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Modeling Health State Utility Values in Ankylosing Spondylitis: Comparisons of Direct and Indirect Methods

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ABSTRACT

Objectives: Cost-effectiveness analyses of technologies for patients with ankylosing spondylitis frequently require estimates of health utilities as a function of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI). **Methods:** Linear regression, bespoke mixture models, and generalized ordered probit models were used to model the EuroQol five-dimensional questionnaire as a function of BASDAI and BASFI. Data were drawn from a large UK cohort study (n = 516 with up to five observations) spanning the full range of disease severity. **Results:** Linear regression was systematically biased. Three- and four-component mixture models and generalized probit models exhibit no such bias and improved fit to the data. The mean, median, mean error, and mean absolute error favored the mixture model approach. Root mean square error favored the generalized ordered probit model approach for the data as a whole. Model fit assessed using these same measures by disease severity quartiles tended to be best using the mixture models. The value of moving from good to poor health may differ substantially according to the chosen method. Simulated data from the mixture and probit models yield a very similar distribution to the original data set. **Conclusions:** These results add to a body of evidence that the statistical model used to estimate health utilities matters. Linear models are not appropriate. The four-class bespoke mixture model approach provides the best performing method to estimate the EuroQol five-dimensional questionnaire values from BASDAI and BASFI.

Keywords: ankylosing spondylitis, EQ-5D, mapping.

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Introduction

A substantial proportion of economic evaluations estimate the incremental cost per quality-adjusted life-year from studies of clinical effectiveness in which no utility-based instrument was administered [1]. They span a broad range of disease areas. Many studies bridge the gap between clinical outcomes measured within a trial and utility-based measures required to calculate quality-adjusted life-years using regression-based methods.

This entails the use of a separate, external data set in which some samples of patients have data recorded simultaneously for both the relevant clinical outcome measure(s) and the desired preference-based measure. A regression can then be constructed with the preference-based measure as the dependent variable and the clinical outcome measures(s) and other covariates as independent variables and the results used to estimate values required in the economic evaluation. The term "mapping" has been used by health economists to describe this process.

Ankylosing spondylitis (AS) is one disease area in which such methods have been widely applied. AS is an inflammatory disease principally affecting the sacroiliac joints at the base of the spine and the spine itself, causing back pain, stiffness, and risk of spinal fracture in later stages of the disease [2–4]. There may be the development of new bone and joint fixation, termed ankylosis. Other large joints may be affected and less commonly the eyes, the bowel, and the cardiovascular system. Symptom onset is typically in late teens or early adult years, with males affected two to three times more commonly than females. The spinal disease is generally progressive and irreversible.

Therapies for AS include drugs used as disease modifiers in rheumatoid arthritis and nonsteroidal anti-inflammatory drugs. Physiotherapy and exercise aim to provide symptomatic relief and spinal mobility improvement. In recent years, biologic drugs such as etanercept and adalimumab have been licensed for use in AS. These are high-cost therapies, obvious candidates for economic evaluation, and consequently feature in most published cost-effectiveness studies.

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The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is the most commonly used instrument to measure disease activity in AS [5]. It comprises six patient-reported questions relating to five major symptoms: fatigue, axial pain, peripheral pain, stiffness, and enthesopathy. Responses are recorded on a 10-cm visual analogue scale or an 11-point numerical rating scale, with higher scores indicating higher disease activity.

The Bath Ankylosing Spondylitis Functional Index (BASFI) is a measure of physical function [6]. It is a patient-assessed, validated, composite index made up of 10 questions that address function and the patient's ability to manage his or her AS. As with the BASDAI, responses are recorded on a 10-cm visual analogue scale or an 11-point numerical rating scale. The BASFI is scored on a 0 to 100 scale, with higher scores indicating a greater degree of functional impairment. These scores are widely applied in clinical practice and studies [7].

Mapping functions that feature in cost-effectiveness studies in AS are all simple linear regressions to estimate the values of Health Utilities Index Mark 3 [8] or the EuroQol five-dimensional questionnaire (EQ-5D) [9–12]. Yet, it is now well established that linear regression models tend to lead to biased results because of several characteristics inherent to health utility instruments. Specifically, utility instruments have upper and lower bounds, have a mass at the upper bound, and can be further characterized by multimodality and skewness. Most statistical models that have been applied in the mapping field, and linear models in particular, systematically underestimate health utilities for those in relatively good health and overestimate utilities for those in poor health, thus underestimating the cost-effectiveness of health technologies. Kobelt et al. [13] recognized that simple regression models are inappropriate and instead simply calculated mean EQ-5D values for each of 25 different BASDAI/BASFI-defined categories for use in their evaluation of infliximab. These features have been demonstrated in diverse disease areas such as cancer [14], heart disease [15], and incontinence [16] as well as in other rheumatological conditions such as rheumatoid arthritis [17–19] and osteoarthritis [20].

There is therefore a need to generate appropriate functions to link BASDAI and BASFI to health utilities to produce unbiased estimates of cost-effectiveness. This article addresses that need by estimating the UK tariff EQ-5D using data from a large UK cohort study. Statistical models estimated are those that have both theoretical and empirical evidence to support their appropriateness in modeling EQ-5D. These are 1) a direct modeling approach based on mixture models comprising distributions bespoke to the EQ-5D and 2) an indirect approach that estimates the probability of being at each of the three levels of the five EQ-5D dimensions followed by calculation of the expected tariff value. These approaches have been compared directly using data from patients with rheumatoid arthritis, linking the Heath Assessment Questionnaire instrument to the EQ-5D [17]. In that setting, both methods overcame the problem of systematic bias and demonstrated performance superior to that of the linear model, with the direct approach achieving better outcomes than the indirect approach. This article aims to provide further comparative evidence of mapping method performance.

Methods

Primary Data Set

Five hundred sixteen patients with AS provided data on up to five occasions to the Population-Based Ankylosing Spondylitis cohort study in Wales, UK. For a full description of the study, see Atkinson et al. [21]. In brief, these patients were recruited by sending letters to patients registered as having AS with rheumatologists in Wales, as well as patients registered with participating family doctors. Participants had to have a diagnosis of AS confirmed by a rheumatologist. Participants completed questionnaires, either online or via a paper-based postal method, every 3 months, including demographic data, measures of severity, work and activity limitations, out-of-pocket expenses, transport to health care appointments and carer assistance, flares, exercise, and coping questions. The study had ethical approval from the London Multi-centre Research Ethics Committee (Research Ethics committee no. 08/H0718/64), and the written consent of participants was obtained according to the Declaration of Helsinki.

Statistical Methods

The distribution of the EQ-5D exhibits many features that render standard approaches to regression analysis inappropriate. The EQ-5D tariff score is bounded at 1 (full health) and exhibits a large gap to the next feasible value of 0.883. There is a lower bound of −0.594, and the remainder of the distribution tends to be bimodal or trimodal. Although the linear regression model is the most widely applied in this field, it has been repeatedly shown to predict values outside the feasible range, to underpredict EQ-5D scores for patients in relatively good health and overpredict EQ-5D scores for patients in severe health states.

In this article, we tested methods that have theoretical relevance for these type of data and have some degree of empirical support in the literature, namely, the direct approach based on bespoke mixture modeling first reported in Hernandez Alava et al. [19] and the indirect approach based on generalized ordered probit models reported in Hernandez Alava et al. [17]. Full details of these statistical models can be found elsewhere [17,19]. We included linear regression for comparative purposes.

The direct approach uses mixture models because of their flexibility to approximate complex nonstandard distributions as a mixture of component distributions. For the EQ-5D, the component distributions are limited above and below at the appropriate level for the UK tariff, and also have a gap between 1 and 0.883 to mirror feasible values in the tariff. The modeling approach is therefore appropriate for the EQ-5D whether it is intended to use results in a cohort or individual simulation-based economic assessment.

The indirect approach is a development of "response mapping" described by Gray et al. [22] but that respects the ordered nature of the responses. Five separate generalized ordered probit models are estimated where the dependent variable is the level ("no problems," "some problems," and "no problems") for each of the five dimensions of health described by the EQ-5D. This stage leads to estimates of the probability of being at each of these three levels. The probability of being in any of the 243 health states described by the EQ-5D can then be calculated conditional on covariates. The expected tariff is then calculated analytically [17].

All analyses were calculated using STATA v13. The indirect method was analyzed using the GOPROBIT command. Previous applications of the direct mixture model approach have used the GAUSS software. For this application, we programmed a new STATA command, ALDVMM.ado, which implements a version of the bespoke mixture model for independent observations and is available as an Appendix in this article's Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.02.016. Models were estimated using maximum likelihood. Reported *P*-values are based on robust standard errors to take into account the repeated observations.

We considered BASDAI, BASFI, age, sex, and disease duration as potential covariates. Alternative models were compared in terms of Akaike and Bayesian information criteria. The overall mean estimates, mean absolute error, and root mean square

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