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Title: First validation of the gout activity score against gout impact scale in a primary care based gout cohort

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Keywords: Gout, disease activity, quality of life

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Abstract: Objectives: To validate the gout activity score (GAS) against the gout impact scale in a primary care based gout cohort.

Methods: This was a single-centre cross-sectional study. People with gout who participated in previous research at Academic Rheumatology, University of Nottingham, UK, and consented for participation in future studies were mailed a questionnaire in September 2015. Those returning completed questionnaires were invited to attend for a study visit at which blood was collected and musculoskeletal examination was performed. The Gout Assessment Questionnaire, which contains the gout impact scale (GIS), and short form (SF) 36v2 questionnaires were completed. The GAS3-step-c score was calculated. Spearman's correlation coefficient was calculated to examine correlation between GAS and SF-36 v2, and GIS. Statistical analyses were performed using PASW v22.

Results: 102 (93% men) of the 150 participants who were mailed a questionnaire attended the study visit. Their mean (SD) age, BMI, serum uric acid and GAS were 67.94 (9.93) years, 29.96 (4.57) kg/m², 5.25 (1.75) mg/dl, and 2.99 (0.74) respectively. There was moderate correlation between GAS and gout concern overall, unmet gout treatment need, and gout concern during an attack components of GIS (r= 0.306 to 0.453), but no to poor correlation between GAS and summary scores and scales of SF-36 v2 (r= -0.090 to -0.251).

Conclusion: This first study to validate GAS against the GIS found moderate correlation. However, this study did not examine the predictive validity of GAS, and prospective studies are needed before GAS can be used widely.

1 First validation of the gout activity score against gout impact scale in a primary care
2 based gout cohort
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Abstract

Objectives To validate the gout activity score (GAS) against the gout impact scale in a primary care based gout cohort.

Methods This was a single-centre cross-sectional study. People with gout who participated in previous research at Academic Rheumatology, University of Nottingham, UK, and consented for participation in future studies were mailed a questionnaire in September 2015. Those returning completed questionnaires were invited to attend for a study visit at which blood was collected and musculoskeletal examination was performed. The Gout Assessment Questionnaire, which contains the gout impact scale (GIS), and short form (SF) 36v2 questionnaires were completed. The GAS_{3-step-c} score was calculated. Spearman's correlation coefficient was calculated to examine correlation between GAS and SF-36 v2, and GIS. Statistical analyses were performed using PASW v22.

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Introduction. Gout is the commonest inflammatory arthritis and affects between 1.4 to 2.5% of the general population (1). It is the only chronic arthritis that can be “cured” by appropriate long-term urate lowering treatment (ULT) (2). Scire and colleagues recently developed the first composite disease activity score (DAS) for gout, the gout activity score (GAS) by employing a Delphi exercise and using a data driven approach (3). Data from a cohort of Italian gout patients recruited from secondary care rheumatology clinics were used for this purpose, and external validation was carried out in a subset of the cohort (3). GAS is simple to use and correlated moderately with the Health Assessment Questionnaire (HAQ) and Short Form-36 (SF-36) physical component score in this cohort (3). However, as GAS was developed in a secondary care gout population which may have an over-representation of people with difficult to treat and/or severe gout, it is important to examine its relationship with gout specific quality of life (QOL) measures in a primary care gout population. Moreover, the relationship between GAS and gout specific QOL measures, such as the Gout Impact Scale (GIS) (4) and its individual domains (e.g. gout concern overall, gout medication side effects etc.) have not been examined before.

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The purpose of this study was to validate GAS in people with gout recruited from primary care. The specific objectives were to examine the correlation between GAS and sub-scales of GIS and summary scores and individual scales of SF-36v2. As GIS is a gout specific QOL instrument, we hypothesized that it will have a stronger correlation with GAS than SF-36v2 which may be influenced by comorbidities.

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Methods *Study design and recruitment.* This was a single-centre cross-sectional study. People with gout who participated in gout research at Academic Rheumatology, University of Nottingham, and gave consent to receive information on future studies were mailed a postal questionnaire in September 2015. These participants had participated in a case-control study aimed at developing a biomarker for gout and osteoarthritis (recruited in 2008) (5), and in an observational study of the effect of physician initiated nurse led treatment of gout on long-term ULT persistence (recruited in 2010-2011) (6). All participants in the case-control study met the preliminary American Rheumatism Association criteria for gout (7), while all participants in the latter study had crystal proven gout (5, 6). Their disease and demographic characteristics have been published previously (5, 6). The current study was approved by the University of Nottingham Medical School Ethics Committee.

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The postal questionnaire enquired about demographic characteristics, comorbidities, medication use, healthcare use for gout and number of gout attacks in the last year, and included the SF-36v2 and Gout Assessment Questionnaire (GAQ) 2.0. Those who returned completed questionnaires were invited to attend for a study visit at which blood was collected for serum uric acid (SUA) and creatinine measurement. Participants' height (metres), weight (kilograms) and blood pressure (mm Hg), were measured, and musculoskeletal examination including tophus count was performed.

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Calculation of GAS and QOL scores Scire *et al* developed two simple to use 4-variable GAS scores, the GAS_{3-step-c} and the GAS_{1-step-c} with slightly different components (4). Of these, the GAS_{3-step-c} had the best metric and was externally validated in a sub-set of the KING cohort (4). We calculated GAS_{3-step-c} using data on self-reported number of gout attacks in the previous 12 months, SUA, patient

1 reported visual analogue score (VAS) about gout and number of tophi ($GAS_{3\text{-step-c}} =$
2 $(0.09 * \text{last 12 month attacks}) + [1.01 * \text{square root (serum uric acid)}] + [0.34 * \text{VAS}$
3 $\text{patient}] + [0.53 * \ln (1+ \text{tophi number})]$) (4) [Appendix A, document S1; See the
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5 supplementary material associated with this article online]. The VAS patient was derived
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7 from the following question of GAQ 2.0 “Considering all the ways gout affects you,
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9 circle a number on the scale for how well you have been doing for the past 4
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11 weeks”(8).
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16 SF-36v2 a global health related QOL measure and GIS were calculated as described
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18 earlier (4, 9). SF-36v2 has eight scales and two summary scores. All scales and
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20 summary scores are scored separately, with higher values indicating better QOL.
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22 GIS evaluates the current impact of gout in five areas, specifically: gout concern
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24 overall; gout medication side effects; unmet gout treatment needs; well-being during
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26 an attack; and gout concern during an attack. All subscales of GIS are scored
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28 separately on a 0 to 100 score [Appendix A, document S2), with higher scores
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30 indicating a greater impact (4). Remission GAS score for gout was defined as no
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32 gout attacks in the last 12 months, no tophi, serum uric acid <6 mg/dl, and both
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34 patient global assessment for gout activity and gout pain ≤ 2 on a 1-10 scale (10).
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42 *Statistical analysis* Number (%), mean (standard deviation (SD)), median
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44 (interquartile range (IQR)) were used for descriptive purposes. Spearman’s
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46 correlation coefficient was calculated to examine the correlation between GAS, SF-
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48 36v2 and GIS as the data were not normally distributed. All statistical analysis were
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50 performed using PASW v22. $p < 0.05$ (two tailed) was regarded as statistically
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52 significant.
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57 **Funding source:** This study was supported by Nottingham University Hospitals
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59 NHS Trust Charity.
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Results 102 of the 150 gout patients who were sent postal questionnaires attended for the study visit. Their mean (SD) age, age of onset of gout, BMI, and SUA level were 67.94 (9.93) years, 50.13 (13.52) years, 29.96 (4.57) kg/m², and 5.25 (1.75) mg/dl. 95 (93.14%) were men, 88 (86.3%) were on ULT, and 2 (1.96%) had tophi. Their mean (SD), and median (IQR) GAS was 2.99 (0.74), and 2.71 (2.48 – 3.38) respectively.

There was moderate correlation between GAS and gout concern overall, unmet gout treatment need, and gout concern during an attack, and weak correlation with gout medication side effects subscales of GIS with $r = 0.383, 0.453, 0.306, 0.227$ respectively (Table S1). However, there was no correlation between GAS and wellbeing during gout attack subscale of GIS.

There was very weak to weak correlation between the mental component summary scale, and bodily pain, general health, mental health, social functioning domains of SF-36 v2 and GAS ($r = -0.196$ to -0.251), (Table S2).

Forty-four participants met the preliminary remission criteria for gout (10). Their mean (SD) GAS was 2.5 (0.2), and ranged from 1.81 to 2.78. On the contrary, the mean (SD) GAS score for participants not in remission was 3.13 (0.55), and ranged between 2.83 and 3.55.

Discussion Until recently there was no composite measure of disease severity in gout. Consequently, the concept of overall gout severity has remained ambiguous and difficult to measure. Scire *et al* developed the first global measure of gout activity in 2016 and externally validated it in a hospital cohort (3). This is the first study to attempt to validate GAS in people with gout recruited from primary care by examining its correlation with GIS. This study found that GAS has a significantly stronger correlation with some components of gout specific QOL measures e.g. gout concern overall, unmet gout treatment need than with a generic overall QOL measure such as SF-36. GAS has the potential of being used as a marker of disease severity, before beginning treatment, and of assessing improvements in gout in a composite way over time. It is easy to measure, can be calculated using web-based calculators just as the disease activity score (DAS) in RA, and provides a measure that will be easy for the patients and their treating doctors to understand. It serves as an important improvement over GIS, which is cumbersome, requires answers on a Likert scale to multiple questions, and cannot be used readily in clinical practice.

This was a well-treated cohort of people with gout and the mean GAS score was low. However, even in this population, there was moderate correlation between GAS and gout concern overall, gout concern during attack and unmet treatment need sub-scales of GIS. As expected, GAS, a measure of intercritical gout disease activity did not correlate with wellbeing during gout attack sub-scale of GIS, and further research is required to develop measures that can measure severity of acute gout. Thus, the findings of this study provide construct and external validity to GAS, even in a population with well treated gout. Apart from this, a GAS score of 2.8 was able to differentiate people in remission.

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Despite being endorsed by OMERACT for use in gout studies, there was a weaker correlation between GAS and SF36 v2 than between GAS and GIS. Moreover, the physical component score and mental component score of SF36 v2 in this study population correlated less well with GAS than in the study by Scire *et al* (3). This may be due to the fact that participants in our study were recruited from the community, and had a significantly lower burden of tophaceous gout and other comorbidities than those participants in the KING study.

Strengths of this study include primary care based recruitment, and systematic assessment for tophus by a single trained research nurse with >10 years' experience of assessing people with gout. We also note some study limitations: this was a cross-sectional study, and we did not directly examine the value of GAS in predicting the occurrence of flare or change ULT dose. Additionally, even though there is a lack of consensus concerning the timeframe over which absence of disease activity defines remission, this study used a single time point, which is not ideal. Also the proportion of gout patients on urate lowering treatment in this study is significantly higher than the proportion on urate lowering treatment in community based studies which may limit the generalisability of our findings.

In summary, this study provides external validity to support the use of an instrument to define disease activity in gout. GAS showed validity in assessing disease-specific health in patients with gout. However, given the study limitations, further prospective studies carried out in less well treated primary care gout cohorts are needed before GAS can be adopted for use.

1 **Conflicts of interest statement:** AA and MD have research grants from Astra
2 Zeneca, and Oxford Immunotech, and MD reports adhoc personal advisory board
3
4 fees from AstraZeneca, Menarini and Nordic Biosciences. Other authors do not have
5
6 any competing interest.
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10 11 12 13 **Appendix A. Supplementary data**

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16 Supplementary data (Documents S1-S2) associated with this article can be found in the online
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18 version at ...
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25 **Highlights:**

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28 • Gout activity score reflects severity of intercritical gout and not of wellbeing
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33 • Gout activity score is only weakly influenced by some measures of overall
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Number of attacks in last year	Serum Uric Acid (mg/dl)
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Table S1 Correlation between Gout Activity Score and individual domains of Gout Impact Scale

	Spearman's correlation coefficient	p value
Gout concern overall	0.383	<0.001
Gout Medication side effect	0.227	0.022
Unmet gout treatment need	0.453	<0.001
Wellbeing during attack	0.077	0.441
Gout concern during attack	0.306	0.002

Table S2 Correlation between Gout Activity Score and summary scales and domains of Short Form-36 v2

	Spearman's correlation coefficient	p value
Physical component summary scale	-0.148	0.136
Mental component summary scale	-0.196	0.049
Physical functioning	-0.090	0.367
Role physical	-0.162	0.162
Bodily pain	-0.235	0.018
General health	-0.204	0.040
Vitality	-0.171	0.085
Role Emotional	-0.190	0.056
Mental health	-0.225	0.023
Social functioning	-0.251	0.011

Calculating the Gout Impact Scale (GIS) subscales

GIS subscales were calculated by transforming the 1-5 responses on a 100-0 scale (1=100, 2=75, 3=50, 4=25, 5=0) for questions 1 a-h and j-l; 2 a-d; and 1-5 responses on a 0-100 scale (1=0, 2=25, 3=50, 4=75, 5=100) for questions 1 i,m, and 3 a-g; and calculating the mean of questions:

Q1 a-d for gout concern overall

Q1 e, k for gout medication side effects

Q1 i, l, m for unmet gout treatment need

Q2 a-d, and 3 a-g for well-being during attack

Q1 f-h, and j for gout concern during attack.

The subscales were calculated if at least half of the items were completed.



To
Prof Marie-Christophe Boissier
Editor, Joint Bone Spine

From
Dr A Abhishek
Academic Rheumatology
University of Nottingham
Nottingham, UK

Date: 6th April 2017

Dear Prof Marie-Christophe Boissier,

It has been a pleasure to revise the manuscript in response to the comments made by the reviewers. The specific comments of the reviewers, our response, and the subsequent changes in the manuscript are itemized below. We hope the revised manuscript meets with your and the reviewers' requirements.

We look forward to hearing from you in due course.

Yours sincerely,

Dr A Abhishek, PhD
Clinical Associate Professor of Rheumatology

Editor

Comment 1: Role of the funding source is missing at the end of the “Methods” section.

Author Response: We have included a sentence after the methods section, “funding source: this study was supported by Nottingham University Hospitals NHS Trust Charity.”

Reviewer 1

No comments

Reviewer 2

Comment 1: New Data of potential interest. Manuscript could be shortened. Tables can be in part presented as supplemental material.

Author Response: We have accepted the reviewer’s comments and have shortened the manuscript. The tables have now been included in the supplementary material.

Reviewer 3

Comment 1: Give a web-based calculator for GAS

Author Response: There are no websites for calculating GAS, and in the absence of dedicated funding we are unable to device and support one. We have included an excel spreadsheet as a supplementary material, where users can insert the number of attacks in the last year, serum uric acid, patient visual analogue score and tophi number. The spreadsheet then produces a GAS automatically.

Comment 2: It could be useful for the rheumatologist to give access to the GAS and GIS in the supplemental data.

Author response: We are unable to include the Gout Impact Scale (GIS) or the Gout Assessment Questionnaire (GAQ) version 2.0 due to copyright issues as this was published in the Journal of Rheumatology previously. However, we have described the

method by which we calculated the GIS in the supplementary material. The GAS can be calculated from the excel spreadsheet we have included as supplementary material.

Comment 3: The main limitation is the study sample which is not representative of a gout population in a primary care setting. 86.3 % being on ULT (vs 82 % in the King study, in a secondary care gout population) and the results are not generalizable.

Author response: We agree with the reviewer's comments, and have discussed this.

Please see page 8, paragraph 2, lines 7-10.