Letter and Reply

Physical symptoms and quality of life in patients on chronic dialysis: results of The Netherlands Cooperative Study on Adequacy of dialysis (NECOSAD)

Sir,

In the recent study by Merkus and co-workers [1] it is concluded ‘… that the symptom burden in dialysis patients can be explained to a limited extent by demographic and clinical variables and not by dialysis variables’. I would suggest that several problems in the design of the study make it necessary to reconsider that bold allegation.

The authors used a cross-sectional design to model the dependencies of several outcome measures on dialysis intensity and demographic and clinical variables. Several problems in the outcome measures are considered, and the authors express some justified doubt as to their relevance as they form conglomerates between measures of quality and intensity. The authors also mention that the outcome measures are fluctuating and imprecise. However, the authors fail to make any assessment as to how these rather problematic characteristics of the dependent variables might influence the conclusion.

As an independent variable, the authors use traditional measures of dialysis quantity. Seemingly this is measured only once, using short-cut formulas to approach Kt/V. From a statistical point of view, the authors could have made assessments of the importance for the conclusions that the measures were imprecise. It is well known that in a regression model imprecision in independent variables may lead to effects being underestimated. Four further problems with the independent variables should be considered.

First, since the amount of dialysis was not controlled by design, it would not be unlikely for a nephrologist to have a more severely affected patient dialysed more in the hope to alleviate symptoms—even though the opposite effect probably was more common in the past.

Second, the amount of dialysis delivered may simply have been too little to have much effect on the symptoms in the relatively short time span considered. I found it disappointing that the authors did not consider the possibility of obtaining improvement in QL by increasing dialysis dose way beyond that used in the study. In any case, the ability to detect the effect of a variable is very much dependent on the range of values of that variable observed, compared to the precision it is measured with.

Third, since the data were collected 3 months after the start of dialysis, to answer the question whether dialysis intensity influences quality of life, one requires that the effect of different dialysis doses should materialize so soon on top of lots of different patient specific confounders. I believe this to be unrealistic.

Finally, the ability of Kt/V to explain dialysis outcomes has been called very much into doubt. As recently discussed in these pages ‘there must be something fundamentally flawed with the concept and one begins to wonder whether in the past, observations were not forcibly made to fit the Procrustes bed of the Kt/V paradigm’ [2,3].

As doctors we are basically seeking interventions that improve some outcome measures for our patients. In other words, our questions are about the effect of a change in something on a change in something in a patient. To model the effects of these interventions efficiently, longitudinal studies are indispensable. In contrast to a cross-sectional design, the longitudinal design makes it natural to incorporate repeated measures of independent variables, taking their possible correlation and imprecision into consideration. Also, in a longitudinal design the effect of unmeasured confounders are made less important by focusing comparisons of treatment effects within patients instead of between patients.

Hence, even after this study [1] we may continue to presume that dialysis dose should be increased and modalities be experimented with in prospective studies, expecting to demonstrate that both the frequency and duration of sessions will have importance—also for QL [4]—not explained by Kt/V.

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Reply

Sir,

We do not agree with Dr Ring that our conclusion that ‘… the symptom burden in dialysis patients can be explained to a limited extent by demographic and clinical variables and not by dialysis variables’ is a bold allegation. In view of our findings, the beginning of our concluding remark that Dr Ring did not cite, is a valid conclusion to our opinion. Namely, we observed that the Kt/V and creatinine clearance could not explain the variation in the perceived symptom burden and quality of life (QL). Additionally, as we discussed in our article, this was not a unique finding of ours but has also been found by others [1–3] as well as in a previous report of our group [4].

With our conclusion we did not have the intention to suggest that there is no need to pay attention to dialysis dose in daily practice. Nor did we beforehand intend to give a verdict on a causal relationship between dose of dialysis and QL. In agreement with Dr Ring, we are well aware of the fact that with a cross-sectional analysis, even with standardization of the treatment duration (as is the case in our study), such a conclusion cannot be drawn and we did not! For an ultimate conclusion on this subject, a randomized trial comparing different doses of dialysis is necessary. Since random-
ized trials in the dialysis context are hard to achieve, a prospective cohort study is the best alternative. In fact, our present analysis is the baseline assessment of a multicentre prospective cohort study. The results on longitudinal follow up of QL obtained in this cohort study have just been published [5].

The objectives of our present report were, as we formulated in the Introduction section: (i) to assess the prevalence and severity of physical symptoms of dialysis patients; (ii) to study the association between demographic and clinical characteristics, dialysis adequacy and dialysis technique on the one hand and physical symptoms on the other; and (iii) to examine the association between symptomatology and patient’s perceived QL. In our article we discussed the fact that the clinimetric properties of the symptom questionnaire and the generic character of the QL questionnaire may have partly obscured more important associations between these outcome measures and dialysis characteristics. It is, however, impossible to quantify the exact impact this might have had.

Regarding Dr Ring’s remarks on the markers of dose of dialysis that we applied (Kt/V and creatinine clearance), we would like to comment that we applied universally used standard estimation methods. Until better parameters of the dose of dialysis are developed, these are the best alternatives. As we discussed in a recently published article of our group [6], small solute mass removal may be a better marker than the conventionally used clearance parameters.

Furthermore, it should be noted that imprecision in independent variables causing associations to be underestimated is not unique to regression analysis but applies to statistical analysis in general. Nor is this phenomenon unique to our study but it is present in all reports that study an association between various parameters. Since the associations between dialysis dose parameters and QL were far from statistically significant, we do not expect that statistically significant associations were obscured by this phenomenon. Moreover, we searched for violations of necessary assumptions in multivariate regression (examination of residuals, the influence of mortality and technique failure in patients ... and possible presence of collinearity) and could not detect any violations.

Finally, we agree with Dr Ring that assessment at 3 months after the start of dialysis may be a too short period to detect an effect of dose of dialysis on QL on top of lots of different patient specific confounders. However, we performed a multivariate analysis, in which we adjusted the association between the dose of dialysis and QL for important patient characteristics such as age, primary kidney disease, comorbidity, nutritional status and residual renal function, and we were still unable to find a relationship between dialysis characteristics and QL. This does not exclude the possibility that haemodialysis regimens applied more frequently than the current ones, such as daily home haemodialysis, might influence patients’ well-being. However, this should be investigated in larger, less selected series than the ones Dr Ring refers to.

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