Critical confounders in the prognostic role of cellular biomarkers


To the Editor: We read with interest the paper by Maruyama et al. recently published in *Kidney International*. The authors report that the level of CD34+ cell count was an independent predictor of cardiovascular events in patients on chronic hemodialysis. Although this result is consistent with the hypothetical role of CD34+ cells in cardiovascular homeostasis and is in line with earlier literature, there are several potential pitfalls in this study that require attention. Most important, the CD34+ cell count was expressed per unit of volume (µl), thus being artificially affected by hemodilution and hemoconcentration, which are extremely common in hemodialysis patients. Thus, as CD34+ cells belong to the white blood cell population, low CD34+ cell count could simply reflect a lower white blood cell count due to hemodilution. The observation that the correlation between the CD34+ cell count and white blood cell count was the strongest and an independent one (Table 1 of the paper) strongly supports this explanation. That hemodilution predicts outcomes in hemodialysis patients would not be surprising. To avoid this artefact, the CD34+ cell count should be always expressed as a fraction of the number of events acquired in flow cytometry analyses. This is of paramount importance in patients subjected to day-to-day changes in body fluids. In addition, the authors failed to report critical details on the methods for CD34+ cell enumeration, such as antibody clones, fluorochromes, and the number of acquired events. Altogether, these limitations make results of the study by Maruyama et al. poorly reproducible.


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Response to ‘Critical confounders in the prognostic role of cellular biomarkers’


We thank Dr Fadini et al. for their interest in our recently published article, showing that a reduced number of circulating CD34+ cells predicts both future cardiovascular events and all-cause deaths in chronic hemodialysis patients.

They raised the point that we expressed the CD34+ cell count as per unit of blood volume. In most earlier studies, the number of endothelial progenitor cells or CD34+ cells has been expressed as a ratio to the number of mononuclear cells. In contrast, we measured the actual number of CD34+ cells and expressed them as per microliter. Our hypothesis was that the circulating endothelial progenitor cells contribute to the maintenance of the vascular endothelium. Therefore, we assumed that the actual number, not the ratio, of circulating CD34+ cells would be of primary importance. In our earlier studies, we have shown successfully that the actual number of circulating CD34+ cells was related to various clinical factors of non-dialysis patients.

Dr Fadini et al. expressed special concern about hemodilution and hemoconcentration in hemodialysis patients. They wondered whether a low CD34+ cell count could reflect simply a low white blood cell count because of hemodilution. It is true that the levels of various factors including albumin, hemoglobin, white blood cell count, and CD34+ cell count are influenced by the fluid status. However, in our study, the Cox analysis showed that the levels of albumin and CD34+ cell count, but not the levels of hemoglobin or WBC count, were independent predictors of prognosis for hemodialysis patients.

Concerning the methodology, not all the information was described in our paper because of space constraints. Instead, we quoted our article which details the precise method to obtain an accurate number of CD34+ cells. One of the advantages of this method is in fact its reproducibility, as described in our papers.

In summary, although it remains to be determined whether it is the ratio or the actual number of CD34+ cells that is the better biomarker, accumulating evidence suggests that circulating progenitor cells contribute to cardiovascular homeostasis.


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