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ORIGINAL ARTICLE

Impact of the combined presence of erosions and ACPA on rheumatoid arthritis disease activity over time: results from the METEOR registry

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ABSTRACT

Objective To investigate associations between baseline presence of erosions and/or anti-citrullinated protein antibodies (ACPA) on functional ability, disease activity and treatment survival over time.

Methods Real life data from newly diagnosed rheumatoid arthritis patients were identified in the international METEOR registry. Patients were grouped according to presence/absence of ACPA and/or erosions at baseline. Associations between the presence of ACPA and/or erosions (four groups) with the change of Disease Activity Score (DAS) and Health Assessment Questionnaire (HAQ) over time were assessed using linear mixed models during maximum 6 or maximum 12 months from baseline. Treatment survival was assessed using multiple failure-times Cox regression.

Results Data were included from 701 ACPA–/erosions–, 334 ACPA–/erosions+, 1585 ACPA+/erosions– and 1993 ACPA+/erosions+ patients. We found statistically significant differences in DAS and HAQ change over time between the four groups, both after maximum follow-up durations of 6 and of 12 months, but after stratification differences proved small and not clinically meaningful. Patients in the ACPA–/erosions– group were less likely to switch treatment compared with the ACPA+/erosions– reference group (p<0.001). The other two ACPA/erosions groups did not differ from the reference group.

Conclusions In this analysis of worldwide real life data, we found statistically significant, but clinically irrelevant differences in treatment response to initial disease modifying anti-rheumatic drug therapies as measured by DAS and HAQ in ACPA–/erosions–, ACPA–/erosions+, ACPA+/erosions– and ACPA+/erosions+ rheumatoid arthritis patients. However, after maximum follow-up durations of 6 and 12 months all groups had a similar response to initial treatment, but with a lower likelihood to switch treatment for ACPA–/erosions– patients during the first year of follow-up.

Key messages

What is already known about this subject?
► Presence of ACPA and erosions are often considered poor prognostic factors, but more recent research has shown that presence of ACPA or erosions may not be relevant for the prediction of early clinical response.

What does this study add?
► The combined presence of ACPA and erosions had no clinically relevant association with response to initial treatment after maximum follow-up durations of 6–12 months.
► ACPA negative/erosions negative patients were less likely to switch treatment during the first 12 months.

How might this impact on clinical practice?
► In newly diagnosed rheumatoid arthritis-patients who are treated according to modern treatment strategies, the (combined) presence of ACPA and erosions does not seem to be a risk factor for worse disease activity or physical functioning.

INTRODUCTION

In rheumatoid arthritis (RA), the association between inflammatory disease activity (over time) and actual as well as future functional disability and future radiological outcomes, is most likely a causal relationship.[1 2] Treatment therefore is targeted at rapidly achieving and maintaining as low a disease activity as possible.[3] Early suppression of disease activity depends on the success of the initial treatment. In general, starting with a combination of conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) with corticosteroids or with a b(iological) DMARD has a higher success rate than starting with a single csDMARD. However, it is still not possible to predict which patient will benefit from which treatment.[4 5] Several patient and disease characteristics have been identified that are associated with response to early treatment and/or late disease outcomes, but to a large extent finding the optimal

treatment still depends on trial and error.[6 7] With the introduction of treatment to target, fewer patients develop significant radiological damage and permanent disability. The success of this approach hinders the identification of poor prognostic factors through paucity of the traditional bad outcomes. Alternative outcomes with which to link prognostic factors are disease activity and inflammation dependent functional ability.[7] Previous research has shown that in newly diagnosed RA-patients functional ability and composite disease activity scores such as the Disease Activity Score (DAS) were associated with symptom duration, functional disability and disease activity at diagnosis, gender, obesity, smoking and the initial treatment.[8–13]

Presence of erosions and ACPA are also often considered poor prognostic factors, mainly based on their association with radiographic damage progression.[14] More recent research has shown that presence of autoantibodies or erosions may not be relevant for the prediction of early clinical response. It remains unclear whether the combined, rather than the individual presence of these potential risk factors is associated with treatment outcomes in real life data.[7 11 15] To test this, we investigated, in a daily practice based cohort, the associations between the presence of erosions and ACPA on functional ability, disease activity scores and treatment survival in the first year of treatment.

METHODS
Data selection
Data were selected from the METEOR registry. This is an international registry capturing daily practice data regarding the treatment of patients with a clinical diagnosis of RA. Data were captured in 128 hospitals in 33 countries on patient and disease characteristics, disease activity, physical functioning and medication use. The presence of ACPA and erosions were defined according to local standards. Data were anonymised and treatment was non-protocolled, therefore medical ethics approval was not required. The METEOR registry has been previously described in detail.[16]

Data were selected from newly diagnosed RA-patients (defined as DMARD start within 3 months after diagnosis), aged >16 years, with at least 3 months of follow-up, available data on ACPA, erosions (present/absent) and medication and at least one visit with available composite disease activity measure (DAS(28), Simple Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) or Routine Assessment of Patient Index Data (RAPID3)). Patients in remission at their first available visit were excluded.

All available follow-up visits were selected until a maximum follow-up duration of 1 year. Timing and frequency of follow-up visits was according to daily practice. Therefore, the total follow-up time and the total number of visits differed per patient.

Statistical analyses
Patients were divided into four groups, based on the presence of ACPA and erosions: (1) ACPA positive/erosions positive, (2) ACPA positive/erosions negative, (3) ACPA negative/erosions positive and (4) ACPA negative/erosions negative. For all analyses comparing these groups the ACPA positive/erosions negative group was chosen as the reference group, to facilitate the comparisons between the double and single positive groups.

Disease activity and physical functioning were compared between these four groups after a maximum follow-up duration of 6 months and of 1 year, using the DAS and the Health Assessment Questionnaire (HAQ), as outcome measures.[17 18] Since frequency and timing of follow-up visits were according to daily practice, actual follow-up may differ per patient. Missing data were imputed using chained equations (40 imputation cycles) with linear regression analysis for continuous variables and (multinomial) logit analysis for categorical variables. Missing data were imputed for the variables HAQ, DAS, CDAI, swollen joint count, Ritchie articular index, patient and physician global assessment of disease activity, patient pain, rheumatoid factor, gender, smoking, weight, height, date of symptom onset and age, based on complete information of ACPA, presence of erosions, medication, country of treatment and time in follow-up. Continuous variables that did not follow a Gaussian distribution were transformed by taking the square root. Subsequent analyses were performed within the imputed database.

Linear mixed model analyses were performed to assess the potential associations between the presence of ACPA and/or erosions and disease outcomes, as measured by DAS28 and HAQ. An interaction term between the ACPA/erosions groups and time in follow-up was added to each model to compare treatment response over time in the four groups. In the presence of a statistically significant interaction ($p < 0.10$), results were stratified by ACPA/erosions group. To account for irregular time intervals between follow-up visits, a random intercept and slope were added to each model, with 'exchangeable' covariance matrix.

To estimate whether the time to a change in treatment (as proxy for treatment failure) differed between the four ACPA/erosions groups over the first year, a conditional risk set model was estimated using a multiple failure-times Cox regression analysis, in which time reflected the length of the time span between events.[19] An event was defined as a change in type of treatment. A change in medication dose or a step-down strategy (eg, from combination therapy of methotrexate and prednisone to methotrexate monotherapy) was not considered a change in type of treatment.

All models were adjusted for the potential confounders gender, smoking, symptom duration, body mass index (BMI), initial medication and country, which were selected based on clinical relevance. Furthermore, it
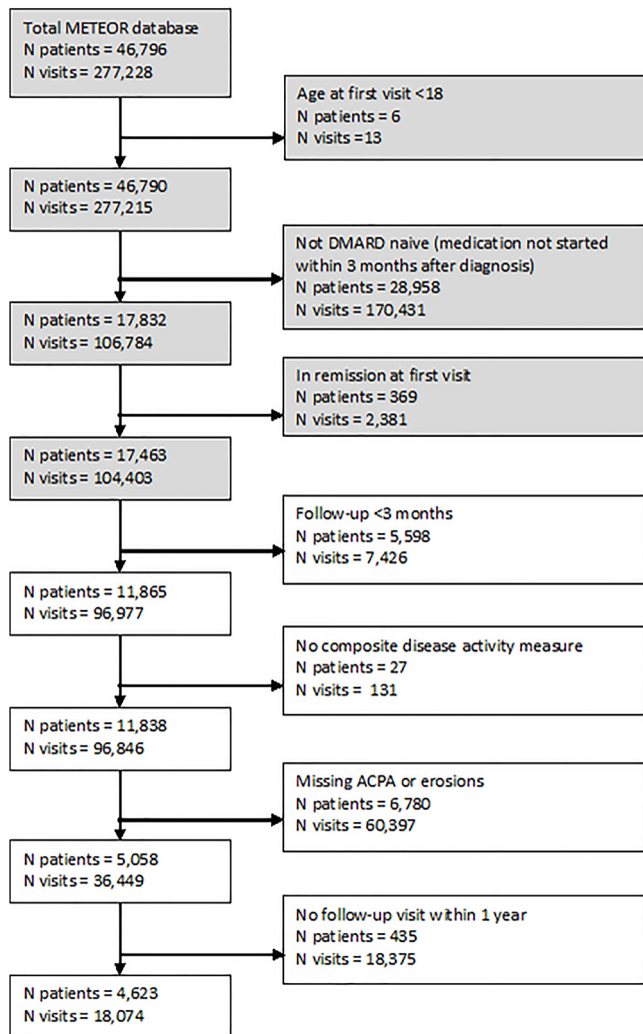
Figure 1 Flow chart of the patient selection. Data extraction performed in February 2018. Grey boxes show the selection of eligible patients, white boxes show patients eligible for the current study, but with insufficient data.

was assessed whether country, initial medication and symptom duration acted as effect modifier, by categorising initial medication (csDMARD monotherapy, csDMARD combination therapy, csDMARD(s)+glucocorticoids, other) and symptom duration (<1 year, 1–2 years, 2–5 years, >10 years) and by adding an interaction term with country, initial medication group or symptom duration group, and ACPA/erosions group and time to the model. If effect modification was not present (p>0.10), results of the different country, medication and symptom duration groups were combined. Analyses were performed using Stata SE V.14 (StataCorp LP).

RESULTS

Data of 4623 patients were selected from the METEOR registry: 701 (15%) were ACPA negative/erosions negative, 344 (7%) were ACPA negative/erosions positive, 1585 (34%) were ACPA positive/erosions negative and

1993 (43%) were ACPA positive/erosions positive. A flow chart of the patient selection is presented in figure 1. Baseline characteristics of included and non-included patients are compared in online supplementary table 1. Non-included patients had longer symptom duration and were more often treated in India, but were otherwise very similar to included patients.

Baseline characteristics of the four ACPA/erosions groups are presented in table 1. Most ACPA positive patients were also rheumatoid factor positive (94%) and the proportion of never smokers was highest in the ACPA positive/erosions positive group (92%). Symptom duration differed between the groups and was lowest in the ACPA negative/erosions negative group (12 (4; 36) months) and highest in the ACPA positive/erosions positive group (48 (19; 108) months). Disease activity and physical functioning were mostly similar between groups, although HAQ was slightly lower in the ACPA positive/erosions negative group and ESR was lower in the ACPA negative/erosions negative group, but higher in the ACPA positive/erosions positive group. Initial medication also differed: erosions negative patients more often used csDMARD monotherapy, whereas erosions positive patients, especially if they were ACPA positive, more often used treatment including glucocorticoids. Median follow-up duration was approximately 9 months, and was very similar between groups.

Since daily practice data were included in the METEOR registry, rheumatologists were free to choose their own outcome measures. Therefore, DAS was missing in 27% of all visits and HAQ was missing in 25% of all visits. However, in 98% of all visits at least one composite disease activity measure (DAS(28), SDAI, CDAI or RAPID3) or HAQ was available.

Based on raw data, DAS and HAQ seemed similar over time between the four ACPA/erosions groups (table 2). However, adjusted analyses on imputed data investigating the associations between the presence of erosions and/or ACPA on the evolution of DAS and HAQ over time revealed statistically significant differences between the groups after maximum follow-up durations of both 6 months and 12 months (table 3). Patients with presence of erosions, with or without positive ACPA, had a statistically significant different DAS response (erosions negative/ACPA positive as reference group) at both time points. For the outcome HAQ, in general all erosions/ACPA groups were statistically significantly different from the reference group, although significance slightly differed after 6-month and 12-month follow-up. Despite these statistically significant differences, after stratification of the different ACPA/erosions groups in the fully adjusted model, numerical differences in both DAS and HAQ over time were small and not clinically relevant, which is in accordance with the raw and unadjusted data (table 2). The maximum difference between the ACPA/ erosions groups was 0.06 per month for DAS and 0.024 per month for HAQ after a maximum follow-up duration of 6 months and 0.03 per month for DAS and 0.011 per month for HAQ after a maximum follow-up duration of 12 months.

Table 1 Baseline characteristics of each ACPA/erosions group

	ACPA negative		ACPA positive	
	Erosions negative n=701	**Erosions positive n=344**	**Erosions negative n=1585**	**Erosions positive n=1993**
Female (%)	83	83.4	81.4	84.9
RF (% positive)	31	33.5	93	95.3
Smoking (%)				
Never	81.2	88.6	85.3	91.6
Current	7.3	4.7	9.3	5.2
Stopped	11.6	6.7	5.4	3.2
Age (years) mean (SD)	51 (16)	50 (14)	48 (13)	49 (12)
BMI mean (SD)	27.7 (6.0)	27.0 (6.0)	25.9 (5.9)	25.7 (5.7)
Symptom duration (months) median (IQR)	12 (4; 36)	36 (12; 72)	18 (6; 48)	48 (19; 108)
HAQ mean (SD)	0.98 (0.61)	1.1 (0.6)	0.88 (0.59)	1.1 (0.6)
DAS mean (SD)	3.5 (0.93)	4.0 (1.0)	3.6 (0.97)	4.0 (0.95)
ESR mean (SD)	47.5 (32.8)	60.1 (37.8)	65.5 (36.0)	72.8 (36.0)
Initial treatment (%)				
csDMARD mono	51.8	42.2	55.5	29.1
csDMARD combi	14.3	17.4	17.9	22.6
csDMARD+GC	27.5	37.2	23.9	45.1
Other	6.43	3.2	2.7	3.2
Country (%)				
Netherlands	19.8	7.9	10.7	3.3
India	41.4	57.8	68.5	68.1
Portugal	9.2	7.3	4.6	2
USA	10.1	5.9	3	1
Mexico	7.5	6.2	1.3	1
South-Africa	1.1	2.7	2	21.4
UK	5.3	1.6	4.2	0.9
Nigeria	1.4	1.7	1.1	0.3
Spain	0.5	0.6	2	0.3
Other	3.7	8.3	2.7	1.7

Based on non-imputed data. Proportion of missing data per variable at baseline: gender 0.4%, RF 0.6%, smoking 3.8%, age 0.4%, BMI 56.8%, symptom duration 4.1%, HAQ 20.0%, DAS 24.9%, ESR 7.8%, initial treatment 0%.

ACPA, anti-citrullinated protein antibodies; BMI, body mass index; combi, combination therapy; csDMARD, conventional synthetic disease modifying anti-rheumatic drug; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; HAQ, Health Assessment Questionnaire; mono, monotherapy; RF, rheumatoid factor.

Sensitivity analyses using CDAI as outcome instead of DAS showed very similar results (data not shown).

Furthermore, as described in the Methods section, we assessed whether effect modification was present for different variables, to test whether results would be likely different for various categories of the variables of interest. We found no effect modification by country, or by initial medication or symptom duration category (p>0.20). Hence, results were not further stratified.

Time to a change in treatment was assessed within a maximum follow-up duration of 12 months, taking into account the possibility that patients changed treatment multiple times. In a fully adjusted model, patients who were erosions negative/ACPA negative were less likely to switch treatment (HR (95% CI) 0.79 (0.69 to 0.90)) compared with a reference group of erosions negative/ACPA positive patients. Patients who were erosions positive/ACPA negative (HR (95% CI) 0.92 (0.79 to 1.08)) or erosions positive/ACPA positive (HR (95% CI) 1.01 (0.92 to 1.10)) were not statistically significantly different from the reference group in their likelihood to switch treatment.

Table 2 DAS, HAQ and follow-up duration at the final available visit

	ACPA negative		ACPA positive	
	Erosions negative	**Erosions positive**	**Erosions negative**	**Erosions positive**
6 months				
DAS, mean (SD)	2.17 (0.91)	2.40 (0.94)	2.32 (0.97)	2.36 (0.92)
HAQ, mean (SD)	0.53 (0.51)	0.62 (0.54)	0.51 (0.49)	0.56 (0.49)
FU duration, median (IQR)	4.1 (3.2; 5.0)	4.1 (3.3; 5.2)	4.1 (3.4; 5.0)	4.0 (3.4; 4.9)
12 months				
DAS, mean (SD)	2.07 (0.96)	2.30 (0.94)	2.27 (0.98)	2.33 (0.95)
HAQ, mean (SD)	0.54 (0.53)	0.61 (0.50)	0.52 (0.49)	0.57 (0.48)
FU duration, median (IQR)	9.2 (6.0; 10.6)	8.8 (6.0; 10.7)	9.0 (6.2; 10.6)	9.3 (6.7; 10.6)

Mean DAS and HAQ are based on non-imputed data, at the final available visit within the mentioned time period (6 or 12 months). Time periods refer to a maximum follow-up duration. Since data is gathered according to daily practice, time intervals between individual patients differ. FU duration indicates the median available follow-up duration per ACPA/erosions group. Proportion of missing data over time 27.4% for DAS and 25.4% for HAQ.

DAS, Disease Activity Score; FU, follow up in months; HAQ, Health Assessment Questionnaire.

DISCUSSION

In view of the changes in treatment options and early treat-to-target aimed at low disease activity or remission, we reinvestigated the association between the presence of erosions and/or ACPA with functional ability and disease activity over time in newly diagnosed RA-patients. We did find statistically significant differences between the four ACPA/erosions groups, but both after 6 and after 12 months differences in HAQ and DAS over time were small and not clinically meaningful. Nevertheless, patients who were both erosions and ACPA negative were less likely to switch treatment within the first year of follow-up.

Traditionally, the presence of ACPA and erosions are seen as risk factors for worse outcomes, and these are therefore considered 'poor prognostic factors' in current recommendations.[14] However, these potential risk factors have been mainly investigated in relation to radiographic damage progression.[7] Preventing radiographic damage progression is still one of the major aims when treating RA patients. But since the majority of patients in both cohorts and clinical trials are currently reported to have no or only very limited radiographic damage, due to early effective treatment, other treatment targets as disease activity and physical functioning are increasingly

Table 3 Associations between the presence of erosions and/or ACPA on the change of DAS and HAQ over time*

Maximum follow-up duration	6 months	12 months	6 months	12 months
	P value†	**P value†**	**B (95% CI)**	**B(95% CI)**
	Interactions with time		Stratified analyses: evolution over time (per month)	
DAS				
Ero– ACPA–	0.481	0.551	–0.24 (–0.27 to –0.22)	–0.11 (–0.12 to –0.10)
Ero+ ACPA–	0.001	<0.001	–0.30 (–0.34 to –0.26)	–0.14 (–0.16 to –0.12)
Ero– ACPA+	Ref.	Ref.	–0.24 (–0.25 to –0.22)	–0.11 (–0.11 to –0.099)
Ero+ ACPA+	<0.001	<0.001	–0.30 (–0.32 to –0.29)	–0.12 (–0.13 to –0.12)
HAQ				
Ero– ACPA–	0.035	0.121	–0.081 (–0.096 to –0.065)	–0.034 (–0.040 to –0.027)
Ero+ ACPA–	0.072	0.034	–0.084 (–0.10 to –0.064)	–0.038 (–0.047 to –0.029)
Ero– ACPA+	Ref	Ref	–0.062 (–0.072 to –0.053)	–0.027 (–0.031 to –0.023)
Ero+ ACPA+	<0.001	0.047	–0.086 (-0.095 to –0.078)	–0.033 (-0.037 to –0.029)

N patients=4623.

*Results stem from multivariable linear mixed models analyses with random intercept and slope and exchangeable covariance matrix, adjusted for age, gender, smoking, symptom duration, BMI, initial medication and country. Results are shown after a maximum follow-up duration of 6 months and of 12 months. Regression coefficients represent the units of change in the outcome per unit of time, in this case, per month. Missing data were imputed using multiple chained equations (40 cycles).

†P values are only shown for the interaction between erosions/ACPA and time in months. In the presence of a statistically significant interaction, results are stratified and the evolution of DAS and HAQ over time is shown for the erosions/ACPA groups separately.

BMI, body mass index; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire.

important.[9 20] A few previous studies investigated the association between ACPA *or* erosions with disease activity outcomes in early RA-patients and none of these studies found them to predict disease activity or functional ability outcomes.[11 15 21 22] We tested whether a combination of ACPA and erosions might be a predictor of treatment outcomes, but found no clinically meaningful difference in treatment response between four ACPA/erosions groups.

We did however observe that patients who were both erosions and ACPA negative were less likely to switch treatment. Probably, a treat-to-target approach has caused most patients to achieve good treatment outcomes over time, as has been previously shown, but patients who were erosions and ACPA negative seemed to require less treatment changes to achieve those outcomes.[23] More research would be required to investigate whether this is due to a better initial treatment response of ACPA negative/erosions negative patients, or a reflection of different treatment decisions of rheumatologists in the absence of ACPA and/or erosions or even differences in the adverse event rate in double-negative patients.

The estimated change in treatment outcomes was larger when modelled over a maximum follow-up duration of 6 months than when estimated over a maximum follow-up duration of 12 months. It is likely that the largest change in treatment outcomes occurred in the first months of follow-up. Furthermore, after longer follow-up more patients may have failed their medication, resulting in a smaller total estimated effect.

We have used real life clinical data from an international registry, which provides the advantages of large patient numbers and better generalisability to daily clinical practice than data from clinical trials. But our study also has several limitations. Since data were gathered during daily practice, measurements were not standardised and non-protocolled. Hence, both ACPA and the presence of erosions were determined locally and slight variability between the centres may exist. Also, local variability may exist in referral, treatment and follow-up of patients. In addition, a part of the data was missing and we had to use multiple imputation to take this into account.

Next to ACPA and erosions, other differences existed between groups at baseline, especially regarding symptom duration and initial treatment. Although we have adjusted for potential confounders and tested several potential effect modifiers, it is always possible that residual bias exists. As expected, ACPA positive/erosions positive patients received most intensive treatment, with less patients receiving csDMARD monotherapy than in the other three groups. It is possible that treatment response to the same treatment would be different between groups, if this would result in inadequate disease suppression in some patients.

Remarkably, patients in the ACPA positive plus erosions positive group smoked slightly less often than patients from the other three groups, whereas an association between ACPA, smoking and erosions has been well established.[24] This can be explained by a large proportion of Indian patients included in this group. Especially the proportion of female smokers in India is known to be very low (approximately 3%).[25] Moreover, smokeless tobacco products, which are not captured in our database, are much more prevalent in India than cigarettes.[26]

In conclusion, we found statistically significant differences in treatment response to initial DMARD therapy between four groups of RA-patients with or without ACPA and/or erosions. However, differences in treatment response measured by DAS and HAQ after maximum follow-up durations of 6 and 12 months, were small and not clinically meaningful. Instead, all groups had a similar response to initial treatment, although patients without ACPA and erosions were less likely to switch treatment. Thus, in newly diagnosed RA-patients who are treated according to modern treatment strategies, the (combined) presence of ACPA and erosions was no risk factor for worse disease activity or physical functioning.

Competing interests EM has received funding from Roche to audit work on behalf of the Scottish Society for Rheumatology and received support from AbbVie and UCB to attend meetings. TWJH the department of rheumatology of the LUMC has received research support/lecture fees/consultancy fees from the Dutch Arthritis Foundation, Abblynx, Merck, UCB, Bristol Myers Squibb, Biotest AG, Janssen, Pfizer, Novartis, Roche, Sanofi-Aventis, Abbott, Crescendo Bioscience, Galapagos, Nycomed, Boeringher, Takeda, Zydus, Epirus and Eli Lilly. The other authors declared no conflicts of interest.

Patient consent for publication Not required.

Ethics approval The METEOR registry contains completely anonymised data which was gathered during daily practice. Treatment, timing of follow-up visits and measurements were non-protocolled. Therefore, medical ethics board approval was not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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