Diagnostic potential of serum biomarkers for left ventricular abnormalities in chronic peritoneal dialysis patients

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Abstract

Background. N-terminal-pro-brain natriuretic peptide, cardiac troponin T (cTnT) and high sensitivity C-reactive protein (hs-CRP) have been shown to predict mortality and cardiovascular outcomes in end-stage renal disease patients. However, it is not known which biomarkers have the strongest diagnostic potential for left ventricular (LV) abnormalities in chronic peritoneal dialysis (PD) patients, nor whether residual renal function may confound the diagnostic potential of these biomarkers.

Methods. Two hundred and thirty chronic PD patients underwent two-dimensional echocardiography to determine LV hypertrophy and ejection fraction and had simultaneous measurement of serum NT-pro-BNP, cTnT and hs-CRP.

Results. A significant gain in predictive power was observed when NT-pro-BNP or cTnT but not hs-CRP was included in the multivariable logistic regression models for severe LV hypertrophy (defined as LV mass index ≥ upper tertile, 247.8 g/m²) and systolic dysfunction (defined as ejection fraction ≤45%). Using ROC curve analysis,
NT-pro-BNP had the highest diagnostic value for severe LV hypertrophy and systolic dysfunction compared to cTnT and hs-CRP, irrespective of residual renal function. An analysis based on the best cut-off threshold showed that NT-pro-BNP and cTnT had a negative predictive value of 87.1% and 92.6% for severe LV hypertrophy and 95.4% and 93.2% for systolic dysfunction, respectively. Furthermore, the best cut-off threshold of NT-pro-BNP and cTnT for excluding severe LV hypertrophy and systolic dysfunction was nearly 3-fold higher in anuric patients than in patients with residual renal function.

**Conclusions.** Serum NT-pro-BNP appeared most useful in excluding systolic dysfunction in chronic PD patients followed by cTnT. hs-CRP was not useful in this regard. Residual renal function confounded the interpretation of these biomarkers and reduced their predictive power. A nearly 30% higher cut-off threshold of NT-pro-BNP and cTnT had to be applied in anuric PD patients.

**Keywords:** cardiac troponin T; left ventricular hypertrophy; natriuretic peptide; peritoneal dialysis; systolic dysfunction

**Introduction**

It is well recognized that end-stage renal disease (ESRD) patients show a very high prevalence of left ventricular (LV) hypertrophy, and both LV hypertrophy and systolic dysfunction have major contributions to this heightened risk of cardiovascular death [1,2]. B-type natriuretic peptide (BNP) is released from ventricular myocytes in response to increased wall stress [3,4] and its generation is increased in the presence of heart failure, cardiac hypertrophy and dysfunction [3,5–8]. Studies in the general population demonstrated superiority of BNP as a hormonal marker of LV hypertrophy and systolic dysfunction over other natriuretic peptides [5]. Mallamaci and co-workers also showed that cardiac natriuretic peptides, in particular BNP, had a high sensitivity in diagnosing LV hypertrophy and systolic dysfunction in dialysis patients [9]. More recently, we showed that N-terminal pro-brain natriuretic peptide (NT-pro-BNP) was correlated with LV hypertrophy and systolic dysfunction and was a powerful prognostic indicator in the chronic peritoneal dialysis (PD) patients [10]. However, the utility of NT-pro-BNP in detecting or excluding LV hypertrophy and systolic dysfunction has so far not been studied in the PD population.

We have shown in the chronic PD patients that C-reactive protein (CRP) and cardiac troponin T (cTnT) were predictive of mortality and cardiovascular outcomes. Of note, even though CRP and cTnT were confounded by residual kidney function [11], elevated cTnT was correlated with LV hypertrophy and systolic dysfunction [12,13] and was predictive of mortality and cardiovascular death independent of residual kidney function in PD patients [12–14]. Likewise, a single time-point measured CRP was shown to be significantly related to LV hypertrophy and predictive of survival and cardiovascular outcomes in PD patients [15]. Furthermore, cTnT enhanced the prognostic value of LV mass and ejection fraction in predicting circulatory congestion in chronic PD patients [16].

Thus, the current study extended further to previous observations in this cohort with the primary objective being to compare the diagnostic potentials of NT-pro-BNP, cTnT and CRP for cardiac hypertrophy and systolic dysfunction in chronic PD patients. Furthermore, we evaluated whether residual renal function may influence the diagnostic potentials of these biomarkers for LV abnormalities in PD patients.

**Methods**

**Protocol**

The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All patients provided informed consent prior to study entry.

**Patients**

Two hundred and thirty patients with ESRD were prospectively and consecutively recruited from a single PD centre in Hong Kong in 1999, and they represented 85% of the total PD population (n = 270) at the centre. Patients were considered eligible for study inclusion if they had received continuous ambulatory PD treatment for ≥3 months. Fifteen percent of the patients were excluded based on the exclusion criteria that included patients with underlying malignancy, chronic liver disease, systemic lupus erythematosus, chronic rheumatic heart disease, congenital heart disease, patients who refused to give consent or patients with incomplete data. All patients were dialyzed using conventional lactate buffered glucose-based PD solutions.

In patients who developed acute coronary syndrome, acute circulatory congestion, peritonitis, exit site infections or any other infective complications, all the above assessments were deferred for at least 1 month after complete resolution of the complication.

**Echocardiography**

Two-dimensional echocardiography was performed using a GE-VingMed System 5 echocardiographic machine (GE-VingMed Sound AB, Horten, Norway) with a 3.3-MHz multifrequency probe in subjects lying in the left decubitus position by a single experienced cardiologist blinded to all clinical, biochemical details and biomarkers results of patients. All echocardiographic data were recorded according to the guidelines of the American Society of Echocardiography [17]. LV hypertrophy was defined as LV mass index >131 g/m² in men and >100 g/m² in women in accordance with Framingham criteria [18]. LV ejection fraction (EF) was obtained using a modified biplane Simpson’s method from apical two- and four-chamber views [19]. Mitral inflow velocities were recorded using pulsed wave Doppler and myocardial velocities were recorded using a tissue Doppler technique as previously described [20]. The ratio of early transmural flow velocity (E) to early diastolic mitral annular velocity (Em) (E/Em ratio) has been shown to be useful in estimating LV filling pressure [21] and was also recently demonstrated to be a powerful predictor of mortality in ESRD patients [20].

**Laboratory measurements**

Fasting EDTA and heparin blood samples were collected from patients at the time of echocardiographic examination for measurement of cTnT, NT-pro-BNP, CRP and other standard biochemical parameters. Troponin T in EDTA plasma and cTnT were measured by the electrochemiluminescence immunoassay (Elecys 2010 analyser, Roche Diagnostic GmbH, Mannheim, Germany). The detection limit of the troponin assay was 0.01 µg/L with an inter-assay CV of 5.9%, 4.8% and 1.5% at 0.024 µg/L, 0.18 µg/L and 1.76 µg/L, respectively. The measuring range of the NT-pro-BNP assay was 5–35 000 pg/mL with a CV of 2.6% at 1068 pg/mL. For samples with NT-pro-BNP concentrations above the measuring range, the final concentrations were taken as 35 000 pg/mL. CRP and albumin in heparin plasma were measured, respectively, using the Tina-quant CRP latex immunoturbidimetric assay (detection limit of 0.88 mg/L and CV of 2.7% at 10.6 mg/L) and the bromocresol purple...
method on the Roche Modular D analyser (Roche Diagnostics GmbH, Mannheim, Germany). Plasma urea, creatinine, calcium and phosphorus were also measured on the Roche modular analyser.

Blood pressure measurements
With a mercury sphygmomanometer, systolic and diastolic blood pressure were measured once on every follow-up visit after a patient was rested for 15 min on either arm at 8-week intervals for 12 months preceding study entry and were then averaged to give the final systolic and diastolic blood pressure.

Assessment of residual renal function and dialysis indices
Residual glomerular filtration rate (GFR) was measured as the average of 24-h urine urea and creatinine clearance [22]. Adequacy of dialysis was estimated by measuring total weekly urea clearance and creatinine clearance using standard methods [23]. Contribution of PD and renal component to the total urea clearance was estimated separately.

Statistical analysis
Continuous data were tested for normality by the Kolmogorov–Smirnov test. Data were expressed as mean ± SD or median (interquartile range, IQR) depending on the distribution. Correlations of the different biomarkers with LV mass index and systolic dysfunction were evaluated using multiple linear regression analysis and multiple logistic regression analysis, respectively. We evaluated the gain in prediction power for severe LV hypertrophy and systolic dysfunction attributable to high sensitivity CRP (hs-CRP), cTnT and NT-pro-BNP by the $-2 \log$ likelihood ($-2 \log L$) test. This test compared different logistic regression models fitted to the same set of data. The smaller is the $-2 \log$ L value, the stronger is 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 provided by the method leading to the lowest $-2 \log L$ value. Statistical analysis was performed using the SPSS software version 14.0 (Chicago, IL, USA).

We compared the usefulness of NT-pro-BNP, cTnT and hs-CRP in predicting severe LV hypertrophy and systolic dysfunction using the ROC curve analysis. The best cut-off was defined on the basis of analysis of the ROC curves by identifying the value of each biomarker that gave the best combination of sensitivity and specificity, that is, the value that maximized the sum of the sensitivity and specificity. The ROC curve analysis was performed using the MedCalc software version 7.50 (Mariakerke, Belgium).

Results
The characteristics of the study population are detailed in Table 1. The background kidney disease was chronic glomerulonephritis in 74 patients (32.2%), diabetic nephropathy in 55 patients (23.9%), hypertensive nephrosclerosis in 31 patients (13.5%), tubulointerstitial disease in 6 patients (2.6%), polycystic kidney disease in 12 patients (5.2%), obstructive uropathy in 13 patients (5.7%) and unidentified in 39 patients (17%). Two hundred and eighteen patients (94.8%) displayed LV hypertrophy on echocardiography. Systolic dysfunction (as defined by EF ≤45%) was present in 38 patients (16.5%). Given the extremely high prevalence of LV hypertrophy, we stratified patients by the upper tertile cut-off of LV mass index (that is, ≥247.8 g/m²) and defined these patients as having severe LV hypertrophy.

NT-pro-BNP was strongly correlated with cTnT ($r = 0.581, P < 0.001$) and hs-CRP ($r = 0.227, P = 0.001$). cTnT was also correlated with hs-CRP ($r = 0.249, P < 0.001$). Adjusting for age, male gender, diabetes mellitus, coronary artery disease, haemoglobin, systolic blood pressure, residual GFR in the multivariate analysis, cTnT [standardized coefficient ($\beta$) = 0.184, $P = 0.004$] and NT-pro-BNP ($\beta = 0.391, P < 0.001$) but not hs-CRP ($P = 1.0$) were significantly associated with LV mass index. Controlling also for the E/Em ratio that is considered a non-invasive marker of LV filling pressure [21], NT-pro-BNP ($\beta = 0.393, P < 0.001$) and cTnT ($\beta = 0.259, P = 0.001$) but not hs-CRP ($\beta = -0.052, P = 0.46$) remained significantly associated with LV mass index. Adjusting for the same covariates in the multiple logistic regression analysis, every 1000 pg/mL increase in NT-pro-BNP was associated with an 8% increase (95% CI, 1.04–1.12; $P < 0.001$) in the risk of systolic dysfunction. Both CRP [Odds ratio (OR), 0.98 (95% CI, 0.94–1.02); $P = 0.24$] and cTnT [OR, 3.15 (95% CI, 0.40–24.97); $P = 0.28$] showed no significant association with systolic dysfunction. After additional adjustment for the E/Em ratio, every 1000 pg/mL increase in NT-pro-BNP

<table>
<thead>
<tr>
<th>Table 1. Patient characteristicsa</th>
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<tr>
<td>Demographic and clinical characteristics</td>
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<tr>
<td>Age (years)</td>
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<td>Male gender (%)</td>
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<td>Positive smoking history (%)</td>
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<td>Body mass index (kg/m²)</td>
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<td>Diabetes (%)</td>
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<td>Background atherosclerotic vascular disease (%)</td>
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<tr>
<td>Background coronary artery disease (%)</td>
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<td>Duration of dialysis (months)b</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
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<td>Medications use</td>
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<tr>
<td>Erythropoietin (%)</td>
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<tr>
<td>Aspirin (%)</td>
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<tr>
<td>HMG-CoA reductase inhibitors (%)</td>
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<tr>
<td>Anti-hypertensive medication (%)</td>
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<tr>
<td>Beta blockers</td>
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<tr>
<td>Calcium channel blockers</td>
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<tr>
<td>Angiotensin converting enzyme inhibitors or angiotensin receptor blockers</td>
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<tr>
<td>Biochemical parameters</td>
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<td>Haemoglobin (g/dL)a</td>
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<td>Albumin (g/L)a</td>
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<td>Calcium (mmol/L)</td>
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<td>Phosphorus (mmol/L)</td>
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<tr>
<td>Intact parathyroid hormone (pmol/L)b</td>
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<tr>
<td>NT-pro-BNP (pg/mL)b</td>
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<td>Cardiac troponin T (µg/L)b</td>
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<tr>
<td>C-reactive protein (mg/L)b</td>
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<td>Dialysis parameters</td>
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<tr>
<td>Total urea clearance</td>
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<td>Total creatinine clearance (L/week/1.73 m²)</td>
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<tr>
<td>Residual glomerular filtration rate (mL/min/1.73 m²)b</td>
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<tr>
<td>Echocardiographic parameters</td>
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<tr>
<td>Left ventricular mass index (g/m²)</td>
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<td>Left ventricular end-diastolic volume index (mL/m²)</td>
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<tr>
<td>Left ventricular ejection fraction (%)</td>
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<td>Left ventricular fractional shortening (%)</td>
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</table>

aContinuous data as mean ± SD unless specified otherwise.
bMedian (interquartile range).
Table 2. Predictive value of NT-pro-BNP and cardiac troponin T for severe LV hypertrophy and systolic dysfunction using the threshold of best cut-off values in overall peritoneal dialysis patients

<table>
<thead>
<tr>
<th></th>
<th>Best cut-off</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe LV hypertrophy (LVMI ≥ upper tertile, 247.8 g/m²) (n = 77)</td>
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<tr>
<td>NT-pro-BNP</td>
<td>8862 pg/mL</td>
<td>76.6 (65.6–85.5)</td>
<td>79.1 (71.8–85.2)</td>
<td>64.8</td>
<td>87.1</td>
</tr>
<tr>
<td>Cardiac troponin T</td>
<td>0.01 µg/L</td>
<td>92.2 (83.8–97.1)</td>
<td>49.0 (40.9–57.2)</td>
<td>47.7</td>
<td>92.6</td>
</tr>
<tr>
<td>Systolic dysfunction (EF ≤ 45%) (n = 38)</td>
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<tr>
<td>NT-pro-BNP</td>
<td>7468 pg/mL</td>
<td>84.2 (68.7–93.9)</td>
<td>64.6 (57.4–71.3)</td>
<td>32.0</td>
<td>95.4</td>
</tr>
<tr>
<td>Cardiac troponin T</td>
<td>0.07 µg/L</td>
<td>76.3 (59.8–88.5)</td>
<td>64.1 (56.8–70.8)</td>
<td>29.6</td>
<td>93.2</td>
</tr>
</tbody>
</table>

LVMI, left ventricular mass index; EF, ejection fraction; PPV, positive predictive value; NPV, negative predictive value.

Table 2 presents the diagnostic value of NT-pro-BNP and cTnT for severe LV hypertrophy and systolic dysfunction in the overall population. The ROC curve analyses in relation to severe LV hypertrophy and systolic dysfunction are shown in Figure 2A and B. NT-pro-BNP, cTnT and hs-CRP had a significant diagnostic value for severe LV hypertrophy because the area under the corresponding ROC curves (AUC) were 0.823 (95% CI, 0.767–0.870; P < 0.0001), 0.730 (95% CI, 0.668–0.786; P < 0.0001) and 0.636 (95% CI, 0.570–0.698; P = 0.0007), respectively, and were significantly greater than the threshold of diagnostic indifference (50%). The AUC of NT-pro-BNP was significantly higher than that of cTnT (P = 0.013) and attributable to adding hs-CRP, cTnT and NT-pro-BNP to the basic model.

Fig. 2. ROC curves for NT-pro-BNP, cardiac troponin T and C-reactive protein in predicting (A) severe left ventricular (LV) hypertrophy and (B) systolic dysfunction in the overall population.

remained associated with a 9% increase [95% CI, 1.03–1.16; P = 0.004] in the risk of systolic dysfunction. cTnT [OR, 0.18 (95% CI, 0.01–5.32); P = 0.32] and CRP [OR, 0.95 (95% CI, 0.88–1.03); P = 0.23] showed insignificant association with systolic dysfunction in the multivariable model. Figure 1A and B shows the gain in predictive power for severe LV hypertrophy and systolic dysfunction attributable to adding hs-CRP, cTnT and NT-pro-BNP to the basic model.

Fig. 1. Percentage gain in the predictive power for (A) severe left ventricular (LV) hypertrophy (defined as LV mass index ≥ upper tertile, 247.8 g/m²) and (B) systolic dysfunction (defined as ejection fraction ≤ 45%) attributable to adding C-reactive protein, cardiac troponin T and NT-pro-BNP to the basic regression model that included age, gender, diabetes mellitus, coronary artery disease, haemoglobin, systolic blood pressure and residual GFR.
hs-CRP (P < 0.001). The AUC of cTnT was also higher than that of hs-CRP (P = 0.056) (Figure 2A).

NT-pro-BNP and cTnT had a significant diagnostic potential for systolic dysfunction as shown by the significantly greater AUC [NT-pro-BNP: 0.799 (95% CI, 0.741–0.849; P < 0.0001); cTnT: 0.750 (95% CI, 0.689–0.805; P < 0.0001)] compared to the threshold of diagnostic indifference (50%). The AUC of hs-CRP for systolic dysfunction was only 0.586 (95% CI, 0.519–0.650) and was statistically insignificant (P = 0.10). The AUC in relation to systolic dysfunction was significantly higher for NT-pro-BNP (P < 0.001) and cTnT (P = 0.006) compared to that for hs-CRP. No significant difference was observed in the AUCs of NT-pro-BNP and cTnT (P = 0.32) for systolic dysfunction (Figure 2B).

Patients were stratified in two groups by the presence or absence of residual renal function (RRF). Figure 3A and B shows the ROC curve analysis in relation to severe LV hypertrophy and systolic dysfunction in patients with RRF. The AUCs in predicting severe LV hypertrophy were 0.793 (95% CI, 0.717–0.856; P < 0.0001), 0.736 (95% CI, 0.655–0.806; P < 0.0001) and 0.625 (95% CI, 0.540–0.704; P = 0.030), respectively, for NT-pro-BNP, cTnT and hs-CRP and were significantly higher than the threshold of diagnostic indifference (50%). The AUC in relation to severe LV hypertrophy was higher for NT-pro-BNP than that for hs-CRP (P = 0.026). The difference in AUCs between NT-pro-BNP and cTnT (P = 0.32) and between cTnT and hs-CRP (P = 0.16) did not reach statistical significance.

The AUCs of NT-pro-BNP and cTnT in predicting systolic dysfunction were 0.803 (95% CI, 0.728–0.864; P < 0.0001) and 0.759 (95% CI, 0.680–0.826; P < 0.0001), respectively, and were significantly higher than the threshold of diagnostic indifference (50%) while that of hs-CRP was insignificant [0.635 (95% CI, 0.550–0.714); P = 0.079]. The AUC in relation to systolic dysfunction was not significantly different between NT-pro-BNP and cTnT (P = 0.58), between cTnT and hs-CRP (P = 0.21) and between NT-pro-BNP and hs-CRP (P = 0.078). Table 3 shows the predictive value of NT-pro-BNP and cTnT for severe LV hypertrophy and systolic dysfunction using the best cut-off threshold in patients with and without RRF.

Figure 3C and D shows the ROC curve analysis in relation to severe LV hypertrophy and systolic dysfunction in anuric PD patients. The AUCs in relation to severe LV hypertrophy were significantly higher for NT-pro-BNP [0.803 (95% CI, 0.704–0.881; P < 0.0001)] and cTnT [0.631 (95% CI, 0.521–0.732; P = 0.035)] than the threshold of diagnostic indifference (50%). The AUC of hs-CRP was insignificant [0.584 (95% CI, 0.474–0.689; P = 0.18)]. The AUC in predicting severe LV hypertrophy differed significantly between NT-pro-BNP and cTnT (P = 0.003), between NT-pro-BNP and hs-CRP (P = 0.003) but not between cTnT and hs-CRP (P = 0.52). The AUCs of NT-pro-BNP and cTnT in relation to systolic dysfunction were 0.751 (95% CI, 0.646–0.837; P < 0.0001) and 0.701 (95% CI, 0.593–0.794; P = 0.002), respectively, and were significantly higher than the threshold of diagnostic indifference (50%) while that of hs-CRP was insignificant [0.483 (95% CI, 0.374–0.593; P = 0.94). The AUC in relation to systolic dysfunction differed significantly between NT-pro-BNP and hs-CRP (P = 0.001), between cTnT and hs-CRP (P = 0.005) but not between NT-pro-BNP and cTnT (P = 0.49).
Patients with residual renal function (n = 143)

Severe LV hypertrophy (n = 33)

<table>
<thead>
<tr>
<th>NT-pro-BNP (µg/L)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6244 pg/mL</td>
<td>78.8 (61.1–91.0)</td>
<td>77.3 (68.3–84.7)</td>
<td>51.0</td>
<td>92.4</td>
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Systolic dysfunction (n = 16)

<table>
<thead>
<tr>
<th>NT-pro-BNP (µg/L)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7924 pg/mL</td>
<td>75.0 (47.6–92.6)</td>
<td>74.8 (66.3–82.1)</td>
<td>27.3</td>
<td>96.0</td>
</tr>
</tbody>
</table>

Anuric patients (n = 87)

Severe LV hypertrophy (n = 44)

<table>
<thead>
<tr>
<th>NT-pro-BNP (µg/L)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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</thead>
<tbody>
<tr>
<td>9600 pg/mL</td>
<td>75.0 (59.7–86.8)</td>
<td>74.4 (58.8–86.5)</td>
<td>75.5</td>
<td>74.4</td>
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Systolic dysfunction (n = 22)

<table>
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<tr>
<th>NT-pro-BNP (µg/L)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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</thead>
<tbody>
<tr>
<td>12494 pg/mL</td>
<td>77.3 (54.6–92.1)</td>
<td>76.7 (54.9–78.8)</td>
<td>44.7</td>
<td>89.8</td>
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<table>
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<tr>
<th>cTnT (µg/L)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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<tbody>
<tr>
<td>0.05 µg/L</td>
<td>81.8 (67.3–91.8)</td>
<td>44.2 (29.1–60.1)</td>
<td>60.0</td>
<td>70.4</td>
</tr>
<tr>
<td>0.19 µg/L</td>
<td>50.0 (28.2–71.8)</td>
<td>87.7 (77.2–94.5)</td>
<td>57.9</td>
<td>83.8</td>
</tr>
</tbody>
</table>

LV, left ventricular; PPV, positive predictive value; NPV, negative predictive value; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; cTnT, cardiac troponin T.

Discussion

In this study, we showed that NT-pro-BNP has the strongest predictive value for severe LV hypertrophy and systolic dysfunction compared to cTnT irrespective of the presence or absence of residual renal function. Close to 13% gain in predictive power was observed when NT-pro-BNP was included in the regression models for severe LV hypertrophy and systolic dysfunction, clearly showing significant predictive value of NT-pro-BNP for severe LV hypertrophy and systolic dysfunction. LV hypertrophy and systolic dysfunction are important predictors of all-cause and cardiovascular mortality in the dialysis population [1,2]. The prevalence of LV hypertrophy has been estimated to range from 60 to 80% [1,2]. In the PD population, the prevalence of LV hypertrophy was even higher, approaching 95% [24]. On the other hand, systolic dysfunction occurred less frequently with a reported prevalence of around 15% [1,2], similar to our current cohort. In addition, a greater progression of LV hypertrophy during dialysis predicts a more adverse cardiovascular outcome [25]. BNP is secreted mainly from the left ventricle in response to increased wall stress [3,4] and increases in proportion to the severity of LV dysfunction [3]. In dialysis patients, cardiac natriuretic peptides are frequently elevated [10,26,27]. In keeping with other studies [28–30], we observed a strong association between NT-pro-BNP and LV mass index and systolic dysfunction in PD patients. Other contributing factors for elevated NT-pro-BNP included extra-cellular volume expansion [31,32], coronary artery disease [33] and decline in residual renal function [10]. In keeping with the Cardiovascular Risk Evaluation Extension (CREED) study [9], our current study showed that NT-pro-BNP had a high negative predictive value (NPV) for systolic dysfunction and a moderately high NPV for severe LV hypertrophy and suggests that NT-pro-BNP could be similarly applied in the PD population to rule out systolic dysfunction, irrespective of residual kidney function. Our data suggest that NT-pro-BNP testing may be utilized to pre-screen and identify high-risk patients for further echocardiographic studies and thus save resources. Our study differed from the CREED study in that we included non-selective PD patients and that patients with previous heart failure were also recruited.

It is of interest that the best NT-pro-BNP cut-off for excluding systolic dysfunction in our PD patients was around 7500 pg/mL and closely approximated that derived from another study of haemodialysis patients [34]. On the other hand, the best NT-pro-BNP cut-off in ruling out severe LV hypertrophy in PD patients was even higher, ~8800 pg/mL. However, the very high prevalence of LVH limits the diagnostic utility and application of NT-pro-BNP in detecting LVH in the clinical setting.

It is well recognized that cTnT is frequently elevated in dialysis patients in the absence of acute coronary syndrome [11–14] and that the elevation may be partly attributed to LV hypertrophy and systolic dysfunction [11,12]. In this study, we showed that cTnT may be useful in ruling out severe LV hypertrophy and systolic dysfunction in PD patients although the AUCs were slightly lower than that of NT-pro-BNP. The gain in predictive power attributable to adding cTnT in the regression models for severe LV hypertrophy and systolic dysfunction was more modest (5% and 3%, respectively) compared to that of NT-pro-BNP. Using the best cut-off of 0.07 µg/L, cTnT had a NPV of 93% for systolic dysfunction, suggesting that cTnT could also be reliably applied in the PD patients to exclude systolic dysfunction. A cTnT cut-off of 0.01 µg/L may also be useful in excluding severe LV hypertrophy as evident by the high NPV for severe LV hypertrophy (92.6%) and a sensitivity of 92.2%, using a cut-off of 0.01 µg/L. Our findings were somewhat contrary to the study by Mallamaci et al. showing a high positive predictive value (PPV) of cTnT for LV hypertrophy but a low NPV for LV hypertrophy [34]. This difference may be partly attributed to difference in the prevalence of LV hypertrophy in the two cohorts (95% for our PD patients and 75% in the study by Mallamaci et al.).
Thus, we used the upper tertile cut-off of LV mass index to define severe LV hypertrophy. In addition, the study by Mallamaci et al. excluded patients with previous history of heart failure while close to one-third of our PD patients had previous history of heart failure. It is, however, important to note that both our study and study by Mallamaci et al. showed a very high NPV of cTnT (both 93%) for systolic dysfunction, clearly confirming the potential diagnostic value of cTnT for excluding systolic dysfunction in the dialysis patients. Conversely, hs-CRP appeared not useful at all in either regard.

As shown in previous studies, a decline in residual renal function may contribute to elevated NT-pro-BNP and cTnT in ESRD patients on maintenance PD [10,11]. In this study, NT-pro-BNP had a moderately strong predictive value for LV systolic dysfunction irrespective of the presence or absence of residual renal function. The NPV of NT-pro-BNP for LV systolic dysfunction was high in both patients with and without residual renal function (96% and 90%, respectively), clearly indicating the usefulness of NT-pro-BNP in screening out systolic dysfunction in PD patients irrespective of residual renal function. It is, however, imperative to note that the best cut-off of NT-pro-BNP for excluding systolic dysfunction was nearly 30% higher among anuric PD patients compared to those with preserved residual renal function. Likewise, the best cut-off in excluding severe LV hypertrophy was also around 30% higher among anuric PD patients compared to those with preserved residual renal function. And, using the best cut-off of NT-pro-BNP, the NPV for severe LV hypertrophy was higher among patients with residual renal function (92%) than anuric patients (74%). This suggests that NT-pro-BNP measurement may have a greater value in excluding severe LV hypertrophy in patients with preserved residual renal function than anuric patients.

Our results suggested that cTnT measurement may also be reliably applied in PD patients with residual renal function to rule out severe LV hypertrophy and systolic dysfunction as evident by the high NPV for severe LV hypertrophy (91.3%) and systolic dysfunction (96%). In contrast, the NPV of cTnT for severe LV hypertrophy and systolic dysfunction appeared much lower in anuric PD patients. The best cut-off threshold of cTnT in excluding systolic dysfunction was nearly 2.5-fold higher in anuric PD patients than in patients with residual renal function.

Our study has some limitations to consider. First, the prevalence of LV hypertrophy was extremely high in our PD population and thus we used an arbitrary upper tertile cut-off of LV mass index to define severe LV hypertrophy. Second, even though the overall population was large, stratifying patients into those with and without residual renal function resulted in smaller subgroups and reduced study power. Thus, our subgroup analysis will need further confirmation in a large-scale study.

In conclusion, our data suggest that NT-pro-BNP appeared most useful in ruling out systolic dysfunction in PD patients followed by cTnT while hs-CRP appeared not useful at all. Furthermore, the best cut-off level in excluding systolic dysfunction should be defined according to the degree of residual renal function.

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End-stage renal failure and regulatory activities of CD4+CD25\textsuperscript{bright}+FoxP3+ T-cells

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Abstract

Background. The defensive immune system in patients with end-stage renal failure is impaired at multiple levels. This state of immune incompetence is associated with continuous activation of the immune system. An additional explanation for this state of activation may be the disturbed function of CD4+CD25\textsuperscript{bright}+FoxP3+ regulatory T-cells.

Methods. The phenotype and function of peripheral regulatory T-cells from patients with end-stage renal failure (N = 80) and healthy controls (N = 17) was studied by flow cytometry, RT-PCR and mixed lymphocyte reaction. Patients were on haemodialysis (N = 40), peritoneal dialysis (N = 26) or not treated with dialysis yet (N = 14). The latter group had a glomerular filtration rate of <20 ml/min/1.73 m\textsuperscript{2}.

Results. The basal IL-2 mRNA level was high in patient-PBMC (P = 0.0002 versus healthy controls). The absolute number of CD4+CD25\textsuperscript{bright}+ T-cells was low in patients (P < 0.05 versus healthy controls). Furthermore, proliferation of patient-PBMC upon allogenic stimulation was impaired (P < 0.0001 versus healthy controls). The regulatory function of CD4+CD25\textsuperscript{bright}+ T-cells was determined in the setting of direct allore cognition. First, the effect of