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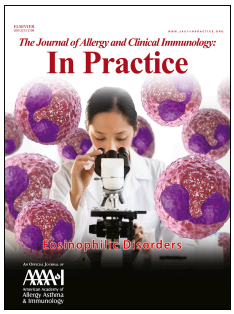

Development and validation of the Anaphylaxis Quality of Life Scale for Adults (A-QoL-Adults)

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TITLE PAGE

Original Article

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Conflicts of Interest

R Knibb: Work on the project paid for by a grant from the Department of Allergy and Immunology, University Hospitals Birmingham NHS Foundation Trust.

AP Huissoon: Speaker fees ALK Abello.

R Baretto: Sponsorship to attend a conference ALK Abello, Novartis. Honoraria for lectures and an educational grant from Thermofisher.

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ABSTRACT

Background: Anaphylaxis is a severe and potentially life-threatening allergic reaction which can have a detrimental impact on quality of life (QoL). There are no validated scales to measure the impact of anaphylaxis on QoL of adults.

Objective: The aim of this study was to develop and assess the reliability and validity of a QoL scale for adults with anaphylaxis (A-QoL-Adults).

Methods: All participants were recruited from a specialist allergy clinic and had a confirmed diagnosis of anaphylaxis (as per the WAO diagnostic criteria) to food, drugs, venom, latex or had spontaneous anaphylaxis. Interviews were conducted with 13 adults; data was analysed using thematic analysis to extract items for a QoL scale. A prototype QoL scale was then completed by 115 participants alongside validated scales to measure generic QoL (WHOQoL BREF), anxiety and depression (HADS) and stress (PSS).

Results: The A-QoL-Adults scale has 21-items demonstrating excellent internal reliability (Cronbach's alpha=0.96). Factor analysis produced 3 sub-scales: Emotional Impact; Social Impact; Limitations on Life. Each have excellent internal reliability (0.92; 0.92; 0.91 respectively). Poorer anaphylaxis-related QoL (total A-QoL-Adults score and sub-scale scores) correlated significantly with poorer general QoL and greater anxiety, depression and stress (all $p<0.01$ with medium to large effect sizes).

Conclusion: The A-QoL-Adults scale is a reliable measure of QoL in adults with anaphylaxis and shows good construct validity. It will offer healthcare professionals a means to further understand the impact of anaphylaxis on adult patients and could help direct and monitor allergy management and the need for further psychological intervention.

Highlights

What is already known?

- Anaphylaxis is potentially fatal, and detrimentally impacts patients' quality of life
- Currently there are no validated scales to measure the impact of anaphylaxis on QoL of adults.

What does this article add to our knowledge?

- We present a reliable and valid scale (A-QoL-Adults) to measure quality of life in adults with anaphylaxis.
- Use of the scale will enable direct comparison of the impact of anaphylaxis across different types of allergens.

How does this study impact current management guidelines?

- The A-QoL-Adults can be used in clinics or research to measure the impact of anaphylaxis on adults, direct allergy management advice and help evaluate formal interventions aimed at improving anaphylaxis management and quality of life.

Key words: Adults, anaphylaxis, quality of life, scale

Abbreviations

A-QoL-Adults: Anaphylaxis Quality of Life scale for Adults

HADS: Hospital Anxiety and Depression Scale

PSS: Perceived Stress Scale

QoL: Quality of life

WAO: World Allergy Organisation

WHOQoL BREF: World Health Organisation Quality of Life Scale (Brief version)

INTRODUCTION

People allergic to foods such as peanuts, nuts and shellfish, drugs such as penicillin or general anaesthetic agents, latex, bee and wasp venom can be at risk of having an anaphylactic reaction if they accidentally come into contact with the allergen[1]. Anaphylaxis is a potentially life-threatening systemic hypersensitivity reaction characterised by cardio-respiratory and muco-cutaneous manifestations requiring prompt administration of epinephrine alongside other supportive measures[2].

The lifetime prevalence of anaphylaxis is approximately 0.05-2.0% in the USA and around 3% in Europe[1] and a number of population studies have noted a rise in its incidence[3]. The risk or experience of anaphylaxis can have a great effect on quality of life. Research examining severe food allergy has found that it has an impact on the quality of life of children and adolescents and their families[4,5] and those with a history of anaphylaxis have reported poorer quality of life and greater anxiety than those with no such history[6]. Similar findings regarding the impact on quality of life have been reported for those with venom allergy[7,8] and drug allergy[9,10].

Recently, validated psychometric scales have been developed for food allergy[11] and venom allergy[7,12] but there is no such tool to measure the impact of the risk of anaphylaxis from any cause. To date, the impact of anaphylaxis has only been measured quantitatively as an item included on scales that measure quality of life for a particular type of allergy. The ability to measure the impact of anaphylaxis itself, the most serious allergic reaction, would provide information for patients and health care professionals and help direct information and support on allergy management, including allergen avoidance, being prepared for a reaction and to help recognise when anaphylaxis is having an impact on mental wellbeing. Such a tool would also enable clinicians and patients to monitor changes in quality of life following interventions aimed at improving anaphylaxis management. In this study we report the development and preliminary validation of an anaphylaxis quality of life scale for adults (A-QoL-Adults).

METHODS

Ethical approval was provided by the NHS Ethics Committees (reference: 16/SC/0238). All participants gave written informed consent.

Item Generation

Participants and procedures

Participants were 13 adults (aged 40-71; 5 males) newly diagnosed with anaphylaxis to drugs, food, venom or spontaneous anaphylaxis. Participants had to meet the World Allergy Organisation (WAO) diagnostic criteria[2] as assessed by a specialist in allergy. They were recruited using purposive sampling (to ensure all anaphylaxis triggers were included in the sample) from allergy clinics in University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.

Interviews and analysis

Interviews were conducted by an experienced psychologist (KN), who was not a member of the direct clinical care team. They were audiotaped, transcribed verbatim and analysed independently by RK and CS using inductive thematic analysis. Full details of the qualitative phase have been published previously[13]. Results of the thematic analysis and a literature review informed the development of items for inclusion in a prototype scale. The items and rating scale were discussed within the study team, which comprised of psychologists and allergy specialist clinicians working with adults with anaphylaxis. Two further items were added and a rating scale was agreed. This process resulted in a 28-item prototype scale of questions that could be answered by an adult with anaphylaxis from any cause. A further 8 questions were added that were specifically related to particular causes: food, insect venom, drugs and spontaneous anaphylaxis. The response scale was from 1-5 with 1=never, 2=rarely, 3=sometimes, 4=most of the time, 5=always.

Scale reliability and validity

Participants and procedure

To assess reliability and validity of the scale, adult participants (aged ≥18 years) with a diagnosis of anaphylaxis meeting WAO diagnostic criteria[2] as assessed by a specialist in allergy were recruited from allergy clinics in UHB, Birmingham, UK. Patients were systematically assessed with clinical

history and allergy tests as per British Society for Allergy and Clinical Immunology and European Association of Allergy and Clinical Immunology guidelines[14-20]. All eligible participants who attended the clinics were provided with a study participant information sheet by health care professionals at the allergy clinic. If they wanted to take part, they were asked to sign a consent form and complete the prototype scale and validation scales in clinic or take them home for completion there. If they took the questionnaires home, they were provided with an envelope with a stamp and the return address, for the participant to post them back to the RK's study team at Aston University, Birmingham. All completed questionnaire packs were separated from consent forms, assigned a study code and analysed anonymously.

Cross-sectional validation measures

Participants completed three scales to assess convergent construct validity. These were the World Health Organisation Quality of Life Scale (Brief version) (WHOQoL BREF)[21] to measure generic quality of life, the Hospital Anxiety and Depression Scale (HADS)[22] to measure anxiety and depression and the Perceived Stress Scale (PSS)[23] to measure stress. Scales were chosen that measured variables that had a relationship with quality of life or were connected with suffering from anaphylaxis. All scales are validated for a general population and have excellent reliability and validity. Further details of each scale can be found in the online repository. Participants were also asked to complete demographic information and information about their anaphylaxis. These data were also extracted from their clinical records and cross-checked with the self-report data.

Statistical analysis

Data analyses were conducted using SPSS version 25. The data was checked for floor and ceiling effects (to ensure no items had very high or very low scores which meant they were not discriminatory across participants). Exploratory factor analysis (maximum likelihood method) was conducted to remove items that reduced internal structural validity and to explore the existence of underlying clusters of variables that would indicate the existence of sub-scales. Cronbach's α coefficient was conducted to assess internal reliability of the scale. Construct validity was conducted by examining correlations between the A-QoL-Adults and the other validated questionnaires using Pearson's bivariate

correlations. Correlations were classed as large if over 0.5, medium if 0.3-0.49 and small if 0.29 or below. All tests were 2-tailed with a significance level set at $p<0.05$.

RESULTS

Scale reliability and validity

A total of 115 participants completed the questionnaires. A diagram showing recruitment can be seen in Figure 1. Demographic information and anaphylaxis characteristics of these participants can be found in Table 1. Participants reported anaphylaxis to food, venom, medication, latex or had spontaneous anaphylaxis, with n=8 reporting anaphylaxis to more than one trigger.

Internal structural validity of the A-QoL-Adults

Mean scores were checked for each item and there were no floor or ceiling effects. Factor analysis using the maximum likelihood method with a varimax rotation was then conducted on the 28 core items of the prototype A-QoL-Adults. The KMO statistic (0.92) showed that the sample size was sufficient for factor analysis and exceeding the recommended value of 0.6[25]. The Bartlett's Test of Sphericity (2024.30, *df* = 210, p<0.001) was significant, indicating that factor analysis on the correlations between items should produce meaningful factors. The solution produced a good fit with the data (goodness of fit χ^2=294.09(150), p<0.001).

Seven items with low factor loadings (less than 0.4, indicating they did not correlate well with other items) were removed and the analysis was re-run, giving a 21-item solution, consisting of three factors (underlying variables on which items correlate together) which explained 65.9% of the total variance in the data. A clear interpretation of factors could be made and they were called: Social Quality of Life, Emotional Quality of Life and Limitations on Life (see Table 2; reported loadings indicate which item relates to each factor or sub-scale of the A-QoL-Adults). To score the A-QoL-Adults, all items are summed and then divided by 21 to get a total mean score between 1 and 5. Sub-scale items are also summed and divided by the number of items in each sub-scale. A higher score indicates a greater impact of anaphylaxis on quality of life. There are no items that need to be reverse scored. The full scale along with the supplementary items (Table E1) and scoring information, including items belonging to each sub-scale (Table E2), can be found in the online repository.

Internal reliability of the A-QoL-Adults

The 21 items of the A-QoL-Adults and each of the three sub-scales had excellent internal consistency with all Cronbach's alpha levels over 0.90 (see Table 2).

Cross-sectional construct validity of A-QoL-Adults

The A-QoL-Adults significantly correlated with general quality of life, anxiety, depression and stress (Table 3). Correlations were generally medium to large in size and indicated that poorer anaphylaxis-related quality of life was related to poorer general quality of life, greater anxiety, greater depression and greater stress (see Table 3). Correlations were also run on the supplementary item scores (Table 4). Significant correlations were found with answers related to venom allergy anaphylaxis and general quality of life (in all but the environmental domain), anxiety, depression and stress. Food allergy anaphylaxis significantly correlated with psychological and environmental quality of life, anxiety and stress. Spontaneous anaphylaxis correlated significantly with anxiety and depression. In all cases, poorer anaphylaxis-related quality of life for the supplementary items was related to poorer generic quality of life, greater anxiety, depression or stress. There were no significant correlations for the two items related to drug allergy anaphylaxis.

Simple regression models were run to assess the ability of the A-QoL-Adults to predict anxiety, depression or stress (Table 5). Anaphylaxis related quality of life significantly predicted levels of stress, anxiety and depression with all models significant at $p<0.001$.

DISCUSSION

The A-QoL-Adults was developed using gold standard guidelines[24,25] for scale development, and preliminary evidence shows it to be both internally reliable and have good convergent construct validity. The prototype scale was developed after interviews with 13 adult participants who experienced anaphylaxis to food, venom, drugs and spontaneous anaphylaxis[13]. The majority of the items extracted from the interviews were relevant for adults with anaphylaxis to any of these triggers or multiple triggers and these core items showed excellent internal reliability with Cronbach's alpha levels over 0.90 for the overall scale and for each sub-scale.

Convergent construct validity was assessed by correlating scores on the A-QoL-Adults with constructs that are related to quality of life or associated with having anaphylaxis. All correlations were medium to large in size, with particularly high correlations seen for anaphylaxis related quality of life and anxiety. Regression models showed that anaphylaxis related quality of life also significantly predicted anxiety, depression and stress. As models were run on cross-sectional data, we cannot state that the scale has predictive validity, but the significance of the models provides some support which could be tested in longitudinal studies. The data suggests that those with poor anaphylaxis related quality of life may not only need help in management of the condition, but psychological support to reduce mental distress and so it is important for clinicians to be aware of this when assessing patients.

Eight further items are included in the scale which are applicable to people who developed anaphylaxis to specific triggers: food, insect venom, drugs and spontaneous anaphylaxis. Only venom and food allergy items demonstrated evidence of construct validity. There was limited evidence of this for spontaneous anaphylaxis, with significant correlations with anxiety and depression, but there were no significant correlations for drug allergy. There are only two supplementary questions per trigger and this may not be enough to demonstrate good construct validity, so these items should be treated with some caution. Nevertheless, they could be used for patients with these particular triggers to provide further specific information on where support might be needed in relation to allergy management such as avoidance of allergens.

Further work is needed on the A-QoL-Adults to confirm reliability and validity across different demographics and presentations of anaphylaxis. Although initial uptake of the study was high, two thirds of participants who had a questionnaire pack sent home did not return them. Completing packs in clinic was more efficient but not always possible and not all participants wished to do this. This level of response is not unusual for this type of study design, but it must be acknowledged that it is unknown if those not responding would have answered differently. There was a wide age range for the current sample and further work would be useful to see if there is a variation in QoL by age, that can be measured by the scale. Both the development and validation of the scale was conducted on predominantly white British participants and so reliability and validity of the scale in other ethnic groups needs to be established. Almost 60% of the current sample were educated to a post-high school level (A levels in the UK education system) and so it would be useful to conduct further testing on adults who have not reached this level of education. There was a fairly even distribution across the different anaphylaxis triggers (albeit with a high proportion of those with spontaneous anaphylaxis), but only three participants reported latex allergy and so the reliability and validity of the scale for this trigger should be treated with caution. In further work on this scale, the factor structure of the scale should be confirmed using confirmatory factor analysis and a test re-test should also be carried out to see if the scale is stable over time. Use of the scale in longitudinal studies, particularly those which include an intervention, will provide evidence of sensitivity to change.

In conclusion, the A-QoL-Adults is a reliable and valid tool to assess quality of life in adults with anaphylaxis to any trigger and can be used in research and clinical practice. Results from the scale could help direct information and support on allergy management, including allergen avoidance, being prepared for a reaction and how to treat it and to help recognise when anaphylaxis is having an impact on mental wellbeing, where referral to a psychologist might be helpful. Importantly the scale measures the impact of anaphylaxis from any cause and can be used with patients with multiple triggers. This means that a clinician is able to use this one scale with any of the adult patients they see with this condition. It will also be possible to directly compare the impact of anaphylaxis on quality of life across different types of allergens using this scale. It will offer healthcare professionals a means to further understand the impact anaphylaxis has on their patients and could help direct and monitor suitable interventions.

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409 **Figure legends**

410

411 Figure 1. Flow diagram showing study recruitment
412

413

414 Table 1 Demographic information and anaphylaxis characteristics

415

		N=115 N (%)
Mean age in years (S.D.)		42.73 (16.85)
Age range in years		18-78
Gender	Male	45 (39.1)
	Female	69 (60)
	Prefer not to say	1 (0.9)
Ethnicity	White	96 (83.5)
	Indian/Pakistani	9 (7.8)
	African/Caribbean	2 (1.7)
	Prefer not to say	2 (1.7)
	Other	5 (4.3)
Highest level of education	Vocational qualification	12 (10.5)
	Secondary/High school level	24 (20.8)
	A level/post High school level	29 (25.2)
	Undergraduate degree	38 (33.0)
	Postgraduate degree	0
	None	4 (6.1)
Mean N of anaphylactic reactions (S.D.)		3.86 (8.26)
Cause of anaphylaxis	Food	43 (37.4)
	Medication/drugs	28 (24.3)
	Wasp/Bee venom	24 (20.9)
	Latex	3 (2.6)
	Unknown/spontaneous	25 (22.6)
Symptoms	Difficulty breathing	77 (67.0)
	Skin rash	75 (65.2)
	Itchy skin	73 (63.5)
	Vomiting	25 (21.7)
	Swelling of mouth, lips or face	76 (66.1)
	Loss of consciousness	21 (18.3)
	Drop in blood pressure	51 (44.3)
Prescription of an epinephrine autoinjector	Yes	97 (84.3)
How often do you carry your epinephrine autoinjector	Never	8 (7.0)
	Rarely	5 (4.3)
	Sometimes	9 (7.8)
	Most of the time	19 (16.5)
	Always	50 (43.5)
Other allergies	Yes	59 (51.3)
Asthma	Yes	16 (13.9)
Eczema	Yes	6 (5.22)
Other physical illness	Yes	45 (39.1)
Family history of allergy	Yes	33 (28.7)

416 Figures represent mean (SD) or number (%). Where totals do not equal 100% there is missing data;
417 where they total more than 100% participants could select more than one option
418

Table 2 Factor analysis with factor loadings (correlation between the item and the factor) of the A-QOL-Adults 21-item scale

Items	Social	Emotional	Limitations
Cronbach's alpha (α) for 21 items = 0.96	**α=0.92**	**α=0.92**	**α=0.91**
I feel isolated because of my anaphylaxis	.754		
I feel I am a burden to my family and friends	.737		
I avoid holidays in the UK because of my anaphylaxis	.658		
I get frustrated that people don't know what anaphylaxis is	.618		
I avoid holidays abroad because of my anaphylaxis	.612		
Having anaphylaxis stops me getting on with my life	.578		
I get frustrated that others don't take anaphylaxis seriously	.575		
I feel out of control of my life because of anaphylaxis	.571		
My work has been affected because of anaphylaxis	.497		
I feel scared that I might have an anaphylactic reaction		.860	
Having another anaphylactic reaction plays on my mind		.815	
I worry that I could have an anaphylactic reaction at any time		.749	
I'm afraid that my next anaphylactic reaction will be worse		.633	
I feel helpless because of my anaphylaxis		.627	
I worry that I might die because of an anaphylactic reaction		.566	
The risk of having a reaction stops me doing things I'd like to do			.814
I get annoyed about missing out on things			.742
I have to plan things in advance to avoid having a reaction			.645
I feel that my anaphylaxis is a nuisance			.546
I get frustrated because of my anaphylaxis			.518
I am less confident about doing things because of my anaphylaxis			.517
Eigenvalues	**5.00**	**4.77**	**4.07**
% variance explained	**23.84**	**22.70**	**19.37**

Table 3 Correlations between the A-QOL-Adults, the WHOQOL BREF, the HADS and the PSS to demonstrate cross-sectional construct validity

Scale	A-QOL-A			
	Total score	**Emotional**	**Social**	**Limitations**
WHOQOL BREF				
Physical QoL	-.45**	-.29**	-.51**	-.38**
Psychological QoL	-.43**	-.39**	-.40**	-.37**
Social QoL	-.35**	-.23*	-.37**	-.38**
Environmental QOL	-.46**	-.36**	-.45**	-.48**
HADS				
Anxiety	.72**	.74**	.67**	.60**
Depression	.51**	.47**	.51**	.43**
PSS				
Stress	.43**	.49**	.38**	.34**

*p<0.05; **p<0.01

Table 4 Correlations between the WHOQOL BREF, the HADS and the PSS and supplementary A-QOL-Adults questions to demonstrate cross-sectional construct validity

Scale	A-QOL-Adults supplementary questions			
	Venom allergy	Food allergy	Drug allergy	Spontaneous allergy
WHOQOL BREF				
Physical QoL	-.38*	-.18	-.14	-.09
Psychological QoL	-.40*	-.35*	-.17	-.27
Social QoL	-.35*	-.19	-.08	-.05
Environmental QOL	-.12	-.40**	-.02	-.24
HADS				
Anxiety	.50**	.50**	.26	.57**
Depression	.38*	.24	.17	.30*
PSS				
Stress	.34*	.43**	.08	.26

*p<0.05;**p<0.01

Table 5 Simple regression models with the A-QOL-Adults total mean score as the predictor and anxiety, depression or stress as the outcome variable.

Outcome variable	Unstandardised Beta	Standardised beta	Lower CI	Upper CI	R^2 (Adj R^2)	F
Stress	3.95	.43	2.32	5.58	.43 (.18)	23.19***
Anxiety	3.67	.72	2.99	4.35	.72 (.52)	114.26***
Depression	2.14	.51	1.43	2.84	.51 (.26)	36.34***

***p<0.001