also performed non-parametric tests on all data and did not find any relevant change of results compared with the data reported in our paper [1].

Vernaglione's interpretation of renal haemodynamic changes in response to N^G-monomethyl-L-arginine (L-NMMA) may be devised from our study. An increase in filtration fraction in response to L-NMMA may be interpreted as a more substantial contribution of NO to efferent than to afferent arteriolar tone. However, this rather simplistic approach contradicts more recent work that the regulation of glomerular filtration is due to the fact of several confounding determinants, of which glomerular pressure is just one. Experimental work mentioned by Vernaglione [3] supports this notion, but other data from animal models indicate a more pronounced role of NO in the regulation of afferent than of efferent arteriolar tone under basal conditions [4]. Strikingly enough, although an increase of filtration fraction due to L-NMMA is a common finding, a decrease of glomerular filtration rate in response to L-NMMA is reported in other studies [2,5], in contrast to our present findings [1] and would be in line with a predominant action of NO on the afferent glomerular arteriole.

Differences in the effect of L-NMMA on renal haemodynamics reported in the literature may derive from differences in study participants and confounding factors, such as sodium (and possibly protein) intake [2]. These contradictory results of experimental and human studies led us to design the current study using pharmacological modification of afferent and efferent arteriolar tone as a new approach to the examination of the contribution of NO to renal haemodynamics in human subjects [1]. As already discussed in our paper, this approach is an indirect one. Discrepancies between our findings on the change or absence of change in the response of renal plasma flow to L-NMMA after amlodipine or valsartan treatment, respectively, and Vernaglione's interpretation of the response of filtration rate to L-NMMA in our study participants clearly demonstrate that evaluation of such data proves to be difficult. While we appreciate Vernaglione's interpretation of a prevalent effect of NO on the efferent arteriole, one cannot neglect the results from our pharmacologically driven approach and data from other authors also pointing towards the afferent arteriole as the major target for NO. Certainly, our study is not the last word about the role of NO in the regulation of glomerular haemodynamics in humans.

Conflict of interest statement. None declared.

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doi:10.1093/ndt/gfh457

Some notes about the usage of the Charlson co-morbidity index

Sir,

We read with great interest the recent paper by Kalantar-Zadeh *et al*. [1] based on a comparison of malnutrition–inflammation markers for outcome predictability. We appreciate its high level in the matter of clinical usefulness and statistical power, but would like to add some critical notes.

In our opinion, Kalantar-Zadeh *et al*. placed insufficient emphasis on the significance of the Charlson co-morbidity index (CCI), despite the fact that the *z*-statistics show the CCI to be the most potent predictive factor in mortality and hospitalization.

Moreover, the method used to calculate CCI—specifically, the exclusion of factors pertaining to age and kidney disease—differs significantly from that employed by Charlson *et al*. [2] and Fried *et al*. [3] in their studies of general populations and dialysis patients, respectively. The absence of these factors makes it difficult to compare the results of Kalantar-Zadeh *et al*. with those of previous studies using CCI.

Furthermore, the final multivariate model incorporates the malnutrition–inflammation score, or MIS, alongside the CCI, even though both indices take into account the same set of diseases: myocardial infarction, chronic obstructive pulmonary disease, major neurology sequelae and malignancies. Similarly, diabetes mellitus was included in the model as an independent factor despite being accounted for in the CCI; the same for serum albumin which is already accounted for in MIS. These overlapping factors could bias the results of the final analysis.

In order to avoid the duplication of similar factors within one model, we suggest comparing several different models, each with its own set of non-overlapping factors, and determining which is most accurate by estimating the –2 log likelihood (–2LL) statistics for each in the Cox analysis. This procedure compares the –2LL for different models fitted to the same set of survival data, assuming that the smaller the –2LL value, the better the agreement between the model and observed data. The difference between models will be termed statistically significant with $P < 0.05$ if it is >3.841.

We used this approach in a retrospective evaluation of survival among 213 non-diabetic and 45 diabetic haemodialysis patients based on the following factors: diabetes mellitus, age, authentic CCI and modified CCI (unpublished data). In our survey, CCI was better than diabetes in predicting survival, but equal to diabetes and age (Table 1). In order to analyse CCI and diabetes together, we modified the CCI by excluding the weight of diabetes with end-organ damage (calculated at 2). This constellation of factors improves the predictive power of the model. Next, we increased the weight of diabetes with end-stage organ damage to 3 on the assumptions that Charlson *et al*. could underestimate diabetes weight, having performed their

Table 1. Survival predictability of models based on different sets of factors

Factors in model	–2LL
Diabetes mellitus	597.734
Diabetes mellitus and age	590.693
CCI	588.522
Diabetes mellitus and modified CCI (without diabetes weight)	581.744
Modified CCI (with diabetes weight calculated at 3)	583.596

research with only 13 patients with diabetes (2.2% of their total population), and that diabetic patients on haemodialysis could suffer from a more pronounced degree of angiopathy than diabetics without renal failure. This modified CCI model achieved the same predictive power as the previous scenario without neglecting any of the components of CCI. (Interestingly, increasing the weight of diabetes to ≥ 4 did not improve the model's predictive power.)

We realize that our results need to be verified by further research. However, in order to compare the results of different studies, a uniform original approach to CCI should be used until modifications are approved by the scientific community.

Another important point is that Kalantar-Zadeh *et al.* fail to resolve whether inflammation–malnutrition markers correlate with CCI, or with any co-morbidities in particular, and whether differences in predictors of mortality and hospitalization may be found between diabetics and non-diabetics. However, these factors may considerably influence the inflammation–malnutrition markers.

Conflict of interest statement. None declared.

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doi:10.1093/ndt/gfh463

Reply

Sir,

The points mentioned by Bikbov are appreciated. However, the focus of our study [1] was to compare the outcome predictability of 10 markers of the malnutrition–inflammation complex syndrome (MICS) with each other. Hence, our finding on the significant association of the Charlson co-morbidity index (CCI), which represented a covariate to adjust for, with mortality and hospitalization deserving only a brief mention in that context. The outcome predictability of CCI and its statistical associations with elements of MICS in maintenance dialysis patients are subjects of another ongoing but separate study within our group, which will be reported in the future.

Other groups have also modified the CCI by excluding age as a component [2]. We believe this is a legitimate approach, especially since age has a strong bearing on mortality and can confound the independent value of co-morbid conditions in predicting outcome. Since all dialysis patients have end-stage kidney disease, there is no statistical gain in including this universally positive component. No other changes were implemented in the CCI in our study. We maintained diabetes mellitus in the CCI, since diabetes is divided into two distinct categories (with and without end-organ damage). It is interesting that Bikbov, too, has decided to modify the CCI by changing the weight factor for diabetes. Such modifications, if they lead to improved correlations, are warranted.

With regard to the malnutrition–inflammation score (MIS), only one out of the 10 MIS components is about co-morbid conditions in a limited format, i.e. with four levels of severity for the entire co-morbidity, whereas the modified CCI we used had a fully quantitative score ranging from 0 to 24 [1]. We, too, believe that CCI is a valuable and practical tool with important clinical applications in risk stratification and outcome prediction in maintenance dialysis patients.

Conflict of interest statement. None declared.

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doi:10.1093/ndt/gfh464