의학박사 학위논문

만성신장질환의 심혈관계 질환 예측을 위한 위험인자 및 바이오마커에 관한 연구

– 사회경제적 지위 및 high-sensitivity Troponin T 를 중심으로 –

Risk factors and biomarkers as predictors for cardiovascular outcomes in chronic kidney disease

– Focusing on socioeconomic status and high-sensitivity troponin T –

2020 년 2 월

서울대학교 대학원

임상의과학과

강 은 정

Abstract

Risk factors and biomarkers as predictors for cardiovascular outcomes in chronic kidney disease

- Focusing on socioeconomic status and high-sensitivity troponin T -

Eunjeong Kang, M.D.
Department of Internal Medicine
The Graduate School
Seoul National University College of Medicine

Introduction: Cardiovascular (CV) diseases are the leading cause of death among patients with chronic kidney disease (CKD). Thus, it is important to identify risk factors for the prevention of CV disease in patients with CKD to facilitate early intervention. Thus, the risk factors and diagnostic biomarkers for subclinical cardiac changes were investigated in this study. In the first part of this study, I aimed to reveal the association between left ventricular (LV) structure, function and socioeconomic status (SES). In the second part of this study, I evaluated the relationship between high-sensitivity troponin T (hs-TnT) and LV structure, function in the CKD population according to the estimated glomerular filtration rate (eGFR).

Methods: Data were collected from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD, NCT01630486 at http://www.clinicaltrials.gov) which is a prospective cohort study with non-dialysis-dependent CKD patients. Echocardiography was conducted for evaluation of left ventricular hypertrophy (LVH), systolic and diastolic dysfunction at baseline and after 4 years. Information on educational attainment and monthly income level, which were captured from patient-reported questionnaires, was used as indicators of SES. Cardiac troponin T levels were measured using high-sensitivity assay, and the participants were categorized into quartiles according to hs-TnT concentrations.

Results: In the analysis regarding SES and LVH, LVH was associated with parameters of SES and these associations had graded responses. Lower education and income level showed a statistically significant determinant of LVH in total participants and a subgroup with age ≥ 50 years, but not age < 50 years in the multivariate analysis. In view of diastolic dysfunction, the monthly income level was associated with diastolic dysfunction in total patients and patients age ≥ 50 years in the multivariable analysis. In the second part of this study, elevated hs-TnT was associated with LVH and diastolic dysfunction at baseline in an adjusted model, but not in systolic dysfunction. These associations remained significant for both eGFR subgroups based on eGFR 60mL/min/1.73m^2, irrespective of renal function. ROC analysis showed that hs-TnT levels as a continuous variable exhibited fair significance for the detection of LVH (Area under the curve [AUC] 0.69) and

diastolic dysfunction (AUC 0.74). Finally, multivariable analysis showed that higher hs-TnT levels at study entry were related to the development of new LVH but not the development of diastolic dysfunction among participants with follow-up echocardiography at 4 years (N=864).

Conclusion: The present study shows that educational attainment and monthly income level are possible risk factors for LVH and monthly income level is a significant determinant of diastolic dysfunction. Additionally, in the view of biomarkers, hs-TnT is strongly associated with alterations of LV structure and diastolic dysfunction regardless of renal function. Baseline hs-TnT levels are predictive of new LVH on follow-up. Further studies regarding novel risk factors and the mechanisms for CV disease in non-dialysis-dependent CKD population is warranted to improve the CV outcomes.

Parts of the results in this thesis have been published in the following articles:

- Eunjeong Kang et al. (2018). "The association between socioeconomic disparities and left ventricular hypertrophy in chronic kidney disease: results from the KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD)". *BMC Nephrology* 19(1):203.
- Eunjeong Kang et al. (2019). "Association Between High-Sensitivity Cardiac Troponin T and Echocardiographic Parameters in Chronic Kidney Disease: Results From the KNOW-CKD Cohort Study". *Journal of American Heart Association* 17;8(18):e013357

Keywords: Chronic kidney disease, cardiovascular disease, left ventricular hypertrophy, systolic dysfunction, diastolic dysfunction, socioeconomic status, high-sensitivity troponin T

***Student Number*:** 2016-30801

Table of Contents

List of Tables

List of Figures

Chapter 1. Introduction

1.1 Backgrounds

The importance of cardiovascular disease in chronic kidney disease

Worldwide, cardiovascular (CV) diseases are the leading cause of death among patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD), irrespective of race and ethnicity,(1) especially, it is reported that CV disease may account for half of the deaths in CKD patients irrespective of biological age.(2) Also, CV disease is the primary cause of death in CKD patients in Korea, accounting for 39% of mortality cases in peritoneal dialysis and 36% in hemodialysis patients.(3)

The presence of CV disease is independently related to kidney function decline.(4) From several epidemiological studies, it is certain that patients with CKD are at higher risk of developing CVD.(5) Many previous studies reported that low estimated glomerular filtration rate (eGFR) and higher level of albuminuria are related to CV diseases and mortality.(6, 7) Especially, the risk of CV mortality linearly inclines with decreasing eGFR below 75 mL/min/1.73m^2 even after adjustment for traditional CV risk factors and albuminuria.(6, 7) According to the CKD stages, the CV mortality rate was twice as high in patients with CKD stage 3 (30-59mL/min/1.73m^2) and three times higher in CKD stage 4 (15-29 mL/min/1.73m^2) compared to those with normal

renal function.(6-8) In the view of albuminuria, the adjusted hazard ratio of CV mortality is more than two folds at the 30-299 mg/g categories, compared with the risk in individuals with normal albuminuria.(6-8) In particular, given that even a small amount of albuminuria increases the risk of CV mortality, physicians and nephrologists should pay attention to the albuminuria itself. Thus, it is important to identify risk factors for the prevention of cardiovascular disease in patients with CKD in order to facilitate treatment in the asymptomatic phase.

The risk factors for adverse cardiovascular event in CKD patients

So far, the underlying mechanisms of the association between CKD and CV risk remain unclear. CKD alters metabolism in the uremic milieu and plenty of risk factors were observed in CKD patients. Various links between the CV and renal systems represent complex associations. These complicated relationships between CKD and CV diseases come from an assembly of multiple CV risk factors, including the "traditional risk factors" and "non-traditional risk factors". Representatively, traditional risk factors that were revealed from the Framingham cohort study, such as age, lifestyle, dyslipidemia, left ventricular hypertrophy, hypertension and diabetes mellitus predict CV mortality from CKD with mild to moderate renal dysfunction.(9) Recently, novel risk factors for CV disease, including inflammation, endothelial cell dysfunction, sympathetic tone over-activation, protein energy-wasting,(10) oxidative

stress, vascular calcification, and volume overload seem to play a more important role for CV disease in CKD patients than general population.(11-14) All of these traditional and non-traditional risk factors interact with each other in CKD populations and have a great influence on the development of CV diseases. However, we need to consider that the association between traditional risk factors and CV diseases is complicated: i.e., the well-known association between traditional risk factors in the general population is not observed in the patients with advanced CKD.(15) The high prevalence of protein-energy wasting, persistent inflammation and volume overload in advanced CKD are the main reasons for the paradoxical association between established risk factors and CV outcomes in this population group.(16, 17)

Pathophysiology of cardiovascular disease in CKD patients

In particular, CKD patients are exposed to pressure overload, volume overload, and CKD-related non-hemodynamic factors that change the myocardium. Pressure overload results from long-standing hypertension and vascular stiffness.(18) It leads to an increment of cardiac afterload and decrement of arterial compliance through concentric thickening of the left ventricular wall. Additionally, volume overload leads to eccentric hypertrophy secondary to the addition of new sarcomeres and may be related to increased extracellular volume and anemia. As a result, increased left

ventricular wall stress from pressure and volume overload induces changes in the myocardium.(2) Left ventricular hypertrophy (LVH) provoked by this process through physiologic adaptation, causes decreased diastolic compliance and leads to ischemic cardiomyopathy, even in the absence of coronary artery disease.(19) More specifically, in a cohort of patients starting dialysis therapy, cardiac enlargement and decreased systolic function exhibited a relationship with ischemic heart disease and cardiac failure.(20) LVH lead to various clinical sequels including myocardial infarction, intradialytic hypotension, angina, heart failure, and sudden cardiac death.(2) The prevalence of LVH is estimated to be between 16-31% in patients with GFR >30mL/min/1.73m^2, and it increases to 60-75% before initiation dialysis also rises to more than 90% after starting renal replacement therapy.(21) Cardiac symptoms may not occur until the changes of heart structure and function are severe, thus, it is important to diagnose subclinical disease including LVH earlier and stratify risks for CV outcomes.

In addition to hemodynamic changes, improper activation of the renin-angiotensin system, oxidative stress, inflammation, and stimulation of many kinds of hypertrophic and fibrogenic factors (transforming growth factorβ, cardiotrophin-1, galectin-3, fibroblast growth factor) are important CV risk factors in CKD patients.(22)

Since both the traditional and CKD-specific non-traditional risk factors aforementioned effect to raise the CV risk, further studies are needed for early detection and interruption of these pathophysiologic mechanisms.

Cardiovascular diseases in CKD patients

The spectrum of CVD in CKD populations is varied since it includes congestive heart failure, arrhythmias, ischemic heart disease, stroke, valvular calcification and peripheral vascular disease.(23-26)

First of all, congestive heart failure (CHF) is the leading CV disease in CKD patients, which is characterized by pulmonary edema and dyspnea.(2) LV dysfunction is observed among CKD patients and is related to the increment of the prevalence of CHF and CV mortality. Especially, diastolic dysfunction may occur in the early stages of CKD, even without LVH. The mortality was slightly higher for diastolic dysfunction than for systolic dysfunction.(27)

In addition, as eGFR decreases, the incidence of coronary artery disease (CAD) increases.(28, 29) In CKD patients, CAD is characterized by diffuse multi-vessel involvement with coronary artery calcification. CKD and ESRD patients rarely show typical manifestations ("oligo-symptomatic") such as chest pain when developing myocardial infarction and CAD; 72% of patients with normal kidney function who

present with acute myocardial infarction complain of chest pain, arm or shoulder pain, while only 44% patients with eGFR <60 mL/min/1.73m^2 develop above symptoms.(30) Thus, differences in the acute manifestations profile in CKD patients should be addressed in real clinical settings.

KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD)

CKD is a rapidly growing disease and worldwide problem. The prevalence of CKD in South Korea is estimated to be at 13.7% in the adult by the population-based study.(31) Recently, several CKD cohorts were established worldwide and most of them are primarily based on the CKD populations with low GFR (less than 60mL/min/1.73m^2).(32-34)

The KNOW-CKD cohort, funded by the Korea Center for Disease Control and Prevention was established in 2011 in South Korea. The main purposes of this cohort are as follows: 1) to establish an adult pre-dialysis CKD cohort covering early, as well as advanced, CKD, 2) to evaluate the natural history of CKD including renal progression, death, CV disease, and other complications, 3) to investigate the etiologic factors for renal progression and cardiovascular complications, 4) to find out the mechanisms between renal dysfunction and adverse outcomes, and 5) to identify

the genetic and molecular effect on renal progression and complications.(35) The strong point of KNOW-CKD is the composition of participants which included a broad range of renal dysfunction – from early to advanced CKD patients. Therefore, KNOW-CKD is suitable for investigating various aspects of CKD.

1.2 The purpose of this study

As mentioned above, it is important to prevent and detect CV disease and complications early in CKD populations for improving the clinical outcomes. In this theses, risk factors and diagnostic biomarker for subclinical cardiac changes were investigated based on the KNOW-CKD Study.

Chapter 2. The association between socioeconomics disparities and echocardiographic parameters in chronic kidney disease

2.1 Background

Socioeconomic status and chronic kidney disease

Socioeconomic status (SES) is a measurement of social and economic wellbeing assessed by three aspects: education, occupation, and income. SES is an important and strong predictor of morbidity and mortality. Generally, education level, occupation, race, housing, social support, and income are key components to be evaluated as SES. Multiple determinants of health care level vary with SES levels, including risk of all-cause mortality,(36) cardiovascular diseases,(37-39) diabetes mellitus,(39, 40) cancer,(41, 42) and CKD.(39, 43) Socioeconomic status may affect health by the availability of resources to maintain health including a safe place to exercise, healthy food, access to health care, and health insurance.(44) Such determinants may interact with and combine to affect the health outcomes in an interconnected mechanism.

CKD is a complex disease of genetic and environmental factors. Social determinants of health might affect environmental components. Because SES might similarly influence CKD patients as it does the general population, it is important to clarify

health-related risk factors in CKD affected by SES. Thus, understanding the social determinants of health is very important. Until now, several studies have reported that low income is associated with albuminuria and eGFR <60mL/min/1.73m in Jackson Heart Study (45) and Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort.(46, 47) Also, lower-income and education were related to lower eGFR in the CRIC study. Besides, the incidence of ESRD was higher in patients with low income and educational attainment.(48, 49)

Socioeconomic status and cardiovascular disease

SES also has a significant impact on CV disease, and the people with low SES levels carry a substantial burden of CV disease and are more likely to experience increased event rates and poorer clinical outcomes (50). There are many studies regarding the association between income level and mortality, myocardial infarction, and coronary heart disease in western countries. All of these studies revealed that low income level is associated with significantly higher rates of events and poorer outcomes compared to the group with higher income level.(51-53) Additionally, in the view of educational attainment, several studies have demonstrated a higher risk of CV disease and mortality.(54) Especially, in South Korea, low education level was associated with an increased risk of three-year cardiac events and all-cause mortality (55).

In one study, Carlos et al.(56) reported that lower SES is an independent risk factor for increased left ventricular mass among hypertensive and normotensive African Americans. Additionally, low family SES at childhood was associated with increased LV mass and diastolic dysfunction after more than 30 years.(57) However, the relationship between SES and risk factors of cardiovascular mortality, including LVH, is less well known among CKD patients.

However, most of the studies were conducted to find out the prevalence of CV disease according to SES in the general population, or reveal the influence of SES on poorer clinical outcomes in the patients with myocardial infarction. Few studies have been conducted regarding SES and CVD in the CKD population.

The purpose of this part of the study

Since some social determinants of health are modifiable through education and governmental health policies, investigating the influence of SES on the outcome of CKD and CVD is crucial. As mentioned above, LVH and diastolic dysfunction are one of the most important factors for subclinical disease in CKD populations. Therefore, here, I investigated the association between LVH and diastolic dysfunction, the representative risk factor for CV mortality in CKD and socioeconomic status,

evaluated by educational attainment and monthly income level, among participants in the KNOW-CKD.

2.2 Materials and methods

Study populations

This study was performed using the database extracted from KNOW-CKD, a Korean multicenter prospective cohort study that enrolled subjects with non-dialysis dependent CKD (stages 1 to 5) from 2011 to 2016. The study protocol was approved by the Institutional Review Board at each participating clinical center. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol summary is registered at ClinicalTrials.gov under accession number NCT01630486. Written informed consent was obtained from all subjects at the time of enrollment. Briefly, a total of 2,238 patients were enrolled in the KNOW-CKD study.

Among them, I excluded 1) individuals who did not respond to the questionnaire regarding SES, 2) with no measured left ventricular (LV) mass and 3) who were lost to follow-up (Figure 1). Finally, 1,648 subjects were included in the analyses.

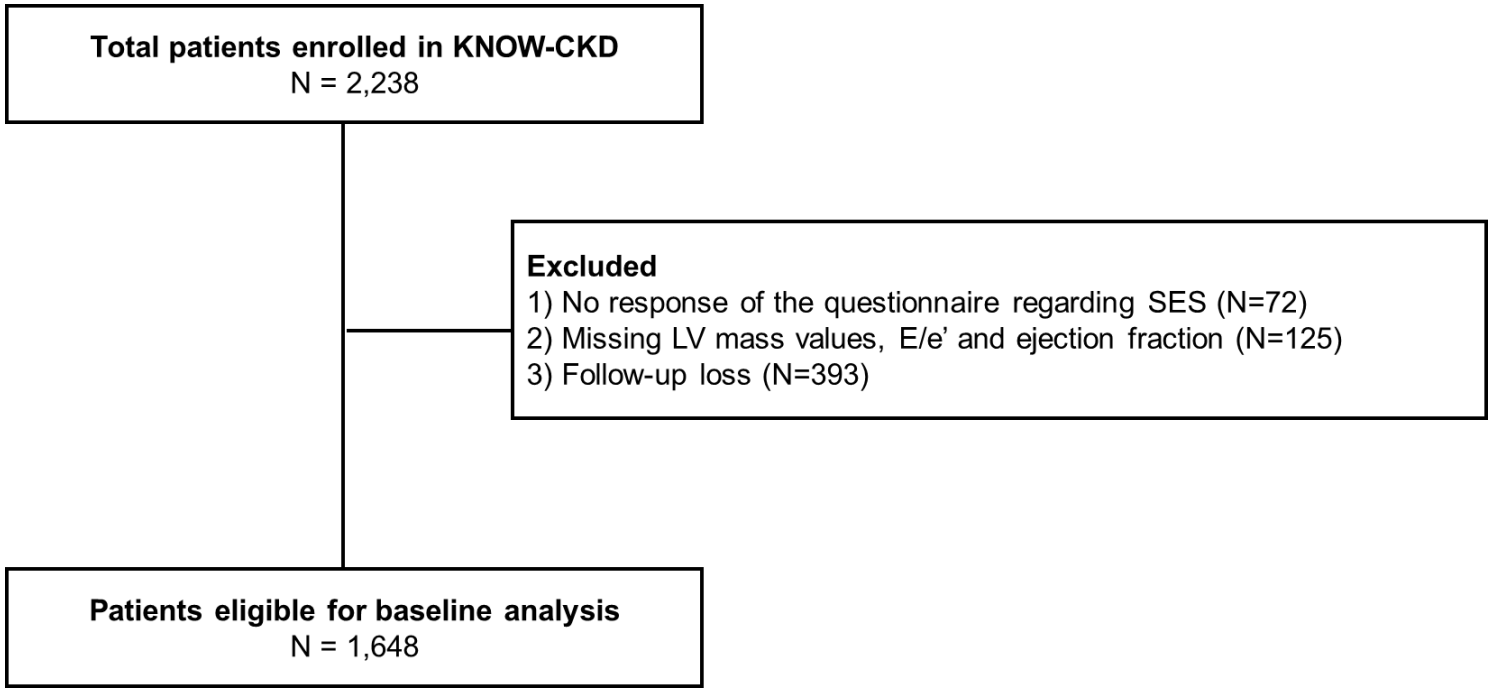


Figure 1 Study flow

Abbreviations: SES, socioeconomic status; LV, left ventricular

Evaluation of socioeconomic status

Information on educational attainment and monthly income level, which were captured from the patient-reported questionnaire, was used as indicators of SES. Monthly income level based on the average household income level was classified into three levels: less than $ 1500, $ 1500 to $ 4500, and over $ 4500 per month. With regard to educational attainment, the patients were asked about the level at which their formal school education was completed. Educational attainment was classified into three levels: “less than high school” included those who never went to high school or who completed only part of high school, “completed high school” included those who had graduated from high school but not completed college, “college degree or beyond” included those who had completed college or a higher degree.

Evaluation of echocardiography

Two-dimensional echocardiography was conducted at study entry and during the 4th year of follow-up to measure cardiac parameters including LV dimensions, geometry, mass, and systolic and diastolic dysfunction. LV mass was calculated using the formula $0.8 \times \{1.04[LVIDd + PWTd + SWTd)^3 - (LVIDd)^3]\} + 0.6$ g, where LVIDd refers to LV end-diastolic internal dimension and PWTd and SWTd are posterior wall thickness at end-diastole and septal wall thickness at end-diastole, respectively.(58)

To account for gender differences and variations in body size, LV mass was indexed to height$^{2.7}$ because LV mass indexed to body surface area is problematic in that weight is affected by volume overload in CKD.(59-61) LVH was defined as an LV mass/height$^{2.7}$ $\geq$ 47 g/m$^{2.7}$ in women and $\geq$ 50 g/m$^{2.7}$ in men. Relative wall thickness (RWT) was calculated as twice the posterior wall thickness / LV internal linear dimension in diastole. RWT values > 0.42 were considered to be increased.(62) LV mass and RWT were used to classify LV geometry: normal (no LVH and RWT $\leq$ 0.42), concentric remodeling (No LVH and RWT > 0.42), eccentric hypertrophy (LVH and RWT $\leq$ 0.42), and concentric hypertrophy (LVH and RWT > 0.42).

Data collection

Demographics, and clinical and laboratory values at enrollment were extracted from an electronic data management system (http://www.phactaX.org). The eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using creatinine.(63) Resting blood pressure was measured with mercury sphygmomanometers and cuffs of appropriate size three times for average blood pressure. Hypertension (HTN) was defined as a blood pressure recording ≥140/90 mmHg, a self-reported history of hypertension, or the use of antihypertensive agents. Diabetes (DM) was defined by self-reporting or the use of hypoglycemic medications. Physical activity was quantified by the International Physical Activity Questionnaire.

Subjects were categorized by total Metabolic Equivalent of Task (MET) - minutes/week; “high” was defined as ≥3000 METs-minutes/week, “moderate” as 600–2999 METs-minutes/week and “low” as < 600 METs-minutes/week. Anemia was defined as hemoglobin < 13 g/dL for males, or < 12 g/dL for females. Body mass index (BMI) was calculated by measuring height and body weight [weight (kg)/height (m^2)]. Smoking status was categorized as current smoker, ex-smoker, or never smoker.

Statistical analysis

Continuous variables are presented as a mean ± standard deviation. Proportions were used for categorical variables, including age groups, sex, CKD stages, and comorbidities. I used a one-way analysis of variance for comparison of continuous variables and the $\chi 2$ test for categorical variables. Statistical significance was determined at $P < 0.05$ using two-sided tests. I conducted logistic regression to evaluate the association between LVH and SES, which is categorized into three education or monthly income levels. I carried out additional subgroup analyses according to age (age < 50 years, ≥ 50 years). The Hosmer-Lemeshow goodness of fit test was performed for determining whether multivariable models are fit of data. Statistical analyses were carried out using the R, version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Ethics statement

The study protocol was approved by the Institutional Review Board at each participating clinical center — i.e., Seoul National University Hospital (1104–089-359), Seoul National University Bundang Hospital (B-1106/129–008), Yonsei University Severance Hospital (4–2011-0163), Kangbuk Samsung Medical Center (2011–01-076), Seoul St. Mary's Hospital (KC11OIMI0441), Gil Hospital (GIRBA2553), Eulji General Hospital (201105–01), Chonnam National University Hospital (CNUH-2011-092), and Pusan Paik Hospital (11–091) in 2011. This study was conducted in accordance with the principles of the Declaration of Helsinki.

2.3 Results

Baseline characteristics of the study population

Baseline characteristics of the study subjects at study entry are shown in Table 1. The Mean age was 52.8 ± 11.9 years, and 1,014 (61.5%) were men. Mean eGFR was 55.0 ± 30.6 mL/min/1.73m^2 and the number of patients with a CKD stage G3a, G3b, G4, and G5 were 274 (16.6%), 362 (22.0%), 311 (18.9%), and 84 (5.1%), respectively. Subjects with DM and HTN comprised 32.6% and 95.7% of the study participants, respectively. Anemia was prevalent in 673 (40.8%) subjects.

Comparison of baseline characteristics according to socioeconomic status

I compared baseline characteristics according to education attainment (Table 1) and monthly income levels (Table 2). With respect to educational strata, the mean age was 11 years older in the lowest educational group. Subjects in the lowest education group exhibited the lowest eGFR (61.3 ± 31.7 mL/min/1.73m^2 for 'college or beyond', 53.8 ± 30.5 mL/min/1.73m^2 for 'completed high school', and 44.1 ± 25.0 mL/min/1.73m^2 for 'less than high school' groups, respectively, *P* for trend < 0.001). The higher education group was associated with higher monthly household income (*P* for trend < 0.001). The prevalence of anemia increased with a decreasing level of educational attainment (32.3%, 43.6%, and 53.7%, respectively; *P* for trend < 0.001). The

proportion of diabetic patients was the highest in the lowest education group. No group differences were exhibited in sodium excretion from 24-hour urine collection.

When the subjects were categorized based on monthly income level, similar trends were observed in terms of age, eGFR, DM, anemia, and 24-hour sodium excretion.

Table 1 Baseline characteristics according to educational attainment

		Total (N=1693)	College or beyond (N=730)	Completed high school (N=600)	Lower than high school (N=363)	*P*	*P* for trend
Age (year, mean ± SD)		52.8 ± 11.9	49.2 ± 12.4	52.9 ± 11.3	60.1 ± 8.0	<0.001	<0.001
Male (N, %)		1014 (61.5%)	521 (73.1%)	339 (57.9%)	154 (44.0%)	<0.001	<0.001
LVH (N, %)		357 (21.7%)	108 (15.1%)	132 (22.6%)	117 (33.4%)	<0.001	<0.001
Systolic dysfunction (N, %)		19 (1.2%)	7 (1.0%)	6 (1.0%)	6 (1.7%)	0.539	0.771
Diastolic dysfunction (N, %)		120 (7.3%)	31 (4.3%)	49 (8.4%)	40 (11.4%)	<0.001	<0.001
eGFR (mL/min/1.73m^2)		55.0 ± 30.6	61.3 ± 31.7	53.8 ± 30.5	44.1 ± 25.0	<0.001	<0.001
BMI (kg/m^2, mean ± SD)		24.6 ± 3.4	24.6 ± 3.4	24.3 ± 3.3	25.0 ± 3.3	0.009	0.063
CKD stage (N, %)						<0.001	<0.001
	Stage 1	284 (17.2%)	158 (22.2%)	99 (16.9%)	27 (7.7%)		
	Stage 2	333 (20.2%)	169 (23.7%)	109 (18.6%)	55 (15.7%)		
	Stage 3a	274 (16.6%)	130 (18.2%)	94 (16.1%)	50 (14.3%)		
	Stage 3b	362 (22.0%)	126 (17.7%)	137 (23.4%)	99 (28.3%)		
	Stage 4	311 (18.9%)	108 (15.1%)	112 (19.1%)	91 (26.0%)		
	Stage 5	84 (5.1%)	22 (3.1%)	34 (5.8%)	28 (8.0%)		

Diabetes mellitus (N, %)		538 (32.6%)	189 (26.5%)	184 (31.5%)	165 (47.1%)	<0.001	<0.001
Hypertension (N, %)		1577 (95.7%)	671 (94.1%)	563 (96.2%)	343 (98.0%)	0.004	0.001
SBP (mmHg, mean ± SD)		127.3 ± 15.3	126.8 ± 14.1	127.0 ± 16.1	128.6 ± 16.3	0.265	0.116
DBP (mmHg, mean ± SD)		77.1 ± 10.6	78.0 ± 10.3	76.8 ± 10.9	75.7 ± 10.7	0.001	<0.001
Monthly income (N, %)						<0.001	<0.001
	> $ 4,500	414 (25.1%)	283 (39.7%)	104 (17.8%)	27 (7.7%)		
	$ 1,500 to 4,500	903 (54.8%)	370 (51.9%)	359 (61.4%)	174 (49.7%)		
	< $ 1,500	331 (20.1%)	60 (8.4%)	122 (20.9%)	149 (42.6%)		
Physical activity (N, %)						0.001	0.094
	High	498 (33.9%)	209 (32.2%)	199 (38.8%)	90 (29.2%)		
	Moderate	594 (40.4%)	291 (44.8%)	182 (35.5%)	121 (39.3%)		
	Low	378 (25.7%)	149 (23.0%)	132 (25.7%)	97 (31.5%)		
Anemia (N, %)		673 (40.8%)	230 (32.3%)	255 (43.6%)	188 (53.7%)	<0.001	<0.001
Serum laboratory findings (mean ± SD)							
	Hemoglobin (g/dL)	13.0 ± 2.0	13.5 ± 1.9	12.8 ± 1.9	12.2 ± 1.9	<0.001	<0.001
	Albumin (g/dL)	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.4	4.1 ± 0.4	<0.001	<0.001
	Calcium (mg/dL)	9.1 ± 0.5	9.2 ± 0.5	9.1 ± 0.5	9.1 ± 0.5	0.100	0.020

	Phosphorus (mg/dL)	3.6 ± 0.7	3.5 ± 0.6	3.7 ± 0.7	3.8 ± 0.7	<0.001	<0.001
	Total cholesterol (mg/dL)	174.4 ± 38.6	174.5 ± 38.4	174.3 ± 37.3	174.5 ± 41.3	0.994	0.872
	LDL (mg/dL)	96.5 ± 31.4	96.5 ± 31.2	97.0 ± 31.7	95.9 ± 31.6	0.864	0.748
	HDL (mg/dL)	49.8 ± 15.3	50.5 ± 15.8	49.9 ± 14.5	48.0 ± 15.4	0.044	0.039
	Triglyceride (mg/dL)	157.2 ± 98.4	155.7 ± 97.3	152.4 ± 87.9	168.3 ± 115.1	0.052	0.074
24hr urinary sodium (mEq/day)		159.6 ± 78.3	155.5 ± 65.1	166.4 ± 95.6	156.3 ± 69.6	0.043	0.750

Abbreviations: SD standard deviation, eGFR estimated glomerular filtration rate, BMI body mass index, CKD chronic kidney disease, LDL low density lipoprotein, HDL high density lipoprotein

Table 2 Baseline characteristics according to monthly income level

		Total (N=1693)	> $ 4,500 (N=422)	$ 1,500 to 4,500 (N=932)	< $ 1,500 (N=339)	*P*	*P* for trend
Age (year, mean ± SD)		52.8 ± 11.9	51.1 ± 10.5	52.0 ± 12.4	57.3 ± 11.3	<0.001	<0.001
Male (N, %)		1014 (61.5%)	282 (68.1%)	529 (58.6%)	203 (61.3%)	0.004	0.005
LVH (N, %)		357 (21.7%)	69 (16.7%)	180 (19.9%)	108 (32.6%)	<0.001	<0.001
Systolic dysfunction (N, %)		19 (1.2%)	4 (1.0%)	9 (1.0%)	6 (1.8%)	0.453	0.242
Diastolic dysfunction (N, %)		120 (7.3%)	16 (3.9%)	61 (6.8%)	43 (13.0%)	<0.001	<0.001
eGFR (mL/min/1.73m^2)		55.0 ± 30.6	59.7 ± 30.1	56.2 ± 31.1	45.5 ± 28.1	<0.001	<0.001
BMI (kg/m^2, mean ± SD)		24.6 ± 3.4	24.5 ± 3.1	24.5 ± 3.5	24.9 ± 3.3	0.108	0.068
CKD stage (N, %)						<0.001	<0.001
	Stage 1	284 (17.2%)	85 (20.5%)	167 (18.5%)	32 (9.7%)		
	Stage 2	333 (20.2%)	96 (23.2%)	184 (20.4%)	53 (16.0%)		
	Stage 3a	274 (16.6%)	76 (18.4%)	152 (16.8%)	46 (13.9%)		
	Stage 3b	362 (22.0%)	83 (20.0%)	199 (22.0%)	80 (24.2%)		
	Stage 4	311 (18.9%)	65 (15.7%)	152 (16.8%)	94 (28.4%)		

	Stage 5	84 (5.1%)	9 (2.2%)	49 (5.4%)	26 (7.9%)		
Diabetes mellitus (N, %)		538 (32.6%)	113 (27.3%)	274 (30.3%)	151 (45.6%)	<0.001	<0.001
Hypertension (N, %)		1577 (95.7%)	400 (96.6%)	859 (95.1%)	318 (96.1%)	0.354	0.645
SBP (mmHg, mean ± SD)		127.3 ± 15.3	126.8 ± 13.5	126.4 ± 15.4	130.2 ± 16.7	0.007	0.003
DBP (mmHg, mean ± SD)		77.1 ± 10.6	78.6 ± 9.9	76.6 ± 10.8	76.6 ± 11.0	0.005	0.008
Educational attainment (N, %)						<0.001	<0.001
	College or beyond	713 (43.3%)	283 (68.4%)	370 (41.0%)	60 (18.1%)		
	Completed high school	585 (35.5%)	104 (25.1%)	359 (39.8%)	122 (36.9%)		
	Lower than high school	350 (21.2%)	27 (6.5%)	174 (19.3%)	149 (45.0%)		
Physical activity (N, %)						0.005	0.053
	High	130 (32.6%)	272 (35.2%)	96 (32.1%)	98 (32.1%)		
	Moderate	182 (45.6%)	308 (39.9%)	104 (34.8%)	107 (35.1%)		
	Low	87 (21.8%)	192 (24.9%)	99 (33.1%)	100 (32.8%)		
Anemia (N, %)		135 (32.6%)	372 (41.2%)	166 (50.2%)	170 (50.1%)	<0.001	<0.001
Serum laboratory findings (mean ± SD)							
	Hemoglobin (g/dL)	13.0 ± 2.0	13.4 ± 1.9	13.0 ± 2.0	12.5 ± 2.0	<0.001	<0.001
	Albumin (g/dL)	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.4	4.1 ± 0.4	<0.001	<0.001

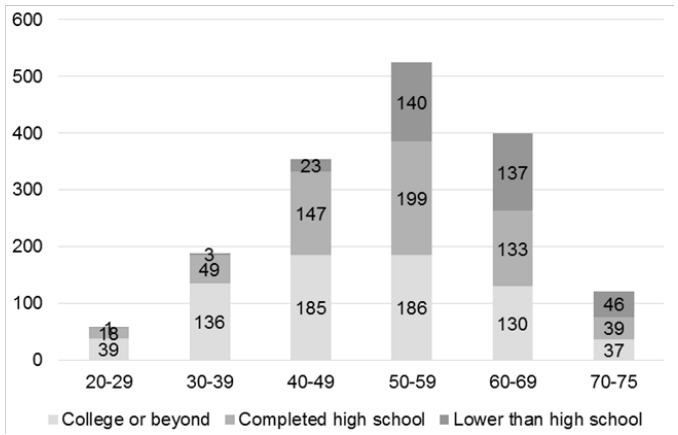
	Calcium (mg/dL)	9.1 ± 0.5	9.2 ± 0.5	9.2 ± 0.5	9.1 ± 0.5	0.002	0.002
	Phosphorus (mg/dL)	3.6 ± 0.7	3.6 ± 0.6	3.7 ± 0.7	3.7 ± 0.8	0.011	0.007
	Total cholesterol (mg/dL)	174.4 ± 38.6	174.1 ± 37.3	175.0 ± 38.8	173.1 ± 40.0	0.774	0.870
	LDL (mg/dL)	96.5 ± 31.4	94.5 ± 30.1	97.7 ± 31.9	95.8 ± 31.8	0.486	0.440
	HDL (mg/dL)	49.8 ± 15.3	51.3 ± 15.3	49.8 ± 15.3	47.9 ± 14.9	0.003	0.006
	Triglyceride (mg/dL)	157.2 ± 98.4	156.5 ± 106.0	155.9 ± 97.6	161.6 ± 90.4	0.523	0.449
24hr urinary sodium (mEq/day)		159.6 ± 78.3	159.4 ± 68.4	155.7 ± 83.4	169.8 ± 75.2	0.116	0.068

Abbreviations: SD standard deviation, eGFR estimated glomerular filtration rate, BMI body mass index, CKD chronic kidney disease, LDL low density lipoprotein, HDL high density lipoprotein

The distribution of socioeconomic status according to age

Concerning educational attainment, the proportion of 'college or beyond' decreased, from 67.2% in their 20s to 30% in their 50s (Figure 2B). In terms of monthly household income level, '$1,500 to $4,500' group accounted for more than half of all age groups, and the proportion of high-income level more than $4,500 is the highest in the 40s. In a comparison of monthly income and educational attainment, the high-income earners were 39.7% of the 'college or beyond' group and the highest percentage of low-income earners under $1,500 was 42.6% in the 'lower than high school' (Figure 4).

(A)



(B)

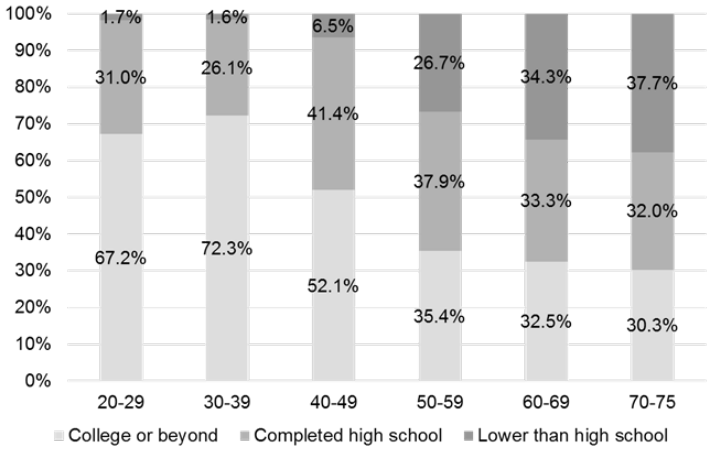


Figure 2 The distribution of educational attainment according to age

(A) The number of participants

(B) The percentages of participants

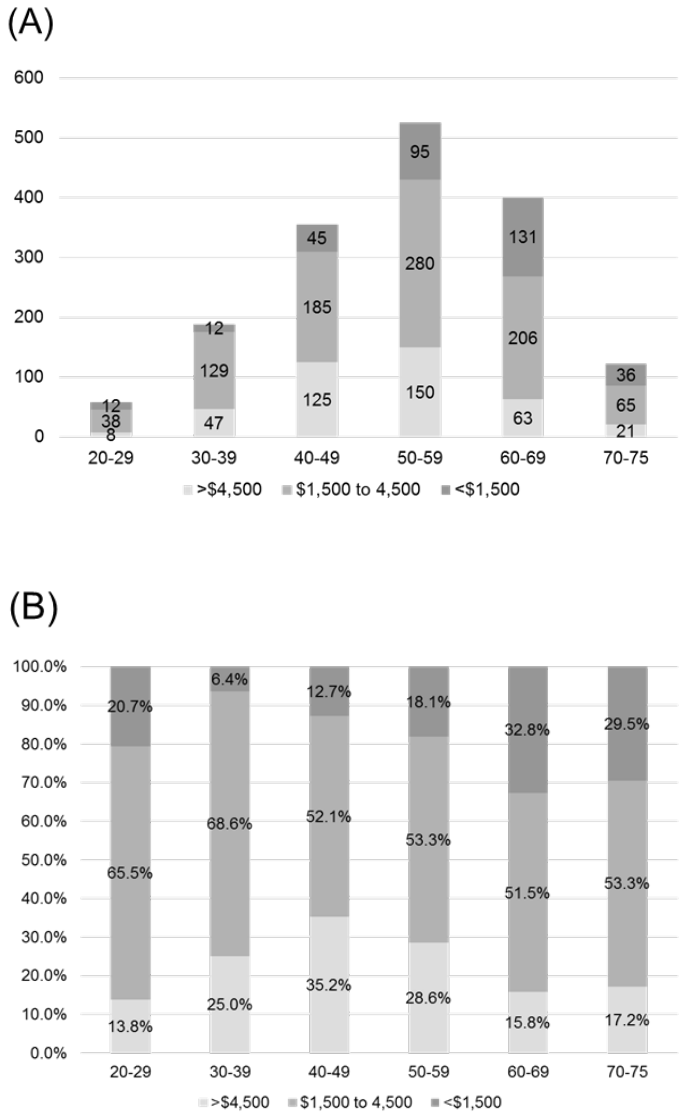


Figure 3 The distribution of monthly income according to age

(A) The number of participants

(B) The percentages of participants

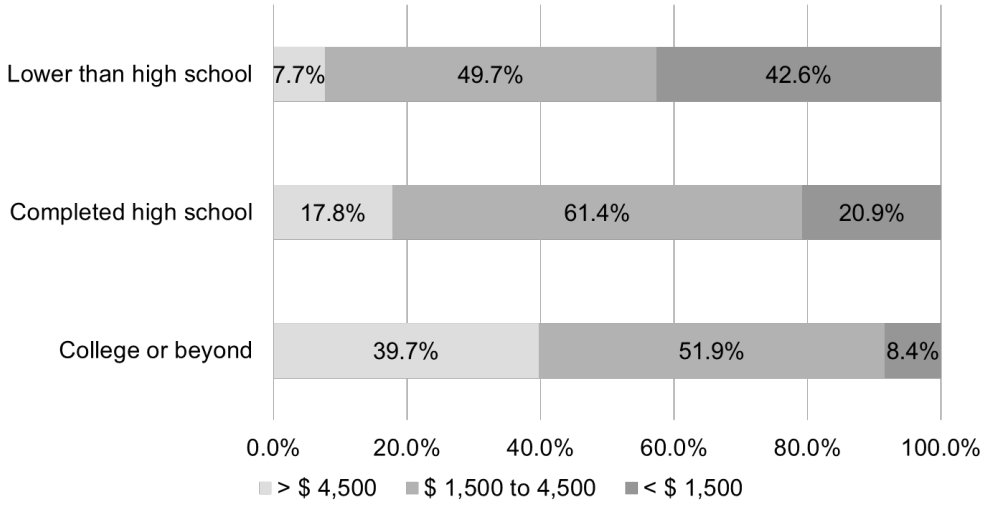


Figure 4 The distribution of educational attainment and monthly income level

Socioeconomic status and left ventricular hypertrophy

The total number of patients diagnosed with LVH on echocardiography was 357 (21.7%). With the increase of the household income level or with the increase of the educational attainment, the prevalence of LVH gradually increased (Table 1 and 2, P for trend <0.001, respectively). In unadjusted analyses, the risk of LVH increased with decreasing levels of education attainment and monthly income level, respectively (Table 3, Table 4 and Figure 5). In particular, the lowest educational level (lower than high school) was independently associated with LVH after adjusting for age, sex, pulse pressure, DM, CKD stage and physical activity ('college or beyond,' reference; 'completed high school', odds ratio [OR] 1.26, 95% CI 0.92–1.72; 'less than high school' OR 1.59, 95% CI 1.11–2.26; Table 3 and Figure 5A). Additionally, when anemia included as a covariate in the multivariable model, the association between the lowest education level and LVH still showed the statistical significance (Table 3). Monthly income level is a risk factor for LVH in a multivariable analysis adjusted age, sex, pulse pressure, diabetes, CKD stage, and physical activity, even if anemia was added to the analysis. In the subgroup analysis according to age, there were no independent relationships between socioeconomic status (educational attainment and monthly income level) and LVH in the subgroup aged <50 years. However, in the group of patients aged ≥50 years, the lowest educational attainment showed a significant association with LVH in univariate and multivariate analysis (Table 3, Figure 5).

Table 3 The relationship between LVH and educational attainment according to age

	Univariate analysis		Multivariate analysis*		Multivariate analysis¶	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Total participants						
≥ College	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
High school	1.60 (1.21-2.12)	0.001	1.26 (0.92-1.72)	0.153	1.26 (0.92-1.72)	0.151
< high school	2.90 (2.16-3.90)	<0.001	1.59 (1.11-2.26)	0.011	1.59 (1.11-2.26)	0.01
Age <50 years						
≥ College	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
High school	1.82 (1.09-3.03)	0.021	1.50 (0.83-2.68)	0.174	1.51 (0.84-2.70)	0.168
< high school	2.26 (0.72-5.94)	0.122	1.42 (0.41-4.38)	0.547	1.37 (0.40-4.13)	0.59
Age ≥50 years						
≥ College	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
High school	1.30 (0.93-1.83)	0.130	1.21 (0.83-1.77)	0.324	1.21 (0.83-1.76)	0.33
< high school	1.99 (1.43-2.80)	<0.001	1.57 (1.06-2.32)	0.024	1.56 (1.06-2.31)	0.026

Abbreviations: LVH, left ventricular hypertrophy; OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease

*Adjusted for age, sex, pulse pressure, diabetes, CKD stage, physical activity

¶Adjusted for age, sex, pulse pressure, diabetes, CKD stage, physical activity and anemia

Table 4 The relationship between LVH and monthly income level according to age

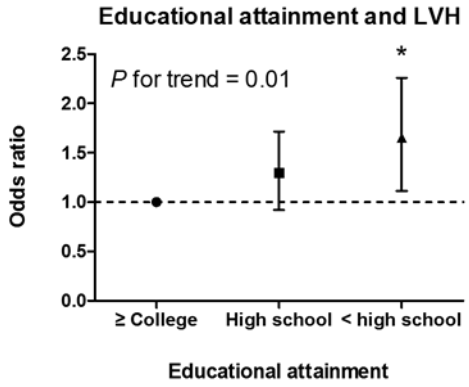
	Univariate analysis		Multivariate analysis*		Multivariate analysis¶	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Total participants						
> $ 4,500	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
$ 1,500 - 4,500	1.23 (0.91-1.67)	0.179	1.13 (0.82-1.57)	0.470	1.13 (0.82-1.57)	0.467
< $ 1,500	2.40 (1.71-3.38)	<0.001	1.52 (1.04-2.23)	0.030	1.52 (1.04-2.23)	0.029
Age <50 years						
> $ 4,500	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
$ 1,500 - 4,500	0.84 (0.48-1.51)	0.546	1.00 (0.54-1.88)	0.992	1.02 (0.55-1.94)	0.947
< $ 1,500	2.52 (1.23-5.13)	0.011	1.67 (0.73-3.76)	0.218	1.70 (0.74-3.82)	0.206
Age ≥50 years						
> $ 4,500	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
$ 1,500 - 4,500	1.33 (0.93-1.93)	0.118	1.19 (0.80-1.77)	0.395	1.18 (0.80-1.76)	0.403
< $ 1,500	1.98 (1.33-2.96)	<0.001	1.49 (0.96-2.31)	0.077	1.48 (0.96-2.31)	0.078

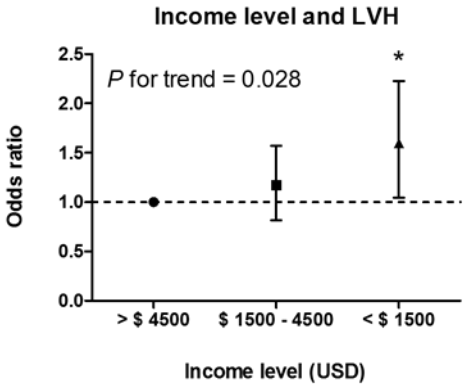
Abbreviations: LVH, left ventricular hypertrophy; OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease

*Adjusted for age, sex, pulse pressure, diabetes, CKD stage, physical activity

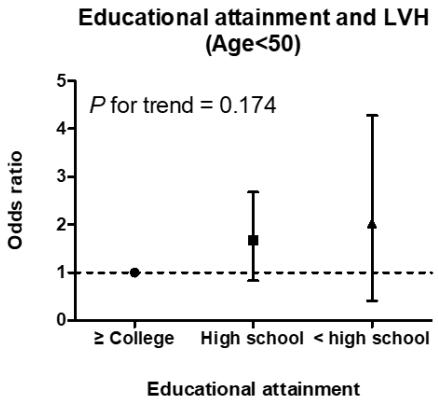
¶Adjusted for age, sex, pulse pressure, diabetes, CKD stage, physical activity and anemia

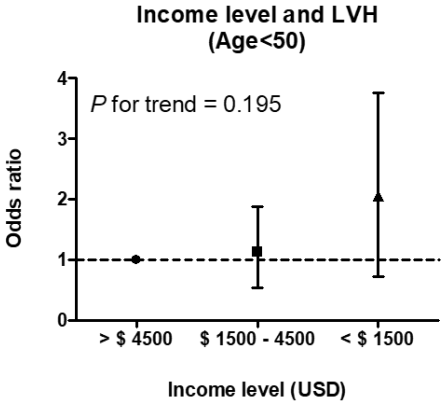
(A)


Educational attainment and LVH
P for trend = 0.01
*
Odds ratio
2.5
2.0
1.5
1.0
0.5
0.0
≥ College
High school
< high school
Educational attainment


Income level and LVH
P for trend = 0.028
*
Odds ratio
2.5
2.0
1.5
1.0
0.5
0.0
> $ 4500
$ 1500 - 4500
< $ 1500
Income level (USD)

(B)


Educational attainment and LVH
(Age<50)
P for trend = 0.174
Odds ratio
5
4
3
2
1
0
≥ College
High school
< high school
Educational attainment


Income level and LVH
(Age<50)
P for trend = 0.195
Odds ratio
4
3
2
1
0
> $ 4500
$ 1500 - 4500
< $ 1500
Income level (USD)

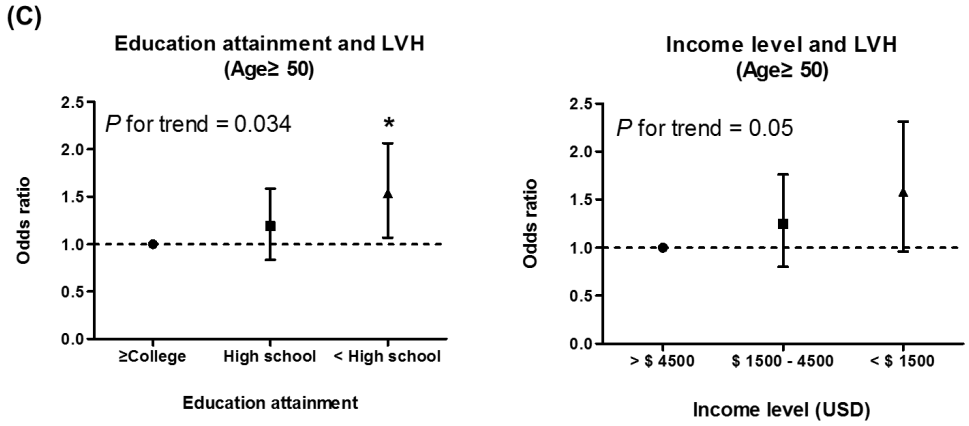


Figure 5 Odds ratio for LVH according to SES in multivariate analysis

(A) Total participants

(B) Age <50 years

(C) Age ≥50 years

Adjusted for age, sex, pulse pressure, diabetes, CKD stage, physical activity

*: P < 0.05

Abbreviations: LVH, left ventricular hypertrophy; SES, Socioeconomic status; CKD, chronic kidney disease; USD, US dollar

Socioeconomic status and diastolic dysfunction

The total number of participants diagnosed with diastolic dysfunction on echocardiography was 120 (7.3%). In terms of educational attainment, the tendency of gradual increment was observed only in the univariate analysis in total participants (Table 5). With the decrement of the monthly income level, the OR of diastolic dysfunction gradually increased in unadjusted and multivariate analysis (Table 6, Figure 6). In the subgroup analysis according to age, there are no significant associations between both socioeconomic status and diastolic dysfunction in the subgroup aged <50 years. In the group of patients aged ≥50 years, the lowest monthly income level showed a significant association with diastolic dysfunction in univariate and multivariate analysis (Table 6, Figure 6).

Table 5 The relationship between diastolic dysfunction and educational attainment according to age

	Univariate analysis		Multivariate analysis*		Multivariate analysis¶	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Total participants						
≥ College	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
High school	2.01 (1.27-3.23)	0.003	1.49 (0.90-2.49)	0.12	1.48 (0.89-2.48)	0.13
< high school	2.84 (1.75-4.65)	<0.001	1.23 (0.70-2.18)	0.47	1.22 (0.69-2.17)	0.48
Age <50 years						
≥ College	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
High school	1.71 (0.58-5.05)	0.32	0.83 (0.21-2.97)	0.78	0.82 (0.21-2.94)	0.77
< high school	1.95 (0.10-11.56)	0.54	1.22 (0.06-9.37)	0.87	1.22 (0.06-9.40)	0.87
Age ≥50 years						
≥ College	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
High school	1.74 (1.04-2.99)	0.04	1.61 (0.92-2.88)	0.10	1.60 (0.91-2.87)	0.11
< high school	1.88 (1.11-3.23)	0.02	1.27 (0.69-2.35)	0.44	1.25 (0.69-2.33)	0.46

Abbreviations: LVH, left ventricular hypertrophy; OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease

*Adjusted for age, sex, pulse pressure, diabetes, CKD stage, physical activity

¶Adjusted for age, sex, pulse pressure, diabetes, CKD stage, physical activity and anemia

Table 6 The relationship between diastolic dysfunction and monthly income level according to age

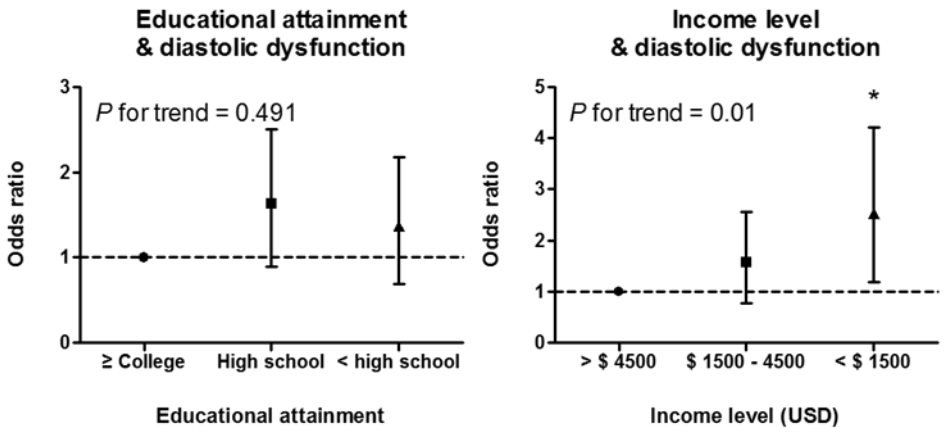
	Univariate analysis		Multivariate analysis*		Multivariate analysis¶	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Total participants						
> $ 4,500	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
$ 1,500 - 4,500	1.79 (1.05-3.25)	0.04	1.38 (0.77-2.58)	0.29	1.37 (0.76-2.56)	0.31
< $ 1,500	3.70 (2.09-6.89)	<0.001	2.20 (1.19-4.23)	0.01	2.19 (1.18-4.21)	0.01
Age <50 years						
> $ 4,500	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
$ 1,500 - 4,500	1.36 (0.39-6.29)	0.65	1.11 (0.27-5.63)	0.89	1.09 (0.26-5.55)	0.91
< $ 1,500	3.58 (0.77-18.56)	0.10	2.04 (0.38-11.70)	0.40	2.03 (0.38-11.16)	0.40
Age ≥50 years						
> $ 4,500	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
$ 1,500 - 4,500	1.80 (0.99-3.51)	0.06	1.40 (0.74-2.83)	0.32	1.40 (0.74-2.81)	0.33
< $ 1,500	2.97 (1.58-5.93)	0.001	2.23 (1.14-4.59)	0.02	2.22 (1.14-4.57)	0.02

Abbreviations: LVH, left ventricular hypertrophy; OR, odds ratio; CI, confidence interval

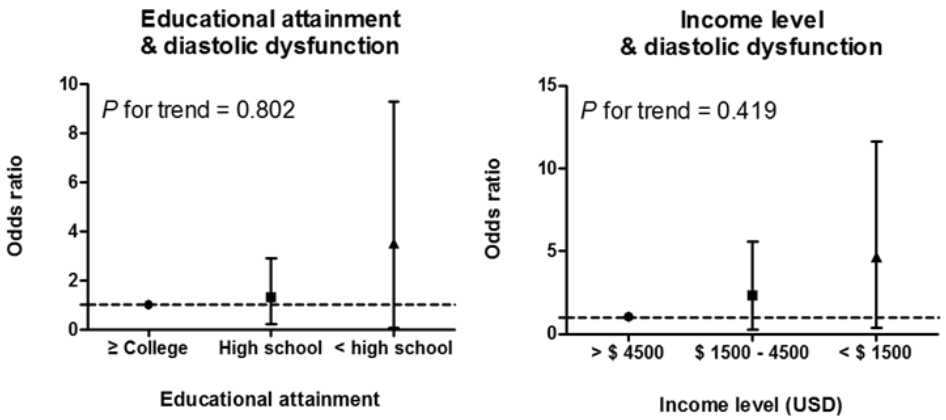
*Adjusted for age, sex, diabetes, CKD stages, physical activity

¶ Adjusted for age, sex, diabetes, CKD stages, physical activity and anemia

(A)


Educational attainment
& diastolic dysfunction
P for trend = 0.491
Odds ratio
0
1
2
3
≥ College
High school
< high school
Educational attainment
Income level
& diastolic dysfunction
P for trend = 0.01
*
Odds ratio
0
1
2
3
4
5
> $ 4500
$ 1500 - 4500
< $ 1500
Income level (USD)

(B)


Educational attainment
& diastolic dysfunction
P for trend = 0.802
Odds ratio
0
2
4
6
8
10
≥ College
High school
< high school
Educational attainment
Income level
& diastolic dysfunction
P for trend = 0.419
Odds ratio
0
5
10
15
> $ 4500
$ 1500 - 4500
< $ 1500
Income level (USD)

(C)

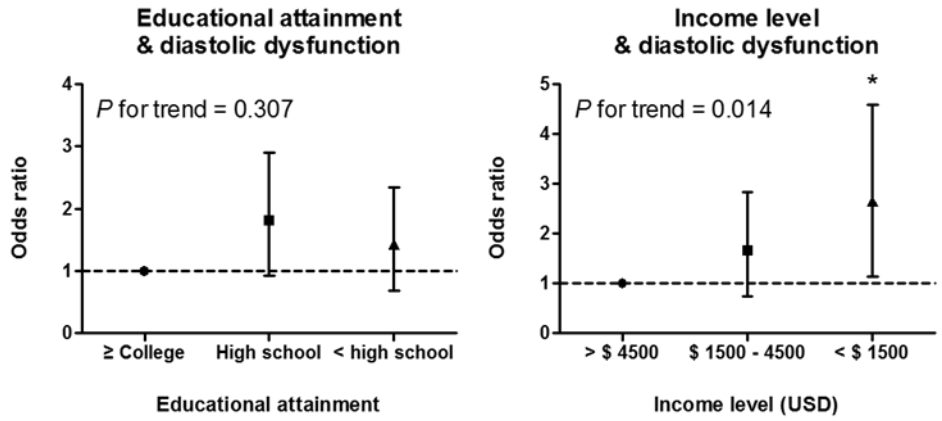


Figure 6 Odds ratio for diastolic dysfunction according to SES in multivariate analysis

(A) Total participants

(B) Age <50 years

(C) Age ≥50 years

Adjusted for age, sex, diabetes, CKD stage, physical activity and anemia

*: P < 0.05

Abbreviations: SES, Socioeconomic status; CKD, chronic kidney disease; USD, US dollar

Chapter 3. The association between high-sensitivity cardiac troponin T and echocardiographic parameters in chronic kidney disease

3.1 Background

Biomarkers of cardiovascular disease: high-sensitivity troponin T

The conventional cardiac troponin T (TnT) assay was developed in 2000 and has since become a widely used biomarker for diagnosing acute coronary syndrome.(58) Since their introduction, troponin assays have continued to evolve, and a high-sensitivity TnT (hs-TnT) assay with detection limits 10 to 100 times lower than conventional assays is now available. Importantly, hs-TnT can be detected in asymptomatic patients with no history of cardiovascular disease.

Sustained elevation of hs-TnT was recently shown to be associated with chronic subclinical myocardial damage in the general population, including left ventricular structure abnormalities (64-66). However, subjects with CKD have persistently elevated TnT levels when compared to those with normal renal function (67). In addition, chronic structural and functional abnormalities of the heart are very common among CKD patients (68). Because hs-TnT is easier to obtain in an outpatient setting

and is relatively low in cost compared to a traditional echocardiogram, there is an important and clinically relevant need to define cardiac structural and functional correlates of hs-TnT levels. Therefore, the ability to interpret elevated troponin levels in CKD patients is critical, as their elevation may predict clinical and subclinical cardiac injury in subjects with or without CKD.

The purpose of this part of the study

In the second part of this study, to better understand the implication of elevated hs-TnT level in CKD patients across a broad range of estimated eGFRs, the association between hs-TnT and left ventricular (LV) structure and function was investigated based on two different eGFR strata in the KNOW-CKD cohort, which comprises subjects with both mild and severe renal dysfunction.

3.2 Materials and methods

Study populations

This study was performed using the database extracted from KNOW-CKD, a Korean multicenter prospective cohort study that enrolled subjects with non-dialysis dependent CKD (stages 1 to 5) from 2011 to 2015. The ethics statement was described in section 2.2.6. Briefly, a total of 2,238 patients were enrolled in the KNOW-CKD study. Subjects were excluded who, at study entry, 1) did not have a hs-TnT measurement at our central laboratory, 2) did not have an LV mass index measurement, or 3) had been diagnosed with heart failure. Finally, a total of 2,017 patients were included in our cross-sectional analysis (Figure 7). Patients who completed follow-up transthoracic echocardiography after 4years were included in a longitudinal analysis of new changes of cardiac structure and function (n= 864, 42.8% of total participants).

Additionally, because hs-TnT could be elevated in patients with coronary artery disease, I conducted a sensitivity analysis in the group of patients without a history of coronary artery disease. A total of 116 participants with a history of coronary artery disease were excluded. In this analysis, finally, a total of 1,901 patients were analyzed.

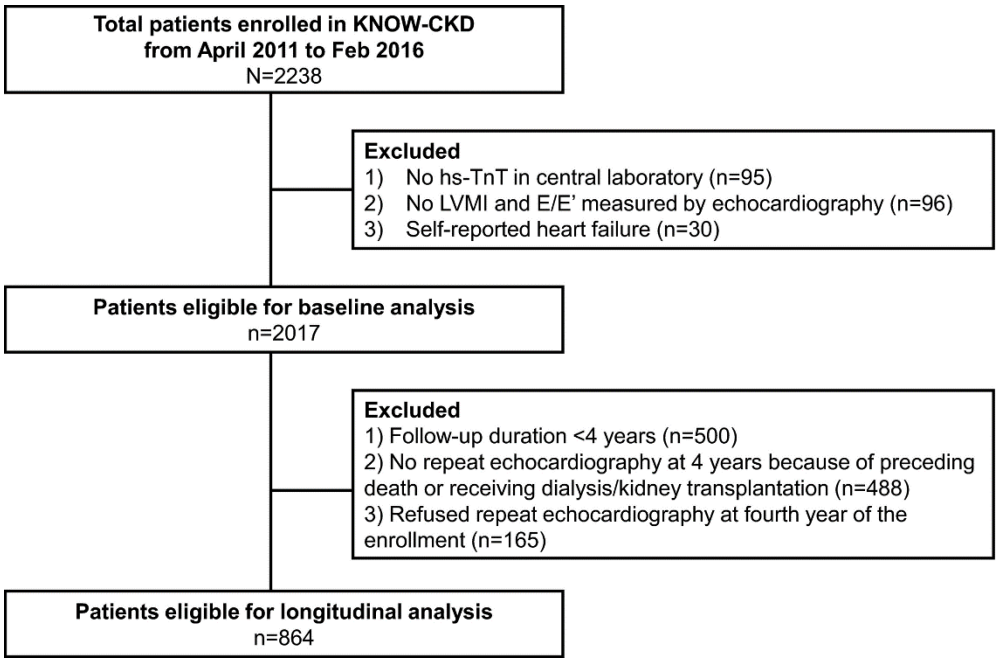


Figure 7 Study flow

Abbreviations: hs-TnT, high-sensitivity cardiac troponin T; KNOW-CKD, KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease; LVMI, left ventricular mass index

Measurement of hs-TnT

Serum hs-TnT was measured using a highly-sensitive electro-chemiluminescence immunoassay on an Elecsys 2010 by Roche Diagnostics Corp. (Basel, Swiss) which has an analytical measurement range of 3-10,000 pg/mL.

Evaluation of left ventricular structure and function in echocardiography

The primary outcome was LVH, systolic and diastolic dysfunction. Two-dimensional echocardiography was conducted at enrollment and 4th year of follow-up. The definitions of LVH and LV geometry were described in the "Evaluation of echocardiography" section (14 page). Additional data regarding systolic and diastolic dysfunction were collected. LV systolic dysfunction was defined as an ejection fraction (EF) <50%.(60) Diastolic dysfunction was defined as an E/e' >15.(61)

Statistical analysis

Continuous variables are presented as the mean ± standard deviation. Categorical variables are presented by proportion and frequency. I used a one-way analysis of variance for comparison of continuous variables and the χ^2 test for categorical variables.

Patients were stratified into four groups according to hs-TnT quartiles. Multivariable logistic regression analysis was used to evaluate an independent association between hs-TnT and outcomes of this study. Univariate analysis for each variable was conducted primarily, the results of which were used to select the covariates included in the multivariate analysis based on P <0.05. Although some variables did not show statistical significance, variables of clinical importance were included based on the judgment of the researchers.

Subjects were stratified into two subgroups based on an eGFR ≥ 60 mL/min/1.73 m^2 or eGFR < 60 mL/min/1.73 m^2 to evaluate the modifying effect of renal impairment on hs-TnT. eGFR strata did not show a statistically significant interaction for the hs-TnT level (P for interactions were 0.07, 0.55 and 0.41 in LVH, systolic dysfunction, and diastolic dysfunction, respectively.). Additional analyses were carried out to investigate whether hs-TnT can be used as a screening test to detect structural and functional abnormalities. Receiver operating characteristic (ROC) analysis was performed for the area under the curve (AUC) determination. Optimal cut-off concentrations for hs-TnT were defined as points of the ROC curves by the Youden method.(69) Additionally, multivariate ROC analysis was conducted with adjustments for the co-variables which were selected in the previous logistic regression, and the AUCs were compared according to renal function. Pairwise comparisons among the AUCs were made using Delong's method.(70)

A two-tailed *P* value of <0.05 was used as the cutoff for statistical significance. All statistical analyses were performed using R (version 3.5.2; The R Foundation for Statistical Computing, Vienna, Austria).

3.3 Results

Distribution of hs-TnT

The overall distribution of hs-TnT was skewed to the right, and an inverse relationship between hs-TnT and eGFR (Figure 8) was observed.

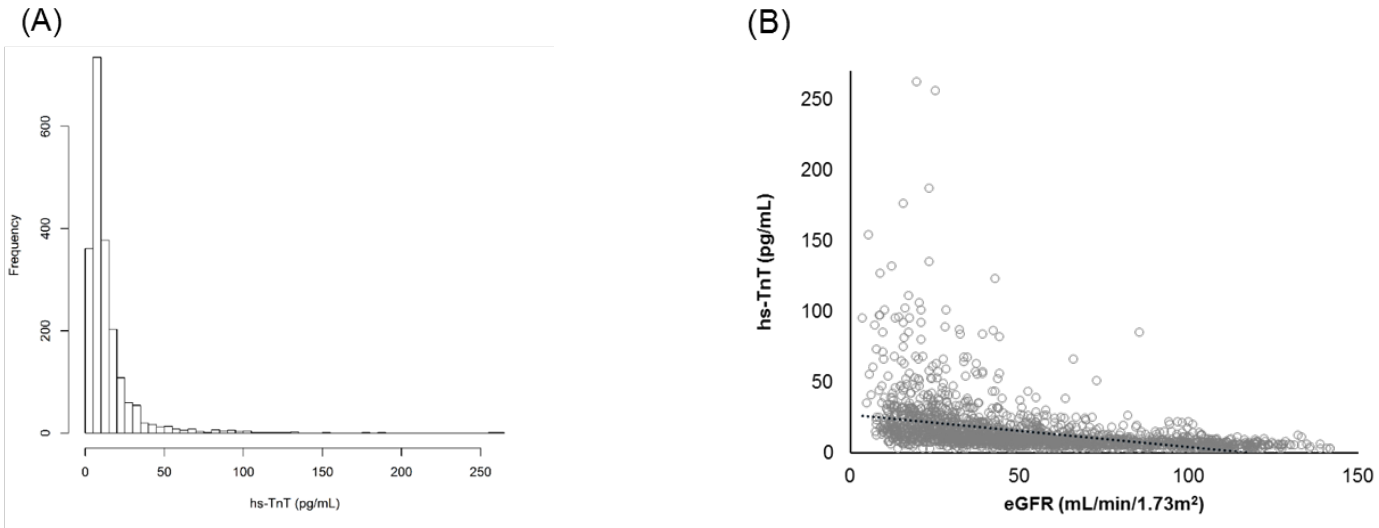


Figure 8 Distributions of hs-TnT in the KNOW-CKD cohort

(A) Histogram according to hs-TnT (B) Distribution of hs-TnT according to eGFR

Abbreviations: hs-TnT, high-sensitivity cardiac troponin T; KNOW-CKD, KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease; eGFR, estimated glomerular filtration rate

Baseline characteristics of the study population

The mean age of the subjects was 53.5 ± 12.2 years, and 1,229 (60.9%) patients were men (Table 7). The median (interquartile range [IQR]) hs-TnT level was 10.0 (6.0-16.0) pg/mL and the mean eGFR was 53.6 ± 30.9 mL/min/1.73 m^2. Subjects with higher hs-TnT levels were older and more likely to be male and tended to have lower eGFRs and higher systolic blood pressures. Additionally, the higher the hs-TnT concentration, the higher the percentage of patients diagnosed with diabetic or hypertensive nephropathy.

Overall, there were 483 patients (23.9%) with LVH on echocardiography. LV mass index increased gradually across the hs-TnT quartile groups. The proportion of concentric LVH, concentric remodeling and eccentric LVH all gradually increased across the quartiles of cardiac troponin T concentration (Figure 9). There were 21 patients (1.0%) with systolic dysfunction and 166 patients (8.2%) with diastolic dysfunction, respectively. The proportions of both LV dysfunction were higher in patients with higher hs-TnT levels than those with lower levels.

Table 7 Baseline characteristics of participants according to hs-TnT level

		Total (N=2,017)	TnT category (pg/mL) ≤6.0 (N=517)	>6.0-10.0 (N=579)	>10.0-16.0 (N=436)	>16.0 (N=485)	*P*	*P* for trend
Age (years)		53.5 ± 12.2	46.0 ± 10.6	51.6 ± 11.4	58.5 ± 10.9	59.1 ± 10.9	<0.001	<0.001
Sex (N, %)							<0.001	<0.001
	Female	788 (39.1)	288 (55.7)	223 (38.5)	155 (35.6)	122 (25.2)		
	Male	1229 (60.9)	229 (44.3)	356 (61.5)	281 (64.4)	363 (74.8)		
Body mass index (kg/m^2)		24.6 ± 3.4	24.0 ± 3.5	24.6 ± 3.2	24.7 ± 3.3	25.1 ± 3.4	<0.001	<0.001
Blood pressure								
	SBP (mmHg)	127.9 ± 16.2	125.0 ± 14.1	126.3 ± 14.8	127.7 ± 15.6	133.2 ± 18.9	<0.001	<0.001
	DBP (mmHg)	77.1 ± 11.1	78.3 ± 10.5	77.5 ± 10.3	75.7 ± 10.7	76.5 ± 12.7	0.002	<0.001
	Mean arterial pressure (mmHg)	94.0 ± 11.6	93.8 ± 10.9	93.8 ± 10.9	9± 11.0	95.4 ± 13.6	0.02	0.20
Current smoker (N, %)		325 (16.1)	79 (15.3)	97 (16.8)	76 (17.4)	73 (15.1)	<0.001	
Diabetes (N, %)		673 (33.4)	60 (11.6)	112 (19.3)	172 (39.4)	329 (67.8)	<0.001	<0.001
Hypertension (N, %)		1937 (96.0)	466 (90.1)	563 (97.2)	432 (99.1)	476 (98.1)	<0.001	<0.001
Coronary artery disease (N, %)		102 (5.1)	4 (0.8)	18 (3.1)	28 (6.4)	52 (10.7)	<0.001	<0.001
Cause of CKD (N, %)							<0.001	0.10
	Diabetic nephropathy	466 (23.1)	21 (4.1)	52 (9.0)	122 (28.0)	271 (55.9)		
	Glomerulonephritis	720 (35.7)	232 (44.9)	283 (48.9)	128 (29.4)	77 (15.9)		
	Hypertensive nephropathy	368 (18.2)	56 (10.8)	100 (17.3)	118 (27.1)	94 (19.4)		

	PKD		344 (17.1)	181 (35.0)	115 (19.9)	35 (8.0)	13 (2.7)	
	Unknown		119 (5.9)	27 (5.2)	29 (5.0)	33 (7.6)	30 (6.2)	
eGFR (mL/min/1.73 m^2)			53.6 ± 30.9	80.9 ± 28.9	58.6 ± 26.2	40.9 ± 21.7	29.8 ± 17.3	<0.001	<0.001
CKD stage (N, %)								<0.001	<0.001
	Stage 1		335 (16.6)	217 (42.0)	91 (15.7)	21 (4.8)	6 (1.2)		
	Stage 2		385 (19.1)	162 (31.3)	152 (26.3)	46 (10.6)	25 (5.2)		
	Stage 3a		328 (16.3)	72 (13.9)	131 (22.6)	85 (19.5)	40 (8.2)		
	Stage 3b		428 (21.2)	50 (9.7)	132 (22.8)	131 (30.0)	115 (23.7)		
	Stage 4		417 (20.7)	14 (2.7)	64 (1)	120 (27.5)	219 (45.2)		
	Stage 5		124 (6.1)	2 (0.4)	9 (1.6)	33 (7.6)	80 (16.5)		
Laboratory findings									
	CRP (mg/dL)		2.0 ± 5.2	1.5 ± 4.3	1.9 ± 4.6	2.2 ± 5.5	2.5 ± 6.5	0.01	<0.001
	HDL (mg/dL)		49.3 ± 15.5	54.2 ± 15.9	50.7 ± 14.7	46.3 ± 13.4	45.0 ± 15.9	<0.001	<0.001
	Triglyceride (mg/dL)		157.4 ± 97.9	144.6 ± 89.9	155.4 ± 98.4	163.2 ± 93.2	167.7 ± 107.5	0.001	
	Hemoglobin (g/dL)		12.9 ± 2.0	13.6 ± 1.7	13.4 ± 1.9	12.5 ± 2.0	11.7 ± 1.9	<0.001	<0.001
Urine protein/creatinine ratio (g/g, IQR)			0.5 (0.1-1.5)	0.3 (0.07-0.7)	0.3 (0.1-0.9)	0.5 (0.2-1.5)	1.4 (0.5-3.4)	<0.001	<0.001
Urine albumin/creatinine ratio (mg/mg, IQR)			347.7 (76.8-1052.1)	167.5 (27.9-530.0)	242.8 (59.1-665.7)	366.4 (83.3-1063.2)	997.0 (350.8-2378.9)	<0.001	<0.001
Data from echocardiography									
	LVM index (g/m$^{2.7}$)		41.9 ± 11.5	36.6 ± 9.0	39.7 ± 9.2	43.8 ± 10.7	48.3 ± 13.5	<0.001	<0.001
	LVH (N, %)		483 (23.9)	56 (10.8)	92 (15.9)	129 (29.6)	206 (42.5)	<0.001	<0.001
	LV geometry (N, %)							<0.001	<0.001
		Normal	1237 (61.3)	392 (75.8)	400 (69.1)	246 (56.4)	199 (41.0)		

Concentric LVH	245 (12.1)	38 (7.4)	58 (10.0)	55 (12.6)	94 (19.4)		
Concentric remodeling	294 (14.6)	57 (11.0)	87 (15.0)	70 (16.1)	80 (16.5)		
Eccentric LVH	236 (11.7)	29 (5.6)	33 (5.7)	64 (14.7)	110 (22.7)		
E/E'	9.9 ± 3.7	8.3 ± 2.4	9.2 ± 3.0	10.4 ± 3.8	11.9 ± 4.4	<0.001	<0.001
Ejection fraction (%)	64.2 ± 5.9	63.8 ± 5.6	64.7 ± 5.6	64.1 ± 5.8	64.2 ± 6.7	0.08	0.04
Systolic dysfunction (N, %)	21 (1.0)	2 (0.4)	4 (0.7)	4 (0.9)	11 (2.3)	<0.001	<0.001
Diastolic dysfunction (N, %)	166 (8.2)	8 (1.5)	26 (4.5)	47 (10.8)	85 (17.5)	<0.001	<0.001

Abbreviations: hs-TnT, high sensitivity troponin T; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; PKD, polycystic kidney disease; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; HDL, high density lipoprotein; IQR, interquartile range; LVM, left ventricular mass; LVH, left ventricular hypertrophy

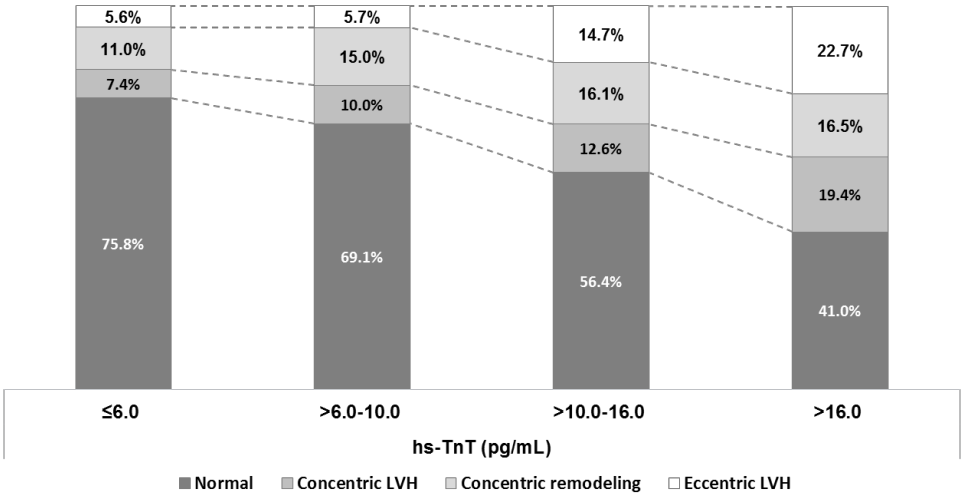


Figure 9 Elevated hs-TnT levels are associated with LVH in patients with CKD

With higher quartiles of hs-TnT, the prevalence of concentric and eccentric LVH and concentric remodeling increased.

Abbreviations: hs-TnT, high-sensitivity cardiac troponin T; LVH, left ventricular hypertrophy; CKD, chronic kidney disease

The association between hs-TnT and echocardiographic parameters

Table 8 summarizes the independent association between hs-TnT and echocardiographic parameters with multivariable analysis. At baseline, the two highest quartiles of hs-TnT were found to have an OR > 1.9 for LVH in the fully adjusted model (Figure 10, *P* for trend < 0.001). All subjects were stratified into two groups, based on eGFR 60 mL/min/1.73 m^2 in order to evaluate the modifying effect of renal impairment on the association between hs-TnT and echocardiographic parameters. The highest quartiles of hs-TnT were significantly associated with LVH in both the eGFR strata, suggesting the results were independent of renal function in multivariable analysis. No significant association between hs-TnT and systolic dysfunction was identified in multivariable analysis. Higher hs-TnT concentrations were independently associated with diastolic dysfunction in our fully adjusted model (*P* for trend < 0.001). In a stratified analysis according to eGFR, diastolic dysfunction continued to show a significant relationship with the highest hs-TnT range for both eGFR strata.

Table 8 Association between hs-TnT and LV structure and functional abnormalities according to eGFR

hs-TnT (pg/mL)	Odds of LVH*	*P*	Odds of systolic dysfunction†	*P*	Odds of diastolic dysfunction§	*P*
Total patients						
≤6.0	1.00 (reference)		1.00 (reference)		1.00 (reference)	
>6.0-10.0	1.13 (0.76-1.70)	0.55	1.06 (0.20-7.87)	0.95	2.52 (0.76-1.70)	0.032
>10.0-16.0	1.93 (1.24-3.02)	0.004	1.23 (0.20-10.07)	0.83	4.75 (1.24-3.02)	<0.001
>16.0	3.08 (1.90-5.04)	<0.001	2.20 (0.41-17.50)	0.39	8.15 (3.47-21.19)	<0.001
eGFR ≥60 mL/min/1.73 m^2						
≤6.0	1.00 (reference)		1.00 (reference)		1.00 (reference)	
>6.0-10.0	1.17 (0.65-3.47)	0.60	1.08 (0.08-14.00)	0.95	1.99 (0.64-6.87)	0.25
>10.0-16.0	1.51 (0.63-3.47)	0.34	3.91 (0.27-55.70)	0.29	2.08 (0.47-9.07)	0.32
>16.0	8.88 (3.06-26.19)	<0.001	6.02 (0.38-94.00)	0.18	8.46 (1.82-39.84)	0.006
eGFR <60 mL/min/1.73 m^2						
≤6.0	1.00 (reference)		1.00 (reference)		1.00 (reference)	
>6.0-10.0	0.92 (0.51-1.68)	0.77	1.05 (0.13-21.79)	0.96	2.04 (0.65-8.99)	0.27
>10.0-16.0	1.61 (0.90-2.94)	0.11	0.86 (0.09-18.87)	0.91	4.18 (1.40-18.08)	0.02
>16.0	2.34 (1.28-4.44)	0.007	1.63 (0.22-33.79)	0.68	6.92 (2.37-30.28)	0.002

Abbreviations: hs-TnT, high-sensitivity troponin T; LVH, left ventricular hypertrophy; eGFR, estimated glomerular filtration rate

*LVH: adjusted for age, sex, pulse pressure, diabetes, hypertension, history of coronary artery disease, chronic kidney disease stage, body mass index, high-density lipoprotein, triglyceride, and hemoglobin

†Systolic dysfunction: adjusted for age, sex, history of coronary artery disease, chronic kidney disease stage

§Diastolic dysfunction: Adjusted for age, sex, pulse pressure, chronic kidney disease stage, history of coronary artery disease, BMI, hemoglobin, HDL cholesterol

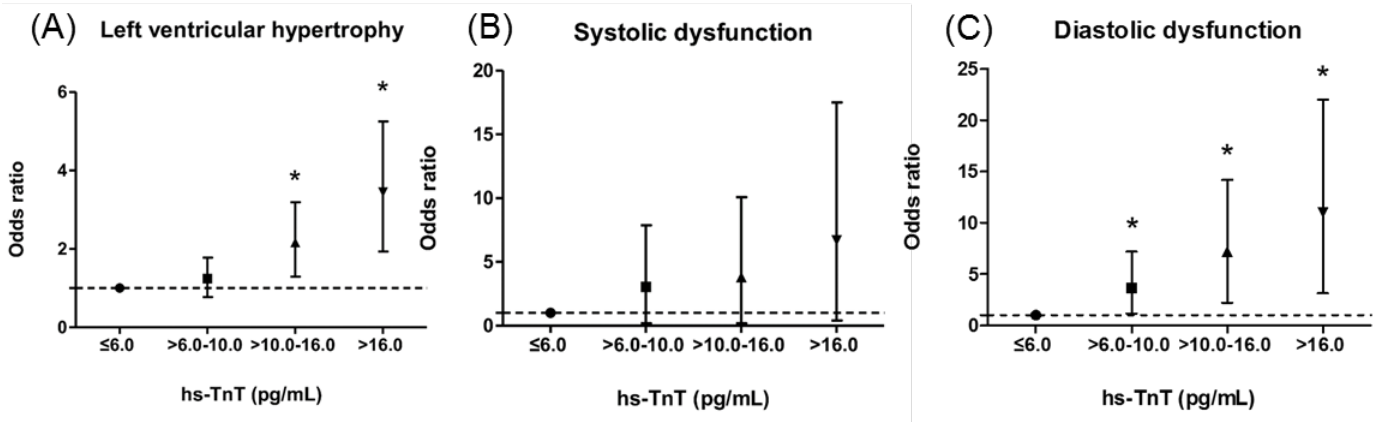


Figure 10 The association between hs-TnT and left ventricular structure and function at baseline echocardiography

(A) LVH: Adjusted for age, sex, pulse pressure, diabetes, hypertension, history of coronary artery disease, chronic kidney disease stage, body mass index, high-density lipoprotein, triglyceride, and hemoglobin

(B) Systolic dysfunction: Adjusted for age, sex, history of coronary artery disease, chronic kidney disease stage

(C) Diastolic dysfunction: Adjusted for age, sex, pulse pressure, chronic kidney disease stage, history of coronary artery disease, body mass index, hemoglobin, HDL cholesterol

Abbreviations: hs-TnT, high-sensitivity troponin T; LVH, left ventricular hypertrophy; HDL, high density lipoprotein

Evaluation of hs-TnT as a screening test for LVH and diastolic dysfunction

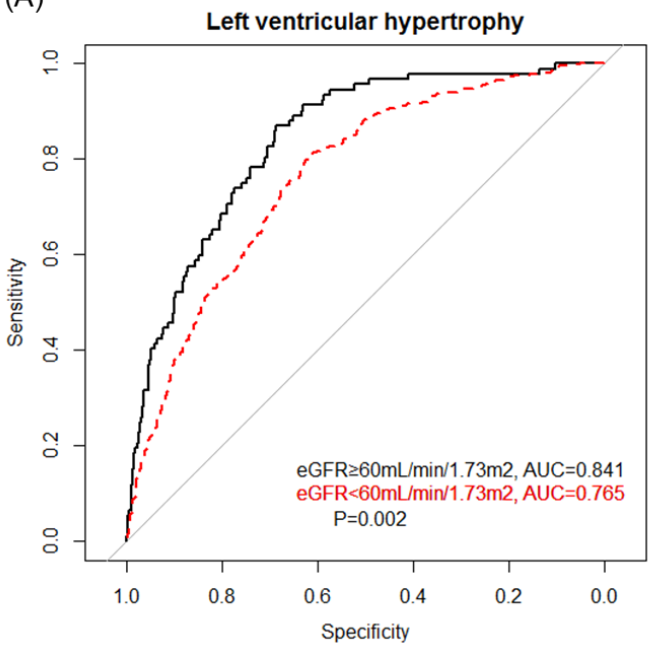
Next, it was evaluated whether hs-TnT as a continuous variable can be used as a screening test for LVH and LV function in the CKD population (Table 9). Levels of hs-TnT exhibited fair significance for the detection of each outcome. By ROC analysis, the optimized hs-TnT cut-off value for LVH was 9 pg/mL for patients with an eGFR ≥ 60 mL/min/1.73 m^2 and 15 pg/mL for those with an eGFR < 60 mL/min/1.73 m^2, respectively. With respect to diastolic dysfunction, the optimized hs-TnT cut-off values were 9 pg/mL and 14pg/mL for patients with eGFRs ≥ 60 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2, respectively. When comparing the multivariable ROC curves with other covariates for the two eGFR strata, the differences between the two curves were statistically significant for both LVH and diastolic dysfunction, not in systolic dysfunction (Figure 11).

Table 9 hs-TnT as a single diagnostic test for LVH and diastolic dysfunction

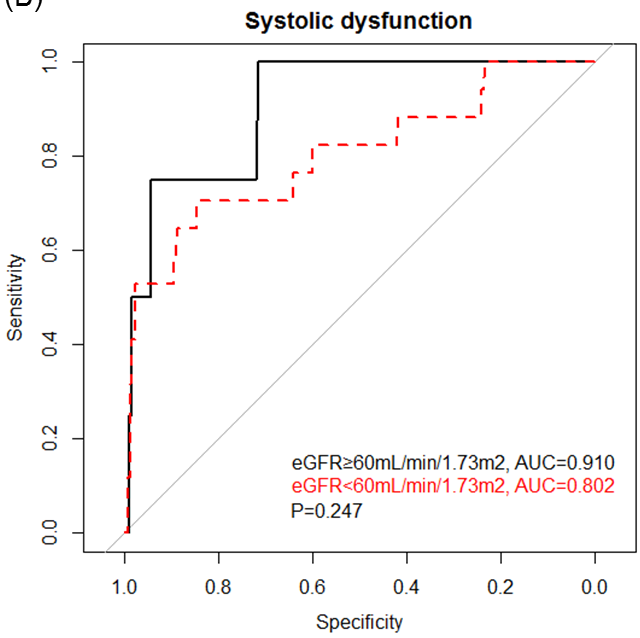
	AUC (95% CI)	Optimal cut off (pg/mL)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Positive likelihood ratio	Negative likelihood ratio
LVH								
Total participants	0.69 (0.66-0.72)	10	69.4	61.8	13.5	83.6	1.8	0.5
eGFR ≥ 60 mL/min/1.73 m^2	0.63 (0.58-0.68)	9	38.7	81.9	11.7	74.5	2.3	0.8
eGFR < 60 mL/min/1.73 m^2	0.64 (0.61-0.68)	15	56.2	63.9	24	57.2	1.4	0.5
Systolic dysfunction								
Total participants	0.69 (0.58-0.80)	16	52.4	76.3	0.7	97.7	2.2	0.4
eGFR ≥ 60 mL/min/1.73 m^2	0.78 (0.56-1.00)	8	75	76.1	0.2	98.3	3.1	0.3
eGFR < 60 mL/min/1.73 m^2	0.64 (0.49-0.79)	31	41.2	88.5	0.9	95.5	3.6	0.7
Diastolic dysfunction								
Total participants	0.74 (0.71-0.78)	12	79.5	57.3	3.5	83.6	2.2	0.4
eGFR ≥ 60 mL/min/1.73 m^2	0.71 (0.63-0.79)	9	54.3	80.2	2.4	90.3	2.2	0.4
eGFR < 60 mL/min/1.73 m^2	0.70 (0.65-0.74)	14	64.2	60.3	4.9	80.6	1.8	0.5

Abbreviations: hs-TnT, high-sensitivity cardiac troponin T; LVH, left ventricular hypertrophy; AUC, area under the curve; CI, confidence interval; eGFR, estimated glomerular filtration rate

(A)


Left ventricular hypertrophy
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
eGFR≥60mL/min/1.73m2, AUC=0.841
eGFR<60mL/min/1.73m2, AUC=0.765
P=0.002
1.0
0.8
0.6
0.4
0.2
0.0
Specificity

(B)


Systolic dysfunction
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
eGFR≥60mL/min/1.73m2, AUC=0.910
eGFR<60mL/min/1.73m2, AUC=0.802
P=0.247
1.0
0.8
0.6
0.4
0.2
0.0
Specificity

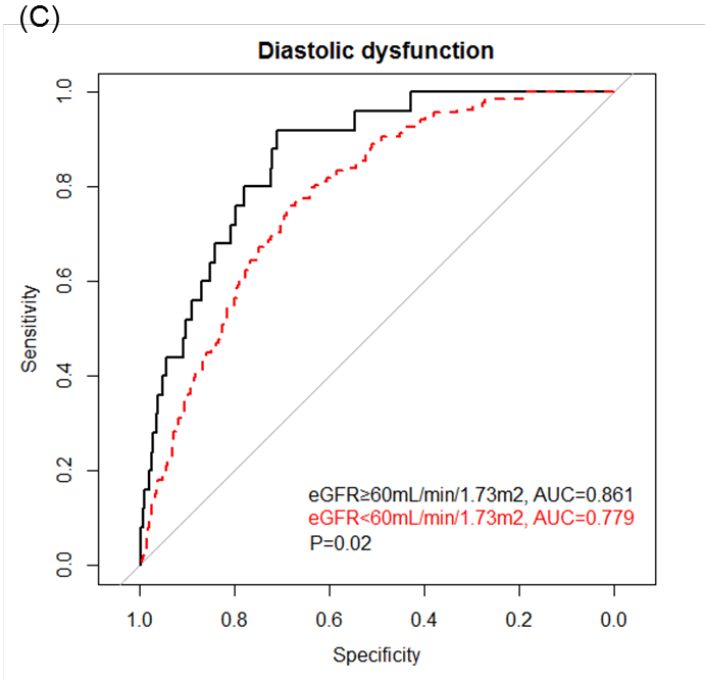


Figure 11 Receiver operating characteristic (ROC) curve and area under the curve (AUC) after adjustment for co-variables according to renal function

(A) LVH: Adjusted for age, sex, pulse pressure, diabetes, hypertension, history of coronary artery disease, chronic kidney disease stage, body mass index, high-density lipoprotein, triglyceride, and hemoglobin

(B) Systolic dysfunction: Adjusted for age, sex, history of coronary artery disease, chronic kidney disease stage

(C) Diastolic dysfunction: Adjusted for age, sex, Pulse Pressure, chronic kidney disease stage, history of coronary artery disease, body mass index, hemoglobin, HDL cholesterol

Abbreviations: LVH, left ventricular hypertrophy; HDL, high density lipoprotein

The association between hs-TnT and new changes in LV structure and function

Among all 2,017 enrolled patients, 864 patients underwent follow-up echocardiography after 4 years of follow-up. Patients were excluded who were previously diagnosed with LVH at baseline echocardiography, 86 (12.3%) out of 698 patients developed new LVH. Among 828 patients who did not have diastolic dysfunction at baseline, 44 (5.3%) patients developed new diastolic dysfunction at 4 years. Only seven patients were diagnosed with new systolic dysfunction. The percentage of patients who developed new LVH and new diastolic dysfunction increased with elevation of hs-TnT levels. In terms of LV geometry at 4 years, the results were similar to the baseline, in that each proportion of concentric LVH, concentric remodeling, and eccentric LVH, respectively, increased across the quartiles of cardiac troponin T concentration (Figure 12). Finally, multivariable analysis showed that increased hs-TnT was related to new LVH (Figure 13A, *P* for trend <0.001), but not to diastolic dysfunction (Figure 13B, *P* for trend = 0.262).

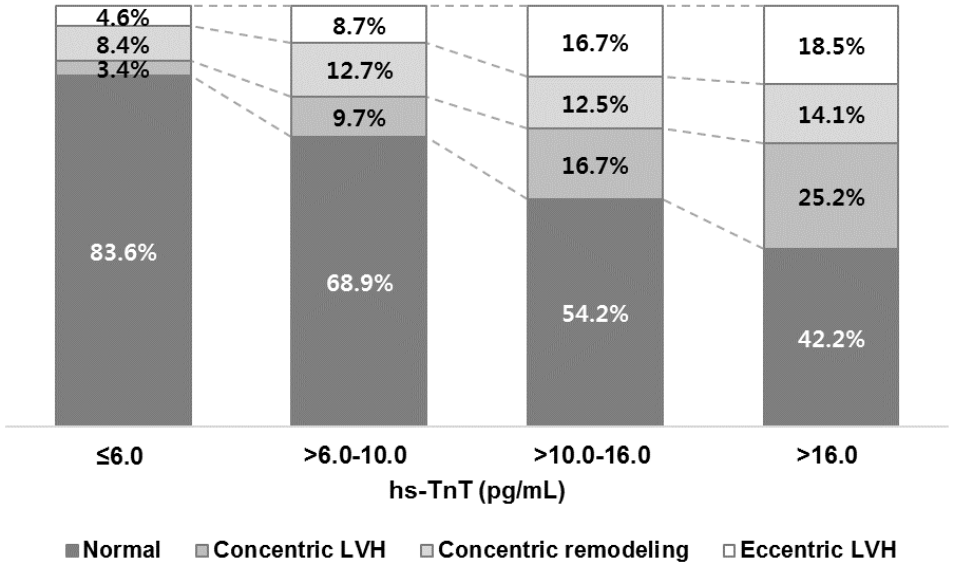


Figure 12 Elevated hs-TnT are associated with new LVH in patients with CKD

Abbreviations: hs-TnT, high-sensitivity cardiac troponin T; LVH, left ventricular hypertrophy; CKD, chronic kidney disease

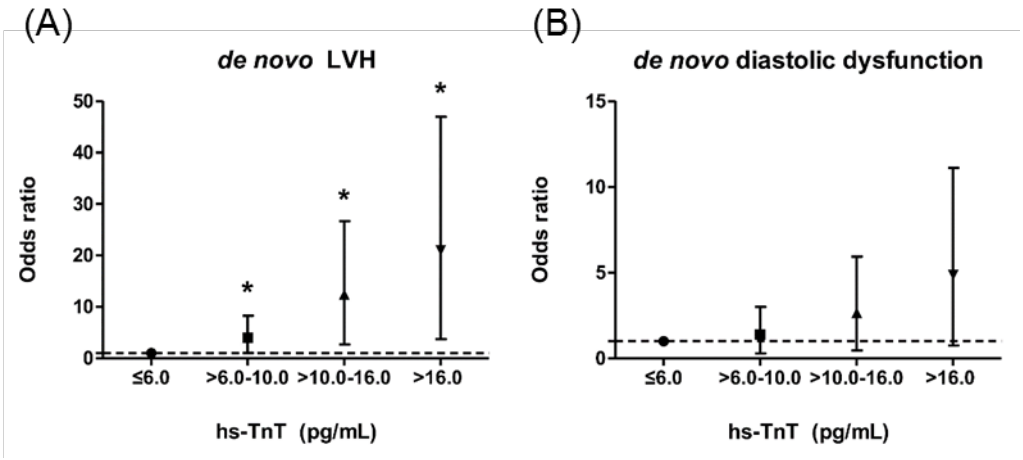


Figure 13 The association between hs-TnT and follow-up echocardiography

(A) LVH: Adjusted for age, sex, pulse pressure, diabetes, hypertension, history of coronary artery disease, chronic kidney disease stage, body mass index, high-density lipoprotein, triglyceride, and hemoglobin

(B) Diastolic dysfunction: Adjusted for age, sex, pulse Pressure, chronic kidney disease stage, history of coronary artery disease, body mass index, hemoglobin, HDL cholesterol

Abbreviations: hs-TnT, high-sensitivity troponin T; LVH, left ventricular hypertrophy; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein;

Sensitivity analysis except for patients previously diagnosed with coronary artery disease

Table 10 summarizes the baseline characteristics of patients without coronary artery disease at study entry. A total of 1,901 patients were included in the sensitivity analysis after the exclusion of the participants with a history of coronary artery disease. LV mass index was increased gradually according to the increment of hs-TnT quartile groups. The proportion of concentric LVH, concentric remodeling and eccentric LVH all gradually increased across the hs-TnT quartile groups. There were 435 patients (22.9%) with LVH, 11 patients (0.6%) with systolic dysfunction and 150 patients (7.9%) with diastolic dysfunction, respectively. The proportions of diastolic dysfunction were higher in patients with higher hs-TnT concentrations than those with lower concentrations. The distribution of most variables was similar to the main analysis.

Table 10 Baseline characteristics according to hs-TnT concentration in the patients without previous history of coronary artery disease

			hs-TnT category (pg/mL)				
		Total	**≤6.0**	**>6.0-10.0**	**>10.0-16.0**	**>16.0**	***P* value**
		(N=1901)	**(N=511)**	**(N=559)**	**(N=407)**	**(N=424)**	
Age (years)		52.9 ± 12.2	45.8 ± 10.5	51.3 ± 11.4	58.1 ± 11.0	58.7 ± 11.0	<0.001
Sex							<0.001
	Female (N, %)	769 (40.5%)	288 (56.4%)	218 (39.0%)	151 (37.1%)	112 (26.4%)	
	Male (N, %)	1132 (59.5%)	223 (43.6%)	341 (61.0%)	256 (62.9%)	312 (73.6%)	
Body mass index (kg/m^2)		24.5 ± 3.4	23.9 ± 3.5	24.6 ± 3.3	24.7 ± 3.4	25.0 ± 3.4	<0.001
Blood pressure							
	SBP (mmHg)	127.8 ± 16.2	124.9 ± 14.1	126.2 ± 14.9	127.6 ± 15.7	133.4 ± 19.1	<0.001
	DBP (mmHg)	77.2 ± 11.1	78.3 ± 10.5	77.6 ± 10.4	75.9 ± 10.8	76.8 ± 12.7	0.008
	Mean arterial pressure (mmHg)	94.1 ± 11.7	93.9 ± 10.9	93.8 ± 11.0	93.1 ± 11.2	95.7 ± 13.7	0.012
Diabetes (N, %)		600 (31.6%)	60 (11.7%)	102 (18.2%)	156 (38.3%)	282 (66.5%)	<0.001
Hypertension (N, %)		1823 (95.9%)	460 (90.0%)	543 (97.1%)	404 (99.3%)	416 (98.1%)	<0.001

Current smoker (N, %)		306 (16.1%)	77 (15.1%)	92 (16.5%)	73 (17.9%)	64 (15.1%)	<0.001
Cause of CKD (N, %)							<0.001
	Diabetic nephropathy	706 (37.1%)	230 (45.0%)	281 (50.3%)	123 (30.2%)	72 (17.0%)	
	Glomerulonephritis	410 (21.6%)	21 (4.1%)	44 (7.9%)	109 (26.8%)	236 (55.7%)	
	Hypertensive nephropathy	335 (17.6%)	53 (10.4%)	92 (16.5%)	108 (26.5%)	82 (19.3%)	
	ADPKD	341 (17.9%)	180 (35.2%)	114 (20.4%)	35 (8.6%)	12 (2.8%)	
	Unknown	109 (5.7%)	27 (5.3%)	28 (5.0%)	32 (7.9%)	22 (5.2%)	
eGFR (mL/min/1.73 m^2)		54.5 ± 31.2	81.1 ± 28.9	58.8 ± 26.4	41.0 ± 21.8	29.6 ± 17.6	<0.001
CKD stage (N, %)							<0.001
	Stage 1	332 (17.5%)	216 (42.3%)	90 (16.1%)	20 (4.9%)	6 (1.4%)	
	Stage 2	371 (19.5%)	160 (31.3%)	147 (26.3%)	43 (10.6%)	21 (5.0%)	
	Stage 3a	306 (16.1%)	70 (13.7%)	124 (22.2%)	80 (19.7%)	32 (7.5%)	
	Stage 3b	399 (21.0%)	49 (9.6%)	128 (22.9%)	121 (29.7%)	101 (23.8%)	
	Stage 4	374 (19.7%)	14 (2.7%)	61 (10.9%)	111 (27.3%)	188 (44.3%)	
	Stage 5	119 (6.3%)	2 (0.4%)	9 (1.6%)	32 (7.9%)	76 (17.9%)	
Laboratory findings							
	CRP (mg/dL)	2.0 ± 5.3	1.5 ± 4.3	1.9 ± 4.6	2.2 ± 5.7	2.6 ± 6.7	0.014
	HDL (mg/dL)	49.6 ± 15.5	54.4 ± 15.9	51.0 ± 14.7	46.8 ± 13.5	44.8 ± 16.0	<0.001

Triglyceride (mg/dL)	157.0 ± 98.9	144.2 ± 89.8	155.4 ± 99.3	162.3 ± 94.8	169.1 ± 110.1	0.001
Hemoglobin (g/dL)	12.9 ± 2.0	13.6 ± 1.7	13.4 ± 1.9	12.5 ± 2.0	11.7 ± 1.9	<0.001
Urine protein/creatinine ratio (g/g, IQR)	1.2 ± 2.0	0.6 ± 0.9	0.8 ± 1.3	1.1 ± 1.6	2.6 ± 3.2	<0.001
Urine albumin/creatinine ratio (mg/mg, IQR)	852.7 ± 1361.9	426.5 ± 642.7	576.3 ± 906.8	798.1 ± 1090.6	1781.4 ± 2100.4	<0.001
Data from echocardiography						
LVM index ($g/m^{2.7}$)	41.5 ± 11.3	36.6 ± 8.9	39.7 ± 9.2	43.5 ± 10.6	47.9 ± 13.5	<0.001
LVH (N, %)	435 (22.9%)	54 (10.6%)	90 (16.1%)	116 (28.5%)	175 (41.3%)	<0.001
LV geometry (N, %)						<0.001
Normal	1190 (62.6%)	387 (75.7%)	391 (69.9%)	232 (57.0%)	180 (42.5%)	
Concentric LVH	223 (11.7%)	38 (7.4%)	56 (10.0%)	50 (12.3%)	79 (18.6%)	
Concentric remodeling	269 (14.2%)	56 (11.0%)	79 (14.1%)	67 (16.5%)	67 (15.8%)	
Eccentric LVH	214 (11.3%)	29 (5.7%)	32 (5.7%)	57 (14.0%)	96 (22.6%)	
E/E’	9.8 ± 3.7	8.3 ± 2.4	9.1 ± 3.0	10.4 ± 3.9	11.9 ± 4.5	<0.001
Ejection fraction (%)	64.4 ± 5.7	63.8 ± 5.5	64.7 ± 5.6	64.3 ± 5.8	64.7 ± 6.0	0.045
Systolic dysfunction (N, %)	11 (0.6%)	1 (0.2%)	4 (0.7%)	4 (1.0%)	2 (0.5%)	0.438
Diastolic dysfunction (N, %)	150 (7.9%)	7 (1.4%)	24 (4.3%)	45 (11.1%)	74 (17.5%)	<0.001

Abbreviations: hs-TnT, high sensitivity troponin T; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; PKD, polycystic kidney disease; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; HDL, high density lipoprotein; IQR, interquartile range; LVM, left ventricular mass; LVH, left ventricular hypertrophy

Table 11 showed the results of the independent relationship between hs-TnT and clinical outcomes. At baseline, the two highest quartiles of hs-TnT exhibited an OR > 1.9 for LVH in the multivariable analysis (Figure 14). LVH continued to show a statistically significant relationship between the highest hs-TnT concentrations for both eGFR strata. No significant association between hs-TnT and systolic dysfunction was observed on multivariable analysis because the number of participants with systolic dysfunction was very low. Additionally, higher hs-TnT levels were related to diastolic dysfunction in the fully adjusted model (*P* for trend <0.001). In a stratified analysis according to eGFR 60mL/min/1.73m^2, statistical significance for the association between diastolic dysfunction and hs-TnT was observed for both eGFR strata.

Table 11 The association between hs-TnT and left ventricular structure according to renal function in the patients without previous history of coronary artery disease

hs-TnT (pg/mL)	Odds of LVH*	*P*	Odds of systolic dysfunction†	*P*	Odds of diastolic dysfunction§	*P*
Total patients						
≤6.0	1.00 (reference)		1.00 (reference)		1.00 (reference)	
>6.0-10.0	1.20 (0.79-1.85)	0.39	2.34 (0.41-24.33)	0.36	3.00 (1.22-8.54)	0.024
>10.0-16.0	1.92 (1.20-3.08)	0.007	4.60 (0.69-52.18)	0.12	5.95 (2.38-17.23)	<0.001
>16.0	3.05 (1.81-5.20)	<0.001	2.71 (0.27-36.51)	0.39	9.78 (3.71-29.61)	<0.001
eGFR ≥60 mL/min/1.73 m^2						
≤6.0	1.00 (reference)		1.00 (reference)		1.00 (reference)	
>6.0-10.0	1.36 (0.74-2.50)	0.33	3.80 (0.19-586.60)	0.39	1.65 (0.44-6.92)	0.46
>10.0-16.0	1.69 (0.69-4.04)	0.24	19.56 (0.93-2999.91)	0.06	1.72 (0.33-8.91)	0.51
>16.0	11.31 (3.49-37.83)	<0.001	34.81 (1.52-5672.45)	0.03	14.45 (2.95-78.34)	0.001
eGFR <60 mL/min/1.73 m^2						
≤6.0	1.00 (reference)		1.00 (reference)		1.00 (reference)	
>6.0-10.0	0.98 (0.54-1.86)	0.96	1.22 (0.19-12.99)	0.84	2.94 (0.79-19.06)	0.16
>10.0-16.0	1.73 (0.96-3.25)	0.08	1.58 (0.23-17.59)	0.65	6.30 (1.79-40.03)	0.02
>16.0	2.72 (1.47-5.23)	0.002	0.58 (0.04-7.81)	0.65	9.35 (2.62-59.85)	0.003

Abbreviations: hs-TnT, high-sensitivity troponin T; LVH, left ventricular hypertrophy; eGFR, estimated glomerular filtration rate

*LVH: adjusted for age, sex, pulse pressure, diabetes, hypertension, chronic kidney disease stage, body mass index, high-density lipoprotein cholesterol, triglyceride, and hemoglobin

†Systolic dysfunction: adjusted for age, sex, chronic kidney disease stage

§Diastolic dysfunction: Adjusted for age, sex, pulse Pressure, chronic kidney disease stage, body mass index, hemoglobin, high-density lipoprotein cholesterol

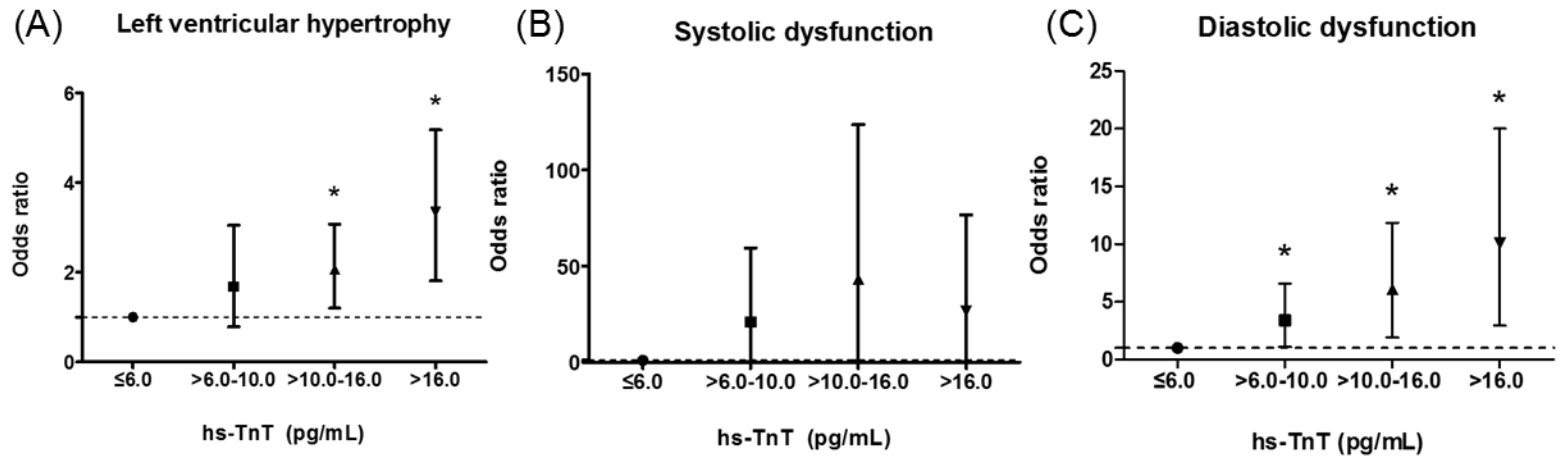


Figure 14 The association between hs-TnT and left ventricular structure and function in the patients without previous history of coronary artery disease

(A) LVH: adjusted for age, sex, pulse pressure, diabetes, hypertension, chronic kidney disease stage, body mass index, high-density lipoprotein cholesterol, triglyceride, and hemoglobin

(B) Systolic dysfunction: adjusted for age, sex, chronic kidney disease stage

(C) Diastolic dysfunction: Adjusted for age, sex, pulse Pressure, chronic kidney disease stage, body mass index, hemoglobin, high-density lipoprotein cholesterol

Abbreviations: hs-TnT, high-sensitivity troponin T; LVH, left ventricular hypertrophy;

Among 1,901 patients, 825 participants received follow-up echocardiography after 4 years of follow-up. Subjects were excluded who were previously diagnosed with LVH at baseline echocardiography, 75 (11.2%) out of 669 patients developed new LVH. Among 774 patients who did not have diastolic dysfunction at baseline, 38 (4.9%) patients developed new diastolic dysfunction in the 4th year after study entry. The percentage of participants who developed new LVH and diastolic dysfunction increased with the increment of hs-TnT concentrations.

Finally, multivariable analysis showed that increment of hs-TnT concentrations had an independent association with new LVH (Figure 15A), but not with new diastolic dysfunction (Figure 15B).

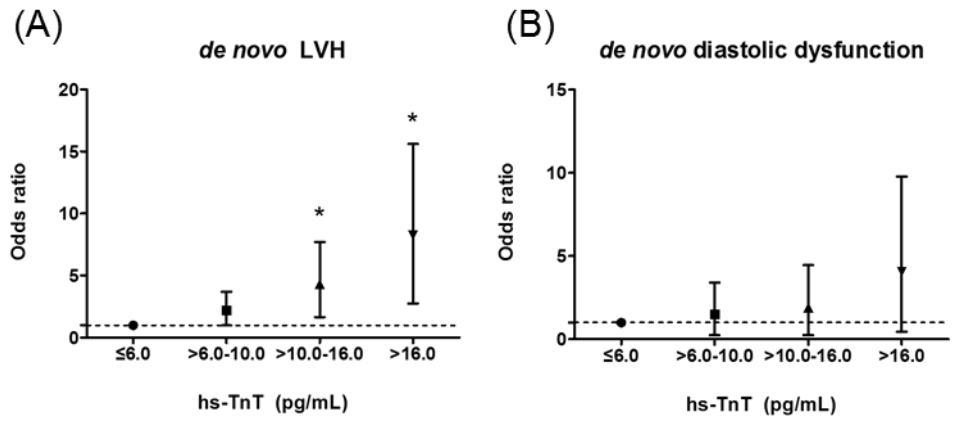


Figure 15 The association between hs-TnT and follow-up echocardiography in the patients without previous history of coronary artery disease

(A) LVH: Adjusted for age, sex, pulse pressure, diabetes, hypertension, chronic kidney disease stage, body mass index, high-density lipoprotein, triglyceride, and hemoglobin

(B) Diastolic dysfunction: Adjusted for age, sex, pulse pressure, chronic kidney disease stage, body mass index, hemoglobin, HDL cholesterol

Abbreviations: hs-TnT, high-sensitivity troponin T; LVH, left ventricular hypertrophy; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein;

Chapter 4. Discussion

4.1 Socioeconomic status and echocardiographic parameters

In the first part of this study, I performed a cross-sectional analysis for the relationships between SES and LVH, diastolic dysfunction in a CKD population using the data from the KNOW-CKD cohort. LVH was associated with parameters of SES, such as educational attainment and monthly income level, and these associations had graded responses. Additional analyses were conducted to clarify the association between SES and LVH, adjusting for BMI, sex, age, blood pressure, DM, CKD stage and physical activity. After adjustment, lower education and income level remained a statistically significant determinant of LVH in total participants and patients with age ≥ 50 years, not with age <50 years. In terms of diastolic dysfunction, the OR for diastolic dysfunction gradually increased with lowering of the monthly income level in the adjusted analysis, however, such a tendency was not observed with respect to educational attainment.

Compared with the statistical data of the Organization for Economic Co-operation and Development (OECD) statistics, the proportions of college graduates or above among the subjects at 25 – 45 years of age, were 69% for Koreans and 42% for the average OECD countries, respectively, while among those at 55-64 years of age,

they are 18% in Korea and 26% in OECD average.(71, 72) Namely, since most of the younger Korean population are college graduates, educational attainment is not a suitable factor for evaluating the SES among younger Korean CKD patients. In such respect, statistical significance according to educational attainment remained only in the subjects at the age of 50 or older. In view of the monthly income level, the value of OR was gradually increased in both groups according to age. However, there is no statistical significance in the younger age group. This is probably due to the low prevalence of LVH in younger patients compared to the older group (11.8% in the patients with age <50 vs. 27.8% in the patients with age ≥50 years.

Usually, SES is defined by education, employment, income and poverty, and these indicators could influence one's access to medical care and social support through insurance, housing stability, and quality, accessibility to healthy food and degree of stress.(44) Since numerous complex interactions between the selected social determinants of health exist, it is difficult to elucidate the mechanism for the association between SES and many clinical outcomes regarding the incidence, progression of disease and mortality. In particular, low educational attainment has indirect effects on one's understanding of the disease and medical treatment. Low income level could affect one's ability to engage in healthy behavior and access to healthcare services. It is important to identify clinical outcomes influenced by SES because some determinants could be modified by government policies, social support for access medical care, and efforts of physicians and community members.

Explanations for the differences in the burden of LVH between various strata of socio-economic status remain speculative, but there are several potential reasons why lower SES could be an independent risk factor for LVH. First, socioeconomically disadvantaged patients tend to receive less vigorous treatment because of poorer access to medical care.(73) It is well known that early referral to a nephrologist improves clinical outcomes in CKD patients (74, 75) due to timely and proper management for the prevention of disease progression. The primary health insurance system of South Korea is the National Health Insurance (NHI), and nearly 96% of the total Korean population joined this NHI program.(75) It guarantees basic medical care including in-patient and out-patient health service, preventive care and prescription drugs, based on the co-payment system.(76) However, with the rapid expansion of the enrolled population, the NHI has been under heavy burdens due to increased medical expenditure.(77) Inevitably, the NHI program had to restrict the range of covered medical services at the possible level.(78) Therefore, some medical services or medical tests at high costs are not covered by the NHI, rendering them not easily accessible to individuals at low SES. Besides, low SES leads to a decreased understanding of treatment plans and poor compliance, which results in late diagnosis and disease progression.

Second, sympathetic stimulation is one of the mechanisms of LVH in low SES. The role of stress in health has been investigated since the 1950s(79) and the association between stress and cardiovascular disease is well known.(80-83)

Sympathetic nervous system activity increases with various environmental factors, including low SES and stress. Lower SES is an important factor in psychosocial stress relative to higher SES.(83) It has been reported that chronic adrenergic stimulation can cause increased left ventricular mass.(84) Moreover, patients with CKD may be unable to adapt easily to stressful situations because stress hormones are metabolized and cleared by the kidney.(85) Patients with CKD may present inappropriate reactions to chronic stress. Thus, CKD patients with lower SES might be subjected both to more stress, and inappropriate responses to the stress.

Dietary differences between low and high SES groups are also related to LVH. One study reported that increased sodium retention might increase the risk of LVH by activation of the renin-angiotensin system and volume expansion.(86) Sodium intake tended to be higher among individuals with low SES.(87-89) In a study carried out among Chinese individuals, more educated participants had a lower intake of salt and soy sauce compared with less-educated individuals.(90) This tendency might also be present in CKD populations, and dietary differences could contribute to a greater risk of LVH by sodium intake differences. Although this study did not collect dietary information, I attempted to evaluate sodium intake by measuring 24-hour urine sodium excretion, as it might reflect dietary sodium intake.(91, 92) However, our data did not show a significant difference in 24-hour urine sodium excretion with respect to educational attainment or income level. Since the main source of sodium intake in the western countries is processed foods

(77% in the United States and 65-70% in the United Kingdom), people with low SES are less likely to have access to fresh food, thus, they are more likely to consume more processed food. In other words, the more processed food consumed, the more sodium intake. However, in South Korea, the main sources of salt intake are Kimchi, soup, and stew, and these are easily accessible to anyone regardless of SES. Therefore, in Korea, personal salt intake depends more heavily on the personal salt preference, rather than on the SES of the individual. In addition, though adults should consume less than 2,000 mg of sodium, or 5 grams of salt per day according to guidelines issued by the World Health Organization (WHO)(93), Korean sodium intake is very high, because Korean food is generally very salty. In fact, looking at the Korea National Health and Nutrition Examination Survey (KNHANES) data, the amount of sodium intake in Korea is 3,669 mg, far exceeding 2,000 mg.(94)

Anemia has been shown to be an independent risk factor for LVH in CKD patients.(95, 96) The relationship between SES and anemia has been assessed primarily among adolescents and reproductive-aged women, for whom low SES is an important risk factor for anemia.(97, 98) Low intake among low SES populations also has been well established.(8, 99) In our subjects, anemia was more prevalent in the lowest educational group. Based on the above findings, I hypothesized that low SES might be associated with anemia, which, in turn, might lead to LVH. This study showed that the inclusion of anemia as a covariate in the

multivariate analysis could not affect the significant association between both SES parameters and LVH in the total participants. Namely, other social determinants affected by SES but not included in the analysis might contribute to LVH. Further studies are warranted for elucidating the interconnected mechanism underlying the association between SES and LVH.

In terms of diastolic dysfunction, various comorbidities associated with the development of heart failure including diabetes,(100) hypertension,(101) peripheral vascular disease,(102) coronary heart disease,(103) anemia(104) and renal dysfunction(105) in the general populations. It was reported that the prevalence and clinical outcomes related to these comorbidities are associated with SES.(97, 106-110) In this study, I could not confirm these comorbidities act as confounders between SES and diastolic dysfunction. Further studies are needed to find out the confounding factors.

This study is the first, to our knowledge, to elucidate that lower SES is an independent risk factor of LVH and diastolic dysfunction among the CKD population. However, several limitations exist. First, although LVH and diastolic dysfunction are influenced by many factors, and I tried to adjust as many factors as possible related to health and dietary behavior, there still remains a possibility for a residual confounder. Since this study was conducted as a cross-sectional analysis, I could not determine causality between SES and changes in

echocardiographic parameters. However, longitudinal follow-up of the same study subjects will show us the causal relationship between SES and CV outcome. Second, I have excluded those who did not respond to the self-questionnaire and LV mass measurement or E/e'. Because these patients are more likely to have poor compliance, it might influence the results. In addition, because information on the income and educational status was based only on the self-report, there may be a reporting bias. Although echocardiography was performed at each of nine participating centers, the data coordinating center of the KNOW-CKD Study collected each measurement parameter, calculated LV mass index, and relative wall thickness and classified LV geometry following uniform criteria from the American Society of Echocardiography.(62) Lastly, the study enrolled only ethnic Korean patients; thus, it cannot provide information on the ethnic disparities in CKD.

In summary, I identified a novel relationship between SES and echocardiographic parameters in CKD patients. Lower SES, defined by educational attainment and monthly income level, is an independent factor for LVH among CKD patients. The monthly income level significantly associated with diastolic dysfunction. Further studies are needed to explore the causal relationships between the SES and adverse cardiovascular outcomes in the CKD population, to address factors related to socio-environmental causes of changes of echocardiographic parameters to develop preventive strategies for CV mortality in patients with kidney disease. Such efforts

will minimize socio-economic disparities, and improve CV outcomes for patients with CKD.

4.2 hs-TnT and echocardiographic parameters

In the second part of the study, the relationship between hs-TnT and LV structure and function was investigated in CKD patients with mild-to-severe renal dysfunction. Consistent with previous reports (111-113), increased TnT was independently associated with LVH. To our knowledge, this is the 1st study regarding the association between diastolic dysfunction and hs-TnT in predialysis CKD patients. Given that hs-TnT is elevated with lowering of renal function (67, 114), further analyses were conducted with stratification of the subjects into two subgroups based on renal function as determined by eGFR. Elevated hs-TnT was significantly associated with LVH and diastolic dysfunction in both eGFR strata.

As techniques for measuring biomarkers have become more sensitive, it is now easier to detect TnT using a highly sensitive assay. Importantly, there is growing evidence that elevated hs-TnT levels in the chronic setting with no cardiac symptoms and without acute coronary syndrome may indicate the presence of chronic subclinical myocardial damage (64-66). However, a previous retrospective observational study showed that a reduced eGFR is associated with a gradual increase in hs-TnT at the

individual and population levels, meaning there is an inverse relationship between hs-TnT and eGFR (114). It is not clear whether chronic elevation of cardiac troponin levels in CKD patients is related to decreased renal clearance or increased cardiac release. Considering the relationship between renal function and hs-TnT, it remains unclear whether the detection of hs-TnT in asymptomatic patients is meaningful for identifying chronic myocardial damage. Thus, one of the greatest advantages of the present study is our assessment of the association between hs-TnT levels and cardiac structural and functional abnormalities across various stages of CKD, from relatively preserved renal function to severe renal dysfunction.

This study showed that the distribution of hs-TnT was different according to the cause of CKD. As mentioned above, there is an inverse relationship between eGFR and hs-TnT concentrations. In the KNOW-CKD cohort, patients with various CKD stages from CKD stage 1 to 5 (predialysis) were included, also, the percentage of advanced CKD (stage 4 and 5) was the highest in our diabetic nephropathy group and the lowest in the polycystic kidney disease group.(115) Thus, the higher hs-TnT concentration, the higher the percentage of patients diagnosed with diabetic or hypertensive nephropathy due to the advanced stage of renal function. One of the other mechanisms of this phenomenon is that people with diabetes have significantly higher hs-TnT values than those without diabetes.(116) Further studies for patients with similar CKD stages within each CKD cause are needed to confirm this observation.

Explanations of the relationship between hs-TnT and LV structural and functional abnormalities remain speculative. LVH is caused by LV pressure and/or volume overload in an attempt to maintain wall stress, which in turn leads to myocyte death that may be further exacerbated by decreased coronary perfusion, and uremia (112, 117). In particular, uremia is one of the important factors for changing myocardial structure regardless of pressure and volume overload in both animal and human studies (118, 119). Renal impairment provokes accumulation of hypertrophic substances related to uremia such as endothelin 1, parathyroid hormone, tumor necrosis factor α, an interleukins 1α and 6 (120). In addition, LVH may lead to a release of hs-TnT in the hypertrophied heart, possibly reflecting changes in cell membrane permeability and myocardial protein turnover (111, 121). Decreased elimination of hs-TnT by the kidney has been suggested as one of the causes (67, 122), however, recently there is a controversy.

Systolic and diastolic dysfunction are associated with increased hs-TnT in both general population (64, 65) and in patients with ESRD (22, 123, 124). Studies on non-dialysis dependent CKD patients are rare, thus the results of the present study may help to enrich our understanding of the relationship between hs-TnT, CKD, and CV disease. Indeed, an independent association was observed between the highest quartile of hs-TnT group and diastolic dysfunction, independent of renal function. In contrast to the CRIC study (111), an association between hs-TnT and systolic dysfunction was not identified in our study; however, hs-TnT was associated with

diastolic dysfunction in the present study. s, Subjects who were previously diagnosed with congestive heart failure (New York Heart Association function class III or IV) were excluded in the enrollment of the KNOW-CKD cohort. Therefore, it was difficult to perform additional analysis for systolic dysfunction.

The results of the present study suggest hs-TnT as a useful screening test for LVH and diastolic dysfunction, irrespective of renal function, prior to additional costly evaluation such as echocardiographic study. Specifically, there were statistically significant differences between the AUCs according to renal function for both LVH and diastolic dysfunction. An additional analysis was carried out to identify the optimal value of hs-TnT and the ideal cut-off values for hs-TnT were higher in patients with a lower eGFR for both LVH and diastolic dysfunction. These findings suggest that hs-TnT might be affected by renal function. However, because of the low prevalence of LVH and diastolic dysfunction among the study participants, the positive predictive values were very low. Positive and negative likelihood ratios were calculated to reduce the influence of low prevalence and the results suggested that hs-TnT alone has some limitation as a definitive screening test for LVH and diastolic dysfunction. However, considering that echocardiography is a very expensive test, the present study showed the possibility of hs-TnT as a simple and cost-effective test for risk stratification for subjects who need further cardiac evaluation.

To elucidate the temporal relationship between hs-TnT and LV structural and functional abnormalities, additional analyses were conducted with longitudinal follow-up data. Follow-up echocardiography at 4 years was offered to all the subjects, irrespective of cardiac symptoms. Subjects who died or developed the end-stage renal disease before 4 years of follow-up, or who have not reached a 4-year follow-up did not perform the repeat echocardiography. Higher hs-TnT levels were associated only with new LVH, and not with diastolic dysfunction. However, because the number of participants who underwent follow-up echocardiography was small, further analyses will be warranted to elucidate the causal relationships between hs-TnT and new changes in cardiac structure and function.

There were several limitations of this study that deserve attention. First, I depended on a single hs-TnT measurement and were thus unable to perform additional analyses into changes of hs-TnT levels over time. Secondly, this study was conducted exclusively in an Asian population without pre-existing severe heart failure. In addition, there were relatively few patients with systolic dysfunction, which limited statistical power. Additionally, echocardiographic interpretations could be prone to poor inter-rater reliability depending on the settings, and the echocardiography was conducted by different echocardiographers. Lastly, echocardiographic follow-up was conducted in less than 50% of the study subjects for various reasons, including dialysis initiation, death, and drop-out.

In summary, hs-TnT was strongly associated with alterations of LV structure and diastolic dysfunction. These tendencies persisted in a stratified analysis according to eGFR. Although the predictive power was limited in the low eGFR subgroup, a hs-TnT measurement from CKD patients, nevertheless, appears to be a useful targeted strategy that can be used for the risk-stratification of patients who may need further cardiac evaluation, irrespective of renal function. The results of a four-year follow-up showed that increased cTnT was associated with the development of LVH. If such a hs-TnT screening test was incorporated, patients identified at higher risk should be encouraged to perform further evaluations regularly, or more targeted interventions in order to reduce their risk of LVH and diastolic dysfunction. Further studies are needed to confirm the ideal cut-off values of hs-TnT in various CKD populations, and such efforts will help early detection of cardiac structural and functional abnormalities and improve CV outcomes for patients with CKD.

Chapter 5. Conclusion

Prevention and early detection of CV disease and complications in the CKD population are essential for improving clinical outcomes including mortality. In this study, I investigated the modifiable risk factors and a diagnostic cardiac biomarker for subclinical cardiac changes.

First of all, SES is one of the most important factors for health including CKD and CKD-related clinical outcomes. Thus, a better understanding of SES and risk stratification are critical first steps in identifying and tailoring interventions to improve CKD-related clinical outcomes. However, there is a lack of studies regarding the association between SES and CV outcomes in CKD populations. In this study, I identified a novel relationship between LVH and SES evaluated by educational attainment and monthly income level in CKD patients. Some determinants of SES could be modified by government policies including the accessibility to health care, and medical information. Therefore, it is crucial to find out clinical outcomes affected by SES.

In the view of biomarkers, decreased renal function may change the concentration of biomarkers. Additionally, we can measure biomarkers with lower concentrations because high-sensitivity tests were developed. Consideration of these situations

should be given for the interpretation of the results. I explored hs-TnT, which is one of the important cardiac markers broadly used. hs-TnT was associated with the change of LV structure and diastolic function even in the subgroup analysis according to eGFR in the cross-sectional study, and development of new LVH. Though predictive power was limited in the low eGFR group, hs-TnT could be a possible strategy for risk stratification of patients who may need further cardiac evaluations in CKD patients.

Prevention and timely diagnosis of CV disease and complications must be achieved to improve the outcome of patients with CKD. In this study, I found that SES is a new marker for LVH, and hs-TnT concentration is associated with LVH and diastolic dysfunction at study entry. It is also associated with new LVH during follow-up. Such an associated was observed in non-dialytic CKD patients regardless of renal function. Further studies regarding novel risk factors and the mechanisms for CV disease in the non-dialytic CKD population are warranted to improve CV outcomes.

References

1. Liu M, Li XC, Lu L, Cao Y, Sun RR, Chen S, et al. Cardiovascular disease and its relationship with chronic kidney disease. European review for medical and pharmacological sciences. 2014;18(19):2918-26.

2. Shastri S, Sarnak MJ. Cardiovascular disease and CKD: core curriculum 2010. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2010;56(2):399-417.

3. Korean Society of Nephrology. Current Renal Replacement Therapy in Korea - Insan Memorial Dialysis Registry. [cited 2019 09 July]. Available from: http://www.ksn.or.kr/file/sinchart/982988834_eddaa4e5_2016_EC9B90EAB3A0.pdf

4. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet (London, England). 2013;382(9889):339-52.

5. Herzog CA, Asinger RW, Berger AK, Charytan DM, Diez J, Hart RG, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney international. 2011;80(6):572-86.

6. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria

with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet (London, England). 2010;375(9731):2073-81.

7. van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney international. 2011;79(12):1341-52.

8. Shimakawa T, Sorlie P, Carpenter MA, Dennis B, Tell GS, Watson R, et al. Dietary intake patterns and sociodemographic factors in the atherosclerosis risk in communities study. ARIC Study Investigators. Preventive medicine. 1994;23(6):769-80.

9. Muntner P, He J, Astor BC, Folsom AR, Coresh J. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. Journal of the American Society of Nephrology : JASN. 2005;16(2):529-38.

10. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney international. 2008;73(4):391-8.

11. Cheung AK, Sarnak MJ, Yan G, Dwyer JT, Heyka RJ, Rocco MV, et al. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney international. 2000;58(1):353-62.

12. Muntner P, Hamm LL, Kusek JW, Chen J, Whelton PK, He J. The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. Annals of internal medicine. 2004;140(1):9-17.

13. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. Kidney international. 2002;62(5):1524-38.

14. Stenvinkel P, Carrero JJ, Axelsson J, Lindholm B, Heimburger O, Massy Z. Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? Clinical journal of the American Society of Nephrology : CJASN. 2008;3(2):505-21.

15. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney international. 2003;63(3):793-808.

16. Suliman M, Stenvinkel P, Qureshi AR, Kalantar-Zadeh K, Barany P, Heimburger O, et al. The reverse epidemiology of plasma total homocysteine as a mortality risk factor is related to the impact of wasting and inflammation. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2007;22(1):209-17.

17. Liu Y, Coresh J, Eustace JA, Longenecker JC, Jaar B, Fink NE, et al. Association between cholesterol level and mortality in dialysis patients: role of

inflammation and malnutrition. Journal of the American Medical Association : JAMA. 2004;291(4):451-9.

18. McCullough PA. Cardiovascular disease in chronic kidney disease from a cardiologist's perspective. Current opinion in nephrology and hypertension. 2004;13(6):591-600.

19. Middleton RJ, Parfrey PS, Foley RN. Left ventricular hypertrophy in the renal patient. Journal of the American Society of Nephrology : JASN. 2001;12(5):1079-84.

20. Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray DC, Barre PE. Outcome and risk factors for left ventricular disorders in chronic uraemia. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 1996;11(7):1277-85.

21. Di Lullo L, Floccari F, Polito P. Right ventricular diastolic function in dialysis patients could be affected by vascular access. Nephron Clinical practice. 2011;118(3):c257-61.

22. Cerasola G, Nardi E, Palermo A, Mule G, Cottone S. Epidemiology and pathophysiology of left ventricular abnormalities in chronic kidney disease: a review. Journal of nephrology. 2011;24(1):1-10.

23. Das M, Aronow WS, McClung JA, Belkin RN. Increased prevalence of coronary artery disease, silent myocardial ischemia, complex ventricular arrhythmias, atrial fibrillation, left ventricular hypertrophy, mitral annular calcium, and aortic

valve calcium in patients with chronic renal insufficiency. Cardiology in review. 2006;14(1):14-7.

24. Schrier RW. Cardiorenal versus renocardiac syndrome: is there a difference? Nature clinical practice Nephrology. 2007;3(12):637.

25. Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, et al. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. European heart journal. 2010;31(6):703-11.

26. Subbiah AK, Chhabra YK, Mahajan S. Cardiovascular disease in patients with chronic kidney disease: a neglected subgroup. Heart Asia. 2016;8(2):56-61.

27. Ahmed A, Rich MW, Sanders PW, Perry GJ, Bakris GL, Zile MR, et al. Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study. The American journal of cardiology. 2007;99(3):393-8.

28. Nakano T, Ninomiya T, Sumiyoshi S, Fujii H, Doi Y, Hirakata H, et al. Association of kidney function with coronary atherosclerosis and calcification in autopsy samples from Japanese elders: the Hisayama study. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2010;55(1):21-30.

29. Chonchol M, Whittle J, Desbien A, Orner MB, Petersen LA, Kressin NR. Chronic kidney disease is associated with angiographic coronary artery disease. American journal of nephrology. 2008;28(2):354-60.

30. Sosnov J, Lessard D, Goldberg RJ, Yarzebski J, Gore JM. Differential symptoms of acute myocardial infarction in patients with kidney disease: a community-wide perspective. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2006;47(3):378-84.

31. Kim S, Lim CS, Han DC, Kim GS, Chin HJ, Kim SJ, et al. The prevalence of chronic kidney disease (CKD) and the associated factors to CKD in urban Korea: a population-based cross-sectional epidemiologic study. Journal of Korean medical science. 2009;24 Suppl:S11-21.

32. Feldman HI, Appel LJ, Chertow GM, Cifelli D, Cizman B, Daugirdas J, et al. The Chronic Renal Insufficiency Cohort (CRIC) Study: Design and Methods. Journal of the American Society of Nephrology : JASN. 2003;14(7 Suppl 2):S148-53.

33. Imai E, Matsuo S, Makino H, Watanabe T, Akizawa T, Nitta K, et al. Chronic Kidney Disease Japan Cohort (CKD-JAC) study: design and methods. Hypertension research : official journal of the Japanese Society of Hypertension. 2008;31(6):1101-7.

34. Levin A, Rigatto C, Brendan B, Madore F, Muirhead N, Holmes D, et al. Cohort profile: Canadian study of prediction of death, dialysis and interim cardiovascular events (CanPREDDICT). BMC nephrology. 2013;14:121.

35. Oh KH, Park SK, Park HC, Chin HJ, Chae DW, Choi KH, et al. KNOW-CKD (KoreaN cohort study for Outcome in patients With Chronic Kidney Disease): design and methods. BMC nephrology. 2014;15:80.

36. Adler NE, Ostrove JM. Socioeconomic status and health: what we know and what we don't. Annals of the New York Academy of Sciences. 1999;896:3-15.

37. Marmot MG, Rose G, Shipley M, Hamilton PJ. Employment grade and coronary heart disease in British civil servants. Journal of epidemiology and community health. 1978;32(4):244-9.

38. Adelstein AM, Bulusu L. Changing social-class distribution of heart disease. British medical journal. 1978;2(6154):1785.

39. Choi AI, Weekley CC, Chen SC, Li S, Kurella Tamura M, Norris KC, et al. Association of educational attainment with chronic disease and mortality: the Kidney Early Evaluation Program (KEEP). American journal of kidney diseases : the official journal of the National Kidney Foundation. 2011;58(2):228-34.

40. Meadows P. Variation of diabetes mellitus prevalence in general practice and its relation to deprivation. Diabetic medicine : a journal of the British Diabetic Association. 1995;12(8):696-700.

41. Berg JW, Ross R, Latourette HB. Economic status and survival of cancer patients. Cancer. 1977;39(2):467-77.

42. Bradley CJ, Given CW, Roberts C. Race, socioeconomic status, and breast cancer treatment and survival. Journal of the National Cancer Institute. 2002;94(7):490-6.

43. Bello AK, Peters J, Rigby J, Rahman AA, El Nahas M. Socioeconomic status and chronic kidney disease at presentation to a renal service in the United Kingdom.

Clinical journal of the American Society of Nephrology : CJASN. 2008;3(5):1316-23.

44. Norton JM, Moxey-Mims MM, Eggers PW, Narva AS, Star RA, Kimmel PL, et al. Social Determinants of Racial Disparities in CKD. Journal of the American Society of Nephrology : JASN. 2016;27(9):2576-95.

45. Bruce MA, Beech BM, Crook ED, Sims M, Wyatt SB, Flessner MF, et al. Association of socioeconomic status and CKD among African Americans: the Jackson Heart Study. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2010;55(6):1001-8.

46. Crews DC, McClellan WM, Shoham DA, Gao L, Warnock DG, Judd S, et al. Low income and albuminuria among REGARDS (Reasons for Geographic and Racial Differences in Stroke) study participants. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2012;60(5):779-86.

47. McClellan WM, Newsome BB, McClure LA, Howard G, Volkova N, Audhya P, et al. Poverty and racial disparities in kidney disease: the REGARDS study. American journal of nephrology. 2010;32(1):38-46.

48. Crews DC, Gutierrez OM, Fedewa SA, Luthi JC, Shoham D, Judd SE, et al. Low income, community poverty and risk of end stage renal disease. BMC nephrology. 2014;15:192.

49. Lipworth L, Mumma MT, Cavanaugh KL, Edwards TL, Ikizler TA, Tarone RE, et al. Incidence and predictors of end stage renal disease among low-income blacks and whites. PloS one. 2012;7(10):e48407.

50. Schultz WM, Kelli HM, Lisko JC, Varghese T, Shen J, Sandesara P, et al. Socioeconomic Status and Cardiovascular Outcomes: Challenges and Interventions. Circulation. 2018;137(20):2166-78.

51. Kucharska-Newton AM, Harald K, Rosamond WD, Rose KM, Rea TD, Salomaa V. Socioeconomic indicators and the risk of acute coronary heart disease events: comparison of population-based data from the United States and Finland. Annals of epidemiology. 2011;21(8):572-9.

52. Gerber Y, Weston SA, Killian JM, Therneau TM, Jacobsen SJ, Roger VL. Neighborhood income and individual education: effect on survival after myocardial infarction. Mayo Clinic proceedings. 2008;83(6):663-9.

53. Stirbu I, Looman C, Nijhof GJ, Reulings PG, Mackenbach JP. Income inequalities in case death of ischaemic heart disease in the Netherlands: a national record-linked study. Journal of epidemiology and community health. 2012;66(12):1159-66.

54. Mehta RH, O'Shea JC, Stebbins AL, Granger CB, Armstrong PW, White HD, et al. Association of mortality with years of education in patients with ST-segment elevation myocardial infarction treated with fibrinolysis. Journal of the American College of Cardiology. 2011;57(2):138-46.

55. Kim JH, Jeong MH. The association of socioeconomic status with three-year clinical outcomes in patients with acute myocardial infarction who underwent percutaneous coronary intervention. Journal of Korean medical science. 2014;29(4):536-43.

56. Rodriguez CJ, Sciacca RR, Diez-Roux AV, Boden-Albala B, Sacco RL, Homma S, et al. Relation between socioeconomic status, race-ethnicity, and left ventricular mass: the Northern Manhattan study. Hypertension (Dallas, Tex : 1979). 2004;43(4):775-9.

57. Laitinen TT, Puolakka E, Ruohonen S, Magnussen CG, Smith KJ, Viikari JSA, et al. Association of Socioeconomic Status in Childhood With Left Ventricular Structure and Diastolic Function in Adulthood: The Cardiovascular Risk in Young Finns Study. JAMA pediatrics. 2017;171(8):781-7.

58. Jaffe AS, Vasile VC, Milone M, Saenger AK, Olson KN, Apple FS. Diseased skeletal muscle: a noncardiac source of increased circulating concentrations of cardiac troponin T. Journal of the American College of Cardiology. 2011;58(17):1819-24.

59. Glassock RJ, Pecoits-Filho R, Barberato SH. Left ventricular mass in chronic kidney disease and ESRD. Clinical journal of the American Society of Nephrology : CJASN. 2009;4 Suppl 1:S79-91.

60. Mahadevan G, Davis RC, Frenneaux MP, Hobbs FD, Lip GY, Sanderson JE, et al. Left ventricular ejection fraction: are the revised cut-off points for defining

systolic dysfunction sufficiently evidence based? Heart (British Cardiac Society). 2008;94(4):426-8.

61. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2016;29(4):277-314.

62. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2005;18(12):1440-63.

63. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Annals of internal medicine. 2009;150(9):604-12.

64. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, et al. Association of troponin T detected with a highly sensitive assay and cardiac

structure and mortality risk in the general population. Journal of the American Medical Association : JAMA. 2010;304(22):2503-12.

65. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. Journal of the American Medical Association : JAMA. 2010;304(22):2494-502.

66. Rubin J, Matsushita K, Ballantyne CM, Hoogeveen R, Coresh J, Selvin E. Chronic hyperglycemia and subclinical myocardial injury. Journal of the American College of Cardiology. 2012;59(5):484-9.

67. deFilippi C, Seliger SL, Kelley W, Duh SH, Hise M, Christenson RH, et al. Interpreting cardiac troponin results from high-sensitivity assays in chronic kidney disease without acute coronary syndrome. Clinical chemistry. 2012;58(9):1342-51.

68. Matsushita K, Ballew SH, Coresh J. Influence of chronic kidney disease on cardiac structure and function. Current Hypertension Reports. 2015;17(9):581.

69. Youden WJ. Index for rating diagnostic tests. Cancer. 1950;3(1):32-5.

70. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837-45.

71. Korea Statistics. National education level (Population distribution by educational attainment). [cited 2019 09 July 2019]. Available from: http://kostat.go.kr/portal/eng/index.action.

72. Organization for Economic Co-operation and Development (OECD). Education at a Glance 2017: OECD indicators [cited 2019 09 July]. Available from: https://www.hm.ee/sites/default/files/eag2017_eng.pdf.

73. Vart P, Gansevoort RT, Crews DC, Reijneveld SA, Bultmann U. Mediators of the association between low socioeconomic status and chronic kidney disease in the United States. American journal of epidemiology. 2015;181(6):385-96.

74. Kim DH, Kim M, Kim H, Kim YL, Kang SW, Yang CW, et al. Early referral to a nephrologist improved patient survival: prospective cohort study for end-stage renal disease in Korea. PloS one. 2013;8(1):e55323.

75. Wavamunno MD, Harris DC. The need for early nephrology referral. Kidney international Supplement. 2005(94):S128-32.

76. Liaropoulos LL. Health services financing in Greece: a role for private health insurance. Health policy (Amsterdam, Netherlands). 1995;34(1):53-62.

77. Kwon S, Reich MR. The changing process and politics of health policy in Korea. Journal of health politics, policy and law. 2005;30(6):1003-26.

78. Shin J. Private health insurance in South Korea: an international comparison. Health policy (Amsterdam, Netherlands). 2012;108(1):76-85.

79. Selye H. The Stess of Life. New York, NY, US: McGraw-Hill; 1956.

80. Theorell T, Karasek RA. Current issues relating to psychosocial job strain and cardiovascular disease research. Journal of occupational health psychology. 1996;1(1):9-26.

81. Dimsdale JE. Psychological stress and cardiovascular disease. Journal of the American College of Cardiology. 2008;51(13):1237-46.

82. Everson-Rose SA, Lewis TT. Psychosocial factors and cardiovascular diseases. Annual review of public health. 2005;26:469-500.

83. Sternberg EM, Chrousos GP, Wilder RL, Gold PW. The stress response and the regulation of inflammatory disease. Annals of internal medicine. 1992;117(10):854-66.

84. Rapaport E. Pathophysiological basis of ventricular hypertrophy. European heart journal. 1982;3 Suppl A:29-33.

85. Cukor D, Cohen SD, Peterson RA, Kimmel PL. Psychosocial aspects of chronic disease: ESRD as a paradigmatic illness. Journal of the American Society of Nephrology : JASN. 2007;18(12):3042-55.

86. de Simone G, Devereux RB, Roman MJ, Schlussel Y, Alderman MH, Laragh JH. Echocardiographic left ventricular mass and electrolyte intake predict arterial hypertension. Annals of internal medicine. 1991;114(3):202-9.

87. Vlismas K, Stavrinos V, Panagiotakos DB. Socio-economic status, dietary habits and health-related outcomes in various parts of the world: a review. Central European journal of public health. 2009;17(2):55-63.

88. Darmon N, Drewnowski A. Does social class predict diet quality? The American journal of clinical nutrition. 2008;87(5):1107-17.

89. Grimes CA, Campbell KJ, Riddell LJ, Nowson CA. Is socioeconomic status associated with dietary sodium intake in Australian children? A cross-sectional study. Britich Medical Journal open : BMJ open. 2013;3(2).

90. Tian HG, Hu G, Dong QN, Yang XL, Nan Y, Pietinen P, et al. Dietary sodium and potassium, socioeconomic status and blood pressure in a Chinese population. Appetite. 1996;26(3):235-46.

91. Ortega RM, Lopez-Sobaler AM, Ballesteros JM, Perez-Farinos N, Rodriguez-Rodriguez E, Aparicio A, et al. Estimation of salt intake by 24 h urinary sodium excretion in a representative sample of Spanish adults. The British journal of nutrition. 2011;105(5):787-94.

92. Ribic CH, Zakotnik JM, Vertnik L, Vegnuti M, Cappuccio FP. Salt intake of the Slovene population assessed by 24 h urinary sodium excretion. Public health nutrition. 2010;13(11):1803-9.

93. World Health Organization (WHO). Diet, nutrition and the prevention of chronic diseases (WHO Technical report series, No. 916). Geneva, Switzerland: World Health Organization Press; 2003.

94. Eduardo Alegria-Ezquerra EA-B. How to quantify salt intake in certain patients [cited 2019 09 July]. Available from: https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-10/How-to-quantify-salt-intake-in-certain-patients.

95. Parfrey PS, Foley RN. The clinical epidemiology of cardiac disease in chronic renal failure. Journal of the American Society of Nephrology : JASN. 1999;10(7):1606-15.

96. Astor BC, Arnett DK, Brown A, Coresh J. Association of kidney function and hemoglobin with left ventricular morphology among African Americans: the Atherosclerosis Risk in Communities (ARIC) study. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2004;43(5):836-45.

97. Kim JY, Shin S, Han K, Lee KC, Kim JH, Choi YS, et al. Relationship between socioeconomic status and anemia prevalence in adolescent girls based on the fourth and fifth Korea National Health and Nutrition Examination Surveys. European journal of clinical nutrition. 2014;68(2):253-8.

98. Nguyen PH, Gonzalez-Casanova I, Nguyen H, Pham H, Truong TV, Nguyen S, et al. Multicausal etiology of anemia among women of reproductive age in Vietnam. European journal of clinical nutrition. 2015;69(1):107-13.

99. Hulshof KF, Brussaard JH, Kruizinga AG, Telman J, Lowik MR. Socio-economic status, dietary intake and 10 y trends: the Dutch National Food Consumption Survey. European journal of clinical nutrition. 2003;57(1):128-37.

100. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. Journal of the American College of Cardiology. 2010;55(4):300-5.

101. Fendler WP, Calais J, Eiber M, Flavell RR, Mishoe A, Feng FY, et al. Assessment of 68Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial. JAMA oncology. 2019;5(6):856-63.

102. Correa de Sa DD, Hodge DO, Slusser JP, Redfield MM, Simari RD, Burnett JC, et al. Progression of preclinical diastolic dysfunction to the development of symptoms. Heart (British Cardiac Society). 2010;96(7):528-32.

103. Ren X, Ristow B, Na B, Ali S, Schiller NB, Whooley MA. Prevalence and prognosis of asymptomatic left ventricular diastolic dysfunction in ambulatory patients with coronary heart disease. The American journal of cardiology. 2007;99(12):1643-7.

104. Lam CS, Lyass A, Kraigher-Krainer E, Massaro JM, Lee DS, Ho JE, et al. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. Circulation. 2011;124(1):24-30.

105. Vogel MW, Slusser JP, Hodge DO, Chen HH. The natural history of preclinical diastolic dysfunction: a population-based study. Circulation Heart failure. 2012;5(2):144-51.

106. Saydah S, Lochner K. Socioeconomic status and risk of diabetes-related mortality in the U.S. Public health reports (Washington, DC : 1974). 2010;125(3):377-88.

107. Suwannaphant K, Laohasiriwong W, Puttanapong N, Saengsuwan J, Phajan T. Association between Socioeconomic Status and Diabetes Mellitus: The National Socioeconomics Survey, 2010 and 2012. Journal of clinical and diagnostic research : JCDR. 2017;11(7):Lc18-lc22.

108. Leng B, Jin Y, Li G, Chen L, Jin N. Socioeconomic status and hypertension: a meta-analysis. Journal of hypertension. 2015;33(2):221-9.

109. Colhoun HM, Hemingway H, Poulter NR. Socio-economic status and blood pressure: an overview analysis. Journal of human hypertension. 1998;12(2):91-110.

110. Pande RL, Creager MA. Socioeconomic inequality and peripheral artery disease prevalence in US adults. Circulation Cardiovascular quality and outcomes. 2014;7(4):532-9.

111. Mishra RK, Li Y, DeFilippi C, Fischer MJ, Yang W, Keane M, et al. Association of cardiac troponin T with left ventricular structure and function in CKD. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2013;61(5):701-9.

112. Mallamaci F, Zoccali C, Parlongo S, Tripepi G, Benedetto FA, Cutrupi S, et al. Troponin is related to left ventricular mass and predicts all-cause and cardiovascular mortality in hemodialysis patients. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2002;40(1):68-75.

113. Bansal N, Hyre Anderson A, Yang W, Christenson RH, deFilippi CR, Deo R, et al. High-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide

(NT-proBNP) and risk of incident heart failure in patients with CKD: the Chronic Renal Insufficiency Cohort (CRIC) Study. Journal of the American Society of Nephrology : JASN. 2015;26(4):946-56.

114. Chung JZ, Dallas Jones GR. Effect of renal function on serum cardiac troponin T--Population and individual effects. Clinical biochemistry. 2015;48(12):807-10.

115. Kang E, Han M, Kim H, Park SK, Lee J, Hyun YY, Kim YS, et al. Baseline General Characteristics of the Korean Chronic Kidney Disease: Report from the KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD). Journal of Korean medical science. 2017;32(2):221-30.

116. Selvin E, Lazo M, Chen Y, Shen L, Rubin J, McEvoy JW, et al. Diabetes mellitus, prediabetes, and incidence of subclinical myocardial damage. Circulation. 2014;130(16):1374-82.

117. Alhaj E, Alhaj N, Rahman I, Niazi TO, Berkowitz R, Klapholz M. Uremic cardiomyopathy: an underdiagnosed disease. Congest Heart Fail. 2013;19(4):E40-5.

118. McMahon AC, Greenwald SE, Dodd SM, Hurst MJ, Raine AE. Prolonged calcium transients and myocardial remodelling in early experimental uraemia. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2002;17(5):759-64.

119. Wolf WC, Yoshida H, Agata J, Chao L, Chao J. Human tissue kallikrein gene delivery attenuates hypertension, renal injury, and cardiac remodeling in chronic renal failure. Kidney International. 2000;58(2):730-9.

120. Winchester JF, Audia PF. Extracorporeal strategies for the removal of middle molecules. Seminars in dialysis. 2006;19(2):110-4.

121. Francis GS, Tang WH. Cardiac troponins in renal insufficiency and other non-ischemic cardiac conditions. Progress in cardiovascular diseases. 2004;47(3):196-206.

122. Diris JH, Hackeng CM, Kooman JP, Pinto YM, Hermens WT, van Dieijen-Visser MP. Impaired renal clearance explains elevated troponin T fragments in hemodialysis patients. Circulation. 2004;109(1):23-5.

123. deFilippi C, Wasserman S, Rosanio S, Tiblier E, Sperger H, Tocchi M, et al. Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. Journal of the American Medical Association : JAMA. 2003;290(3):353-9.

124. Sharma R, Gaze DC, Pellerin D, Mehta RL, Gregson H, Streather CP, et al. Cardiac structural and functional abnormalities in end stage renal disease patients with elevated cardiac troponin T. Heart. 2006;92(6):804-9.

요약 (국문초록)

심혈관계 질환은 만성신장질환 환자의 주요 사망원인이므로, 심혈관계 질환의 예방을 위해 위험인자를 조기 발견하여 치료하는 것이 매우 중요하다. 따라서 본 연구에서는 증상이 아직 나타나지 않은 심장 구조 및 기능의 변화에 대한 위험 인자 및 진단적 바이오마커에 대해 연구하였다. 첫번째는 만성신장질환 환자에서 사회경제적 지위와 좌심실 구조 및 기능 변화와의 관계에 대해서, 두번째는 만성신장질환 환자에서 추정 사구체 여과율에 따라 high-sensitivity troponin T (hs-TnT)와 좌심실 구조 및 기능과의 관계에 대해 평가해 보고자 하였다.

본 연구는 투석 이전의 만성신장병 환자를 대상으로 하는 전향적 코호트인 한국인 만성신장병 장기 추적 코호트 (KNOW-CKD)의 데이터를 이용하여 진행되었다. 심장초음파 검사는 연구 등록 당시 및 4 년 후에 시행되었으며 이를 통해 좌심실 구조 및 기능 장애에 대한 평가를 시행하였다. 등록 당시 시행한 설문지에서 교육 수준과 가구별 월 소득 수준에 대한 정보를 수집하여 사회경제적 지위의 지표로 사용하였다. Troponin T 의 경우 high-sensitivity 로 측정하였고, 사분위수로 분류하여 분석을 시행하였다.

첫번째 파트인 사회경제적 지위 및 좌심실 구조에 대한 분석에서 좌심실 비대는 사회경제적 지위(교육 수준 및 월 소득 수준)가 낮을수록 증가하는 것으로 확인되었다. 낮은 교육 수준과 월 소득 수준 모두 전체 환자에서 다변량 분석 시 좌심실 비대와 통계적으로 유의한 것으로 확인되었으나, 50 세 미만에서는 유의성을 나타내지 않았다. 이완기 기능 장애의 경우, 낮은 소득 수준만이 전체 환자 및 50 세 이상의 환자에서 시행한 다변량 분석에서 유의한 것으로 확인되었다.

두번째 파트에서는 등록 당시의 높은 hs-TnT 가 좌심실 비대 및 이완기 기능 장애와 통계적으로 유의한 연관성을 보였으나, 수축기 기능 장애와는 이러한 연관성을 보이지 않았다. 이러한 결과는 추정 사구체 여과율 60mL/min/1.73m^2 를 기준으로 두 그룹으로 나누어 분석한 하위집단 분석에서도 동일하게 유지되었다. hs-TnT 를 연속변수로 두고

시행한 수신자 조작 특성 곡선(Receive Operating Curve, ROC) 분석에서 좌심실 비대(Area under the curve [AUC] 0.69) 및 이완기 기능장애(AUC 0.74)의 진단에 상당한 의미를 가지는 것으로 확인되었다. 마지막으로, 다변량 분석 결과 등록 당시의 높은 hs-TnT 는 4 년 후 시행한 심초음파에서 새롭게 발생하는 좌심실 비대와 연관성이 있으나, 새로 진단되는 이완기 기능 장애와는 연관성을 보이지 않았다.

본 연구는 교육 수준 및 월 소득 수준이 좌심실 비대의 위험 요소이며, 특히 월 소득 수준은 이완기 기능장애의 위험인자임을 밝혔다. 또한 바이오마커의 관점에서는, 등록 당시의 hs-TnT 가 높을수록 신기능에 관계없이 좌심실 비대 및 이완기 기능 장애와 단면적 연구에서 강한 연관성을 보임을 확인하였으며, 4 년 뒤의 좌심실 비대를 예측할 수 있음을 본 연구에서 확인하였다.

주요어: 만성콩팥병, 심혈관계 질환, 사망률, 바이오마커, 사회경제적 지위, high-sensitivity troponin T

학번: 2016-30801