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Which Biomarker is the Best for Predicting Mortality in Incident Peritoneal Dialysis Patients: NT-ProBNP, Cardiac TnT, or hsCRP?

A Prospective Observational Study

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Abstract: Although numerous previous studies have explored various biomarkers for their ability to predict mortality in end-stage renal disease (ESRD) patients, these studies have been limited by retrospective analyses, mostly prevalent dialysis patients, and the measurement of only 1 or 2 biomarkers. This prospective study was aimed to evaluate the association between 3 biomarkers and mortality in incident 335 ESRD patients starting continuous ambulatory peritoneal dialysis (CAPD) in Korea. According to the baseline NT-proBNP, cTnT, and hsCRP levels, the patients were stratified into tertiles, and cardiovascular (CV) and all-cause mortalities were compared. Additionally, time-dependent ROC curves were constructed, and the net reclassification index (NRI) and integrated discrimination improvement (IDI) of the models with various biomarkers were calculated. We found the upper tertile of NT-proBNP was significantly associated with increased risk of both CV and all-cause mortalities. However, the upper tertile of hsCRP was significantly related only to the high risk of all-cause mortality even after adjustment for age, sex, and white blood cell counts. Moreover, NT-proBNP had the highest predictive power for CV mortality, whereas hsCRP was the best prognostic marker for all-cause mortality among these biomarkers. In conclusions, NT-proBNP is a more significant prognostic factor for CV mortality than cTnT and hsCRP, whereas hsCRP is a more significant predictor than NT-proBNP and cTnT for all-cause mortality in incident peritoneal dialysis patients.

(*Medicine* 94(44):e1636)

Abbreviations: CAD = coronary arterial disease, CAPD = continuous ambulatory peritoneal dialysis, cTnT = cardiac troponin T, CVD = cardiovascular disease, ECG = electrocardiogram, ESRD = end-stage renal disease, HD = hemodialysis, hsCRP = high-sensitivity C-reactive protein, LAD = left atrial dimension, LVEF = left ventricular ejection fraction, LVH = left ventricular hypertrophy, LVMI = left ventricular mass index, NT-proBNP = N-terminal pro B-type natriuretic peptide, PAD = peripheral arterial disease.

INTRODUCTION

Cardiovascular disease (CVD) is a prevalent disease, and is the most common cause of death in patients with end-stage renal disease (ESRD).[1–4] Even though traditional risk factors for CVD, such as advanced age, diabetes mellitus (DM), hypertension, volume overload, and dyslipidemia, are frequently accompanied by ESRD,[5,6] it is difficult to conclude that the high prevalence of CVD is entirely due to these traditional risk factors. Therefore, numerous studies have investigated alternative ways to stratify CVD risk in this population.[7] Recently, several biochemical markers, such as B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP), cardiac troponin T (cTnT), and high-sensitivity C-reactive protein (hsCRP) have been demonstrated to provide additional help in CVD risk stratification[7-10].

Plasma BNP and NT-proBNP concentrations are increased in patients with abnormal left ventricular (LV) structure and function,[11,12] whereas cTnT, a component of the contractile apparatus of the heart muscle, is increased in myocardial infarction patients.[7,13] Previous studies have shown that BNP, NT-proBNP, and cTnT are significant predictors of CV and all-cause mortalities not only in the general population, but also in patients with specific diseases, including ESRD.[7,9,10,14,15] Meanwhile, uremia-related nontraditional risk factors, such as inflammation, play a role in the pathogenesis and are associated with the clinical outcomes of CVD in ESRD patients on dialysis.[16,17] Supporting this notion, a number of prior studies have found that there is a significant correlation between the levels of hsCRP, a marker of inflammation, and mortality in these patients[6,10,18,19].

Editor: Costas Fourtounas.
Received: June 8, 2015; revised: August 25, 2015; accepted: August 26, 2015.
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This work was supported by the Brain Korea 21 Project for Medical Science, Yonsei University, by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (No. 2011–0030711), and by a grant of the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (A102065).
All authors have no conflict of interests to declare.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001636

As aforementioned, several biomarkers have been demonstrated to be significantly associated with CV and all-cause mortalities in ESRD patients, but the majority of the previous studies were retrospective, included small numbers of patients and mostly prevalent dialysis patients, and measured only 1 or 2 biomarkers.[8–10,15] In this study, therefore, we compared the prognostic power of NT-proBNP, cTnT, and hsCRP for CV and all-cause mortalities in the Korean incident ESRD patients who commenced with the continuous ambulatory peritoneal dialysis (CAPD). In addition, the association between these 3 biomarkers and echocardiographic parameters was assessed.

PATIENTS AND METHODS

Patients

All ESRD patients who started CAPD between August 1, 2009 and December 31, 2012 at the 36 centers of the Clinical Research Center for ESRD in Korea were initially recruited for this prospective observational multicenter study. This study was part of the nationwide multicenter joint network prospective cohort study on ESRD patients in Korea, designed to improve survival rates and quality of life, and to draw up effective treatment guidelines (clinicaltrial.gov NCT00931970). Among these patients, we excluded patients who were younger than 18 years, had a history of hemodialysis (HD) or kidney transplantation before CAPD, had an underlying active malignancy, or were expected to survive <3 months. Patients who died within 3 months of the initiation of CAPD or failed to maintain CAPD for >3 months were also excluded. Ultimately, a total of 335 incident CAPD patients were included in the final analysis.

The study protocol was approved by the Institutional Review Board of each participating center and all patients provided their written informed consent to participate in the study.

Data Collection

Patients' demographic and clinical data, such as age and sex, body mass index (BMI), comorbid conditions, and medications, were collected at the time of study enrollment. Cardiovascular disease was defined when the patients had a history of coronary, cerebrovascular, and/or peripheral vascular disease. We specified coronary artery disease (CAD) when the patients had a history of angina, myocardial infarction, coronary angioplasty, or coronary artery bypass grafts, cerebrovascular disease when they have experienced transient ischemic attack, stroke, or carotid endarterectomy, and peripheral arterial disease (PAD) when there was a history of claudication, any peripheral revascularization procedure, or ischemic limb loss and/or ulceration. The following laboratory data were measured from fasting blood samples, which were drawn at 2 hours after the first peritoneal dialysis (PD) exchange with 1.5% dextrose dialysate, at the time of study enrollment and every 3 months thereafter: hemoglobin (Hb), white blood cell (WBC) count, calcium, phosphorus, intact parathyroid hormone (iPTH), albumin, total cholesterol, triglyceride, sodium, potassium, bicarbonate, NT-proBNP, cTnT, and hsCRP. The preceding overnight dwell was regulated to 1.5% dextrose dialysate to make the glucose load same. Body weight was checked in the morning, on the same day as when the first dialysate was drained out.

The Elecsys proBNP electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN) and a third-generation electrochemiluminescence immunoassay (Elecsys Troponin T STAT Immunoassay, Roche Diagnostics) were used to determine NT-proBNP and cTnT concentrations, respectively. Moreover, a latex-enhanced immunonephelometric method using a BNII analyzer (Dade Behring, Newark, DE) was applied for the measurement of hsCRP levels. The modified peritoneal equilibration test was performed with 4.25% glucose dialysis solution as described previously.[20] Furthermore, peritoneal transport characteristics were classified as high, high average, low average, and low based on the results of dialysate-to-plasma creatinine (D/P Cr) and glucose (D/D0 glucose) concentration ratios at 4 hours of dwell.

Electrocardiogram and Echocardiography

LV hypertrophy (LVH) was determined by the results of baseline electrocardiogram (ECG) and echocardiography. By ECG, LV hypertrophy was defined if the products of the Cornell voltage combination (with 6 mm added in women) multiplied by QRS duration was $\geq$2440 mm/msec.[21] Echocardiography was performed with an empty abdomen close to the time of discharge, when the patients were considered to be clinically stable and in a euvolemic state. Two-dimensional echocardiography was performed with patients lying in the left decubitus position, based on the imaging protocol recommended by the American Society of Echocardiography.[22] The LV ejection fraction (LVEF), which was assessed with a modified biplane Simpson method from the apical 2-chamber and 4-chamber views, was regarded as an index of LV systolic function. In addition, the method of Devereux[23] was used to determine LV mass, and LV mass index (LVMI) was calculated by dividing the LV mass by the body surface area (g/m^2). According to the leading-edge-to-leading-edge convention, left atrial dimension (LAD) was measured at the aortic valve level at the ventricular end-systolic point. We also evaluated multiple reproducibility, intrareader reliability, inter-reader reliability, and reader drift analyses at Kyungpook National University (Daegu, Korea), a core echocardiography laboratory using a random sample of 3% of the entire cohort every year. The intra-class correlation coefficients for the echocardiographic measures were revealed to be 0.822, 0.801, and 0.796 for LVEF, LVMI, and LAD, respectively. Systolic and diastolic blood pressures (BPs) were measured at the time of echocardiography after resting for 15 min.

Assessment of Residual Renal Function and Dialysis Indices

Residual renal function (RRF) and dialysis adequacy were measured at 1 month after PD initiation. RRF was calculated as an average of the 24-hour urine urea and creatinine clearances.[24] To assess the dialysis adequacy, weekly Kt/V urea was calculated as the ratio of the 24-hour urinary and drained dialysate urea clearance to total body water, which was derived using the Watson formula.[25–27] Peritoneal transport characteristics were determined using the equilibration ratios between dialysate and plasma creatinine.

Outcome Measures

All patients were followed up prospectively after all the baseline assessments. All mortality events were retrieved from the database and carefully reviewed. CV mortality was defined as death from myocardial infarction or ischemia, congestive heart failure, pulmonary edema, and cerebrovascular disorder, or peripheral vascular disease. The primary and secondary endpoints were CV and all-cause mortalities, respectively. Loss to follow-up, renal transplantation, transfer to HD, and recovery of renal function after the first 3 months of PD

TABLE 1. Baseline Clinical Characteristics and Biomarkers of the Study Population

Variables	Total (N = 335)	NT-proBNP, pg/mL[†]			cTnT, ng/mL[§]			hsCRP, mg/dL[¶]		
		Lower (N = 111)	Middle (N = 111)	Upper (N = 113)	Lower (N = 114)	Middle (N = 108)	Upper (N = 113)	Lower (N = 113)	Middle (N = 109)	Upper (N = 113)
Age, y	53.5 ± 13.1	52.9 ± 13.4	57.3 ± 13.2	55.2 ± 13.0	52.3 ± 14.3	57.8 ± 13.5	54.6 ± 12.3	51.7 ± 12.6	53.4 ± 12.7	56.3 ± 14.1*
Male, n (%)	204 (60.9)	75 (67.6)	60 (54.1)	69 (61.1)	62 (54.4)	63 (58.3)	79 (69.9)	65 (57.5)	68 (62.4)	71 (62.8)
BMI (kg/m^2)	22.8 ± 3.4	22.7 ± 3.0	22.5 ± 3.5	22.9 ± 3.9	22.6 ± 3.3	22.9 ± 3.7	22.7 ± 3.9	22.1 ± 3.3	23.1 ± 3.2	23.2 ± 3.4
Comorbid diseases, n (%)										
DM	140 (41.8)	32 (28.8)	49 (44.1)	59 (52.2)*	22 (19.3)	43 (39.8)	73† (64.6)	42 (37.2)	53 (48.6)	45 (39.8)
Hypertension	161 (48.1)	56 (50.5)	51 (45.9)	54 (47.8)	58 (50.9)	48 (44.4)	55 (48.7)	55 (48.7)	52 (47.7)	54 (47.8)
Coronary arterial disease	38 (11.3)	10 (9.0)	16 (14.4)	12 (10.6)	11 (9.9)	10 (9.0)	17 (15.0)	12 (10.6)	13 (11.9)	13 (11.5)
Peripheral arterial disease	25 (7.5)	4 (3.6)	7 (6.3)	14 (12.4)	4 (3.6)	8 (7.2)	13 (11.5)	5 (4.4)	8 (7.3)	12 (10.6)
Charlson Comorbidity Index	4.9 ± 2.4	4.5 ± 2.4	5.4 ± 2.4	5.9 ± 2.3	4.5 ± 2.2	5.6 ± 2.6	6.1 ± 2.3	4.7 ± 2.3	5.1 ± 2.4	5.3 ± 2.4
Mean arterial pressure, mmHg	98.3 ± 15.6	95.7 ± 12.7	99.3 ± 14.7	100.5 ± 16.2	99.1 ± 14.9	95.9 ± 14.6	100.7 ± 13.1	100.5 ± 18.2	96.6 ± 15.8	97.5 ± 12.7
Dialysis parameters										
Total weekly Kt/V	2.0 ± 0.2	1.9 ± 0.3	2.0 ± 0.4	1.9 ± 0.4	1.8 ± 0.3	1.8 ± 0.4	1.9 ± 0.3	2.0 ± 0.2	2.0 ± 0.3	1.9 ± 0.3
Total weekly CCr (L/wk/1.73 m^2)	57.1 ± 21.0	59.2 ± 22.1	57.3 ± 19.8	55.7 ± 20.6	63.3 ± 25.4	60.8 ± 23.1	59.9 ± 21.8	59.4 ± 19.4	55.4 ± 20.5	56.5 ± 19.9
PD Kt/V	1.5 ± 0.4	1.6 ± 0.4	1.6 ± 0.5	1.5 ± 0.5	1.7 ± 0.4	1.5 ± 0.4	1.5 ± 0.5	1.6 ± 0.5	1.5 ± 0.4	1.5 ± 0.5
Dialysate to plasma creatinine ratio	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.2	0.6 ± 0.2	0.7 ± 0.2	0.6 ± 0.3	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.2	0.7 ± 0.2
Icodextrin use daily	99 (29.6)	39 (35.1)	27 (23.9)	33 (29.7)	36 (31.6)	33 (30.6)	30 (26.5)	33 (29.2)	31 (28.4)	35 (31.0)
2.5% and/or 4.25% dialysate use daily	79 (23.6)	27 (23.9)	27 (23.9)	25 (22.1)	28 (24.6)	24 (22.2)	27 (23.9)	28 (24.8)	26 (23.9)	25 (22.1)
Dwell time, h/d	19.1	19.0	18.7	19.2	18.9	18.8	20.1	19.2	19.0	19.7
Residual GFR (mL/min/1.73 m^2)	1.1 ± 0.5	1.4 ± 0.5	1.2 ± 0.3	0.9 ± 0.3*	1.3 ± 0.4	1.2 ± 0.4	1.2 ± 0.5	1.1 ± 0.5	1.1 ± 0.4	0.9 ± 0.4
Daily net PD ultrafiltration volume, L	1.1 ± 0.8	1.1 ± 0.7	1.0 ± 0.8	1.0 ± 0.7	1.0 ± 0.9	1.1 ± 0.9	0.9 ± 0.7	1.1 ± 0.8	1.1 ± 0.7	1.0 ± 0.8
Used dialysate volume, L/d	7.7 ± 1.4	7.8 ± 1.5	7.7 ± 1.3	7.6 ± 1.4*	7.7 ± 1.1	7.6 ± 1.0	7.7 ± 1.5	7.5 ± 1.8	7.7 ± 1.7	7.7 ± 1.3
Daily urine volume, L	0.5 ± 0.5	0.7 ± 0.4	0.5 ± 0.5	0.5 ± 0.6*	0.6 ± 0.6	0.5 ± 0.6	0.5 ± 0.5	0.5 ± 0.6	0.6 ± 0.6	0.5 ± 0.5
Total daily net PD + urine ultrafiltration volume, L	1.5 ± 1.1	1.8 ± 1.0	1.5 ± 1.2	1.5 ± 1.2	1.5 ± 1.4	1.6 ± 1.3	1.4 ± 1.2	1.5 ± 1.2	1.6 ± 1.2	1.5 ± 1.3
PD duration, mo	21.5 ± 8.5	22.0 ± 8.7	22.0 ± 8.7	21.9 ± 8.6	20.4 ± 6.9	21.3 ± 8.1	22.2 ± 9.4	22.2 ± 7.3	21.8 ± 8.5	21.9 ± 8.1
Groups of peritoneal equilibration test, n (%)										
High	49 (14.6)	16 (14.4)	16 (14.4)	17 (15.0)	17 (14.9)	15 (13.9)	17 (15.0)	17 (15.0)	15 (13.8)	17 (15.0)
High average	182 (54.3)	60 (54.1)	59 (53.2)	63 (55.8)	61 (53.5)	59 (54.6)	62 (54.9)	62 (54.9)	59 (54.1)	61 (54.0)
Low average	99 (29.6)	34 (30.6)	32 (28.8)	33 (29.2)	35 (30.7)	32 (29.6)	32 (28.3)	33 (29.2)	32 (29.3)	34 (30.1)
Low	5 (1.5)	1 (0.9)	4 (3.6)	—	1 (0.9)	2 (1.9)	2 (1.8)	1 (0.9)	3 (2.8)	1 (0.9)
Biochemical parameters										
WBC, cells/mm^3	7005.4 ± 2579.8	7085.9 ± 3418.6	6830.7 ± 2269.6	7957.1 ± 3150.4*	6984.0 ± 3581.2	6383.7 ± 2117.7	7622.4 ± 2861.9	6577.3 ± 1874.4	6823.7 ± 2052.3	7685.6 ± 3608.3*
Hb, g/dL	9.4 ± 1.6	9.5 ± 1.4	9.2 ± 1.8	8.7 ± 1.4*	9.1 ± 1.4	8.7 ± 1.4	9.0 ± 1.3	9.7 ± 1.5	9.5 ± 1.7	8.8 ± 1.4†
Uric acid, mg/dL	8.1 ± 2.4	8.6 ± 2.1	7.6 ± 2.3	8.3 ± 2.9	8.5 ± 2.5	8.1 ± 2.4	8.1 ± 2.9	8.0 ± 2.1	7.8 ± 2.4	8.5 ± 2.6
Sodium, mEq/L	137.2 ± 5.2	138.1 ± 4.3	137.0 ± 4.4	137.5 ± 4.9	137.2 ± 5.2	137.1 ± 5.0	136.6 ± 4.9	137.7 ± 5.1	136.8 ± 5.2	137.2 ± 5.2
Potassium, mEq/L	4.7 ± 2.1	4.5 ± 1.0	5.46 ± 4.6	4.7 ± 0.9	5.2 ± 0.7	4.5 ± 1.0	4.5 ± 0.7	4.7 ± 0.9	4.6 ± 1.0	4.9 ± 1.5
Bicarbonate, mEq/L	19.3 ± 5.7	19.1 ± 5.7	18.7 ± 6.3	19.2 ± 5.4*	18.9 ± 6.4	18.2 ± 6.2	20.2 ± 5.0	19.6 ± 4.8	19.2 ± 5.9	19.0 ± 6.5
Ca, mg/dL	8.1 ± 1.2	8.6 ± 1.2	7.8 ± 1.2	8.0 ± 1.1*	8.1 ± 1.3	8.3 ± 1.1	8.0 ± 1.5	8.0 ± 1.3	7.9 ± 1.4	8.3 ± 1.0
P, mg/dL	5.0 ± 1.9	4.6 ± 1.7	5.1 ± 2.0	4.7 ± 1.8*	4.8 ± 1.7	4.9 ± 2.1	4.9 ± 2.0	5.0 ± 2.0	4.9 ± 1.4	5.1 ± 2.3
iPTH, pg/mL	246.8 ± 182.8	293.5 ± 234.1	201.8 ± 122.8	281.5 ± 196.4*	280.6 ± 218.5	230.3 ± 143.8	214.6 ± 151.2	231.1 ± 184.9	253.4 ± 184.0	227.3 ± 164.9
Albumin, g/dL	3.4 ± 0.6	3.6 ± 0.6	3.3 ± 0.6	3.2 ± 0.7*	3.6 ± 0.6	3.4 ± 0.5	2.9 ± 0.6†	3.6 ± 0.6	3.4 ± 0.7	3.3 ± 0.6*
Total cholesterol, mg/dL	161.2 ± 48.2	152.8 ± 50.1	158.8 ± 57.9	160.8 ± 40.2	165.1 ± 51.9	154.6 ± 38.7	153.0 ± 48.8	171.3 ± 49.8	161.7 ± 50.8	155.2 ± 46.3
Triglyceride, mg/dL	136.4 ± 80.7	131.6 ± 67.9	133.4 ± 76.5	130.6 ± 71.6	128.5 ± 61.5	131.0 ± 97.5	125.0 ± 69.1	133.3 ± 67.0	135.2 ± 61.2	128.1 ± 94.4
LVH on ECG, n (%)	87 (26.0)	24 (21.6)	28 (25.2)	35 (31.0)*	26 (22.8)	28 (25.9)	33 (29.2)*	32 (28.3)	22 (20.2)	33 (29.2)
Echocardiographic biomarkers										
LVEF (%)	57.5 ± 11.4	63.4 ± 8.4	58.0 ± 8.7	48.3 ± 12.4†*	61.5 ± 10.4	58.2 ± 10.8	56.8 ± 12.2†*	60.0 ± 9.3	55.2 ± 11.6	56.9 ± 12.9
LVMI, g/m^2	185.8 ± 72.6	169.6 ± 67.6	193.4 ± 81.3	208.4 ± 72.6*	181.5 ± 67.3	176.1 ± 59.1	224.5 ± 80.4*	174.0 ± 70.5	194.2 ± 74.4	187.1 ± 68.1
LAD, cm	4.0 ± 0.7	3.7 ± 0.7	3.9 ± 0.6	4.4 ± 0.7†	3.8 ± 0.6	4.2 ± 0.8	4.3 ± 0.7*	3.9 ± 0.6	4.1 ± 0.7	4.1 ± 0.7

Variables	Total (N = 335)	NT-proBNP, pg/mL[‡]			cTnT, ng/mL[§]			hsCRP, mg/dL[¶]		
		Lower (N = 111)	Middle (N = 111)	Upper (N = 113)	Lower (N = 114)	Middle (N = 108)	Upper (N = 113)	Lower (N = 113)	Middle (N = 109)	Upper (N = 113)
Medications										
No. of antihypertensive drugs (n)	2.4 ± 1.2	2.5 ± 1.2	2.3 ± 1.2	2.5 ± 1.0	2.2 ± 1.2	2.4 ± 1.2	2.4 ± 1.1	2.6 ± 1.2	2.3 ± 1.2	2.3 ± 1.2
Diuretics use, n (%)	196 (58.5)	68 (61.3)	56 (50.5)	72 (63.7)	71 (62.3)	71 (65.7)	54 (47.8)	71 (62.8)	61 (56.0)	64 (56.6)
Erythropoietin drugs use, n (%)	220 (65.7)	68 (61.3)	76 (68.5)	76 (67.3)	74 (64.9)	79 (73.1)	67 (59.3)	70 (61.9)	73 (67.0)	77 (68.1)
Phosphate binders use, n (%)	168 (50.1)	56 (50.4)	61 (55.0)	51 (45.1)	59 (51.8)	59 (54.6)	50 (44.2)	59 (52.2)	56 (51.4)	53 (46.9)
Vitamin D supplements or analogues, n (%)	143 (42.7)	49 (44.1)	51 (45.9)	43 (38.1)	50 (43.9)	49 (45.4)	44 (38.9)	50 (44.2)	46 (42.2)	47 (41.6)

Data are presented as n (%) or mean ± SD. BMI = body mass index, Ca = calcium, cTnT = cardiac troponin T, DM = diabetes mellitus, Hb = hemoglobin, hsCRP = high-sensitivity C-reactive protein, iPTH = intact parathyroid hormone, LAD = left atrial dimension, LVEF = left ventricular ejection fraction, LVH on ECG = left ventricular hypertrophy on electrocardiogram, LVMI = left ventricular mass index, No = number, NT-proBNP = N-terminal proB-type natriuretic peptide, P = phosphorus, PD = peritoneal dialysis, WBC = white blood cell counts.

* Comparison among the 3 tertiles and the $P < 0.05$.

† Comparison among the 3 tertiles and the $P < 0.01$.

‡ The tertile of NT-proBNP was 1255.8 and 8720.5 pg/mL.

§ The tertile of cTnT was 0.027 and 0.06 ng/mL.

¶ The tertile of hsCRP was 0.07 and 0.65 mg/dL.

commencement were censored at the end of the PD treatment. When a patient died within 3 months after being transferred to HD, the death was regarded as a mortality event.

Statistical Analysis

Statistical analyses were performed using the SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL) and SAS 9.2 version (SAS Institute Inc, Cary, NC). Continuous variables were expressed as mean ± standard deviation and categorical variables as a number (percentage). According to the baseline NT-proBNP, cTnT, and hsCRP levels, the patients were stratified into tertiles (lower, middle, and upper groups), and the baseline characteristics were compared among the 3 groups using ANOVA for continuous variables and the χ^2 test for categorical variables. The relationships among NT-proBNP, cTnT, hsCRP, WBC, LVEF, LVMI, and LAD were determined by the Pearson correlation analysis. Cumulative survival curves were created by the Kaplan-Meier method, and between-group survival was compared by a log-rank test. To assess the additional effect of each biomarker on the null model, moreover, multivariate regression analyses with a null model (including age and sex, and WBC count) and each biomarker were performed. For the null model, we applied the backward method (specifies the significance level for entering effects and removing effects = 0.05) to the candidate list of traditional risk factors; age and sex, BMI, DM, hypertension, Charlson Comorbidity Index, mean arterial pressure (MAP), 24-hour urine output, Hb, WBC count, and serum albumin and total cholesterol levels, and found that the WBC count was only a significant risk factor for CV and/or all-cause mortality. Therefore, age and sex, and the WBC count were chosen for the variables of the null model. Furthermore, a time-dependent receiver-operating characteristic (ROC) curve was created to determine which biomarkers added up the higher predictive value.[28–30] We compared the global concordance probability (integrated area under the curve [iAUC]) between the null model and each biomarker by using the R Statistical package ver. 3.0.1 (www.R-project.org). The net reclassification index (NRI) and the integrated discrimination improvement (IDI) were also estimated to assess the power of the models with biomarkers to correctly reclassify patients compared with the model without biomarkers (model including the null model and each biomarker). Since the definition of risk strata for NRI was needed, 3 risk strata was defined for CV and all-cause mortalities based on 3 point: <33.3%, 33.3% to 66.6%, and >66.6%. In the NRI, only the changes in predicted probabilities, which indicate a change from one to another category, were considered. Therefore, the NRI could explain the global net improvement in reclassification with the new model. For the IDI, in contrast, we considered the change in the predicted probabilities as a continuous variable because the IDI did not need a prior definition of risk strata.[31] P values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics

Baseline patient characteristics are shown in Table 1. When baseline patient characteristics were compared among the 3 groups based on the tertile values of NT-proBNP (1255.8 and 8720.5 pg/mL), cTnT (0.027 and 0.06 ng/mL), and hsCRP (0.07 and 0.65 mg/dL), the mean values of LVMI and LAD, and the proportions of patients with DM and LVH on ECG, increased significantly across the three tertiles of NT-proBNP

TABLE 2. Comparisons of Clinical Outcomes Between Each Group Stratified Based on the Tertile Value of Cardiac Biomarkers

		NT-proBNP, pg/mL[‡]			cTnT, ng/mL[§]			hsCRP, mg/dL[¶]		
Variables	**Total (N = 335)**	**Lower (N = 111)**	**Middle (N = 111)**	**Upper (N = 113)**	**Lower (N = 114)**	**Middle (N = 108)**	**Upper (N = 113)**	**Lower (N = 113)**	**Middle (N = 109)**	**Upper (N = 113)**
Follow-up duration, mo	21.5 ± 8.5	22.0 ± 8.7	22.0 ± 8.7	21.9 ± 8.6	20.4 ± 6.9	21.3 ± 8.1	22.2 ± 9.4	22.2 ± 7.3	21.8 ± 8.5	21.9 ± 8.1
All-cause mortality, n (%)	39 (11.6%)	4 (3.6%)	6 (5.4%)	29 (25.7%)[†]	3 (2.6%)	16 (14.8%)	20 (17.7%)	3 (2.7%)	9 (8.3%)	27 (23.9%)[*]
Cardiovascular mortality, n (%)	22 (6.6%)	2 (1.8%)	4 (3.6%)	16 (14.2%)[*]	3 (2.6%)	7 (6.5%)	12 (10.6%)[*]	3 (2.7%)	7 (6.4%)	12 (10.6%)

Data are presented as n (%) or mean ± SD. cTnT = cardiac troponin T, hsCRP = high-sensitivity C-reactive protein, NT-proBNP = N-terminal proB-type natriuretic peptide.
[*] Comparison among the 3 tertiles and the $P < 0.05$.
[†] Comparison among the 3 tertiles and the $P < 0.01$.
[‡] The tertile of NT-proBNP was 1255.8 and 8720.5 pg/mL.
[§] The tertile of cTnT was 0.027 and 0.06 ng/mL.
[¶] The tertile of hsCRP was 0.07 and 0.65 mg/dL.

and cTnT. In contrast, serum albumin concentrations and LVEF decreased significantly across the 3 tertiles of NT-proBNP and cTnT. In the hsCRP group, however, significant increases in age and WBC counts and significant decreases in Hb and serum albumin levels were observed across the 3 tertiles of hsCRP. However, there were no significant differences in Charlson Comorbidity Index, MAP, iPTH concentrations, PD-related variables, and the proportion of patients treated with vitamin D supplements or analogues among the tertiles of NT-proBNP, cTnT, and hsCRP (Table 1).

Next, we compared CV and all-cause mortalities among each tertile group. There were significant increases in CV and all-cause mortalities across the 3 tertiles of NT-proBNP (CV mortality: 14.2% vs 3.6% vs 1.8%, $P < 0.05$; all-cause mortality: 25.7% vs 5.4% vs 3.6%, $P < 0.01$). On the contrary, only CV mortality and only all-cause mortality were significantly different among the tertile groups of cTnT (10.6%, 6.5%, and 2.6%, $P < 0.05$) and hsCRP (23.9%, 8.3%, and 2.7%, $P < 0.05$) (Table 2), respectively.

Correlations Among Biomarkers and Other Parameters

Baseline NT-proBNP concentrations had positive correlations with cTnT levels ($r = 0.236$, $P = 0.004$), WBC counts ($r = 0.156$, $P = 0.047$), LVMI ($r = 0.233$, $P = 0.004$), and LAD ($r = 0.304$, $P < 0.001$). An inverse relationship was demonstrated between NT-proBNP levels and LVEF ($r = -0.502$, $P < 0.001$). In addition, there were positive associations of cTnT values with hsCRP concentrations ($r = 0.234$, $P = 0.002$), WBC counts ($r = 0.127$, $P = 0.029$), LVMI ($r = 0.158$, $P = 0.044$), and LAD ($r = 0.194$, $P = 0.015$). A negative correlation was observed between cTnT concentrations and LVEF ($r = -0.335$, $P < 0.001$). There was also a positive association of baseline hsCRP levels with WBC counts ($r = 0.201$, $P = 0.013$) (Table 3). Additionally, we performed Pearson correlation analysis including NT-proBNP, MAP, and daily urine volume and PD ultrafiltration volume. NT-proBNP levels were not significantly associated with MAP and daily PD ultrafiltration volume. However, there was a significantly negative association between NT-proBNP concentrations and daily urinary volume ($r = -0.137$, $P = 0.002$) in spite of comparable amount of daily urinary and PD ultrafiltration volumes among the tertile of NT-proBNP. Furthermore, serum albumin levels were significantly and inversely correlated with all these biomarkers ($r = -0.172$, $P = 0.031$ for NT-proBNP; $r = -0.190$, $P = 0.027$ for cTnT; and $r = -0.079$, $P = 0.042$ for hsCRP), whereas there were no significant associations of the amount of urinary protein excretion with all these biomarkers ($r = 0.132$, $P = 0.211$ for NT-proBNP; $r = 0.090$, $P = 0.177$ for cTnT; $r = 0.079$, $P = 0.453$ for hsCRP). Meanwhile, there were no significant differences in NT-proBNP, CRP levels, and iPTH concentrations between patients with and without vitamin D supplements or analogues treatment.

TABLE 3. Pearson Correlations Among Biomarkers and Other Parameters

	NT-proBNP, pg/mL	**cTnT, ng/mL**	**hsCRP, mg/dL**	**WBC, cells/mm^3**	**LVEF (%)**	**LVMI (g/m^2)**	**LAD, cm**
NT-proBNP, pg/mL	1	0.236, $P = 0.004$	0.114, $P = 0.079$	0.156, $P = 0.047$	−0.502, $P < 0.001$	0.233, $P = 0.004$	0.304, $P < 0.001$
cTnT, ng/mL		1	0.234, $P = 0.002$	0.127, $P = 0.029$	−0.335, $P < 0.001$	0.158, $P = 0.044$	0.194, $P = 0.015$
hsCRP, mg/dL			1	0.201, $P = 0.013$	0.062, $P = 0.187$	−0.067, $P = 0.174$	0.100, $P = 0.080$
WBC, cells/mm^3				1	−0.074, $P = 0.276$	0.113, $P = 0.104$	0.140, $P = 0.043$
LVEF (%)					1	−0.210, $P = 0.001$	−0.332, $P < 0.001$
LVMI, g/m^2						1	0.163, $P = 0.011$
LAD, cm							1

cTnT = cardiac troponin T, hsCRP = high-sensitivity C-reactive protein, LAD = left atrial dimension, LVEF = left ventricular ejection fraction, LVMI = left ventricular mass index, NT-proBNP = N-terminal proB-type natriuretic peptide, WBC = white blood cell counts.

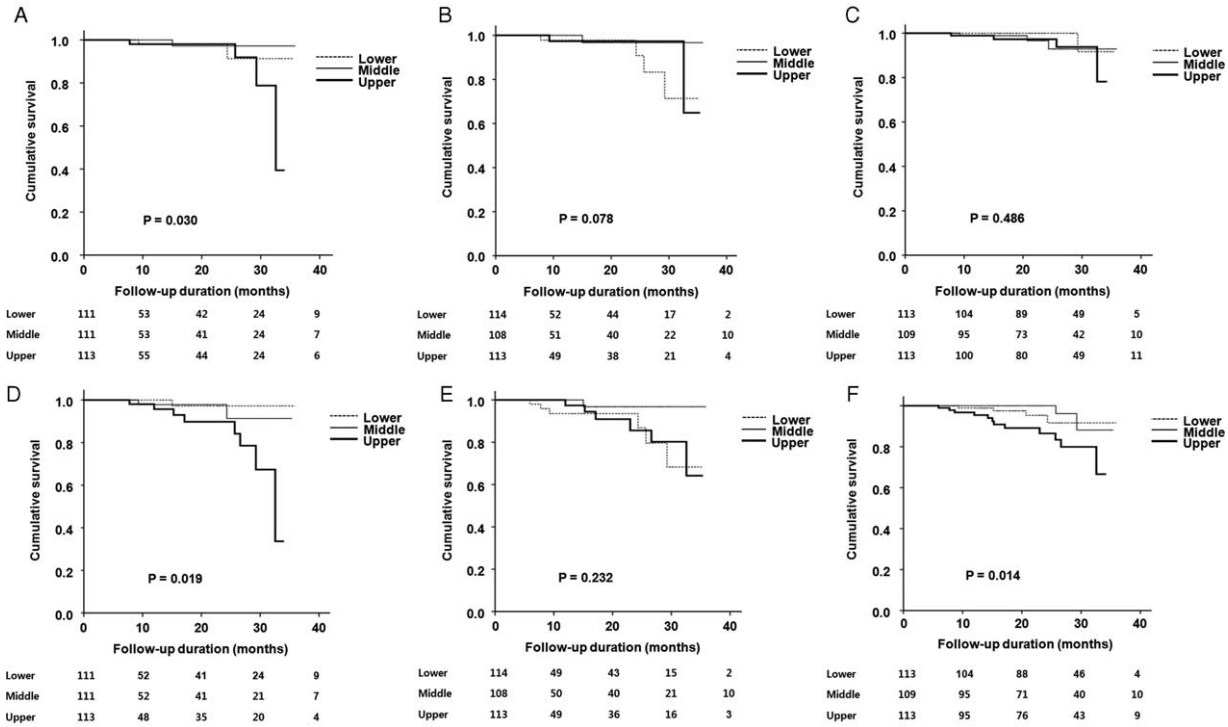

FIGURE 1. Kaplan-Meier survival curves for cardiovascular and all-cause mortality based on the median baseline values of NT-proBNP (A/D), cTnT (B/E), and hsCRP (C/F). The CV survival rates were significantly lower in the ''high'' NT-proBNP and cTnT groups compared with the corresponding ''low'' groups, whereas there was no significant difference in CV survival rates between the ''high'' and ''low'' hsCRP groups (A, B, and C). However, the all-cause mortality rates were significantly higher in all 3 ''high'' groups (D, E, and F). cTnT = cardiac troponin T, CV = cardiovascular, hsCRP = high-sensitivity C-reactive protein, NT-proBNP = N-terminal proB-type natriuretic peptide.

Clinical Outcomes Based on Biomarker Concentrations

During a mean follow-up duration of 21.5 ± 8.5 months, 39 patients (11.6%) died. Among them, 22 patients (56.4%) died from CV causes, and 11 patients (28.2%) due to infection. Furthermore, 26 patients (7.8%) were transferred to HD, and 21 patients (6.3%) received a kidney transplant. As shown in Figure 1, CV mortality rates were significantly higher in the ''upper'' tertile of NT-proBNP compared with the ''middle'' and ''lower'' tertiles of NT-proBNP ($P = 0.030$), but there were

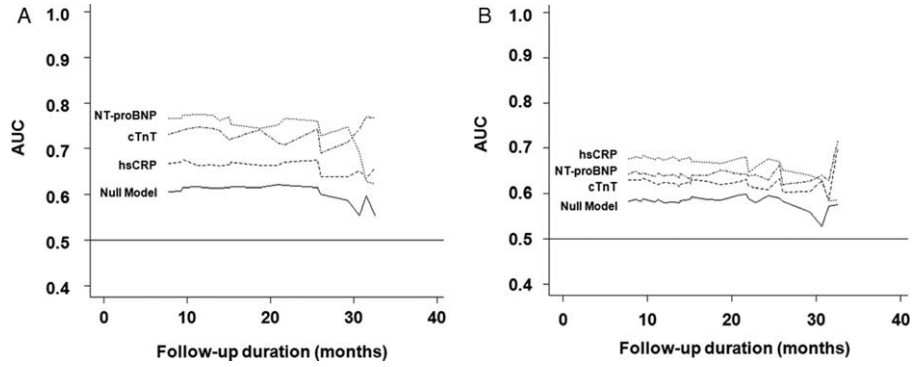

FIGURE 2. Time-dependent ROC curve analyses for cardiovascular (A) and all-cause mortality (B). iAUC values for CV mortality were 0.620 (95% CI, 0.545–0.694) for null model, 0.725 (95% CI, 0.602–0.771) for null model with NT-proBNP, 0.685 (95% CI, 0.650–0.792) for null model plus cTnT, and 0.663 (95% CI, 0.592–0.703) for null model with hsCRP. The estimated difference in iAUC was 0.105 (95% CI, 0.041–0.178) for NT-proBNP, 0.064 (95% CI, 0.005–0.156) for cTnT, and 0.043 (95% CI, 0.001–0.152) for hsCRP, indicating that all of these 3 biomarkers were additional significant prognostic factors for CV mortality, but NT-proBNP was revealed to be the significantly most predictive factor for CV mortality among them. On the contrary, iAUC values for all-cause mortality were 0.621 (95% CI, 0.534–0.722) for null model, 0.669 (95% CI, 0.571–0.771) for null model plus NT-proBNP, and 0.675 (95% CI, 0.564–0.786) for null model with hsCRP, and the ESD in iAUC values for all-cause mortality were 0.048 (95% CI, 0.001–0.158) for NT-proBNP and 0.055 (95% CI, 0.001–0.163) for hsCRP. However, iAUC for all-cause mortality was 0.640 (95% CI, 0.551–0.739) for the null model plus cTnT, and the ESD in iAUC of cTnT for all-cause mortality was only 0.019 (95% CI, −0.005 to 0.093). CI = confidence interval, cTnT = cardiac troponin T, CV = cardiovascular, ESD = estimated difference, hsCRP = high-sensitivity C-reactive protein, iAUC = integrated area under curve, NT-proBNP = N-terminal proB-type natriuretic peptide, ROC = receiver-operating curve.

no significant differences in CV mortality among the tertiles of cTnT ($P = 0.078$) and hsCRP ($P = 0.486$). Meanwhile, all-cause mortality rates increased significantly across the 3 tertiles of NT-proBNP and hsCRP groups (NT-proBNP group, $P = 0.019$; hsCRP group; $P = 0.014$), but not among the cTnT tertiles ($P = 0.232$).

Time-dependent ROC curves over the entire follow-up period are presented in Figure 2. iAUC values for CV mortality were 0.620 (95% CI, 0.545–0.694) for the null model (including age, sex, and WBC counts), 0.725 (95% CI, 0.602–0.771) for the null model with NT-proBNP, 0.685 (95% CI, 0.650–0.792) for the null model plus cTnT, and 0.663 (95% CI, 0.592–0.703) for the null model with hsCRP. The estimated differences (ESDs) in iAUC were 0.105 (95% CI, 0.041–0.178) for NT-proBNP, 0.064 (95% CI, 0.005–0.156) for cTnT, and 0.043 (95% CI, 0.001–0.152) for hsCRP, indicating that all of these 3 biomarkers provided additional significant prognostic values for CV mortality. However, among them, NT-proBNP was the most significant additional predictive factor for CV mortality. In contrast, iAUC values for all-cause mortality were 0.621 (95% CI, 0.534–0.722) for the null model, 0.669 (95% CI, 0.571–0.771) for the null model plus NT-proBNP, and 0.675 (95% CI, 0.564–0.786) for the null model with hsCRP. The ESDs in iAUC values for all-cause mortality were 0.048 (95% CI, 0.001–0.158) for NT-proBNP, and 0.055 (95% CI, 0.001–0.163) for hsCRP, suggesting that both NT-proBNP and hsCRP were additional significant prognostic factors for all-cause mortality. Furthermore, hsCRP was considered to be more significantly predictive for all-cause mortality than NT-proBNP. However, iAUC for all-cause mortality was 0.640 (95% CI, 0.551–0.739) for the null model plus cTnT, and the ESD in iAUC of cTnT for all-cause mortality was only 0.019 (95% CI, −0.005 to 0.093).

Biomarkers as Predictors of Mortality

The univariate Cox proportional hazard regression analysis revealed that the ''upper'' tertiles of NT-proBNP and cTnT were significantly associated with higher risks of both CV (NT-proBNP: HR = 4.975, $P = 0.012$; cTnT: HR = 3.794, $P = 0.040$) and all-cause mortalities (NT-proBNP: HR = 4.199, $P = 0.010$; hsCRP: HR = 4.867, $P = 0.001$) compared with the corresponding ''lower'' tertile groups. In addition, the ''upper'' tertile of hsCRP was significantly associated only with the increases in the risk for all-cause mortality. Serum albumin levels and WBC counts were also found to significantly predict all-cause mortality but not CV mortality (Table 4). In the multivariate Cox models, the ''upper'' tertiles of NT-proBNP and cTnT were still significantly related to the higher risks of CV mortality (NT-proBNP: HR = 4.702, $P = 0.018$; cTnT: HR = 4.483, $P = 0.021$); there were significant associations of the ''upper'' tertiles of NT-proBNP and hsCRP with all-cause mortality (NT-proBNP: HR = 4.174, $P = 0.012$; hsCRP: HR = 4.550, $P = 0.003$), even after adjusting for age, sex, and WBC counts (Table 5). Moreover, we calculated the NRI and IDI to assess the ability of the models with biomarkers to correctly reclassify patients compared with the

TABLE 4. Univariate Cox Proportional Regression Analysis for Cardiovascular and All-Cause Mortality

	Cardiovascular Mortality		All-Cause Mortality	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, y	0.995 (0.965-1.026)	0.753	1.018 (0.993–1.044)	0.163
Male (vs female)	0.680 (0.318–1.452)	0.319	0.848 (0.450–1.598)	0.609
BMI, kg/m^2	1.067 (0.955–1.193)	0.252	1.101 (0.782–2.367)	0.121
DM (vs non-DM)	1.597 (0.730–3.495)	0.241	1.680 (0.872–3.236)	0.121
CCI	1.083 (0.933–1.256)	0.295	1.106 (0.984–1.244)	0.091
MAP, mmHg	0.984 (0.958–1.011)	0.236	0.994 (0.973–1.014)	0.549
Urine output, mL/day	1.000 (0.999–1.000)	0.516	1.000 (0.999–1.000)	0.461
Hb, g/dL	0.957 (0.750–1.221)	0.723	0.970 (0.793–1.187)	0.769
WBC, cells/mm^3	1.118 (0.997–1.254)	0.056	1.110 (1.008–1.222)	0.034
Serum albumin, g/dL	0.724 (0.415–1.265)	0.257	0.622 (0.406–0.951)	0.028
Total cholesterol, mg/dL	0.992 (0.982–1.001)	0.085	1.110 (1.008–1.222)	0.034
Bicarbonate, mEq/L	0.968 (0.905–1.036)	0.350	0.954 (0.905–1.005)	0.077
LVH on ECG	2.180 (0.640–7.425)	0.213	1.938 (0.917–6.972)	0.055
LVEF (%)	0.998 (0.960–1.038)	0.928	0.981 (0.952–1.011)	0.213
LVMI, g/m^2	1.003 (0.996–1.009)	0.406	1.003 (0.997–1.008)	0.357
LAD, cm	0.888 (0.445–1.769)	0.735	1.164 (0.661–2.049)	0.599
NT-proBNP*				
Tertile 1	Ref	—	Ref	—
Tertile 2	1.974 (0.493–7.897)	0.336	2.216 (0.682–7.201)	0.186
Tertile 3	4.975 (1.417–17.47)	0.012	4.199 (1.408–12.52)	0.010
cTnT†				
Tertile 1	Ref	—	Ref	—
Tertile 2	1.384 (0.339–5.645)	0.651	1.653 (0.567–4.818)	0.360
Tertile 3	3.794 (1.066–13.51)	0.040	3.015 (0.864–8.261)	0.231
hsCRP‡				
Tertile 1	Ref	—	Ref	—
Tertile 2	2.752 (0.729–10.40)	0.135	1.947 (0.652–5.817)	0.223
Tertile 3	4.910 (0.916–17.02)	0.112	4.867 (1.852–12.79)	0.001

BMI = body mass index, CCI = Charlson Comorbidity Index, CI = confidence interval, cTnT = cardiac troponin T, DM = diabetes mellitus, Hb = hemoglobin, HR = hazard ratio, hsCRP = high-sensitivity C-reactive protein, LAD = left atrial dimension, LVEF = left ventricular ejection fraction, LVH on ECG = left ventricular hypertrophy on electrocardiogram, LVMI = left ventricular mass index, MAP = mean arterial pressure, NT-proBNP = N-terminal proB-type natriuretic peptide, WBC = white blood cell counts.

* The tertile of NT-proBNP was 1255.8 and 8720.5 pg/mL.

† The tertile of cTnT was 0.027 and 0.06 ng/mL.

‡ The tertile of hsCRP was 0.07 and 0.65 mg/dL.

TABLE 5(A). Multivariate Cox Proportional Regression Analysis for Cardiovascular Mortality

	Null Model		Model 1		Model 2		Model 3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (per year)	1.001 (0.972–1.031)	0.944	1.006 (0.972–1.041)	0.750	0.982 (0.948–1.017)	0.311	0.992 (0.962–1.023)	0.618
Male (vs female)	0.690 (0.319–1.490)	0.344	0.563 (0.238–1.330)	0.190	0.422 (0.172–1.033)	0.059	0.498 (0.223–1.114)	0.090
WBC (increase by 1000 cells/mm^3	1.114 (0.992–1.251)	0.068	1.009 (0.883–1.152)	0.899	1.111 (0.970–1.272)	0.129	1.036 (0.916–1.172)	0.574
NT-proBNP*								
Tertile1			Ref	—				
Tertile2			1.751 (0.431–7.109)	0.433				
Tertile3			4.702 (1.299–17.03)	0.018				
cTnT†								
Tertile1					Ref	—		
Tertile2					1.463 (0.348–6.152)	0.603		
Tertile3					4.483 (1.174–15.40)	0.021		
hsCRP‡								
Tertile1							Ref	—
Tertile2							3.028 (0.794–11.55)	0.105
Tertile3							5.412 (0.815–20.00)	0.091

Table 5(B). Multivariate Cox Proportional Regression Analysis for All-Cause Mortality

	Null model		Model 1		Model 2		Model 3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (per year)	1.022 (0.997–1.048)	0.082	1.022 (0.992–1.053)	0.145	0.999 (0.971–1.029)	0.970	1.013 (0.988–1.039)	0.301
Male (vs female)	0.812 (0.427–1.545)	0.526	0.649 (0.307–1.371)	0.258	0.574 (0.28–1.176)	0.129	0.624 (0.321–1.21)	0.163
WBC (increase by 1000 cells/mm^3)	1.127 (1.018–1.249)	0.022	1.028 (0.914–1.157)	0.642	1.102 (0.984–1.234)	0.094	1.048 (0.943–1.165)	0.385
NT-proBNP								
Tertile1			Ref	—				
Tertile2			1.897 (0.573–6.277)	0.294				
Tertile3			4.174 (1.368–12.74)	0.012				
cTnT								
Tertile1					Ref	—		
Tertile2					1.710 (0.576–5.074)	0.334		
Tertile3					3.562 (0.865–10.03)	0.214		
hsCRP								
Tertile1							Ref	—
Tertile2							2.064 (0.686–6.206)	0.197
Tertile3							4.550 (1.665–12.44)	0.003

CI = confidence interval, cTnT = cardiac troponin T, HR = hazard ratio, hsCRP = high-sensitivity C-reactive protein, NT-proBNP = N-terminal proB-type natriuretic peptide, WBC = white blood cell counts. Null model: age, sex, and white blood cell counts; Model 1: Null model + tertile of NT-proBNP; Model 2: Null model + tertile of cTnT; Model 3: Null model + tertile of hsCRP.

*The tertile of NT-proBNP was 1255.8 and 8720.5 pg/mL.

†The tertile of cTnT was 0.027 and 0.06 ng/mL.

‡The tertile of hsCRP was 0.07 and 0.65 mg/dL.

model without biomarkers (including the null model and each biomarker). The prognostic powers of the null model and each biomarker model are shown in Table 6. There were significant differences in both the CV and all-cause mortalities between the null model and the null model plus NT-proBNP, whereas cTnT and hsCRP had significant associations with only CV and all-cause mortalities, respectively (Table 6).

DISCUSSION

Several previous studies demonstrated that NT-proBNP, cTnT, and hsCRP predicted CV mortality in ESRD patients, but most of the patients included in these studies were prevalent HD patients.[9,10,15] The present study found that NT-proBNP was independently associated with both CV and all-cause mortalities in incident CAPD patients; however, cTnT was related only to the CV mortality, and hsCRP was related only to the all-cause mortality. Among these 3 biomarkers, NT-proBNP was revealed to be the most significant predictor of CV mortality,

TABLE 6. Prognostic Power for Cardiovascular and All-Cause Mortality for Null and Each Cardiac Biomarker Models Using NRI and IDI

	Cardiovascular Mortality				All-Cause Mortality			
	NRI	*P*	IDI	*P*	NRI	*P*	IDI	*P*
Model 1	0.204	0.050	0.078	0.002	0.116	0.15	0.039	0.037
Model 2	0.280	0.091	0.052	0.017	0.005	0.912	0.016	0.176
Model 3	0.010	0.317	0.010	0.239	0.249	0.015	0.052	0.008

IDI = integrated discrimination improvement, NRI = net reclassification index. Null model: age, sex, and white blood cell counts; Model 1: Null model + tertile of NT-proBNP; Model 2: Null model + tertile of cTnTl; Model 3: Null model + tertile of hsCRP.

*The data were analyzed with tertile groups of cardiac biomarkers.

†The tertile of NT-proBNP was 1255.8 and 8720.5 pg/mL.

‡The tertile of cTnT was 0.027 and 0.06 ng/mL.

§The tertile of hsCRP was 0.07 and 0.65 mg/dL.

whereas hsCRP was shown to be the most significant prognostic factor for all-cause mortality in incident CAPD patients. To our knowledge, the present study is the first to investigate and compare the predictive value of various biomarkers at the time of dialysis initiation on CV and all-cause mortalities in a large, ethnically homogeneous, incident CAPD patient cohort.

The first noticeable finding of this study was that NT-proBNP and cTnT but not hsCRP had a significant predictive power for CV mortality. The exact reason for the conflicting impacts of these 3 biomarkers is not yet defined. One possible explanation is that NT-proBNP and cTnT are more closely linked to LVH, which is known to be significantly associated with clinical outcomes in patients with chronic kidney disease.[9,11,12,15] A number of previous studies have shown that LVH is a powerful independent predictor of CV mortality in ESRD patients on dialysis. Moreover, the change in LVH has been demonstrated as a strong prognostic factor in these patients.[32,33] London et al[32] found that 10% reduction in left ventricular mass (LVM) during a mean follow-up duration of 54 months resulted in a 28% decrease in CV mortality and a 22% decrease in all-cause mortality in ESRD patients. LVM regression was also independently associated with better patient survival even after adjustment for age, sex, diabetes, history of CVD, and all the nonspecific CV risk factors.[32] Although the study used LVM and LVMI, assessed by echocardiography, as an indicator of LVH, similar findings were observed in hypertensive patients with LVH on ECG.[34,35] In addition, persistent ECG-based LVH at baseline and follow-up identified patients with greater LVM and higher prevalence of echocardiographic LVH, suggesting that these patients may be at a higher risk for subsequent CV morbidity and mortality.[36] In the present study, the proportions of patients with LVH on ECG and LVMI were significantly higher in the ''upper'' tertiles of NT-proBNP and cTnT. Moreover, in these groups, there was a significant decrease in LVEF and a significant increase in LAD, which were revealed to be associated with CV mortality in dialysis patients. Furthermore, NT-proBNP and cTnT were significantly correlated with LVEF, LVMI, and LAD. In contrast, there were no significant differences in the proportion of patients with LVH on ECG, LVEF, LVMI, and LAD among the tertiles of hsCRP. Additionally, there were no significant correlations of hsCRP with LVEF, LVMI, and LAD. Based on these findings, we surmise that the better predictability of NT-proBNP and cTnT, but not hsCRP, for CV mortality was attributed to their strong associations with LVH and systolic and diastolic dysfunction.

The cutoff value of cTnT for the ''middle'' and ''upper'' groups (0.06 ng/mL) in our study was less than the reference cTnT concentration (0.1 ng/mL) used in most previous studies,[37–39] whereas that of NT-proBNP (8720.5 pg/mL) was comparable with the value used in other studies.[9,10,15] In addition, the proportion of CV mortality among the all-cause mortality (22/39 [56.4%]) was somewhat lower than that of the other studies. However, the proportion of infection-related mortality (11/39 [28.2%]) was similar to or slightly higher than that of the others.[37,39–41] These findings may in part contribute to a relatively lower prognostic value of cTnT for CV mortality compared with NT-proBNP. Nevertheless, further studies are needed to determine whether a weaker association between cTnT and CV mortality is attributed to more meticulous care and more intensive treatment provided for these patients.

hsCRP, a well-known inflammatory marker, has been demonstrated to be associated with CVD because of a significant pathogenic role of inflammation in the development and progression of atherosclerosis.[16,17] Moreover, a number of previous studies have revealed that serum hsCRP levels can predict future CV events as well as CV mortality in the general population.[16] However, the results of previous studies on the impact of serum hsCRP concentrations on CVD or CV mortality in ESRD patients were not consistent,[10,15] which may partly be due to the differences in the study population, the duration of dialysis, comorbid diseases, and measurement methods. However, increased serum hsCRP levels are usually observed in patients with diabetes, insulin resistance, and dyslipidemia, all of which are prevalent in dialysis patients.[11,42] Furthermore, most of ESRD patients, especially CAPD patients, are suggested to have underlying chronic low-grade inflammation,[43] and the concentrations of serum hsCRP levels are also known to vary widely, both intra- and interindividually.[44,45] Taken together, the prognostic value of serum hsCRP levels for CV mortality could be lessened in our study patients. In contrast, we found that all-cause mortality was significantly higher in the ''upper'' tertile of hsCRP compared with the other tertiles (23.9% vs 8.3% and 2.7%, $P < 0.05$). The Kaplan-Meier plot also showed that there was a significant difference in all-cause mortality rates among the tertiles of hsCRP ($P = 0.014$). Moreover, the WBC count was significantly higher in the ''upper'' tertile of hsCRP and significantly correlated with hsCRP ($r = 0.201$, $P = 0.013$). Based on these findings, it was submitted that higher all-cause mortality in the ''upper'' hsCRP group might be attributed to deaths from infection. In fact, infection-related mortality was significantly higher in the ''upper'' tertile of hsCRP (5.3% vs 2.8% and 1.8%, $P < 0.05$); this possibly explains why hsCRP had a higher predictive value for all-cause mortality than other biomarkers in incident CAPD patients. Since there were a relatively small number of deaths from infection, and hsCRP concentrations and WBC counts were determined only once at the time of the study entry, it was difficult to confirm the clear-cut association between hsCRP and infection-related mortality in our study subjects.

At baseline, 143 patients were taking vitamin D supplements or analogues. In the present study, additional analysis revealed that there were no significant differences in NT-proBNP, CRP levels, and PTH levels between patients with and without vitamin D supplements or analogues treatment. Even though several previous studies showed that stimulation of vitamin D receptors reduced BNP levels,[46–51] some recent published data demonstrated that there was no significant association between vitamin D supplements and NT-proBNP concentrations in dialysis patients,[52–54] supporting the results of the present study.

There are several limitations to this study. First, since the patients of the present study were all Korean ESRD patients starting CAPD, the associations between various biomarkers and mortality may not be applicable to other populations. Second, we included only CAPD patients because automated PD (APD) was not widely performed in Korea and the timing of the change from CAPD to APD was not uniform. Third, CV and all-cause mortality rates in this study were lower compared with those in previous studies on Western dialysis patients.[9,10,15] We propose that a difference in ethnicities is what mainly contributes to these disparate results because the mortality rates of our incident CAPD patients were comparable with those of the Japanese ESRD patients on dialysis.[55] Fourth, the measurement of biomarkers and echocardiography were performed only once at the time of PD initiation. Therefore, it is difficult to clarify why some biomarkers did not associate with CV and/or all-cause mortality and to examine whether the changes in these

biomarkers had any impact on patient clinical outcomes. Fifth, the patients were arbitrarily divided into the 3 groups based on the tertile values of each biomarker. As aforementioned, the cutoff values for each biomarker used in previous studies were quite different.[9,10,14,15] Therefore, it is necessary to define the best cutoff levels for the various biomarkers in CAPD patients. Sixth, unfortunately, even though an objective fluid balance monitoring, such as inferior vena cava diameter, bioimpedance, and continuous blood volume measurements, were not carried out in the present study, the physicians performed routine chest X-rays and physical examination to evaluate the volume status of these patients, and these cardiac biomarkers were determined at the time close to discharge. Thus, we considered the patients to be clinically euvolemic at the time of enrollment. Lastly, the follow-up duration was relatively short. However, since this prospective cohort study is still ongoing, the long-term association between the biomarkers and clinical outcomes can be elucidated in the near future. Despite these limitations, to our knowledge, the present study is the first one to investigate and to compare the association of baseline NT-proBNP, cTnT, and hsCRP concentrations with CV and all-cause mortalities in a large, ethnically homogeneous, incident CAPD patient cohort. Moreover, based on the data of the present study demonstrating that among the 3 biomarkers the concentrations of NT-proBNP and hsCRP in incident CAPD patients even at baseline are the most significant predictor of CV and all-cause mortality, respectively, we surmise that the present study may provide some useful information to the physicians; They may have to closely monitor incident CAPD patients, especially whose baseline levels of these biomarkers are high.

In conclusion, among the 3 biomarkers, NT-proBNP and hsCRP were the best prognostic factors for CV and all-cause mortalities, respectively, in the Korean incident CAPD patients.

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