


Routinely measured cardiac troponin I and N-terminal pro-B-type natriuretic peptide as predictors of mortality in haemodialysis patients

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Abstract

Aims Cardiac troponin (cTn) and B-type natriuretic peptide (BNP) are elevated in haemodialysis (HD) patients, and this elevation is associated with HD-induced myocardial stunning/myocardial strain. However, studies using data from the international Dialysis Outcomes and Practice Patterns Study (DOPPS) have shown that these cardiac biomarkers are measured in <2% of HD patients in real-world practice. This study aimed to examine whether routinely measured N-terminal pro-BNP (NT-proBNP) and cTnI (contemporary assay) are more appropriate than clinical models for reclassifying the risk of HD patients who have the highest risk of death.

Methods and results Pre-dialysis levels of cTnI and NT-proBNP at study enrolment were measured in 1152 HD patients (Japan DOPPS Phase 5). The patients were prospectively followed for 3 years. Cox regression was used to test the associations of cardiac biomarkers with all-cause mortality, adjusting for potential confounders. Subgroup analyses were performed to assess potential effect modification of clinical characteristics, such as age, systolic blood pressure, HD vintage, diabetes mellitus, coronary artery disease, and a history of congestive heart failure. At baseline, 337 (29%) patients had elevated cTnI (99th percentile of a healthy population: >0.04 ng/mL) with a median (inter-quartile range) level of 0.020 (0.005–0.041) ng/mL, and 1140 (99%) patients had elevated NT-proBNP (cut-off for heart failure: >125 pg/mL) with a median level of 3658 (1689–9356) pg/mL. There were 167 deaths during a median follow-up of 2.8 (2.2–2.8) years. Higher levels of both cardiac biomarkers were incrementally associated with mortality after adjustment for potential confounders. Even after adjustment for alternative cardiac biomarkers, the overall *P* value for the association was <0.01 for both biomarkers. However, the prognostic significance of NT-proBNP was moderately diminished when cTnI was added to the model. The hazard ratios of mortality for cTnI > 0.04 ng/mL (vs. cTnI < 0.006 ng/mL) and NT-proBNP > 8000 pg/mL (vs. NT-proBNP < 2000 pg/mL) were 2.56 (95% confidence interval: 1.37–4.81) and 1.90 (95% confidence interval: 0.95–3.79), respectively. Subgroup analyses showed that the associations of both cardiac biomarkers with mortality were generally consistent between stratified groups.

Conclusions Routinely measured NT-proBNP and cTnI levels are strongly associated with mortality among prevalent HD patients. These associations remain robust, even after adjustment for alternative biomarkers, suggesting that cTnI and NT-proBNP have identical prognostic significance and may reflect different pathological aspects of cardiac abnormalities.

Keywords Cardiac troponin I; Cardiovascular disease; Haemodialysis; Mortality; NT-proBNP

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Introduction

Cardiovascular disease (CVD) is prevalent in haemodialysis (HD) patients and is the leading cause of mortality with a risk

of ~9 times that in the general population.¹ B-type natriuretic peptide (BNP)² and cardiac troponin (cTn)³ are widely used in the setting of heart failure (HF) and suspected acute coronary syndrome (ACS), respectively. However, studies using interna-

tional data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) have shown that these cardiac biomarkers are measured in <2% of HD patients in real-world practice (analyses not shown).

Among patients without chronic kidney disease (CKD), the diagnostic cut-offs of 35 pg/mL for BNP and 125 pg/mL for N-terminal pro-BNP (NT-proBNP) are recommended to indicate the presence of chronic HF in the clinical guidelines from the European Society of Cardiology.⁴ However, almost 100% of HD patients have values above these threshold levels.⁵ These values could be 10-fold to 100-fold higher than those in non-CKD patients⁶ because of deficits in renal and extrarenal clearance⁷ and other unknown mechanisms of increased cardiac production.⁸

Similar to natriuretic peptides, cardiac troponin T (cTnT) and troponin I (cTnI) concentrations are also elevated in HD patients. A cut-off value for cTn that exceeds the 99th percentile of a healthy population indicates myocardial injury and is generally considered as suspected acute myocardial infarction if there is an acute rise in cTn concentrations.⁹ When this cut-off value is used, >90% and ~30% of HD patients have increased cTnT¹⁰ and cTnI concentrations with high-sensitivity or contemporary (clinically prevalent sensitive) assays, respectively.^{10–12} This chronic subtle elevation in cTn concentrations in HD patients without ACS is associated with subclinical cardiac diseases,^{13,14} especially 'dialysis-induced myocardial stunning/myocardial strain'.^{15,16}

Although BNP and cTn concentrations are increased in HD patients, they are both associated with poor outcomes, including CVD and mortality.^{17,18} Nevertheless, guidelines do not provide specific diagnostic and prognostic cut-offs of these cardiac biomarkers for patients on HD.^{2,4}

This study aimed to examine whether routinely measured NT-proBNP and cTnI (contemporary assay) can be more appropriate than clinical models for reclassifying the risk of mortality in HD patients who have the highest risk of death. Specifically, we compared the prognostic value of NT-proBNP, which shows an increase in almost all patients on HD, and cTnI, which is relatively unaffected by this increase compared with cTnT.

Methods

Study design and participants

This study is a part of the DOPPS, which is an international prospective cohort study of the relationships between HD care practices and HD patient outcomes.¹⁹ The Japan DOPPS Phase 5 (J-DOPPS 5) (2012–15) enrolled prevalent HD patients 18 years or older and randomly selected from 45 dialysis facilities in Japan. The participants were prospectively followed-up from July 2012 to July 2015 (for 3 years).

Data collection

Demographic and baseline clinical status variables were collected at study entry. These data, including demographics, medication, and co-morbidity, were collected using a globally unified format questionnaire. Laboratory test values and renal medications were collected at study entry and monthly thereafter. In an ancillary study to J-DOPPS 5, biosamples were collected from study patients annually to ascertain laboratory data that are not commonly collected in dialysis practice, including the cardiac biomarkers cTnI and NT-proBNP. Baseline ancillary biosample data were collected between 6 August 2012 and 25 September 2012. These data were merged with contemporary baseline and monthly J-DOPPS 5 data records dated no more than 120 days before the biosample collection date. All biosamples were sent to a single laboratory, which measured serum Ca, P, Alb, iPTH, FGF23, 1.25(OH)2D, 25(OH)D, ALP, hs-CRP, and cardiac biomarkers including cTnI and NT-proBNP.

Cardiac biomarker assay measurements

Exposures of interest in this study were cTnI and NT-proBNP at baseline measurement. Serum cTnI was measured using a contemporary cTn assay (TnI-Ultra Troponin Kit; Siemens Medical, Solutions Diagnostics). The 99th percentile upper reference limit for the assay is 0.04 ng/mL with a coefficient of variation (CV) of 10% at 0.03 ng/mL and a detection limit at 0.006 ng/mL. Patients who had troponin measurements below the level of detection had their values imputed and set to 0.005 ng/mL for inclusion in the analysis. Serum NT-proBNP was measured using an electrochemiluminescence immunoassay and the ECLusys 2010 analyser (NT-proBNP II, Roche Diagnostics K.K.). The acceptable assay range was 5–35 000 pg/mL, and the <10% CV range was 22 to ~30 000 pg/mL.

Outcome measurements

The primary outcome was all-cause mortality, and the secondary outcome was the occurrence of major adverse cardiovascular events (MACE). MACE were defined as the composite of cardiovascular death, non-fatal myocardial infarction, angina, or stroke. The clinical outcome was prospectively observed for 3 years unless patients departed from the J-DOPPS (typically due to transfer out of the study site).

Statistical analysis

Cox proportional hazards regression models were used to evaluate the association between cardiac biomarker levels

and clinical outcomes. The time at risk started at the moment of biomarker collection to when an outcome occurred, 7 days after leaving the facility due to transfer or a change in kidney replacement therapy modality, loss to follow-up, or the end of the study phase (whichever event occurred first) in July 2015. We analysed stratified models of the primary analysis by possible effect modifiers (history of coronary artery disease, congestive HF, hypertension, or diabetes, age, dialysis vintage, and systolic blood pressure). We selected candidate model covariates on the basis of expected clinical relevance and known associations suggested by previous studies. Model results were estimated using three progressive sets of potential confounders as follows: (i) sex, age, body mass index, and the time on haemodialysis (Model 1); (ii) the same variables as those in Model 1 plus a history of diabetes, hypertension, coronary artery disease, or congestive HF (Model 2); (iii) the same variables as those in Model 2 plus albumin, creatinine, haemoglobin, serum phosphorus, C-reactive protein, pre-haemodialysis systolic blood pressure, use of aldosterone antagonists, aspirin, angiotensin receptor blocker/angiotensin-converting enzyme inhibitors, beta-blockers, vasodilators, statins, lung disease, and cerebrovascular disease (main model); and (iv) the same variables as those in Model 3, plus quartiles of alternative cardiac biomarkers. To deal with missing model covariate data, we used multiple imputation and assumed that data were missing at random. Missing covariate values were imputed using the Sequential Regression Multiple Imputation Method by IVEware.²⁰ Model results were estimated separately by imputation and combined using SAS PROC MIANALYZE

(SAS Institute Inc., Cary, NC, USA). Data management and statistical analyses were performed using SAS 9.4.

Results

Baseline characteristics of the cohort

Initially, 1668 HD patients were enrolled in the J-DOPPS 5 at the time of selection to the biomarker collection. Among these patients, 1194 had ancillary biosamples for a cardiac biomarker and were followed in the DOPPS cohort. In the final study sample, we selected 1152 patients who had both cTnI and NT-proBNP levels measured at baseline (*Figure 1*).

Both cardiac biomarkers levels in the 1152 participants were markedly elevated compared with reported values for the normal population. *Figure 2A* and *2B* shows histograms of cTnI and NT-proBNP levels at baseline, respectively. The median [inter-quartile range (IQR)] baseline cTnI level was 0.020 (0.005–0.041) ng/mL. cTnI levels were unmeasurable in 308 (27%) patients (detection limit at <0.006 ng/mL). When using the cut-off level of 0.04 ng/mL (99th percentile of a healthy population), which is generally designated as indicating the presence of acute myocardial infarction,⁹ 337 (29%) patients had elevated cTnI levels above the cut-off at baseline. The median (IQR) baseline NT-proBNP level was 3658 (1689–9356) pg/mL. A total of 1140 (>99%) patients had elevated NT-proBNP levels at baseline (cut-off for HF: >125 pg/mL). *Figure 3* shows the relationship

Figure 1 STROBE diagram, illustrating the selection criteria for the study sample.

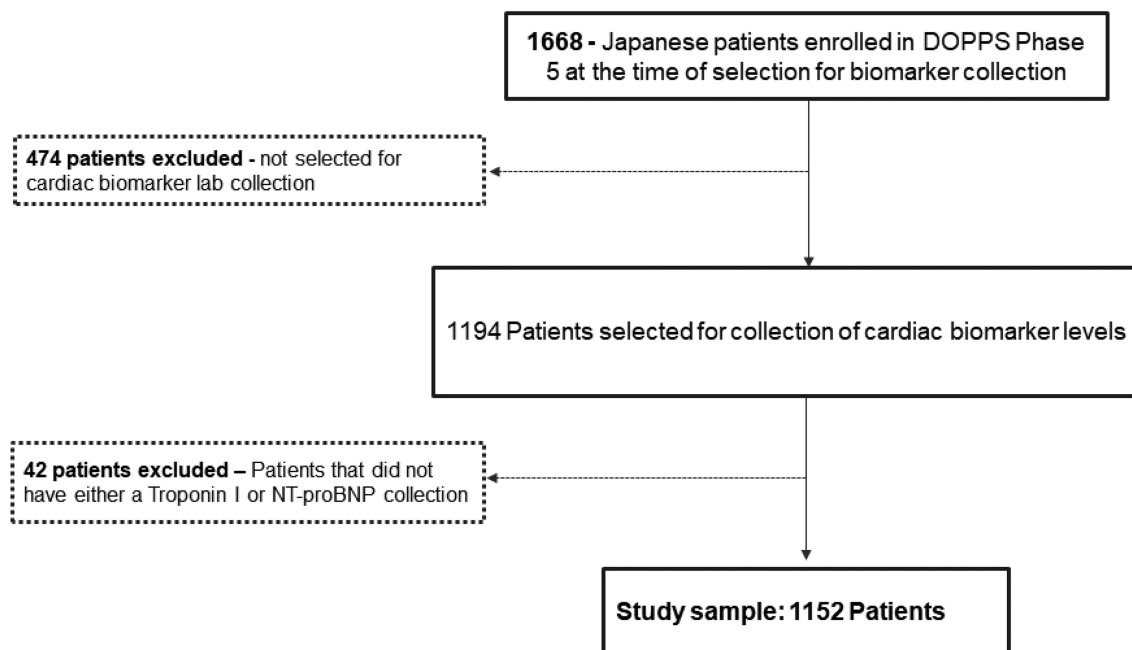


Figure 2 (A) Distribution of troponin I levels in Japan DOPPS 5 patients (2012, $n = 1152$). For measurement of cTnI, the TnI-Ultra Troponin Kit (contemporary assay) was used. At baseline, 308 (27%) patients had unmeasurable levels of cTnI (detection limit at <0.006 ng/mL), and 289 (25%) patients had elevated cTnI (above the 99th percentile of a healthy population: >0.04 ng/mL) with a median [IQR] level of 0.020 [0.005–0.041] ng/mL. (B) Distribution of NT-proBNP levels in Japan DOPPS 5 patients (2012, $n = 1152$). For measurement of NT-proBNP, the NT-proBNP II kit (ECLusys 2010 analyser) was used. At baseline, 1140 (99%) patients had elevated NT-proBNP (cut-off of chronic heart failure for general population: >125 pg/mL) with a median [IQR] level of 3658 [1689–9356] pg/mL.

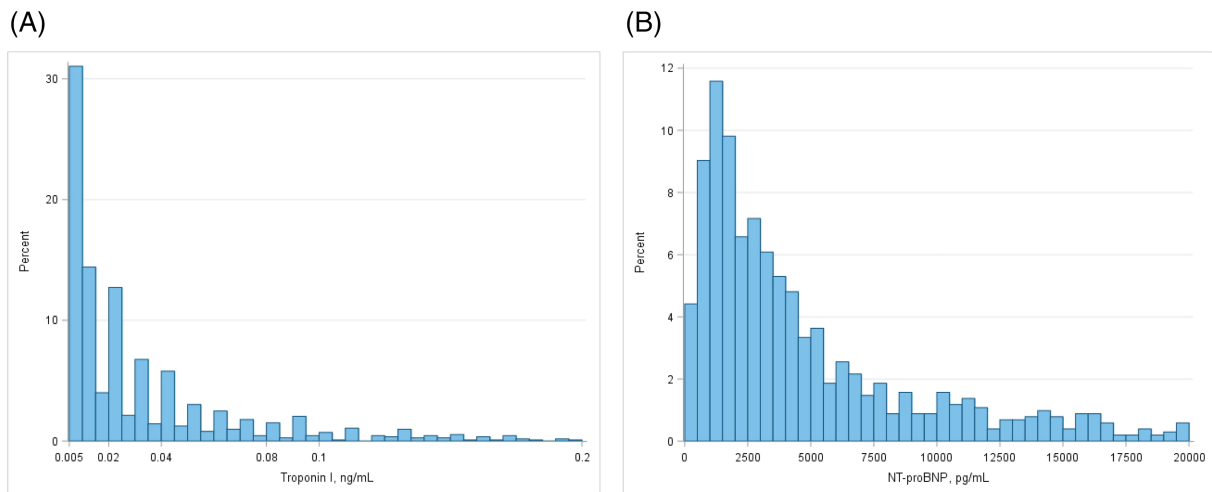
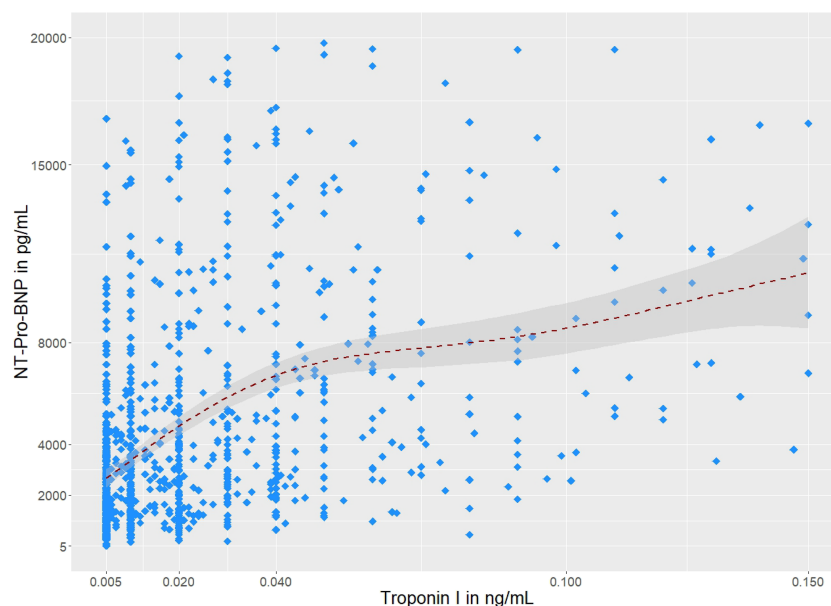


Figure 3 Relationship of cTnI and NT-proBNP. The values displayed include those below the level of detection for troponin I ($TnI < 0.006$), which were set to $TnI = 0.005$ ng/mL. Performed locally estimated scatter plot smoothing (LOESS) to plot the line. Bands represent the 95% confidence interval for the estimate. Restricted to observations with $TnI < 0.15$ ng/mL and $NT\text{-}proBNP < 20\,000$ pg/mL ($N = 989$). A positive correlation between the two cardiac biomarkers was observed. However, this positive correlation was weakened at the cTnI levels above the 99th percentile of a healthy population (0.04 ng/mL).



between cTnI and NT-proBNP concentrations. There was a positive correlation between these two cardiac biomarkers, and it persisted when the scale of these biomarkers was log-transformed (Supporting Information, *Figure S1*).

Categories of biomarkers were chosen on the basis of their distribution among sampled patients with the goal of informing the development of prognostic cut-offs for this population.

Baseline patients' characteristics by these categories of biomarkers are shown in *Tables 1A* and *1B*. Patients with higher cardiac biomarker levels were likely to be older had a higher rate of CVD, including coronary artery disease, history of congestive HF, cerebrovascular disease, and peripheral vascular disease. Patients with higher cardiac biomarker levels also had a longer HD vintage, a lower body mass index, lower creatinine, albumin, and haemoglobin levels and higher systolic blood pressure, C-reactive protein levels, and antihypertensive drug use. Higher levels of cTnI, but not NT-proBNP levels, were associated with a higher rate of hypertension, a higher rate of using an aldosterone antagonist, and a lower proportion of female sex. However, higher levels of NT-proBNP but not cTnI were associated with higher phosphate levels and beta-blocker use.

Relationships of cardiac troponin I and N-terminal pro-B-type natriuretic peptide with mortality and major adverse cardiovascular events

Participants with baseline cTnI and NT-proBNP measurements experienced 167 deaths and 170 MACE during a median (IQR) follow-up of 2.8 (2.2–2.8) years. The hazard ratios (HRs) for mortality associated with quasi-quartiles of cTnI and NT-proBNP are shown in *Tables 2A* and *2B*, respectively. Higher levels of both cardiac biomarkers were incrementally associated with a greater risk of mortality. There was a strong association of the third or higher category of cardiac biomarkers (cTnI > 0.02 ng/mL and NT-proBNP > 4000 pg/mL) with mortality in the main model (adjusted for patients' covariates, including demographics, comorbidity, and other confounders, but not alternative cardiac biomarkers). After adjustment for alternative cardiac biomarkers in addition to the main model, the HRs for mortality in the highest category of cTnI (>0.04 ng/mL) and NT-proBNP (>8000 pg/mL) vs. the references (cTnI < 0.006 ng/mL and NT-proBNP < 2000 pg/mL) were 2.56 [95% confidence interval (CI): 1.37–4.81] and 1.90 (95% CI: 0.95–3.79), respectively (Supporting Information, *Table S1*). However, the overall *P* values were <0.01 for the associations of both cTnI and NT-proBNP with mortality in this model. Additionally, there was no synergistic effect when both biomarkers were added to the model because the *P* value for the interaction of cTnI and NT-proBNP with mortality was 0.561. When cTnI and NT-proBNP were used as log-transformed continuous variables, the adjusted HR per 10% higher cTnI concentrations was 1.05 (95% CI: 1.03–1.07) and that per 10% higher NT-proBNP concentrations was also 1.05 (95% CI: 1.03–1.06). The *P* value for the interaction was 0.36 (Supporting Information, *Table S2*).

Similar associations were observed for MACE (*Table 3*). In the main model, the adjusted HRs (95% CI) for MACE in the third category (>0.02–0.04 ng/mL) and the highest category

(>0.04 ng/mL) of cTnI vs. the reference (<0.006 ng/mL) were 2.66 (1.58–4.45) and 3.01 (1.77–5.13), respectively. With regard to NT-proBNP, only the highest category (>8000 pg/mL) was associated with MACE (2.57 [1.65–4.01]). These associations remained significant even after adjustment for alternative cardiac biomarkers in addition to the main model. The HRs for MACE in the highest category of cTnI (>0.04 ng/mL) and NT-proBNP (>8000 pg/mL) vs. the references (cTnI < 0.006 ng/mL and NT-proBNP < 2000 pg/mL) were 2.25 (95% CI: 1.30–3.90) and 1.94 (95% CI: 1.25–3.01), respectively (Supporting Information, *Table S3*). Similar associations were found when cTnI and NT-proBNP were used as continuous variables. After full adjustment for clinically relevant factors, HRs (95% CI) per 10% higher cTnI and NT-proBNP concentrations for MACE were 1.03 (1.02–1.05) and 1.03 (1.01–1.04), respectively. The *P* value for the interaction was 0.62 (Supporting Information, *Table S4*).

Subgroup analyses

Tables 4A and *4B* show subgroup analyses of the association of cardiac biomarkers with mortality across specified groups of patients. Diabetes mellitus, coronary artery disease, systolic blood pressure, HD vintage, age, and sex did not modify the association of cTnI or NT-proBNP with mortality (each *P* value for interaction was >0.10). The association between NT-proBNP concentrations and mortality appeared to be weaker in patients with prior diagnoses indicating congestive HF. However, there was a lack of substantial evidence to conclude that this association was different for the interaction between congestive HF and NT-proBNP. This is supported by the finding that, after Benjamini Hochberg adjustment for multiple comparisons, the *P* value for this interaction was >0.20. *Figure 4A* and *4B* shows adjusted HR for mortality in each category vs. the reference (lowest category of cardiac biomarkers in the non-HF patients). Patients with HF without elevated BNP or troponin levels had an elevated risk of mortality compared with non-HF patients. Among the patients with elevated biomarkers, those without a diagnosis of HF had a similar risk of mortality as that in patients with HF.

Discussion

We prospectively examined the associations of baseline levels of cTnI and NT-proBNP with mortality and MACE in a multicentre cohort of Japanese HD patients. At baseline, 25% of patients had elevated cTnI (>99th percentile of a healthy population: >0.04 ng/mL), and 99% of patients had elevated NT-proBNP (cut-off of chronic HF: >125 pg/mL). The prevalence of elevated cTnI and NT-proBNP in HD patients in this study is similar to that in previous reports.^{5,10–12} NT-proBNP levels in HD patients were >10 times higher than

Table 1A Patient characteristics by troponin I in Japan DOPPS Phase 5 (2012)

Variable	Troponin I categories				P for trend	% missing
	<0.006 ng/mL ^a	0.006 to <0.02 ng/mL	0.02 to <0.04 ng/mL	≥0.04 ng/mL		
Number of patients	308 (27%)	248 (22%)	259 (22%)	337 (29%)		
Biomarkers						
Troponin I (ng/mL)	0.005 [0.005–0.005]	0.010 [0.010–0.013]	0.022 [0.020–0.030]	0.070 [0.050–0.111]	—	—
NT-proBNP (pg/mL)	1683 [933–3167]	3026 [1569–5338]	4023 [1998–9960]	10 344 [5020–22 749]	<0.01	—
Demographics						
Age	59.0 (12.8)	64.6 (11.4)	68.8 (10.2)	69.4 (10.5)	<0.01	0%
HD vintage (years)	5.13 [2.25–10.6]	5.78 [2.59–13.2]	6.89 [2.91–12.8]	6.68 [3.07–12.6]	<0.01	<1%
Female sex	46%	35%	34%	33%	<0.01	0%
BMI (kg/m ²)	21.9 (3.60)	21.7 (3.65)	21.4 (3.62)	20.9 (3.46)	<0.01	7%
Systolic BP (mmHg) ^b	145 (21.7)	145 (20.7)	149 (21.5)	151 (23.7)	<0.01	2%
IDWG (% of body weight)	3.93 (1.62)	3.99 (1.40)	4.00 (1.46)	4.43 (1.57)	<0.01	3%
Active smoker	11%	6%	8%	13%	0.2	0%
Cause of kidney failure						
Diabetes	33%	30%	35%	41%	0.03	5%
Hypertension	5%	6%	10%	7%	0.12	5%
Glomerular disease	40%	45%	38%	31%	<0.01	5%
Polycystic kidney disease	7%	8%	3%	3%	<0.01	5%
Other	15%	11%	14%	18%	0.13	5%
Cause of death						
Heart disease	2%	2%	4%	9%	<0.01	—
Vascular	0%	0%	2%	1%	0.06	—
Cancer	1%	1%	1%	2%	0.12	—
Other	2%	5%	10%	16%	<0.01	—
Missing	0%	1%	2%	5%	<0.01	14%
Laboratory						
Phosphorus (mg/dL)	5.1 (1.2)	5.0 (1.2)	5.0 (1.2)	5.2 (1.4)	0.39	0%
Ferritin (ng/mL)	104 (114)	134 (322)	114 (142)	158 (430)	0.16	52%
Haemoglobin (g/dL)	10.8 (1.1)	10.6 (1.1)	10.5 (1.1)	10.5 (1.3)	<0.01	<1%
Albumin (g/dL)	3.7 (0.3)	3.7 (0.3)	3.6 (0.4)	3.6 (0.4)	<0.01	0%
Creatinine (mg/dL)	11.1 (3.0)	11.2 (2.7)	10.5 (2.7)	10.1 (2.5)	<0.01	1%
PTH (pg/mL)	167 (143)	171 (172)	153 (133)	161 (193)	0.4	0%
CRP (mg/dL)	0.06 [0.02–0.18]	0.07 [0.03–0.21]	0.09 [0.03–0.25]	0.12 [0.05–0.38]	0.06	<1%
Co-morbidities						
Coronary artery disease	16%	17%	32%	35%	<0.01	<1%
Diabetes	36%	36%	36%	42%	0.1	<1%
Hypertension	78%	79%	82%	85%	<0.01	<1%
Congestive heart failure	11%	15%	19%	23%	<0.01	<1%
Cerebrovascular disease	7%	13%	14%	14%	0.02	<1%
Lung disease	3%	3%	3%	5%	0.348	<1%
Peripheral vascular disease	9%	11%	14%	22%	<0.01	<1%
Medication						
Antihypertensive use ^c	83%	89%	87%	94%	<0.01	1%
ARB/ACE inhibitor use	51%	47%	46%	46%	0.154	1%
Beta-blocker use	24%	28%	27%	24%	0.9	1%

(Continues)

Table 1A (continued)

Variable	Troponin I categories				P for trend	% missing
	<0.006 ng/mL ^a	0.006 to <0.02 ng/mL	0.02 to <0.04 ng/mL	≥0.04 ng/mL		
Aldosterone antagonist use	0%	1%	0%	4%	<0.01	1%
Vasodilator use	39%	52%	49%	66%	<0.01	1%
Aspirin use	22%	28%	36%	35%	<0.01	1%
Statin use	18%	22%	20%	20%	0.78	1%

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; HD, haemodialysis; IDWG, interdialytic weight gain; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PTH, parathyroid hormone.

Results shown as mean (standard deviation), prevalence, or median [inter-quartile range].

^aFirst column characteristics come from patients who had troponin levels below the level of detection (troponin I < 0.006 ng/mL), set to troponin I = 0.005 ng/mL.

^bMean of systolic blood pressure measured before three haemodialysis sessions.

^cAntihypertensive use includes the following major medication classes: ARB/ACE inhibitors, beta-blockers, calcium channel blockers, and vasodilators.

those in the general population, whereas cTnI levels in HD patients were relatively similarly to those in the general population. Even though the magnitude of the CKD-related increase in NT-proBNP levels was much higher than that for cTnI, a positive correlation was observed between these two cardiac biomarkers in this HD cohort. However, this correlation was not observed when cTnI levels were greater than the 99th percentile of a healthy population (0.04 ng/mL). This finding suggests that cTnI and NT-proBNP can be used to determine different aspects of cardiac abnormalities in patients at a high risk of CVD and mortality.

Although cTnI and NT-proBNP (especially NT-proBNP) levels in HD patients were expected to be higher than those in the general population, the prognostic and predictive significance of these biomarkers were maintained and comparable. Higher levels of both cardiac biomarkers were associated with mortality and MACE after adjustment for potentially confounding factors. Even after adjustment for alternative biomarkers, the overall *P* values for the associations of cTnI and NT-proBNP with mortality were significant. However, the prognostic significance of NT-proBNP (the highest category vs. the reference) was moderately diminished when cTnI was added to the model. Nonetheless, these data indicate that cTnI and NT-proBNP may reflect different pathological aspects of cardiac abnormalities. Our finding that cTnI and BNP/NT-proBNP were strong risk indicators and provided incremental information to alternative biomarkers was also reported in patients with HF²¹ and non-dialysis CKD.²² In our study, patients with elevated biomarkers, albeit without HF, had a comparable risk with those with HF, which suggested the presence of undiagnosed heart abnormalities in this subgroup of patients.

In this study, the third (0.02–0.04 ng/mL) and highest (>0.04 ng/mL) categories of cTnI were associated with mortality in the fully adjusted main model. Therefore, even a slight increase in cTnI levels below the 99th percentile (0.04 ng/mL) would be predictive for mortality in HD patients. Elevated cTnI levels do not always indicate necrosis of cardiomyocytes (irreversible injury by ACS).^{23–25} The detection of cTnI in the blood without necrosis or apoptosis of cardiomyocytes can be explained by a normal myocyte turnover, cellular release of proteolytic degradation products, increased cell wall permeability, and the formation and release of membranous blebs.²⁴ These cTnI can be released from viable cardiomyocytes subjected to stress by plasma membrane shedding of vesicular blebs containing unbound cTnI from the cytosolic pool.²⁵ A small increase in cTnI, which carry strong prognostic information for mortality or incipient and/or worsening HF, is associated with increased left ventricular filling pressure. This increase results in myocardial wall stress, toxicity from inflammatory cytokines, oxidative stress, or catecholamine excess and direct cellular damage.^{23,24} Generally, patients have increased cTnI levels compared with those in the general population. Increased

Table 1B Patient characteristics by NT-proBNP in Japan DOPPS Phase 5 (2012)

Characteristics	NT-proBNP categories				P for trend	% missing
	<2000 pg/mL	2000–4000 pg/mL	>4000–8000 pg/mL	>8000 pg/mL		
Number of patients	355 (31%)	256 (22%)	221 (19%)	320 (28%)		
Biomarkers						
Troponin I (ng/mL)	0.005 [0.005–0.018]	0.013 [0.005–0.030]	0.020 [0.010–0.050]	0.049 [0.023–0.090]	<0.01	—
NT-proBNP (pg/mL)	1197 [763–1585]	2883 [2484–3412]	5370 [4552–6544]	16 366 [11 409–30 896]	—	—
Demographics						
Age	60.0 (13.0)	66.1 (10.8)	67.2 (11.0)	69.8 (10.4)	<0.01	0%
HD vintage (years)	4.40 [1.76–10.0]	6.17 [3.03–12.6]	7.47 [3.15–14.7]	6.84 [3.47–12.4]	<0.01	<1%
Female sex	35%	40%	41%	35%	0.9	0%
BMI (kg/m ²)	22.8 (3.77)	21.4 (3.54)	21.0 (3.35)	20.2 (3.01)	<0.01	7%
Systolic BP (mmHg) ^a	145 (21.3)	147 (21.7)	147 (22.2)	152 (22.9)	<0.01	2%
IDWG (% of body weight)	3.80 (1.53)	4.21 (1.44)	3.96 (1.46)	4.48 (1.59)	<0.01	3%
Active smoker	11%	7%	7%	13%	0.5	0%
Cause of kidney failure						
Diabetes	34%	35%	34%	38%	0.4	5%
Hypertension	6%	6%	8%	8%	0.2	5%
Glomerular disease	38%	40%	39%	35%	0.5	5%
Polycystic kidney disease	9%	4%	5%	3%	<0.01	5%
Other	13%	16%	14%	16%	0.4	5%
Cause of death						
Heart disease	2%	3%	2%	10%	<0.01	—
Vascular	1%	1%	0%	3%	0.03	—
Cancer	1%	2%	0%	2%	0.2	—
Other	3%	4%	12%	17%	<0.01	—
Missing	1%	1%	2%	5%	<0.01	14%
Laboratory						
Phosphorus (mg/dL)	5.3 (1.2)	5.1 (1.2)	5.0 (1.3)	4.9 (1.3)	<0.01	0%
Ferritin (ng/mL)	98.6 (159)	143 (223)	113 (178)	161 (452)	0.1	52%
Haemoglobin (g/dL)	10.9 (1.1)	10.6 (1.0)	10.5 (1.1)	10.4 (1.3)	<0.01	<1%
Albumin (g/dL)	3.8 (0.3)	3.7 (0.3)	3.6 (0.3)	3.6 (0.4)	<0.01	0%
Creatinine (mg/dL)	11.6 (3.0)	10.9 (2.6)	10.5 (2.3)	9.7 (2.6)	<0.01	1%
PTH (pg/mL)	173 (155)	157 (124)	176 (231)	148 (142)	0.1	0%
CRP (mg/dL)	0.06 [0.02–0.15]	0.07 [0.03–0.19]	0.08 [0.03–0.22]	0.16 [0.05–0.51]	<0.01	<1%
Co-morbidities						
Coronary artery disease	17%	24%	26%	33%	<0.01	<1%
Diabetes	39%	36%	36%	39%	0.9	<1%
Hypertension	82%	79%	82%	81%	0.9	<1%
Congestive heart failure	12%	20%	14%	24%	<0.01	<1%
Cerebrovascular disease	8%	11%	14%	15%	<0.01	<1%
Lung disease	2%	2%	4%	6%	0.03	<1%
Peripheral vascular disease	7%	13%	18%	21%	<0.01	<1%
Medications						
Antihypertensive use ^b	83%	87%	89%	94%	<0.01	1%
ARB/ACE inhibitor use	45%	46%	47%	51%	0.169	1%
Beta-blocker use	22%	24%	25%	31%	<0.01	1%

(Continues)

Table 1B (continued)

Characteristics	NT-proBNP categories				P for trend	% missing
	<2000 pg/mL	2000–4000 pg/mL	>4000–8000 pg/mL	>8000 pg/mL		
Aldosterone antagonist use	1%	1%	3%	2%	0.1	1%
Vasodilator use	43%	55%	50%	62%	<0.01	1%
Aspirin use	26%	30%	30%	36%	0.01	1%
Statin use	23%	22%	18%	15%	<0.01	1%

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; HD, haemodialysis; IDWG, interdialytic weight gain; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PTH, parathyroid hormone.

Results shown as mean (standard deviation), prevalence, or median (inter-quartile range).

^aMean of systolic blood pressure measured before three haemodialysis sessions.

^bAntihypertensive use includes the following major medication classes: ARB/ACE inhibitors, beta-blockers, calcium channel blockers, and vasodilators.

cTn levels in CKD patients reduce the rule-in performance, but not the rule-out performance, of high-sensitivity cTn for myocardial infarction.²⁶ However, the prognostic performance of cTn for mortality and the incidence of CVD has been established in CKD patients,¹⁸ which is consistent with our study. The underlying mechanism of baseline elevated cTn concentrations in CKD patients is not completely known. Hypothesized mechanisms include subclinical myocyte damage/structural changes associated with cardio-renal interaction, a decreased clearance of cTns,²⁷ CKD-related cardiomyopathy (e.g., uraemic cardiomyopathy),²⁸ and dialyzer membranes.²⁹ In this study, we used the cTnI assay. This assay appears to have an advantage in HD patients¹⁰ because of a lower incidence of elevated cTnI concentrations compared with that of elevated cTnT concentrations.^{10–12} An explanation for this observation remains highly controversial, but it may be because of the differential release, degradation, and clearance of cTns in the circulation.³⁰ Accumulated evidence suggests that cTnT is more affected by renal clearance than cTnI.^{31,32} A reason for this possibility is that circulating cTnT easily degrade into fragmentation (small molecules), which facilitates renal clearance,³² whereas cTnI might be predominantly cleared by other pathways such as the liver.³³

In this HD cohort, almost all of the patients had elevated NT-proBNP levels. This finding is consistent with that in previous reports.⁵ Baseline BNP/NT-proBNP levels in HD patients are 10-fold to 100-fold greater than those in patients without CKD.⁶ However, a meta-analysis that pooled 27 studies showed that an increase in the BNP/NT-proBNP level was still a strong predictor for all-cause mortality (odds ratio: 3.85; 95% CI: 3.11–4.75) and CV mortality (odds ratio: 4.05; 95% CI: 2.53–6.84), despite limited diagnostic accuracy for HF.¹⁷ Similar to previous studies, we found that elevated NT-proBNP levels (>4000 pg/mL) were associated with mortality and the incidence of MACE compared with reference NT-proBNP levels (<2000 pg/mL) in the fully adjusted main model. This finding indicated a much higher NT-proBNP level as a prognostic cut-off for HD patients than that in other patient populations.^{22,34} The CRIC study examined the association of NT-proBNP and cTnT with the incidence of HF in non-dialysis CKD patients (mean glomerular filtration rate: 45.7 mL/min/1.73 m²).²² The median NT-proBNP level of this study was 135 pg/mL (IQR: 59–336 pg/mL), and even modest elevations in NT-proBNP were directly associated with the rate of HF. Another study in patients with stable coronary heart disease described predictive information for mortality and MACE.³⁴ Among the patients with a median NT-proBNP level of 175 pg/mL (IQR: 74–459 pg/mL), NT-proBNP levels were incrementally associated with a greater risk of mortality and the incidence of MACE, and 100 pg/mL of NT-proBNP may be optimal for distinguishing the risk of MACE. These results suggest that different cut-offs of BNP/NT-proBNP are necessary for specific patient populations, including HD pa-

Table 2A Association of quasi-quartiles of troponin I with mortality, by level of adjustment in Japan DOPPS Phase 5 (2012)

Troponin I categories	Hazard ratio (95% confidence interval) for mortality		
	Model 1 ^a	Model 2 ^b	Model 3 ^c
<0.006 ng/mL	1 (ref)	1 (ref)	1 (ref)
0.01 to <0.02 ng/mL	1.19 (0.63–2.26)	1.19 (0.62–2.28)	1.35 (0.68–2.69)
0.02 to <0.04 ng/mL	1.99 (1.14–3.49)	1.92 (1.08–3.41)	1.97 (1.09–3.57)
≥0.04 ng/mL	4.01 (2.30–7.00)	3.72 (2.13–6.50)	3.65 (2.10–6.34)

N = 1152 patients and 167 mortality events.

^aModel 1 adjustments: sex, age, body mass index, and years since start of haemodialysis; model accounts for facility clustering.

^bModel 2 adjustments: Model 1 + history of diabetes, hypertension, coronary artery disease, and congestive heart failure.

^cModel 3 adjustments: Model 2 + albumin, creatinine, haemoglobin, serum phosphorus, C-reactive protein, pre-haemodialysis systolic blood pressure, use of aldosterone antagonists, aspirin, angiotensin receptor blocker/angiotensin-converting enzyme inhibitors, beta-blockers, vasodilators, statin, lung disease, and cerebrovascular disease (main model).

Table 2B Association of quasi-quartiles of NT-proBNP with mortality, by level of adjustment in Japan DOPPS Phase 5 (2012)

NT-proBNP categories	Hazard ratio (95% confidence interval) for mortality		
	Model 1 ^a	Model 2 ^b	Model 3 ^c
<2000 pg/mL	1 (ref)	1 (ref)	1 (ref)
2000–4000 pg/mL	1.35 (0.73–2.48)	1.29 (0.69–2.41)	1.19 (0.62–2.28)
>4000–8000 pg/mL	2.03 (1.21–3.38)	2.00 (1.20–3.32)	1.95 (1.17–3.24)
>8000 pg/mL	4.19 (2.40–7.30)	3.90 (2.21–6.89)	3.08 (1.62–5.88)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

N = 1152 patients and 167 mortality events.

^aModel 1 adjustments: sex, age, body mass index, and years since start of haemodialysis; model accounts for facility clustering.

^bModel 2 adjustments: Model 1 + history of diabetes, hypertension, coronary artery disease, and congestive heart failure.

^cModel 3 adjustments: Model 2 + albumin, creatinine, haemoglobin, serum phosphorus, C-reactive protein, pre-haemodialysis systolic blood pressure, use of aldosterone antagonists, aspirin, ARB/ACE inhibitors, beta-blockers, vasodilators, statin, lung disease, and cerebrovascular disease (main model).

Table 3 Association of quasi-quartiles of troponin I and NT-proBNP with MACE in Japan DOPPS Phase 5 (2012)

Hazard ratio (95% confidence interval) for MACE			
Troponin I categories	NT-proBNP categories		
<0.006 ng/mL	1 (ref)	<2000 pg/mL	1 (ref)
0.006 to <0.02 ng/mL	2.05 (1.12–3.74)	2000–4000 pg/mL	1.47 (0.91–2.36)
0.02 to <0.04 ng/mL	2.66 (1.58–4.45)	>4000–8000 pg/mL	1.50 (0.97–2.31)
≥0.04 ng/mL	3.01 (1.77–5.13)	>8000 pg/mL	2.57 (1.65–4.01)

Notes: MACE defined as the composite of cardiovascular death, non-fatal myocardial infarction, angina, or stroke. Separate models for troponin I and NT-proBNP. Both models adjusted for sex, age, body mass index, years since start of haemodialysis, history of diabetes, hypertension, coronary artery disease, congestive heart failure, albumin, creatinine, haemoglobin, serum phosphorus, C-reactive protein, pre-haemodialysis systolic blood pressure, use of aldosterone antagonists, aspirin, ARB/ACE inhibitors, beta-blockers, vasodilators, statin, lung disease, and cerebrovascular disease (main model).

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MACE, major adverse cardiovascular events; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

N = 1152 patients and 170 events (MACE).

tients. With regard to age, the educational recommendation from the IFCC recommends stratified cut-offs for BNP/NT-proBNP.² Additionally, the ICON-RELOADED study showed that age-stratified diagnostic cut-offs for NT-proBNP of 450, 900, and 1800 pg/mL for the age categories of <50, 50–75, and >75 years, respectively, were optimal to rule in acute HF.³⁵ BNP/NT-proBNP levels are affected by many factors, such as age,³⁵ sex (testosterone concentrations),³⁶ body mass index,³⁷ and renal diseases.⁸ Renal disease is associated with high BNP/NT-proBNP concentrations with complex mecha-

nisms that are poorly understood.⁶ NT-proBNP could be more dependent on renal clearance than BNP. BNP is eliminated from the plasma by binding to natriuretic peptide receptor type C (a clearance receptor) or through proteolysis by neutral endopeptidases (neprilysin), as well as renal excretion by glomerular filtration. In contrast, NT-proBNP is principally cleared by renal excretion.³⁰ In this study, we used NT-proBNP to assess natriuretic peptides. NT-proBNP appears to be superior to BNP for predicting mortality and MACE in CKD patients,³⁸ but this has not been proven.³⁹

Table 4A Association of troponin I with mortality, stratified by possible effect modifiers in Japan DOPPS Phase 5 (2012)

Group ^a	N ^b	Events	Hazard ratio (95% confidence interval) for mortality, by troponin I categories				P for interaction ^c
			<0.006 ng/mL	0.006 to <0.02 ng/mL	0.02 to <0.04 ng/mL	≥0.04 ng/mL	
Overall	1152	167	1 (ref)	1.35 (0.67–2.72)	2.08 (1.16–3.74)	3.68 (2.15–6.31)	—
Diabetes	434	77	1 (ref)	1.25 (0.47–3.32)	2.70 (1.30–5.61)	4.33 (2.10–8.92)	0.7
No diabetes	713	90	1 (ref)	1.47 (0.48–4.57)	1.79 (0.67–4.76)	3.87 (1.61–9.30)	
CAD	288	62	1 (ref)	0.58 (0.14–2.45)	1.09 (0.37–3.15)	3.44 (1.34–8.80)	0.2
No CAD	863	105	1 (ref)	1.73 (0.70–4.30)	2.76 (1.23–6.16)	3.84 (1.73–8.52)	
Congestive HF	199	44	1 (ref)	0.22 (0.03–1.94)	1.82 (0.65–5.07)	1.83 (0.64–5.21)	0.13
No congestive HF	952	123	1 (ref)	1.92 (0.85–4.33)	2.27 (1.15–4.49)	4.89 (2.56–9.34)	
SBP > 140 mmHg	709	103	1 (ref)	1.54 (0.67–3.52)	1.79 (0.97–3.33)	3.05 (1.47–6.33)	0.6
SBP ≤ 140 mmHg	443	64	1 (ref)	1.11 (0.33–3.75)	2.46 (0.75–8.02)	5.30 (1.92–14.7)	
Age > median	575	122	1 (ref)	1.09 (0.44–2.41)	2.04 (0.94–4.40)	3.72 (1.85–7.49)	0.4
Age ≤ median	577	45	1 (ref)	2.25 (0.72–7.02)	2.67 (0.98–7.29)	3.29 (1.10–9.88)	
HD vintage > median	572	70	1 (ref)	0.79 (0.14–4.62)	2.76 (0.74–10.3)	5.22 (1.44–19.0)	0.3
HD vintage ≤ median	580	97	1 (ref)	1.53 (0.70–3.33)	1.86 (0.85–4.11)	2.90 (1.45–5.82)	
Women	431	47	1 (ref)	1.58 (0.44–5.75)	3.18 (1.26–8.04)	3.44 (1.17–10.1)	0.4
Men	720	120	1 (ref)	1.32 (0.53–3.27)	1.83 (0.82–4.07)	3.95 (1.92–8.14)	

CAD, coronary artery disease; CRP, C-reactive protein; HD, haemodialysis; HF, heart failure; SBP, systolic blood pressure.

^aSeparate models for each group; all models adjusted for sex, age, body mass index, HD vintage, history of diabetes, hypertension, CAD, congestive heart failure, CRP, and pre-haemodialysis SBP.

^bWe reported the number of patients (N) from the observed dataset; the hazard ratio and P values were estimated with observed and multiple imputed data.

^cP values reported were calculated from the joint test of the effect estimate of the interaction term of each possible effect modifier with troponin I, included in the main model.

Table 4B Association of NT-proBNP with mortality, stratified by possible effect modifiers in Japan DOPPS Phase 5 (2012)

Group ^a	N ^b	Events	Hazard ratio (95% confidence interval) for mortality, by NT-proBNP categories				P for interaction ^c
			<2000 pg/mL	2000–4000 pg/mL	>4000–8000 pg/mL	>8000 pg/mL	
Overall	1152	167	1 (ref)	1.20 (0.63–2.30)	1.98 (1.17–3.34)	3.07 (1.60–5.89)	—
Diabetes	434	77	1 (ref)	0.68 (0.23–2.02)	1.76 (0.89–3.47)	2.45 (0.97–6.18)	0.2
No diabetes	713	90	1 (ref)	2.29 (0.89–5.84)	2.77 (1.13–6.78)	5.05 (1.81–14.1)	
CAD	288	62	1 (ref)	0.51 (0.14–1.85)	1.63 (0.58–4.56)	2.21 (0.83–5.88)	0.4
No CAD	863	105	1 (ref)	1.69 (0.76–3.77)	1.96 (0.95–4.02)	3.56 (1.59–8.02)	
Congestive HF	199	44	1 (ref)	0.29 (0.06–1.53)	1.47 (0.36–6.07)	1.61 (0.45–5.79)	0.03
No congestive HF	952	123	1 (ref)	1.86 (0.93–3.74)	2.20 (1.26–3.82)	4.34 (2.26–8.34)	
SBP > 140 mmHg	709	103	1 (ref)	1.73 (0.70–4.28)	1.88 (0.84–4.20)	3.02 (1.38–6.58)	0.4
SBP ≤ 140 mmHg	443	64	1 (ref)	0.78 (0.23–2.65)	2.24 (0.94–5.33)	3.87 (1.33–11.3)	
Age > median	575	122	1 (ref)	1.36 (0.60–3.09)	1.77 (0.86–3.64)	2.55 (1.26–5.16)	0.2
Age ≤ median	577	45	1 (ref)	0.76 (0.18–3.13)	2.48 (0.94–6.54)	3.74 (1.50–9.33)	
HD vintage > median	572	70	1 (ref)	0.90 (0.19–4.21)	2.95 (0.82–10.7)	4.35 (1.20–15.7)	0.2
HD vintage ≤ median	580	97	1 (ref)	1.58 (0.79–3.15)	1.62 (0.88–2.99)	2.76 (1.15–6.61)	
Women	431	47	1 (ref)	1.81 (0.57–5.79)	1.69 (0.56–5.08)	2.92 (1.17–7.30)	0.4
Men	720	120	1 (ref)	1.22 (0.59–2.51)	2.25 (1.21–4.21)	3.47 (1.60–7.49)	

CAD, coronary artery disease; CRP, C-reactive protein; HD, haemodialysis; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.

^aSeparate models for each group; all models adjusted for sex, age, body mass index, HD vintage, history of diabetes, hypertension, CAD, congestive heart failure, CRP, and pre-haemodialysis SBP.

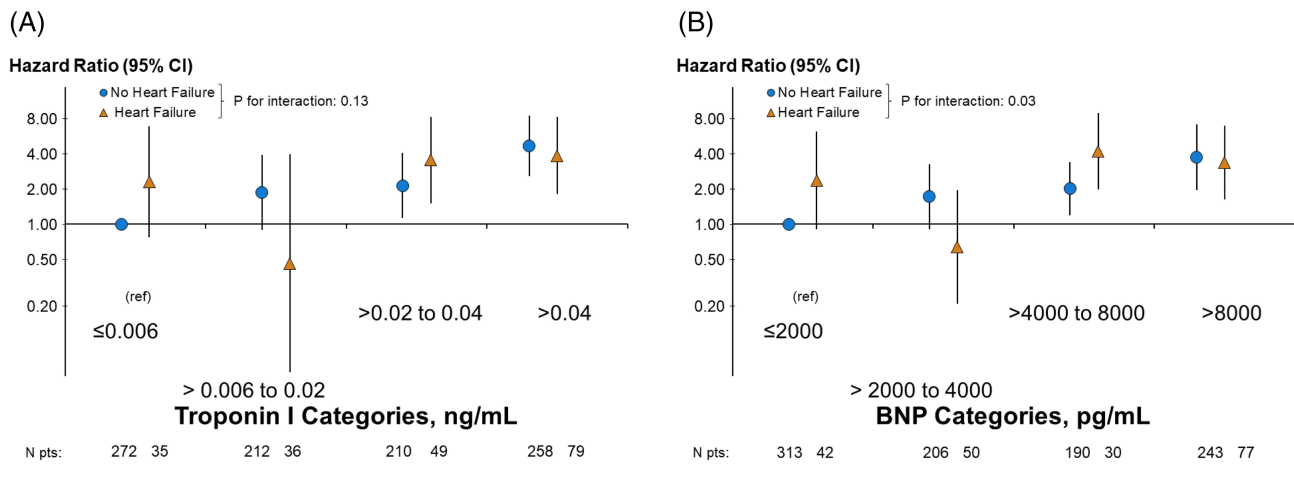
^bWe reported the number of patients (N) from the observed dataset; the hazard ratio and P values were estimated with observed and multiple imputed data.

^cP values reported were calculated from the joint test of the effect estimate of the interaction term of each possible effect modifier with NT-proBNP, included in the main model.

This study has some limitations. First, the cTnI assay used in this study was a contemporary assay (clinically prevalent sensitive but not a high-sensitivity assay). High-sensitivity cTn assays enable detection of low cTn concentrations, which may be present in the blood of healthy individuals, possibly because of cardiomyocyte turnover. However, the contemporary cTn assay does not affect cTn concentrations above the 99th percentile compared with the high-sensitivity assay.⁴⁰

Moreover, the IFCC statement described that the cTn assay is considered 'guideline acceptable' if it has a %CV of ≤10% at the 99th percentile.⁴¹ The 99th percentile upper reference limit of this contemporary cTnI assay is 0.04 ng/mL with a CV of 10% at 0.03 ng/mL. We believe that this is sensitive enough to evaluate HD patients, and the proportion of unmeasurable cTnI concentrations in this assay was only 27% in this study.

Figure 4 (A) Risk (hazard ratio and 95% CI) of all-cause mortality based on troponin I levels and diagnostic of congestive heart failure (reference group: patients in the lower troponin level group without congestive heart failure). Number of deaths: 167. Adjusted for sex, age, body mass index, years since start of haemodialysis, history of diabetes, hypertension, coronary artery disease, congestive heart failure, albumin, creatinine, haemoglobin, serum phosphorus, C-reactive protein, pre-haemodialysis systolic blood pressure, use of aldosterone antagonists, beta-blockers, and vasodilators. (B) Risk (hazard ratio and 95% CI) of all-cause mortality based on NT-proBNP levels and diagnostic of congestive heart failure (reference group: patients in the lower NT-proBNP level group without congestive heart failure). Number of deaths: 167. Adjusted for sex, age, body mass index, years since start of haemodialysis, history of diabetes, hypertension, coronary artery disease, congestive heart failure, albumin, creatinine, haemoglobin, serum phosphorus, C-reactive protein, pre-haemodialysis systolic blood pressure, use of aldosterone antagonists, beta-blockers, and vasodilators.



Second, we examined the prognostic ability of cardiac biomarkers, but cardiac biomarkers assays, especially cTnI assays,⁴¹ are not well harmonized and standardized. Because there is only one source of antibodies and calibrators for NT-proBNP (Roche), harmonization of NT-proBNP assays should not be a problem. However, new NT-proBNP assays are currently being developed.² Further studies need to validate our cut-offs with other cardiac biomarker assays.

Third, race/ethnicity might have been an issue. This study only included Japanese HD patients. The mortality rate and CVD incidence in Japanese HD patients are much lower than those in other countries. In this study, there were 167 (14%) deaths and 170 (15%) MACE over 3 years. In contrast, the CHOICE study, which examined cardiac biomarkers and mortality in 446 HD patients in the USA, showed 323 (72%) deaths and 271 (61%) CVD events during a median follow-up of 3.1 years.⁴² Although there is a large difference in the mortality rate and CVD incidence between this study and the CHOICE study, both studies showed the same finding that elevated cTnI and NT-proBNP levels were directly associated with adverse outcomes. Notably, despite the large difference in the mortality rate and CVD incidence between these two studies, the prevalence of elevated cTnI and BNP/NT-proBNP levels was strikingly similar.

In conclusion, in Japanese HD patients, elevated cTnI and NT-proBNP concentrations were much higher than those in the general population, but were still associated with the

mortality rate and incidence of MACE, even after adjustment for clinically relevant confounders. These associations remained robust after adjustment for alternative biomarkers. In the current study, we lacked evidence to conclude that one of the two biomarkers studied had a substantially better prognostic predictive ability than the other. Because cardiac biomarker concentrations markedly changed depending on the patient population and measurement method (ELISA), additional studies from another cohort/ELISA are required to validate the conclusion.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Relationship between log transformed Troponin I and log transformed NT-ProBNP.

Table S1. Association of quasi-quartiles of Troponin I and

NT-ProBNP with mortality, after adjustment for the alternative cardiac biomarker.

Table S2. Association of Troponin I and NT-proBNP as a continuous variable with mortality, per 10% increase in biomarkers' serum levels.

Table S3. Association of quasi-quartiles of Troponin I and NT-ProBNP with major adverse cardiovascular (MACE) events, after adjustment for the alternative cardiac biomarker.

Table S4. Association of Troponin I and NT-proBNP as a continuous variable with major adverse cardiovascular (MACE) events, per 10% increase in biomarkers' serum levels.

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