Long-term mortality and cardiovascular risk stratification of peritoneal dialysis patients using a combination of inflammation and calcification markers

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Abstract

Background. It remains unknown whether a composite of inflammation and calcification markers provides better mortality and cardiovascular risk stratification in chronic peritoneal dialysis (PD) patients.

Methods. We performed a 4-year prospective follow-up study in 231 chronic PD patients from a single regional dialysis centre in Hong Kong. Valvular calcification was detected using echocardiography, and fasting venous blood was collected to measure a panel of inflammation markers. The patients were stratified into five groups on the basis of 0, 1, 2, 3 and all 4 inflammation and calcification risk markers, namely high C-reactive protein (CRP) (CRP in upper tertile), high interleukin-6 (IL-6) (IL-6 in upper tertile), low fetuin-A (fetuin-A in lower tertile) and valvular calcification. Study outcomes included all-cause and cardiovascular mortality and fatal or non-fatal cardiovascular events (CVEs).

Results. The patients with 4, 3, 2 and 1 markers had an adjusted hazard ratio (HR) of 5.17 (95% CI, 1.81–14.77, P = 0.002), 3.38 (95% CI, 1.50–7.60; P = 0.003), 2.17 (95% CI, 0.98–4.77; P = 0.056) and 2.42 (95% CI, 1.18–4.96; P = 0.016), respectively, for mortality at 4 years than those with 0 risk marker. The adjusted HRs for fatal or non-fatal CVEs were 4.33 (95% CI, 1.70–11.03; P = 0.002), 1.60 (95% CI, 0.73–3.52; P = 0.24), 1.92 (95% CI, 0.95–3.90; P = 0.07) and 1.33 (95% CI, 0.67–2.62; P = 0.42), respectively, for patients with 4, 3, 2 and 1 markers than those with 0 risk markers.

Conclusions. A composite of inflammation and calcification markers provides long-term prognostication and identifies the sickest PD patients with the worst clinical outcomes. Since these parameters can all be obtained quite readily, our data support the adoption of a multiinflammation and calcification risk marker approach for mortality and cardiovascular risk stratification in PD patients.

Keywords: calcification; cardiovascular events; inflammation; mortality; peritoneal dialysis

Introduction

The mortality of end-stage renal disease (ESRD) patients is at least 10- to 100-fold greater than age- and gender-matched controls, and is largely attributed to the high prevalence of cardiovascular complications [1]. Hence, one of the clinical goals is to identify serum biomarkers or other markers that are useful for early cardiovascular risk prediction and stratification in the ESRD population.

Using non-invasive echocardiography, heart valve calcification has been shown to be an important predictor of mortality and cardiovascular death in ESRD patients receiving chronic peritoneal dialysis (PD) therapy [2]. Heart valve calcification not only reflects deranged mineral metabolism with abnormally elevated calcium × phosphorus products but is also a marker of atherosclerotic burden in ESRD patients [3].

On the other hand, it is well recognized that inflammation plays a pivotal role in atherosclerosis [4]. Despite being non-specific markers of inflammation, C-reactive protein (CRP) and interleukin-6 (IL-6) have both been shown to predict mortality and cardiovascular outcomes in ESRD patients and are regarded as the prototype biomarkers for cardiovascular risk stratification [5–10]. There are also recent data that IL-6 may better predict mortality and cardiovascular risk than CRP in ESRD patients [7,11–13]. IL-6 induces the synthesis of CRP and is increasingly recognized to play a central regulatory role in the inflammatory response [14,15]. Additionally, fetuin-A, which is a negative acute phase protein as well as a calcification inhibitor protein [16], has also been associated with inflammation,
malnutrition and atherosclerosis/calcification syndrome and predicts mortality and cardiovascular death in ESRD patients [16–18]. Of note, even though the prognostic value of these different inflammatory proteins has been reported individually, there was so far no prospective data that investigated whether a composite of these inflammatory and calcification markers may improve prognostication in the PD population.

Given this background, the objective of this study is to determine whether the combined use of a panel of inflammation and calcification markers allows better mortality and cardiovascular event (CVE) risk stratification in chronic PD patients.

Methods

Study protocol

This is a prospective cohort study performed in a single dialysis centre in Hong Kong. The study protocol was approved by the Human Research Ethics Committee of the Chinese University of Hong Kong. Informed consent was obtained from all study participants.

Study subjects

The patients were considered eligible for study inclusion if they have ESRD and have been maintained on continuous PD treatment for 3 months or more. Exclusion criteria included patients with underlying malignancy, systemic lupus erythematosus, chronic rheumatic heart disease or congenital heart disease or patients with incomplete data. Based on the predicted study inclusion and exclusion criteria, we recruited 231 chronic PD patients and they represented 86% of the total PD population (n = 270) at the unit. All patients were dialysed using conventional lactate-buffered glucose-based PD solutions.

Measurements

Predictors. Heart valve calcification is defined as bright echoes of >1 mm on one or more cusps of the aortic valve or mitral valve or mitral annulus and is determined by two-dimensional echocardiography, performed using a 3.3 MHz multishape array probe (Vivid 5, GE-Vingmed Sound AB, Horten, Norway) with subjects lying in left decubitus position. Echocardiography was performed according to the recommendations of the American Society of Echocardiography [19] and images were analysed by a single experienced cardiologist who was blinded to all the clinical details. Sensitivity and specificity for echocardiographic detection of calcium in the mitral valve or mitral annulus and aortic valve were reported to be 76% and 89–94%, respectively [20]. The intra-observer agreement for echocardiographic detection of heart valve calcification was 90% (kappa = 0.76) in our study.

Biochemical parameters including high-sensitivity CRP (hs-CRP), IL-6 and fetuin-A were measured from fasting venous blood collected at the time of echocardiography. Serum CRP was measured using the Tina-quant CRP (Latex) ultrasensitive assay (Roche Diagnostics GmbH, Mannheim, Germany). The coefficient of variation of the CRP assay was 4.7% and 1.6% at concentrations of 4.3 mg/L and 2.0 mg/L, respectively. IL-6 was measured using the enzyme-linked immunosorbent assay (ELISA) (BioSource International Inc., Camarillo, CA, USA) with a detection limit of 2 pg/mL and intra-assay coefficient of variation of 5.7% at 19.8 pg/mL. Fetuin-A was determined using a human fetuin-A ELISA kit (Epitope Diagnostics, San Diego, CA, USA). The intra-assay precision was 4.8%–5.5% and inter-assay precision was 5.7%–6.8%.

Covariates. Multivariable Cox regression models included demographic (age, gender), clinical (diabetes, hypertension, background atherosclerotic vascular disease, duration of diabetes, biofilm bacterial serum albumin, haemoglobin, phosphate, low-density lipoprotein [serum cholesterol] and dialysis covariates (residual glomerular filtration rate). Baseline clinical and demographic data were collected at study entry. Background atherosclerotic vascular disease was defined as the presence of ischaemic heart disease, history of angina, previous myocardial infarction with or without coronary artery bypass surgery or stenting operation, ischaemic cerebrovascular event, transient ischaemic attack or peripheral vascular disease with or without amputation or revascularization surgery.

Fasting serum samples were used to measure albumin, calcium, phosphorus, intact parathyroid hormone, total cholesterol and triglyceride. Serum albumin was measured using the bromocresol purple method. Calcium and phosphorus concentrations were measured using dye-binding methods on the Dimension AR automatic analyser (Du Pont Co, Wilmington, DE, USA). Intact parathyroid hormone was determined by the chemiluminescence immunoassay on the Immulite analyser (Diagnostic Products Corp, Los Angeles, CA, USA). Total cholesterol and triglycerides were assayed enzymatically (Hitachi 911 analyser, Roche Diagnostics GmbH, Mannheim, Germany). LDL-cholesterol was calculated using the Friedewald equation [21].

Residual glomerular filtration rate was measured at the time of echocardiography as the average of 24-h urine urea and creatinine clearance [22]. Adequacy of dialysis was estimated by the measurement of total weekly urea and creatinine clearance using the standard method [23]. Contribution of PD and renal component to the total urea clearance was estimated separately.

Outcomes

All patients were followed up prospectively for 4 years from the day of baseline assessment at study entry or until death or permanent transfer to alternative renal replacement therapy including haemodialysis or kidney transplantation. No patient was lost to follow-up. The clinical outcomes evaluated were death from all causes, cardiovascular death and first fatal or non-fatal CVE. Fatal or non-fatal CVE included electrocardiographically documented myocardial ischaemia or infarction, sustained atrial or ventricular arrhythmia, transient ischaemic attack and ischaemic cerebrovascular event, all of which were defined according to standard clinical criteria, peripheral vascular disease or sudden death. Peripheral vascular disease was defined as the presence of intermittent claudication with angiographic or sonographic detection of ≥50% stenosis of the major arteries of the lower limb, with or without revascularization procedures, ischaemic leg ulceration, gangrene with or without amputation and aortic aneurysm. Sudden death was defined as unexpected natural death within 1 h from the symptom onset and without any prior condition that would appear fatal [24,25]. The exact cause of death and the nature of first CVE were provided by the attending physician. In the case of death out of hospital, family members were interviewed by telephone to ascertain the circumstances surrounding death. For patients who had multiple CVEs, survival analysis in relation to CVE was limited to the first event.

Statistical analysis

Continuous data were expressed as mean ± SD or median (interquartile range, IQR) depending on the distribution. Between-group comparisons were performed using the t-test or the Mann–Whitney test for continuous data where appropriate and using the chi-square test for categorical data. The patients were first stratified into tertiles according to CRP, IL-6 and fetuin-A, respectively. Those with fetuin-A in the lower tertile (fetuin-A ≥14.07 pg/mL) were defined as having high CRP and high IL-6, respectively. Those with fetuin-A in the lower tertile (fetuin-A ≥0.28 g/L) were defined as having low fetuin-A. The patients were stratified into five groups on the basis of the presence of 0, any 1, 2, 3 and all 4 inflammation and calcification markers, namely high CRP, high IL-6, low fetuin-A and the presence of heart valve calcification.

Survival curves were generated by means of the Kaplan–Meier estimates, and differences in survival between groups were compared by the log-rank test. The patients who underwent kidney transplant or permanently transferred to haemodialysis were censored at the time of transfer to alternative renal replacement therapy. If a patient died within 3 months of transfer to haemodialysis, then he or she was not censored as the early mortality was considered to reflect the health status during the period of failing PD treatment. Cox proportional hazards regression analysis for all-cause mortality, cardiovascular death and fatal or non-fatal CVEs were used to calculate the HR (95% CI) in relation to the presence of 0, any 1, 2, 3 and all 4 inflammation and calcification risk markers with and without adjusting for potential confounding covariates. The rule of 10 events per covariate was relaxed in this situation in order to allow adequate control of confounders [26]. We compared the gain in prediction power attributable to each inflammation and calcification risk marker and a combination of these markers by using the −2 log likelihood (−2 Log L)
This test compared different Cox models fitted to the same set of data, and the smaller the $-2 \log L$ value, the stronger the agreement between the model and the observed data. A 3.841 difference in $-2 \log L$ coincides with a significance level of 0.05 in a $\chi^2$ distribution with 1 degree of freedom and indicates a better prediction of risk estimate provided by the method leading to the lowest $-2 \log L$ value. A risk score for each subject based on each model was calculated by multiplying the coefficient estimate for each variable from the fully adjusted Cox model by the value of the variable for each patient and then adding these figures for each patient. This risk score was then used in the ROC curve analysis. A $P$-value of $<0.05$ was considered to be statistically significant. Statistical analysis was performed using SPSS version 13.0 (SPSS, Inc., Chicago, IL, USA).

**Results**

The baseline characteristics of the study population are shown in Table 1.

The underlying cause of kidney disease was chronic glomerulonephritis in 75 patients (32.5%), diabetic nephropathy in 55 patients (23.8%), hypertensive nephrosclerosis in 31 patients (13.4%), polycystic kidney disease in 12 patients (5.2%), obstructive uropathy in 13 patients (5.6%) and tubulointerstitial disease in 6 patients (2.6%) and not identified in 39 patients (16.9%). Of the 231 patients, 29.9% had background diabetes but 6.1% did not have diabetic nephropathy as the cause of kidney disease.

The patients were stratified into five groups on the basis of the presence of 0, any 1, 2, 3 and all 4 inflammatory and calcification risk markers, namely the presence of heart valve calcification, high CRP, high IL-6 and low fetuin-A. The baseline characteristics across the five groups of patients are detailed in Table 1. There was a significant increasing trend effect in the percentage of patients with preserved residual renal function across the five groups of patients with increasing inflammation and calcification risk markers ($P < 0.001$).

Compared to patients with no heart valve calcification, those with heart valve calcification had significantly higher CRP [5.35 (1.66, 14.64) versus 1.82 (0.83, 5.80) mg/L; $P = 0.001$], higher IL-6 [13.70 (7.05, 22.85) versus 8.55 (5.00, 16.00) pg/mL; $P = 0.002$] and lower fetuin-A (0.287 ± 0.059 versus 0.316 ± 0.067 g/L; $P = 0.004$). The correlation matrix of these inflammation and calcification risk markers is shown in Table 2.

During the 4-year follow-up, 87 patients died, 30 patients underwent kidney transplantation and 26 patients were permanently switched to haemodialysis. Of the 87 deaths, 55 were cardiovascular causes and 32 were non-cardiovascular causes. The detailed causes of death are listed in Table 3.

Eighty-nine patients developed one or more fatal or non-fatal CVEs. The nature of the first CVE was ischaemic heart disease in 26 patients, cerebrovascular disease in 28 patients, peripheral vascular disease in 6 patients, sudden cardiac death in 16 patients and arrhythmia in 13 patients.

The Kaplan–Meier estimates of overall survival, fatal CVE-free survival and first fatal or non-fatal CVE-free survival are shown in Figure 1.
Table 1. Baseline characteristics

Inflammation and calcification risk markers

<table>
<thead>
<tr>
<th>Total (n = 231)</th>
<th>0 (n = 82)</th>
<th>Any 1 (n = 57)</th>
<th>2 (n = 48)</th>
<th>3 (n = 30)</th>
<th>4 (n = 14)</th>
<th>P for trend</th>
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<tbody>
<tr>
<td><strong>Clinical and demographic factors</strong></td>
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<tr>
<td>Age (years)</td>
<td>55.5 ± 16.3</td>
<td>51.0 ± 11.7</td>
<td>55.7 ± 11.1</td>
<td>58.1 ± 12.1</td>
<td>61.2 ± 8.6</td>
<td>60.0 ± 8.3</td>
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<td>% male</td>
<td>51.1</td>
<td>56.1</td>
<td>42.1</td>
<td>54.2</td>
<td>56.7</td>
<td>35.7</td>
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<td>% diabetes mellitus</td>
<td>29.9</td>
<td>15.9</td>
<td>28.1</td>
<td>43.8</td>
<td>43.3</td>
<td>42.9</td>
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<tr>
<td>% positive smoking history</td>
<td>37.7</td>
<td>39.0</td>
<td>29.8</td>
<td>41.7</td>
<td>40.0</td>
<td>42.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.1 ± 3.4</td>
<td>22.3 ± 3.6</td>
<td>22.5 ± 2.8</td>
<td>24.4 ± 3.0</td>
<td>24.2 ± 3.2</td>
<td>24.0 ± 3.6</td>
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<tr>
<td>Duration of dialysis (months)</td>
<td>37.0 ± 29.4</td>
<td>36.2 ± 27.4</td>
<td>35.6 ± 30.6</td>
<td>30.9 ± 29.2</td>
<td>43.9 ± 33.2</td>
<td>52.9 ± 22.5</td>
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<tr>
<td>Hypertension (%)</td>
<td>85.3</td>
<td>85.4</td>
<td>82.5</td>
<td>85.4</td>
<td>90.0</td>
<td>85.7</td>
</tr>
<tr>
<td>Background atherosclerotic vascular disease (%)</td>
<td>22.5</td>
<td>0</td>
<td>21.1</td>
<td>39.6</td>
<td>43.3</td>
<td>100</td>
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<td>Echocardiographic parameters</td>
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<tr>
<td>Heart valve calcification (%)</td>
<td>25.1</td>
<td>0</td>
<td>21.1</td>
<td>39.6</td>
<td>43.3</td>
<td>100</td>
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<tr>
<td>LVM index (g/m²)</td>
<td>224 ± 84</td>
<td>199 ± 73</td>
<td>214 ± 74</td>
<td>235 ± 81</td>
<td>267 ± 87</td>
<td>282 ± 125</td>
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<tr>
<td>Dialysis parameters</td>
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<tr>
<td>Total weekly urea clearance</td>
<td>1.81 ± 0.43</td>
<td>1.83 ± 0.45</td>
<td>1.89 ± 0.46</td>
<td>1.72 ± 0.36</td>
<td>1.80 ± 0.47</td>
<td>1.73 ± 0.34</td>
</tr>
<tr>
<td>PD urea clearance</td>
<td>1.52 ± 0.36</td>
<td>1.49 ± 0.36</td>
<td>1.60 ± 0.41</td>
<td>1.46 ± 0.28</td>
<td>1.48 ± 0.36</td>
<td>1.66 ± 0.41</td>
</tr>
<tr>
<td>Total weekly creatinine clearance (L/wk/1.73 m²)</td>
<td>56 ± 21</td>
<td>58 ± 22</td>
<td>56 ± 19</td>
<td>55 ± 21</td>
<td>58 ± 26</td>
<td>50 ± 11</td>
</tr>
<tr>
<td>% with RRF</td>
<td>62.3</td>
<td>72.0</td>
<td>68.4</td>
<td>56.3</td>
<td>50.0</td>
<td>28.6</td>
</tr>
<tr>
<td>Residual GFR (mL/min/1.73 m²)b</td>
<td>0 (0.63, 1.94)</td>
<td>0.86 (0, 2.11)</td>
<td>0.68 (0, 1.86)</td>
<td>0.56 (0, 1.78)</td>
<td>0.28 (0, 2.39)</td>
<td>0 (0, 0.15)</td>
</tr>
<tr>
<td>Biochemical parameters</td>
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<tr>
<td>Haemoglobin (g/dL)</td>
<td>9.18 ± 1.69</td>
<td>9.48 ± 1.77</td>
<td>9.24 ± 1.44</td>
<td>9.11 ± 1.67</td>
<td>8.92 ± 1.97</td>
<td>7.99 ± 1.10</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>28.6 ± 5.1</td>
<td>30.5 ± 4.0</td>
<td>28.2 ± 4.0</td>
<td>28.3 ± 5.4</td>
<td>26.7 ± 7.2</td>
<td>24.5 ± 5.4</td>
</tr>
<tr>
<td>Calciumb phosphorus (mmol²/L²)</td>
<td>4.32 ± 1.35</td>
<td>4.33 ± 1.29</td>
<td>4.20 ± 1.19</td>
<td>4.31 ± 1.65</td>
<td>4.31 ± 1.31</td>
<td>4.71 ± 1.32</td>
</tr>
<tr>
<td>Intact PTH (pmol/L)b</td>
<td>40.7 (17.9, 73.9)</td>
<td>46.0 (18.7, 77.8)</td>
<td>36.9 (11.5, 64.1)</td>
<td>33.1 (16.0, 65.7)</td>
<td>44.3 (19.4, 72.6)</td>
<td>104.7 (18.4, 134.5)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.4 ± 1.2</td>
<td>5.5 ± 1.2</td>
<td>5.4 ± 1.2</td>
<td>5.4 ± 1.1</td>
<td>5.1 ± 1.0</td>
<td>5.1 ± 1.6</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.24 ± 0.42</td>
<td>1.28 ± 0.41</td>
<td>1.33 ± 0.44</td>
<td>1.11 ± 0.44</td>
<td>1.15 ± 0.33</td>
<td>1.27 ± 0.46</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>3.29 ± 0.98</td>
<td>3.47 ± 1.07</td>
<td>3.17 ± 0.90</td>
<td>3.36 ± 0.83</td>
<td>2.99 ± 0.76</td>
<td>3.04 ± 1.41</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>2.06 ± 1.46</td>
<td>1.80 ± 1.01</td>
<td>1.95 ± 1.12</td>
<td>2.57 ± 2.09</td>
<td>2.21 ± 1.71</td>
<td>2.02 ± 1.39</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)b</td>
<td>2.60 (0.92, 7.94)</td>
<td>0.93 (0.51, 1.68)</td>
<td>2.60 (0.97, 4.22)</td>
<td>5.58 (1.53, 13.64)</td>
<td>11.60 (6.20, 28.86)</td>
<td>18.95 (12.95, 30.86)</td>
</tr>
<tr>
<td>Interleukin-6 (pg/mL)b</td>
<td>5.20 (9.70, 17.80)</td>
<td>5.40 (3.20, 8.03)</td>
<td>9.30 (5.20, 11.80)</td>
<td>15.20 (8.73, 19.25)</td>
<td>21.15 (17.33, 31.98)</td>
<td>35.10 (24.45, 45.28)</td>
</tr>
<tr>
<td>Fetuin-A (g/L)</td>
<td>0.31 ± 0.07</td>
<td>0.36 ± 0.05</td>
<td>0.30 ± 0.05</td>
<td>0.29 ± 0.06</td>
<td>0.25 ± 0.05</td>
<td>0.24 ± 0.03</td>
</tr>
</tbody>
</table>

LVM, left ventricular mass; RRF, residual renal function; GFR, glomerular filtration rate; PTH, parathyroid hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

aContinuous data are expressed as mean ± SD unless specified otherwise.
bMedian (interquartile range).
Multivariable Cox regression analysis of all-cause mortality, cardiovascular death and fatal or non-fatal CVE-free survival in relation to the presence of any 1, 2, 3 and all 4 risk markers with adjustment for potential confounding covariates are detailed in Table 4. The patients having all four risk markers, namely high CRP, high IL-6, low fetuin-A and heart valve calcification, had the highest adjusted risk of all-cause mortality, cardiovascular death and fatal or non-fatal CVE. The percentage gain in prediction power for all-cause mortality, cardiovascular death, fatal or non-fatal CVE attributable to each inflammation and calcification risk marker and a combination of the risk markers in the multivariable Cox regression models are presented in Figure 2A–C, respectively.

The ability of a composite of inflammation and calcification risk markers to predict mortality, cardiovascular death and first fatal or non-fatal CVE at 4 years was also investigated by means of the ROC curve analysis (Table 5). A combination of all four inflammation and calcification risk markers (model 6) increased predictive value across all outcomes, including mortality, cardiovascular death and first fatal or non-fatal CVE compared to any of the risk markers when considered alone (models 1–4). In the model including age, gender, clinical, biochemical and dialysis parameters (model 7), adding a composite of inflammation and calcification risk markers increased the predictive value across all outcomes including all-cause mortality, cardiovascular death and fatal or non-fatal CVE (model 8).

### Discussion

The importance of CRP, IL-6, fetuin-A and valvular calcification in predicting outcome of ESRD patients has been individually reported in numerous previous studies [2,5–9,16–18]. This study is the first to explore the use of a multimarker approach in chronic PD patients. Our results showed that a composite of inflammation and calcification risk markers, namely CRP, IL-6, fetuin-A and valvular calcification, provides significant gain in prediction power for long-term all-cause mortality, cardiovascular death and fatal or non-fatal CVE in chronic PD patients compared to individual risk markers, clearly demonstrating the value of adopting a multimarker approach for long-term mortality and CVE risk stratification in chronic PD patients. Furthermore, adding the composite of inflammation and calcification risk markers to a model including standard clinical, demographic, biochemical and dialysis parameters increased the area under the curves (AUCs) in relation to all-cause mortality, cardiovascular death and fatal or non-fatal CVEs at 4 years, clearly suggesting that a composite of
inflammation and calcification risk markers had additional prognostic value beyond the standard clinical, biochemical and dialysis parameters in chronic PD patients.

It is well established that inflammation plays a pivotal role in arterial damage [4]. Valvular calcification, being a marker of subclinical atherosclerosis in ESRD patients, has also been shown to be associated with inflammation [3]. Thus, it is not surprising to find that CRP, IL-6, fetuin-A and valvular calcification were all interrelated to varying degrees. In this study, we observed the strongest correlation between CRP and IL-6, followed by IL-6 and fetuin-A. However, the long-term mortality and CVE risk of chronic PD patients are better predicted using a composite of inflammation and calcification risk markers as evidenced by the higher AUCs in relation to the different outcomes than using a single risk marker. PD patients being positive for all four risk markers at baseline had a 4-year all-cause mortality and cardiovascular death approaching 85% and 60%, respectively. On the other hand, those with 0 risk markers had a 4-year all-cause mortality and cardiovascular death of 20% and 10%, respectively, while those with any 1, 2 or 3 risk markers had more intermediate outcomes. As CRP and IL-6 are relatively non-specific inflammation markers and 20% and 10%, respectively, while those with any 1, 2 or 3 risk markers had more intermediate outcomes. As CRP and IL-6 are relatively non-specific inflammation markers and can become elevated secondary to any inter-current clinical event such as infections, surgical interventions or other inflammatory or injurious conditions that result in tissue damage, using a composite of inflammation and calcification risk markers rather than individual risk markers allows a more precise definition of the degree of inflammation and severity of cardiovascular risk burden, as clearly demonstrated by our results. In addition, a composite of inflammation and calcification risk markers reflects the residual variance not captured by a single risk marker alone.

Residual renal function is now recognized as an important predictor of outcomes in chronic PD patients [27], and inflammation has been suggested to partly contribute...
to the association between loss of residual renal function and adverse outcomes in these patients [28–30]. Increased pro-inflammatory cytokines and markers of endothelial dysfunction have been observed with deterioration of renal function in pre-dialysis chronic kidney disease patients [31,32]. In chronic PD patients, loss of residual renal function was associated with an increased inflammatory response and endothelial activation as evidenced by higher CRP and adhesion molecules [29,30]. Our current study showed that patients being positive for all four inflammation and calcification risk markers indeed had the lowest residual renal function, providing further evidence that loss of residual renal function was associated with an amplified inflammatory and calcification milieu in PD patients. There is experimental evidence to suggest that loss of residual renal function or uraemia per se may enhance an inflammatory response via increased oxidative stress and may lead to monocyte activation and cytokine production [33]. Impaired cytokine clearance as evidenced in nephrectomized rats [34] has been suggested as the other possible mechanism that explained the link between loss of residual renal function and inflammation. Conversely, the presence of inflammation may also accelerate the decline of residual renal function [35].

Our results differed from previous studies suggesting that IL-6 has stronger predictive value for mortality and cardiovascular risk than CRP [12,36] and may be related to difference in the study population in that ours was done in PD patients while these studies were mostly done in haemodialysis patients. The other potential explanations may relate to difference in the CRP and IL-6 assays used and difference in the follow-up duration. The previous study showed superiority of IL-6 as a predictor of all-cause mortality and cardiovascular death over other inflammation markers including CRP, tumour necrosis factor, adhesion molecule, interleukin-1β and interleukin-18 but the risk estimate of CRP was reported to be reasonably close to that of IL-6 [12]. Another study comparing four different biomarkers including serum albumin, CRP, IL-6 and fetuin-A also concluded that IL-6 may be the most reliable predictor of 2-year mortality and cardiovascular disease in ESRD patients [36]. These observations somewhat differed from our current findings that CRP had the highest AUCs for mortality and cardiovascular death up to 4 years, while IL-6 had the highest AUCs for CVEs, when each of the risk markers was considered separately. However, it is important to caution that the actual difference in the AUCs across all outcomes for CRP and IL-6 was very small and may not be of real clinical significance. Nevertheless, our findings favour the adoption of a multimarker approach rather than using a single risk marker for prognostication in chronic PD patients, given the variability with a one-off determination of serum inflammation markers.

There are several limitations of this study that need consideration. First, a single baseline measurement of these markers was used to predict outcome; thus serial changes in these biomarkers with time on dialysis were not accounted for in the analysis. However, given that this is a prognostic rather than etiologic study, our study also reproduced the typical situation of everyday clinical practice and demonstrated the usefulness of this single time-point multimarker approach in early identification of the sickest PD patients for more aggressive intervention. Second, the study included only prevalent but not incident patients and may introduce prevalence-incidence bias, resulting in either an under- or over-estimation of the true risk associated with inflammation and valvular calcification. Third, the number of patients with any 1, 2 or 3 or all 4 risk markers was relatively small and was not powered enough to stratify further into subgroups as to which specific 1, 2 or 3 risk markers were represented.

In conclusion, our data suggest that a composite of inflammation and calcification risk markers is useful in identifying the sickest PD patients with the worst long-term outcomes. Since these parameters can all be obtained quite readily in clinical practice, our data support the adoption of a multimarker approach, incorporating both inflammation and calcification markers in the multivariable Cox regression models are detailed in Table 4. *P < 0.05
and calcification risk markers for better mortality and cardiovascular risk stratification in chronic PD patients.

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Conflict of interest statement. None declared

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