Arthritis Care & Research
DOI 10.1002/acr.22896

Survey definitions of gout for epidemiological studies: comparison with crystal identification as the gold standard

Nicola Dalbeth[1], H. Ralph Schumacher[2], Jaap Fransen[3], Tuhina Neogi[4], Tim L Jansen[5], Melanie Brown[6], Worawit Louthrenoo[7], Janitzia Vazquez-Mellado[8], Maxim Eliseev[9], Geraldine McCarthy[10,11], Lisa K. Stamp[12], Fernando Perez-Ruiz[13], Francisca Sivera[14], Hang-Korng Ea[15,16], Martijn Gerritsen[17], Carlo A. Scire[18], Lorenzo Cavagna [19], Chingtsai Lin[20], Yin-Yi Chou[21], Anne-Kathrin Tausche[22], Geraldo da Rocha Castelar-Pinheiro[23], Matthijs Janssen[24], Jiunn-Horng Chen[25, 26], Marco A. Cimmino[27], Till Uhlig[28], William J Taylor[6].

Institutions and higher degrees

1. Nicola Dalbeth, MD FRACP, University of Auckland, New Zealand
2. H. Ralph Schumacher, MD, University of Pennsylvania, Philadelphia PA.
3. Jaap Fransen, PhD, Radboud University Medical Centre, Nijmegen, Netherlands
4. Tuhina Neogi, MD PhD FRCPC, Boston University School of Medicine, Boston MA
5. Tim L Jansen, MD, Viecuri Medical Center, Venlo, Netherlands
6. Melanie Brown, MHealSc; William J Taylor, PhD FRACP, University of Otago Wellington, New Zealand
7. Worawit Louthrenoo, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Received: Dec 09, 2015; Revised: Feb 18, 2016; Accepted: Mar 22, 2016

8. Janitzia Vazquez-Mellado, MD PhD, Servicio de Reumatología, Hospital General de México, México City, México

9. Maxim Eliseev, MD, Nasonova Research Institute of Rheumatology of Russia, Moscow, Russia

10. Geraldine McCarthy, MD FRCPI, School of Medicine and Medical Science, University College Dublin, Ireland

11. Geraldine McCarthy, MD FRCPI, Mater Misericordiae University Hospital, Eccles St, Dublin, Ireland

12. Lisa K. Stamp, PhD FRACP, Department of Medicine, University of Otago Christchurch, New Zealand

13. Fernando Perez-Ruiz, MD, Rheumatology Division, Hospital Universitario Cruces & BioCruces Health Research Institute, Vizcaya, Spain

14. Francisca Sivera, MD, Department Reumatologia, Hospital General Universitario de Elda, Alicante, Spain

15. Hang-Korng Ea, MD, Univ. Paris Diderot, Sorbonne Paris Cité, UFR de Médecine, F-75205 Paris, France; INSERM, UMR 1132, Hôpital Lariboisière, F-75475 Paris, France

16. Hang-Korng Ea, MD, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Lariboisière, Service de Rhumatologie, Centre Viggo Petersen, Pôle Appareil Locomoteur, 2, Rue Ambroise Paré, F-75010 Paris, France

17. Martijn Gerritsen, MD, Amsterdam Rheumatology Immunology Center (ARC), Department of Rheumatology, Westfries Gasthuis, Hoorn, The Netherlands

18. Carlo A. Scire, MD PhD, Epidemiology Unit, Italian Society for Rheumatology (SIR), via Turati 40, 20121, Milan, Italy

19. Lorenzo Cavagna, MD, Division of Rheumatology, University and IRCCS Policlinico S. Matteo Foundation, Viale Golgi 3, 27100, Pavia, Italy

20. Chingtsai Lin, MD, Division of Rheumatology, Immunology and Allergy, Taichung Veteran's General Hospital, Taichung, Taiwan, ROC

21. Yin-Yi Chou, MD, Taichung Veterans' General Hospital, 160 Taichung Road Section 3, Taichung, Taiwan 40705, ROC

22. Anne-Kathrin Tausche, MD, Division of Rheumatology, Department of Internal Medicine III, University Hospital Carl Gustav Carus, Fetscherstrasse 74, D-01307 Dresden, Germany

23. Geraldo da Rocha Castelar-Pinheiro, MD, Division of Rheumatology, Department of Internal Medicine, Universidade do Estado do Rio de Janeiro, Brasil

24. Matthijs Janssen, MD, Rijnstate Hospital, Arnhem, The Netherlands

25. Jiunn-Horng Chen, MD, School of Medicine, China Medical University, Taichung, Taiwan, ROC

26. Jiunn-Horng Chen, MD, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan, ROC

27. Marco A. Cimmino, MD, Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Italy

28. Till Uhlig, MD, National Advisory Unit on Rehabilitation in Rheumatology, Department of Rheumatology, Diakonhjemmet Hospital, Box 23 Vinderen, 0319 Oslo, Norway.

Corresponding author: Prof Nicola Dalbeth, Department of Medicine, University of Auckland, Private Bag 92019, 85 Park Road, Grafton, Auckland, New Zealand. Phone +64 9 3737999 x82568, Fax +64 9 3737677 Email: n.dalbeth@auckland.ac.nz

Keywords: gout, survey, epidemiology

Word count: 1,277, **Tables**: 2, **Figures**: 1, **Supplementary tables**: 1.

Funding statement: This study was supported by the American College of Rheumatology, European League against Rheumatism, Arthritis New Zealand, Association Rhumatisme et Travail, and Asociación de Reumatólogos del Hospital de Cruces.

Financial disclosures statement

Nicola Dalbeth: consultancy, honoraria or speaker fees from Takeda (<$10,000), Teijin (<$10,000), Menarini (<$10,000), Pfizer (<$10,000), ArdeaBiosciences/AstraZeneca (>$10,000), Cymabay (<$10,000), and Crealta (<$10,000).

H. Ralph Schumacher: consultancy, honoraria or speaker fees from Novartis, Regeneron, Metabolex and AstraZeneca (all<$10,000)

Jaap Fransen: no disclosures

Tuhina Neogi: no disclosures

Tim L Jansen: consultancy, honoraria or speaker fees from Abbvie, AstraZeneca, Bristol-Myers-Squib, Menarini and Roche (all <$10,000)

Melanie Brown: no disclosures

Worawit Louthrenoo: no disclosures

Janitzia Vazquez-Mellado: no disclosures

Maxim Eliseev: no disclosures

Geraldine McCarthy: no disclosures

Lisa K. Stamp: consultancy fees from AstraZeneca (<$10,000)

Fernando Perez-Ruiz: consultancy, honoraria or speaker fees from Menarini, Sobi, Pfizer, AstraZeneca, Novartis (all <$10,000)

Francisca Sivera: no disclosures

Hang-Korng Ea: no disclosures

Martijn Gerritsen: speaking fees or consultancy from Sobi and Menarini (all<$10,000)

Carlo A. Scire: no disclosures

Lorenzo Cavagna: no disclosures

Chingtsai Lin: no disclosures

Yin-Yi Chou: no disclosures

Anne-Kathrin Tausche: consulting fees/speaking fees from Berlin-Chemie Menarini, Ardea Biosciences/AstraZeneca and Novartis (all <$10,000)

Geraldo da Rocha Castelar-Pinheiro: no disclosures

Matthijs Janssen: no disclosures

Jiunn-Horng Chen: no disclosures

Marco A. Cimmino: consulting fees from Menarini (<$10,000)

Till Uhlig: consultancy fees for AstraZeneca and Sobi (<$10,000)

William J Taylor: consultancy, honoraria or speaker fees from Pfizer (<$10,000), educational grants from Abbvie, Roche, Pfizer (all <$10,000)

ABSTRACT

Aim: To identify the best performing survey definition of gout from items usually available in epidemiological studies.

Methods: Survey definitions of gout were identified from 34 epidemiological studies contributing to the Global Urate Genetics Consortium (GUGC) genome-wide association study. Data from the Study for Updated Gout Classification Criteria (SUGAR) were randomly divided into development and test datasets. A data-driven case-definition was formed using logistic regression in the development dataset. This definition, along with definitions used in GUGC studies and the 2015 ACR-EULAR Gout Classification criteria were applied to the test dataset, using monosodium urate crystal identification as the gold-standard.

Results: For all tested GUGC definitions, the simple definition of 'self-report of gout or urate-lowering therapy use' had the best test performance characteristics (sensitivity 82%, specificity 72%). The simple definition had similar performance to a SUGAR data-driven case-definition with five weighted items: self-report, self-report of doctor diagnosis, colchicine use, urate-lowering therapy use and hyperuricaemia (sensitivity 87%, specificity 70%). Both of these definitions performed better than the 1977 American Rheumatism Association survey criteria (sensitivity 82%, specificity 67%). Of all tested definitions, the 2015 ACR-EULAR criteria had the best performance (sensitivity 92%, specificity 89%).

Conclusions: A simple definition of 'self-report of gout or urate-lowering therapy use' has the best test performance characteristics of existing definitions that use routinely available data. A more complex combination of features is more sensitive, but still lacks good specificity. If more accurate case-definition is required for a particular study, the 2015 ACR-

EULAR Gout Classification criteria should be considered.

SIGNIFICANCE AND INNOVATIONS

- Gout epidemiology studies are hampered by the lack of a consistently used survey definition of gout.

- This large international study, using MSU crystal identification as the gold standard, has identified a simple survey definition with good test performance characteristics.

- However, the 2015 ACR-EULAR Gout Classification criteria have substantially better performance characteristics than any tested survey definitions.

INTRODUCTION

Limited information is usually available for the case-definition of gout in epidemiological studies, particularly for multipurpose cohorts. A standard and accurate method of case-definition is important for epidemiological studies, for reasons of efficiency and validity. However, many different combinations of data available from surveys or multipurpose cohorts have been used to identify gout cases in large population studies (1), and different case definitions of disease can lead to major variation in estimates of disease incidence and prevalence (2, 3). The aim of this study was to construct the best performing case-definition for gout from the limited items available in survey studies and multipurpose cohorts, testing these for accuracy against monosodium urate (MSU) crystal identification as the gold standard.

METHODS

Data from the Study for Updated Gout Classification Criteria (SUGAR) were analyzed. The methods of this study have been described in detail (4, 5); briefly, this was a large multinational cross-sectional study of 983 consecutive rheumatology clinic patients with at least one swollen joint or suspected subcutaneous tophus designed to identify clinical features that accurately distinguish gout from non-gout. At a standardized study visit, clinical features were recorded using case record forms, in addition to independent synovial fluid microscopy by a certified observer. Gout status was defined by synovial fluid or tophus aspirate microscopy result in all patients.

Items and combinations of these items used for definitions of gout in various surveys were identified from 32 studies contributing to the Global Urate Genetics Consortium (GUGC) genome wide association study of hyperuricaemia and gout (6), and were tested in the SUGAR dataset. The GUGC is a large genetic epidemiology study (>140,000 participants of European ancestry), 15 different definitions of gout were used, including the 1977 preliminary American Rheumatism Association survey definition (7) (Supplementary Table 1). Five items for survey definitions of gout were abstracted from the GUGC studies: patient self-report of gout, patient self-report of doctor diagnosis of gout, allopurinol or other urate-lowering therapy use, colchicine use, and self-report of elevated serum urate. These variables were all available in SUGAR with the exception of self-report of elevated serum urate, so actual serum urate level was used instead. Elevated serum urate (hyperuricaemia) was defined as serum urate greater than the upper limit of normal for the local laboratory.

Data from SUGAR were randomly divided into a development data subset (2/3) and test data subset (1/3). Items from the GUGC gout definitions were entered into a logistic regression analysis in the SUGAR development data subset to construct a data-driven case-definition, using MSU crystal defined gout/non-gout status as the dependent variable and backward selection. The score for the data-driven definition was derived from the beta coefficients in this model. The data-driven case-definition and definitions used in the GUGC studies (n=10 definitions with available data in SUGAR, including 7 composite definitions (Supplementary Table 1) were applied to the SUGAR test data subset and the sensitivity and specificity of each definition were calculated. The 2015 American College of Rheumatology (ACR)-European League Against Rheumatism (EULAR) Gout Classification Criteria were also applied to the test data subset (8, 9). Data were analyzed using SPSS v22 (SPSS Inc., Chicago, IL).

RESULTS

Development data subset

In the development data subset, all five items (patient self-report, patient self-report of doctor diagnosis, allopurinol or other urate-lowering therapy use, colchicine use, and elevated serum urate) independently contributed to the regression model (Table 1). Using these data, a score for case definition was derived from the five items: self-report of gout (3 points), self-report of doctor diagnosis of gout (2 points), colchicine use (1 point), urate-lowering therapy use (2 points), hyperuricaemia (3 points) (Table 1). The points were derived from rounding the beta coefficient from the multivariate model to the nearest 0.5 and multiplying by 2. A cut-point of >5 for the data-driven SUGAR survey definition provided maximal sensitivity and specificity according to the receiver operating characteristic curve (Figure 1).

Test data subset

The sensitivity and specificity for the data-driven SUGAR survey definition along with individual items, other definitions from GUGC studies, and the 2015 ACR-EULAR Gout Classification criteria were calculated in the SUGAR test data subset (Table 2). 'Self-report of gout' had the best overall performance as a single item (sensitivity 80%, specificity 72%). 'Use of urate-lowering therapy' as a single item had high specificity (91%), but very low sensitivity (36%). For all tested GUGC definitions, the simple definition of 'self-report of gout or urate-lowering therapy use' had the best test performance characteristics of existing definitions with sensitivity of 82% and specificity of 72%.

The data-driven SUGAR survey definition had a sensitivity of 87% and specificity of 70% in the test data subset. Overall, this performance was similar to the simple definition of 'self-report of gout or urate-lowering therapy use'. The simple definition of 'self-report of gout or urate-lowering therapy use' and the data-driven SUGAR survey definition both performed better than the 1977 American Rheumatism Association survey criteria (sensitivity 82%, specificity 67%). Of all tested definitions, the 2015 ACR-EULAR Gout Classification criteria had the best performance (sensitivity 92%, specificity 89%).

CONCLUSIONS

This analysis has identified that a simple definition of 'self-report of gout or urate-lowering therapy use' has the best, although not without limitations, test performance characteristics of existing survey definitions with sensitivity of 82% and specificity of 72%. Given the design features of SUGAR, the specificity is likely to be an under-estimate of test-performance for population studies and these values are therefore helpful in estimating worst-case misclassification rates from population studies. A more complex combination of features available from routinely collected data is more sensitive, but still lacks very high specificity. Importantly, none of these survey definitions perform as well as the 2015 ACR-EULAR Gout Classification criteria. However, the 2015 ACR-EULAR Gout Classification criteria require a patient interview for typical clinical characteristics of gout, physical examination and laboratory testing, with or without imaging assessment (8, 9). For large multipurpose epidemiological studies, particularly general cohorts not focused on gout or established before the 2015 Gout Classification criteria were published, such detailed information may not feasible or available, and for this reason survey definitions may be required.

Limitations of this study include recruitment for SUGAR from rheumatology clinics. Patients presenting to secondary care may not be representative of people with gout in a community or general population setting due to disease severity or comorbid conditions. It is also likely that the predictive properties of all definitions will differ in a general population cohort in which the majority of participants do not have gout. In addition, although the specificity of all these case-definitions are likely to be even higher among general population non-gout controls, it is likely that the same order of specificity values we observed in SUGAR would hold true in a general population sample. SUGAR did not collect information about self-report of elevated serum urate, and this variable may have different properties to hyperuricaemia defined by a laboratory test. It is also possible that different serum urate cut-points may alter sensitivity and specificity of a survey definition. This study has a number of strengths. SUGAR is a large, multinational study designed specifically to identify features that classify gout. The case definition of gout using the pathological gold standard of crystal identification is a major strength. The findings of this study are likely to be widely applicable, noting that the items 'self-report of gout or urate-lowering therapy use' are available in many surveys and multipurpose cohorts.

In summary, a simple definition of 'self-report of gout or urate-lowering therapy use' has the best test performance of existing survey definitions for epidemiological gout studies. If more accurate case-definition is required for a particular study, the 2015 ACR-EULAR Gout Classification criteria should be considered.

ACKNOWLEDGEMENTS

We gratefully acknowledge the help of Ole Slot (Copenhagen University Hospital Glostrup DK-2600, Denmark), Joung-Liang Lan, Chien-Chung Huang, Po-Hao Huang, Hui-Ju Lin and Su-Ting Chang (China Medical University Hospital, Taiwan), Anne Madigan (Dublin, Ireland), Yi-hsing Chen (Taichung, Taiwan), Alain Sanchez-Rodríguez and Eduardo Aranda-Arreola (Mexico City, Mexico), Viktoria Fana (Copenhagen, Denmark), Panomkorn Lhakum and Kanon Jatuworapruk (Chiang Mai, Thailand), Dianne Berendsen (Nijmegen, Netherlands), Femke Lamers-Karnebeek (Amsterdam, Netherlands), Olivier Peyr (Paris, France), Ana Beatriz Vargas dos Santos (Rio de Janeiro, Brasil), Fatima Kudaeva (Moscow, Russia), Angelo Gaffo (Birmingham AL, USA), Douglas White (Hamilton, New Zealand), Giovanni Cagnotto (Pavia, Italy) and Juris Lazovskis (Sydney, Canada) with data collection, crystal examination or patient referral. We are grateful to Eliseo Pascual (Alicante, Spain) for help with MSU observer certification.

AUTHORSHIP CONTRIBUTION STATEMENT

Nicola Dalbeth: 1a, 1c, 2, 3

H. Ralph Schumacher: 1a, 1c, 2, 3

Jaap Fransen: 1a, 1c, 2, 3

Tuhina Neogi: 1a, 1b, 1c, 2, 3

Tim L Jansen: 1a, 1c, 2, 3

Melanie Brown: 1b, 2, 3

Worawit Louthrenoo: 1b, 2, 3

Janitzia Vazquez-Mellado: 1b, 2, 3

Maxim Eliseev: 1b, 2, 3

Geraldine McCarthy: 1b, 2, 3

Lisa K. Stamp: 1b, 2, 3

Fernando Perez-Ruiz: 1b, 2, 3

Francisca Sivera: 1b, 2, 3

Hang-Korng Ea: 1b, 2, 3

Martijn Gerritsen: 1b, 2, 3

Carlo A. Scire: 1b, 2, 3

Lorenzo Cavagna: 1b, 2, 3

Chingtsai Lin: 1b, 2, 3

Yin-Yi Chou: 1b, 2, 3

Anne-Kathrin Tausche: 1b, 2, 3

Geraldo da Rocha Castelar-Pinheiro: 1b, 2, 3

Matthijs Janssen: 1b, 2, 3

Jiunn-Horng Chen: 1b, 2, 3

Marco A. Cimmino: 1b, 2, 3

Till Uhlig: 1b, 2, 3

William J Taylor: 1a, 1c, 2, 3

REFERENCES

1. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol. 2015;11:649-62.

2. Bardin T, Bouee S, Clerson P, Chales G, Flipo RM, Liote F, et al. Prevalence of gout in the adult population of France. Arthritis Care Res (Hoboken). 2015; Epub ahead of rpint.

3. Richette P, Clerson P, Bouee S, Chales G, Doherty M, Flipo RM, et al. Identification of patients with gout: elaboration of a questionnaire for epidemiological studies. Ann Rheum Dis. 2015;74:1684-90.

4. Taylor WJ, Fransen J, Dalbeth N, Neogi T, Schumacher HR, Brown M, et al. Performance of classification criteria for gout in early and established disease. Ann Rheum Dis. 2014; Epub ahead of print.

5. Taylor WJ, Fransen J, Jansen TL, Dalbeth N, Schumacher HR, Brown M, et al. Study for Updated Gout Classification Criteria (SUGAR): identification of features to classify gout. Arthritis Care Res (Hoboken). 2015; Epub ahead of print.

6. Kottgen A, Albrecht E, Teumer A, Vitart V, Krumsiek J, Hundertmark C, et al. Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. Nat Genet. 2013;45:145-54.

7. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum. 1977;20:895-900.

8. Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2015;74:1789-98.

9. Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. 2015 Gout Classification Criteria: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arthritis Rheumatol. 2015;67:2557-68.

Table 1. Regression model of individual survey items using the development data subset and data-driven SUGAR survey definition of gout. For the data-driven SUGAR survey definition of gout, a cut-point >5 points provided optimal sensitivity and specificity in the development data subset. Regression model chi-square 305, df 5, p<0.001, R-squared 0.54.

Item	Odds ratio (95% CI)	B coefficient (SE)	Points
Self-report of gout	4.1 (2.4, 6.8)	1.40 (0.26)	3
Self-report of doctor diagnosis of gout	3.1 (1.8, 5.1)	1.12 (0.26)	2
Hyperuricaemia	5.3 (3.3, 8.4)	1.67 (0.24)	3
Colchicine use	1.6 (1.0, 2.6)	0.49 (0.24)	1
Urate-lowering therapy use	2.2 (1.2, 3.9)	0.77 (0.31)	2

Table 2. Performance of individual items and composite survey definitions in the SUGAR test data subset.

	Sensitivity	Specificity	Youden index†
Single items used in the Global Urate Genetics Consortium study			
Self-report of gout	80%	72%	0.52
Self-report of doctor diagnosis of gout	80%	69%	0.49
Hyperuricaemia	85%	60%	0.45
Colchicine use	48%	76%	0.24
Urate-lowering therapy (ULT) use	36%	91%	0.27
Composite definitions reported in the Global Urate Genetics Consortium study			
Self-report of gout or ULT use	82%	72%	0.54
Hyperuricaemia and ULT use	31%	94%	0.25
Gout specific medications (colchicine or ULT)	61%	72%	0.32
Self-report of gout or gout specific medications	87%	61%	0.48
Self-report of gout and gout specific medications	53%	83%	0.36
Self-report of gout or hyperuricaemia	96%	50%	0.46
1977 preliminary ARA survey criteria	82%	67%	0.49
New composite definitions			
Data-driven SUGAR survey definition	87%	70%	0.57
2015 ACR-EULAR gout classification criteria	92%	89%	0.81

†Youden index = sensitivity + specificity - 1 (perfect test is 1, test no better than chance is 0)

ARA: American Rheumatism Association, ACR-EULAR: American College of Rheumatology-European League Against Rheumatism

FIGURE LEGENDS

Figure 1. Receiver operator characteristic (ROC) curve for the data-driven SUGAR survey definition in the development data subset. AUC (95% CI) for curve 0.83 (0.78, 0.88).

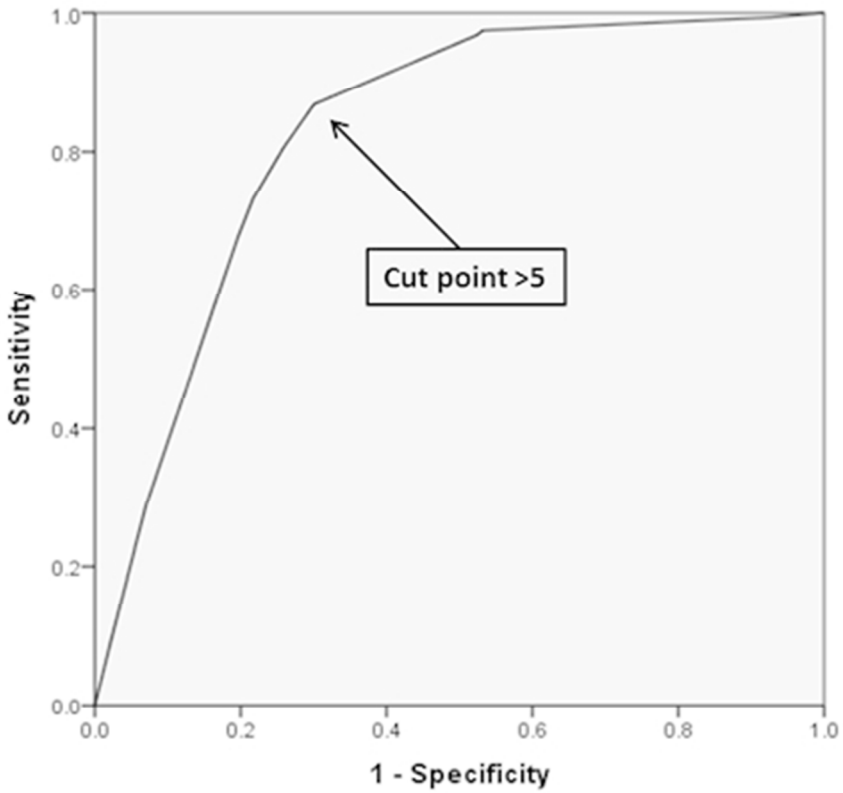

Figure 1. Receiver operator characteristic (ROC) curve for the data-driven SUGAR survey definition in the development data subset. AUC (95% CI) for curve 0.83 (0.78, 0.88).
40x34mm (300 x 300 DPI)