Letters to the Editor

Rheumatology 2002;41:701

Re: Chehata et al. Mortality in rheumatoid arthritis: relationship to single and composite measures of disease activity

Sir, The authors’ finding that the presence of nodules and rheumatoid factor titre are independently related to mortality in rheumatoid arthritis is striking. I have some concerns about the statistical method they have used to include rheumatoid factor; this may have biased their Cox regression model.

Rheumatoid factor was included in the model as the reciprocal of its titre. This results in a very skewed distribution (see Table 2; the standard deviation of rheumatoid factor is far larger than the mean value). At baseline, the univariate regression coefficient and hazard ratio quoted for rheumatoid arthritis latex (RAL) titre seem inconsistent with the P value of <0.001 (Table 4).

In the stepwise model, the authors state that for every 100-unit rise in this reciprocal, there is a 1.09 increase in hazard ratio. This equates to an increase in hazard of 1.14 for titre 1:160 (1.09(160/100)), 3.0 for titre 1:1280 (1.09(1280/100)) and 9.1 for titre 1:2560 (1.09(2560/100)) [1]. This progression seems improbable; the reason is that the underlying assumption of proportional hazards has been violated by including rheumatoid factor in this way (see [1] for discussion). It would have been more appropriate to log-transform the rheumatoid factor titre prior to inclusion in the model—failure to do so may overestimate its effect. Re-running the analysis with log-transformed RAL titre might allow other variables, previously lost in the stepwise regression, to show their true effects.

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Reply

We thank Dr Grove for his contribution. Taking logs of rheumatoid arthritis latex titre (RAL) in the analysis in Table 4 results in it becoming non-significant (P = 0.07). Re-running the analyses in Table 4 for the non-transformed RAL confirms the results apart from the regression coefficient being 0.0012 rather than 0.012. The effect in the stepwise routine of using log RAL is to choose only age and the presence of nodules.

On reflection, it would probably have been better to treat RAL as an ordinal categorical variable rather than a continuous variable. We re-ran the Cox regression analysis using this transformation with the result that the hazard functions were approximately parallel and that the two largest values in RAL (1280 and 2560) showed much larger hazard ratios than all lower values. If the RAL is expressed as a binary variable, where >1280 is compared with <1280 in a Cox regression with age, sex and history, this yields the following: regression coefficient = 1.593, hazard ratio = 4.922 (95% confidence interval 2.201–11), P < 0.001. In the stepwise routine, age, presence of nodules and binary RAL (P < 0.002) were chosen.

Our objective in looking at RAL was to study whether increased RAL resulted in higher mortality. This was confirmed in this new analysis for the high RAL values. The main message of the paper is unchanged.

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