Original Article

Cardiothoracic Ratio as a Predictor of Cardiovascular Events in a Cohort of Hemodialysis Patients

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Aim: The cardiothoracic ratio (CTR) on a chest X-ray is an indicator of cardiac enlargement, although its predictive power for cardiovascular disease (CVD) events in chronic kidney disease is unknown. We examined it in a cohort of hemodialysis patients, as compared with an N-terminal fragment of probrain natriuretic peptide (NT-proBNP).

Method: This was an observational study with cross-sectional and longitudinal analyses including 517 maintenance hemodialysis patients and 122 healthy control subjects. The main predictors were CTR and serum NT-proBNP, and the main outcome was CVD events in 5 years.

Results: At baseline, the hemodialysis patients had higher median (interquartile range) levels of CTR [0.487 (0.457–0.520)] than the control group [0.458 (0.432–0.497)]. In the hemodialysis group, CTR was positively correlated with NT-proBNP (Spearman's $r = 0.44$, $P < 0.001$). During follow-up, 190 CVD events occurred. CTR was significantly associated with the risk of CVD [HR 2.12 (95% CI, 1.38–3.25) for the fourth quartile as compared with the second quartile of CTR] in a multivariate Cox model. In the same model, NT-proBNP (fourth versus first quartile) showed a HR of 3.27 (2.02–5.31). When CTR and NT-proBNP were simultaneously included as predictors, only NT-proBNP remained a significant predictor of CVD events, all-cause mortality and composite of CVD plus all-cause mortality.

Conclusions: We showed that CTR was a significant and independent predictor of CVD in hemodialysis patients. CTR can be used for CVD risk stratification in hemodialysis patients when NT-proBNP is not available.

Key words: Cardiothoracic ratio (CTR), NT-proBNP, Cardiovascular event, Hemodialysis, Cohort

Introduction

Patients treated with hemodialysis (HD) have an elevated risk for death from and events of cardiovascular disease (CVD)[1]. Among many CVD risk factors[2-5], left ventricular hypertrophy as measured by ultrasonography was shown to be a strong predictor for worse clinical events[6].

Ventricular myocardium synthesizes probrain natriuretic peptide (proBNP), which is processed to a mature 32-amino-acid polypeptide BNP and a 76-amino-acid polypeptide N-terminal fragment (NT-proBNP). These polypeptides are secreted at equal molar ratios into the circulation in response to stretching of cardiomyocytes to promote excretion of sodium into urine resulting in reduction of extracellular fluid volume. Thus, BNP and NT-proBNP reflect volume overload. In addition, these measurements serve as serum biomarkers for cardiac hypertrophy since left

ventricular mass index by echo cardiography is correlated well with serum levels of BNP[7] or NT-proBNP[8]. Cohort studies showed that cardiovascular endpoints were predicted by higher levels of BNP[7] and by NT-proBNP[9] in hemodialysis patients. However, these biomarker levels are markedly increased in patients with renal failure due to their renal elimination, which may limit their clinical usefulness in some situations.

Historically, the cardiothoracic ratio (CTR) on a chest X-ray has been used as an index of cardiac enlargement[10]. Unlike serum NT-proBNP, CTR is not influenced by renal function itself. In Japan, CTR has been routinely measured in HD practice for the assessment of cardiac hypertrophy and volume overload[11]. Therefore, if CTR can be used in place of NT-proBNP and other costly biomarkers, it would serve in CVD risk stratification of HD patients. However, there are only two studies[12, 13] in patients on HD showing that CTR was an independent predictor of all-cause and/or cardiovascular mortality. So far, no study examined CTR as a possible predictor of future CVD events, not death from CVD, as an endpoint in patients with chronic kidney disease (CKD). In addition, no previous studies explored which is more predictive of poor clinical outcomes, CTR or NT-proBNP.

Aim

The purpose of this study was to evaluate CTR as a predictor of CVD events and other outcomes in comparison with serum NT-proBNP in a cohort of HD patients.

Methods

Study Design

This is an observational study including cross-sectional and longitudinal analyses. The participants were prevalent hemodialysis patients and healthy control subjects. In the cross-sectional study, we compared CTRs between the HD and control groups and examined the correlation between CTR and NT-proBNP in HD patients. In the longitudinal analysis, we performed a cohort study in the HD group. The main exposures were CTR (primary) and serum NT-proBNP levels (secondary). The main outcome was CVD events, and additional outcomes were all-cause mortality and the composite of CVD events plus all-cause mortality during the 5 year follow-up period.

Participants

The HD patients derived from a single center,

prospective cohort study with a total of 518 prevalent HD patients named "DREAM" (Dialysis-Related Endocrine and Metabolic Changes Affecting Cardiovascular Disease) at Inoue hospital, Suita City, Osaka, Japan. The aim of the DREAM cohort was to investigate endocrine, metabolic, or other factors as predictors for outcomes including CVD in HD patients. This study adhered to the Declaration of Helsinki, was approved by the ethics committee at Inoue Hospital (approval No. 121), and was registered at UMIN-CTR (University Hospital Medical Information Network-Clinical Trials Registry; www.umin.ac.jp/ctr/index.htm; study number: UMIN000006168). Some results of the DREAM cohort study have been published elsewhere[14, 15].

The healthy control subjects derived of 122 persons extracted from our database consisted of more than 1500 participants of a health check program in Osaka City. They were selected in a blinded manner, so that their age and sex were comparable to the HD patients. They gave written informed consent prior to the study. None had fasting hyperglycemia (>126 mg/dL) or proteinuria by dip-stick. No one was taking medications for hypertension, diabetes mellitus, or dyslipidemia.

Measurement of CTR

CTR was measured by the method of Danzer[10]. Briefly, CTR was defined as the ratio of the width of the heart to the thoracic width on a posterior to anterior view of a chest X-ray (120–130 kV) taken at full inspiration in a standing position. Cardiac width was measured as the sum of the right and left greatest diameters from midline. The thoracic width was measured as the greatest diameter of the inner borders of the ribs. The coefficient of variation of the CTR measurement was 1.4% when we assessed the reproducibility of our CTR measurement by two independent examiners using chest X-rays taken from 46 HD patients.

For practical reasons, a chest X-ray was taken just after HD sessions for those treated in the AM shift, and it was taken just before HD sessions for those treated in the PM shift (afternoon or evening sessions). Chest X-rays of the control group were taken in the morning.

Blood Sampling and Assay of Serum NT-ProBNP

At baseline, we collected blood samples of the HD patients from arteriovenous fistula before the first HD session in a week. Routine laboratory tests were done within the same day by an automated analyzer, and NT-proBNP was assayed later by using freshly frozen samples kept at −80℃. NT-proBNP was mea-

sured using electrochemiluminescence immunoassay (ECLIA) using a commercially available kit (ECLusys NT-proBNP II, Roche Diagnostics Japan, Inc, Tokyo, Japan) by SRL Inc (Tokyo, Japan). Intra- and interassay coefficients of variation were 1.41% or smaller for three pooled serum standards with different NT-proBNP concentrations (145, 4828, and 8202 pg/mL). In the control group, fasting blood was collected in the morning, and serum samples were kept frozen until the assay.

Definition of CVD

In the DREAM cohort, CVD comprised ischemic heart disease (IHD), stroke, peripheral artery disease (PAD), congestive heart failure (CHF), and cardiac valve disease. The definitions of these diseases were described in detail previously[14]. Shortly, IHD included myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting. Angina pectoris was included in IHD only when myocardial ischemia was evident by electrocardiogram and/or stress myocardial scintigraphy. Stroke was defined by neurological deficit with sudden onset lasting for more than 24 h confirmed by magnetic resonance imaging (MRI) and/or X-ray computed tomography (CT) of the brain. Transient ischemic attack was not included in stroke. On the basis of the available information, stroke was classified into ischemic stroke, hemorrhagic stroke, and unspecified. PAD was diagnosed when the patient had history of amputation of lower limb, percutaneous transluminal angioplasty, and/or bypass grafting due to ischemic limb. We did not include intermittent claudication, leg pain at rest, or foot ulceration in PAD if none of the above mentioned treatment was performed. In this cohort, CHF was defined by severe pulmonary edema requiring hospitalization, excluding pneumonia, but not excluding noncardiac circulatory failure. Valve disease was diagnosed when the patient had valve replacement. The same definitions were used for pre-existing CVD as of December 2004 and the new onset of CVD events during the follow-up.

Other Variables

We recorded age, sex, dialysis duration, clinical diagnosis of underlying renal disease (not necessarily biopsy proven), pre-existing CVD, and dialysis shift (dialysis sessions in AM or PM) as case-mix variables. As classic risk factors, we included current smoking status, hypertension, high-density lipoprotein cholesterol (HDL-C), and non-high-density lipoprotein cholesterol (non-HDL-C). Hypertension was defined as blood pressure of 140/90 mmHg or higher and/or use of any antihypertensive medication. Non-HDL-C was

calculated by subtracting HDL-C from total cholesterol. As indicators of protein-energy wasting (PEW) and inflammation, body mass index (BMI) after dialysis, serum albumin, and C-reactive protein (CRP) were recorded. Serum calcium, phosphate, intact parathyroid hormone (PTH), and use of vitamin D receptor activator (VDRA) were also recorded as parameters of CKD-mineral bone disorder (CKD-MBD). Regarding renal anemia, we included hematocrit, dose of erythropoiesis stimulating agent (ESA), and use of intravenous iron injections at baseline. In 2004, we used only recombinant human erythropoietin preparations (epoetins *α* and *β*) as ESA.

Follow-Up of the Cohort

The cohort was followed for 5 years until the end of 2009. At the end of each year, attending physicians filled an annual follow-up sheet to report new onsets of CVD events, if any, using the same definitions as indicated above. The annual follow-up sheet also included dates of death (cause of death), change in modality of renal replacement therapy, and moving away to other dialysis unit.

Statistical Methods

Data were summarized as number, percentage, or median (interquartile range) as appropriate. In cross-sectional analyses, comparisons in prevalence and median values between groups were performed by the chi-squared test and Mann-Whitney *U*-test or Kruskal-Wallis test, respectively. Correlations were examined by nonparametric Spearman's rank correlation. Here $P < 0.05$ was taken as statistically significant.

In longitudinal analyses, survival curves were constructed by the Kaplan-Meier method and evaluated by log-rank test. We calculated hazard ratios (HRs) and 95% confidence intervals (95% CI) by Cox proportional hazard models using time to the first CVD event, all-cause death, or the composite of the two. The cohort was divided by the quartile of the main exposure (CTR or NT-proBNP), and unadjusted HR was calculated with the quartile of the lowest hazard as referent (model 1). The main model was adjusted for the case-mix variables including age, sex, dialysis duration, diabetic nephropathy or not, pre-existing CVD, and dialysis shift (model 2). In addition to these six covariates, further adjustment was done for the classic coronary risk factors (model 3), the factors of PEW and inflammation (model 4), the factors of CKD-MBD (model 5), or the factors of renal anemia (model 6).

The linear trends in risks of quartile were evaluated by entering the medians for each categorical level of the exposure. We evaluated nonlinear effects of

continuous independent variables by using quadratic, square root, and log transformations. Since CRP showed nonlinear associations with CVD, we fit models using log transformation of CRP. Proportional hazards assumption was confirmed by using log minus log plot, time-dependent variables, or the Schoenfeld residuals in the main model (model 2), and all independent variables met the assumption. Regarding the association of CTR or NT-proBNP with the main outcome (CVD events), we tested the possible effect modification by the case-mix variables by the insertion of first-order interaction terms.

As additional analyses, we calculated hazard ratios for all-cause mortality and the composite of CVD events plus all-cause mortality as alternative endpoints.

These statistical calculations were performed using statistical software STATA 14 (StataCorp, Texas, USA) for Windows personal computers.

Results

Flow of the HD Patients

Among the 518 HD patients of the DREAM cohort, one patient was excluded due to missing data of CTR. The remaining 517 patients were the subjects of this study. The numbers of new CVD, all-cause death, and the composite of the two were 190, 107, and 235, respectively, during the 5-year follow-up.

Baseline Characteristics of the Participants

Table 1 shows baseline characteristics of the HD patients and the controls. Age and sex were not different between the two groups. Across the quartiles of CTR in the HD patients, there were significant differences in age, sex, pre-existing CVD, BMI, CRP, use of IV-iron, and NT-proBNP. The HD group had a higher median CTR than the control subjects.

Correlation between CTR and NT-ProBNP

CTR and NT-proBNP were positively correlated (Spearman's $r=0.44$, $P<0.001$) in the HD patients.

CTR and Risk of CVD Events

Kaplan-Meier curves show that the risk of CVD events was significantly different across by the quartiles of CTR, with the higher quartiles being at the higher risk (**Fig. 1**).

Table 2 shows the results with Cox models. Because the second quartile (Q2) of CTR showed the lowest incidence rate of CVD events, we determined Q2 as the referent. In an unadjusted model (model 1), the highest two quartiles (Q4 and Q3) showed significantly higher risks for CVD events than the referent.

This was true after adjustment for the case-mix variables (model 2) and further adjustment for the classic coronary risk factors such as hypertension, smoking and dyslipidemia (model 3), or the variables relating to PEW and inflammation (model 4), CKD-MBD (model 5), or renal anemia (model 6).

Since we found a significant effect modification by age on the association between CTR and CVD events, we performed a stratified analysis in the younger (<61 years old) and older (61 years or older) subgroups using the median age as the cutoff. In the model with case-mix covariates, the association of CTR was closer in the younger subgroup with a hazard ratio of 3.70 (1.63–8.42) as compared with a hazard ratio of 1.74 (1.06–2.88) in the older subgroup.

Although the Cox models were adjusted for the timing of CTR measurement (namely, AM or PM shift), we performed the following analyses: (1) We compared CTR between the groups treated in AM (0.488, 0.460–0.525) and PM shifts (0.487, 0.456–0.515), but there was no statistically significant difference. (2) We examined a possible effect modification by the timing of CTR evaluation (AM or PM shift) on the association between CTR and outcomes by inserting the interaction term (CTR×HD shift). However, we did not find such effect modification. (3) We performed stratified analysis by the timing of CTR evaluation (AM and PM shift), but the results only in the AM or PM shift patients were essentially the same as the results in the total subjects.

NT-ProBNP and Risk of CVD Events

Fig. 1 gives Kaplan-Meier curves showing that risk of CVD event was higher in the higher quartiles of NT-proBNP. Because the Q1 of NT-proBNP showed the lowest incidence rate of CVD, we determined Q1 as the referent in Cox models. In an unadjusted model (model 1), the highest two quartiles (Q4 and Q3) showed significantly higher risks for CVD than the referent. This was also true after adjustment for the case-mix variables (model 2). The higher risk in Q4 and Q3 remained significant even after additional adjustment for the variables relating to the classic coronary risk factors (model 3), PEW and inflammation (model 4), CKD-MBD (model 5), or renal anemia (model 6).

We found no significant effect modification by age on the association between NT-proBNP and CVD. However, we noticed a significant effect modification by history of prior CVD, with the HR of NT-proBNP being lower in the subgroup with prior CVD as compared with that in those without prior CVD. Even in the patients with prior CVD, the HR of the highest quartile of NT-proBNP (2.60, 95% CI 1.34–

Table 1. Baseline characteristics of the hemodialysis cohort by quartiles of CTR and the healthy controls

	CTR quartile			
	Q1	Q2	Q3	Q4
CTR	0.439 (0.426-0.451)	0.473 (0.466-0.481)	0.503 (0.496-0.512)	0.549 (0.535-0.569)
NT-proBNP (pg/mL)	3230 (1680-6520)	4440 (2210-10600)	6900 (3020-14500)	15750 (7160-33300)
Age (years)	56 (51-63)	60 (54-68)	62 (57-68)	64 (60-73)
Sex (%male)	67.7	70.8	62.0	50.8
Dialysis duration (month)	92 (35-189)	124 (53-184)	125 (68-228)	117 (51-180)
Diabetic nephropathy (%)	19.2	23.1	18.6	24.2
Pre-existing CVD (%)	19.2	33.1	36.4	45.3
HD shift (%AM)	49.2	54.6	47.3	58.6
Hypertension (%)	84.6	84.6	88.4	87.5
Smoker (%)	40.8	40.8	41.1	42.2
HDL-C (mg/dL)	43.1 (34.7-58.6)	44.0 (35.4-53.2)	44.4 (36.0-52.3)	45.4 (37.7-55.5)
Non-HDL-C (mg/dL)	108 (90-135)	119 (97-146)	111 (87-143)	115 (90-135)
BMI (kg/m^2)	21.1 (19.7-23.3)	22.2 (19.8-24.1)	21.5 (19.9-23.7)	21.4 (19.3-22.9)
Serum albumin (g/dL)	3.8 (3.6-3.9)	3.7 (3.5-3.9)	3.7 (3.5-3.9)	3.7 (3.5-3.9)
CRP (mg/dL)	0.07 (0.04-0.18)	0.16 (0.05-0.51)	0.16 (0.06-0.41)	0.17 (0.06-0.52)
Calcium (mg/dL)	9.1 (8.7-9.7)	9.2 (8.6-9.9)	9.1 (8.5-9.8)	9.2 (8.4-9.8)
Phosphate (mg/dL)	6.0 (5.2-6.7)	5.8 (5.0-6.7)	5.6 (5.0-6.5)	5.8 (4.7-6.6)
Intact PTH (pg/mL)	109 (34-212)	120 (46-214)	130 (45-231)	108 (40-205)
Use of VDRA (%)	46.2	49.2	40.3	41.4
Hematocrit (%)	30.8 (29-32.6)	30.7 (29.1-32.6)	30.7 (28.6-32.3)	30.5 (27.9-32)
ESA dose (units/wk)	9000 (6000-9000)	9000 (7500-9000)	9000 (7500-9000)	9000 (7500-9000)
Use of IV iron (%)	47.7	60.0	61.2	64.1

	Difference across quartile	Total HD cohort	Healthy control	Difference between HD and control
	P	(*N*=517)	(*N*=122)	*P*
CTR	<0.001	0.487 (0.457-0.52)	0.458 (0.432-0.497)	<0.001
NT-proBNP (pg/mL)	<0.001	6360 (2550-15200)	-	-
Age (years)	<0.001	61 (54-68)	62 (53-67)	0.4
Sex (%male)	0.005	62.9	59.0	0.4
Dialysis duration (month)	0.1	113 (47-191)	-	-
Diabetic nephropathy (%)	0.6	21.3	-	-
Pre-existing CVD (%)	<0.001	33.5	-	-
HD shift (%AM)	0.3	52.4	-	-
Hypertension (%)	0.7	86.3	13.9	<0.001
Smoker (%)	0.995	41.2	41.0	0.965
HDL-C (mg/dL)	0.6	44 (36-54)	60 (51-73)	<0.001
Non-HDL-C (mg/dL)	0.3	115 (91-138)	158 (133-183)	<0.001
BMI (kg/m^2)	0.04	21.6 (19.6-23.5)	22.7 (21.1-24.6)	<0.001
Serum albumin (g/dL)	0.4	3.7 (3.5-3.9)	-	-
CRP (mg/dL)	<0.001	0.14 (0.05-0.41)	0.05 (0.02-0.10)	<0.001
Calcium (mg/dL)	0.6	9.1 (8.6-9.8)	-	-
Phosphate (mg/dL)	0.2	5.8 (5.0-6.6)	-	-
Intact PTH (pg/mL)	0.8	118 (41-214)	-	-
Use of VDRA (%)	0.4	44.3	-	-
Hematocrit (%)	0.2	30.7 (28.6-32.4)	-	-
ESA dose (units/wk)	0.7	9000 (7500-9000)	-	-
Use of IV iron (%)	0.04	58.2	-	-

The table gives median (interquartile range) for continuous variables and percentages for categorical variables.
P values by Mann-Whitney *U*-test, Kruskal-Wallis test, or chi-squared test.
Abbreviations: CTR, cardiothoracic ratio; Q, quartile; CVD, cardiovascular disease; HDL, high-density lipoprotein; BMI, body mass index; CRP, C-reactive protein; PTH, parathyroid hormone; VDRA, vitamin D receptor activator; ESA, erythropoiesis stimulating agent; iv-iron, intravenous iron preparation; NT-proBNP, N-terminal fragment of probrain natriuretic peptide; HD, hemodialysis.
Conversion factors for units: HDL-C and Non-HDL-C in mg/dL to mmol/L, x 0.02586; phosphorus in mg/dL to mmol/L, x 0.3229.
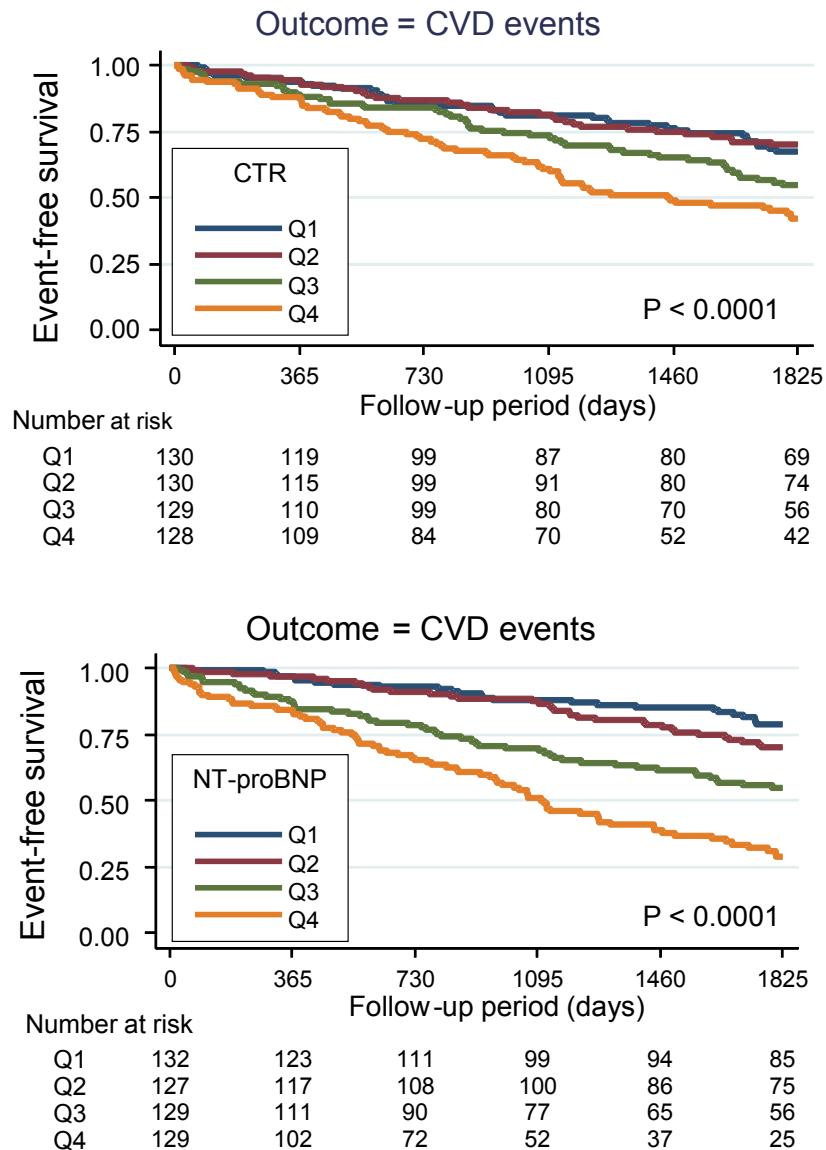
Fig. 1. Kaplan–Meier curves of CVD events by quartiles of CTR and NT-proBNP

The figure shows the CVD-event free survival by quartiles of CTR (upper panel) and by quartiles of NT-proBNP (lower panel). *P*-values by log-rank test.
Abbreviations: CTR, cardiothoracic ratio; CVD, cardiovascular disease; Q, quartile.

5.04) was not smaller than that of the highest quartile of CTR (2.31, 95% CI 1.32–4.06).

CTR, NT-ProBNP, and CVD Risk

To examine whether CTR and NT-proBNP independently predict CVD, we put both CTR and NT-proBNP simultaneously into the Cox model (**Fig. 2**). In such analysis, CTR was not a significant predictor of CVD independent of NT-proBNP, whereas NT-proBNP remained a significant predictor of CVD independent of CTR and the case-mix variables.

Additional Analyses with Other Endpoints

Additional analyses were performed using all-cause mortality and the composite of CVD events plus all-cause mortality as alternative endpoints using the main model (**Fig. 2**). CTR was not significantly associated with all-cause mortality, whereas Q4 of CTR showed a significantly higher risk for the composite endpoint as compared with the referent. In contrast, the risk of all-cause mortality was significantly higher in Q4 of NT-proBNP, and the risk of the composite endpoint was significantly higher in Q3 and Q4 of NT-proBNP. When CTR and NT-proBNP

Table 2. Risk of CVD by quartile of CTR

Models	Adjustment	Quartile of CTR				
		Q1	Q2	Q3	Q4	
Endpoint: CVD events						
	Number of Cases	37	34	52	67	
	Total person-years	488	485	445	395	
	Incidence rate per 100 person-years	7.6	7.0	11.7	17.0	
Hazard ratios						
						P for trend
1	Unadjusted	1.08	1	1.68*	2.44***	<0.001
		(0.68-1.72)	(Referent)	(1.09-2.58)	(1.62-3.69)	
2	Age, Sex, Diabetic Nephropathy, Dialysis duration,	1.53	1	1.64*	2.12**	0.01
	Pre-existing CVD, and HD shift	(0.95-2.46)	(Referent)	(1.06-2.54)	(1.38-3.25)	
3	Model 2	1.51	1	1.56*	2.03**	0.03
	+HTN, Smoking, HDL-C, Non-HDL-C	(0.94-2.43)	(Referent)	(1.01-2.42)	(1.32-3.12)	
4	Model 2	1.59	1	1.68*	2.08**	0.02
	+BMI, Serum albumin, Log CRP	(0.98-2.58)	(Referent)	(1.09-2.59)	(1.36-3.19)	
5	Model 2	1.53	1	1.70*	2.13**	0.01
	+Ca, P, intact PTH, Use of VDRA	(0.95-2.47)	(Referent)	(1.10-2.62)	(1.39-3.28)	
6	Model 2	1.59	1	1.67*	2.11**	0.02
	+Hematocrit, Dose of ESA, Use of iv-iron	(0.99-2.57)	(Referent)	(1.08-2.58)	(1.37-3.23)	

The table gives the number of cases, total person-years, incidence rate, and hazards ratios (95% confidence intervals) for each CTR quartiles for CVD events in 517 hemodialysis patients.
*$P<0.05$, **$P<0.01$, ***$P<0.001$.
Abbreviations: CTR, cardiothoracic ratio; Q, quartile; CVD, cardiovascular disease; HD, hemodialysis; HTN, hypertension; HDL, high-density lipoprotein; BMI, body mass index; CRP, C-reactive protein; Ca, calcium; P, phosphate; PTH, parathyroid hormone; VDRA, vitamin D receptor activator; ESA, erythropoiesis stimulating agent; iv-iron, intravenous iron preparation.

were simultaneously included in the model, NT-proBNP was significantly associated with CVD events, all-cause mortality, and the composite of the two independent of CTR, whereas CTR was no longer predictive of any of the three endpoints.

Discussion

Cardiac hypertrophy is an established risk factor of poor prognosis in HD patients[1, 16]. Although previous studies showed that serum biomarkers of cardiac hypertrophy, BNP[7, 17] and NT-proBNP[9, 18], are useful in predicting all-cause mortality and CVD events in dialysis populations, no study examined the relationship between CTR and risk for CVD events in patients with CKD. In this study, we confirmed the previous findings regarding NT-proBNP. We further revealed that CTR was a significant predictor for CVD events in HD patients. However, the predictive power of CTR was less impressive than that of NT-proBNP as judged by their HRs, particularly in the

older age subgroup. When CTR and NT-proBNP were included simultaneously, only NT-proBNP remained a significant predictor for CVD events, all-cause mortality, and the composite of the two. These results indicate that CTR is a significant predictor of CVD independent of the relevant clinical factors, and that it can be used in CVD risk stratification of hemodialysis patients when NT-proBNP is not available.

There are only a few studies reporting the association of CTR with risk of worse clinical endpoints in dialysis populations. Chen *et al.*[12] showed that CTR was predictive of death from all-cause and from CVD in 468 nondiabetic HD patients. The same group[13] reported that CTR was associated with all-cause mortality in 179 diabetic HD patients. Regarding peritoneal dialysis (PD) patients, Chen *et al.*[19] reported that a larger CTR was a significant predictor of higher mortality risk, whereas Gao *et al.* reported that mortality risk was not predicted by either baseline CTR[20] or a change in CTR during the preceding year[21]. Interestingly, Gao *et al.* found that CTR was a signifi-
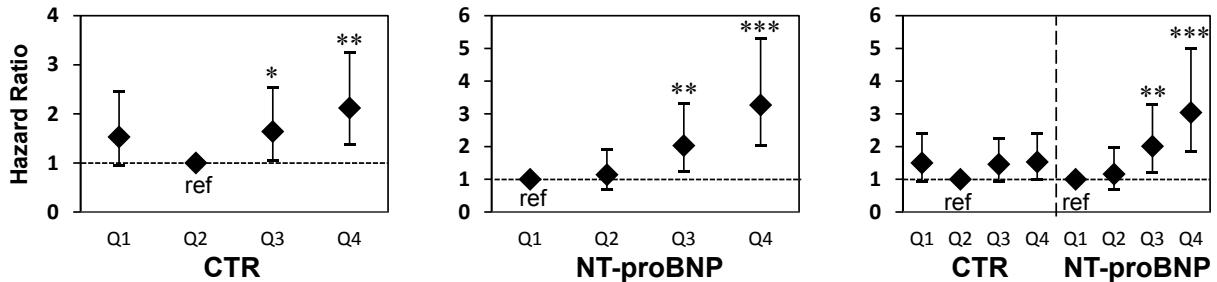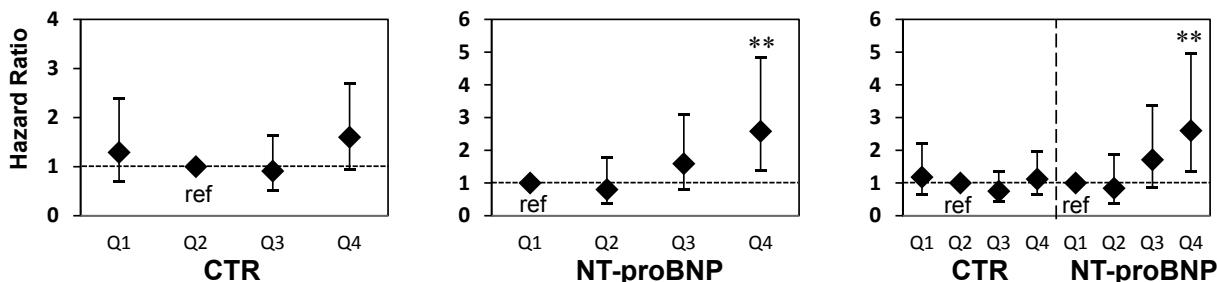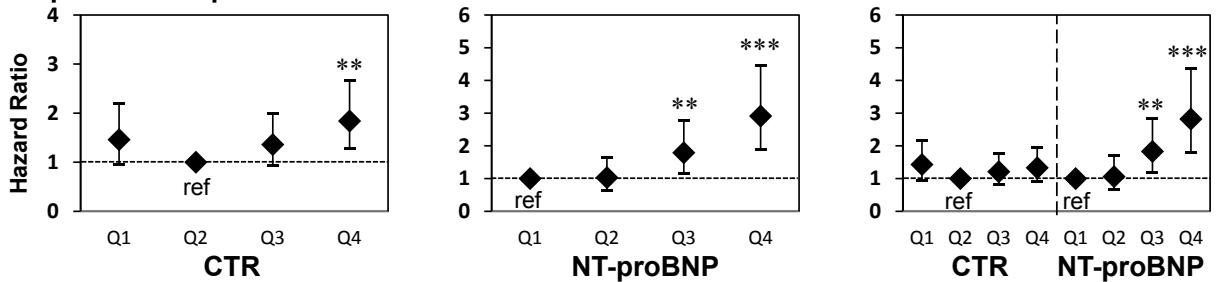
Fig. 2. Additional analyses with other endpoints

The figure shows the hazard ratios (diamonds) and 95% confidence intervals (vertical bars) for CTR and NT-proBNP in the association with three endpoints, namely, CVD events (top panels), all-cause mortality (middle panels), and composite of the two (bottom panels). Risks of these endpoints were predicted by CTR alone (left panels), by NT-proBNP alone (middle panels), and by both CTR and NT-proBNP (right panels), using Cox model adjusted for age, sex, dialysis duration, diabetic nephropathy, pre-existing CVD, and HD shift.

Abbreviations: CTR, cardiothoracic ratio; NT-proBNP, N-terminal fragment of probrain natriuretic peptide; CVD, cardiovascular disease; HD, hemodialysis; Q, quartile.

$*P<0.05$, $**P<0.01$, $***P<0.001$.

cant predictor of hospitalization due mainly to CVD in the PD cohort[21]. In the present study with a larger cohort size than the previous studies, we newly found that CTR was significantly associated with CVD events but not with all-cause mortality. Thus, the association between CTR and all-cause mortality in dialysis populations is not consistent between studies. We interpret these studies to indicate that the predictive value of CTR is more selective to CVD events than noncardiovascular outcomes in dialysis populations.

We have advanced the knowledge of predictive powers of CTR and NT-proBNP by comparing the two markers. First, NT-proBNP was an independent

predictor of both CVD events and all-cause mortality, while CTR was a significant predictor of CVD events but not of all-cause mortality. Second, in the prediction of CVD events, CTR was less powerful than NT-proBNP as shown by their hazard ratios. Third, the effect modification by age was significant for CTR but not for NT-proBNP in the association with CVD events, and CTR was less predictive of CVD in the older subgroup. Fourth, the association of NT-proBNP with CVD events was independent of CTR. In contrast, the association between CTR and CVD events was no longer significant in the models including NT-proBNP as an additional covariate. These

results indicate that CTR can be used in CVD risk stratification of hemodialysis patients when NT-proBNP is not available and that NT-proBNP provides more information when both CTR and NT-proBNP are available.

There are possible explanations for the better predictive power of NT-proBNP than that of CTR. First, NT-proBNP may be a more direct marker of cardiac hypertrophy[22] than CTR is. CTR is increased with cardiac hypertrophy, but CTR is influenced by other factors such as extracellular volume. According to a study by Zoccali *et al.*[7], although human atrial natriuretic peptide (hANP), a biomarker of extracellular volume[23], was a prognostic factor, BNP was more powerful predictor of CVD in HD patients. Also, they revealed that left ventricular mass index was more strongly correlated with BNP than hANP level. Thus, although serum NT-proBNP is affected by renal function, it can serve as a better predictor of CVD events than CTR within the HD patients.

Second, a low CTR may be an unfavorable sign in some conditions. For example, inappropriately low setting of "dry weight" could result in hypovolemia and a lower CTR, whereas it would induce HD-associated hypotension, an independent factor predicting higher mortality in HD patients[24]. In this study, we noticed a higher risk of CVD events, although not statistically significant, in the lowest quartile as compared to the second quartile of CTR. This may indicate the increased risk associated with hypovolemia.

Third, CTR could be influenced by noncardiac factors. Patients with chronic obstructive pulmonary disease would have larger lung volumes and relatively lower CTRs, whereas those with such disease are at an increased risk for CVD[25]. On the contrary, a larger CTR could be resulted from a smaller thoracic size. Elderly patients often have reduced bone mineral density and "bell-shaped" costal deformity, which could lead to a higher CTR on chest X-ray. This may explain the observation that the association of CTR with CVD event was modified by age. Pericardial fat may also affect CTR.

There are several limitations in this study. First, we do not have data of the left ventricular mass by echo cardiography or magnetic resonance, the gold standard for cardiac hypertrophy. Therefore, we cannot discuss the correlation of CTR or NT-proBNP with the gold standard measurement. Second, the results were based on single measurements of the exposure variables. Therefore, the results may overestimate or underestimate the true association. Third, the results of this observational study do not necessarily indicate causality. Therefore, this study does not provide the target range of CTR or NT-proBNP in clinical practice. Fourth, since this is a cohort study in a large dialysis center in an urban area in Japan, our results need confirmation in other settings.

Conclusion

We showed for the first time that a high CTR was an independent predictor of CVD events in HD patients indicating the usefulness of CTR in CVD risk stratification of this population. We additionally revealed that NT-proBNP gives more information than CTR when both CTR and NT-proBNP are available. Further studies are needed to confirm our results in other settings.

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