Letter and Reply

Crippling of inflammatory markers as predictors of death by dichotomization and multicollinearity

Sir,

Caravaca et al. [1] recently addressed the important issue of whether the determination of inflammatory markers, in particular C-reactive protein (CRP), in patients with chronic kidney disease (CKD) adds to their prognostic evaluation in terms of mortality. They conclude that the determination of inflammatory markers is not helpful if age and comorbidity are taken into account. It would, however, be appropriate if some further analyses were performed before such a conclusion is advanced. The conclusion of Caravaca et al. [1] is based on a multivariate Cox-regression analysis in which the significance of CRP as a predictor of mortality is lost after adjustment for other variables. For this analysis, CRP and other inflammatory markers are dichotomized, while other variables, including age, are left unchanged with retention of full variance. Entrance of dichotomized and continuous variables together in one Cox-regression model is like amputating a swimmer’s legs before competition. If a predictor, like CRP, has a continuous distribution, dichotomization along the median results in a loss of predictive power by 35% [2,3]. Another issue is that of multicollinearity. When different domains of the same phenomenon, such as inflammation, are studied simultaneously, the variables tend to correlate with each other, thus violating the assumptions of multivariate regression models [4]. Caravaca et al. [1] do not report whether or not there were significant correlations between CRP, white blood cell counts and counts of polymorphonuclear leucocytes. However, significant correlations of all these parameters with the negative acute phase response marker, serum albumin, existed. The authors should thus at least repeat their multivariate analysis with inflammatory markers as continuous variables, in the absence of serum albumin as a variable in the model. If the other inflammatory markers are found to be correlated, this analysis should ideally be repeated for each of the markers separately. Then, if the authors still find the same loss of significance of each of the inflammatory markers as a predictor of mortality in the multivariate model(s), their conclusion is valid.

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Department of Medicine
Stephan J. L. Bakker
University Medical Center Groningen
University of Groningen
The Netherlands
Email: s.j.l.bakker@int.umcg.nl

Reply

Sir,

We would like to apologize for not showing a more complete presentation of the analyses originally done in our study. Of course, C-reactive protein (CRP) was analysed as a continuous variable, log-transformed for normalization of its distribution. Different Cox-regression models were performed with varying degrees of covariate adjustment. The first multivariate model included the age and comorbidity index. In order to establish the predictive information added by CRP levels, this variable was entered into this first model in several forms: as a log-transformed continuous variable, and as nominal scale covariates (above or below median, tertiles, above or below 3 mg/l, or as above or below the best predictive value over mortality). None of these covariates added predictive information to that provided by age and comorbid index. For instance, the hazard ratio of log-CRP in this model—in which serum albumin or other inflammatory markers were not included—was 1.28 (95% CI: 0.90–1.82).

We would like to emphasize that the dichotomization of CRP values in this study was performed after assessing the cut-off values best related with the mortality of the study group. By doing that, and using the same metaphor which Dr Bakker used, we did not intend to amputate the leg of the swimmer, but provide him a couple of flippers.

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Servicio Nefrologı´a
Hospital Infanta Cristina
Badojoz, Spain
Email: fcaravaca@senefro.org

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