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Rheumatoid arthritis disease progression in a South African cohort: Bayesian multistate chronic disease, dynamic modelling

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Monitoring of disease progression in rheumatoid arthritis patients

Rheumatoid arthritis (RA) is a chronic disease, that affects many tissues and organs, but mainly flexible joints making them tender or swollen (1). RA can lead to permanent disability or substantial loss of functioning and mobility if not adequately treated. Arthritis is the most common physical reason for people, especially the elderly, becoming disabled and encountering difficulty in performing activities of daily living (2). A clinical measure useful for monitoring disease progression (remission, low, moderate and high) is the 28 joint disease activity score (DAS28) (3). When patients respond well to treatment they generally move from high disease activity (DAS28 > 5.1) to moderate, low disease activity and eventually remission (DAS28 < 2.8).

Globally chronic disease treatment pose a great financial burden on patients, government health support structures and medical schemes (4). The primary goal of this article is to model the forces (rates) of recovery, relapse and mortality for patients started on RA standard treatment and the effect of adjusting for body functionality.

A multistate semi-parametric Cox survival Bayesian model

A four state model inclusive of the absorbing state 'death' was fit to these data. A consequence of an improved health is better body functionality, which was measured using a health assessment disability index (HAQ-DI). Bayesian based models were fit to the data adjusting for HAQ-DI to assess the effect of other variables to the forces of recovery and/or relapse.

The modelling was done using a member of the generalised additive mixed models (GAMMs) which utilise nonparametric functions adjusting for over-dispersion and correlation (5). This approach allows us to fit the often numerically intractable (non-integrable) GAMMs such as clustered, nested, hierarchical and spatial models. These models were fit using the free statistical software R-cran (6) and BayesX (7).

The four multistate model fit is an extension of the Cox semi-parametric model. The Cox model is a special case of the multistate model, with only two mono-directional states (8). The two states and multistate models are discussed in Appendix 1, giving the linkage between the two.

Gauteng Region Early Arthritis Trial (GREAT)

The RA data were from a longitudinal study on patients diagnosed within two years of disease onset who were disease modifying drugs (DMARDs) naive, from Baragwaneth and Steve Biko teaching hospitals in Gauteng Province, South Africa (9). There were 171 patients whose average age was 47 (±12.5) years, 84% was rheumatoid factor positive, the majority (82%) were females and 23% were smokers. The average years in school was 8.9 (±3.2) and the average months of illness duration before treatment was 11.7(±7.0).

The patients would move multi-directionally within the states: remission, moderate and severe disease activity, or permanently into the absorbing state (death). On fitting a model with no covariates, we found that the average time patients spent in severe, moderate or remission was 8.0, 1.3 and 7.0 months respectively, as show in Figure 1 (left hand side). A patient starting with moderate disease is 3.75 times (7.084/1.89) more likely to get worse than get better if we do not adjust for HAQ-DI. When adjusting for better functionality the rates of worsening disease diminished significantly, for example from moderate to remission a 2.22 (4.197/1.89) times greater, and the time spent in the remission state was more than halved from 7 months to 3.1 (-12/-3.857) months reduction in rate (Figure 1 right hand side). Based on the higher forces from moderate to severe compared to remission it is desirable to keep patients in the remitting state to increase their likelihood of full recovery. Body functionality compliments the recovery process of RA patients on DMARDs treatment and also reduces the mortality rates significantly.

In conclusion, we advocate that patients should be treated until the disease activity score is in remission or lowest possible to enable greater physical functionality whilst alleviating disability and reducing mortality due to RA. Interventions like physiotherapy or exercise can have a positive impact on increasing body functionality thereby expediting the recovery process for RA patients. Lastly since

the patients were observed within two years of disease onset, there is value in advocating for public health awareness for people to present early before much bodily damage has occurred to enable better response to treatment.

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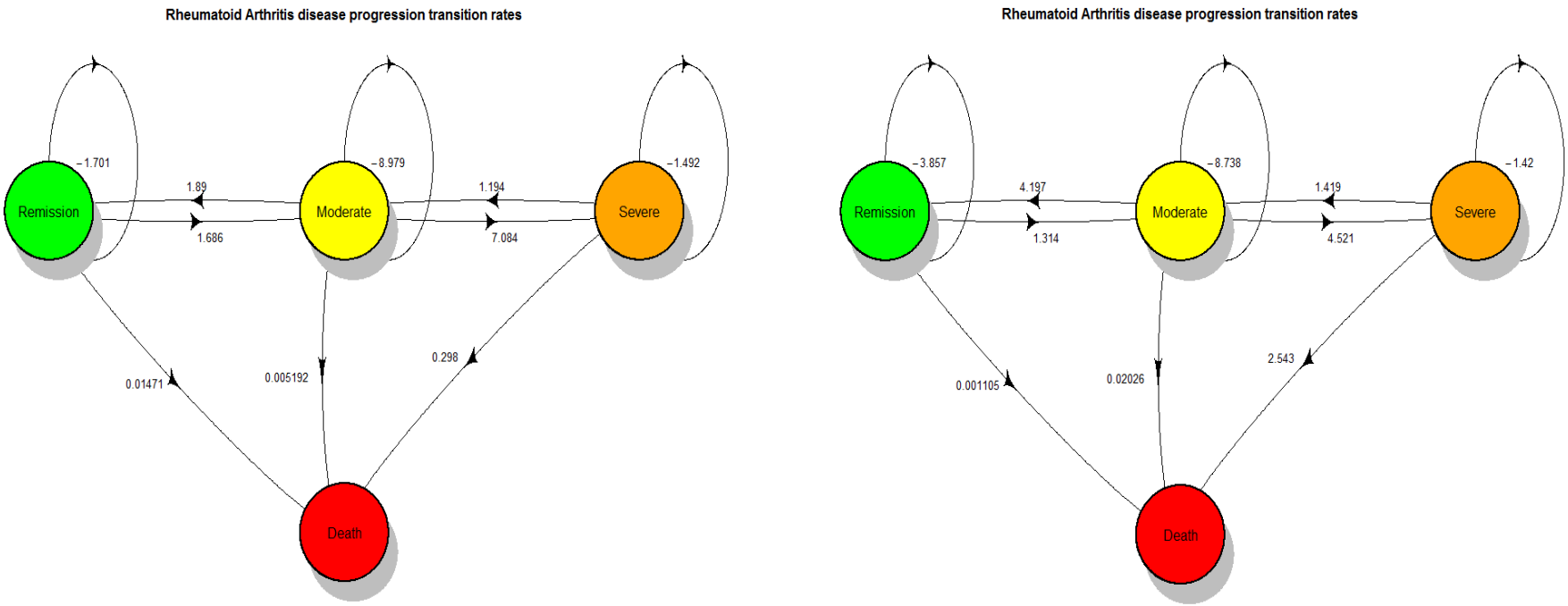

Figure 1: Four states rheumatoid arthritis model for the GREAT cohort from South Africa: Model without covariates (left hand side) and model adjusting for HAQ-DI (right hand side)