uptake higher than liver uptake was defined as positive. The qualitative FDG uptake in the aorta, its aortic branches (carotid, axillary, and subclavian arteries), iliofemoral and cranial arteries was also registered. An overall interpretation of the whole FDG-PET/CT scan was made and was registered as a dichotomous variable: consistent with LVV or not consistent with LVV.

### Temporal artery biopsy

Biopsy results were reported as positive or negative for GCA based on the report of the pathologist. A positive biopsy was defined as a biopsy showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, with or without the presence of multinucleated giant cells [14].

### Statistical analysis

Chi-square test or Fisher's exact test were used to analyse differences between proportions; Student's *t*-test was used for comparison between means. The sensitivity and specificity of US and FDG-PET/CT were calculated with the clinical diagnosis as the reference standard. All tests were two-sided; $p$ values $< .05$ 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 (JMC07-RHEUM0321) and written informed consent was determined to be not mandatory.

## Results

### Patient characteristics

We analysed data from 113 patients referred to the FTP, of whom 74.3% were female and the mean age was 74 years. The patient flow diagram is shown in Figure 1. Polymyalgia rheumatica (PMR) diagnosis before US examination was present in 35 (31%) patients, but none of the patients included in the study had LVV prior to diagnosis. After 6 months of follow-up, 37 (32.7%) patients were diagnosed with LVV, 34 patients with GCA, and 3 patients with Takayasu. Clinical, laboratory, and imaging findings of patients with and without LVV are shown in Table 1. LVV patients had higher acute phase reactants (APR) and presented more frequently with headache and scalp tenderness. Among the 76 patients in whom the clinical diagnosis of LVV was excluded, the most common diagnosis were: 32 (42.1%) polymyalgia rheumatica (PMR), 7 (9.2%) other autoimmune diseases (one rheumatoide arthritis (RA), one sarcoidosis, one Sjögren's syndrome, one essential mixed cryoglobulinemia, one spondyloartrhitis, one IgA vasculitis, and one IgG4-related disease), 5 (6.6%) tension headache, 4 (5.3%) migraine, 4 (5.3%) infection, 3 (3.9%) visual loss due to atherosclerosis, 3 (3.9%) microcrystalline arthritis, one congestive heart failure, one ischaemic stroke, and one trigeminal neuralgia, and one fever of unknown origin. Finally, 14 (18.4%) patients had no definite diagnosis at 6 months of follow-up according to the medical health records. Seventeen patients with LVV clinical diagnosis did not fulfil the 1990 ACR classification criteria for GCA. The majority of these patients had extracranial involvement in the US scan (64.7%), while only 5 (29.4%) patients had US TA involvement.

Only 28 (24.8%) patients underwent a FDG-PET/CT scan according to the treating clinician criteria and 23 (20.4%) patients have available results for TA biopsy (Table 1). From a total of 70 patients with no additional ancillary studies apart from US, 7 (10%) patients had clinical diagnosis confirmation of LVV at 6 months. Of the 37 LVV patients, 18 patients underwent FDG-PET/CT and 11 patients were positive for extracranial LVV (Figure 1).

### Diagnostic accuracy of ultrasound in cranial and extracranial LVV

Only 3 (3.9%) patients without LVV versus 32 (86.5%) patients with LVV had positive US findings. Among patients with LVV, 24 (64.9%) patients had TA involvement and 16 (43.2%) patients had extracranial LVV according to US examination (37.8% axillary, 29.7% subclavian, and 32.4% carotid artery involvement). We found a mixed pattern with involvement of both TA and LV arteries in 8 (21.6%) patients. PMR-like symptoms were found in 22 (59.5%) patients with LVV clinical diagnosis. Considering all LVV patients, sensitivity and specificity of US were 86.5% and 96.1%, respectively (85.7% and 87.1% for intracranial and 94.1% and 80.2% for extracranial involvement, respectively) (Table 2). When analysing only patients with PMR-like symptoms, sensitivity and specificity of US were 95.5% and 94.7%, respectively. Specifically, the sensitivity and specificity of the halo sign for LVV diagnosis were 81.1% and 98.7% (Figure 2) (Video 1), and of the compression sign was 48.6% and 98.7%, respectively. Stenosis was found in 21.6% of patients with LVV, and in none of non-LVV group. Of them, six cases of stenosis were found in temporal arteries, whereas only two cases were found in extracranial arteries (both in patients with Takayasu).

### Diagnostic accuracy of FDG-PET/CT in cranial and extracranial LVV

A total of 28 patients underwent a FDG-PET/CT, of whom 12 (42.9%) patients showed positive findings. The mean (SD) time from the US scan and FDG-PET/CT evaluation was 23.4 (28.9) days. Ten (35.7%) patients initiated glucocorticoid treatment before the examination. Overall, the sensitivity and specificity of FDG-PET/CT for LVV were 61.1% and 90%, respectively (55.6% and 63.2% for intracranial and 84.6% and 93.3% for extracranial LVV) (Table 2). Considering only patients with clinical diagnosis of Takayasu, FDG-PET/CT was able to correctly detect all cases (sensitivity 100%). However, FDG-PET/CT showed cranial artery uptake in none of the patients (all positive FDG-PET/CT findings in cranial LVV patients rely on the coexistence of extracranial LVV artery uptake).

### Value of US with FDG-PET/CT as the reference

When FDG-PET/CT was applied as the external criteria for LVV diagnosis, the US showed positive extracranial findings in 10 (83.3%) of those 12 patients. Concerning the two patients in whom US did not show LV artery

**Table 1.** Clinical, laboratory and imaging findings of patients included in the fast-track pathway with and without LVV.

| | Total $n=113$ | Patients with LVV $n=37$ (32.7%) | Patients without LVV $n=76$ (67.3%) |
|---|---|---|---|
| Demographics | | | |
| Age, mean (SD) | 74 [11] | 74.9 (10.8) | 73 (11.2) |
| Female, *n* (%) | 84 (74.3%) | 27 (73%) | 57.6 (75%) |
| Clinical variables | | | |
| Baseline use of steroids, *n* (%) | 57 (50.9%) | 17 (47.2%) | 40 (52.6%) |
| PMR diagnosis before US examination, *n* (%) | 35 (31%) | 8 (21.6%) | 27 (31.5%) |
| Headache, *n* (%) | 54 (47.8%) | 24 (64.9%) | 30 (39.5%)* |
| Scalp tenderness, *n* (%) | 12 (10.6%) | 8 (21.6%) | 4 (5.3%)* |
| Jaw claudication, *n* (%) | 16 (14.2%) | 11 (29.7%) | 5 (6.6%)** |
| Visual symptoms, *n* (%) | 23 (20.4%) | 11 (29.7%) | 12 (15.8%) |
| Ocular ischaemia, *n* (%) | 9 (8%) | 4 (10.8%) | 5 (6.6%) |
| Weight loss, *n* (%) | 34 (30.1%) | 15 (40.5%) | 19 (25%) |
| Fever, *n* (%) | 16 (14.2%) | 5 (13.5%) | 11 (14.5%) |
| Myalgias, *n* (%) | 60 (53.1%) | 22 (59.5%) | 38 (50%) |
| Abnormal TA clinical examination, *n* (%) | 10 (8.8%) | 7 (18.9%) | 3 (3.9%)* |
| Laboratory findings | | | |
| CRP (mg/dL), mean (SD) | 5 (6.2) | 8.7 (7.4) | 3.1 (4.5)*** |
| ESR (mm/h), mean (SD) | 55 (34.6) | 70.9 (33.2) | 46 (32.3)** |
| Haemoglobin (g/dL), mean (SD) | 12.4 (1.8) | 11.7 (1.5) | 12.7 (1.8)** |
| Platelets $10^9$/L, mean (SD) | 298 (122.3) | 354.3 (135.4) | 270.2 (105.6)** |
| Fulfilling 1990 GCA criteria, *n* (%) | 34 (30.1%) | 20 (54.1%) | 14 (18.4%)*** |
| Histology | | | |
| Temporal artery biopsy positive $n=23$****, *n* (%) | 8 (34.8%) | 8 (40%) | 0 (0%) |
| Imaging | | | |
| FDG-PET/CT positive $n=28$****, *n* (%) | 12 (42.9%) | 11 (61.1%) | 1 (10%)** |
| Aorta uptake $n=28$****, *n* (%) | 11 (39.3%) | 10 (55.6%) | 1 (10%)* |
| Subclavian uptake $n=28$****, *n* (%) | 8 (28.6%) | 8 (44.4%) | 0 (0%)* |
| Axillary uptake $n=28$****, *n* (%) | 4 (14.3%) | 4 (22.2%) | 0 (0%) |
| Carotid uptake $n=28$****, *n* (%) | 6 (21.4%) | 6 (33.3%) | 0 (0%)* |
| Iliac uptake $n=28$****, *n* (%) | 6 (21.4%) | 5 (27.8%) | 1 (10%) |
| Cranial arteries uptake $n=28$****, *n* (%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Positive US findings, *n* (%) | 35 (31%) | 32 (86.5%) | 3 (3.9%)*** |
| Temporal artery positive, *n* (%) | 25 (22.1%) | 24 (64.9%) | 1 (1.3%)*** |
| Large vessel arteries positive, *n* (%) | 18 (15.9%) | 16 (43.2%) | 2 (2.6%)*** |
| Axillary positive, *n* (%) | 16 (14.2%) | 14 (37.8%) | 2 (2.6%)*** |
| Subclavian positive, *n* (%) | 11 (9.7%) | 11 (29.7%) | 0 (0%)*** |
| Carotid positive, *n* (%) | 12(10.6%) | 12 (32.4%) | 0 (0%)*** |
| Temporal + large vessel arteries positive, *n* (%) | 8 (7.1%) | 8 (21.6%) | 0 (0%)*** |
| Halo sign positive, *n* (%) | 31 (27.4%) | 30 (81.1%) | 1 (1.3%)*** |
| Compression sign positive, *n* (%) | 19 (16.8%) | 18 (48.6%) | 1 (1.3%)*** |
| Stenosis positive, *n* (%) | 8 (7.1%) | 8 (21.6%) | 0 (0%)*** |

SD: standard deviation.
*$p<.05$;
**$p<.01$;
***$p<.001$ in comparisons between groups;
****Number of patients undergoing the procedure.

**Table 2.** Diagnostic accuracy of US and FDG-PET/CT with clinical diagnosis as external criteria in all LVV, patients with cranial LVV, extracranial LVV, and PMR LVV.

| | Sens | Spec | LR+ | LR- | |
|---|---|---|---|---|---|
| All LVV patients, $n=37$ | US | 86.5% | 96.1% | 22.18 | 0.14 |
| | FDG-PET/CT | 61.1% | 90% | 6.11 | 0.43 |
| Cranial LVV, $n=28$ | US | 85.7% | 87.1% | 6.64 | 0.16 |
| | FDG-PET/CT | 55.6% | 63.2% | 1.51 | 0.702 |
| Extracanial LVV, $n=17$ | US | 94.1% | 80.2% | 4.75 | 0.07 |
| | FDG-PET/CT | 84.6% | 93.3% | 12.63 | 0.16 |
| PMR LVV, $n=22$ | US | 95.5% | 94.7% | 18.02 | 0.05 |
| | FDG-PET/CT | 66.7% | 100% | - | 0.33 |

LR+, positive likelihood ratio; LR–, negative likelihood ratio; Sens, sensitivity; Spec, specificity.

involvement with positive FDG-PET/CT findings, one patient presented isolated aortitis and the other one aorta and iliac artery involvement (Table 4). Additionally, the US was able to detect two (12.5%) additional cases of large vessel involvement with negative FDG-PET/CT examination (Table 3).

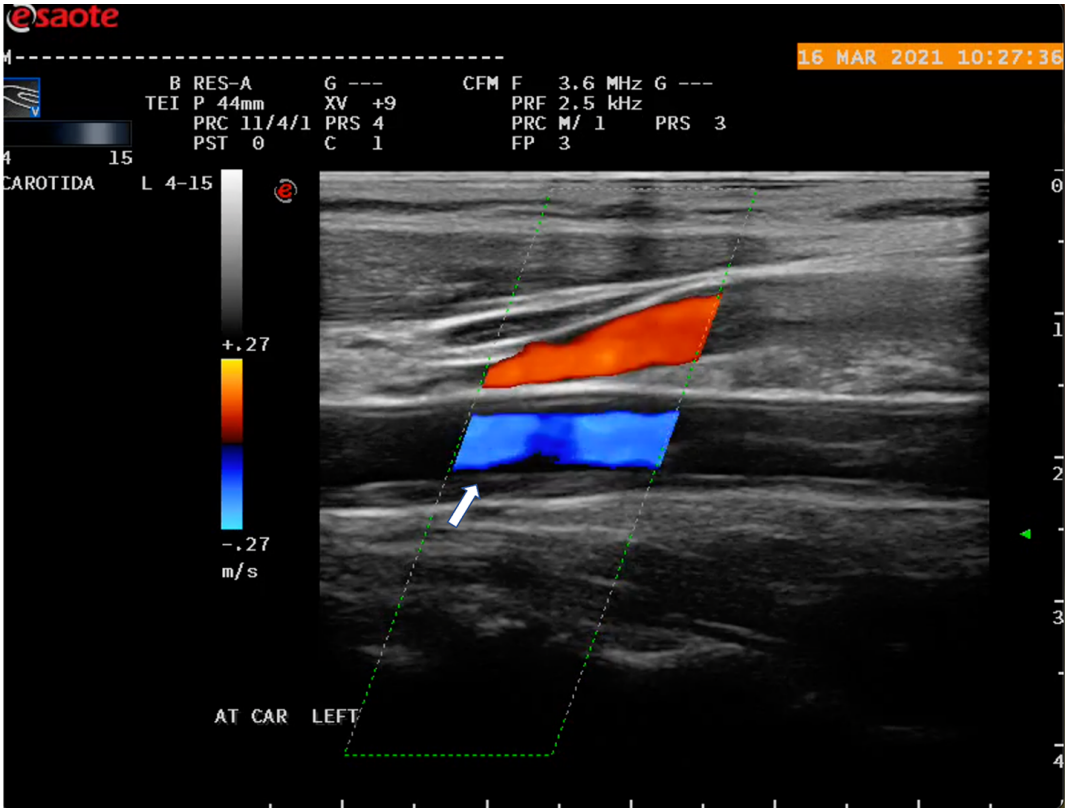


**Figure 2.** Longitudinal ultrasound scan of the left carotid artery showing a 'halo sign' with increased intima-media thickness. White arrow: artery wall with increased intima-media thickness.

## Discussion

In this observational cross-sectional study, we evaluated the diagnostic value of US to identify extracranial involvement in patients with suspected LVV. We found that US exhibits higher sensitivity to detect extracranial involvement versus FDG-PET/CT, with slightly lower specificity. Our findings open new insights in the imaging assessment of LVV patients and provide more data on the usefulness of the US to detect extracranial artery involvement.

The US is a valid tool to detect GCA and quantify the extent of vascular inflammation [15–21]. Although most studies include the examination of axillary arteries as part of the diagnostic work-up, the value of US in assessing extracranial involvement in GCA and which arteries should be examined is unclear [2, 22, 23] and FDG-PET/CT has been traditionally considered the reference standard for detecting extracranial involvement. In agreement with our results, Löffler *et al.* described a high sensitivity (80%) for US to identify inflammation in 30 patients with FDG-PET/CT-proven LVV [10]. In our population, the sensitivity of US using FDG-PET/CT as external criteria was similar (83.3%). An adequate training in detecting US supraaortic inflammation may improve the sensitivity of US as this technique is highly dependent on the operator's experience. In our fast-track clinic, two additional cases of LVV with negative FDG-PET/CT examination were identified. In a longitudinal study by Nielsen *et al.*, including 46 patients with FDG-PET/CT-proven LVV [11],

**Table 3.** Ultrasound findings of patients included in the fast-track pathway taking FDG-PET/CT as the reference for large vessel vasculitis.

| | Total $n = 28$ | FDG-PET/CT positive for LLV $n = 12$* (%) | FDG-PET/CT negative for LLV $n = 16$ (%) |
|---|---|---|---|
| Positive US findings, *n* (%) | 16 (57.1%) | 10 (83.3%) | 6 (37.5%)* |
| Temporal artery positive, *n* (%) | 9 (32.1%) | 5 (41.7%) | 4 (25%) |
| Large vessel arteries positive, *n* (%) | 12 (42.9%) | 10 (83.3%) | 2 (12.5%)*** |
| Axillary positive, *n* (%) | 11 (39.3%) | 9 (75%) | 2 (12.5%)** |
| Subclavian positive, *n* (%) | 9 (32.1%) | 8 (66.7%) | 1 (6.3%)** |
| Carotid positive, *n* (%) | 9(32.1%) | 8 (66.7%) | 1 (6.3%)** |

LLV: large vessel vasculitis.
#One patient with isolated aortitis in the context of IgG4-related disease has been included in the analysis.
*$p < .05$;
**$p < .01$;
***$p < .001$ in comparisons between groups.

**Table 4.** Comparison between US and FDG-PET/CT findings in patients with FDG-PET/CT-proven LVV. Specific arterial territories involvement of patients with FDG-PET/CT positive findings for LVV are summarized for each patient. Ultrasound detected no signs of inflammation in two patients with positive FDG-PET/CT.

| | Ultrasound | | | | FDG-PET/CT | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Patient | TA | CA | SA | AA | TA | CA | SA | AA | Aorta | IA |
| 1[a] | + | + | - | - | - | + | - | - | - | - |
| 2[b] | - | - | - | - | - | - | - | - | + | + |
| 3[a] | + | - | + | + | - | + | + | - | + | + |
| 4[a] | + | - | + | + | - | + | + | + | + | - |
| 5[a] | - | + | + | + | - | - | - | - | + | + |
| 6[a] | + | + | + | + | - | - | + | - | + | + |
| 7[a] | - | + | + | + | - | + | + | + | + | + |
| 8[a] | - | + | + | + | - | + | + | + | + | + |
| 9[c] | - | - | - | - | - | - | - | - | + | - |
| 10[b] | - | + | + | + | - | - | + | - | + | - |
| 11[a] | + | + | + | + | - | + | + | + | + | - |
| 12[a] | + | + | + | + | - | - | + | - | + | - |

+ positive findings for LVV; –negative findings for LVV; CA: carotid artery; SA: subclavian artery; AA: axillary artery; IA: iliac artery;
[a]Giant cell arteritis;
[b]Takayasu;
[c]Isolated aortitis in the context of IgG4-related disease.

they found that the majority of FDG-PET/CT positive axillary arteries were US positive (only 20 of 73 axillary arteries were US negative and FDG-PET/CT positive). Overall, they found a sensitivity and specificity of US for LVV of 78% and 100%, respectively. Our findings yielded higher sensitivity and lower specificity of US for extracranial involvement (94.1% and 80.2%, respectively). Although, very dependent on the ultrasonographer's experience, it has been shown that atherosclerosis is a potencial pitfall when evaluating cranial and large vessel arteries [24]. Thus, high specificities are seldom achieved. An interesting finding of their results is that all patients with FDG-PET/CT positive findings in the axillary artery presented a bilateral uptake, whereas patients with positive US in axillary arteries sometimes were unilateral. Thus, axillary US using FDG-PET/CT as the reference, on a segment level, decreased sensitivity from 78% to 73%. Finally, similarly to our findings, they found two GCA patients with cranial and LV artery involvement on the US (one carotid and one axillary) with LV FDG-PET/CT negative. More recently, Hop *et al.* compared the diagnostic accuracy of axillary US in 13 patients with FDG-PET/TC proven axillary artery inflammation [12]. They found, an axillary halo in 8 of these 13 patients. Additionally, they demonstrated that adding axillary artery examination to the TA alone improved sensitivity from 52% to 71%.

Regardless of the excellent resolution of US compared with FDG-PET/CT, only structural changes that occur after the inflammatory phase of the disease can be identified. Thus, an increased FDG-PET/CT signal of the artery wall without enough intima-media thickening to cause a halo or compression sign on the US may occur in some cases. In consequence, FDG-PET/CT may detect inflammation at an earlier stage of the disease than US [25]. Moreover, aortic, intraabdominal, and lower extremity artery manifestations, are often missed by US and easily assessed by FDG-PET/CT. This may explain the lower sensitivity of US to detect LVV when using FDG-PET/CT as the reference, in agreement with previous studies [10–12].

Although FDG-PET/CT is able to detect glucose uptake in the complete LV vascular tree, it is a very expensive and not always available imaging modality, usually performed weeks after glucocorticoid treatment initiation that may decrease the intensity of 18F-FDG uptake [26]. We have found that the US, despite the assessment of only a limited number of TA and large vessels, showed an excellent diagnostic accuracy and was able to detect two additional cases of large vessel involvement with negative FDG-PET/CT examination and a final clinical diagnosis of LVV. In both patients, FDG-PET/CT was performed after treatment initiation. Based on our findings, we believed that US should always be the first-line investigation, provided the sonographer is adequately skilled and the examination is promptly available, not only in suspected cranial but also in extracranial LVV. However, the US showed a relatively low specificity (80.2%) for extracranial LVV taking clinical diagnosis as the reference and low sensitivity (83.3%) when taking FDG-PET/CT as the reference for LVV. Thus, the US cannot replace FDG-PET/CT when extracranial artery involvement is suspected and, if negative, FDG-PET/CT should be performed.

Including large vessel arteries, such as axillary, in the US examination has been deeply discussed in the literature with discordant results. Previous studies by Diamantopoulus *et al.* [8] and Luqmani *et al.* [9] showed that adding axillary artery US to TA assessment slightly improved the sensitivity of the examination. In our cohort, almost half of the patients (43.2%) had large vessel involvement and 10 (27%) patients had exclusively large vessel inflammation without the involvement of TA. In consequence, the inclusion of these arteries increased the diagnostic yield of US. This means that, without scanning large vessel arteries as part of the routine examination, we would miss almost 3 out of 10 patients with LVV. Our results are in line with previous findings by Schmidt *et al.*, reporting a substantial part of the extracranial GCA patients (20 out of 53) had no TA involvement on the US [2]. Recently, Hop *et al.* [12] demonstrated that adding axillary artery results substantially improved sensitivity from 52% to 71%, while specificity did not change.

An additional interesting finding is the low sensitivity and specificity of FDG-PET/CT to detect patients with cranial involvement (55.6% and 63.2%, respectively), and these

results are based on the coexistence of extracranial LVV artery uptake, as FDG-PET/CT did not detect TA artery uptake in any of the patients. Although FDG-PET/CT has not been recommended for the assessment of inflammation in cranial arteries [7], FDG-PET/CT uptake in cranial arteries in GCA has been described [27, 28]. Our findings are in line with EULAR recommendations on the limited value of FDG-PET/CT for the assessment of inflammation of cranial arteries. However, further studies are necessary to better characterize the role of FDG-PET/CT in detecting cranial involvement in LVV patients. On the other hand, the US is of limited value for the assessment of the aorta given the limitations of the technique.

Our study has limitations including the retrospective design and the limited data for some ancillary studies such as TA biopsy and FDG-PET/CT that were only performed according to clinician criteria, consistent with real-world clinical practice. Baseline use of steroids was relatively high, in almost half of patients and especially in patients with a previous diagnosis of PMR, and the partial control of inflammation after treatment may affect the sensitivity of both US and FDG-PET/CT. Moreover, delays in the FDG-PET/CT evaluation occurred due to the low availability of the exam which may potentially negativize the results. On the other hand, specific cardiovascular risk assessment was not performed and the presence of atherosclerosis was not collected that may impact the US results. Reliability analysis of the US examination was not performed, so a less-experienced examiner may lead to less diagnostic accuracy to detect LVV. Finally, the ultrasonographer was not blinded to clinical data but all FDG-PET/CT examinations were performed after the US exam.

In conclusion, the US and FDG-PET/CT are accurate and valid imaging tools to detect extracranial involvement in patients with LVV. The presence of US extracranial artery inflammation is consistent with FDG-PET/CT examination. However, if the US is negative and extracranial involvement is suspected, FDG-PET/CT should be performed. Our findings provide more evidence to support the use of US as the first-line imaging study in patients not only suspected of cranial involvement but also when large vessel involvement is suspected.

## Acknowledgements

The authors thank all the patients who participated in this study.

## Supplementary data

Supplementary data is available at *Modern Rheumatology* online.

## Conflict of interest

None declared.

## Funding

The authors received no specific funding for this work.

## 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.

## Ethics approval

The research protocol has been approved by the Research Ethical Committee of Hospital General Universitario Gregorio Marañón, and informed written consent was not mandatory for their participation in the study.

## Contributors

All authors made substantial contributions to the conception and design of this study. Study design, subject recruitment, US examinations, and collection of the epidemiological and clinical data were performed by JMC. JMC and IC performed the statistical analysis. JMC, IC, JR, JMB, JCN-G, KL, FM, LT, CG, and JAG drafted the manuscript. All co-authors revised the final manuscript.

## Data availability

The data underlying this article are available in the article and in its online supplementary material.

## References

[1] Jennette JC, Falk RJ, Bacon PA *et al.* 2012 revised international chapel hill consensus conference nomenclature of vasculitides. *Arthritis Rheum* 2013;**65**:1–11.
[2] Schmidt WA, Seifert A, Gromnica-Ihle E *et al.* Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis. *Rheumatology (Oxford)* 2008;**47**:96–101.
[3] Brack A, Martinez-Taboada V, Stanson A *et al.* Disease pattern in cranial and large-vessel giant cell arteritis. *Arthritis Rheum* 1999;**42**:311–7.
[4] Muratore F, Kermani TA, Crowson CS *et al.* Large-vessel giant cell arteritis: a cohort study. *Rheumatology (Oxford)* 2015;**54**:463–70.
[5] Diamantopoulos AP, Haugeberg G, Lindland A *et al.* 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)* 2016;**55**:66–70.
[6] Seeliger B, Sznajd J, Robson JC *et al.* Are the 1990 American College of Rheumatology vasculitis classification criteria still valid? *Rheumatology (Oxford)* 2017;**56**:1154–61.
[7] Dejaco C, Ramiro S, Duftner C *et al.* EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis* 2018;**77**:636–43.
[8] Diamantopoulos AP, Haugeberg G, Hetland H *et al.* Diagnostic value of color Doppler ultrasonography of temporal arteries and large vessels in giant cell arteritis: a consecutive case series. *Arthritis Care Res (Hoboken)* 2014;**66**:113–9.
[9] Luqmani R, Lee E, Singh S *et al.* The role of ultrasound compared to biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study. *Health Technol Assess* 2016;**20**:1–238.
[10] Löffler C, Hoffend J, Benck U *et al.* The value of ultrasound in diagnosing extracranial large-vessel vasculitis compared to FDG-PET/CT: a retrospective study. *Clin Rheumatol* 2017;**36**:2079–86.

[11] Nielsen BD, Hansen IT, Keller KK *et al.* Diagnostic accuracy of ultrasound for detecting large-vessel giant cell arteritis using FDG PET/CT as the reference. *Rheumatology (Oxford)* 2020;**59**:2062–73.
[12] Hop H, Mulder DJ, Sandovici M *et al.* Diagnostic value of axillary artery ultrasound in patients with suspected giant cell arteritis. *Rheumatology (Oxford)* 2020;**59**:3676–84.
[13] Chrysidis S, Duftner C, Dejaco C *et al.* Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group. *RMD Open* 2018;**4**:e000598.
[14] Hunder GG, Bloch DA, Michel BA *et al.* The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990;**33**:1122–8.
[15] Schmidt WA, Kraft HE, Vorpahl K *et al.* Color duplex ultrasonography in the diagnosis of temporal arteritis. *N Engl J Med* 1997;**337**:1336–42.
[16] Ball EL, Walsh SR, Tang TY *et al.* Role of ultrasonography in the diagnosis of temporal arteritis. *Br J Surg* 2010;**97**:1765–71.
[17] Arida A, Kyprianou M, Kanakis M *et al.* 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.
[18] Karassa FB, Matsagas MI, Schmidt WA *et al.* Meta-analysis: test performance of ultrasonography for giant-cell arteritis. *Ann Intern Med* 2005;**142**:359–69.
[19] Rinagel M, Chatelus E, Jousse-Joulin S *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**:56–61.
[20] van der Geest KSM, Borg F, Kayani A *et al.* Novel ultrasonographic Halo Score for giant cell arteritis: assessment of diagnostic accuracy and association with ocular ischaemia. *Ann Rheum Dis* 2020;**79**:393–9.
[21] Molina Collada J, Martínez-Barrio J, Serrano-Benavente B *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. 10.1136/annrheumdis-2020-218631.
[22] Duftner C, Dejaco C, Sepriano A *et al.* Imaging in diagnosis, outcome prediction and monitoring of large vessel vasculitis: a systematic literature review and meta-analysis informing the EULAR recommendations. *RMD Open* 2018;**4**:e000612.
[23] Molina Collada J, Martínez-Barrio J, Serrano-Benavente B *et al.* Subclavian artery involvement in patients with giant cell arteritis: do we need a modified Halo Score? *Clin Rheumatol* 2021;**40**:2821–7.
[24] Fernández-Fernández E, Monjo-Henry I, Bonilla G *et al.* False positives in the ultrasound diagnosis of giant cell arteritis: some diseases can also show the halo sign. *Rheumatology (Oxford)* 2020;**59**:2443–7.
[25] Jiemy WF, Heeringa P, Kamps JAAM *et al.* Positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging of macrophages in large vessel vasculitis: current status and future prospects. *Autoimmun Rev* 2018;**17**:715–26.
[26] Prieto-Peña D, Calderón-Goercke M, Martínez-Rodríguez I *et al.* Fri0646 effect of long-term medium-dose steroid treatment on 18f-Fdg Pet/Ct findings to assess vascular and Musculoeskeletal involvement in patientswith polymyalgia reumatica. *Ann Rheum Dis* 2019;**78**:1020–1.
[27] Rehák Z, Szturz P, Křen L *et al.* Upsampling from aorta and aortic branches: PET/CT hybrid imaging identified 18F-FDG hypermetabolism in inflamed temporal and occipital arteries. *Clin Nucl Med* 2014;**39**:e84–6.
[28] Nielsen BD, Hansen IT, Kramer S *et al.* Simple dichotomous assessment of cranial artery inflammation by conventional 18F-FDG PET/CT shows high accuracy for the diagnosis of giant cell arteritis: a case-control study. *Eur J Nucl Med Mol Imaging* 2019;**46**:184–93.

## 4. Impact of ultrasound limitation to assess aortitis in patients with giant cell arteritis: comparative study with FDG-PET/CT

Molina-Collada J, Castrejón I, Monjo-Henry I, Fernández-Fernández E, Torres Ortiz G, Martínez-Barrio J, Álvaro-Gracia JM, de Miguel E. Impact of ultrasound limitation to assess aortitis in patients with giant cell arteritis: comparative study with FDG-PET/CT. RMD Open. 2023 Aug;9(3):e003329. doi: 10.1136/rmdopen-2023-003329.

RMD Open
Rheumatic & Musculoskeletal Diseases

SHORT REPORT

# Impact of ultrasound limitation to assess aortitis in patients with giant cell arteritis: comparative study with FDG-PET/CT

Juan Molina-Collada ,[1,2] Isabel Castrejón,[1,2,3] Irene Monjo-Henry ,[4] Elisa Fernández-Fernández ,[4] Gabriela Torres Ortiz,[4] Julia Martínez-Barrio,[1,2] José María Álvaro-Gracia,[1,2,3] Eugenio de Miguel [4]

**To cite:** Molina-Collada J, Castrejón I, Monjo-Henry I, *et al*. Impact of ultrasound limitation to assess aortitis in patients with giant cell arteritis: comparative study with FDG-PET/CT. *RMD Open* 2023;**9**:e003329. doi:10.1136/rmdopen-2023-003329

Received 20 May 2023
Accepted 3 August 2023



[1]Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[2]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain
[3]Faculty of Medicine. Complutense University of Madrid, Madrid, Spain
[4]Department of Rheumatology, Hospital Universitario La Paz, Madrid, Spain

**Correspondence to**
Dr Juan Molina-Collada;
molinacolladajuan@gmail.com

## ABSTRACT

**Objective** To determine the impact of ultrasound (US) intrinsic limitation to assess aortitis versus FDG-PET/CT in patients with US-proven giant cell arteritis (GCA) and to identify factors associated with aortic involvement.

**Methods** Retrospective observational study of patients referred to US fast-track clinics at two academic centres over a 4-year period. Only patients with GCA confirmed by US were included. Temporal arteries (TA) and extracranial arteries US were performed at baseline. FDG-PET/CT was performed according to clinician's criteria. An FDG artery uptake at the aorta higher than liver uptake was considered positive for aortitis.

**Results** Seventy-two of 186 patients with US-proven GCA underwent an FDG-PET/CT; 29 (40.3%) had a positive FDG-PET/CT and 24 (33.3%) presented aortitis. Only 6 (20.7%) patients with positive FDG-PET/CT had negative US findings of large vessel (LV)-GCA. Among patients with aortitis in FDG-PET/CT, only two (8.3%) had negative US findings of LV-GCA. Patients with aortitis were younger (68.9 vs 81;p<0.001), more frequently females (79.2% vs 39.6%;p=0.002) and had higher platelets count (413.4 vs 311.1;p=0014). Patients with aortitis presented positive TA US less frequently (41.7% vs 83.3%;p<0.001), but more LV US involvement (91.7% vs 41.7%; p<0.001) versus patients without aortitis. None of the patients with aortitis exhibited visual symptoms (0% vs 31.2%;p=0.001).

**Conclusions** FDG-PET/CT can detect aortitis in one out of every three patients with US-proven GCA. However, a negative US examination for LV-GCA suggests a low risk of aortitis. Younger and female GCA patients with thrombocytosis, absence of visual manifestations and LV-GCA on US may more frequently present aortitis by FDG-PET/CT.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Aortitis is a serious potential complication of patients with giant cell arteritis (GCA) and may lead to dilation, aneurysms or dissection.
⇒ Since ultrasound (US) has limited access to detect aortitis, comparative studies with other imaging modalities to determine the clinical impact of this limitation and the specific situations warranting their use are needed.

### WHAT THIS STUDY ADDS

⇒ A negative US examination for large vessel-GCA (LV-GCA) suggests a low risk of aortitis detected by FDG-PET/CT.
⇒ Younger and female GCA patients with thrombocytosis, absence of visual manifestations and LV-GCA on US may more frequently present aortitis by FDG-PET/CT in comparison with patients without aortitis.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings may guide decisions on when and how to investigate the presence of aortitis in patients with US-confirmed GCA. Further research in at-risk populations is needed to confirm these results.

## INTRODUCTION

Giant cell arteritis (GCA) is the most common form of vasculitis in the older adults.[1] In the last decades, the increasing availability of modern imaging techniques has shown that involvement of extracranial arteries, known as large vessel (LV)-GCA, may be present in up to 50% of patients.[2–5] According to European Alliance of Associations for Rheumatology (EULAR) recommendations on the use of imaging in LV vasculitis, ultrasound (US), fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT), MRI or CT can be useful for detecting mural inflammation or luminal changes in extracranial arteries to support a diagnosis of LV-GCA.[6] US can detect signs of LV-GCA in axillary, subclavian or carotid arteries among other regions, but has limited access to the thoracic aorta. The

first portion of the ascending aorta, the aortic arch and the abdominal aorta may be visible with appropriate probes (sector or convex). The prevalence of aortitis, the most frequent region affected in LV-GCA, has been estimated at 45%–65%,[2 7 8] although the exact incidence is unknown as it is not routinely evaluated in all patients at diagnosis or during follow-up. Aortitis is a serious diagnosis as it can result in a life-threatening situation due to serious complications such as dilation, aneurysms or dissection.[9–12] Some cohort studies have shown that LV-GCA patients have a higher risk of developing aortic dilation.[13 14] Given the limitation of US to assess the aorta, comparative studies on the usefulness of different imaging tools in clinical practice and the specific situations warranting their use are needed.

The primary objective of this study was to investigate the impact of US limitation to detect aortitis versus FDG-PET/CT examination in patients with US-proven GCA. Secondary objectives included the identification of factors associated with aortic involvement.

## METHODS

### Patient selection and data collection

This was a retrospective cross-sectional study including a cohort of patients referred to GCA fast-track clinics at two academic centres over a 4-year period (January 2018–January 2022). US vascular assessment within 24–48 hours was performed on all patients with suspected GCA. For the purpose of this study, only those patients with a GCA diagnosis confirmed by the clinicians and positive US in whom an FDG-PET/CT was performed were selected. We retrospectively collected patients' data from their electronic health records: demographics, symptoms including headache, scalp tenderness, jaw claudication, visual loss or ischaemic complications such as ocular ischaemia diagnosed by an ophthalmologist, morning stiffness, fever and abnormal findings on the temporal artery (TA) examination. Laboratory tests such as C reactive protein, erythrocyte sedimentation rate, haemoglobin and platelets, and TA biopsy findings (if available) were collected. The study was performed under routine clinical practice conditions.

### Imaging assessment

All patients underwent a protocolised vascular bilateral US examination of the cranial arteries (common superficial TA, its parietal and frontal branches) and extracranial arteries (carotid, subclavian and axillary). The entire axillary artery was evaluated including its three parts from the anterior side or the axillar fossa. The proximal region of the brachial artery was also scanned. The US examination was performed by three experienced ultrasonographers (EdM, IM and JM-C) with two sets of US equipment including an Esaote MyLab8 (Esaote, Genoa) with a 12–18 MHz (for TA) and 6–15 MHz transducer (for extracranial arteries) and an Esaote MylabTwice with a 10–22 MHz (for TA) and 4–13 MHz transducers (for extracranial arteries). The presence of a halo and/or compression sign in TA or the presence of a halo in the extracranial arteries in the absence of atherosclerosis was considered sufficient for a positive US examination.[15] The ultrasonographers were not blinded to the clinical information of the patients.

FDG-PET/CT was performed per clinician's criteria according to routine clinical care if considered necessary to support diagnosis, despite the positive US examination, usually in patients with high suspicion of extracranial involvement (fever, constitutional symptoms, bruits or arm claudication). Additionally, clinician experience interpreting US or FDG/PET-CT may also guide the decision of performing the latest, despite the absence of LV symptoms. All FDG-PET/CT scans were assessed by expert nuclear medicine physicians and performed at the two centres included in the study, using a Siemens Biograph 6–4R TruePoint PET/CT Scanner and a Siemens Biograph Vision PET/CT Scanner 128 slices (Siemens Medical Systems, Knoxville, Tennessee, USA). An FDG artery uptake at the thoracic or abdominal aorta higher than liver uptake was defined as aortitis. The qualitative FDG uptake in the aortic branches (carotid, axillary and subclavian arteries), iliofemoral and cranial arteries was also registered.

### Statistical analysis

Simple descriptions are presented as mean (SD) or total number (%). A $\chi^2$ test or Fisher's exact test was used to analyse differences between proportions; a Student's t-test was used for comparisons between means. All tests were two sided; p values <0.05 were considered statistically significant.

## RESULTS

### Patient characteristics

A total of 186 patients with US-proven GCA were evaluated at the two US fast-track clinics during the study period. Of these, 72 patients underwent an FDG-PET/CT and were included for analysis. Mean age was 77 years and 52.8% were females. The clinical, laboratory and histology findings of patients with or without aortic involvement are depicted in table 1. A total of 38 (52.8%) and 68 (94.4%) patients fulfilled the 1990 American College of Rheumatology (ACR) and the 2022 ACR/EULAR classification criteria for GCA, respectively, and 15 (20.8%) had been diagnosed with PMR before the US examination.

### Imaging findings

A total of 48 (66.7%) patients had LV-GCA imaging findings based on US or FDG-PET/CT examinations. US revealed cranial involvement in 50 (69.4%) patients and LV-GCA in 42 (58.3%) (table 2). Twenty-one (29.2%) had carotid, 29 (40.3%) subclavian and 35 (48.6%) axillary involvement. A mixed pattern

**Table 1** Clinical, laboratory and histology findings of patients with and without aortic involvement

| | Total n=72 | Patients with aortic involvement in FDG-PET/CT n=24 (33.3%) | Patients without aortic involvement in FDG-PET/CT n=48 (66.7%) | P value |
|---|---|---|---|---|
| Demographics | | | | |
| Age, mean (SD) | 77 (9.1) | 68.9 (8.1) | 81 (6.5) | <0.001 |
| Female, n (%) | 38 (52.8) | 19 (79.2) | 19 (39.6) | 0.002 |
| Clinical variables | | | | |
| PMR diagnosis before US examination, n (%) | 15 (20.8) | 3 (12.5) | 12 (25) | 0.432 |
| Headache, n (%) | 49 (68.1) | 14 (58.3) | 35 (72.9) | 0.211 |
| Scalp tenderness, n (%) | 16 (22.2) | 3 (12.5) | 13 (27.1) | 0.232 |
| Jaw claudication, n (%) | 16 (22.2) | 4 (16.7) | 12 (25) | 0.423 |
| Visual symptoms, n (%) | 15 (20.8) | 0 (0) | 15 (31.2) | 0.001 |
| Ocular ischaemia, n (%) | 6 (8.3) | 0 (0) | 6 (12.5) | 0.07 |
| Constitutional symptoms, n (%) | 42 (58.3) | 17 (70.8) | 25 (52.1) | 0.128 |
| Fever, n (%) | 19 (26.4) | 9 (37.5) | 10 (20.8) | 0.130 |
| Morning stiffness in shoulders/neck, n (%) | 38 (52.8) | 10 (41.7) | 28 (58.3) | 0.182 |
| Abnormal TA clinical examination, n (%) | 11 (15.3) | 3 (12.5) | 8 (16.7) | 0.643 |
| Fulfilled 1990 ACR GCA classification criteria, n (%) | 38 (52.8) | 9 (37.5) | 29 (60.4) | 0.066 |
| Fulfilled 2022 ACR/EULAR GCA classification criteria, n (%) | 68 (94.4) | 22 (91.7) | 46 (95.8) | 0.467 |
| Laboratory findings | | | | |
| CRP (mg/L), mean (SD) | 85.8 (79.6) | 101.8 (77.8) | 77.8 (80.4) | 0.230 |
| ESR (mm/hour), mean (SD) | 68.6 (33.6) | 69.7 (31.8) | 68 (34.7) | 0.839 |
| Haemoglobin (g/L), mean (SD) | 119 (16) | 115 (15) | 121 (17) | 0.139 |
| Platelets $10^9$/L, mean (SD) | 345.7 (152.1) | 413.4 (169.7) | 311.11 (131.1) | 0.014 |

ACR, American College of Rheumatology; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; TA, temporal artery.

of cranial and extracranial US involvement was found in 20 (27.8%) patients. A total of 29 (40.3%) patients had positive FDG-PET/CT findings for LV-GCA, 24 (33.3%) presenting aortitis. Moreover, 21 (29.2%) had subclavian, 15 (20.8%) carotid, 9 (12.5%) iliofemoral, 7 (9.7%) axillary, 3 (4.2%) vertebral and 1 (1.4%) TA involvement, based on FDG-PET/CT findings. Mean time from glucocorticoid initiation and FDG-PET/CT was 46.4 days. Taking FDG-PET/CT as the reference standard, six (20.7%) patients had negative US findings for LV-GCA but positive FDG-PET/CT. Among patients with aortitis in FDG-PET/CT, two (8.3%) presented negative US findings of LV-GCA (one patient presented with isolated aortitis and the other had aortic and iliac involvement). None of these patients had supraortic arteries involvement reported in FDG-PET/

**Table 2** US patterns of vascular involvement in patients with or without aortitis in FDG-PET/CT

| | Total n=72 | Patients with aortic involvement in FDG-PET/CT n=24 (33.3%) | Patients without aortic involvement in FDG-PET/CT n=48 (66.7%) | P value |
|---|---|---|---|---|
| Positive cranial GCA US, n (%) | 50 (69.4) | 10 (41.7) | 40 (83.3) | <0.001 |
| Positive LV-GCA US, n (%) | 42 (58.3) | 22 (91.7) | 20 (41.7) | <0.001 |
| Negative LV-GCA US, n (%) | 30 (41.7) | 2 (8.3) | 28 (58.3) | <0.001 |
| Isolated positive LV-GCA US, n (%) | 22 (30.6) | 14 (58.3) | 8 (16.7) | <0.001 |
| Positive cranial+LV GCA US, n (%) | 20 (27.8) | 8 (33.3) | 12 (25) | 0.457 |

GCA, giant cell arteritis; LV, large vessel; US, ultrasound.

CT. In contrast, 19 (45.2%) patients with US findings of LV-GCA had a negative FDG-PET/CT.

### Factors associated with aortitis on FDG-PET/CT

Patients with aortitis were younger (68.9 vs 81; p<0.001) and more frequently females (79.2% vs 39.6%;p=0.002) compared with patients without aortitis. Regarding laboratory markers, patients with aortitis had higher (mean) platelet count (413.4 vs $311.1\times10^9$/L; p=0014). The best threshold to differentiate between aortic and non-aortic involvement was $354.5\times10^9$/L (AUC 0.663; Sens 58.3%, Spec 66%). The absence of visual symptoms was the only clinical variable associated with aortitis (0% vs 31.2%;p=0.001) (table 1). US comparison between groups showed that when aortitis was present by FDG-PET/CT, positive TA US was less frequent (41.7% vs 83.3%; p<0.001), whereas US signs of LV-GCA were more frequent (91.7% vs 41.7%; p<0.001) in comparison with patients without aortic involvement (table 2).

## DISCUSSION

According to EULAR recommendations, in patients in whom there is a high clinical suspicion of GCA and a positive imaging result, the diagnosis of GCA may be made without additional tests (biopsy or further imaging).[6] LV involvement, particularly the aorta, is frequent in patients with GCA.[2–5] Indeed, the screening of LV-GCA by US, at least the axillary arteries, is recommended in patients with suspected GCA.[6] However, US is of limited value for assessing the thoracic aorta, although the first portion of the ascending aorta, the aortic arch and the abdominal aorta may be visible depending on the characteristic of the patient with appropriate probes (sector or convex) and adequate training. Nowadays, an increased number of fast-track clinics use US as their preferred diagnostic tool when GCA is suspected. Consequently, our study sought to investigate the usefulness of performing FDG-PET/CT in patients with US-confirmed GCA, as the presence of aortitis have an increased risk for the development of aortic dilatation, aneurysms, dissection or rupture.[9–12] Moreover, GCA patients with an aortic aneurysm have a higher mortality compared with those without aortic complications or with the general population.[16 17] Therefore, it is necessary to determine the clinical impact of US intrinsic limitations to assess aortitis. Our results demonstrate that FDG-PET/CT may be useful for detecting aortitis in certain patients with US-confirmed GCA, although a negative US examination for LV-GCA suggests a low risk of aortitis.

Several studies have compared the ability of US and FDG-PET/CT to detect LV-GCA, showing good, but not excellent agreement between both techniques.[4 18–20] However, for most studies comparing different imaging tools, the patients included are usually investigated based on either clinical or imaging findings of LV-GCA, which could potentially lead to circularity. To our knowledge, no studies have been specifically designed to assess the added value of FDG-PET/CT in patients with GCA and positive US findings. According to our results, 33.3% of patients with US-confirmed GCA have aortitis in FDG-PET/CT. These results are of value, not only for diagnostic and prognostic purposes, but also for monitoring activity during treatment, as baseline assessment of involved vascular regions are helpful for detecting new or recurrent involvement during follow-up.[21] However, it is important to note that the majority of patients with aortitis had signs of LV involvement on US examination (only two patients had negative US findings of LV-GCA but positive aortitis in FDG-PET/CT), minimising the need of FDG-PET/CT in US negative findings for LV-GCA. Thus, US correctly classifies as LV-GCA the majority of patients with aortitis. Although it is well known that aortitis is a factor associated with poorer prognosis in GCA, it is still a matter of debate whether these patients would benefit from more intensive treatment versus patients without aortic involvement.

On the other hand, the routine use FDG-PET/CT in patients with suspected GCA is limited not only by its cost, lower availability and radiation exposure, but also by its sensitivity according to our results. Performing US and FDG-PET/CT scans in all patients and yet detecting only 8.3% of aortitis cases without US signs of LV involvement seems an unfeasible screening strategy. Thus, it would be necessary to investigate factors associated with aortic involvement and then select those patients who would most benefit from undergoing FDG-PET/CT. In this context, we have identified several variables associated with the presence of aortitis in patients with US-confirmed GCA such as female gender, younger age, thrombocytosis and the absence of visual manifestations. Our results should be confirmed by other studies. These variables may be helpful for identifying which patients can benefit from an additional FDG-PET/CT in order to properly identify aortitis, especially in patients with low or intermediate pretest probability.[22] On the other hand, some US findings may indicate the need for FDG-PET/CT in this specific population due to the US pattern of LV-GCA, which was significantly more frequent in patients with aortitis.

Some limitations of our study should be noted. First, the sensitivity of FDG-PET/CT may be affected by glucocorticoid treatment.[23 24] Thus, sensitivity results of FDG-PET/CT should be interpreted with caution and in keeping with the context of this study, which was conducted under clinical practice conditions where delays in performing FDG-PET/CT may occur and patients can be undergoing glucocorticoid treatment at the time of the imaging study. Second, due to the absence of an appropriate gold standard, either for GCA or for LV-GCA diagnosis, diagnostic studies of LV-GCA are always limited by the fact that one imaging method is usually required to verify the presence of vasculitis, serving as the gold standard. In our study, since US-confirmed GCA was selected as an inclusion criterion, the exact sensitivity of FDG-PET/CT in all GCA patients (including also those with negative US)

was not investigated. Third, the decision of performing FDG-PET/CT was made per clinician's criteria, usually in patients with high suspicion of LV involvement, what may lead to a selection bias with a higher probability of aortitis. Finally, the inclusion of other extracranial arteries (as the vertebral arteries or the visible regions of the aorta) in the US examination could potentially increase the sensitivity for extracranial GCA.

In summary, FDG-PET/CT may detect aortitis in patients with US-confirmed GCA in certain situations. However, US is able to detect signs of LV-GCA in the majority of patients presenting with aortitis, thus minimising the need for routinely FDG-PET/CT, especially in negative US patients for LV-GCA. Female gender, younger age, thrombocytosis, absence of visual manifestations and an US-pattern of LV-GCA are all associated with the presence of aortitis in FDG-PET/CT.

**Twitter** Juan Molina-Collada @jmolinacollada, Isabel Castrejón @CastrejonIsabel, Elisa Fernández-Fernández @EliFdezFdez and José María Álvaro-Gracia @AlvaroGraciaSER

**Acknowledgements** The authors would like to thank all of the patients who participated in this study. The authors also thank the Spanish Foundation of Rheumatology for providing medical writing/editorial assistance during the preparation of the manuscript (FERBT2023). The preliminary results of this paper were presented at 2023 EULAR congress as an oral presentation (OP0171).[25]

**Contributors** All authors made substantial contributions to the conception and design of this study. The study was designed by EdM, IC and JM-C. Subject recruitment and US examinations were performed by EdM, IM and JM-C. Collection of the epidemiological and clinical data were performed by JM-C and GTO. EdM and JM-C performed the statistical analysis. JM-C, IC and EdM drafted the manuscript. All coauthors revised the final manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** This study was performed in accordance with the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki of 1975, as revised in 1983. Research ethics committee approval for the protocol was obtained at each centre prior to commencing the study (JMC08-RHEUM0722, HULP PI3040).

**Provenance and peer review** Not commissioned; externally peer reviewed.



**ORCID iDs**
Juan Molina-Collada http://orcid.org/0000-0001-5191-7802
Irene Monjo-Henry http://orcid.org/0000-0002-3252-8016
Elisa Fernández-Fernández http://orcid.org/0000-0002-1628-5042
Eugenio de Miguel http://orcid.org/0000-0001-5146-1964

## REFERENCES

1 Hunder GG, Bloch DA, Michel BA, *et al*. The American college of rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990;33:1122–8.
2 Prieto-González S, Arguis P, García-Martínez A, *et al*. Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. *Ann Rheum Dis* 2012;71:1170–6.
3 Henry IM, Fernández Fernández E, Peiteado D, *et al*. Diagnostic validity of ultrasound including extra-cranial arteries in giant cell arteritis. *Clin Rheumatol* 2023;42:1163–9.
4 Molina-Collada J, Castrejón I, Rivera J, *et al*. The role of ultrasound and FDG-PET/CT to detect Extracranial artery involvement in patients with suspected large vessel vasculitis. *Mod Rheumatol* 2023;33:549–56.
5 Dejaco C, Duftner C, Buttgereit F, *et al*. The spectrum of giant cell arteritis and Polymyalgia Rheumatica: revisiting the concept of the disease. *Rheumatology (Oxford)* 2017;56:506–15.
6 Dejaco C, Ramiro S, Duftner C, *et al*. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis* 2018;77:636–43.
7 Agard C, Barrier J-H, Dupas B, *et al*. Aortic involvement in recent-onset giant cell (temporal) arteritis: a case-control prospective study using Helical aortic computed Tomodensitometric scan. *Arthritis Rheum* 2008;59:670–6.
8 Espitia O, Agard C. Aortitis in giant cell arteritis and its complications. *Rev Med Interne* 2013;34:412–20.
9 Robson JC, Kiran A, Maskell J, *et al*. The relative risk of aortic aneurysm in patients with giant cell arteritis compared with the general population of the UK. *Ann Rheum Dis* 2015;74:129–35.
10 Gonzalez-Gay MA, Garcia-Porrua C, Piñeiro A, *et al*. Aortic aneurysm and dissection in patients with biopsy-proven giant cell arteritis from Northwestern Spain: a population-based study. *Medicine (Baltimore)* 2004;83:335–41.
11 Nuenninghoff DM, Hunder GG, Christianson TJH, *et al*. Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. *Arthritis Rheum* 2003;48:3532–7.
12 Evans JM, O'Fallon WM, Hunder GG. Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis. A population-based study. *Ann Intern Med* 1995;122:502–7.
13 de Boysson H, Daumas A, Vautier M, *et al*. Large-vessel involvement and aortic dilation in giant-cell arteritis. A multicenter study of 549 patients. *Autoimmun Rev* 2018;17:391–8.
14 Blockmans D, Coudyzer W, Vanderschueren S, *et al*. Relationship between Fluorodeoxyglucose uptake in the large vessels and late aortic diameter in giant cell arteritis. *Rheumatology (Oxford)* 2008;47:1179–84.
15 Chrysidis S, Duftner C, Dejaco C, *et al*. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT large vessel vasculitis ultrasound working group. *RMD Open* 2018;4:e000598.
16 Baslund B, Helleberg M, Faurschou M, *et al*. Mortality in patients with giant cell arteritis. *Rheumatology (Oxford)* 2015;54:139–43.
17 Kermani TA, Warrington KJ, Crowson CS, *et al*. Large-vessel involvement in giant cell arteritis: a population-based cohort study of the incidence-trends and prognosis. *Ann Rheum Dis* 2013;72:1989–94.
18 Hop H, Mulder DJ, Sandovici M, *et al*. Diagnostic value of Axillary artery ultrasound in patients with suspected giant cell arteritis. *Rheumatology (Oxford)* 2020;59:3676–84.
19 Förster S, Tato F, Weiss M, *et al*. Patterns of Extracranial involvement in newly diagnosed giant cell arteritis assessed by physical examination, colour coded duplex Sonography and FDG-PET. *Vasa* 2011;40:219–27.
20 Nielsen BD, Hansen IT, Keller KK, *et al*. Diagnostic accuracy of ultrasound for detecting large-vessel giant cell arteritis using FDG PET/CT as the reference. *Rheumatology (Oxford)* 2020;59:2062–73.
21 Ponte C, Monti S, Scirè CA, *et al*. Ultrasound halo sign as a potential monitoring tool for patients with giant cell arteritis: a prospective analysis. *Ann Rheum Dis* 2021;80:1475–82.
22 Fernández-Fernández E, Monjo I, Peiteado D, *et al*. Validity of the EULAR recommendations on the use of ultrasound in the diagnosis of giant cell arteritis. *RMD Open* 2022;8:e002120.
23 Blockmans D, de Ceuninck L, Vanderschueren S, *et al*. Repetitive 18F-Fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. *Arthritis Rheum* 2006;55:131–7.
24 Prieto-González S, Depetris M, García-Martínez A, *et al*. Positron emission tomography assessment of large vessel inflammation in patients with newly diagnosed, biopsy-proven giant cell arteritis: a prospective, case-control study. *Ann Rheum Dis* 2014;73:1388–92.
25 Molina Collada J, Castrejon I, Monjo I, *et al*. Op0171 ADDED value of Fdg-pet/ct to detect aortic involvement in patients with ultrasound proven giant cell arteritis. *Ann Rheum Dis* 2023;82:113.

## 5. Performance of the 2022 ACR/EULAR giant cell arteritis classification criteria for diagnosis in patients with suspected giant cell arteritis in routine clinical care.

Molina-Collada J, Castrejón I, Monjo I, Fernández-Fernández E, Torres Ortiz G, Álvaro-Gracia JM, de Miguel E. Performance of the 2022 ACR/EULAR giant cell arteritis classification criteria for diagnosis in patients with suspected giant cell arteritis in routine clinical care. RMD Open. 2023 Apr;9(2):e002970. doi: 10.1136/rmdopen-2022-002970.

RMD Open
Rheumatic & Musculoskeletal Diseases

SHORT REPORT

# Performance of the 2022 ACR/EULAR giant cell arteritis classification criteria for diagnosis in patients with suspected giant cell arteritis in routine clinical care

Juan Molina-Collada ,[1,2] Isabel Castrejón,[1,2,3] Irene Monjo ,[4] Elisa Fernández-Fernández ,[4] Gabriela Torres Ortiz,[4] Jose María Álvaro-Gracia,[1,2,3] Eugenio de Miguel [4]

**To cite:** Molina-Collada J, Castrejón I, Monjo I, *et al*. Performance of the 2022 ACR/EULAR giant cell arteritis classification criteria for diagnosis in patients with suspected giant cell arteritis in routine clinical care. *RMD Open* 2023;**9**:e002970. doi:10.1136/rmdopen-2022-002970

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2022-002970).

Received 28 December 2022
Accepted 3 April 2023



[1]Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[2]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain
[3]Universidad Complutense de Madrid, Madrid, Spain
[4]Department of Rheumatology, Hospital Universitario La Paz, Madrid, Spain

**Correspondence to**
Dr Juan Molina-Collada; molinacolladajuan@gmail.com

## ABSTRACT

**Objective** To examine the performance of the new 2022 American College of Rheumatology (ACR)/EULAR giant cell arteritis (GCA) classification criteria for diagnosis in routine clinical care.

**Methods** Multicentric retrospective observational study of patients referred to two ultrasound (US) fast track clinics. Patients with GCA were compared with unselected controls with suspected GCA. The gold standard for GCA diagnosis has been clinical confirmation after 6 months of follow-up. All patients underwent an US exam of temporal and extracranial arteries (carotid, subclavian and axillary) at baseline. Fluorodeoxyglucose-positron emission tomography/CT was performed according to standard clinician criteria. The performance of the new 2022 ACR/EULAR GCA classification criteria was evaluated in all patients with GCA across different subsets of the disease.

**Results** A total of 319 patients (188 cases, 131 controls) were included for analysis (mean age 76 years, 58.9% females). Overall, the 2022 EULAR/ACR GCA classification criteria had a sensitivity of 92.6% and a specificity of 71.8%, using GCA clinical diagnosis as external criterion and the area under the curve (AUC) was 0.928 (95% CI 0.899 to 0.957). Isolated large vessel-GCA showed a sensitivity of 62.2% and a specificity of 71.8% (AUC 0.691 (0.592 to 0.790)), while biopsy-proven GCA showed a sensitivity of 100% and a specificity of 71.8% (AUC 0.989 (0.976 to 1)). Overall sensitivity and specificity of the 1990 ACR criteria was 53.2% and 80.2%, respectively.

**Conclusions** The new 2022 ACR/EULAR GCA classification criteria showed adequate diagnostic accuracy in patients with suspected GCA under routine care, and an improvement on the sensitivity and specificity of the 1990 ACR classification criteria in all patient subsets.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Vascular imaging modalities are more frequently used nowadays to evaluate patients with suspected giant cell arteritis (GCA) replacing temporal artery biopsy as a first-line diagnostic test and leading to greater diagnosis of extracranial involvement.
⇒ The 2022 American College of Rheumatology (ACR)/EULAR GCA classification criteria have been recently developed to reflect this change in the diagnostic approach.

### WHAT THIS STUDY ADDS

⇒ This is the first external validation of the 2022 ACR/EULAR GCA classification criteria for diagnosis of patients with suspected GCA in routine clinical practice.
⇒ The new criteria performed adequately in supporting GCA clinical diagnosis and improved the diagnostic accuracy of the 1990 ACR GCA classification criteria.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The 2022 ACR/EULAR GCA classification may be useful to support the diagnosis of GCA in clinical practice.
⇒ Further studies are necessary to better determine their diagnostic accuracy in different GCA populations.

## INTRODUCTION

In 1990, the American College of Rheumatology (ACR) published criteria for the classification of seven types of systemic vasculitis, including giant cell arteritis (GCA).[1] These criteria were meant to assist in the classification of patients for inclusion in clinical trials. However, their potential use for diagnostic purposes has been explored showing poor sensitivity (Sens).[2] At the time they were developed, non-invasive imaging modalities were not available, so they were focused on clinical features, laboratory and histology findings on temporal artery biopsy (TAB). In addition, these criteria only included features of cranial GCA and did not perform well when classifying patients with large vessel (LV) involvement, commonly

termed LV-GCA. Nowadays, vascular imaging modalities have increasingly been incorporated into patient assessments; indeed, in more than half of suspected GCA cases showing LV-GCA.[3–6] Moreover, EULAR recommendations place ultrasound (US) of temporal (TA) and axillary arteries as first-line imaging tests and a non-compressible halo sign may replace the need for TAB in patients with high pretest probability.[7] Newer randomised controlled trials have applied additional inclusion criteria for patients with GCA such as polymyalgia rheumatica, C reactive protein (CRP) or imaging (US, fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT, MRI or CT)[8–11] and TAB has been replaced by imaging as the first-line diagnostic test in patients with suspected GCA in clinical practice.[12] Therefore, new classification criteria were needed to better reflect current practice.

The 2022 ACR/EULAR GCA classification criteria have been recently published using a very consistent methodology, including both a developmental cohort and a validation cohort, yielding a Sens of 87.0% and a specificity (Spec) of 94.8%.[13] These new criteria incorporate modern imaging techniques, reflecting their growing use in routine care. Although these criteria have been developed for the purpose of patient classification in research settings, a comparison between their diagnostic performance versus the classic 1990 ACR GCA classification criteria in routine care may prove informative since validation is a continuous process.

The primary objective of this study was to examine the performance of the 2022 ACR/EULAR GCA classification criteria for diagnosis in patients with suspected GCA in routine care.

## METHODS

### Patients

This retrospective cross-sectional study included patients referred to an US fast-track clinics (FTC) at two academic centres for the screening of possible GCA over a 4-year period (January 2018–January 2022). Patients with suspected GCA were referred for US evaluation by various specialties (rheumatology, internal medicine, emergency care, neurology) within 24–48 hours, per the protocol (excluding weekends, with delays up to 72 hours). The gold standard for GCA diagnosis was clinical confirmation by the treating clinician after at least 6 months of follow-up. All patients with a final GCA diagnosis over the study period were compared with a cohort of unselected controls with suspected GCA evaluated at the US FTC during a 1-year period. The study was performed under routine clinical practice conditions.

### Data collection

All variables included in the 2022 ACR/EULAR GCA classification criteria were collected retrospectively from the electronic medical records, to include: demographics; presenting symptoms, including new-onset headache, scalp tenderness, jaw claudication, visual loss and ocular ischaemia diagnosed by an ophthalmologist; morning stiffness in shoulders/neck and abnormal findings on the TA examination. Additionally, we have collected the proportion of patients who have previously had a diagnosis of polymyalgia rheumatica (PMR) before the US scan. US findings are systematically registered as part of the routine practice of the fast-track clinics. Laboratory tests such as CRP, erythrocyte sedimentation rate (ESR), haemoglobin and platelets and TAB findings (if available) were also collected. Following EULAR recommendations,[7] TAB was only performed according to clinician criteria in case of uncertainty (negative imaging findings in patients with moderate/high pretest probability or positive imaging findings in patients with low pretest probability). TAB results were reported as positive or negative for GCA based on the report of the pathologists, with >5 years of experience. A positive TAB was considered as a biopsy showing vasculitis characterised by a predominance of mononuclear cell infiltration or granulomatous inflammation, with or without the presence of multinucleated giant cells.[1]

### Imaging assessments

All patients underwent a US exam of TA, including common superficial TA, its parietal and frontal branches and an LV scan of the carotid, subclavian and axillary arteries. The US exam was performed by three ultrasonographers (EdM, IM and JM-C) with >15, 10 and 5 years of experience performing vascular US, respectively. We have used two US machines, including an EsaoteMyLab8 (Esaote, Genoa) with a 12–18 MHz (for TA) and 6–15 MHz transducers (for LV), as well as an Esaote MyLabTwice with a 10–22 MHz (for TA) and 4–13 MHz transducers (for LV). The presence of a halo and/or compression sign in TA, or the presence of a halo in LV in the absence of atherosclerosis was considered sufficient for a positive US examination, in agreement with the OMERACT definitions.[14] In cases of uncertainty, the intima-media thickness was measured to confirm the findings according to published proposed cut-off values.[15–18] The ultrasonographers were not blinded to the clinical data.

An FDG-PET/CT was performed per clinician criteria if necessary for diagnosis, usually in patients with high suspicion of extracranial involvement (fever, constitutional symptoms, bruits or arm claudication) or patients with negative US scan but high pretest probability of GCA. All PET images were assessed by expert nuclear medicine physicians with >5 years of experience using a Siemens Biograph 6-4R TruePoint PET/CT Scanner and a Siemens Biograph Vision PET/CT Scanner 128 slices (Siemens Medical Systems, Knoxville, Tennessee, USA). An arterial FDG uptake higher than the liver uptake was defined as positive.[7 19] The qualitative FDG uptakes in the aorta, its aortic branches (carotid, axillary and subclavian arteries), iliofemoral and cranial arteries were also recorded.

### Application of the 2022 ACR/EULAR GCA classification criteria

All clinical variables were scored according to the 2022 classification criteria[13] as follows: morning stiffness in shoulders/neck (+2), sudden visual loss (+3), jaw/tongue claudication (+2), new temporal headache (+2), scalp tenderness (+2), abnormal examination of TA (+2), ESR ≥50 mm/hour or CRP ≥10 mg/L (+3), positive TAB (if performed) or halo sign on TA US (+5), bilateral axillary involvement in angiography, US or FDG-PET/CT (+2) and FDG uptake throughout the aorta on FDG-PET/CT (+2). Age restriction ≥50 was applied. GCA classification criteria were considered fulfilled when a total score ≥6 of the sum of the 10 items was recorded.

### Statistical analysis

The performance of the new criteria was evaluated in all patients with GCA, as well as in four different patient subsets: 1) isolated cranial GCA, 2) isolated LV-GCA, 3) TAB-proven GCA and 4) all LV-GCA (with or without cranial GCA). Quantitative data are expressed as the mean (SD) and qualitative variables as absolute frequencies (percentages). As we had a very low percentage of missing data which happened at a random fashion, a complete case analysis or listwise deletion was conducted (default option for analysis in the statistical software package). A $\chi^2$ test or Fisher's exact test was used to analyse differences between proportions; Student's t-test was used for comparisons between means. Criterion validity was evaluated using receiver operating characteristic (ROC) curves with GCA clinical diagnosis as the external criterion. All tests were two-sided; p values <0.05 were considered statistically significant. SPSS software (V.25.0, IBM, USA) was used for the statistical analysis.

## RESULTS

### Patient characteristics

A total of 319 patients, including all 188 patients with GCA and 131 consecutive non-selected controls (of the 502 patients without GCA) evaluated at our FTCs during the study period, were included for analysis (mean age 76 years, 58.9% females). Clinical, laboratory and imaging findings of patients, with and without GCA, are presented in table 1. Different patient subsets were determined by the treating clinician at the time of diagnosis, based on clinical or imaging findings: 83 patients had isolated cranial GCA and 37 patients had isolated LV-GCA. TAB was performed in 57 patients; 21 (42%) patients with GCA had positive histology findings according to the pathologist's criteria. Controls included 55 (42%) PMR, 10 (7.6%) cases of non-specific or tensional headache, 6 (4.6%) non-vasculitis ocular ischaemia, 5 (3.8%) fever of unknown origin and 55 (41.9%) other diagnosis (including cancer, infections, inflammatory arthritis or other forms of vasculitis).

### Imaging findings

Positive US findings were found in 183 (97.3%) cases with GCA, and in only 5 (3.8%) controls (p<0.001). Remarkably, 98 (52.1%) patients had US signs of LV-GCA and 32 (17%) isolated LV-GCA, based only on US examination, without considering the findings of other imaging tests. FDG-PET/CT was performed in 99 patients per clinician criteria, with 32 (32.3%) showing positive findings. A total of 30 (40.5%) patients with GCA and FDG-PET/CT had abnormal artery uptake, while only 2 (8%) controls had positive findings (one patient with an IgG4-related disease diagnosis and another with non-vasculitic diffuse infiltrative disease) (p<0.01). Aortic uptake was the most frequent involvement in GCA (33.8%).

### Performance of the 2022 ACR/EULAR GCA classification criteria

Overall, the new criteria had a Sens of 92.6% and a Spec of 71.8% for GCA clinical diagnosis (table 2), with the AUC measuring 0.928 (95% CI 0.899 to 0.957). The performance of each individual item included in the criteria with GCA clinical diagnosis as external criterion is detailed in table 3. The diagnostic accuracies of the 2022 ACR/EULAR and the 1990 ACR GCA classification criteria in different subsets of patients are shown in table 2. In patients with isolated cranial GCA, the new criteria showed the highest Sens (96.4%), with an AUC of 0.962 (95% CI 0.930 to 0.993), while the group of isolated LV-GCA cases showed a lower Sens: 62.2% with an AUC of 0.691 (95% CI 0.592 to 0.790). When we included only those patients with biopsy-proven GCA, the Sens was 100%. The 1990 criteria only performed well in the biopsy-proven GCA group (Sens 95.2 and Spec 80.2), while the Sens was low in the overall GCA population (53.2%), particularly in the isolated LV-GCA group (18.9%), with an AUC of 0.554 (95% CI 0.455 to 0.653). We have additionally calculated the accuracy of the criteria in the subgroup of patients who underwent a TAB (negative or positive for GCA). Sens and Spec for the new criteria in this population was 100% and 0%, respectively, and for the 1990 ACR criteria was 72% and 28.6%, respectively. Higher scores of the criteria (≥7 or ≥8, instead of ≥6 points) decreased Sens to 92% and 84.6%, but increased Spec to 74% and 88.5%, respectively, for GCA clinical diagnosis.

We further tested the performance of the criteria by including as scoring criteria (+2) bilateral axillary involvement, and any positive imaging findings on US or FDG/PET-TC pertaining to the carotid or subclavian arteries with either unilateral or bilateral involvement (online supplemental material 1). While the overall Sens of these modified criteria slightly improved when applied to the general GCA population (from 92.6% to 94.7%), Spec findings remained the same. However, in the patient subset presenting isolated LV-GCA, the Sens considerably increased, from 62.2% to 73%.

## DISCUSSION

This is the first study evaluating the performance of the 2022 ACR/EULAR GCA classification criteria[13] for

**Table 1** Clinical, laboratory and imaging findings of patients with and without GCA

| | Patients with GCA n=188 | Patients without GCA n=131 | P value |
|---|---|---|---|
| Demographics | | | |
| Age, mean (SD) | 78.2 (8.5) | 72.9 (11.4) | **<0.001** |
| Female, n (%) | 100 (53.2%) | 88 (67.2%) | **0.013** |
| Clinical variables | | | |
| PMR diagnosis before US examination, n (%) | 53 (28.2%) | 40 (30.5%) | 0.07 |
| New temporal headache, n (%) | 147 (78.2%) | 51 (38.9%) | **<0.001** |
| Scalp tenderness, n (%) | 46 (24.5%) | 5 (3.8%) | **<0.001** |
| Jaw/Tongue claudication, n (%) | 47 (25%) | 9 (6.9%) | **<0.001** |
| Sudden visual loss, n (%) | 57 (30.3%) | 18 (13.7%) | **<0.01** |
| Diplopia, n (%) | 14 (7.4 %) | 2 (1.5%) | **0.017** |
| Transient visual loss, n (%) | 42 (22.3 %) | 10 (7.6 %) | **<0.001** |
| Permanent visual loss, n (%) | 15 (8 %) | 8 (6.1%) | 0.517 |
| Ocular ischaemia, n (%) | 24 (12.8%) | 10 (7.6%) | 0.144 |
| Constitutional symptoms, n (%) | 100 (53.2%) | 36 (27.5%) | **<0.001** |
| Fever, n (%) | 29 (15.4%) | 28 (21.4%) | 0.172 |
| Morning stiffness in shoulders or neck, n (%) | 91 (48.4%) | 66 (50.4%) | 0.728 |
| Abnormal examination of the TA, n (%) | 42 (22.3%) | 4 (3.1%) | **<0.001** |
| Laboratory findings | | | |
| CRP (mg/L), mean (SD) | 60.9 (68.2) | 40 (52.5) | **<0.01** |
| ESR (mm/hour), mean (SD) | 58.1 (34.2) | 46.5 (31.2) | **<0.01** |
| Haemoglobin (g/L), mean (SD) | 134 (110) | 141 (194) | 0.685 |
| Platelets $10^9$/L, mean (SD) | 326.5 (128.1) | 279.4 (113.2) | **<0.01** |
| Histology | | | |
| Temporal artery biopsy positive n=57, n (%) | 21 (42%) | 0 (0%) | **0.031** |
| Imaging | | | |
| FDG-PET/CT positive n=99, n (%) | 30 (40.5%) | 2 (8%) | **<0.01** |
| Aorta uptake n=99, n (%) | 25 (33.8%) | 2 (8%) | **0.012** |
| Subclavian uptake n=99, n (%) | 21 (28.4%) | 1 (4%) | **0.011** |
| Axillary uptake n=99, n (%) | 7 (9.5%) | 1 (4%) | 0.387 |
| Carotid uptake n=99, n (%) | 15 (20.5%) | 0 (0%) | **0.014** |
| Vertebral uptake n=99, n (%) | 3 (4.1%) | 0 (0%) | 0.303 |
| Iliac uptake n=99, n (%) | 9 (12.3%) | 1 (4%) | 0.235 |
| Cranial arteries uptake n=99, n (%) | 1 (1.4%) | 0 (0%) | 0.564 |
| Positive US findings, n (%) | 183 (97.3%) | 5 (3.8%) | **<0.001** |
| Temporal arteries positive, n (%) | 151 (80.3%) | 2 (1.5%) | **<0.001** |
| Large vessel arteries positive, n (%) | 98 (52.1%) | 3 (2.3%) | **<0.001** |
| Temporal+Large vessel arteries positive, n (%) | 66 (35.1%) | 0 (0%) | **<0.001** |
| Isolated temporal artery positive, n (%) | 85 (45.2%) | 2 (1.5%) | **<0.001** |
| Isolated large vessels arteries positive, n (%) | 32 (17%) | 3 (2.3%) | **<0.001** |

*Number of patients who underwent the procedure.
CRP, C reactive protein; ESR, erythrocyte sedimentation rate; FDG, fluorodeoxyglucose; GCA, giant cell arteritis; PET, positron emission tomography; PMR, polymyalgia rheumatica; TA, temporal artery; US, ultrasound.

**Table 2** Diagnostic accuracy of the new 2022 ACR/EULAR GCA and the 1990 ACR/EULAR classification criteria, with clinical diagnosis serving as the external criteria in all patients with GCA, as well as those with isolated cranial GCA, isolated LV-GCA, all LV-GCA and biopsy-proven GCA

| | | Sens (%) | Spec (%) | LR+ | LR− | AUC (95% CI) |
|---|---|---|---|---|---|---|
| All GCA (n=188) vs controls (n=131) | 2022 ACR/EULAR criteria | 92.6 | 71.8 | 3.28 | 0.1 | 0.928 (0.899 to 0.957) |
| | 1990 ACR criteria | 53.2 | 80.2 | 2.68 | 0.58 | 0.719 (0.663 to 0.775) |
| Isolated cranial GCA (n=83) vs controls (n=131) | 2022 ACR/EULAR criteria | 96.4 | 71.8 | 3.41 | 0.05 | 0.962 (0.930 to 0.993) |
| | 1990 ACR criteria | 61.4 | 80.2 | 3.1 | 0.48 | 0.764 (0.699 to 0.829) |
| Isolated LV-GCA (n=37) vs controls (n=131) | 2022 ACR/EULAR criteria | 62.2 | 71.8 | 2.21 | 0.53 | 0.691 (0.592 to 0.790) |
| | 1990 ACR criteria | 18.9 | 80.2 | 0.95 | 1.01 | 0.554 (0.455 to 0.653) |
| LV-GCA (with or without cranial GCA) (n=105) vs controls (n=131) | 2022 ACR/EULAR criteria | 89.5 | 71.8 | 3.17 | 0.15 | 0.901 (0.859 to 0.942) |
| | 1990 ACR criteria | 46.7 | 80.2 | 2.36 | 0.66 | 0.683 (0.616 to 0.751) |
| Biopsy-proven GCA (n=21) vs controls (n=131) | 2022 ACR/EULAR criteria | 100 | 71.8 | 3.55 | 0 | 0.989 (0.976 to 1) |
| | 1990 ACR criteria | 95.2 | 80.2 | 4.81 | 0.06 | 0.931 (0.877 to 0.985) |
| Biopsy-negative GCA (n=29) vs controls (n=131) | 2022 ACR/EULAR criteria | 100 | 71.8 | 3.55 | 0 | 0.970 (0.946 to 0.995) |
| | 1990 ACR criteria | 55.2 | 80.2 | 2.79 | 0.31 | 0.735 (0.642 to 0.829) |

ACR, American College of Rheumatology; AUC, area under the curve; GCA, giant cell arteritis; LR+, positive likelihood ratio; LR−, negative likelihood ratio; LV, large vessel; Sens, sensitivity; Spec, specificity.

**Table 3** Diagnostic accuracy of each item included in the new 2022 ACR/EULAR GCA classification criteria, with clinical diagnosis serving as the external criteria

| | Patients with GCA n=188 | Patients without GCA n=131 | Sens (%) | Spec (%) | LR+ | LR− |
|---|---|---|---|---|---|---|
| Morning stiffness in shoulders or neck (+2) | 91 (48.4%) | 66 (50.4%) | 48.4 | 49.6 | 0.96 | 1.04 |
| Sudden visual loss (+3) | 57 (30.3%) | 18 (13.7%) | 30.3 | 86.3 | 2.21 | 0.81 |
| Jaw/Tongue claudication (+2) | 47 (25%) | 9 (6.9%) | 25 | 93.1 | 3.62 | 0.81 |
| New temporal headache (+2) | 147 (78.2%) | 51 (38.9%) | 78.2 | 61.1 | 2.03 | 1.28 |
| Scalp tenderness (+2) | 46 (24.5%) | 5 (3.8%) | 24.5 | 96.2 | 6.44 | 0.79 |
| Abnormal examination of the TA (+2) | 42 (22.3%) | 4 (3.1%) | 22.3 | 96.9 | 7.19 | 0.8 |
| Maximum ESR ≥50 mm/hour or maximum CRP ≥10 mg/L (+3) | 157 (83.5%) | 102 (77.9%) | 83.5 | 22.1 | 1.07 | 0.75 |
| Positive TAB or halo sign on TA US (+5) | 151 (80.3%) | 2 (1.5%) | 80.3 | 98.5 | 53.53 | 0.2 |
| Bilateral axillary involvement (+2) | 42 (22.3%) | 1 (0.8%) | 22.3 | 99.2 | 22.5 | 0.78 |
| FDG-PET/CT activity throughout aorta (+2) | 25 (13.3%) | 2 (1.5%) | 13.3 | 98.5 | 8.87 | 0.88 |

ACR, American College of Rheumatology; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; FDG, fluorodeoxyglucose; LR+, positive likelihood ratio; LR−, negative likelihood ratio; PET, positron emission tomography; Sens, sensitivity; Spec, specificity; TA, temporal artery.

diagnosis in patients with suspected GCA within a routine clinical care setting. Our analysis demonstrates that the diagnostic accuracy of the new criteria versus a clinical diagnosis after 6 months of follow-up in routine clinical practice is adequate, and substantially improves on the Sens and Spec of the 1990 ACR classification criteria.[1]

The 1990 criteria did facilitate research in vasculitis and have been widely used in clinical trials and observational studies. However, they were designed before the introduction of modern imaging techniques, which have considerably impacted diagnosis and monitoring of the disease.[7 20] Importantly, these criteria were not designed as a diagnostic tool, although many rheumatologists use them as an aid for diagnostic purposes.[21] The same applies to the 2022 ACR/EULAR criteria, as they were developed to differentiate patients with varying types of medium or LV vasculitis, after excluding potential mimics.[13] However, in the absence of a suitable gold standard for GCA diagnosis, validation of the proposed criteria in other populations is needed. Although not developed for diagnostic purposes, these criteria may also be helpful for guiding treatment decisions in clinical practice.[22]

The new classification criteria have been developed using a very consistent methodology, including both a developmental cohort and a validation cohort. As comparators, they included Takayasu (33.5%), other vasculitis that mimic GCA and Takayasu (33.4%) and other mimics of LV vasculitis such as atherosclerosis and unspecific headaches (33.1%). Thus, there was a predominance of vasculitis cases among the comparators. Our study shows a different approach; we focused on routine care and analysed patients with suspected GCA referred to FTC. According to our findings, the performance of the criteria when applied to routine care was adequate and improved on traditional criteria across every subtype, especially in the LV-GCA group, in which the 1990 ACR criteria showed very low Sens. Overall, the new criteria had a Sens of 92.6% vs GCA clinical diagnosis, which was higher than that in the original publication. However, the Spec was lower (71.8%), as we included controls evaluated in our FTC, involving symptoms that usually mimic GCA (eg, new headaches), as well as PMR-like symptoms or visual disturbances related to other conditions, all of which led to higher rates of false positives. The low Spec of the new criteria may be problematic when used as diagnostic criteria, as overdiagnosis may lead to unnecessary glucocorticoid treatment. Higher scores (≥7 or ≥8) may be necessary to be used as diagnostic criteria, increasing Spec but decreasing Sens.

Special consideration should be given to the patient subset with isolated LV-GCA, in whom diagnosis can be challenging due to their non-specific spectrum of symptoms. According to the study by Ponte *et al*, the Sens of the new criteria in this specific population is quite low (55.7%), which is in line with our own results (Sens 62.2%). Recent studies have shown that the inclusion of subclavian arteries in tandem with the US may improve the Sens of the examination to better support a clinical diagnosis.[4] Interestingly, if we include bilateral axillary involvement as single criterion, and positive imaging findings on US or FDG/PET-TC in carotid or subclavian arteries with unilateral or bilateral involvement, the Sens increases considerably (from 62.2% to 73%) in this specific patients subset. While encouraging, these new possibilities should be further tested in larger cohorts.

Our study has certain limitations. First, its retrospective design and the limited data for some ancillary studies such as TAB and FDG-PET/CT, which were only performed using clinician-based criteria, leading to selection bias. Second, the limited data for TAB could underestimate the diagnostic accuracy of the 1990 ACR criteria when compared with the new 2022 ACR/EULAR criteria. Third, interobserver reliability was not investigated for this study, but our group has performed reliability analysis in previous cohort with ICC between 0.958 and 0.979.[4] Finally, our cohort of patients with GCA are older and the proportion of men is greater than in other populations,[23 24] which may suggest a selection bias by the referring clinician. Additionally, we found few patients with abnormal examination of TA, suggesting a possible bias leading to a decrease in the Sens of the criteria.

In summary, the performance of the 2022 EULAR/ACR GCA classification criteria,[13] when applied in routine care, proved adequate and may support GCA diagnosis confirmation in tandem with clinician-based criteria. However, these results need to be confirmed in additional populations.

**Twitter** Juan Molina-Collada @jmolinacollada, Isabel Castrejón @CastrejonIsabel and Elisa Fernández-Fernández @EliFdezFdez

**Acknowledgements** The authors thank the Spanish Foundation of Rheumatology for providing medical writing/editorial assistance during the preparation of the manuscript (FERBT2022).

**Contributors** All authors made substantial contributions to the conception and design of this study. The study design was conducted by EdM, IC and JM-C. Subject recruitment and US examinations were carried out by EdM, IM and JM-C. Collection of the epidemiological and clinical data were performed by JM-C, EFF and GTO. EdM and JM-C performed the statistical analysis. JM-C, IC, IM, EFF, GTO, JMÁG and EdM drafted the manuscript. All coauthors revised the final manuscript.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** The research ethics committee approval was obtained from each centre prior to commencing the study (JMC08-RHEUM0722,HULP PI3040). The 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. Informed written consent was not mandatory for patient participation in this study.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**ORCID iDs**
Juan Molina-Collada http://orcid.org/0000-0001-5191-7802
Irene Monjo http://orcid.org/0000-0002-3252-8016
Elisa Fernández-Fernández http://orcid.org/0000-0002-1628-5042
Eugenio de Miguel http://orcid.org/0000-0001-5146-1964

## REFERENCES

1 Hunder GG, Bloch DA, Michel BA, *et al*. The American College of rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis & Rheumatism* 1990;33:1122–8.
2 Seeliger B, Sznajd J, Robson JC, *et al*. Are the 1990 American College of rheumatology vasculitis classification criteria still valid? *Rheumatology (Oxford)* 2017;56:1154–61.
3 Prieto-González S, Arguis P, García-Martínez A, *et al*. Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. *Ann Rheum Dis* 2012;71:1170–6.
4 Henry IM, Fernández Fernández E, Peiteado D, *et al*. Diagnostic validity of ultrasound including extra-cranial arteries in giant cell arteritis. *Clin Rheumatol* 2023;42:1163–9.
5 Molina-Collada J, Castrejón I, Rivera J, *et al*. The role of ultrasound and FDG-PET/CT to detect extracranial artery involvement in patients with suspected large vessel vasculitis. *Mod Rheumatol* 2022.
6 Blockmans D, de Ceuninck L, Vanderschueren S, *et al*. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. *Arthritis Rheum* 2006;55:131–7.
7 Dejaco C, Ramiro S, Duftner C, *et al*. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis* 2018;77:636–43.
8 Schmidt WA, Dasgupta B, Luqmani R, *et al*. A multicentre, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of sirukumab in the treatment of giant cell arteritis. *Rheumatol Ther* 2020;7:793–810.
9 Venhoff N, Schmidt WA, Lamprecht P, *et al*. Efficacy and safety of secukinumab in patients with giant cell arteritis: study protocol for a randomized, parallel group, double-blind, placebo-controlled phase II trial. *Trials* 2021;22:543.
10 Cid MC, Unizony SH, Blockmans D, *et al*. Efficacy and safety of mavrilimumab in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2022;81:653–61.
11 Stone JH, Tuckwell K, Dimonaco S, *et al*. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med* 2017;377:317–28.
12 de Miguel E, Sanchez-Costa JT, Estrada P, *et al*. Influence of the EULAR recommendations for the use of imaging in large vessel vasculitis in the diagnosis of giant cell arteritis: results of the ARTESER register. *RMD Open* 2022;8:e002507.
13 Ponte C, Grayson PC, Robson JC, *et al*. 2022 American College of rheumatology/EULAR classification criteria for giant cell arteritis. *Ann Rheum Dis* 2022;81:1647–53.
14 Chrysidis S, Duftner C, Dejaco C, *et al*. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT large vessel vasculitis ultrasound working group. *RMD Open* 2018;4:e000598.
15 López-Gloria K, Castrejón I, Nieto-González JC, *et al*. n.d. Ultrasound intima media thickness cut-off values for cranial and extracranial arteries in patients with suspected giant cell arteritis. *Front Med*;9.
16 Schäfer VS, Juche A, Ramiro S, *et al*. Ultrasound cut-off values for intima-media thickness of temporal, facial and axillary arteries in giant cell arteritis. *Rheumatology (Oxford)* 2017;56:1632.
17 Ješe R, Rotar Ž, Tomšič M, *et al*. The cut-off values for the intima-media complex thickness assessed by colour doppler sonography in seven cranial and aortic arch arteries. *Rheumatology (Oxford)* 2021;60:1346–52.
18 Czihal M, Schröttle A, Baustel K, *et al*. B-Mode sonography wall thickness assessment of the temporal and axillary arteries for the diagnosis of giant cell arteritis: a cohort study. *Clin Exp Rheumatol* 2017;35 Suppl 103:128–33.
19 Slart R. Writing group, reviewer group, members of EANM cardiovascular, members of EANM infection & inflammation, members of committees, SNMMI cardiovascular, et al. FDG-PET/CT(A) imaging in large vessel vasculitis and polymyalgia rheumatica: joint procedural recommendation of the EANM, SNMMI, and the PET interest group (PIG), and endorsed by the ASNC. *Eur J Nucl Med Mol Imaging* 2018;45:1250–69.
20 Duftner C, Dejaco C, Sepriano A, *et al*. Imaging in diagnosis, outcome prediction and monitoring of large vessel vasculitis: a systematic literature review and meta-analysis informing the EULAR recommendations. *RMD Open* 2018;4:e000612.
21 Rao JK, Allen NB, Pincus T. Limitations of the 1990 American College of rheumatology classification criteria in the diagnosis of vasculitis. *Ann Intern Med* 1998;129:345–52.
22 Yazici H, Yazici Y. Diagnosis and/or classification of vasculitis: different? *Curr Opin Rheumatol* 2016;28:3–7.
23 Sharma A, Mohammad AJ, Turesson C. Incidence and prevalence of giant cell arteritis and polymyalgia rheumatica: a systematic literature review. *Semin Arthritis Rheum* 2020;50:1040–8.
24 Brekke LK, Diamantopoulos AP, Fevang BT, *et al*. Incidence of giant cell arteritis in Western Norway 1972-2012: a retrospective cohort study. *Arthritis Res Ther* 2017;19:278.

## 6. Different giant cell arteritis phenotypes may present distinct types of ischemic complications

- Amar Muñoz HM, Molina-Collada J, Castrejón I, Monjo-Henry I, Fernández-Fernández E, Álvaro-Gracia JM, De Miguel E. Different giant cell arteritis phenotypes may present distinct types of ischemic complications. Clin Exp Rheumatol. 2024 Sep (In press)

# Different giant cell arteritis phenotypes may present distinct types of ischaemic complications

H.M. Amar Muñoz[1], J. Molina-Collada[1,2], I. Castrejón[1,2], I. Monjo-Henry[3], E. Fernández-Fernández[3], J.M. Álvaro-Gracia[1,2], E. de Miguel[3]

*[1]Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid; [2]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid; [3]Department of Rheumatology, Hospital Universitario La Paz, Madrid, Spain.*

## Abstract

### Objective

*To determine if the subtype of vascular ultrasound (US) presentation is associated with different types of ischaemic complications (IC) in giant cell arteritis (GCA).*

### Methods

*Retrospective observational analysis of GCA clinically confirmed patients referred to US fast-track clinics at two centres. All patients underwent baseline US of cranial and extracranial arteries (carotid, subclavian and axillary). Two patterns of IC were analysed: the occurrence of acute anterior ischaemic optic neuropathy (AION) or the presence of a non-AION pattern (including stroke, acute coronary syndrome, pulmonary embolism or peripheral artery disease) at diagnosis and in the following 3 months, excluding other potentially implicated causes.*

### Results

*Of 188 clinically confirmed GCA patients, 43 (22.9%) had IC: 24 (12.8%) AION and 19 (10.1%) non-AION. Patients with AION more often exhibited US cranial involvement versus those with non-AION IC and without IC (100%, 63.2%, and 79.3%, respectively; p=0.009). Patients with AION less frequently presented signs of US large vessel (LV)-GCA than those with non-AION IC and without IC (25%, 63.2% and 55.2%, respectively; p=0.014). Patients with previous polymyalgia rheumatica (PMR) (p=0.049) or concomitant PMR symptoms at the time of diagnosis (p=0.014) showed less frequent AION. In contrast, patients with non-AION IC more frequently had positive LV-GCA US findings vs the other two groups (63.2%, 25% and 55.2%, respectively; p=0.014).*

### Conclusions

*The subtype of vascular US presentation influences the IC in GCA. US cranial-GCA patients more frequently present AION, while predominantly US LV-GCA more frequently exhibit non-AION IC.*

**Key words**

ultrasound, ischaemic complications, large vessel vasculitis, giant cell arteritis, polymyalgia rheumatica

*Helena M. Amar Muñoz*, MD*
*Juan Molina-Collada*, MD, PhD*
*Isabel Castrejón, MD, PhD*
*Irene Monjo-Henry, MD*
*Elisa Fernández-Fernández, MD*
*José María Álvaro-Gracia, MD, PhD*
*Eugenio de Miguel, MD, PhD*

*H.M. Amar Muñoz and J. Molina-Collada contributed equally to this work and share first authorship.

*Please address correspondence to:*
*Helena M. Amar Muñoz*
*Department of Rheumatology,*
*Hospital General Universitario Gregorio Marañón,*
*Calle del Dr. Esquerdo 46,*
*28007 Madrid, Spain.*
*E-mail: helenaamar@hotmail.com*

*Received on May 21, 2024; accepted in revised form on August 30, 2024.*



*ORCID iD:*
*H.M. Amar Muñoz: 0009-0002-6231-1747*
*J. Molina-Collada: 0000-0001-5191-7802*
*I. Castrejón: 0000-0003-1811-2417*
*I. Monjo-Henry: 0000-0002-3252-8016*
*E. Fernández-Fernández: 0000-0002-1628-5042*
*J.M. Álvaro-Gracia: 0000-0002-0343-3747*
*E. de Miguel: 0000-0001-5146-1964*

*Competing interests: none declared.*

## Introduction

The most common vasculitis diagnosed in the elderly is giant cell arteritis (GCA), which predominantly affects the large arteries, particularly the branches of the carotid artery. Symptoms typically include diplopia or blurred vision, headache, scalp tenderness, jaw claudication/pain, polymyalgia rheumatica (PMR) symptoms, fever and/or constitutional symptoms. GCA can lead to serious complications if not treated promptly. Among the most concerning are ischaemic complications (IC), which are associated with significant morbidity and increased mortality (1-4). Identifying patients at risk of IC is crucial for improving long-term outcomes. Over the last decade, several studies have assessed risk factors for IC, such as visual complications or stroke, in patients with GCA, yielding varying conclusions (4-17). Some studies have reported an association with less pronounced clinical or laboratory systemic inflammation (6, 7, 9, 13-16). Others have also described a positive association between traditional atherosclerosis risk factors or established vascular disease and IC-related GCA (5, 6, 8, 9, 11, 12, 14-17). The value of ultrasound (US) in the diagnosis of GCA and, as a consequence, the risk of IC has been studied over the last decades. However, individualisation of the risk based on the subtype of vascular involvement as a predictor of different types of IC has not yet been established.

The recently updated 2023 EULAR recommendations on the use of imaging in large vessel vasculitis prioritise US of the temporal and axillary arteries as first-line imaging test for evaluating patients with suspected GCA (18). Indeed, its implementation in clinical practice could improve the diagnosis of GCA (19, 20). However, these recommendations do not endorse routine imaging for follow-up and to date there remain very few studies that examine the prognostic value of US in predicting ischaemic complications in patients with GCA (21).

Our main objective was to determine if the subtype of vascular US presentation is associated with different types of IC in GCA patients.

## Methods

### *Patients*

This was a retrospective observational study that included patients referred to US fast-track clinics at two academic centres for the screening of possible GCA over a 4-year period. Per protocol, patients with suspected GCA were referred to this US clinic for examination within 72 hours. For the purposes of this study, only consecutive patients with clinically confirmed GCA at 6 months of follow-up were included for analysis. This study was performed under routine clinical practice conditions.

### *Data collection*

The following variables were collected from the electronic health records: demographics (*e.g.*, age and sex), presenting symptoms (headache, scalp tenderness, jaw claudication, visual symptoms and ocular ischemia diagnosis by an ophthalmologist, fever, previous PMR diagnosis, PMR symptoms at GCA onset, and constitutional symptoms, previous use of glucocorticoids, and laboratory variables (*e.g.*, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), haemoglobin, and platelets). The gold standard for GCA diagnosis was clinical confirmation by the treating clinician after at least 6 months of follow-up. IC was categorised as either the occurrence of acute anterior ischaemic optic neuropathy (AION) (diagnosed by an ophthalmologist or neurologist) or non-AION (including stroke, acute coronary syndrome, pulmonary embolism or peripheral artery disease) at diagnosis and in the following 3 months, and after excluding other potentially implicated causes. Other complementary tests, such as temporal artery biopsy or other imaging tests (PET/CT), were requested at the clinician's discretion if necessary for the diagnosis and they were not performed systematically.

### *Ultrasound assessment*

The three temporal arteries (TA) segments (common superficial trunk and its parietal and frontal branches) and extracranial (carotid, subclavian and

**Table I**. Baseline characteristics, clinical and laboratory variables according to the presence and type of ischemic complications.

| | All patients n=188 | No ischaemic complication n=145 (77.1%) | AION n=24 (12.8%) | Non-AION IC n=19 (10.1%) | *p* |
|---|---|---|---|---|---|
| **Demographics** | | | | | |
| Age, mean (SD) | 78.2 (8.5) | 77.7 (8.9) | 81.1 (5.8) | 78.6 (8.5) | 0.183 |
| Female, n (%) | 88 (46.8%) | 69 (47.6%) | 10 (41.7%) | 9 (47.4%) | 0.864 |
| **Clinical variables** | | | | | |
| Headache, n (%) | 147 (78.2%) | 115 (79.3%) | 18 (75%) | 14 (73.7%) | 0.788 |
| Scalp tenderness, n (%) | 46 (24.5%) | 38 (26.2%) | 3 (12.5%) | 5 (26.3%) | 0.344 |
| Jaw claudication, n (%) | 47 (25%) | 37 (25.5%) | 6 (25%) | 4 (21.1%) | 0.915 |
| Constitutional symptoms, n (%) | 100 (53.2%) | 81 (55.9%) | 10 (41.7%) | 9 (47.4%) | 0.376 |
| Fever, n (%) | 29 (15.4%) | 25 (17.2%) | 0 (0%) | 4 (21.1%) | 0.074 |
| Concomitant PMR symptoms, n (%) | 91 (48.4%) | 77 (53.1%) | 5 (20.8%) | 9 (47.4%) | **0.014** |
| Previous PMR diagnosis, n (%) | 53 (28.2%) | 45 (31%) | 2 (8.3%) | 6 (31.6%) | **0.049** |
| Abnormal TA clinical examination, n (%) | 42 (22.3%) | 31 (21.4%) | 5 (20.8%) | 6 (31.6%) | 0.594 |
| SCORE CVR score, mean (SD) | 21.8 (14.7) | 20.9 (14.8) | 25.5 (13) | 24 (15.4) | 0.275 |
| **Laboratory findings** | | | | | |
| CRP (mg/L), mean (SD) | 36.4 (54.3) | 40.3 (57.6) | 26.3 (48.8) | 20.1 (24.6) | 0.194 |
| ESR (mm/h), mean (SD) | 58.1 (34.2) | 56.1 (35.1) | 73.7 (25.8) | 54.4 (32.5) | 0.072 |
| Haemoglobin (g/dL), mean (SD) | 13.4 (11) | 13.8 (12.5) | 12 (1.8) | 12 (2) | 0.658 |
| Platelets $10^9$/L, mean (SD) | 326.5 (128.1) | 334.7 (126) | 297.1 (151.4) | 302.6 (108.1) | 0.288 |
| **Histology** | | | | | |
| Temporal artery biopsy positive, n/total number of biopsies performed (%) | 21/50 (42%) | 15/38 (39.5%) | 6/8 (75%) | 0/4 (0%) | **0.037** |
| Outcomes | | | | | |
| Relapse at 6 months follow-up, n (%) | 24 (12.8%) | 16 (11%) | 5 (20.8%) | 3 (15.8%) | 0.377 |

AION: acute anterior ischaemic optic neuropathy; PMR: polymyalgia rheumatica; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; US: ultrasound; LV: large-vessel; SD: standard deviation; CVR: cardiovascular risk.

distal and proximal axillary) arteries were bilaterally evaluated by US in all patients within 24 hours per protocol (excluding weekends with delays up to 72 h). The patient, in a supine position, was examined by three experienced ultrasonographers (EdM, IM-H and JM-C) using an EsaoteMyLab8 (Esaote, Genoa) with a 12–18 MHz (for TA) and 6–15 MHz transducer (for extracranial arteries) and an Esaote Mylab X8 system (Esaote, Genoa) with a 12–25 MHz (for TA) and 4–15 MHz transducers (for extracranial arteries). The distal axillary arteries were scanned from the axillary fossa. The focus was positioned 5 mm below the skin for the TA and 2–3 cm for the axillary arteries. The pulse repetition frequency was 2–3 kHz. The colour box was set at an angle between sound waves and the artery at <60°. The presence of a halo and/or compression sign in TA or the presence of a halo in extracranial arteries in the absence of atherosclerosis was considered sufficient for a positive US examination (22). The ultrasonographer was not blinded to the clinical information of the patients.

*Statistical analysis*

Quantitative data were described as the mean (standard deviation, SD) and qualitative variables as the absolute frequency (percentages). A Chi-square test or Fisher's exact test was used to analyse the differences between proportions; a Student's t test was used for comparisons between the means. All tests were two-sided; *p* values <0.05 were considered statistically significant. SPSS software (version 23.0; IBM, USA) was used for statistical analysis.

*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. The research protocol was approved by the Research Ethics Committee of the Hospital General Universitario Gregorio Marañón (JMC08-RHEUM0722) and the Research Ethics Committee of the Hospital Universitario La Paz (PI3040). Informed written consent was not mandatory for patient participation in this study.

## Results

*Patient characteristics*

A total of 188 patients with GCA clinical confirmation referred to fast-track clinics were included for analysis; 88 (46.8%) were female, with a mean age of 78.2 years. A total of 172 (91.5%) patients fulfilled the ACR/EULAR 2022 GCA classification criteria (23). Table I summarises the baseline characteristic, as well as the clinical and laboratory variables of the patients included. A TA biopsy was performed per clinician criteria in 50 patients, with positive results in 21 (42%) of the GCA patients. Regarding the most notable clinical variables, 147 patients (78.2%) presented headache, 100 (53.2%) constitutional symptoms, 88 (46.8%) morning stiffness in proximal girdles suggestive of PMR, 53 (28.2%) had a previous diagnosis of PMR, 47 (25%) jaw claudication and 29 (15.4%) fever.

*GCA vascular subtypes*

A total of 183 (97.3%) patients presented positive US findings. Of these, 151 (80.3%) patients had cranial involvement, 85 (45.2%) had isolated cranial

**Table II**. Ultrasound findings of GCA patients according to the presence and type of ischaemic complications.

| | All patients n=188 | No ischaemic complication n=145 (77.1%) | AION n=24 (12.8%) | Non-AION IC n=19 (10.1%) | *p* |
|---|---|---|---|---|---|
| US findings | | | | | |
| Positive US, n (%) | 183 (97.3%) | 140 (96.6%) | 24 (100%) | 19 (100%) | 0.467 |
| Positive cranial GCA US, n (%) | 151 (80.3%) | 115 (79.3%) | 24 (100%) | 12 (63.2%) | **0.009** |
| Positive isolated cranial GCA US, n (%) | 85 (45.2%) | 60 (41.4%) | 18 (75%) | 7 (36.8%) | **0.007** |
| Positive large vessel-GCA US, n (%) | 98 (52.1%) | 80 (55.2%) | 6 (25%) | 12 (63.2%) | **0.014** |
| Isolated positive large vessel-GCA US, n (%) | 32 (17%) | 25 (17.2%) | 0 (0%) | 7 (36.8%) | **0.006** |
| Mixed cranial + large vessel GCA US, n (%) | 66 (35.1%) | 55 (37.9%) | 6 (25%) | 5 (26.3%) | 0.328 |

involvement, 98 (52.12%) had positive large vessel (LV)-CGA, and 32 (17%) had isolated positive LV-GCA. Among the 5 (2.7%) patients with GCA diagnosis and negative US, one had positive FDG-PET/CT findings and the others, despite negative imaging, were presumed to have GCA based on the evaluation of the attending physician.

*Ischaemic complications*

Patient characteristics according to IC type are shown in Table I. A total of 43 (22.9%) patients had an IC at diagnosis or in the following 3 months of follow-up, 24 (12.8%) an AION and 19 (10.1%) a non-AION IC (9 had experienced a stroke, 4 acute coronary syndrome, 3 peripheral artery disease, 2 pulmonary embolism and 1 ischaemic colitis). Patients with AION more frequently showed evidence of US cranial involvement (100%) versus those with non-AION IC (63.2%) and without IC (79.3%); $p$=0.009. All patients with AION presented positive cranial US findings (18 with isolated cranial involvement and 6 with mixed involvement), whereas none presented isolated LV US. In contrast, patients with non-AION IC more frequently presented signs of US LV-GCA (63.2%) versus those with AION (25%) or without IC (55.2%), $p$=0.014. Regarding a previous diagnosis of PMR, 2 (8.3%) patients with AION had a previous diagnosis of PMR versus 6 (31.6%) with non-AION and 6 (31%) without IC; $p$=0.049. Patients with morning stiffness in proximal girdles suggestive of PMR at GCA diagnosis less frequently presented AION (20.8%) *vs*. the other groups ($p$=0.014). No significant differences were observed in the frequency of PMR diagnosis (30.6% *vs*. 25.6%; $p$=0.695) or PMR symptoms at the time of diagnosis (51% *vs*. 45.6%; $p$=0.454) between patients with and without LV-GCA US, respectively.

## Discussion

We have demonstrated a potential association between different patterns of vascular US involvement and distinct types of IC in patients with GCA. Our findings suggest that a vascular US pattern may serve as a valuable indicator for identifying specific subgroups of GCA patients at higher risk for specific types of IC. Understanding these associations could aid in developing more targeted and personalised approaches for the management and prevention of IC in individuals diagnosed with GCA. Traditionally, GCA and PMR have been considered distinct inflammatory conditions, albeit closely related, with similar epidemiological distributions (24, 25). The relationship between GCA and PMR is complex, with a significant percentage of patients having both conditions (26). Both conditions are thought to be part of the same spectrum of disease (GCA-PMR spectrum disease) with different risks and potential treatments (27). Approximately half of GCA patients experience PMR either at the time of diagnosis or during relapse, while about a fifth may have a history of PMR (27). A recent study has demonstrated that the risk of relapse in patients with PMR varies depending on the presence or absence of subclinical vasculitis (28). Therefore, knowledge gaps in the relationship between PMR and GCA persist (26), and the prognostic role, including the frequency of ischaemic complications, remains unknown when PMR precedes or coexists at the onset of GCA.

We can differentiate three patterns of US vascular involvement in GCA patients: the classic cranial pattern (cranial GCA), the extracranial large vessel pattern (LV-GCA) and a combination of these two patterns (mixed-GCA) (29, 30). While studies of GCA have traditionally focused on temporal arteries, there is growing evidence that LV involvement is more frequent than previously thought. In this context, we have determined that patients with AION more frequently exhibited US cranial involvement compared to those with non-AION IC or without IC. Moreover, all patients with AION presented cranial involvement (isolated or mixed), whereas none presented isolated LV-GCA. Our results are in line with previous studies that have identified cranial symptoms as predictors of visual involvement in GCA (4, 31, 32). In contrast, patients with non-AION IC more frequently presented signs of US LV-GCA versus those with AION or without IC. These data are novel and demonstrate that in LV-GCA, there is also an associated risk of IC, including severe forms such as cerebrovascular accidents. Strokes and non-AION IC are more frequent when LV involvement is also present. However, a lack of cranial involvement in mixed forms can increase the risk of non-AION IC. While encouraging, these new findings should be further tested in larger cohorts. After AION, stroke is the second most frequent ischaemic complication in GCA, followed by acute coronary syndrome and peripheral artery disease. Previously identified predictors of stroke include male gender (5, 16), presence of visual symptoms (5 ,9, 16), hypertension (5, 16), smoking (16), and absence of anaemia (5, 9, 16).

On the other hand, the presence of PMR in patients with GCA has traditionally been associated with a reduced risk of

IC, although such patients tend to relapse more frequently during follow-up (24). According to our results, patients with previous or concomitant PMR symptoms may be at less risk of developing AION. It is important to note that while PMR symptoms are usually associated with LV-GCA, in our cohort no differences were observed in the frequency of a previous PMR diagnosis or PMR symptoms at the time of GCA diagnosis between patients with and without US LV-GCA, respectively. Some limitations affecting our study should be noted. First, it was retrospective in nature and there may be some recorded inaccuracies or incomplete data. Second, the small sample size of each group may limit the study's statistical power. Third, the ultrasonographer was not blinded to the clinical data. Another potential limitation is that intra- and inter-observer reliability was not specifically investigated for this study, although previous reliability studies have been performed within the same research group (33). Finally, the arteries of the lower limbs were not included in the US examination, which could limit the detection of LV-GCA.

In summary, different patterns of vascular involvement based on US are associated with varying ischaemic complications in patients with GCA. Predominantly cranial-GCA patients more frequently experience AION, whereas predominantly LV-GCA patients have a higher incidence of non-AION ischaemic complications. This underscores the importance of additional validation and replication studies across different settings in order to strengthen the robustness of these findings in various contexts and patient groups.

**Take home messages**

- The different vascular subtypes of GCA are associated with distinct types of IC.
- US cranial-GCA patients more frequently present AION IC.
- US LV-GCA patients more frequently present non-AION IC.

**Acknowledgements**

The authors would like to thank all of the patients who participated in this study. The authors would also like to thank the Spanish Foundation of Rheumatology for providing medical writing/editorial assistance during the preparation of the manuscript (FERBT2023).

**References**

1. HOČEVAR A, JEŠE R, TOMŠIČ M, ROTAR Ž: Risk factors for severe cranial ischaemic complications in giant cell arteritis. *Rheumatology* (Oxford) 2020; 59(10): 2953-9. https://doi.org/10.1093/rheumatology/keaa058
2. CHAZAL T, COUTURE P, ROSSO C *et al*.: Cerebrovascular events are associated with lower survival in giant cell arteritis: A case-controlled multicenter study. *Joint Bone Spine* 2018; 85(3): 383-5. https://doi.org/10.1016/j.jbspin.2017.05.017
3. LIOZON E, DELMAS C, DUMONTEIL S *et al*.: Features and prognosis of giant cell arteritis in patients over 85 years of age: A case-control study. *Semin Arthritis Rheum* 2019; 49(2): 288-95. https://doi.org/10.1016/j.semarthrit.2019.02.011
4. MOLINA-COLLADA J, DOMÍNGUEZ-ÁLVARO M, MELERO-GONZÁLEZ RB *et al*.: Visual manifestations in giant cell arteritis: identification of risk factors from the ARTESER Registry. *Rheumatology* 2024 Jan 20. https://doi.org/10.1093/rheumatology/keae042
5. SAMSON M, JACQUIN A, AUDIA S *et al*.: Stroke associated with giant cell arteritis: a population-based study. *J Neurol Neurosurg Psychiatry* 2015; 86(2): 216-21. https://doi.org/10.1136/jnnp-2014-307614
6. LIOZON E, DALMAY F, LALLOUE F *et al*.: Risk Factors for Permanent Visual Loss in Biopsy-proven Giant Cell Arteritis: A Study of 339 Patients. *J Rheumatol* 2016; 43(7): 1393-9. https://doi.org/10.3899/jrheum.151135
7. SALEH M, TURESSON C, ENGLUND M, MERKEL PA, MOHAMMAD AJ: Visual Complications in Patients with Biopsy-proven Giant Cell Arteritis: A Population-based Study. *J Rheumatol* 2016; 43(8): 1559-65. https://doi.org/10.3899/jrheum.151033
8. YATES M, MACGREGOR AJ, ROBSON J *et al*.: The association of vascular risk factors with visual loss in giant cell arteritis. *Rheumatology* 2017; 56(4): 524-8. https://doi.org/10.1093/rheumatology/kew397
9. DE BOYSSON H, LIOZON E, LARIVIÈRE D *et al*.: Giant Cell Arteritis–related Stroke: A Retrospective Multicenter Case-control Study. *J Rheumatol* 2017; 44(3): 297-303. https://doi.org/10.3899/jrheum.161033
10. JI J, DIMITRIJEVIC I, SUNDQUIST J, SUNDQUIST K, ZÖLLER B: Risk of ocular manifestations in patients with giant cell arteritis: a nationwide study in Sweden. *Scand J Rheumatol* 2017; 46(6): 484-9. https://doi.org/10.1080/03009742.2016.1266030
11. PARIENTE A, GUÉDON A, ALAMOWITCH S *et al*.: Ischemic stroke in giant-cell arteritis: French retrospective study. *J Autoimmun* 2019; 99: 48-51. https://doi.org/10.1016/j.jaut.2019.01.009
12. CZIHAL M, TSCHAIDSE J, BERNAU C *et al*.: Ocular ischaemic complications in giant cell arteritis: CHADS2-score predicts risk of permanent visual impairment. *Clin Exp Rheumatol* 2019; 37 (Suppl. 117): S61-4.
13. LIOZON E, HERRMANN F, LY K *et al*.: Risk factors for visual loss in giant cell (temporal) arteritis: a prospective study of 174 patients. *Am J Med* 2001; 111(3): 211-7. https://doi.org/10.1016/s0002-9343(01)00770-7
14. PEGO-REIGOSA R, GARCIA-PORRUA C, PIÑEIRO A, DIERSSEN T, LLORCA J, GONZALEZ-GAY MA: Predictors of cerebrovascular accidents in giant cell arteritis in a defined population. *Clin Exp Rheumatol* 2004; 22 (Suppl. 36): S13-17.
15. SALVARANI C, CIMINO L, MACCHIONI P *et al*.: Risk factors for visual loss in an Italian population-based cohort of patients with giant cell arteritis. *Arthritis Rheum* 2005; 53(2): 293-7. https://doi.org/10.1002/art.21075
16. GONZALEZ-GAY MA, VAZQUEZ-RODRIGUEZ TR, GOMEZ-ACEBO I *et al*.: Strokes at time of disease diagnosis in a series of 287 patients with biopsy-proven giant cell arteritis. *Medicine* (Baltimore) 2009; 88(4): 227-35. https://doi.org/10.1097/MD.0b013e3181af4518
17. ZENONE T, PUGET M: Characteristics of cerebrovascular accidents at time of diagnosis in a series of 98 patients with giant cell arteritis. *Rheumatol Int* 2013; 33(12): 3017-23. https://doi.org/10.1007/s00296-013-2814-0
18. DEJACO C, RAMIRO S, BOND M *et al*.: EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice: 2023 update. *Ann Rheum Dis* 2024; 83(6): 741-51. https://doi.org/10.1136/ard-2023-224543
19. MOLINA-COLLADA J, CASTREJÓN I, MONJO I *et al*.: Performance of the 2022 ACR/EULAR giant cell arteritis classification criteria for diagnosis in patients with suspected giant cell arteritis in routine clinical care. *RMD Open* 2023; 9(2): e002970. https://doi.org/10.1136/rmdopen-2022-002970
20. MORETTI M, TREPPO E, MONTI S *et al*.: Systemic vasculitis: one year in review 2023. *Clin Exp Rheumatol* 2023; 41(4): 765-73. https://doi.org/10.55563/clinexprheumatol/zf4daj
21. VAN DER GEEST KSM, WOLFE K, BORG F *et al*.: Ultrasonographic Halo Score in giant cell arteritis: association with intimal hyperplasia and ischaemic sight loss. *Rheumatology* (Oxford) 2021; 60(9): 4361-6. https://doi.org/10.1093/rheumatology/keaa806
22. CHRYSIDIS S, DUFTNER C, DEJACO C *et al*.: Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group. *RMD Open* 2018; 4(1): e000598. https://doi.org/10.1136/rmdopen-2017-000598
23. PONTE C, GRAYSON PC, ROBSON JC *et al*.: 2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis. *Ann Rheum Dis* 2022; 81(12): 1647-53. https://doi.org/10.1136/ard-2022-223480
24. SALVARANI C, CANTINI F, BOIARDI L, HUNDER GG: Polymyalgia Rheumatica and Giant-Cell Arteritis. *N Engl J Med* 2002;

347(4): 261-71. https://doi.org/10.1056/NEJMra011913
25. HERNÁNDEZ-RODRÍGUEZ J, FONT C, GARCÍA-MARTÍNEZ A *et al.*: Development of ischemic complications in patients with giant cell arteritis presenting with apparently isolated polymyalgia rheumatica: study of a series of 100 patients. *Medicine* (Baltimore) 2007; 86(4): 233-41. https://doi.org/10.1097/MD.0b013e318145275c
26. BOND M, DEJACO C: Polymyalgia rheumatica: crafting the future of a simple (but not easy!) clinical syndrome. *Ann Rheum Dis* 2024; 83(3): 271-3. https://doi.org/10.1136/ard-2023-225192
27. SALVARANI C, PADOAN R, IORIO L *et al.*: Subclinical giant cell arteritis in polymyalgia rheumatica: Concurrent conditions or a common spectrum of inflammatory diseases? *Autoimmun Rev* 2024; 23(1): 103415. https://doi.org/10.1016/j.autrev.2023.103415
28. DE MIGUEL E, KARALILOVA R, MACCHIONI P *et al.*: Subclinical giant cell arteritis increases the risk of relapse in polymyalgia rheumatica. *Ann Rheum Dis* 2024; 83(3): 335-41. https://doi.org/10.1136/ard-2023-224768
29. PRIETO-GONZÁLEZ S, ARGUIS P, GARCÍA-MARTÍNEZ A *et al.*: Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. *Ann Rheum Dis* 2012; 71(7): 1170-6. https://doi.org/10.1136/annrheumdis-2011-200865
30. DIAMANTOPOULOS AP, HAUGEBERG G, HETLAND H, SOLDAL DM, BIE R, MYKLEBUST G: Diagnostic value of color Doppler ultrasonography of temporal arteries and large vessels in giant cell arteritis: a consecutive case series. *Arthritis Care Res* (Hoboken) 2014; 66(1): 113-9. https://doi.org/10.1002/acr.22178
31. SINGH AG, KERMANI TA, CROWSON CS, WEYAND CM, MATTESON EL, WARRINGTON KJ: Visual Manifestations in Giant Cell Arteritis: Trend over Five Decades in a Population-based Cohort. *J Rheumatol* 2015; 42(2): 309-15. https://doi.org/10.3899/jrheum.140188
32. GONZÁLEZ-GAY MA, BLANCO R, RODRÍGUEZ-VALVERDE V *et al.*: Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. *Arthritis Rheum* 1998; 41(8): 1497-504. https://doi.org/10.1002/1529-0131(199808)41:8<1497::AID-ART22>3.0.CO;2-Z
33. HENRY IM, FERNÁNDEZ FERNÁNDEZ E, PEITEADO D, BALSA A, DE MIGUEL E: Diagnostic validity of ultrasound including extracranial arteries in giant cell arteritis. *Clin Rheumatol* 2023; 42(4): 1163-9. https://doi.org/10.1007/s10067-022-06420-8

## 7. The OMERACT Giant cell arteritis Ultrasonography Score: a potential predictive outcome to assess the risk of relapse during follow-up

Molina-Collada J, Monjo-Henry I, Fernández-Fernández E, Álvaro-Gracia JM, de Miguel E. The OMERACT Giant cell arteritis Ultrasonography Score: a potential predictive outcome to assess the risk of relapse during follow-up. Rheumatology (Oxford). 2024 May 8:keae260. doi: 10.1093/rheumatology/keae260.

*Rheumatology*, 2024, **00**, 1–5
https://doi.org/10.1093/rheumatology/keae260
Advance access publication 8 May 2024
**Concise Report**



Clinical science

# The OMERACT giant cell arteritis ultrasonography score: a potential predictive outcome for assessing the risk of relapse during follow-up

**Juan Molina-Collada [1,2,*], Irene Monjo-Henry [3], Elisa Fernández-Fernández [3], José María Álvaro-Gracia [1,2], Eugenio de Miguel [3]**

[1]Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[2]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain
[3]Department of Rheumatology, Hospital Universitario La Paz, Madrid, Spain

*Correspondence to: Juan Molina-Collada, Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Calle del Dr Esquerdo, 46, 28007 Madrid, Spain. E-mail: molinacolladajuan@gmail.com

## Abstract

**Objective:** The objective of this study was to determine whether the OMERACT GCA US Score (OGUS) change after treatment can be used for assessing the probability of relapse.

**Methods:** This study was a multicentre retrospective study of GCA patients referred to two US GCA fast-track clinics over 2 years. The patients underwent US evaluation at baseline, and at 3 and 6 months. EULAR criteria for remission and relapse were checked at 3 and 6 months. OGUS changes at 0–3 months and 0–6 months were compared between patients with and without relapse at 6 months, as well as between those with and without remission at 6 months.

**Results:** A total of 76 patients were included (mean age 77.2 years, 55.3% females). Nineteen (26%) patients relapsed at 6 months, of whom 14 (19.1%) showed a minor relapse and 5 (6.8%) a major relapse. EULAR remission at 6 months was achieved in 32 (43.8%) patients. The standardized mean difference in OGUS between baseline and 3 months and between 3 months and 6 months was −0.25 and −0.38, respectively. OGUS significantly improved between baseline and 6 months (1.18 to 0.99, $P=0.004$) and from 3–6 months (1.08 to 0.99, $P=0.04$) in non-relapsing patients, whereas no significant changes at 3 (1.17 to 1.17; $P=0.736$) and 6 months (1.17 to 1.21; $P=0.343$) months were observed in those who experienced relapse. The mean 0–6-month OGUS improvement was lower in patients who relapsed (−0.1 to 0.16, $P=0.037$). The mean 0–6-months OGUS improvement (decrease) was greater in patients who achieved remission at 6 months (0.28 to −0.07, $P=0.001$).

**Conclusion:** The absence of OGUS improvement during follow-up in GCA may be used to assess the probability of relapse and the absence of remission at 6 months.

**Keywords:** ultrasound, giant cell arteritis, OGUS, relapse, remission.

**Rheumatology key messages**

- OGUS shows sensitivity to change during follow-up in GCA patients.
- OGUS changes during follow-up may be used to assess the probability of relapse and remission in GCA.

## Introduction

Imaging has transformed the diagnosis of patients with GCA in recent decades [1]. It is now an integral part of the new 2022 ACR/EULAR GCA classification criteria [2], reflecting its expanding role in clinical practice [3, 4]. Specifically, US is endorsed by EULAR as the primary imaging modality for patients suspected of having GCA [5].

Once the diagnostic potential of imaging techniques in GCA [5–10] becomes widely recognized, our efforts can shift towards enhancing their sensitivity to change and their role in monitoring disease activity, treatment response, and predicting outcomes. Several indices have been published with the goal of quantifying vessel wall inflammation using US in GCA [11–13]. However, the optimal score for use in clinical practice and research remains unknown. To solve this question, the OMERACT US LV vasculitis working group has developed and validated the OMERACT GCA US Score (OGUS), demonstrating its reliability, construct validity, and sensitivity to change in tracking vascular involvement in GCA over time [14].

Although pending validation, it has also been recently proposed as a potentially useful tool for defining relapse and remission [15]. However, its predictive role for identifying

**Received:** 8 March 2024. **Accepted:** 23 April 2024

worse outcomes in GCA has not yet been studied. On the other hand, the updated EULAR recommendations on the use of imaging in large-vessel (LV) vasculitis highlight the broader utility of imaging in GCA [5], emphasizing its potential role not only in diagnosis but also in assessing inflammatory activity, identifying relapses, and evaluating structural damage during follow-up. Nevertheless, the research agenda emphasizes the need to investigate the value of composite scores for GCA monitoring and prognosis. Therefore, our study aimed to assess the responsiveness to treatment of OGUS in GCA patients and its value in assessing the probability of future relapses during subsequent follow-up.

## Methods

### Patient selection and data collection

This was a multicentre observational retrospective study that included a cohort of patients referred to GCA fast-track clinics at two academic centres over a 2-year period (June 2019—June 2021). The inclusion criteria for this study required any GCA diagnosis to be confirmed by clinicians at least after 6 months of follow-up. We retrospectively collected data from their electronic health records at each visit, including demographics, presenting symptoms and physical findings from temporal artery (TA) examinations at baseline. Additionally, laboratory tests such as CRP, ESR, haemoglobin, and platelet counts, as well as TA biopsy (TAB) findings (if available), were collected. Disease activity was evaluated following routine care. As per protocol, the treating clinician was not blinded to US findings. We used the EULAR definition of remission ('absence of all clinical signs and symptoms attributable to active LVV and normalization of ESR and CRP; in addition, for patients with extracranial disease there should be no evidence of progressive vessel narrowing or dilatation') and the EULAR definitions of major relapse ['recurrence of active disease with either of the following: a. Clinical features of ischaemia (including jaw claudication, visual symptoms, visual loss attributable to GCA, scalp necrosis, stroke, limb claudication). b. Evidence of active aortic inflammation resulting in progressive aortic or large vessel dilatation, stenosis or dissection'] and minor relapse ('recurrence of active disease, not fulfilling the criteria for a major relapse') [16]. EULAR remission, as well as major and minor relapse, were checked for every patient at 3 months and 6 months. Patients were treated according to their clinical response with standard therapy.

### US assessment

All patients underwent a protocolized vascular bilateral US of the cranial arteries (common superficial TA, and its parietal and frontal branches) and extracranial arteries (carotid, subclavian and axillary) at baseline and at each visit. The entire axillary artery was evaluated, including its three parts from the anterior side or the axillary fossa. The US exam was performed by three experienced ultrasonographers (E.d.M., I. M.-H. and J.M.-C.) with two sets of US equipment, including an Esaote MyLab8 (Esaote, Genoa, Italy) with a 12–18 MHz transducer (for the TA) and a 6–15 MHz transducer (for the extracranial arteries), and an Esaote MyLabX8eXP with a 12–25 MHz transducer (for the TA) and a 4–15 MHz transducer (for the extracranial arteries). The presence of a halo and/or compression sign in the TA, or the presence of a halo in the extracranial arteries in the absence of atherosclerosis, was considered sufficient for a positive US examination [6]. OGUS [14] calculations of recorded images and videos were performed both at the initial baseline assessment and during subsequent visits. OGUS was calculated as the sum of the intima media thickness (IMT) in every segment divided by the rounded cut-off values of IMTs in each segment (0.4 mm for the common trunk of the superficial TA, 0.3 mm for the parietal and frontal branches and 1 mm for the axillary arteries). The total sum was divided by the number of segments available. The ultrasonographers were not blinded to the clinical information of the patients.

### Statistical analysis

Statistical analysis was performed using SPSS software (version 20; SPSS, IBM Corp., Armonk, NY, USA). Qualitative variables are presented using frequencies and percentages, and continuous variables as mean (S.D.). OGUS' sensitivity to change was calculated as negative values of the standardized mean difference for each visit separately. The paired $t$ test was used for comparing baseline and follow-up OGUS assessments. The 0–3 and 0–6 months OGUS changes were calculated by simply calculating the difference between the baseline OGUS and the OGUS at 3 months and 6 months, respectively. A lower value for the difference indicated less improvement, and a negative result indicated worsening of the OGUS, i.e. a higher OGUS, at the last visit compared with baseline. The 0–3 and 0–6 months OGUS changes were compared between patients with and without relapse at 6 months, and with and without achievement of remission at 6 months. All tests were two-sided, and $P$ values of $<0.05$ were considered statistically significant.

### Ethics approval

This study was performed in accordance with the Declaration of Helsinki of 1975, revised in 1983. The research protocol was approved by the Research Ethics Committee of the Hospital General Universitario Gregorio Marañón (JMC08-RHEUM0722) and the Research Ethics Committee of the Hospital Universitario La Paz (PI3040). Informed written consent was not mandatory for patient participation in the study.

## Results

### Patient characteristics

A total of 76 patients were included for analysis during the study period. The mean (S.D.) age was 77.2 (9.2) years and 42 (55.3%) were females. Data for clinical, laboratory and the main US variables are shown in detail in Table 1. All patients received glucocorticoid treatment upon diagnosis. During the 6-months follow-up, 16 (21.1%) patients underwent tocilizumab therapy and 14 (18.4%) received MTX

### Relapses during follow-up

A total of 73 patients completed the US exam at 6 months. Nineteen patients (26%) relapsed at 6 months; of these, 14 (19.1%) showed a minor relapse and 5 (6.8%) a major relapse. Among the latter, two patients presented with visual symptoms or jaw claudication, as clinical features of ischaemia, while the others showed progressive involvement of large arteries by imaging, either fluorodeoxyglucose (FDG)-PET/CT, US, angio-MRI or CT. At the time of relapse, the mean CRP and ESR were 53.9 and 32.8, respectively. The

**Table 1.** Clinical, laboratory, histology and US findings for patients with GCA who participated in the study

| | Positive cranial GCA US $n = 53$ | Positive LV-GCA US $n = 55$ | Positive mixed-GCA (cranial + LV) US $n = 33$ | Total $n = 76$ |
|---|---|---|---|---|
| **Demographics** | | | | |
| **Age, mean** (S.D.) | 79.1 (6.7) | 76 (8.1) | 76.9 (6.8) | 77.2 (9.2) |
| **Female, *n*** (%) | 27 (50.9%) | 27 (49.1%) | 13 (39.4%) | 42 (55.3%) |
| **Clinical variables** | | | | |
| **Symptoms duration (days), median (IQR)** | 40 (20-120) | 60 (30-150) | 90 (30-120) | 60 (22.8-120) |
| **PMR diagnosis before US examination, *n*** (%) | 9 (17%) | 15 (27.3%) | 8 (24.2%) | 16 (21.1%) |
| **Headache, *n*** (%) | 40 (75.5%) | 32 (58.2%) | 23 (69.7%) | 49 (64.5%) |
| **Scalp tenderness, *n*** (%) | 14 (26.4%) | 6 (10.9%) | 4 (12.1%) | 16 (21.1%) |
| **Jaw claudication, *n*** (%) | 19 (35.8%) | 9 (16.4%) | 8 (24.2%) | 20 (26.3%) |
| **Visual symptoms, *n*** (%) | 14 (26.4%) | 8 (14.5%) | 6 (18.2%) | 16 (21.1%) |
| **Ocular ischaemia, *n*** (%) | 6 (11.3%) | 1 (1.8%) | 1 (3%) | 7 (9.2%) |
| **Constitutional symptoms, *n*** (%) | 21 (39.6%) | 26 (47.3%) | 16 (48.5%) | 32 (42.1%) |
| **Fever, *n*** (%) | 10 (18.9%) | 14 (25.5%) | 8 (24.2%) | 16 (21.1%) |
| **Morning stiffness in shoulders/neck, *n*** (%) | 22 (41.5%) | 30 (54.5%) | 17 (51.5%) | 35 (46.1%) |
| **Abnormal TA clinical examination, *n*** (%) | 10 (18.9%) | 3 (5.5%) | 3 (9.1%) | 10 (13.2%) |
| **Positive TA biopsy, *n*/total TA biopsy performed** (%) | 9/17 (52.9%) | 4/9 (44.4%) | 4/6 (66.7%) | 9/20 (45%) |
| **Laboratory findings** | | | | |
| **CRP (mg/dl), mean** (S.D.) | 38.9 (50.7) | 39.3 (50.3) | 52.3 (57.2) | 33 (45.9) |
| **ESR (mm/h), mean** (S.D.) | 63.3 (34.4) | 58.8 (37.2) | 59.4 (38.5) | 62.2 (34.9) |
| **Haemoglobin (g/dl), mean** (S.D.) | 12.1 (1.6) | 12.1 (1.7) | 12 (1.7) | 12.1 (1.6) |
| **Platelets $10^9$/l, mean** (S.D.) | 332.1 (134.6) | 333.7 (144.9) | 334.4 (147.6) | 335.8 (139.1) |
| **US findings** | | | | |
| **Positive US findings, *n*** (%) | 53 (100%) | 54 (98.2%) | 33 (100%) | 75 (98.7%) |

IQR: interquartile range; LV: large vessel; TA: temporal artery.

mean prednisone dose at relapse was 8.5 mg daily. A total of 5 (26.3%) patients were on MTX at relapse. EULAR remission at 6 months was achieved by 32 (43.8%) patients. Only 2 patients in our cohort were in remission without glucocorticoids at 6 months.

### Baseline and follow-up US findings

At diagnosis, positive US findings were found in 75 patients (98.7%), with involvement of the cranial arteries in 53 patients (69.7%), LV involvement in 55 (72.4%) and a mixed pattern of cranial and LV-GCA in 33 (43.4%). The mean baseline OGUS was 1.18 (0.32). In the overall patient population, OGUS numerically improved (decreased) at 3 months (1.18 *vs* 1.1, $P = 0.108$) and 6 months (1.18 *vs* 1.06, $P < 0.71$), although these differences were not statistically significant (Supplementary Table S1, available at *Rheumatology* online). The standardized mean difference in OGUS between baseline and 3 months and between baseline and 6 months was −0.25 and −0.38, respectively. OGUS significantly improved (decreased) from baseline to 6 months (1.18 to 0.99, $P = 0.004$) and from 3 to 6 months (1.08 to 0.99, $P = 0.04$) in non-relapsing patients, whereas no significant changes from baseline to 3 months (1.17 to 1.17; $P = 0.736$) or baseline to 6 months (1.17 *vs* 1.21; $P = 0.343$) were observed in patients who relapsed (Supplementary Table S1 and Supplementary Fig. S1, available at *Rheumatology* online). Supplementary Fig. S2, available at *Rheumatology* online, depicts OGUS change between baseline, 3 months and 6 months, according to the achievement of EULAR remission at 6 months. The 0–3 months and 0–6 months OGUS change in patients who did and did not relapse at 6 months, as well as in those who did and did not achieve remission at 6 months are shown in detail in Table 2. No significant differences were found in OGUS changes at 3 months between patients who did and did not relapse. At the 6 months follow-up visit, OGUS was significantly higher in patients who relapsed compared with in those who did not. The mean 0–6 months OGUS improvement was significantly less (or it worsened) in patients who relapsed at 6 months (−0.1 to 0.16, $P = 0.037$). On the other hand, the mean 0–6 months OGUS improvement was greater in patients who achieved remission at 6 months (0.28 to −0.07, $P = 0.001$).

## Discussion

We evaluated changes in OGUS during follow-up to detect relapses. Our preliminary data indicated that, while patients who relapsed at 6 months showed no OGUS improvements, those who did not relapse showed OGUS improvement at 3 months, with significant improvement evident at 6 months.

Due to insufficient evidence, EULAR does not recommend routine imaging in GCA patients in remission. Its use may be considered in cases of suspected relapse, particularly when laboratory markers of disease activity are unreliable, and also for the long-term monitoring of structural damage, particularly at sites that previously showed vascular inflammation. This recommendation relies on several studies, suggesting the potential usefulness of US for assessing disease activity and treatment response in GCA [17–20]. The frequency of screening, as well as the imaging method applied, should be decided on an individual basis [5].

While it has been demonstrated that the IMT decreases after treatment, the decrease is slower in the extracranial arteries compared with the cranial arteries [17]. Aschwanden *et al.* conducted a study involving 42 GCA patients with LV involvement at 6, 12 and 24 months post-diagnosis. They found a reduction in LV wall thickening in 45% of patients during follow-up. Conversely, a reduction in vessel wall thickening in the TA was observed in 85% of patients [19]. Ponte *et al.* demonstrated in a prospective study of 49 GCA patients that the number of TA segments with a halo and sum and a maximum TA halo IMT showed a significant correlation (Spearman's correlation coefficient) with the ESR

**Table 2.** Baseline, 3- and 6-months OGUS, and 0–3 and 0–6 months OGUS change in patients with and without relapse at 6 months and with and without achievement of remission at 6 months

| Parameter | All patients $n = 76$ | Relapse at 6-months follow-up $n = 19$ | No relapse at 6-months follow-up $n = 54$ | *P* | EULAR remission at 6-months follow-up $n = 32$[a] | No EULAR remission at 6-months follow-up $n = 41$[a] | *P* |
|---|---|---|---|---|---|---|---|
| **Baseline OGUS, mean** (S.D.) | 1.18 (0.32) | 1.17 | 1.18 | 0.902 | 1.23 | 1.14 | 0.255 |
| **3-months OGUS, mean** (S.D.) | 1.1 (0.34) | 1.17 | 1.08 | 0.439 | 1.07 | 1.14 | 0.415 |
| **6-months OGUS, mean** (S.D.) | 1.06 (0.27) | 1.21 | 0.99 | **0.01** | 0.98 | 1.13 | 0.061 |
| **0–3-months OGUS change, mean** (S.D.) | 0.07 (0.48) | 0.05 (0.48) | 0.07 (0.50) | 0.854 | 0.12 (0.41) | 0.01 (0.57) | 0.439 |
| **0–6-months OGUS change, mean** (S.D.) | 0.08 (0.39) | −0.1 (0.38) | 0.16 (0.38) | **0.037** | 0.28 (0.32) | −0.07 (0.39) | **0.001** |
| **3–6-months OGUS change, mean** (S.D.) | 0.08 (0.34) | −0.08 (0.51) | 0.15 (0.23) | 0.071 | 0.15 (0.19) | 0.01 (0.46) | 0.09 |

[a] A total of 73 patients completed an US exam at 6 months. Bold text indicates *P* values of <0.05, which were considered statistically significant. OGUS: OMERACT GCA Ultrasonography Score.

(0.41), CRP (0.34), BVAS (0.29) and glucocorticoid cumulative dose (−0.34), although no significant correlation was found for the axillary halo features [17]. De Miguel *et al.* in a study including 30 GCA patients, showed that halo disappearance occurred in the majority of patients (95%), but was rare before 2 weeks, and frequently persisted during the first 2 months after glucocorticoid initiation [20]. While these studies suggest the potential usefulness of US for assessing disease activity and response to treatment in GCA, to our knowledge the value of the US change in determining the risk of relapse has not yet been studied.

Some studies have already shown sensitivity to change in OGUS during follow-up in GCA. Nielsen *et al.* [15] previously observed similar results in a smaller retrospective study aimed at determining the sensitivity to change of different vascular US indices. In their cohort, 10 (21%) of the 47 patients followed-up at 6 months relapsed. OGUS increased from 2 to 6 months in the group of patients who relapsed, and there was a higher OGUS at 6 months than in those patients who did not relapse. Patients who experienced a relapse had a mean OGUS increase from 2 to 6 months (95% CI) of 0.26 (0.18–0.35). In our cohort, this increase was considerably smaller, possibly due to the different definitions of relapse used in the two studies. While we used the EULAR definition of relapse (with stricter criteria), Nielsen *et al.* used a clinical definition of relapse. Nevertheless, our results are similar and confirm the previous observation that OGUS improves to a lesser degree, or even worsens in patients relapsing at 6 months. Another relevant question is whether early OGUS change (within the first 3 months) can predict which patients will experience relapse in the future. From our results, we have not been able to demonstrate this association. Although improvement in OGUS from 0 to 3 months was numerically lower in patients who experienced relapses, these differences are not statistically significant. A larger sample size or longer follow-up time may be needed to clarify this issue.

In this study, we have also demonstrated sensitivity to change in OGUS during follow-up. OGUS significantly improved (decreased) at 6 months and from 3–6 months in non-relapsing patients, whereas no improvement was observed at 3 and 6 months in patients who relapsed. Our results are in line with previous observations confirming the sensitivity of OGUS to change [14, 15].

Some limitations of our study include those intrinsic to any retrospective study, such as potential inaccuracies in relapse recording leading to misclassification. On the other hand, our sample size complicates comparisons between groups. Neither the clinician nor the sonographer were blinded to clinical and laboratory data, which may have led to biases. Among the strengths, ours was a multicentre study, including fast-track clinics with over 5 years of experience, and US scans included as part of a well-defined protocol in which all US data are systematically collected.

In conclusion, the change in OGUS during follow-up may be useful both in assessing the probability of relapse and in defining remission in patients with GCA. This study lays the groundwork for conducting prospective studies to determine the predictive value of OGUS for outcomes in GCA, as well as for other complications such as ischaemic manifestations.

## Supplementary material

Supplementary material is available at *Rheumatology* online.

## Data availability

The data underlying this article are available in the article and in the online supplementary material.

## Contribution statement

All authors made substantial contributions to the conception and design of this study. The study was designed by E.d.M., I.M.-H. and J.M.-C. Subject recruitment and US examinations were performed by E.d.M., I.M.-H. and J.M.-C. Collection of the epidemiological and clinical data was performed by J.M.-C. and I.M.-H. E.d.M. and J.M.-C. performed the statistical analysis. J.M.-C. and E.d.M. drafted the manuscript. All co-authors revised the final manuscript.

## Funding

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

*Disclosure statement:* The authors have declared no conflicts of interest.

## Acknowledgements

The authors would like to thank all of the patients who participated in this study. The authors would also like to thank the Spanish Foundation of Rheumatology for providing medical writing/editorial assistance during the preparation of the manuscript (FERBT2023).

## References

1. Ponte C, Martins-Martinho J, Luqmani RA. Diagnosis of giant cell arteritis. Rheumatology (Oxford) 2020;59:iii5–16.
2. Ponte C, Grayson PC, Robson JC *et al.*; DCVAS Study Group. 2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis. Ann Rheum Dis 2022;81:1647–53.
3. Molina-Collada J, Castrejón I, Monjo I *et al.* Performance of the 2022 ACR/EULAR giant cell arteritis classification criteria for diagnosis in patients with suspected giant cell arteritis in routine clinical care. RMD Open 2023;9:e002970.
4. van Nieuwland M, van Bon L, Vermeer M, Brouwer E, Alves C. External validation of the 2022 ACR/EULAR classification criteria in patients with suspected giant cell arteritis in a Dutch fast-track clinic. RMD Open 2023;9:e003080.
5. Dejaco C, Ramiro S, Bond M *et al.* EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice: 2023 update. Ann Rheum Dis 2024;83:741–51.
6. Bosch P, Bond M, Dejaco C *et al.* Imaging in diagnosis, monitoring and outcome prediction of large vessel vasculitis: a systematic literature review and meta-analysis informing the 2023 update of the EULAR recommendations. RMD Open 2023;9:e003379.
7. López-Gloria K, Castrejón I, Nieto-González JC *et al.* Ultrasound intima media thickness cut-off values for cranial and extracranial arteries in patients with suspected giant cell arteritis. Front Med (Lausanne) 2022;9:981804.
8. Schäfer VS, Juche A, Ramiro S, Krause A, Schmidt WA. Ultrasound cut-off values for intima-media thickness of temporal, facial and axillary arteries in giant cell arteritis. Rheumatology (Oxford) 2017;56:1479–83.
9. Ješe R, Rotar Ž, Tomšič M, Hočevar A. The cut-off values for the intima-media complex thickness assessed by colour Doppler sonography in seven cranial and aortic arch arteries. Rheumatology (Oxford) 2021;60:1346–52.
10. Czihal M, Schröttle A, Baustel K *et al.* B-mode sonography wall thickness assessment of the temporal and axillary arteries for the diagnosis of giant cell arteritis: a cohort study. Clin Exp Rheumatol 2017;35(Suppl 103):128–33.
11. van der Geest KSM, Borg F, Kayani A *et al.* Novel ultrasonographic Halo Score for giant cell arteritis: assessment of diagnostic accuracy and association with ocular ischaemia. Ann Rheum Dis 2020;79:393–9.
12. Molina Collada J, Martínez-Barrio J, Serrano-Benavente B *et al.* Diagnostic value of ultrasound halo count and Halo Score in giant cell arteritis: a retrospective study from routine care. Ann Rheum Dis 2022;81:e175.
13. Molina Collada J, Martínez-Barrio J, Serrano-Benavente B *et al.* Subclavian artery involvement in patients with giant cell arteritis: do we need a modified Halo Score? Clin Rheumatol 2021; 40:2821–7.
14. Dejaco C, Ponte C, Monti S *et al.* The provisional OMERACT ultrasonography score for giant cell arteritis. Ann Rheum Dis 2022; 82:556–64.
15. Nielsen BD, Therkildsen P, Keller KK *et al.* Ultrasonography in the assessment of disease activity in cranial and large-vessel giant cell arteritis: a prospective follow-up study. Rheumatology (Oxford) 2023;62:3084–94.
16. Hellmich B, Agueda A, Monti S *et al.* 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79:19–30.
17. Ponte C, Monti S, Scirè CA *et al.* Ultrasound halo sign as a potential monitoring tool for patients with giant cell arteritis: a prospective analysis. Ann Rheum Dis 2021;80:1475–82.
18. Schäfer VS, Chrysidis S, Schmidt WA *et al.* OMERACT definition and reliability assessment of chronic ultrasound lesions of the axillary artery in giant cell arteritis. Semin Arthritis Rheum 2021; 51:951–6.
19. Aschwanden M, Schegk E, Imfeld S *et al.* Vessel wall plasticity in large vessel giant cell arteritis: an ultrasound follow-up study. Rheumatology (Oxford) 2019;58:792–7.
20. De Miguel E, Roxo A, Castillo C *et al.* Martín-Mola E. The utility and sensitivity of colour Doppler ultrasound in monitoring changes in giant cell arteritis. Clin Exp Rheumatol 2012;30:S34–8.


Rheumatology, 2024, 00, 1–5
https://doi.org/10.1093/rheumatology/keae260
Concise Report

## 8. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice: 2023 update

Dejaco C, Ramiro S, Bond M, Bosch P, Ponte C, Mackie SL, Bley TA, Blockmans D, Brolin S, Bolek EC, Cassie R, Cid MC, Molina-Collada J, Dasgupta B, Nielsen BD, De Miguel E, Direskeneli H, Duftner C, Hočevar A, Molto A, Schäfer VS, Seitz L, Slart RHJA, Schmidt WA. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice: 2023 update. Ann Rheum Dis. 2024 May 15;83(6):741-751. doi: 10.1136/ard-2023-224543.

# EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice: 2023 update

Christian Dejaco ,[1,2] Sofia Ramiro ,[3,4] Milena Bond ,[2] Philipp Bosch ,[1] Cristina Ponte ,[5,6] Sarah Louise Mackie,[7,8] Thorsten A Bley,[9] Daniel Blockmans ,[10,11] Sara Brolin ,[12,13] Ertugrul Cagri Bolek ,[14] Rebecca Cassie,[15] Maria C Cid ,[16] Juan Molina-Collada ,[17] Bhaskar Dasgupta ,[18,19] Berit Dalsgaard Nielsen,[20,21] Eugenio De Miguel ,[22] Haner Direskeneli ,[23] Christina Duftner ,[24] Alojzija Hočevar ,[25,26] Anna Molto ,[27,28] Valentin Sebastian Schäfer ,[29] Luca Seitz,[30] Riemer H J A Slart,[31,32] Wolfgang A Schmidt [33]

**Handling editor** Josef S Smolen

For numbered affiliations see end of article.

**Correspondence to**
Dr Christian Dejaco, Department of Rheumatology and Immunology, Medical University of Graz, Graz, Steiermark, Austria;
christian.dejaco@gmx.net

The results of this study have been presented at EULAR 2023 (LB0009).

Received 6 June 2023
Accepted 18 July 2023
Published Online First 7 August 2023



**To cite:** Dejaco C, Ramiro S, Bond M, *et al*. *Ann Rheum Dis* 2024;**83**:741–751.

## ABSTRACT

**Objectives** To update the EULAR recommendations for the use of imaging modalities in primary large vessel vasculitis (LVV).

**Methods** A systematic literature review update was performed to retrieve new evidence on ultrasound, MRI, CT and [$^{18}$F]-fluorodeoxyglucose positron emission tomography (FDG-PET) for diagnosis, monitoring and outcome prediction in LVV. The task force consisted of 24 physicians, health professionals and patients from 14 countries. The recommendations were updated based on evidence and expert opinion, iterating until voting indicated consensus. The level of agreement was determined by anonymous votes.

**Results** Three overarching principles and eight recommendations were agreed. Compared to the 2018 version, ultrasound is now recommended as first-line imaging test in all patients with suspected giant cell arteritis, and axillary arteries should be included in the standard examination. As an alternative to ultrasound, cranial and extracranial arteries can be examined by FDG-PET or MRI. For Takayasu arteritis, MRI is the preferred imaging modality; FDG-PET, CT or ultrasound are alternatives. Although imaging is not routinely recommended for follow-up, ultrasound, FDG-PET or MRI may be used for assessing vessel abnormalities in LVV patients with suspected relapse, particularly when laboratory markers of inflammation are unreliable. MR-angiography, CT-angiography or ultrasound may be used for long-term monitoring of structural damage, particularly at sites of preceding vascular inflammation.

**Conclusions** The 2023 EULAR recommendations provide up-to-date guidance for the role of imaging in the diagnosis and assessment of patients with LVV.

## INTRODUCTION

Giant cell arteritis (GCA) and Takayasu arteritis (TAK) are the most common primary large vessel vasculitides (LVV).[1 2] Temporal artery biopsy (TAB) and conventional angiography have been considered for decades the 'golden standards' for diagnosing GCA and TAK, respectively. In the last years, however, imaging modalities including ultrasound, MRI and [$^{18}$F]-fluorodeoxyglucose positron emission tomography (FDG-PET) have become an integral part of the diagnosis, supported by the 2018 EULAR recommendations for the use of imaging in LVV.[3]

Since 2018, new studies on imaging in LVV have been published, some of them prompting a reconsideration of the original statements. FDG-PET, for example, was previously considered inadequate for the assessment of temporal arteries because of the proximity to the brain.[3] However, recent studies report that FDG-PET can detect temporal arteritis with high sensitivity and specificity.[4–6]

Glucocorticoids (GC) are the mainstay in the treatment of GCA and TAK, but recently, the interleukin-6 receptor (IL-6R) inhibitor tocilizumab has become part of the standard treatment for GCA.[7] Studies indicate that this drug is also effective in TAK, although approval for this indication by the Food and Drug Administration (FDA) and the European Medicines Agency is still lacking.[8] The IL-6 R inhibitor sarilumab has been approved by FDA for Polymyalgia rheumatica (PMR), a disease that is considered to be part of the GCA-PMR spectrum.[9 10] These agents interfere with the ability to produce an acute phase response as evaluated by erythrocyte sedimentation rate (ESR) or C reactive protein (CRP), reducing the impact of these biomarkers on clinical assessment of disease activity in LVV. Imaging modalities therefore may contribute to a more comprehensive assessment of patients with GCA and TAK.[11]

The American College of Rheumatology (ACR) has recently published management guidelines for GCA expressing their preference for TAB over ultrasound and MRI of cranial arteries in the diagnosis of GCA, which contrasts with the 2018 EULAR recommendations[12] and other recommendations.[13–16] The ACR clarifies that these recommendations relate in part to the lack of technical expertise of clinicians in the USA with these modalities.[12]

These and other developments have prompted us to re-evaluate and update the original EULAR recommendations, particularly addressing uncertainties about the choice of the imaging technique for diagnosis and assessment of patients with GCA

and TAK. The objectives, target population and target users of this update remain unchanged compared with the previous version.[3] These recommendations are intended to advise physicians on the use of imaging modalities in patients with suspected or established primary LVV, specifically GCA and TAK.

## METHODS

After approval by the EULAR Council, the convenors (CDejaco and WAS) and the methodologist (SR) led a task force guided by the 2014 updated EULAR Standardised Operating Procedures (SOP), complying also with the principles stipulated in the 2022 EULAR SOPs.[17 18] The 24 task force members from 14 countries consisted of rheumatologists, a radiologist, nuclear medicine specialists, an internist, epidemiologists, a patient representative (the second patient could not attend the meeting for health reasons), a health professional in rheumatology and 2 EMerging EUlar NETwork representatives. Five members were recruited through an open call to EULAR countries via a competitive application process. All members disclosed their potential conflicts of interest before starting the process. A single face-to-face task force meeting took place. In preparation of that meeting, several online conferences of the steering committee (CDejaco, SR, WAS, MB, PB, CP and SLM) were conducted. For the systematic literature review (SLR), we used the same Population, Intervention, Control, Oucome (PICO) questions and inclusion/exclusion criteria as in the original project,[19] covering the role of ultrasound, MRI, CT, FDG-PET in the (1) diagnosis and (2) monitoring of inflammation and damage, (3) prediction of outcome and (4) required technical standards for imaging. The steering committee made a single modification of the original PICO questions including optical coherence tomography and fluorescein angiography (FA) as additional imaging techniques in the search.

The SLR was conducted by two fellows (MB and PB) under the guidance of the methodologist (SR). Papers published between March 2017 and 16 November 2022 were considered. Some articles were identified by both the original[19] and the present SLR and were therefore excluded manually from the current update. Only prospective and cross-sectional studies conducted in >20 adult patients with suspected and/or established GCA or TAK were included. We chose a cut-off of 20, because studies with a lower number of participants were concerned to be of lower quality and would therefore be less relevant for the task force. The evidence summarised in the SLR was presented to the task force in the form of tables summarising the findings, including an assessment of the risk of bias (RoB).[20 21] The evidence collected in the previous SLR was also considered and summarised to the task force.[19] Given the large number of studies included in the complete SLR (original and current update), a conscious choice was made to favour evidence stemming from studies with low RoB. The present SLR is published separately[11]; however, the SLR and the present recommendations manuscript form an integral and inseparable part and should be read as such.

Based on new evidence and expert opinion, the steering committee prepared proposals for updated recommendations which were subsequently discussed and refined by the entire group during the task force meeting. Following the EULAR SOP, a modification of the original statements had to be approved by >75% of the task force members, followed by a second voting on the final wording of the rephrased recommendation.[18] Consensus was accepted if >75% of the members voted in favour of the statement in the first round, >66% in the second round and in the third round >50% was accepted. The 2011 Oxford Centre for Evidence Based Medicine levels of evidence (LoE) derived from the SLR were added to each recommendation.[22]

Finally, each task force member anonymously indicated the level of agreement via Survey Monkey (LoA, 0–10 numeric rating scale with 0=do not agree and 10=fully agree). The mean and SD of the LoA, as well as the percentage of task force members with an agreement ≥8 are presented.

The task force specified that CT and MRI also refer to the specific angiography techniques such as CT-angiography (CTA) and MR-angiography (MRA), respectively, and PET is commonly used in conjunction with CT or CTA, and occasionally in combination with MRI/MRA.

The original research agenda was checked as to whether any of the gaps in evidence have meanwhile been filled with evidence.[3] New issues arising during the task force meeting were added to the research agenda presented in this paper. The final manuscript was reviewed and approved by all task force members and by the EULAR Council.

## RESULTS

### General aspects

In 2018, 12 recommendations were formulated, while the update includes three overarching principles and eight specific recommendations. Compared with the original statements, two (new numbers 5+6) remained unchanged, two underwent minor (4+8) and four major modifications (1–3, 7). The former recommendation five on CT and FDG-PET for the assessment of cranial arteries was deleted (see online supplemental table 1 for a comparison between the original and the updated statements).

The updated recommendations are depicted in table 1 (including the LoE and LoA) and are explained in detail below.

### Overarching principles

Overarching principles are statements of generic nature and are not necessarily based on direct evidence. They reflect principles of good clinical practice and build the framework for the subsequent specific recommendations.

#### Overarching principle A

In patients with suspected GCA, an early imaging test is recommended to support the clinical diagnosis of GCA, assuming high expertise and prompt availability of the imaging technique. Imaging should not delay initiation of treatment.

This statement remained largely unchanged compared with the original recommendation.[3] The task force emphasised that an imaging test should be considered in every patient with suspected GCA. TAB is also an adequate option, particularly when imaging is not readily available or expertise with imaging in GCA is insufficient. It is commonly believed that operator dependency is the major limitation of imaging, particularly of ultrasound. However, all diagnostic procedures including TAB are subject to operator dependency; and reproducibility can be improved by specific training.[23 24] In addition, a multicentre study including sonographers with a mixed level of experience revealed that inter-reader reliability of ultrasound images was comparable to that of digital histological images.[25]

The main point of discussion within the task force was whether treatment could be delayed while waiting for imaging to be done. It was felt that patients with strongly suspected GCA, particularly if there are ischaemic manifestations of concern (eg, transient visual loss or jaw claudication), must be treated immediately due to the risk of imminent and permanent visual

**Table 1** 2023 EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice

| | | LoA (0–10) | |
|---|---|---|---|
| **Overarching principles** | | **Mean (SD)** | **% with LoA≥8** |
| A. In patients with suspected GCA, an early imaging test is recommended to support the clinical diagnosis of GCA, assuming high expertise and prompt availability of the imaging technique. Imaging should not delay initiation of treatment. | | 9.1 (1.9) | 88 |
| B. Imaging examination should be done by a trained specialist using appropriate equipment, standardised operational procedures and settings. | | 9.8 (0.4) | 100 |
| C. In patients in whom there is a high clinical suspicion of GCA and a positive imaging result, the diagnosis of GCA may be made without an additional test (biopsy or further imaging). In patients with a low clinical probability and a negative imaging result, the diagnosis of GCA can be considered unlikely. In all other situations (including the case of an inconclusive imaging result), additional efforts towards a diagnosis are necessary. | | 9.4 (1.0) | 96 |
| Recommendations | LoE | | |
| 1. Ultrasound of temporal and axillary arteries should be considered as the first imaging modality to investigate mural inflammatory changes in patients with suspected GCA. | 1 | 9.6 (1.0) | 96 |
| 2. High-resolution MRI or FDG-PET* can be used as alternatives to ultrasound for the assessment of cranial arteries† in patients with suspected GCA. | 1 | 9.4 (1.1) | 88 |
| 3. FDG-PET*, alternatively MRI or CT, can be used for the detection of mural inflammation or luminal changes of extracranial arteries in patients with suspected GCA. | 1 (PET), 3 (CT), 5 (MRI) | 9.6 (0.9) | 92 |
| 4. In patients with suspected TAK, MRI to investigate mural inflammation or luminal changes should be used as the first imaging test to make a diagnosis of TAK. | 3 | 9.5 (0.8) | 96 |
| 5. FDG-PET, CT or ultrasound may be used as alternative imaging modalities in patients with suspected TAK. Ultrasound is of limited value for assessment of the thoracic aorta. | 3 (CT) and 5 (PET and US) | 9.7 (0.6) | 100 |
| 6. Conventional angiography is not recommended for the diagnosis of GCA or TAK as it has been superseded by the previously mentioned imaging modalities. | 5 | 9.8 (0.5) | 100 |
| 7. In case of a suspected relapse of GCA or TAK, particularly when laboratory markers of disease activity are unreliable, ultrasound, FDG-PET or alternatively MRI may be considered for the assessment of vessel abnormalities. Imaging is not routinely recommended for patients in clinical and biochemical remission. | 5 | 9.3 (1.4) | 88 |
| 8. In patients with GCA or TAK, MRA, CTA or ultrasound of extracranial vessels may be used for long-term monitoring of structural damage, particularly at sites of preceding vascular inflammation. The frequency of screening as well as the imaging method applied should be decided on an individual basis. | 5 | 9.5 (0.9) | 96 |

Numbers in the columns 'LoA' indicate the mean and SD (in parenthesis) of the LoA (assessed on a scale from 0=no agreement to 10=full agreement), and the proportion of task force members with a score of at least 8/10.
The LoE was assessed according to the Oxford Centre for Evidence-Based Medicine 2011 LoE[22]: LoE 1 indicates a systematic review of cross-sectional studies with consistently applied reference standard and blinding; LoE 3 reflects non-consecutive studies, or studies without consistently applied reference standards; LoE 5 indicates mechanism-based reasoning. Downgrading or upgrading of evidence levels is possible as detailed in reference 22.
*FDG-PET is commonly combined with low-dose CT or CTA, optionally with MRI or MRA.
†Cranial arteries: MRI of the head can visualise superficial temporal, posterior auricular, superficial occipital branches and vertebral arteries, and FDG-PET of the head can visualise superficial temporal, facial, maxillary, superficial occipital branches and vertebral arteries.
CTA, CT-angiography; FDG-PET, [$^{18}$F]-fluorodeoxyglucose positron emission tomography; GCA, giant cell arteritis; LoA, level of agreement; LoE, Level of evidence; LV-GCA, large vessel GCA; MRA, MR-angiography; TAK, Takayasu arteritis.

loss. Blindness and other ischaemic complications of GCA tend to occur almost exclusively before initiation of GC therapy.[26] For patients presenting with polymyalgia or systemic symptoms only and in whom GCA is a possible diagnosis, FDG-PET and MRI to detect large vessel involvement might not be available immediately when requested. One study demonstrated that the sensitivity of a FDG-PET for the diagnosis of GCA conducted 72 hours after the start of 60 mg prednisone remained equal to the pretreatment FDG-PET, but dropped to 36% after 10 days of GCs.[27] Similarly, ultrasound of temporal arteries performed within 1 day of GC therapy revealed a significantly higher intima-media thickness (IMT) than scans performed (in different patients) after 1 week.[28] The task force, therefore, concluded that imaging should best be performed before, or at least, within 72 hours after commencing GC therapy.

The task force urged rapid access to diagnostic imaging tests, commensurate with fast-track clinics for patients with suspected GCA.[29–31] While ultrasound has become a point-of-care tool in many of these fast-track services, long waiting lists are still a major limitation of other imaging modalities. The task force was reluctant to define case scenarios where treatment could be withheld until imaging becomes available. This would not only be counterproductive for the development of rapid access pathways for imaging, but would also expose people with GCA to an unnecessary risk of blindness and other ischaemic manifestations, given that not all patients who develop GCA-related visual loss have characteristic symptoms of cranial GCA.[32]

### Overarching principle B

Imaging examination should be done by a trained specialist using appropriate equipment, standardised operational procedures and settings.

Specific training in vasculitis imaging, rather than general training in musculoskeletal or vascular imaging, is pivotal to guarantee high-quality results.[24] A dedicated training curriculum for rheumatologists still has to be defined. According to expert opinion such a curriculum should include teaching about the signs and symptoms of LVV (in order to appropriately estimate the pretest probability of the disease), specific training in vascular ultrasound as well as instructions on how to correctly interpret the results of additional tests, including other imaging modalities. Recommended technical and operational parameters are detailed in box 1.

### Overarching principle C

In patients in whom there is a high clinical suspicion of GCA and a positive imaging result, the diagnosis of GCA may be made without an additional test (biopsy or further imaging). In patients with a low clinical probability and a

## Recommendation

**Box 1 Suggestions for technical and operational parameters on imaging modalities in large vessel vasculitis**

Ultrasound
⇒ High-quality modern equipment is essential. Linear probes are recommended for supra-aortic arteries; sector or convex probes for ascending aorta; convex, sector or linear probes for the aortic arch; and convex or linear probes for abdominal aorta. Settings may vary slightly according to equipment.
⇒ The B-mode frequency should be ≥15 MHz (preferably ≥18 MHz) for temporal arteries and 7–15 MHz for extracranial supra-aortic arteries. Image depth should be 10–20 mm for temporal arteries and 30–40 mm for extracranial supra-aortic arteries.
⇒ The focus should be at the level of the artery. The B-mode gain should be adjusted to avoid anechoic appearance of the artery wall.
⇒ Colour Doppler is the preferred modality to show the blood flow, but other techniques may be used as well. The gain should be adjusted to avoid underfilling or overfilling of the vessel lumen.
⇒ Doppler frequency and pulse repetition frequency (PRF) settings depend on the equipment. Frequencies of 7–12 MHz and 4–8 MHz as well as PRFs of 2–7 KHz and 3–8 KHz are commonly applied for temporal and extracranial supra-aortic arteries, respectively. The colour box should be angled in longitudinal scans to avoid perpendicularity between sound waves and artery.

CT*
⇒ Multislice CT-scanner should be used.
⇒ Collimation 0.6 mm, individual tube voltage and tube current time product determined by automatic dose modulation.
⇒ Reconstruction slice thickness should be between 0.5 and 1.0 mm.
⇒ Patient and CT technology adapted injection of 50–100 mL of non-ionic iodinated contrast agent (≥350 mg/mL) using a power injector (≥4 mL/s).
⇒ Arterial phase: bolus-tracking method (threshold of 100 HU); ECG triggering.
⇒ Venous phase: 50 s after finishing the arterial phase acquisition.
⇒ Angulated reconstructions for assessment of individual vessel segments.

MRI*
Cranial MRI technique**:
⇒ 3.0T MRI scanner, minimum 16-channel head-coil.
⇒ T1w Spin Echo, Gadolinium contrast enhanced, fat-suppressed, high-resolution (in-plane<1 $mm^2$, eg, 195×260 $\mu m^2$, slice thickness 3 mm, TR/TE 500/22 ms).
⇒ Transversal slices angulated parallel to skull base.
⇒ Reformatted 3D contrast-enhanced vessel-wall MRI may be considered.

Body MRI technique:
⇒ 1.5 T, preferentially 3.0 T MRI scanner, minimum 16-channel head and neck coil and 16-channel body-coil.
⇒ MR-angiography (MRA) of aorta and major branches from carotid bifurcation to abdominal and preferentially pelvic arteries in coronal acquisition to include axillary and brachial arteries → detection of vessel lumen (stenosis, occlusion, aneurysm).

Continued

**Box 1 Continued**

⇒ T1w, fat-suppressed, contrast enhanced, black blood imaging (eg, navigated 3D Turbo Spin Echo (TSE), spatial resolution 1.2×1.3×2 $mm^3$, Repetition Time (TR) / Echo Time (TE) 1000/35 ms) → assessment of mural inflammation.

[$^{18}$F]-fluorodeoxyglucose positron emission tomography (FDG-PET)***
⇒ Position of patient is supine, position of the arms should be arms down.
⇒ Body parts to include: from top of head to at least mid-thigh, preferably to below the knees.
⇒ Blood glucose levels: preferred <7 mmol/L (126 mg/dL), <10 mmol/L (180 mg/dL) acceptable.
⇒ Interval between FDG infusion and image acquisition should be at least 60 min, preferably 90–120 min.
⇒ For evaluation of the cranial arteries, 5 min instead of 2–3 min acquisition time of the head should be used in case of non-digital FDG-PET imaging.
⇒ Scoring of [$^{18}$F]-FDG-uptake: qualitative visual grading; if result is unclear, compare it to the liver background (grading 0–3).
⇒ Digital FDG-PET may be used in order to reduce imaging time, radiation dose and to improve the image quality.
⇒ FDG-PET is commonly combined with low-dose CT, optionally with CT-angiography (CTA). It can also be combined with MRI or MRA.

*CT and MRI also refer to specific angiography techniques such as CTA and MRA.
**MRI of the head can visualise superficial temporal, posterior auricular, superficial occipital branches and vertebral arteries.
***FDG-PET of the head can visualise superficial temporal, facial, maxillary, superficial occipital branches and vertebral arteries.

negative imaging result, the diagnosis of GCA can be considered unlikely. In all other situations (including the case of an inconclusive imaging result), additional efforts towards a diagnosis are necessary.

This statement is unchanged from the 2018 version.[3] It remains at the discretion of the clinician to determine the pretest probability for GCA, considering all available clinical and laboratory data. The precision of the pretest estimates depends largely on the experience of the clinician, which may (similar to imaging) be improved by specific training. A probability score combining demographic, clinical and laboratory parameters, as well as respective cut-offs defining low, intermediate and high probability for GCA has been proposed and initially validated by several centres[33–35]; however, this awaits further experience.

The present recommendation emphasises the dependence of the (post-test) diagnosis on the pretest probability and the imaging test result. While in clinical practice, a global report of the imaging exam is usually provided ('positive'/'negative'), the confidence in this result may vary. For instance, there is a lower confidence in a positive result for patients in whom a limited vessel wall thickening was documented compared with those with extensive swelling of several vessels. If imaging results are inconclusive, such as when wall thickness is only slightly above the normal cut-off or when arteriosclerosis complicates the assessment, additional testing is necessary to establish or exclude GCA. This is also the case if positive imaging occurs in situations with low

pretest probability. Additional testing is also important if GCA mimickers are suspected.[36] In some diseases such as granulomatosis with polyangiitis, lymphoma or amyloidosis, imaging abnormalities similar to those found in GCA have been described; relevant differential diagnoses need therefore to be excluded on clinical grounds, by laboratory exams and/or histology.[37–40]

## Recommendations

### Recommendation 1

Ultrasound of temporal and axillary arteries should be considered as the first imaging modality to investigate mural inflammatory changes in patients with suspected GCA.

Ultrasound is the first imaging modality for the diagnosis of GCA because of strong evidence for a high diagnostic value, with a pooled sensitivity from studies with low RoB of 88% and a specificity of 96%, using clinical diagnosis as the reference standard.[11] Furthermore, ultrasound is known for low resource consumption, easy and prompt availability in many institutions and the absence of radiation. Reliability of ultrasound findings has been high among trained experts,[24 41] and it was comparable to that of reading biopsies by pathologists.[25] The task force chose the term 'should be considered' rather than 'should be used' acknowledging that rapid conduction of ultrasound is not feasible in every setting, particularly in non-tertiary hospitals, and that not all specialists diagnosing GCA have sufficient training in this technique. In these situations, other imaging techniques can be used (see outlined below) and TAB is also an adequate alternative.[3]

While in 2018, a distinction was made between cranial and extracranial phenotypes, and ultrasound was recommended in first place for the former subset,[3] the task force now recognised that GCA represents a single disease spectrum with overlapping phenotypes.[42] Overall, 35%–80% of patients with dominant 'cranial' manifestations have large vessel involvement in imaging studies, and patients with predominantly 'extracranial' manifestations at disease onset might develop cranial disease at later stages.[43–45] The assessment of axillary arteries is now recommended for every patient with suspected GCA as it increases the diagnostic yield and can serve as a baseline for the comparison with possible future examinations. Studies (particularly with low RoB) investigating both temporal and axillary arteries revealed consistently higher sensitivities than those focusing on temporal arteries only.[11] In situations where a scan of temporal and axillary arteries is non-diagnostic, and the clinical suspicion for GCA is still high, additional vessels such as facial, occipital, carotid, vertebral, subclavian and femoral arteries as well as the aorta can be investigated.[46–49]

Ultrasound composite scores have recently been proposed for diagnostic and monitoring purposes in GCA.[50 51] One of these, the Southend score, positively correlated with the diagnostic specificity for GCA, and patients with higher scores were more likely to have positive TAB and visual complications than patients with lower scores.[50 52] The provisional OMERACT ultrasonography score (OGUS) has been developed for the follow-up of patients in research studies and will be described below.[51] Despite these interesting developments, the task force was reluctant to recommend any ultrasound composite score at this stage outside the research setting, encouraging their further validation.

The broad description 'mural inflammatory changes' was used in the update, rather than the term 'non-compressible halo sign' stipulated in the original recommendations.[3] The compression sign for axillary and other extracranial arteries has not been tested in clinical studies so far, and patients with a new diagnosis of GCA may reveal signs of chronic vasculitis (eg, when GCA is newly diagnosed in a patient with long-standing PMR). The ultrasound appearance of chronic vasculitis has recently been described as 'mid-hyperechoic wall thickening with a multilinear pattern' that can clearly be distinguished from the 'halo' sign that is described as homogenous, hypoechoic wall thickening reflecting acute inflammation.[53 54] Cut-off values for the thickness of the intima-media complex have been proposed for follow-up studies (common superficial temporal artery 0.42–0.44 mm, parietal branch 0.29–0.36 mm, frontal branch 0.34 mm, axillary artery 1.0 mm (0.9 mm for chronic vasculitis)).[55–58] They may also aid in distinguishing normal from acute or chronic vasculitis; however, further studies are required to validate these values, particularly in people with advanced age or with severe arteriosclerosis.[59–61]

### Recommendation 2

High-resolution MRI or FDG-PET can be used as alternatives to ultrasound for the assessment of cranial arteries in patients with suspected GCA.

In the original recommendation,[3] the use of FDG-PET and CT were discouraged for the assessment of cranial arteries as there was insufficient evidence to suggest that these vessels were visible by these techniques. Since then, a number of studies supported the utility of FDG-PET for the diagnosis of temporal arteritis, and clinical experience indicates the potential visualisation of superficial cranial vessels by CT.[4 5 62] This technique, however, was not included in the updated recommendation because of the absence of prospective data.

The task force decided to maintain separate recommendations for cranial and extracranial arteries concerning MRI and FDG-PET. The evidence supports the use of high-resolution MRI for cranial arteries, with a pooled sensitivity of 81% and a specificity of 98% (studies with low RoB) using clinical diagnosis as reference standard,[11] while for FDG-PET, studies were mainly conducted to assess extracranial (and only to a lesser extent cranial) vessels. FDG-PET of cranial and extracranial arteries yielded a pooled sensitivity of 76% and a specificity of 95% (studies with low RoB) applying clinical diagnosis as reference standard.[11] The advantages of MRI and FDG-PET over ultrasound are a higher standardisation of data acquisition and the possibility to investigate multiple vessels at the same time. The main limitations are the restricted availability, high costs and possible adverse effects of contrast agents (MRI) and radiation (FDG-PET).[63]

It could be argued that MRI should still be preferred over FDG-PET to image cranial vessels given that at this site, MRI is supported by a higher number of studies. In addition, MRI does not imply radiation and, in some centres, it is available at lower costs.[11] Rapid availability of MRI, as specified in our overarching principles, is still restricted to a small number of centres with a special interest in the field. However, our recommendations might encourage the development of fast-track imaging pathways, including MRI or FDG-PET organised within a few days, ideally within 72 hours of commencing GC therapy.[27]

### Recommendation 3

FDG-PET, alternatively MRI or CT, can be used for the detection of mural inflammation or luminal changes of extracranial arteries in patients with suspected GCA.

## Recommendation

FDG-PET should be considered the first imaging alternative to ultrasound of extracranial vessels because of evidence supporting a high diagnostic value (sensitivity 76%, specificity 95%, clinical diagnosis as reference standard),[11] and the possibility of detecting other serious pathologies such as infections or tumours, particularly in patients with atypical symptoms.[5] Although prospective evidence for the performance of MRI and CT of extracranial vessels is scarce,[19] some members of the task force reported their clinical experience that these techniques may be valid alternatives to ultrasound and FDG-PET when these are not available or inadequate. We intentionally listed CT as last in the list of recommended imaging modalities because there is no evidence that CT performs better than MRI in this indication, but exposes the patient to radiation.[64] On the other hand, there might be practical reasons why CT is preferred in certain situations such as the lower acquisition time and shorter waiting lists.

Direct comparisons between imaging modalities are scarce. One study reported that ultrasound of temporal arteries revealed a higher sensitivity than FDG-PET, while FDG-PET performed better at subclavian and carotid arteries.[65] At axillary arteries, ultrasound detected 76% of cases with vasculitis using FDG-PET as reference.[66] Another study concluded that in patients with LVV, FDG-PET better captures inflammatory activity, while MRI is better suited to assess disease extent.[67] These studies were not included in the SLR because of their case–control design, and their results need to be confirmed by prospective cohort studies before conclusions can be applied to clinical practice.

FDG-PET is usually combined with low-dose CT (or CTA) and optionally with MRI/MRA.[68] The evaluation of luminal changes is therefore possible with FDG-PET, however, MRA or CTA (without FDG-PET) may be sufficient for this indication.[67] A prospective comparison between MRA and CTA for the evaluation of arterial stenoses or aneurysms in GCA has not been conducted so far, and therefore, this aspect has been added to the research agenda.

### Recommendation 4

In patients with suspected TAK, MRI to investigate mural inflammation or luminal changes should be used as the first imaging test to make a diagnosis of TAK.

### Recommendation 5

FDG-PET, CT or ultrasound may be used as alternative imaging modalities in patients with suspected TAK. Ultrasound is of limited value for assessment of the thoracic aorta.

### Recommendation 6

Conventional angiography is not recommended for the diagnosis of GCA or TAK as it has been superseded by the previously mentioned imaging modalities.

Recommendations 4–6, which concern the use of imaging methodologies for the diagnosis of TAK, remain largely unchanged compared with the 2018 version given the absence of new prospective data.[3] MRI is preferred over the other imaging modalities for the diagnosis of TAK because of the absence of radiation (taking into account that serial imaging is required in many patients) and because of the ability to investigate several vessels simultaneously, including the aorta. The descending thoracic aorta, which is frequently affected in patients with TAK, is not accessible to conventional ultrasound. Whether transoesophageal echocardiography, enabling a comprehensive assessment of the thoracic aorta, is helpful in these patients needs to be studied further.[69] The task force emphasised that conventional angiography is indicated for vascular interventions rather than for diagnosis. It should be conducted in a quiescent phase of the disease.[7]

### Recommendation 7

In case of a suspected relapse, particularly when laboratory markers of disease activity are unreliable, ultrasound, FDG-PET or alternatively MRI may be considered for the assessment of vessel abnormalities. Imaging is not routinely recommended for patients in clinical and biochemical remission.

Since the publication of the 2018 recommendations, several new studies have become available investigating the value of ultrasound and FDG-PET for the assessment of GCA patients during follow-up, and to a lesser extent of patients with TAK.[11] Two major ultrasound composite scores have been developed, the Southend score and the OGUS. Both include eight arterial segments (bilateral common, frontal and parietal branches of temporal arteries and axillary arteries) with semiquantitative (0–3) or quantitative scoring of each segment, respectively.[50 51] For FDG-PET, the PET Vascular Activity Score or Total Vascular Score have mostly been used, which evaluate nine (ascending, descending thoracic and abdominal aorta, aortic arch, brachiocephalic, bilateral carotids and subclavian arteries) or twelve (thoracic aorta, abdominal aorta, subclavian arteries, axillary arteries, carotid arteries, iliac arteries and femoral arteries) vascular territories, respectively, on a semiquantitative scale (0–3).[70 71] Most studies applying these imaging composite scores revealed a good sensitivity to change as well as moderate correlations with markers of disease activity.[11 72] No new studies were available for MRI in this regard.

Despite these important advances, the task force concluded that evidence is not strong enough to recommend imaging-based follow-up assessment of inflammation in all patients with LVV. Particularly, there are no studies demonstrating the added value of regular imaging of patients with GCA or TAK over clinical and laboratory monitoring alone. A specific situation in which imaging can be useful is the case of non-specific symptoms with increased inflammatory markers, or the occurrence of a new ischaemic event/worsening of disease-related ischemia. Another example is the evaluation of a possible relapse in patients treated with drugs blocking the interleukin-6 pathway, given that ESR and CRP are not clinically informative in these patients. The GUSTO trial, not included in the SLR because <20 patients were recruited, demonstrated an improvement of the IMT assessed by ultrasound after GC pulse therapy and subsequent worsening of the IMT once GCs were stopped.[73 74] During treatment with tocilizumab, which was started immediately after GC pulses, IMT gradually decreased.

Another indication for imaging is the identification of the disease subtype in TAK.[75] During the follow-up of patients with GCA or TAK, imaging could be used for the stratification of disease such as the identification of the number of vessels involved (including the aorta) and the graduation of inflammation at the single vessel, particularly in patients with refractory or relapsing disease.[42] An imaging composite score might be valuable for this purpose; however, all available imaging-based scores require further validation. Besides, imaging scores are used in a research setting, but have not yet been demonstrated to add value in daily clinical practice.[50 51 76–78]

Imaging is not routinely recommended to evaluate vascular inflammation in patients in clinical remission. Nevertheless, the interpretation of imaging results obtained at the time of a

suspected relapse can be facilitated by the comparison with a previous imaging examination, which also includes an assessment conducted at the time of inactive disease. The main reason for the reluctance of the task force to recommend imaging in patients in remission is the unclear clinical significance of persistent imaging abnormalities (reported by several studies), and whether these should lead to a change in treatment.[70 77 78] Some studies indicate that the risk of a clinical relapse is associated with the intensity of FDG-PET uptake in remission,[71] however, others did not confirm these findings.[70 79]

Another point of discussion was whether worsening of existing or new damage (eg, a new stenosis) may support the clinical suspicion of relapse. While this might sound intuitive, the question of whether pre-existing damage might progress independently of active inflammation is unclear yet; hence, this aspect has been added to the research agenda.

### Recommendation 8

In patients with GCA or TAK, MRA, CTA or ultrasound of extracranial vessels may be used for long-term monitoring of structural damage, particularly at sites of preceding vascular inflammation. The frequency of screening as well as the imaging method applied should be decided on an individual basis.

The key modification of this recommendation is the incorporation of the concept that vascular damage mainly occurs at sites of preceding vascular inflammation.[3] This suggestion is based on the results of one study of 32 GCA and 28 TAK patients, reporting that 80% of territories subsequently developing angiographic changes (stenosis or aneurysms) during follow-up displayed a significant FDG-uptake at baseline.[80] On the other hand, 92% of territories with baseline FDG-PET activity did not yield angiographic changes over time. The present statement should therefore not be understood as a recommendation to perform vascular screening by FDG-PET in every GCA or TAK patient at baseline given the absence of data on the cost-effectiveness of such an approach.

The term 'vascular damage' relates to all types of vascular structural deformities identified by imaging including stenosis, occlusion, dilatation and/or aneurysms, as well as arteriosclerosis and fibrosis. Aortic dilatation appears to be more common in patients with GCA than in the general population.[81 82] Mortality in GCA is increased in patients with aortic aneurysm and dissection as compared with those without.[83] Risk factors for aortic dilatation are male sex, hypertension, smoking history and imaging evidence of aortitis according to some studies,[81 84] while others found aneurysms more frequently among females aged under 70 years and positive TAB.[82] Despite the increased risk of aneurysm development, it is still unclear how many GCA patients need to be screened to prevent one additional rupture/dissection or to detect one additional aneurysm requiring surgery.[85–87] Another point of uncertainty is the frequency and minimum duration of screening, given that aortic dilatation may develop several years after GCA onset despite prolonged clinical remission.[82 87] Routine assessment of all patients for damage is therefore not recommended; the task force suggests, as in 2018, to screen patients with signs or symptoms of stenosis/occlusion or aneurysms for damage, as well as those with recurrent or persistent inflammation of large arteries including the aorta.

No recommendation was made on the value of imaging modalities for outcome prediction of patients with established GCA. The SLR retrieved five studies (three on ultrasound, two on FDG-PET) indicating that baseline imaging did neither predict response to treatment, nor occurrence of relapses or ischaemic complications.[11]

None of the items listed in the research agenda published in 2018 has been sufficiently filled with evidence.[3] Based on the points of discussion during the current task force meeting, a research agenda has been proposed addressing new aspects that have emerged since the publication of the original imaging recommendations (see box 2).

## DISCUSSION

The EULAR recommendations for the use of imaging in LVV in clinical practice have been updated into a set of three overarching principles and eight recommendations. This update led to important changes in some statements from the original recommendations, particularly concerning the investigation of axillary arteries by ultrasound in patients with suspected GCA, the use of FDG-PET for the diagnosis of GCA and the use of imaging for the assessment of patients with GCA or TAK during follow-up.[3] As emphasised in 2018 and also in this manuscript, it is not the intention of the EULAR imaging recommendations to dismiss the role of TAB in GCA; however, when imaging is rapidly available and reveals clear signs that are in concordance with the clinical picture, the added value of performing a TAB is uncertain. In such situations, TAB would expose patients to an unnecessary, although small, risk of complications from the surgical procedure as well as to unnecessary GC treatment until histology results become available.[88] In contrast, the 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of GCA and TAK recommended that TAB should be the primary diagnostic test in GCA.[12] The ACR committee argued that 'rheumatologists and radiologists in the USA are less experienced in using ultrasound to diagnose temporal artery involvement in GCA compared with their counterparts in Europe'. This raises the question whether recommendations should reflect current reality or whether they can be aspirational and be used to promote a change of clinical routine, particularly when the supporting evidence is strong.[11]

The value of imaging for monitoring was one of the topics that were discussed most during the meeting. The task force recognised the need for new objective markers of inflammation in GCA and TAK, given that several new drugs directly influence acute phase reactants rendering them unreliable for the assessment of disease activity.[89] Studies investigating clinical+imaging-based monitoring in comparison to clinical monitoring alone, currently lacking, have therefore a high priority on the current research agenda. Another hot topic was the assessment of vascular damage during follow-up. While it is generally agreed that vascular damage including aortic dilatation is more common in patients with GCA than in the general population, it is less clear how many emergency surgical interventions or deaths from dissections can be prevented if regular imaging is conducted.[82] A related question is to what extent relapsing PMR with constitutional symptoms may be a reservoir for LV-GCA and unexplored vascular damage.[10 42] Other aspects that arose during the discussion were the value of imaging for treat-to-target strategies in GCA and TAK, the value of imaging for the assessment of treatment response in GCA, the role of artificial intelligence in evaluating images from vasculitis patients and the value of contrast-enhanced ultrasound for the assessment of vascular inflammation.[50 51 90–93] These aspects have been added to the research agenda which should stimulate investigators to address the numerous open questions in the field.

**Box 2 Research agenda**

⇒ To investigate and compare the value of imaging composite scores (total scores, (semi)quantitative (cut-off) scores, number of involved vessels, cranial vs extracranial vessels) for diagnosis, monitoring and prognosis of giant cell arteritis (GCA) and Takayasu arteritis (TAK).
⇒ To investigate the prognostic value of positive imaging findings in patients in clinical and biochemical remission, value of repeated imaging for comparison of imaging findings in remission and relapse.
⇒ To better investigate the added value of 'optical coherence tomography' and 'fluorescein angiography' for diagnosis and prognosis of GCA.
⇒ To investigate the value of ultrasound of all supra-aortic vessels as compared with the assessment of the axillary artery only, in addition to the temporal arteries.
⇒ To investigate the value of assessing the aorta for vasculitic involvement in patients with imaging evidence of cranial vasculitis versus extracranial vasculitis.
⇒ To investigate the timing at which imaging should be conducted to detect vessel wall damage.
⇒ To study the role of artificial intelligence in the assessment of large vessel vasculitis by various imaging methods.
⇒ To study positron emission tomography (PET) with novel tracers such as ligands targeting immune cells.
⇒ To study the influence of sodium-glucose cotransporter-2 inhibitors on [$^{18}$F]-fluorodeoxyglucose-PET results.
⇒ To investigate the value (short-term and long-term outcomes) of imaging in addition to clinical monitoring versus clinical monitoring only.
⇒ To investigate the value of imaging in a treat-to-target approach in GCA and TAK.
⇒ To investigate the value of imaging for response assessment and correlation with patient-reported outcomes in GCA and TAK.
⇒ To investigate the association of imaging results with novel laboratory biomarkers in GCA and TAK.
⇒ To define remission of imaging results in GCA and TAK.
⇒ Validate cut-off values for intima–media thickness at several vessels in special patient populations such as those at advanced age or with severe arteriosclerosis.
⇒ To compare the performance of MR-angiography and CT-angiography for the evaluation of arterial stenoses and aneurysms in GCA and TAK.
⇒ To study the value of echocardiography (transthoracic and transoesophageal) for the diagnosis and follow-up of aortitis.
⇒ To investigate the optimal frequency and modality to screen for vascular damage in GCA and TAK patients; to identify predictors of vascular damage.
⇒ To determine the added value of very high-resolution ultrasound (≥50 MHz) of temporal arteries.
⇒ To calculate the number of patients needed to screen with imaging for preventing one additional aortic complication (aneurysm or dissection).
⇒ To investigate the sensitivity and specificity of imaging to detect ongoing or relapsing inflammation versus remodelling or structural damage of vessels.
⇒ To study the association between the progression of vascular damage and imaging detected inflammation, particularly whether inflammatory lesions at the aorta and other large arteries progress to structural damage once they are resolved.
⇒ To test imaging as an outcome tool in randomised controlled trials.

The voice of the patient representative (the second could not participate due to health reasons) was critical in the formulation of some recommendations. She particularly emphasised the importance of early treatment for patients with suspected LVV rather than withholding therapy until all diagnostic tests have been concluded. Also, the need for training of physicians and broad availability of imaging techniques, particularly ultrasound, were other important points emphasised by the task force.

A limitation of these recommendations is their restriction to GCA and TAK, excluding other types of LVV such as (vascular) Behçet's disease, IgG4-related disease or LVV secondary to rheumatoid arthritis or other rheumatic diseases. Another limitation is circular reasoning in some diagnostic studies, meaning that the imaging result was used (at least in part) by the clinician to establish the final diagnosis. While this is sometimes unavoidable because of the uncertainty related to the clinical diagnosis, it might lead to an overestimation of the value of the imaging technique. We, therefore, conducted subanalyses excluding studies with circular reasoning to confirm the robustness of the primary results.[11] Virtually no new evidence has been generated for the use of imaging in TAK, consequently, the respective recommendations remained largely unchanged.[11] Despite these limitations, we believe that the updated recommendations represent a step forward towards a better diagnosis and follow-up of patients with GCA and TAK.

Implementation of these recommendations is another critical step, as also emphasised by an EULAR initiative on the implementation of recommendations.[94] We plan to present and discuss the updated recommendations at national and international conferences, and to continue promoting training courses in imaging for these diseases at a national and international level. Anchoring imaging in training curricula for rheumatologists would also be a fundamental step to ensure implementation of these recommendations in practice. In addition, we envision adaption of the recommendations to the local requirements, promoted by our task force members residing in different EULAR countries. We plan to assess possible barriers and facilitators to identify points for improvement. The lack of availability of technical equipment, specifically high-end ultrasound machines in the rheumatology outpatient clinics, might be an important barrier to implementation, and we hope that these recommendations will help to convince payors that adequate equipment is required to deliver high-quality care to patients with suspected GCA and TAK. The delay between the clinical consultation and the conduction of imaging as well as the percentage of patients with suspected LVV undergoing imaging might be important quality indicators for the level of implementation of these recommendations.

In summary, three overarching principles and eight recommendations are available to guide the use of imaging for the diagnosis and follow-up assessment of GCA and TAK in clinical practice. These recommendations are based on evidence and expert consensus. The research agenda is also an important product of this work, highlighting the gaps of knowledge and areas for further studies. The next update is expected to be

undertaken when sufficient new evidence has become available on imaging in LVV. It is our vision that these recommendations standardise and optimise the use of imaging in the diagnosis and assessment of people living with GCA and TAK.

**Author affiliations**
[1]Department of Rheumatology and Immunology, Medical University of Graz, Graz, Austria
[2]Department of Rheumatology, Teaching Hospital of the Paracelsius Medical University, Brunico Hospital (ASAA-SABES), Brunico, Italy
[3]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[4]Department of Rheumatology, Zuyderland Medical Centre Heerlen, Heerlen, The Netherlands
[5]Department of Rheumatology, Centro Hospitalar Universitario Lisboa Norte EPE, Lisboa, Portugal
[6]Rheumatology Research Unit, Instituto de Medicina Molecular, Lisboa, Portugal
[7]Leeds Institute for Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK
[8]NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[9]Diagnostic and Interventional Radiology, University Medical Center, Wuerzburg, Germany
[10]Clinical Department of General Internal Medicine Department, Research Department of Microbiology and Immunology, Laboratory of Clinical Infectious and Inflammatory Disorders, University Hospitals Leuven, Leuven, Belgium
[11]General Internal Medicine Department, Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium
[12]Department of Medicine, Karolinska Institutet, Stockholm, Sweden
[13]Department of Gastroenterology, Dermatology and Rheumatology, Karolinska University Hospital, Stockholm, Sweden
[14]Department of Internal Medicine, Division of Rheumatology, Hacettepe Universitesi Tip Fakultesi, Ankara, Turkey
[15]Patient Representative, Leicester, UK
[16]Department of Autoimmune Diseases, Hospital Clínic, University of Barcelona. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[17]Department of Rheumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[18]Rheumatology, Southend University Hospital NHS Foundation Trust, Basildon, UK
[19]Anglia Ruskin University, Chelmsford, UK
[20]Department of Rheumatology, Aarhus Universitetshospital, Aarhus, Denmark
[21]Department of Medicine, Regional Hospital Horsens, Horsens, Denmark
[22]Department of Rheumatology, La Paz University Hospital, Madrid, Spain
[23]Department of Internal Medicine, Division of Rheumatology, Marmara University School of Medicine, Istanbul, Turkey
[24]Department of Internal Medicine, Clinical Division of Internal Medicine II, Medical University of Innsbruck, Innsbruck, Austria
[25]Department of Rheumatology, University Medical Centre, Ljubljana, Slovenia
[26]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia
[27]Department of Rheumatology, Cochin Hospital, Assistance Publique Hôpitaux de Paris, Paris, France
[28]INSERM (U1153) Center of Research in Epidemiology and Statistics (CRESS), Université Paris-Cité, Paris, France
[29]Clinic of Internal Medicine III, Section Rheumatology and Clinical Immunology, University Hospital Bonn, Bonn, Germany
[30]Department of Rheumatology and Immunology, Inselspital, University Hospital Bern, University of Bern, Bern, Switzerland
[31]Medical Imaging Centre, Department of Nuclear Medicine and Molecular Imaging, University Medical Center, Groningen, The Netherlands
[32]Department of Biomedical Photonic Imaging, Universiteit Twente, Enschede, The Netherlands
[33]Department of Rheumatology, Immanuel Krankenhaus Berlin, Medical Centre for Rheumatology Berlin-Buch, Berlin, Germany

**X** Sofia Ramiro @sofiaramiro82, Philipp Bosch @philipp_j_bosch, Cristina Ponte @cristinadbponte, Sarah Louise Mackie @Sarah_L_Mackie, Ertugrul Cagri Bolek @ertugrul_cagri, Juan Molina-Collada @jmolinacollada, Bhaskar Dasgupta @profbdasgupta and Anna Molto @annamolto

**Acknowledgements** The authors would like to thank Louise Falzon for her work in the development of the literature search strategy. We also thank Lorna Neill, Luca Cimino and Fabrizio Gozzi for their help with the update of the PICO questions.

**Contributors** All authors were involved in the discussion and formulation of the recommendations. CDejaco wrote the first version of the manuscript. All authors reviewed it and made extensive comments and appropriate changes to it. All authors approved the final version of the manuscript.

**Funding** Funding was provided by the European Alliance of Associations for Rheumatology (Project number: QoC13).

**Disclaimer** The views expressed in this article are those of the authors and not necessarily those of the NIHR, the NIHR Leeds Biomedical Research Centre, the National Health Service or the UK Department of Health and Social Care.

**Competing interests** CDejaco has received consulting/speaker's fees from Abbvie, Eli Lilly, Janssen, Novartis, Pfizer, Roche, Galapagos, Sparrow and Sanofi; grant support from AbbVie and Novartis, all unrelated to this manuscript. He is an editorial board member of ARD. SR has received research grants and/or consultancy fees From AbbVie, Eli Lilly, Galapagos, MSD, Novartis, Pfizer, Sanofi, UCB. MB: consultancy fees from AbbVie PB has received speaker fees by Janssen and project grants by Pfizer. CP has received research grants and/or consultancy fees from AbbVie, Vifor, Roche, GlaxoSmithKline and AstraZeneca, all unrelated to this manuscript. SLM reports: Consultancy on behalf of her institution for Roche/Chugai, Sanofi, AbbVie, AstraZeneca; Investigator on clinical trials for Sanofi, GSK, Sparrow; speaking/lecturing on behalf of her institution for Roche/Chugai, Vifor, Pfizer and Novartis; chief investigator on STERLING-PMR trial, funded by NIHR; patron of the charity PMRGCAuk. No personal remuneration was received for any of the above activities. Support from Roche/Chugai to attend EULAR2019 in person and from Pfizer to attend ACR Convergence 2021 virtually. SLM is supported in part by the NIHR Leeds Biomedical Research Centre. TAB reports research grants from Deutsche Forschungsgemeinschaft (DFG) and Siemens Healthineers on behalf of his Department. He has received consulting/speaker's fees from BioTel Research, Chugai, Guerbet, Novartis, Roche, Sanofi and Siemens Healthineers. DB consultancy fees from Roche and GSKSara Brolin: Grant from Novartis. MCC has received consulting fees from GSK, SCL-Vifor, AbbVie, AstraZeneca and Janssen, and a research grant form Kiniksa Pharmaceuticals. JM-C has received consulting/speaker's fees from Abbvie, Lilly, Janssen, Novartis, Pfizer, UCB, MSD, all unrelated to this manuscript. BD has received consultancies and educational grants from Novartis, Abbvie, Roche, Chugai, Sanofi. BDN has received consulting/speaker's fees from Roche and Novartis all unrelated to this manuscript. EDM Research funding/consulting and conferences fees from: Abbvie, Novartis, Pfizer, Roche, Janssen, Lilly, MSD, BMS, UCB, Grunental and Sanofi. CDuftner has received consulting/speaker's fees from Abbvie, AOP Orphan, Astra-Zeneca, Bristol-Myers-Squibb, Eli-Lilly, Janssen, Galapagos, Merck-Sharp-Dohme, Novartis, Pfizer, Roche, Sandoz, UCB, Vifor, and grant/research support from Eli-Lilly, Pfizer, UCBHaner Direskeneli is investigator in clinical trials for Abbvie and Novartis, had educational support from Pfizer, Amgene, Celltrion, UCB and Roche unrelated to this manuscript. AM has received research grants and/or consultancy fees From AbbVie, BMS, Biogen, Eli Lilly, Galapagos, Janssen, MSD, Novartis and UCB. LS has received grant support from the Swiss Society of Rheumatology, iQone and Sandoz and support for travel expenses from Sanofi; all unrelated to this manuscript. RHJAS has received independent research grants of Siemens Healtineers and WAS has received consultancy fees, honoraria and travel expenses from Abbvie, Chugai, GlaxoSmithKline, Medac, Novartis, Roche, and Sanofi and is principal investigator in trials sponsored by Abbvie, GlaxoSmithKline, Novartis and Sanofi.

**Patient and public involvement statement** Patient research partners were involved in the design, conduct, reporting, and dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.



**ORCID iDs**
Christian Dejaco http://orcid.org/0000-0002-0173-0668
Sofia Ramiro http://orcid.org/0000-0002-8899-9087
Milena Bond http://orcid.org/0000-0002-5400-2955
Philipp Bosch http://orcid.org/0000-0002-6783-6422
Cristina Ponte http://orcid.org/0000-0002-3989-1192
Daniel Blockmans http://orcid.org/0000-0001-9783-1780
Sara Brolin http://orcid.org/0000-0002-1815-6033
Ertugrul Cagri Bolek http://orcid.org/0000-0003-3886-2813
Maria C Cid http://orcid.org/0000-0002-4730-0938
Juan Molina-Collada http://orcid.org/0000-0001-5191-7802
Bhaskar Dasgupta http://orcid.org/0000-0002-5523-6534
Eugenio De Miguel http://orcid.org/0000-0001-5146-1964
Haner Direskeneli http://orcid.org/0000-0003-2598-5806
Christina Duftner http://orcid.org/0000-0003-3137-8834
Alojzija Hočevar http://orcid.org/0000-0002-7361-6549

Anna Molto http://orcid.org/0000-0003-2246-1986
Valentin Sebastian Schäfer http://orcid.org/0000-0002-6591-5936
Wolfgang A Schmidt http://orcid.org/0000-0001-7831-8738

## REFERENCES


1 Berti A, Dejaco C. Update on the epidemiology, risk factors, and outcomes of systemic Vasculitides. *Best Pract Res Clin Rheumatol* 2018;32:271–94.
2 Pugh D, Karabayas M, Basu N, *et al*. Large-vessel vasculitis. *Nat Rev Dis Primers* 2022;7:93.
3 Dejaco C, Ramiro S, Duftner C, *et al*. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis* 2018;77:636–43.
4 Nielsen BD, Hansen IT, Kramer S, *et al*. Simple dichotomous assessment of cranial artery inflammation by conventional 18F-FDG PET/CT shows high accuracy for the diagnosis of giant cell arteritis: a case-control study. *Eur J Nucl Med Mol Imaging* 2019;46:184–93.
5 Sammel AM, Hsiao E, Schembri G, *et al*. Diagnostic accuracy of positron emission tomography/computed tomography of the head, neck, and chest for giant cell arteritis: a prospective, double-blind, cross-sectional study. *Arthritis Rheumatol* 2019;71:1319–28.
6 Nienhuis PH, Sandovici M, Glaudemans AW, *et al*. Visual and semiquantitative assessment of cranial artery inflammation with FDG-PET/CT in giant cell arteritis. *Semin Arthritis Rheum* 2020;50:616–23.
7 Hellmich B, Agueda A, Monti S, *et al*. 2018 update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis* 2020;79:19–30.
8 Misra DP, Singh K, Rathore U, *et al*. The effectiveness of tocilizumab and its comparison with tumor necrosis factor alpha inhibitors for takayasu arteritis: a systematic review and meta-analysis. *Autoimmun Rev* 2023;22:103275.
9 Dasgupta B, Unizony S, Warrington KJ, *et al*. Lb0006 Sarilumab in patients with relapsing Polymyalgia Rheumatica: a phase 3 multicenter, randomized, double blind, placebo controlled trial (Saphyr). *Ann Rheum Dis* 2022;81:210.
10 Tomelleri A, van der GeestKSM, Khurshid MA, *et al*. Disease stratification in giant cell arteritis and polymyalgia rheumatica: state of the art and future perspectives. *Nat Rev Rheumatol* 2023;19:446–59.
11 Bosch P, Bond M, Dejaco C, *et al*. Imaging in diagnosis, monitoring and outcome prediction of large vessel vasculitis: a systematic literature review and meta-analysis informing the 2023 update of the EULAR recommendations. *Ann Rheum Dis* 2023;82:124–5.
12 Maz M, Chung SA, Abril A, *et al*. 2021 American college of rheumatology/vasculitis foundation guideline for the management of giant cell arteritis and takayasu arteritis. *Arthritis Care Res (Hoboken)* 2021;73:1071–87.
13 Mackie SL, Dejaco C, Appenzeller S, *et al*. British society for rheumatology guideline on diagnosis and treatment of giant cell arteritis: executive summary. *Rheumatology (Oxford)* 2020;59:487–94.
14 Haaversen AB, Brekke LK, Bakland G, *et al*. Norwegian society of rheumatology recommendations on diagnosis and treatment of patients with giant cell arteritis. *Front Med (Lausanne)* 2022;9.
15 Ughi N, Padoan R, Crotti C, *et al*. The Italian society of rheumatology clinical practice guidelines for the management of large vessel vasculitis. *Reumatismo* 2022;73.
16 Schirmer JH, Aries PM, Balzer K, *et al*. S2K-Leitlinie: management der Großgefäßvaskulitiden. *Z Rheumatol* 2020;79:67–95.
17 van der Heijde D, Aletaha D, Carmona L, *et al*. Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
18 EULAR council. Standard EULAR procedure (Sops) for recommendation projects. 2022. Available: https://www.eular.org/document/share/228/44d096ad-57d8-45db-bf73-284d6fff4db4 [Accessed 16 Feb 2023].
19 Duftner C, Dejaco C, Sepriano A, *et al*. Imaging in diagnosis, monitoring and outcome prediction of large vessel vasculitis: a systematic literature review and meta-analysis informing the EULAR recommendations. *RMD Open* 2018;4.
20 Whiting PF, Rutjes AWS, Westwood ME, *et al*. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529–36.
21 Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006;144:427–37.
22 OCEBM levels of evidence working group. The Oxford 2011 levels of evidence. 2011. Available: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence
23 De MiguelE, Castillo C, Rodríguez A, *et al*. Learning and reliability of colour doppler ultrasound in giant cell arteritis. *Clin Exp Rheumatol*;27:S53–8.
24 Chrysidis S, Terslev L, Christensen R, *et al*. Vascular ultrasound for the diagnosis of giant cell arteritis: a Reliability and agreement study based on a standardised training programme. *RMD Open* 2020;6.
25 Luqmani R, Lee E, Singh S, *et al*. The role of ultrasound compared to biopsy of temporal arteries in the diagnosis and treatment of giant cell arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study. *Health Technol Assess* 2016;20:1–238.
26 Salvarani C, Cimino L, Macchioni P, *et al*. Risk factors for visual loss in an Italian population-based cohort of patients with giant cell arteritis. *Arthritis Rheum* 2005;53:293–7.
27 Nielsen BD, Gormsen LC, Hansen IT, *et al*. Three days of high-dose glucocorticoid treatment attenuates large-vessel 18F-FDG uptake in large-vessel giant cell arteritis but with a limited impact on diagnostic accuracy. *Eur J Nucl Med Mol Imaging* 2018;45:1119–28.
28 Ponte C, Serafim AS, Monti S, *et al*. Early variation of ultrasound halo sign with treatment and relation with clinical features in patients with giant cell arteritis. *Rheumatology (Oxford)* 2020;59:3717–26.
29 Patil P, Williams M, Maw WW, *et al*. Fast track pathway reduces sight loss in giant cell arteritis: results of a longitudinal observational cohort study. *Clin Exp Rheumatol* 2015;33:S103–6.
30 Diamantopoulos AP, Haugeberg G, Lindland A, *et al*. 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)* 2016;55:66–70.
31 Monti S, Bartoletti A, Bellis E, *et al*. Fast-track ultrasound clinic for the diagnosis of giant cell arteritis changes the prognosis of the disease but not the risk of future relapse. *Front Med (Lausanne)* 2020;7.
32 Baalbaki H, Jalaledin D, Lachance C, *et al*. Characterization of visual manifestations and identification of risk factors for permanent vision loss in patients with giant cell arteritis. *Clin Rheumatol* 2021;40:3207–17.
33 Laskou F, Coath F, Mackie SL, *et al*. A probability score to aid the diagnosis of suspected giant cell arteritis. *Clin Exp Rheumatol* 2019;37 Suppl 117:104–8.
34 Sebastian A, Tomelleri A, Kayani A, *et al*. Probability-based algorithm using ultrasound and additional tests for suspected GCA in a fast-track clinic. *RMD Open* 2020;6.
35 Melville AR, Donaldson K, Dale J, *et al*. Validation of the Southend giant cell arteritis probability score in a Scottish single-centre fast-track pathway. *Rheumatol Adv Pract* 2022;6.
36 Griner PF, Mayewski RJ, Mushlin AI, *et al*. Selection and interpretation of diagnostic tests and procedures. *Ann Intern Med* 1981;94:557–92.
37 Fernández-Fernández E, Monjo-Henry I, Bonilla G, *et al*. False positives in the ultrasound diagnosis of giant cell arteritis: some diseases can also show the halo sign. *Rheumatology (Oxford)* 2020;59:2443–7.
38 Lötscher F, Pop R, Seitz P, *et al*. Spectrum of Large- and medium-vessel vasculitis in adults: neoplastic, infectious, drug-induced, autoinflammatory, and primary immunodeficiency diseases. *Curr Rheumatol Rep* 2022;24:293–309.
39 Seitz L, Seitz P, Pop R, *et al*. Spectrum of large and medium vessel vasculitis in adults: primary vasculitides, arthritides, connective tissue, and fibroinflammatory diseases. *Curr Rheumatol Rep* 2022;24:352–70.
40 Molina Collada J, Ruíz Bravo-Burguillos E, Monjo I, *et al*. Positive ultrasound halo sign of temporal arteries due to amyloidosis. *Rheumatology (Oxford)* 2019;58:2067–9.
41 Schäfer VS, Chrysidis S, Dejaco C, *et al*. Assessing vasculitis in giant cell arteritis by ultrasound: results of OMERACT patient-based reliability exercises. *J Rheumatol* 2018;45:1289–95.
42 Tomelleri A, van der Geest KSM, Sebastian A, *et al*. Disease stratification in giant cell arteritis to reduce relapses and prevent long-term vascular damage. *The Lancet Rheumatology* 2021;3:e886–95.
43 Prieto-González S, Depetris M, García-Martínez A, *et al*. Positron emission tomography assessment of large vessel inflammation in patients with newly diagnosed, biopsy-proven giant cell arteritis: a prospective, case-control study. *Ann Rheum Dis* 2014;73:1388–92.
44 Narváez J, Estrada P, López-Vives L, *et al*. Prevalence of ischemic complications in patients with giant cell arteritis presenting with apparently isolated Polymyalgia Rheumatica. *Semin Arthritis Rheum* 2015;45:328–33.
45 Fernández-Fernández E, Monjo I, Peiteado D, *et al*. Validity of the EULAR recommendations on the use of ultrasound in the diagnosis of giant cell arteritis. *RMD Open* 2022;8.
46 Diamantopoulos AP, Haugeberg G, Hetland H, *et al*. Diagnostic value of color doppler ultrasonography of temporal arteries and large vessels in giant cell arteritis: a consecutive case series. *Arthritis Care Res (Hoboken)* 2014;66:113–9.
47 Chrysidis S, Døhn UM, Terslev L, *et al*. Diagnostic accuracy of vascular ultrasound in patients with suspected giant cell arteritis (EUREKA): a prospective, multicentre, non-Interventional, cohort study. *The Lancet Rheumatology* 2021;3:e865–73.
48 Ješe R, Rotar Ž, Tomšič M, *et al*. The role of colour Doppler Ultrasonography of facial and occipital arteries in patients with giant cell arteritis: a prospective study. *Eur J Radiol* 2017;95:9–12.
49 Palmers P-J, Ameloot K, De Wever W, *et al*. An echocardiographic finding leading to the diagnosis of giant cell arteritis. *Eur Heart J Cardiovasc Imaging* 2013;14.
50 van der Geest KSM, Borg F, Kayani A, *et al*. Novel ultrasonographic halo score for giant cell arteritis: assessment of diagnostic accuracy and association with ocular ischaemia. *Ann Rheum Dis* 2020;79:393–9.
51 Dejaco C, Ponte C, Monti S, *et al*. The provisional OMERACT Ultrasonography score for giant cell arteritis. *Ann Rheum Dis* 2023;82:556–64.
52 van der Geest KSM, Wolfe K, Borg F, *et al*. Ultrasonographic halo score in giant cell arteritis: association with intimal hyperplasia and ischaemic sight loss. *Rheumatology (Oxford)* 2021;60:4361–6.

53 Chrysidis S, Duftner C, Dejaco C, *et al*. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT large vessel vasculitis ultrasound working group. *RMD Open* 2018;4.
54 Schäfer VS, Chrysidis S, Schmidt WA, *et al*. OMERACT definition and reliability assessment of chronic ultrasound lesions of the Axillary artery in giant cell arteritis. *Semin Arthritis Rheum* 2021;51:951–6.
55 Bosch P, Dejaco C, Schmidt WA, *et al*. Ultrasound for diagnosis and follow-up of chronic Axillary vasculitis in patients with long-standing giant cell arteritis. *Ther Adv Musculoskelet Dis* 2021;13.
56 Ješe R, Rotar Ž, Tomšič M, *et al*. The cut-off values for the intima-media complex thickness assessed by colour doppler sonography in seven cranial and aortic arch arteries. *Rheumatology (Oxford)* 2021;60:1346–52.
57 Schäfer VS, Juche A, Ramiro S, *et al*. Ultrasound cut-off values for intima-media thickness of temporal, facial and axillary arteries in giant cell arteritis. *Rheumatology (Oxford)* 2017;56:1632.
58 López-Gloria K, Castrejón I, Nieto-González JC, *et al*. Ultrasound intima media thickness cut-off values for cranial and Extracranial arteries in patients with suspected giant cell arteritis. *Front Med (Lausanne)* 2022;9.
59 De Miguel E, Beltran LM, Monjo I, *et al*. Atherosclerosis as a potential pitfall in the diagnosis of giant cell arteritis. *Rheumatology (Oxford)* 2018;57:318–21.
60 Milchert M, Fliciński J, Brzosko M. Intima-media thickness cut-off values depicting 'halo sign' and potential Confounder analysis for the best diagnosis of large vessel giant cell arteritis by ultrasonography. *Front Med (Lausanne)* 2022;9.
61 Molina-Collada J, López Gloria K, Castrejón I, *et al*. Impact of cardiovascular risk on the diagnostic accuracy of the ultrasound halo score for giant cell arteritis. *Arthritis Res Ther* 2022;24:232.
62 Conway R, Smyth AE, Kavanagh RG, *et al*. Diagnostic utility of computed tomographic angiography in giant-cell arteritis. *Stroke* 2018;49:2233–6.
63 American College of Radiology. ACR manual on contrast media. Available: 2022. https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf [Accessed 16 Feb 2023].
64 European Union Council. Council directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to Ionising radiation, and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom a. 2014. Available: http://data.europa.eu/eli/dir/2013/59/oj
65 Imfeld S, Aschwanden M, Rottenburger C, *et al*. [18F]FDG positron emission tomography and ultrasound in the diagnosis of giant cell arteritis: congruent or complementary imaging methods. *Rheumatology (Oxford)* 2020;59:772–8.
66 Nielsen BD, Hansen IT, Keller KK, *et al*. Diagnostic accuracy of ultrasound for detecting large-vessel giant cell arteritis using FDG PET/CT as the reference. *Rheumatology (Oxford)* 2020;59:2062–73.
67 Quinn KA, Ahlman MA, Malayeri AA, *et al*. Comparison of magnetic resonance angiography and $^{18}$F-fluorodeoxyglucose positron emission tomography in large-vessel vasculitis. *Ann Rheum Dis* 2018;77:1165–71.
68 Laurent C, Ricard L, Fain O, *et al*. PET/MRI in large-vessel vasculitis: clinical value for diagnosis and assessment of disease activity. *Sci Rep* 2019;9.
69 Bezerra Lira-Filho E, Campos O, Lazaro Andrade J, *et al*. Thoracic aorta evaluation in patients with takayasu's arteritis by transesophageal echocardiography. *J Am Soc Echocardiogr* 2006;19:829–34.
70 Blockmans D, de Ceuninck L, Vanderschueren S, *et al*. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. *Arthritis Rheum* 2006;55:131–7.
71 Grayson PC, Alehashemi S, Bagheri AA, *et al*. $^{18}$ F-Fluorodeoxyglucose-positron emission tomography as an imaging biomarker in a prospective, longitudinal cohort of patients with large vessel vasculitis. *Arthritis Rheumatol* 2018;70:439–49.
72 Nielsen BD, Therkildsen P, Keller KK, *et al*. Ultrasonography in the assessment of disease activity in cranial and large-vessel giant cell arteritis: a prospective follow-up study. *Rheumatology (Oxford)* 2023.
73 Seitz L, Christ L, Lötscher F, *et al*. Quantitative ultrasound to monitor the vascular response to tocilizumab in giant cell arteritis. *Rheumatology (Oxford)* 2021;60:5052–9.
74 Christ L, Seitz L, Scholz G, *et al*. Tocilizumab monotherapy after ultra-short glucocorticoid administration in giant cell arteritis: a single-arm, open-label, proof-of-concept study. *The Lancet Rheumatology* 2021;3:e619–26.
75 Hata A, Noda M, Moriwaki R, *et al*. Angiographic findings of takayasu arteritis: new classification. *Int J Cardiol* 1996;54:S155–63.
76 Dashora HR, Rosenblum JS, Quinn KA, *et al*. Comparing semiquantitative and qualitative methods of vascular $^{18}$F-FDG PET activity measurement in large-vessel vasculitis. *J Nucl Med* 2022;63:280–6.
77 Sammel AM, Hsiao E, Schembri G, *et al*. Cranial and large vessel activity on positron emission tomography scan at diagnosis and 6 months in giant cell arteritis. *Int J Rheum Dis* 2020;23:582–8.
78 Quinn KA, Dashora H, Novakovich E, *et al*. Use of 18F-fluorodeoxyglucose positron emission tomography to monitor Tocilizumab effect on vascular inflammation in giant cell arteritis. *Rheumatology (Oxford)* 2021;60:4384–9.
79 Galli E, Muratore F, Mancuso P, *et al*. The role of PET/CT in disease activity assessment in patients with large vessel vasculitis. *Rheumatology (Oxford)* 2022;61:4809–16.
80 Quinn KA, Ahlman MA, Alessi HD, *et al*. Association of 18 F-Fluorodeoxyglucose-positron emission tomography activity with angiographic progression of disease in large vessel vasculitis. *Arthritis Rheumatol* 2023;75:98–107.
81 Robson JC, Kiran A, Maskell J, *et al*. The relative risk of aortic aneurysm in patients with giant cell arteritis compared with the general population of the UK. *Ann Rheum Dis* 2015;74:129–35.
82 Therkildsen P, de Thurah A, Nielsen BD, *et al*. Increased risk of thoracic aortic complications among patients with giant cell arteritis: a nationwide, population-based cohort study. *Rheumatology (Oxford)* 2022;61:2931–41.
83 Aouba A, Gonzalez Chiappe S, Eb M, *et al*. Mortality causes and trends associated with giant cell arteritis: analysis of the French national death certificate database (1980-2011). *Rheumatology (Oxford)* 2018;57:1047–55.
84 Blockmans D, Coudyzer W, Vanderschueren S, *et al*. Relationship between fluorodeoxyglucose uptake in the large vessels and late aortic diameter in giant cell arteritis. *Rheumatology (Oxford)* 2008;47:1179–84.
85 Jud P, Verheyen N, Dejaco C, *et al*. Prevalence and Prognostic factors for aortic dilatation in giant cell arteritis - a longitudinal study. *Semin Arthritis Rheum* 2021;51:911–8.
86 García-Martínez A, Hernández-Rodríguez J, Arguis P, *et al*. Development of aortic aneurysm/dilatation during the followup of patients with giant cell arteritis: a cross-sectional screening of fifty-four prospectively followed patients. *Arthritis Rheum* 2008;59:422–30.
87 García-Martínez A, Arguis P, Prieto-González S, *et al*. Prospective long term follow-up of a cohort of patients with giant cell arteritis screened for aortic structural damage (aneurysm or dilatation). *Ann Rheum Dis* 2014;73:1826–32.
88 Gunawardene AR, Chant H. Facial nerve injury during temporal artery biopsy. *Ann R Coll Surg Engl* 2014;96:257–60.
89 Stone J, Tuckwell K, Dimonaco S, *et al*. Tocilizumab for sustained glucocorticoid-free remission in giant cell arteritis. *N Engl J Med* 2017;377:317–28.
90 Dejaco C, Ramiro S, Touma Z, *et al*. What is a response in randomised controlled trials in giant cell arteritis. *Ann Rheum Dis* 2023;82:897–900.
91 Dejaco C, Kerschbaumer A, Aletaha D, *et al*. Treat-to-target recommendations in giant cell arteritis and Polymyalgia Rheumatica. *Ann Rheum Dis* 2024;83:48–57.
92 Roncato C, Perez L, Brochet-Guégan A, *et al*. Colour doppler ultrasound of temporal arteries for the diagnosis of giant cell arteritis: a multicentre deep learning study. *Clin Exp Rheumatol* 2020;38:120–5.
93 Ding J, Wu D, Han Q, *et al*. Follow-up contrast-enhanced ultrasonography of the carotid artery in patients with takayasu arteritis: a retrospective study. *J Rheumatol* 2022;49:1242–9.
94 Loza E, Carmona L, Woolf A, *et al*. Implementation of recommendations in rheumatic and musculoskeletal diseases: considerations for development and uptake. *Ann Rheum Dis* 2022;81:1344–7.

# DISCUSIÓN

# DISCUSIÓN

## Validez del GIM para el diagnóstico por ecografía de pacientes con ACG

Gracias a la mejora en los equipos de ecografía y al empleo de sondas de muy alta resolución, en los últimos años ha crecido el interés por determinar mediante ecografía el GIM de la pared arterial. Esta medición se ha propuesto como medida adicional a los signos cualitativos clásicos para el diagnóstico de ACG, así como con fines de monitorización. Las últimas recomendaciones EULAR del 2023 sobre el uso de imagen en vasculitis de vaso grande sugieren que la medición del GIM podría ser de utilidad para diferenciar entre arterias normales y aquellas con signos de vasculitis, tanto aguda como crónica (66).

En este sentido, uno de los objetivos de nuestro estudio fue determinar puntos de corte óptimos del GIM, tanto en arterias craneales como en extracraneales, para discriminar entre pacientes con y sin ACG (67). Analizamos un total de 157 pacientes con sospecha de ACG evaluados en una consulta de diagnóstico rápido de ACG, de los cuales 47 (29.9%) fueron diagnosticados clínicamente de ACG tras seis meses de seguimiento. Utilizando el diagnóstico clínico como referencia, la ecografía mostró una sensibilidad del 87.2% para la detección de ACG. Los puntos de corte óptimos del GIM que identificamos para el diagnóstico de ACG fueron: 0,44 mm para la arteria temporal común; 0,34 mm para la rama frontal; 0,36 mm para la rama parietal; 1,1 mm para la arteria carótida y 1 mm para las arterias subclavias y axilares.

Aunque algunos autores han propuesto previamente puntos de corte del GIM para identificar ACG (0,3 mm (56), 0,4 mm (68), 0,5 mm (69) y 1 mm (70) para las arterias temporales; 1.5 mm para las arterias axilares (7)), no han sido desarrollados mediante estudios de validación que incluya pacientes y controles. En 2017 Schäfer et al., publican el primer estudio bien diseñado para determinar puntos de corte del GIM en arterias temporales, faciales y axilares (35). En líneas generales, sus resultados son similares a los de nuestro grupo. Sin embargo, la limitación fundamental es la inclusión de controles sanos en lugar de pacientes con sospecha de ACG, que son los que evaluamos de forma rutinaria en las consultas de diagnóstico rápido. Por otro lado, el uso de sondas de distinta frecuencia (22 MHz en el estudio de Schäfer et al. (35) y 18 MHz en el nuestro (67), puede influir de forma sustancial en la variabilidad de estas mediciones. En un estudio posterior, Czihal et al., proponen un enfoque similar pero en este caso midiendo el grosor de la arteria temporal aplicando el signo de la compresión (lo que equivale a una medición conjunta del GIM superficial y profundo de la arteria) (33). Un punto de corte de 0,7 mm aplicando el signo de la compresión (lo que equivaldría a un GIM aproximado de 0,35 mm) ofrece una sensibilidad del 85% y especificidad del 95% para el diagnóstico de ACG. En el caso de las arterias axilares (donde el signo de la compresión no puede ser aplicado), proponen un punto de corte del GIM de 1.2 mm (sensibilidad 81,3%, especificidad 96,1%). La principal limitación de su estudio es que la determinación del GIM a través del signo de la compresión supone una medida indirecta y, por tanto, aproximada y menos fiable que la medición directa en corte longitudinal como la realizada en nuestro estudio. Por último, Ješe et al. estudian puntos de corte del GIM en distintas regiones arteriales, incluyendo por primera vez, además de las arterias temporales y axilares, las arterias

occipitales, vertebrales, carótidas y subclavias (34). Los resultados son similares para arterias temporales, faciales y occipitales (0,4 mm) y para axilares, subclavias y carótidas (1 mm). Estos autores proponen 0,7 mm como punto de corte para arterias vertebrales. Por último, de Miguel et al. estudian el impacto de la aterosclerosis en el GIM de arterias temporales de sujetos sanos, y proponen un GIM >0,34 mm en al menos 2 segmentos arteriales para minimizar la tasa de falsos positivos (37).

Los resultados de nuestro estudio confirman que la medición del GIM puede ser de utilidad para el diagnóstico de pacientes con ACG y, en general nuestros resultados están en línea con los publicados previamente. Sin embargo, nuestros resultados sugieren usar puntos de corte ligeramente superiores para el tronco común superficial (0,44 mm) y la rama parietal (0,36 mm). Estas diferencias podrían explicarse por el uso de sondas de distinta frecuencia y por la inclusión de diferentes grupos control. Cabe resaltar que en nuestro estudio no se evaluó específicamente el riesgo cardiovascular en el grupo control lo cual también puede haber influido en las pequeñas diferencias observadas.

Entre las limitaciones del trabajo se encuentra el diseño retrospectivo y que la evaluación ecográfica de los pacientes incluidos no fue ciega respecto a datos clínicos y de laboratorio. En cualquier caso, las variaciones en los valores de GIM obtenidas en nuestro estudio respecto a otras publicadas en la literatura (33–35,37) son mínimas, entorno a 0,02 mm tanto en la arteria temporal común como en la rama parietal, siendo estas diferencias atribuibles a la variabilidad de medidas intermáquina e interobservador.

Aunque la medición del GIM parece ser útil para apoyar el diagnóstico de pacientes con sospecha de ACG, son necesarios estudios adicionales de validación de puntos de corte en otras poblaciones, especialmente en pacientes mayores o con alto riesgo cardiovascular (36,37). También es necesario investigar la correcta interpretación de hallazgos en relación al ciclo cardiaco, ya que el GIM puede variar en función de su medición en sístole o diástole (38).

### Impacto del riesgo cardiovascular en el diagnóstico por ecografía de pacientes con ACG

Es importante tener en cuenta que el GIM de arterias temporales puede superar los límites propuestos en algunas patologías distintas a la ACG, resultando en falsos positivos para el diagnóstico de ACG, a pesar de la presencia de hallazgos ecográficos positivos. Aunque esta situación es infrecuente (menos del 5% de pacientes con sospecha de ACG (71)), puede ocurrir en el caso de pacientes con aterosclerosis (37), hiperplasia de la íntima en biopsia (72) o en otras patologías como la amiloidosis (73), otras vasculitis o linfoma (71).
La aterosclerosis puede suponer hasta el 21% de falsos positivos en ecografía (71) y tanto la aterosclerosis como un elevado riesgo cardiovascular pueden producir un signo de la compresión positivo (72), conduciendo a un falso diagnóstico ecográfico de ACG. Por este motivo, parece relevante evaluar qué impacto tiene el riesgo cardiovascular en el diagnóstico por ecografía de ACG.

Por otro lado, en los últimos años se han publicado diversos índices ecográficos con el objetivo de cuantificar el grado de inflamación vascular en ecografía. Aunque cada uno tiene características diferenciales, la mayoría se basan en la medición del GIM en distintas regiones arteriales para calcular un índice compuesto. Uno de estos índices ecográficos es el Halo Count que consiste en un contaje simple del número de arterias afectadas incluyendo las arterias temporales común superficial y sus ramas frontales y parietales, así como las arterias axilares, de forma bilateral. También se ha descrito el Halo Score que incluye las mismas regiones arteriales y aporta distintos grados en función del GIM de cada segmento. Ambos índices han demostrado ser válidos tanto para el diagnóstico (57,60) como para evaluar la respuesta al tratamiento (62).
Más recientemente, el grupo OMERACT de ecografía en vasculitis de vaso grande ha publicado el índice OGUS (OMERACT Giant Cell Arteritis Ultrasonography Score, por sus siglas en inglés), con el objetivo de estandarizar la cuantificación de la inflamación vascular mediante ecografía en la ACG (63). El cálculo de OGUS se lleva a cabo mediante la suma del GIM dividido por el punto de corte del GIM de cada segmento, aplicando un factor corrector en función del número de vasos evaluados. El índice OGUS ha demostrado ser un índice fiable y sensible al cambio (63). De los 3 índices comentados, el OGUS presenta la mayor sensibilidad al cambio durante la monitorización de pacientes con ACG (64) y ha sido elaborado con la metodología estandarizada y validada del grupo OMERACT.

De cara a determinar el impacto del riesgo cardiovascular el diagnóstico por ecografía de pacientes con ACG, hemos evaluado el impacto del mismo en la precisión diagnóstica del índice Southend Halo Score (74). De los 157 pacientes con sospecha de ACG evaluados en la consulta de diagnóstico rápido de ACG durante un periodo de 2 años, 47 (29.9%) fueron diagnosticados de ACG según criterio clínico tras 6 meses de seguimiento. La evaluación del riesgo cardiovascular se llevó a cabo mediante el cálculo del riesgo de enfermedad cardiovascular de la Sociedad Europea de Cardiología (SCORE) (75). El hallazgo más relevante de este estudio es que el GIM de las arterias extracraneales fue significativamente mayor en pacientes con riesgo cardiovascular alto o muy alto respecto a pacientes con riesgo cardiovascular bajo o moderado, en el grupo de pacientes sin ACG. Adicionalmente, los pacientes sin ACG con riesgo cardiovascular alto o muy alto presentaron valores de Halo Score significativamente más altos respecto a pacientes con riesgo cardiovascular bajo o moderado (9,38 [5,93] vs 6,16 [5,22]; p=0,007). El área bajo la curva ROC del Halo Score para identificar pacientes con ACG fue de 0.835 (95% IC 0,756–0.914); significativamente mayor en pacientes con bajo/moderado riesgo cardiovascular (0,965 [95% IC 0,911–1,00]) respecto a pacientes con alto/muy alto riesgo cardiovascular (0,798 [95% IC 0,702–0,895]). También observamos una correlación estadísticamente significativa positiva, aunque débil, entre el Halo Score y el SCORE (r 0,245; p=0,002).

Este estudio pone de manifiesto que el riesgo cardiovascular puede influir en la validez de la ecografía vascular para el diagnóstico de ACG, aunque el impacto es leve. Nuestros resultados están en línea con observaciones previas del grupo de Martire et al (36). Estos autores demostraron que los pacientes con elevado riesgo cardiovascular presentan un GIM significativamente mayor tanto en arterias temporales como en axilares. Aunque su estudio incluyó únicamente pacientes sin diagnóstico de ACG ni PMR, sentaron las bases

para el estudio del riesgo cardiovascular a la hora de determinar el GIM en pacientes con sospecha de ACG. Aunque en nuestro estudio no evaluamos específicamente la presencia de aterosclerosis, nuestras conclusiones están también en línea con datos previos del grupo de de Miguel et al (37). Estudiaron a 40 pacientes con riesgo cardiovascular elevado sin signos ni síntomas de ACG y observaron que la presencia de aterosclerosis en arterias carótidas aumenta el GIM en arterias temporales y puede producir signo del halo. De cara a diferenciar aterosclerosis de vasculitis, se ha descrito el llamado "slope sign" (77). Al contrario que en pacientes con aterosclerosis, la transición de la pared arterial normal hasta el engrosamiento del GIM en vasculitis es lenta, homogénea y continua. Aunque este signo ecográfico puede ser de gran ayuda, en ocasiones la aterosclerosis también puede presentarse como una placa difusa que simula el engrosamiento de la pared vascular de la ACG.

Nuestros resultados subrayan la importancia de la correcta interpretación de la medición del GIM en la evaluación de pacientes con sospecha de ACG, especialmente ante la presencia de alto o muy alto riesgo cardiovascular. Hay que recordar que las recomendaciones EULAR señalan la importancia de la imagen en el contexto de una alta o baja probabilidad pretest para poder confirmar o descartar el diagnóstico de la enfermedad (27).

## Validez de la ecografía en el diagnóstico de ACG-GV.

De acuerdo a datos previos, hasta un 30% de los pacientes con ACG pueden presentar síntomas compatibles con ACG-GV. Este tipo de afectación supone un reto diagnóstico ya que los síntomas pueden ser muy inespecíficos, como por ejemplo la fiebre y pérdida de peso. Por otro lado, la frecuencia de ACG-GV en estudios de imagen puede alcanzar hasta el 68-83% del total de pacientes con ACG (78). Por ello, la afectación extracraneal puede ser infradiagnosticada en ausencia del uso rutinario de técnicas de imagen. Las recomendaciones EULAR del 2018 (27) no dan prioridad a ninguna de las pruebas de imagen para la evaluación de la afectación extracraneal, salvo en el caso de la aortitis torácica, y los estudios que comparan distintas técnicas en esta afectación son muy limitados (39,79,80).

En vista a estas consideraciones, uno de nuestros objetivos fue comparar el valor diagnóstico de la ecografía respecto a la TEP/TC en la detección de afectación extracraneal en pacientes con ACG (81). De los 113 pacientes incluidos, 37 (32,7%) fueron diagnosticados de vasculitis de gran vaso. La sensibilidad y especificidad de la ecografía fue del 86,5% y 96,1%, respectivamente. La sensibilidad y especificidad de la TEP/TC fue del 61,1% y 90%, respectivamente. Tomando a la TEP/TC como referencia, la ecografía detectó ACG-GV en 10/12 (83,3%) pacientes y detectó dos casos adicionales con TEP/TC negativa. Sin embargo, la TEP/TC fue positiva en dos pacientes con ecografía negativa.

Estos resultados demuestran que la ecografía es una técnica válida para detectar ACG-GV y globalmente los resultados son consistentes con la TEP/TC. No obstante, una ecografía

negativa para ACG-GV no excluye totalmente la presencia de afectación extracraneal, y puede ser necesario el uso de TEP/TC en determinadas situaciones. En base a nuestros resultados, proponemos el uso de la ecografía como primera línea, no solo en afectación craneal sino también en ACG-GV, teniendo en cuenta su alta precisión diagnóstica, su coste, disponibilidad y ausencia de uso de radiaciones ionizantes. En caso de sospecha alta o moderada de ACG-GV y ecografía negativa, la TEP/TC puede ser una alternativa de utilidad para el diagnóstico.

Nuestros resultados están en consonancia con las conclusiones de un estudio previo de Nielsen et al. (79), en el que evalúan prospectivamente a 46 pacientes con ACG-GV confirmado por TEP/TC. La sensibilidad y especificidad de la ecografía axilar (definido como un GIM >1) para el diagnóstico de ACG-GV fue del 74% y 92%, respectivamente. En un estudio con menor tamaño muestral, Hop et al. (39), determinaron la sensibilidad de la ecografía axilar en 13 pacientes con ACG-GV confirmado por TEP/TC. La ecografía detectó afectación axilar en 8 de los 13 pacientes (61.5%). En la misma línea que los estudio previos, Löffler et al. (80), investigaron la sensibilidad y especificidad de la ecografía para la detección de ACG-GV en 30 casos confirmados por TEP/TC y 20 controles. La sensibilidad global de la ecografía para la detección de ACG-GV fue del 80%. Sin embargo, al estudiar distintos territorios arteriales observaron que la sensibilidad de la evaluación de las arterias subclavias y axilares era mayor (71,4% y 72,2%, respectivamente), pero la sensibilidad disminuía considerablemente en la evaluación de la aorta (26,1%) y arterias femorales (16,7%).

A pesar de la excelente resolución de la ecografía para determinar el GIM en arterias extracraneales, solo podemos observar la alteración de la pared arterial que ocurre tras la inflamación. Por tanto, la TEP/TC podría detectar inflamaciones que aún no han producido un incremento del GIM visible en ecografía, lo que explica la relativamente menor sensibilidad de la ecografía al compararlo con la TEP/TC. Además, la ecografía tiene limitaciones para la evaluación de la aorta y las arterias de los miembros inferiores. Tan solo podemos evaluar en algunos pacientes la porción más proximal de la aorta ascendente y es necesario estandarizar la evaluación de la aorta abdominal. Sin embargo, la TEP/TC es cara, tiene menor disponibilidad y usa radiación ionizante lo que puede limitar su uso para el diagnóstico. Por ello, la utilización de la ecografía como primera prueba de imagen a realizar en pacientes con sospecha de ACG, tanto craneal como extracraneal, podría ser una estrategia eficiente.

Siguiendo esta línea de investigación en ACG-GV, intentamos cuantificar el impacto de la limitación de la ecografía para evaluar la aorta en comparación con la TEP/TC en el diagnóstico de ACG (82). En este sentido, evaluamos retrospectivamente un total de 72 pacientes con ACG confirmada por ecografía en los que se había realizado TEP/TC, según criterio clínico. De estos, 29 (40.3%) pacientes presentaron incremento de la captación del radiotrazador en TEP/TC, y un 24 (33,3%) presentaron aortitis. Un total de 6 (20,7%) pacientes presentaron ecografía negativa para ACG-GV y TEP/TC positiva. De los pacientes con aortitis en TEP/TC solo 2 (8,3%) presentaron ecografía negativa para ACG-GV. Algunas características de los pacientes con mayor riesgo de aortitis fueron sexo femenino, menor edad, trombocitosis, ausencia de síntomas visuales y afectación ecográfica de ACG-GV. De acuerdo a nuestros resultados, el riesgo de presentar aortitis si no hay datos de ACG-GV

en ecografía es bajo. En otras palabras, la mayoría de pacientes con aortitis tienen signos de ACG-GV en ecografía, lo que podría disminuir la necesidad de uso de TEP/TC en todos los pacientes.

A pesar de que la afectación aórtica puede asociarse a peor pronóstico y mayor riesgo de recidivas en ACG, a día de hoy no hay evidencia para establecer distintas estrategias de tratamiento en función de la presencia o ausencia de aortitis. De nuevo, nuestros resultados apoyan el uso de la ecografía en primera línea para el diagnóstico de ACG. Entre las limitaciones del estudio cabe destacar el carácter retrospectivo y el hecho de que la sensibilidad de la TEP/TC puede verse afectada por el uso de corticoides en práctica clínica que podrían infraestimar la frecuencia de aortitis. Por último, la elección de realizar la TEP/TC en este estudio fue el criterio clínico, lo cual puede implicar sesgos de selección al incluir a pacientes con mayor riesgo de aortitis.

### Validez diagnóstica de los nuevos criterios de clasificación ACR/EULAR 2022 de arteritis de células gigantes

Recientemente se han publicado los nuevos criterios de clasificación ACR/EULAR de ACG (26). El objetivo de aplicar estos criterios es el de distinguir entre distintos tipos de vasculitis u otras enfermedades una vez se ha realizado el diagnóstico de ACG. Por tanto, no son criterios diagnósticos y su desarrollo se llevó a cabo para incluir poblaciones homogéneas en ensayos clínicos. La principal novedad de estos criterios de clasificación es la inclusión de técnicas de imagen por primera vez desde la publicación de los criterios previos ACR del 1990 (24). Para clasificar a un paciente con ACG se requiere una puntuación de al menos 6 puntos. La presencia de signo del halo en ecografía de arteria temporal o la positividad de una biopsia de arteria temporal aporta 5 puntos, por lo que en muchos casos no será necesaria esta última para la clasificación del paciente. Aunque estos criterios no fueron desarrollados para el diagnóstico, a día de hoy no existen criterios diagnósticos en ACG y el patrón oro continúa siendo el criterio del clínico, en general, tras al menos 6 meses de seguimiento, una vez comprobada la correcta respuesta al tratamiento y evolución. Por ello, es de gran interés conocer cuál es la aplicabilidad de los nuevos criterios con fines diagnósticos en la práctica clínica habitual. En este sentido, nos marcamos como uno de los objetivos de esta línea de investigación determinar el valor diagnóstico de los nuevos criterios de clasificación ACR/EULAR 2022 (83). Nuestros resultados fueron pioneros ya que fuimos el primer grupo a nivel mundial en validar los nuevos criterios para el diagnóstico. Posteriormente otros grupos confirmaron y avalaron nuestras observaciones.

Estudiamos a un total de 319 pacientes, incluyendo a 188 casos de ACG y 131 controles (pacientes con PMR, cefalea tensional, isquemia ocular no arterítica, fiebre de origen desconocido u otros diagnósticos). Asumiendo el diagnóstico del clínico como criterio de referencia, la sensibilidad y especificidad global de los nuevos criterios de clasificación fue del 92,6% y 71,8%, respectivamente. Sin embargo, la validez diagnóstica puede variar en función del fenotipo de ACG. En los pacientes con ACG-GV aislada, la sensibilidad y especificidad fue del 62,2% y 71,8%, respectivamente, mientras que en los pacientes con ACG confirmada por biopsia fue del 100% y 71,8%. La sensibilidad y especificidad de los

criterios de clasificación ACR de 1990 fue sustancialmente menor para todos los subtipos de ACG en comparación con los nuevos criterios.

Nuestros resultados ponen de manifiesto que los nuevos criterios de clasificación mejoran la validez de los previos de 1990 para su uso con fines diagnósticos. Sin embargo, la especificad global de los nuevos criterios continúa siendo insuficiente para el diagnóstico. Ello se debe a que en nuestra cohorte de validación se incluyeron controles atendidos habitualmente en consultas de diagnóstico rápido de ecografía que pueden simular ACG y que incluían pacientes con cefalea, PMR o afectación visual por otras causas no arteríticas, dando lugar a una mayor tasa de falsos positivos que en la cohorte de validación original donde se incluyeron únicamente pacientes con otras vasculitis. La relativa baja especificidad de los criterios puede llevar a un sobretratamiento de pacientes como consecuencia de un sobrediagnóstico. Un punto de corte superior (p.e >7 o >8 puntos) puede ser necesario para el diagnóstico para aumentar la especificidad, aunque sea a costa de disminuir sensibilidad.

Tras los resultados publicados por nuestro grupo, otras validaciones externas confirmaron nuestras observaciones. El grupo de van Nieuwland et al. (84), estudiaron la validez diagnóstica de los nuevos criterios en una cohorte menor de 133 pacientes neerlandeses, aportando una sensibilidad del 98% y especificidad del 57,5%, en línea con nuestros resultados. En una serie de casos, se observó una sensibilidad del 100% al aplicar los nuevos criterios de clasificación a 9 pacientes coreanos con ACG (85). Asimismo el grupo de Andel et al. (86), determinaron la sensibilidad (97.2%) de los nuevos criterios en una cohorte de pacientes noruegos con ACG en comparación con los previos del 1990 (69%). Por último, Narváez et al. (87), demostraron una sensibilidad del 92.6% y especificidad del 85,2% en 136 pacientes con ACG al aplicar los nuevos criterios para el diagnóstico en práctica clínica.

En general, los nuevos criterios de clasificación ACR/EULAR 2022 suponen una mejora respecto a los criterios previos. Sin embargo, su relativa baja especificidad impide su uso rutinario en práctica clínica, así como en determinados subgrupos de pacientes, especialmente en ACG-GV. La inclusión de otros vasos potencialmente afectados en ACG, como las arterias subclavias, podría aumentar la sensibilidad en este subgrupos de pacientes de un 62,2% al 73% (83), aunque estos resultados han de confirmarse en futuros estudios.

## Complicaciones isquémicas y su relación con distintos fenotipos de ACG

En ausencia de tratamiento adecuado y precoz, los pacientes con ACG pueden presentar complicaciones isquémicas, de especial relevancia ceguera y accidente cerebrovascular, cuya aparición se asocia a un aumento de la morbimortalidad (12,88,89). En las últimas décadas, se han evaluado factores de riesgo para predecir la aparición de complicaciones isquémicas, con resultados variables. Algunos estudios han observado una asociación con menor inflamación clínica o analítica (90–92). Otros han descrito asociación con factores de riesgo cardiovascular tradicionales (90,93–95). La ecografía ha demostrado ser válida en el diagnóstico de ACG y, como consecuencia, en la determinación de complicaciones

isquémicas. Sin embargo, la individualización del riesgo de complicaciones isquémicas en base al subtipo de afectación vascular ecográfica aún no se ha estudiado.

Por ello, uno de nuestros objetivos fue determinar si el fenotipo de ACG, identificado por el subtipo de afectación vascular en la ecografía, se asocia a distintos tipos de complicaciones isquémicas en pacientes con ACG (96). Para ello, analizamos a 188 pacientes con ACG, de los cuales 43 (22,9%) presentaron complicaciones isquémicas (12,8% NOIA y 10,1% otras complicaciones isquémicas distintas a la NOIA, como accidente cerebrovascular, infarto de miocardio o arteriopatía periférica). Los pacientes con NOIA presentaron más frecuentemente ACG craneal en ecografía respecto a pacientes con otras complicaciones isquémicas o sin complicaciones isquémicas (100%, 63.2%, y 79.3%, respectivamente; p=0.009). Por el contrario, los pacientes con otras complicaciones isquémicas presentaron más frecuentemente ACG-GV en ecografía respecto a pacientes con NOIA o sin complicaciones isquémicas (63.2%, 25% y 55.2%, respectivamente; p=0.014).

En base a nuestro estudio, hemos demostrado por primera vez la probable asociación entre distintos fenotipos de ACG determinados por ecografía y distintos tipos de complicaciones isquémicas. Por tanto, la ecografía puede ser un indicador de gran valor en la identificación de subtipos de pacientes con mayor riesgo de complicaciones isquémicas. Nuestros resultados están en línea con observaciones previas que identifican la afectación craneal como un predictor de NOIA (12,97) y por ello, tradicionalmente se ha asociado la presencia de complicaciones isquémicas al fenotipo de ACG craneal. Sin embargo, hemos observado que los pacientes con otras complicaciones isquémicas distintas a la NOIA, sobre todo accidentes cerebrovasculares, presentan más frecuentemente ACG-GV en ecografía. Esta observación es novedosa y demuestra que en ACG-GV también existe riesgo de complicaciones isquémicas, pero distintas a las observadas en ACG craneal. No obstante, este estudio tiene limitaciones, como el relativamente reducido tamaño muestral para identificar complicaciones isquémicas infrecuentes como accidentes cerebrovasculares o su diseño retrospectivo, con posibles sesgos de selección como el de mortalidad.

Muy recientemente, se han publicado datos del registro español de arteritis de células gigantes de la Sociedad Española de Reumatología (ARTESER) que avalan nuestros resultados. Martín-Gutierrez et al., analizan la prevalencia y factores predictores de accidentes cerebrovasculares en una gran cohorte de 1540 pacientes con ACG representativos de todo el territorio nacional español (88). Un total de 61 (3.96%) pacientes presentaron accidente cerebrovascular. Entre los factores predictores de accidente cerebrovascular identificados se encuentran la presencia de ataque isquémico transitorio (OR 8,63), ACG-GV confirmada por técnicas de imagen (OR 2,79) y la presencia de manifestaciones visuales concomitantes (OR 2,73). En línea con nuestros resultados, este estudio demuestra que la identificación por imagen de ACG-GV puede tener importancia en la detección de otras complicaciones isquémicas distintas a la NOIA, como los accidentes cerebrovasculares.

## Valor de la cuantificación de inflamación por ecografía vascular en la predicción de recidivas en ACG

Según las recomendaciones EULAR de 2018, no se recomienda el uso de la imagen en pacientes con ACG en remisión clínica y analítica, aunque si podría ser de ayuda en caso de sospecha de recidiva (27). Esta recomendación se basa en la limitada evidencia científica con escasez de estudios que avalen el valor añadido del uso de la imagen respecto la valoración clínica y analítica tradicional en el seguimiento de los pacientes. No obstante, la ecografía sí ha demostrado sensibilidad al cambio durante la monitorización de pacientes con ACG. En el ensayo clínico GUSTO (98), se demostró mejoría del GIM en ecografía tras pulsos de corticoides y posterior empeoramiento tras la suspensión de los mismos. Durante el tratamiento con tocilizumab el GIM mejoró gradualmente. Ponte et al. (53), demostraron en un estudio prospectivo de 49 pacientes con ACG la correlación entre el número de segmentos de arterias temporales con signo del halo y la suma del GIM con VSG, PCR y el índice Birmingham Vasculitis Activity Score. Sin embargo, esta correlación no se demostró para el GIM en arterias axilares. El grupo de de Miguel et al. (56), en un estudio que incluyó a 30 pacientes con ACG, demostraron la resolución del signo del halo en la mayoría de pacientes (95%), pero excepcionalmente antes de las dos semanas de tratamiento, y generalmente persistió hasta los dos meses. Estos estudios sugieren que la ecografía podría utilizarse para la evaluación de la actividad de la enfermedad en ACG en el futuro. Sin embargo, un aspecto menos estudiado es el valor que tienen los cambios en imagen en los primeros meses de tratamiento para predecir el riesgo de recidivas futuras.

En este sentido, uno de nuestros objetivos fue el de determinar si el cambio tras el tratamiento de la inflamación vascular determinada por ecografía puede ser de utilidad para evaluar la probabilidad de recidiva futura en pacientes con ACG (99). Para ello, estudiamos a 76 pacientes con ACG seguidos durante 6 meses. Un total de 19 (26%) recidivaron durante el seguimiento. OGUS mejoró significativamente a los 6 meses (de 1,18 a 0,99, p=0,004) y desde los 3 a los 6 meses (de 1,08 a 0,99, p=0,04) en pacientes que no recidivaron, mientras que no se observaron cambios en pacientes con recidiva. Nuestros resultados están en línea con observaciones previas del grupo de Nielsen et al (64). En un estudio retrospectivo de menor tamaño muestral, demostraron empeoramiento de OGUS desde los 2 a los 6 meses en pacientes con recidiva. Nuestro estudio no pudo demostrar la hipótesis inicial de que los cambios en OGUS durante los primeros meses de tratamiento (p.e. a los 3 meses) predicen recidivas futuras. A pesar de la mejoría de OGUS desde basal a 3 meses fue numéricamente menor en pacientes que presentaron recidiva, estas diferencias no fueron estadísticamente significativas. Por tanto, son necesarios estudios con mayor tamaño muestral o mayor periodo de seguimiento para confirmar dicha hipótesis.

## Recomendaciones EULAR para el uso de la imagen en vasculitis de vaso grande: actualización del 2023

Las recomendaciones EULAR del 2018 para el uso de la imagen en vasculitis de vaso grande han supuesto un punto de inflexión ya que posicionan la ecografía como la primera prueba de imagen a realizar en pacientes con sospecha de ACG (27). Esto ha

tenido como resultado un mayor uso de la imagen en detrimento de la biopsia de arteria temporal en práctica clínica (100). Desde su publicación, han aparecido nuevos estudios de imagen en ACG que han obligado a una actualización de las recomendaciones con el fin de incluir cambios sustanciales en relación a la ecografía.
A través de los procedimientos operativos normalizados de EULAR del 2014 (101), se seleccionó un grupo de trabajo formado por 24 miembros entre los que se incluyeron reumatólogos, un radiólogo, especialistas de medicina nuclear, un representante de pacientes y dos representantes de grupo EMEUNET (EMerging EUlar NETwork). Se llevó a cabo una revisión sistemática de la literatura para informar al grupo de expertos de la evidencia disponible actualizada sobre el uso de la ecografía, RM, TEP/TC y TC para el diagnóstico, monitorización y predicción del riesgo en vasculitis de vaso grande. El grupo coordinador propuso una actualización de las recomendaciones en base a la evidencia disponible, estas recomendaciones se redefinieron y se votó el grado de acuerdo entre los expertos de forma anónima en rondas consecutivas. Se acordó aceptar aquellas recomendaciones que alcanzaron un consenso superior al 75% entre los expertos participantes en la primera votación, >66% en la segunda o >50% en la tercera.

Entre los aspectos más novedosos y relevantes de la actualización de las recomendaciones EULAR del 2023 (66) destacan:

1. “La ecografía de arterias temporales y axilares debe ser considerada como la primera prueba de imagen para el estudio de los cambios inflamatorios en la pared arterial de pacientes con sospecha de ACG”. Por un lado, se elimina el concepto de pacientes con predominio de ACG craneal y se hace referencia a todos los pacientes con ACG, considerada un espectro de enfermedad en la que los fenotipos se pueden solapar (muchos pacientes con ACG craneal clínica también tienen ACG-GV en imagen y pacientes con ACG craneal al inicio pueden progresar a ACG-GV). Por otro lado, la inclusión de arterias axilares ya no se considera opcional, ya que hay evidencia de que su inclusión aumenta sustancialmente la sensibilidad, sin reducir significativamente la especificidad (40,102–104).

2. “La RM de alta resolución o la TEP/TC pueden utilizarse como alternativas a la ecografía para la evaluación de arterias craneales en pacientes con sospecha de ACG”. Las recomendaciones del 2018 abogaban en contra del uso de la TEP/TC para la evaluación de arterias temporales debido a su proximidad al parénquima craneal. En los últimos años se han publicado nuevos estudios que avalan el uso de la TEP/TC para la visualización de arterias craneales (44,45).

3. “En caso de sospecha de recidiva de ACG o Takayasu, especialmente cuando los parámetros de laboratorio de actividad de la enfermedad no sean fiables, se puede considerar el uso de la ecografía, la TEP/TC o, como alternativa, la RM para la evaluación de alteraciones en los vasos. No se recomienda el uso de la imagen en pacientes en remisión clínica y analítica”. Los nuevos datos de la utilidad de la ecografía y la TEP/TC demostrando una adecuada sensibilidad al cambio y moderada correlación con otros marcadores de actividad, han conducido a la inclusión de la posibilidad del uso de la imagen en sospecha de recidiva. No obstante, dado que no hay estudios que avalen el

valor añadido de la imagen respecto a la valoración clínica y analítica tradicional, no se recomienda el uso rutinario de la imagen en remisión clínica y analítica.

# CONCLUSIONES

## CONCLUSIONES

- La identificación de puntos de corte del grosor íntima-media mediante ecografía contribuye a una mejor discriminación diagnóstica en ACG, especialmente cuando los signos ecográficos tradicionales no son concluyentes.
- El riesgo cardiovascular debe ser considerado en la interpretación de la ecografía, ya que puede reducir su precisión diagnóstica.
- La ecografía y la TEP/TC son técnicas válidas y complementarias para el diagnóstico de ACG con afectación de vaso grande, aunque una ecografía negativa no excluye totalmente esta afectación.
- Las limitaciones de la ecografía en la detección de aortitis tienen bajo impacto clínico.
- La incorporación de la imagen en los nuevos criterios de clasificación ACR/EULAR 2022 mejora su utilidad diagnóstica, aunque su relativa baja especificidad limita su aplicación como criterios diagnósticos en la práctica clínica.
- Existen distintos fenotipos ecográficos asociados a diferentes perfiles de riesgo isquémico; los pacientes con ACG de vaso grande presentan mayor riesgo de eventos cerebrovasculares.
- La cuantificación ecográfica del grosor de la pared vascular al diagnóstico de ACG podría ser una herramienta útil en la predicción de recidivas, lo que la posiciona como una técnica valiosa para el seguimiento clínico.

# REFERENCIAS

## REFERENCIAS


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. 2013;65(1):1-11.

2. Li KJ, Semenov D, Turk M, Pope J. A meta-analysis of the epidemiology of giant cell arteritis across time and space. Arthritis Res Ther. 2021;23(1):82.

3. Ponte C, Águeda AF, Luqmani RA. Clinical features and structured clinical evaluation of vasculitis. Best Pract Res Clin Rheumatol. 2018;32(1):31-51.

4. Bosch P, Espigol-Frigolé G, Cid MC, Mollan SP, Schmidt WA. Cranial involvement in giant cell arteritis. Lancet Rheumatol. 2024;6(6):e384-96.

5. Blockmans D, de Ceuninck L, Vanderschueren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. Arthritis Rheum. 2006;55(1):131-7.

6. García-Martínez A, Hernández-Rodríguez J, Arguis P, Paredes P, Segarra M, Lozano E, et al. Development of aortic aneurysm/dilatation during the followup of patients with giant cell arteritis: a cross-sectional screening of fifty-four prospectively followed patients. Arthritis Rheum. 2008;59(3):422-30.

7. 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 (Oxford). 2008;47(1):96-101.

8. Muratore F, Kermani TA, Crowson CS, Green AB, Salvarani C, Matteson EL, et al. Large-vessel giant cell arteritis: a cohort study. Rheumatology (Oxford). 2015;54(3):463-70.

9. Nuenninghoff DM, Hunder GG, Christianson TJH, McClelland RL, Matteson EL. Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. Arthritis Rheum. 2003;48(12):3522-31.

10. De Miguel E, Macchioni P, Conticini E, Campochiaro C, Karalilova R, Monti S, et al. Prevalence and characteristics of subclinical giant cell arteritis in polymyalgia rheumatica. Rheumatology (Oxford). 2023;kead189.

11. Tomelleri A, van der Geest KSM, Khurshid MA, Sebastian A, Coath F, Robbins D, et al. Disease stratification in GCA and PMR: state of the art and future perspectives. Nat Rev Rheumatol. 2023;19(7):446-59.

12. Molina-Collada J, Domínguez-Álvaro M, Melero-González RB, Fernández-Fernández E, Silva-Díaz M, Valero JA, et al. Visual manifestations in giant cell arteritis: identification of risk factors from the ARTESER Registry. Rheumatology (Oxford). 2024;keae042.

13. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Gomez-Acebo I, Pego-Reigosa R, Lopez-Diaz MJ, Vazquez-Triñanes MC, et al. Strokes at time of disease diagnosis in a series of 287 patients with biopsy-proven giant cell arteritis. Medicine (Baltimore). 2009;88(4):227-35.

14. Molina-Collada J, Domínguez-Álvaro M, Melero-González RB, de Miguel E, Silva-Díaz M, Valero Jaimes JA, et al. Mortality in patients with giant cell arteritis in Spain: results from the ARTESER registry. Arthritis Res Ther. 2025;27(1):4.

15. Breuer GS, Poltorak V, Nesher G. Survival of patients with giant cell arteritis: a controversial issue. Clin Exp Rheumatol. 2020;38 Suppl 124(2):210-3.

16. Cid MC, Unizony SH, Blockmans D, Brouwer E, Dagna L, Dasgupta B, et al. Efficacy and safety of mavrilimumab in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2022;81(5):653-61.

17. Mazlumzadeh M, Hunder GG, Easley KA, Calamia KT, Matteson EL, Griffing WL, et al. Treatment of giant cell arteritis using induction therapy with high-dose glucocorticoids: a double-blind, placebo-controlled, randomized prospective clinical trial. Arthritis Rheum. 2006;54(10):3310-8.

18. Proven A, Gabriel SE, Orces C, O'Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum. 2003;49(5):703-8.

19. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of Tocilizumab in Giant-Cell Arteritis. N Engl J Med. 2017;377(4):317-28.

20. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2020;79(1):19-30.

21. Maz M, Chung SA, Abril A, Langford CA, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. Arthritis Rheumatol. 2021;73(8):1349-65.

22. Jover JA, Hernández-García C, Morado IC, Vargas E, Bañares A, Fernández-Gutiérrez B. Combined treatment of giant-cell arteritis with methotrexate and prednisone. a randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2001;134(2):106-14.

23. Rubenstein E, Maldini C, Gonzalez-Chiappe S, Chevret S, Mahr A. Sensitivity of temporal artery biopsy in the diagnosis of giant cell arteritis: a systematic literature review and meta-analysis. Rheumatology (Oxford). 2020;59(5):1011-20.

24. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;33(8):1122-8.

25. Seeliger B, Sznajd J, Robson JC, Judge A, Craven A, Grayson PC, et al. Are the 1990 American College of Rheumatology vasculitis classification criteria still valid? Rheumatology (Oxford). 2017;56(7):1154-61.

26. Ponte C, Grayson PC, Robson JC, Suppiah R, Gribbons KB, Judge A, et al. 2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis. Ann Rheum Dis. 2022;81(12):1647-53.

27. 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.

28. Schmidt WA, Kraft HE, Völker L, Vorpahl K, Gromnica-Ihle EJ. Colour Doppler sonography to diagnose temporal arteritis. Lancet. 1995;345(8953):866.

29. Patil P, Williams M, Maw WW, Achilleos K, Elsideeg S, Dejaco C, et al. Fast track pathway reduces sight loss in giant cell arteritis: results of a longitudinal observational cohort study. Clin Exp Rheumatol. 2015;33(2 Suppl 89):S-103-106.

30. 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). 2016;55(1):66-70.

31. Chrysidis S, Duftner C, Dejaco C, Schäfer VS, Ramiro S, Carrara G, et al. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group. RMD Open. 2018;4(1):e000598.

32. Bosch P, Bond M, Dejaco C, Ponte C, Mackie SL, Falzon L, et al. Imaging in diagnosis, monitoring and outcome prediction of large vessel vasculitis: a systematic literature review and meta-analysis informing the 2023 update of the EULAR recommendations. RMD Open. 2023;9(3):e003379.

33. Czihal M, Schröttle A, Baustel K, Lottspeich C, Dechant C, Treitl KM, et al. B-mode sonography wall thickness assessment of the temporal and axillary arteries for the diagnosis of giant cell arteritis: a cohort study. Clin Exp Rheumatol. 2017;35 Suppl 103(1):128-33.

34. Ješe R, Rotar Ž, Tomšič M, Hočevar A. The cut-off values for the intima-media complex thickness assessed by colour Doppler sonography in seven cranial and aortic arch arteries. Rheumatology (Oxford). 2021;60(3):1346-52.

35. Schäfer VS, Juche A, Ramiro S, Krause A, Schmidt WA. Ultrasound cut-off values for intima-media thickness of temporal, facial and axillary arteries in giant cell arteritis. Rheumatology (Oxford). 2017;56(9):1479-83.

36. Martire MV, Cipolletta E, Di Matteo A, Di Carlo M, Jesus D, Grassi W, et al. Is the intima-media thickness of temporal and axillary arteries influenced by cardiovascular risk? Rheumatology (Oxford). 2021;60(11):5362-8.

37. De Miguel E, Beltran LM, Monjo I, Deodati F, Schmidt WA, Garcia-Puig J. Atherosclerosis as a potential pitfall in the diagnosis of giant cell arteritis. Rheumatology (Oxford). 2018;57(2):318-21.

38. Fernández-Fernández E, Brugarolas E, Monjo-Henry I, Novella-Navarro M, Balsa A, De Miguel E. The influence of the cardiac cycle on the halo sign and its impact on the ultrasound diagnosis of giant cell arteritis. Rheumatology (Oxford). 2024;keae289.

39. Hop H, Mulder DJ, Sandovici M, Glaudemans AWJM, van Roon AM, Slart RHJA, et al. Diagnostic value of axillary artery ultrasound in patients with suspected giant cell arteritis. Rheumatology (Oxford). 2020;59(12):3676-84.

40. Prearo I, Dekorsy FJ, Brendel M, Lottspeich C, Dechant C, Schulze-Koops H, et al. Diagnostic yield of axillary artery ultrasound in addition to temporal artery ultrasound for the diagnosis of giant cell arteritis. Clin Exp Rheumatol. 2022;40(4):819-25.

41. Skoog J, Svensson C, Eriksson P, Sjöwall C, Zachrisson H. The Diagnostic Performance of an Extended Ultrasound Protocol in Patients With Clinically Suspected Giant Cell Arteritis. Front Med (Lausanne). 2021;8:807996.

42. Bley TA, Reinhard M, Hauenstein C, Markl M, Warnatz K, Hetzel A, et al. Comparison of duplex sonography and high-resolution magnetic resonance imaging in the diagnosis of giant cell (temporal) arteritis. Arthritis & Rheumatism. 2008;58(8):2574-8.

43. Sommer NN, Treitl KM, Coppenrath E, Kooijman H, Dechant C, Czihal M, et al. Three-Dimensional High-Resolution Black-Blood Magnetic Resonance Imaging for Detection of Arteritic Anterior Ischemic Optic Neuropathy in Patients With Giant Cell Arteritis. Investigative Radiology. 2018;53(11):698.

44. Nielsen BD, Hansen IT, Kramer S, Haraldsen A, Hjorthaug K, Bogsrud TV, et al. Simple dichotomous assessment of cranial artery inflammation by conventional 18F-FDG PET/CT shows high accuracy for the diagnosis of giant cell arteritis: a case-control study. Eur J Nucl Med Mol Imaging. 2019;46(1):184-93.

45. Sammel AM, Hsiao E, Schembri G, Nguyen K, Brewer J, Schrieber L, et al. Diagnostic Accuracy of Positron Emission Tomography/Computed Tomography of the Head, Neck, and Chest for Giant Cell Arteritis: A Prospective, Double-Blind, Cross-Sectional Study. Arthritis Rheumatol. agosto de 2019;71(8):1319-28.

46. Balink H, Tan SS, Veeger NJGM, Holleman F, van Eck-Smit BLF, Bennink RJ, et al. 18F-FDG PET/CT in inflammation of unknown origin: a cost-effectiveness pilot-study. Eur J Nucl Med Mol Imaging. 2015;42(9):1408-13.

47. Stone JH, Han J, Aringer M, Blockmans D, Brouwer E, Cid MC, et al. Long-term effect of tocilizumab in patients with giant cell arteritis: open-label extension phase of the Giant Cell Arteritis Actemra (GiACTA) trial. The Lancet Rheumatology. 2021;3(5):e328-36.

48. de Boysson H, Daumas A, Vautier M, Parienti JJ, Liozon E, Lambert M, et al. Large-vessel involvement and aortic dilation in giant-cell arteritis. A multicenter study of 549 patients. Autoimmun Rev. 2018;17(4):391-8.

49. Espitia O, Blonz G, Urbanski G, Landron C, Connault J, Lavigne C, et al. Symptomatic aortitis at giant cell arteritis diagnosis: a prognostic factor of aortic event. Arthritis Res Ther. 2021;23(1):14.

50. Schmidt WA, Kraft HE, Vorpahl K, Völker L, Gromnica-Ihle EJ. Color duplex ultrasonography in the diagnosis of temporal arteritis. N Engl J Med. 1997;337(19):1336-42.

51. Ponte C, Serafim AS, Monti S, Fernandes E, Lee E, Singh S, et al. Early variation of ultrasound halo sign with treatment and relation with clinical features in patients with giant cell arteritis. Rheumatology (Oxford). 2020;59(12):3717-26.

52. Hauenstein C, Reinhard M, Geiger J, Markl M, Hetzel A, Treszl A, et al. Effects of early corticosteroid treatment on magnetic resonance imaging and ultrasonography findings in giant cell arteritis. Rheumatology (Oxford). 2012;51(11):1999-2003.

53. Ponte C, Monti S, Scirè CA, Delvino P, Khmelinskii N, Milanesi A, et al. Ultrasound halo sign as a potential monitoring tool for patients with giant cell arteritis: a prospective analysis. Ann Rheum Dis. 2021;80(11):1475-82.

54. Schmidt WA, Moll A, Seifert A, Schicke B, Gromnica-Ihle E, Krause A. Prognosis of large-vessel giant cell arteritis. Rheumatology (Oxford). 2008;47(9):1406-8.

55. Bosch P, Dejaco C, Schmidt WA, Schlüter KD, Pregartner G, Schäfer VS. Ultrasound for diagnosis and follow-up of chronic axillary vasculitis in patients with long-standing giant cell arteritis. Ther Adv Musculoskelet Dis. 2021;13:1759720X21998505.

56. De Miguel E, Roxo A, Castillo C, Peiteado D, Villalba A, Martín-Mola E. The utility and sensitivity of colour Doppler ultrasound in monitoring changes in giant cell arteritis. Clin Exp Rheumatol. 2012;30(1 Suppl 70):S34-38.

57. 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.

58. Chattopadhyay A, Ghosh A. «Halo Score»: missing large-vessel giant cell arteritis-do we need a «modified Halo Score»? Ann Rheum Dis. 2020;

59. Molina Collada J, Martínez-Barrio J, Serrano-Benavente B, Castrejón I, Nieto-González JC, Caballero Motta LR, et al. Subclavian artery involvement in patients with

giant cell arteritis: do we need a modified Halo Score? Clin Rheumatol. 2021;40(7):2821-7.

60. 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;

61. Conticini E, Falsetti P, Al Khayyat SG, Grazzini S, Baldi C, Bellisai F, et al. Diagnostic accuracy of OGUS, Southend halo score and halo count in giant cell arteritis. Front Med (Lausanne). 2024;11:1320076.

62. Sebastian A, Kayani A, Prieto-Pena D, Tomelleri A, Whitlock M, Mo J, et al. Efficacy and safety of tocilizumab in giant cell arteritis: a single centre NHS experience using imaging (ultrasound and PET-CT) as a diagnostic and monitoring tool. RMD Open. 2020;6(3):e001417.

63. Dejaco C, Ponte C, Monti S, Rozza D, Scirè CA, Terslev L, et al. The provisional OMERACT ultrasonography score for giant cell arteritis. Ann Rheum Dis. 2022;ard-2022-223367.

64. Nielsen BD, Therkildsen P, Keller KK, Gormsen LC, Hansen IT, Hauge EM. Ultrasonography in the assessment of disease activity in cranial and large-vessel giant cell arteritis: a prospective follow-up study. Rheumatology (Oxford). 2023;kead028.

65. Quinn KA, Ahlman MA, Malayeri AA, Marko J, Civelek AC, Rosenblum JS, et al. Comparison of magnetic resonance angiography and 18F-fluorodeoxyglucose positron emission tomography in large-vessel vasculitis. Annals of the Rheumatic Diseases. 2018;77(8):1165-71.

66. Dejaco C, Ramiro S, Bond M, Bosch P, Ponte C, Mackie SL, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice: 2023 update. Ann Rheum Dis. 2023;ard-2023-224543.

67. López-Gloria K, Castrejón I, Nieto-González JC, Rodríguez-Merlos P, Serrano-Benavente B, González CM, et al. Ultrasound intima media thickness cut-off values for cranial and extracranial arteries in patients with suspected giant cell arteritis. Front Med (Lausanne). 2022;9:981804.

68. Muratore F, Boiardi L, Restuccia G, Macchioni P, Pazzola G, Nicolini A, et al. Comparison between colour duplex sonography findings and different histological patterns of temporal artery. Rheumatology (Oxford). 2013;52(12):2268-74.

69. Habib HM, Essa AA, Hassan AA. Color duplex ultrasonography of temporal arteries: role in diagnosis and follow-up of suspected cases of temporal arteritis. Clin Rheumatol. 2012;31(2):231-7.

70. Salvarani C, Silingardi M, Ghirarduzzi A, Lo Scocco G, Macchioni P, Bajocchi G, et al. Is duplex ultrasonography useful for the diagnosis of giant-cell arteritis? Ann Intern Med. 2002;137(4):232-8.

71. Fernández-Fernández E, Monjo-Henry I, Bonilla G, Plasencia C, Miranda-Carús ME, Balsa A, et al. False positives in the ultrasound diagnosis of giant cell arteritis: some diseases can also show the halo sign. Rheumatology (Oxford). 2020;59(9):2443-7.

72. Seitz L, Lötscher F. The intima-media thickness in suspected giant cell arteritis-sometimes it is worth taking a closer look. Rheumatology (Oxford). 2021;60(7):3039-41.

73. Molina Collada J, Ruíz Bravo-Burguillos E, Monjo I, Bonilla G, Fernández E, Balsa A, et al. Positive ultrasound halo sign of temporal arteries due to amyloidosis. Rheumatology (Oxford). 2019;58(11):2067-9.

74. Molina-Collada J, López Gloria K, Castrejón I, Nieto-González JC, Martínez-Barrio J, Anzola Alfaro AM, et al. Impact of cardiovascular risk on the diagnostic accuracy of the ultrasound Halo Score for giant cell arteritis. Arthritis Res Ther. 2022;24(1):232.

75. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur J Prev Cardiol. 2021;zwab154.

76. Monjo-Henry I, Fernández-Fernández E, Mostaza JM, Lahoz C, Molina-Collada J, de Miguel E. Ultrasound halo count in the differential diagnosis of atherosclerosis and large vessel giant cell arteritis. Arthritis Res Ther. 2023;25(1):23.

77. Dasgupta B, Smith K, Khan AAS, Coath F, Wakefield RJ. 'Slope sign': a feature of large vessel vasculitis? Annals of the Rheumatic Diseases. 2019;78(12):1738-1738.

78. Geest KSM van der, Sandovici M, Bley TA, Stone JR, Slart RHJA, Brouwer E. Large vessel giant cell arteritis. The Lancet Rheumatology. 2024;6(6):e397-408.

79. Nielsen BD, Hansen IT, Keller KK, Therkildsen P, Gormsen LC, Hauge EM. Diagnostic accuracy of ultrasound for detecting large-vessel giant cell arteritis using FDG PET/CT as the reference. Rheumatology (Oxford). 2020;59(8):2062-73.

80. 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.

81. Molina-Collada J, Castrejón I, Rivera J, Martínez-Barrio J, Nieto-González JC, López K, et al. The Role of Ultrasound and FDG-PET/CT to Detect Extracranial Artery Involvement in Patients with Suspected Large Vessel Vasculitis. Mod Rheumatol. 2022;roac058.

82. Molina-Collada J, Castrejón I, Monjo-Henry I, Fernández-Fernández E, Torres Ortiz G, Martínez-Barrio J, et al. Impact of ultrasound limitation to assess aortitis in patients with giant cell arteritis: comparative study with FDG-PET/CT. RMD Open. 2023;9(3):e003329.

83. Molina-Collada J, Castrejón I, Monjo I, Fernández-Fernández E, Torres Ortiz G, Álvaro-Gracia JM, et al. Performance of the 2022 ACR/EULAR giant cell arteritis classification criteria for diagnosis in patients with suspected giant cell arteritis in routine clinical care. RMD Open. 2023;9(2):e002970.

84. van Nieuwland M, van Bon L, Vermeer M, Brouwer E, Alves C. External validation of the 2022 ACR/EULAR classification criteria in patients with suspected giant cell arteritis in a Dutch fast-track clinic. RMD Open. 2023;9(3):e003080.

85. Ha JW, Song JJ, Park YB, Lee SW. Validation of the 2022 ACR/EULAR classification criteria for giant cell arteritis in Korean patients with giant cell arteritis. Modern Rheumatology. 2025;roae110.

86. Andel PM, Diamantopoulos AP, Myklebust G, Haugeberg G. Vasculitis distribution and clinical characteristics in giant cell arteritis: a retrospective study using the new 2022 ACR/EULAR classification criteria. Front Med (Lausanne). 2023;10:1286601.

87. Narváez J, Estrada P, Vidal-Montal P, Nolla JM. Performance of the new 2022 ACR/EULAR classification criteria for giant cell arteritis in clinical practice in relation to its clinical phenotypes. Autoimmun Rev. 2023;22(10):103413.

88. Martín-Gutiérrez A, Molina-Collada J, Domínguez-Álvaro M, Melero-González RB, Fernández-Fernández E, Silva-Díaz M, et al. Cerebrovascular accidents in giant cell arteritis: prevalence and predictive factors from the ARTESER registry. Rheumatology (Oxford). 2025;keaf051.

89. Hočevar A, Ješe R, Tomšič M, Rotar Ž. Risk factors for severe cranial ischaemic complications in giant cell arteritis. Rheumatology (Oxford). 2020;59(10):2953-9.

90. Liozon E, Herrmann F, Ly K, Robert PY, Loustaud V, Soria P, et al. Risk factors for visual loss in giant cell (temporal) arteritis: a prospective study of 174 patients. Am J Med. 2001;111(3):211-7.

91. Saleh M, Turesson C, Englund M, Merkel PA, Mohammad AJ. Visual Complications in Patients with Biopsy-proven Giant Cell Arteritis: A Population-based Study. J Rheumatol. 2016;43(8):1559-65.

92. Pego-Reigosa R, Garcia-Porrua C, Piñeiro A, Dierssen T, Llorca J, Gonzalez-Gay MA. Predictors of cerebrovascular accidents in giant cell arteritis in a defined population. Clin Exp Rheumatol. 2004;22(6 Suppl 36):S13-17.

93. Samson M, Jacquin A, Audia S, Daubail B, Devilliers H, Petrella T, et al. Stroke associated with giant cell arteritis: a population-based study. J Neurol Neurosurg Psychiatry. 2015;86(2):216-21.

94. Yates M, MacGregor AJ, Robson J, Craven A, Merkel PA, Luqmani RA, et al. The association of vascular risk factors with visual loss in giant cell arteritis. Rheumatology (Oxford). 2017;56(4):524-8.

95. de Boysson H, Liozon E, Larivière D, Samson M, Parienti JJ, Boutemy J, et al. Giant Cell Arteritis-related Stroke: A Retrospective Multicenter Case-control Study. J Rheumatol. 2017;44(3):297-303.

96. Amar Muñoz HM, Molina-Collada J, Castrejón I, Monjo-Henry I, Fernández-Fernández E, Álvaro-Gracia JM, et al. Different giant cell arteritis phenotypes may present distinct types of ischaemic complications. Clin Exp Rheumatol. 2024;

97. Singh AG, Kermani TA, Crowson CS, Weyand CM, Matteson EL, Warrington KJ. Visual manifestations in giant cell arteritis: trend over 5 decades in a population-based cohort. J Rheumatol. 2015;42(2):309-15.

98. Seitz L, Christ L, Lötscher F, Scholz G, Sarbu AC, Bütikofer L, et al. Quantitative ultrasound to monitor the vascular response to tocilizumab in giant cell arteritis. Rheumatology. 2021;60(11):5052-9.

99. Molina-Collada J, Monjo-Henry I, Fernández-Fernández E, Álvaro-Gracia JM, de Miguel E. The OMERACT Giant cell arteritis Ultrasonography Score: a potential predictive outcome to assess the risk of relapse during follow-up. Rheumatology (Oxford). 2024;keae260.

100. De Miguel E, Sanchez-Costa JT, Estrada P, Muñoz A, Valero Martínez C, Moya Alvarado P, et al. Influence of the EULAR recommendations for the use of imaging in large vessel vasculitis in the diagnosis of giant cell arteritis: results of the ARTESER register. RMD Open. 2022;8(2):e002507.

101. Heijde D van der, Aletaha D, Carmona L, Edwards CJ, Kvien TK, Kouloumas M, et al. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. Annals of the Rheumatic Diseases. 2015;74(1):8-13.

102. Diamantopoulos AP, Haugeberg G, Hetland H, Soldal DM, Bie R, Myklebust G. Diagnostic value of color Doppler ultrasonography of temporal arteries and large vessels in giant cell arteritis: a consecutive case series. Arthritis Care Res (Hoboken). 2014;66(1):113-9.

103. Henry IM, Fernández Fernández E, Peiteado D, Balsa A, de Miguel E. Diagnostic validity of ultrasound including extra-cranial arteries in giant cell arteritis. Clin Rheumatol. 2022;

104. 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 (Oxford). 2008;47(1):96-101.