Risk factors associated with left ventricular mass index using echocardiography in chronic kidney disease patients

Running title: Risk factors for LVMI in CKD patients

Mayumi Matsumoto, Hiroaki Io, Masako Furukawa, Kozue Okumura, Atsumi Masuda, Takuya Seto, Miyuki Takagi, Michiko Sato, Lili Nagahama, Keisuke Omote, Atsuko Hisada, Satoshi Horikoshi and Yasuhiko Tomino

Affiliation : Division of Nephrology, Department of Internal Medicine, Juntendo University Faculty of Medicine

Address correspondence and reprint requests to Yasuhiko Tomino M.D., PhD.
Division of Nephrology, Department of Internal Medicine, Juntendo University Faculty of Medicine,
2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan.
Tel & Fax No. 81-3-5802-1064 or -1065
E-mail: yasu@juntendo.ac.jp

The manuscripts has been seen and approved by all authors and that is not under consideration for publication elsewhere in a similar form, in any language, except in abstract form.

Disclosures : None.

ABSTRACT

Background: It is still not clear which factors are associated with left ventricular mass index (LVMI) in chronic kidney disease (CKD) patients based on the patient's physical and biochemical parameters at the time of echocardiography. The objective of the present study was to identify factors associated with LVMI in CKD patients (pre-dialysis patients) using echocardiography.

Methods: Physical, biochemical and LVMI data evaluated by echocardiography were retrospectively analyzed in 930 CKD patients in Juntendo University Hospital, Tokyo, Japan.

Results: Levels of systolic blood pressure (SBP) and hemoglobin (Hb) were independent risk factors for LVMI in multivariate regression analysis. SBP was significantly correlated with LVMI ($r=0.314$, $p<0.0001$). The level of Hb was inversely correlated with LVMI ($r=-0.372$, $p<0.0001$). LVMI increased with decreasing renal function. SBP was significantly higher in patients with LVH in stages Ⅱ and Ⅴ, and Hb was significantly lower in patients with LVH in stages Ⅳ and Ⅴ than in the group without LVH.

Conclusions: It is important to treat hypertension and anemia to prevent left ventricular hypertrophy in CKD patients. These findings have some therapeutic implications in treatment strategies for pre-dialysis patients.

Key words: left ventricular hypertrophy (LVH), left ventricular mass index (LVMI), chronic kidney disease (CKD), echocardiography, blood pressure (BP), anemia

INTRODUCTION

Left ventricular hypertrophy (LVH) has been prevalent in patients with chronic kidney disease (CKD) for many decades (1). LVH is related to a high incidence of cardiovascular events such as congestive heart failure and arrhythmia. The mechanisms underlying heart abnormalities such as LVH, intermyocardial cell fibrosis and capillary loss in CKD patients are diverse but involve afterload and preload factors or are not afterload or preload related . Afterload related factors include systemic arterial resistance, elevated systolic arterial BP, and large vessel compliance. The latter factors could be related in part to the common phenomenon of aortic calcification observed in CKD. Preload related factors include expansion of intravascular volume and anemia (2).

We have several methods to diagnose of LVH such as physical examination by palpation of maximum impulse, evaluation of the cardiothoracic index and electrocardiography. These examinations are simple, inexpensive and non-invasive, but they are not sensitive. Echocardiography (M-Mode and 2-D echocardiography) is widely used because it is more

specific and reproducible, and also far more sensitive for detecting and quantifying heart abnormalities (2). An increase in LVMI is a prerequisite for development of LVH. Accurate echocardiographic screening of patients with CKD seems to be able to rule out the presence of LVH.

We previously reported that SBP, residual glomerular filtration rate (rGFR) and serum albumin levels are predictive factors for LVMI at the initiation of hemodialysis (3). It is still not clear which factors are associated with LVMI in CKD patients based on the patient's physical and biochemical parameters at the time of echocardiography. The objective of the present study was to identify factors associated with LVMI in 930 CKD patients using echocardiography and clinical data.

SUBJECTS AND METHODS

Study Design

The criterion for enrollment in this study was patients who underwent routine laboratory measurements and transthoracic echocardiography from 1999 through 2009 in Juntendo University Hospital, Tokyo, Japan. Patients received echocardiography in hospital on routine visits to the outpatient clinic. Patients on dialysis treatment or with renal transplants were excluded. We enrolled 930 patients with CKD (male/female: 610/320, mean age: 59.5±15.8 years old) in this study. In accordance with the Declaration of Helsinki and institutional guidelines, the protocol was approved by the Ethical Committee of Juntendo University Hospital.

Glomerular filtration rate (GFR) was estimated by using the modification of diet in renal disease (MDRD) formula, as $194 \times Cr^{-1.094} \times Age^{-0.287} \times$ (0.739 if female) (4). CKD patients were stratified using the National Kidney Foundation (NKF); Kidney Disease Outcome Quality Initiative (K/DOQI) classification (5). The enrolled patients were classified as follows: 50 patients (5%) were in stage Ⅰ CKD, 123 patients (13%) in stage Ⅱ, 91 patients (10%) in stage Ⅲ, 128 patients (14%) in stage Ⅳ and 538 patients (58%) in stage Ⅴ. We recorded the patient's physical and biochemical parameters related to LVMI obtained by echocardiography. LVM was calculated according to the Devereux formula and indexed to height$^{2.7}$ (6). LVH was defined as a LVMI of over 47 g/m$^{2.7}$ in women or over 50 g/m$^{2.7}$ in men.

Blood pressure (BP) measurements

BP was measured with a manual sphygmomanometer before the echocardiographic studies or at routine visits to the outpatient clinic in Juntendo University Hospital. Measurements of BP were performed in the sitting position after 5 minutes of rest.

Laboratory Parameters

The investigated parameters were as follows: systolic blood pressure (SBP), level of hemoglobin (Hb), concentrations of serum albumin, creatinine and phosphorus, Fe, intact parathormone, urine protein / urine creatinine ratio and dose of erythropoietin per month. Measurement of these parameters was performed close to the time of echocardiography.

Echocardiography

Echocardiographic examinations were performed in all patients with a Toshiba ultrasound system (model 260 SS-A equipped with a 2.5 MHz phased array transducer, Tokyo, Japan) by one experienced investigator. All examinations were performed in the left lateral recumbent position, and all echocardiographic data were evaluated according to the guidelines of American Society of Echocardiography. The left atrial (LA) and ventricular size, intraventricular septal thickness (IVST) and left ventricular posterior wall thickness (PWT) were measured by two-dimensional and M-mode echocardiography (7).

Statistical Analysis

The univariate regression analysis test was used to determine interrelated factors for LVMI. Variables with P-values of less than 0.05 were analyzed using a stepwise linear regression analysis. We performed a stepwise multiple regression analysis to determine the risk factors for LV geometry. The F-value for entry or removal of candidate variables from the discriminant function was set at 4.0. Repeated ANOVA was performed for comparisons of serial changes of the clinical data and echocardiographic parameters. All calculations were performed using Stat View version 5.0. The P value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 shows clinical data of the CKD patients in a comparison of characteristics in each stage of CKD. Data are expressed as mean ± SD or number of patients. **Table 2** shows the major clinical and hemodynamic data at each CKD stage. LVMI increased with decreasing renal function (Table 2). SBP in stages Ⅳ and Ⅴ was significantly higher than that in stages Ⅰ and Ⅱ ($p < 0.001$). Conversely, the Hb level was lower in advanced stages of CKD. The Hb level in stages Ⅲ, Ⅳ and Ⅴ was significantly lower than that in stages Ⅰ and Ⅱ ($p < 0.0001$). The prevalence of LVH increased with advanced CKD ($p < 0.001$). The prevalence of LVH were 56.5% in patients with CKD stage Ⅰ, 52.2% in CKD stage Ⅱ, 73.3 % in CKD stage Ⅲ, 81.3% in CKD stage Ⅳ, and 89.1% in CKD stage Ⅴ.

When compared of mean SBP and Hb with and without LVH in each CKD stage, SBP was significantly higher in patients with LVH in stage Ⅱand Ⅴ, and Hb was significantly lower in patients with LVH in stages Ⅳand Ⅴ than in the group without LVH (Table 3).

SBP was directly correlated with LVMI (r=0.314, p＜0.0001) (**Figure 1**). The Hb level was inversely correlated with LVMI (r=-0.372, p＜0.0001) (**Figure 2**). LVMI in stages Ⅳ and Ⅴ was significantly higher than that in stages Ⅰ and Ⅱ (p＜0.001, **Figure 3**).

Factors associated with LVMI：

In univariate analysis, SBP, urine protein / urine creatinine ratio, serum creatinine, phosphorus and dose of erythropoietin were directly correlated with LVMI (p＜0.01). The levels of Hb, serum albumin and Fe were inversely correlated with LVMI (p＜0.0001). In a stepwise linear regression analysis of the above factors associated with LVMI, SBP and Hb were independent risk factors for LVMI (**Table 4**).

Factors associated with eGFR：

In univariate analysis, age, LVMI, urine protein / urine creatinine ratio, serum albumin, level of Hb, dose of erythropoietin, phosphorus and serum Fe were significantly correlated with eGFR (p＜0.0001).

DISCUSSION

LVH is a common independent risk factor for cardiac death in CKD and ESKD patients. The prevalence and severity of LVH increase in parallel with the severity of CKD. LVH reduces coronary reserve and induces cardiac ischemia, which may in turn promote myocardial infarction and lethal arrhythmia (1).

The pathogenesis of LVH in ESKD is multifactorial. The left arterial (LA) size is associated very strongly with LVH and its monitoring by echocardiography has recently emerged as an independent prognostic predictor of cardiovascular risk in patients with ESKD (8). In this study, there was a significant correlation with LA size and LVMI (p＜0.0001). Recently we demonstrated that there is a significant correlation between LA volume index and LVMI in CKD stages Ⅳand Ⅴin nondiabetie patients (9)**,** and LA size represents the integration of LV diastolic compliance over time (10). Recent studies also established that the soluble Receptor for Advanced Glycation End Products (RAGE), a member of the immunoglobulin super family that is located at the cell surface of several cell species and the adhesion molecule E-selectin that mediates leukocyte rolling on the activated endothelium are inverse markers of the LVH in ESKD patients (11,12). LVH is closely connected with arterial stiffness (13). Age is an important determinant of arterial stiffness. In this study, age was significantly correlated with LVMI. Vascular aging occurs with advancing age, and is associated with vascular wall changes, which can increase arterial stiffness. AGE link proteins have been shown to increase arterial stiffness in diabetes and ageing (14). Recently, the pulse pressure / stroke index ratio (PP/SVi) method is regarded as a surrogate index to measure arterial stiffness (15). In this study,

the pulse pressure directly correlated with LVMI ($p < 0.0001$). Diabetes is both the most frequent cause of ESKD and also an established risk factor for cardiovascular disease (16). The ectonucleotide pyrophosphatase phosphodiesterase 1 (ENPP1) gene, a regulator of insulin sensitivity whose variability has been associated with insulin resistance (IR) in ESKD and IR is also a relevant factor in the pathogenesis of LVH (17). We also found that LVMI in diabetic patients was higher than that in non-diabetic patients. There was significant association with LVMI. In advanced CKD, renal phosphorus excretion is insufficient to remove the amount of dietary phosphorus that is absorbed daily (18). Several reports have noted the ability of serum phosphorus to stimulate phenotypic transformation of vascular smooth muscle cells into osteoblasts (19, 20). In this environment, hyperphosphatemia is associated with the development of myocardial hypertrophy (21). In this study, the level of serum phosphorus was significantly correlated with LVMI and one quarter of patients were on vitamin D treatment. LVH was present in 238 patients (55%) on non-vitamin D therapy and 94 patients (22%) on therapy. Recent evidence is emerging that vitamin D is important in the development and physiology of cardiac tissue (22). The B allele of the Bsml Vitamin D Receptor (VDR) gene polymorphism may serve as a marker of altered vitamin D signaling in ESKD patients and was independently related to LVH and LVH progression in ESKD patients (23).

In this study, We found that the prevalence of LVH was high especially in CKD stages Ⅳ and Ⅴ. There was a significant correlation between Hb and LVMI ($p < 0.05$) in stage Ⅳ and age, SBP and LVMI ($p < 0.0001$) in stage Ⅴ. And the SBP and Hb were identified as independent risk factors associated with LVMI in stepwise multivariate regression analysis. We also investigated the SBP ($F=6.384$) and Hb ($F=17.911$) were independent risk factors in patients with LVH.

Elevated SBP has a continuous, graded and independent association with risk of coronary heart disease, stroke and ESKD (24). LVH might be a beneficial compensatory process in patients with CKD, allowing the left ventricle to produce additional force to increase cardiac work and maintain constant wall tension (25). In this study, SBP was significantly higher in patients with LVH than in the group without LVH especially in CKD stage Ⅴ. Maintenance of SBP is predicted to have beneficial effects on the course of LVH. Fluid volume management and maintenance of a near euvolemic state are crucial for the amelioration of LVH (26, 27).

CKD, especially in patients with at least a moderately decreased glomerular filtration rate (GFR $<$ 60mL/min/1.73m^2), is associated with anemia and increased risk for cardiovascular disease and death (28). In this study, Hb was significantly lower in patients with LVH than in the group without LVH especially in CKD stages Ⅳand Ⅴ. And 53.1%

patients were on concurrent recombinant human erythropoietin treatment, and a graded decrease in hemoglobin level and increase in the dose of erythropoietin appeared with the progression of CKD. The impact of treatment of anemia with erythropoietin on LVH in CKD or ESKD has also been examined in numerous randomized controlled trials (29). Correction for anemia with erythropoietin improves oxygen delivery to tissue and may protect against oxidative stress induced tubular damage and fibrosis, both of which are linked to progression of CKD (30).

There are some potential limitations of our study. First, this is a cross-sectional study with all its limitations, it has a selection bias associated with its retrospective nature and was not carried out in a double-blind manner. Also this is an observational study, it can establish an association but not a causal relationship between SBP, Hb and LVH. Another limitation is uncertainty about averaging 24-hour home ambulatory BP monitoring and patient compliance during the use of antihypertensive medication prior to the examination. 24-hour ambulatory BP monitoring (ABPM) was considered to be an effective tool to assess the average BP over the day compared with office BP. Left ventricular diastolic function was found to be closely related to ambulatory, rather than office BP, the mean nocturnal diastolic BP being a powerful marker of LV filling impairment (31). In addition, in the past 10 years, cardiac MRI has become established as the new gold standard because of its high precision, reliability, and ability to measure LVMI (32), this new method will certainly refine the relative role of LVM in the risk assessment of patients with ESKD.

In conclusion, this study showed that patients with CKD have a high prevalence of inappropriate LVMI, especially in advanced CKD stages. Anemia and hypertension can be the factors for progression to LVH. Therefore, it is hypothesized that maintaining lower SBP and treatment of anemia may retard the progression of cardiac alterations in CKD patients. It is important to treat hypertension and anemia to prevent LV hypertrophy in CKD patients. These findings have some therapeutic implications in the treatment strategies of pre-dialysis patients.

ACKNOWLEDGMENTS

We are indebted to the nephrologists and patients at Juntendo University Hospital for their cooperating in this study.

REFERENCES

1. Li S, Collins AJ. Association of hematocrit value with cardiovascular morbidity and

mortality in incident hemodialysis patients. Kidney Int. 2004; 65: 626-633.
2. Glassock RJ, Filho RP, Barberato SH. Left ventricular mass in chronic kidney disease and ESRD. Clin J Am Soc Nephrol. 2009; 4: S79-S91.
3. Io H, Matsumoto M, Okumura K, Sato M, Masuda A, Furukawa M, Nohara N, Tanimoto M, Kodama F, Hagiwara S, Gohda T, Shimizu Y, Tomino Y. Predictive factors associated with left ventricular hypertrophy at baseline and in the follow-up period in non-diabetic hemodialysis patients. Seminars in Dialysis. 2011; 24(3): 349-354.
4. Matsuo S, Imai E, Horio Y, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A: Collaborators developing the Japanese equation for estimated GFR. Am J Kidney Dis. 2009; 53: 982-992.
5. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39 (Suppl 1): S1-S266.
6. De Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MA, de Divitiis O, Alderman MH: Left ventricular mass and body size in normotensive children and adults: as assessment of allometric relations and impact of overweight. J Am Coll Cardiol. 1992; 20: 1251-1260.
7. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellika PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Chamber Quantification Writing Group; American Society of Echocardiography's Guideline and Standard Committee; European Association of Echocardiography. J Am Soc Echocardiography. 2005; 18 (12): 1440-1463.
8. Tripepi G, Benedetto FA, Mallamaci F, Tripepi R,Malatino L, Zoccali C. Left atrial volume monitoring and cardiovascular risk in patients with end-stage renal diseas: A prospective cohort study. J Am Soc Nephrol. 2007; 18: 1316-1322.
9. Furukawa M, Io H, Tanimoto M, Hagiwara S, Horikoshi S, Tomino T. Predictive Factors Associated with the Period of Time before Initiation of Hemodialysis in CKD Stages 4 and 5. Nephron Clin Pract. 2011; 117: c341-c347.
10. Io H, Ro Y, Sekiguchi Y, Shimaoka T, Inuma J, Hotta Y, Aruga S, Inami Y, Sato M, Kobayashi T, Masuda A, Kaneko K, Hamada C, Ohtaki E, Horikoshi S, Tomino Y. Cardiac function and structure in longitudinal analysis of echocardiography in peritoneal dialysis patients. Peritoneal Dial Int. 2010; 30(3): 353-361.
11. Leonardis D, Besta G, Mallamaci F, Cutrupi S, Pizzini P, Tripepi G, De Caterina R, Zoccali C. Circulating soluble receptor for advanced glycation end product (sRAGE) and left ventricular hypertrophy in patients with chronic kidney disease (CKD). Nutr metab Cardiovasc Dis. 2010; 1-8.

12. Stancanelli B, Makatino LS, Cataliotti A, Bellanuova I, Mallamaci F, Tripepi G, Benedetto FA, leonardis D, Fatuzzo P, Rapisarda F, Zoccali C. Soluble e-selectin is an inverse and independent preditctor of left ventricular wall thickness in end-stage renal disease patients. Nephron Clin Pract. 2010; 114: c74-c80.
13. Nitta K, Akiba T, Uchida K, Otsubo S, Otsubo Y, Takei T, Ogawa T, Yumura W, Kabaya T, Nihei H. Left ventricular hypertrophy is associated with arterial stiffness and vascular calcification in hemodialysis patients.Hypertensions Res. 2004; 27: 47-52.
14. Jani B, Rajkumar C: Ageing and vascular ageing. Postgrad med J. 2006; 82: 357-362.
15. Palmieri V, Bella JN, Roman MJ, Gerdts E, Papademetriou V, Wachtell K, Nieminen MS, Dahlöf B, Devereux RB. Pulse pressure/stroke index and left ventricular geometry and function: the LIFE Study. J Hypertens. 2003; 21: 781-7.
16. United State Renal Data System: USRDS 2002 annual data report. Bethesda (MD): National Institute of Health, National Institute of Diabetes and Digestive and Kidney Disease. 2002
17. Spoto B, Testa A, Parlongo RM, Tripepi G, Trischitta V, Mallamaci F, Zoccali C. Iinsulin resistance and left ventricular hypertrophy in end-stage renal disease: association between the ENNP1 gene and left ventricular concentric remodeling. Nephrol Dial Transplant. 2011; 0: 1-6.
18. Berndt T and Kumar R. Novel mechanisms in the regulation of phosphorus homeostasis. Physioology. 2009; 24: 17-25.
19. Moe SM, Duan D, Doehle BP, O'Neill KD, Chen NX: Uremia induces the osteoblast differentiation factor Cbfal in human blood vessels. Kidney Int. 2003; 63: 1003-1011.
20. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK: Association of elevated serum PO(4), Ca x PO(4) product,and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol.* 2001; 12:2131–2138.
21. Neves KR, Graciolli FG, Dos Reis LM, Pasqualucci CA, Moysés RM.A, Jorgett V: Adverse effects of hyperphosphatemia on myocardial hypertrophy, renal function, and bone in rats with renal failure. Kidney Int. 2004; 66: 2237-2244.
22. Achinger SG and Ayus JC. The role of vitamin D in left ventrivcular hypertrophy and cardiac function. Kidney Int. 2005; 67 (Suppl 95): S37-S42.
23. Testa A, Mallamaci F, Benedetto FA, Pisano A, Tripepi G, Malatino L, Thadhani R, Zoccali C: Vitamin D Receptor (VDR) gene polymorphism is associated with left ventricular (LV) mass and predicts left ventricular hypertrophy (LVH) progression in end-stage renal disease (ESRD) patients. J Bone Miner Res. 2010; 25: 313-319.

24. Locatelli F, Bommer J, London GM, Martín-Malo A, Wanner C, Yaqoob M, Zoccali C. Cardiovascular disease determinants in chronic renal failure: clinical approach and treatment. Nephrol Dial Transplant. 2001; 16: 459-468.
25. London G. Pathophysiology of cardiovascular damage in the early renal population. Nephrol Dial Transplant. 2001; 16 (Suppl 2) : S3-S6
26. Guyton AC, Coleman TG, Wilcox CS. Quantitative analysis of the pathophysiology of hypertension. J Am Soc Nephrol. 1999; 10: 2248-2249.
27. Charra B, Calemard E, Laurent G. Importance of treatment time and blood pressure control in achieving long-term survival on dialysis. Am J Nephrol 16: 35-44, 1996
28. Go AS, Chertow GM, Fan D, MuCulloch CE, Hsu CY. Chronic kidney disease and risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2003; 351: 1296-1305.
29. Rossert J, Levin A, Roger SD, Hörl WH, Fouqueray B, Gassmann-Mayer C, Frei D, McCellan WM. Effect of early correction of anemia on the progression of CKD. Am J Kidney Dis. 2006; 47: 738-750.
30. Rossert J, Fouqueray B, Boffa JJ. Anemia management and the delay of chronic renal failure progression. J Am Soc Nephrol. 2003; 14: S173-S177.
31. Galderisi M, Petrocelli A, Alfieri A, Garofalo M, de Divitiis O. Impact of ambulatory blood pressure on left ventricular diastolic dysfunction in uncomplicated arterial systemic hypertension. Am J Cardiol. 1996; 77:597–601.
32. Aqabiti RE, Muiesan ML, Salvetti M: New approaches to the assessment of left ventricular hypertrophy. Ther Adv Cardiovasc Dis. 2007; 1: 119-128.

Table 1 Patient characteristics in each CKD stage

Stage	Ⅰ	Ⅱ	Ⅲ	Ⅳ	Ⅴ
Number	50	123	91	128	538
Gender (% male)	58	59	68	71	66
Age	48.0±19.3 *	52.4±17.2†	61.0±14.8	61.4±15.2	61.7±14.2
Primary kidney disease (%)					
Glomerulonephritis	32	29	34	17	20
Hypertensive nephrosclerosis	32	31	24	26	18
Polycystic kidney disease	0	3	5	3	3
Diabetic nephritis	28	25	27	34	40
Others	8	12	10	20	19

Data are shown as mean ± SD, or number of patients.
*p＜0.0001 stage Ⅰ vs Ⅲ,Ⅳ,Ⅴ. †p ＜0.0001 stage Ⅱ vs Ⅲ,Ⅳ,Ⅴ

Table 2 Clinical parameters in each CKD stage

	Stage Ⅰ	Ⅱ	Ⅲ	Ⅳ	Ⅴ	*P*
s-Cre(mg/dL)	0.6±0.1	1.1±2.5	1.2±0.3	2.5±1.6	6.7±2.3	
LVMI ($g/m^{2.7}$)	53.7±17.5	53.0±16.2	61.6±18.9	66.4±19.4 *	75.3±24.5 *	0.0001
Systolic BP (mmHg)	128.1±20.1	131.8±22.5	136.1±21.6	141.3±24.7 #	144.5±20.1 #	0.0001
Hemoglobin (g/dL)	13.9±1.8	13.9±1.8	12.6±2.0 †	11.1±2.3 †	9.0±1.4 †	0.0001
u-Pro/u-Cre (g/g· Cr)	0.4±0.9	1.2±3.4	2.1±3.0	2.7±03.0	3.4±3.6	0.0001
Albumin (g/dL)	4.4±1.5	4.3±3.6	3.5±0.8 ‡	3.5±0.7 ‡	3.4±0.7 ‡	0.0001
Phosphorus (mg/dL)	3.5±0.5	3.6±0.5	3.6±0.6	3.9±0.8	5.1±1.1 $	0.0001
iPTH (pg/mL)	77.3±95.4	61.5±61.5	56.7±27.7	101.2±70.8	250.7±159.5 §	0.0001
Fe (μg/dL)	100.8±47.3	87.8±44.1	78.9±36.9	68.2±27.7	63.5±34.2 **	0.0001
Erythropoietin (IU/month)	0	0	146±926	2849±6296	15970±10929 ##	0.0001

Data are shown as mean ± SD.
LVMI: left ventricular mass index, BP: blood pressure, u-Pro/u-Cre: urine protein/urine creatinine, s-Cre: serum creatinine level, iPTH: intact parathormone
*P＜0.0001 stage Ⅰ, Ⅱ vs Ⅳ, Ⅴ. # P＜0.0001 stage Ⅰ, Ⅱ vs Ⅳ, Ⅴ. † P ＜0.0001 stage Ⅰ, Ⅱ vs Ⅲ, Ⅳ, Ⅴ.
‡ P＜0.0001 stage Ⅰ, Ⅱ vs Ⅲ, Ⅳ, Ⅴ. $ P＜0.0001 stage Ⅰ, Ⅱ, Ⅲ, Ⅳ vs Ⅴ. § P ＜0.0001 stage Ⅱ, Ⅲ, Ⅳ vs Ⅴ.
** P＜0.0001 stage Ⅰ, Ⅱ vs Ⅴ. ## P＜0.0001 stage Ⅰ, Ⅱ, Ⅲ, Ⅳ vs Ⅴ.

Table 3. Comparison of clinical parameters with and without LVH in each CKD stages

	Without LVH	With LVH	p
CKD stage Ⅰ	44%	57%	
Mean SBP (mmHg)	123.4 ± 19.3	132.0 ± 21.0	0.1642
Mean Hb (g/dL)	13.7 ± 1.9	14.1 ± 1.8	0.4822
CKD stage Ⅱ	48%	52%	
Mean SBP (mmHg)	126.8 ± 21.5	138.0 ± 21.7	**0.0076**
Mean Hb (g/dL)	14.1 ± 1.7	13.7 ± 2.0	0.3787
CKD stage Ⅲ	27%	73%	
Mean SBP (mmHg)	129.7 ± 19.6	139.4 ± 22.0	0.0648
Mean Hb (g/dL)	13.0 ± 1.9	12.5 ± 2.1	0.3152
CKD stage Ⅳ	19%	81%	
Mean SBP (mmHg)	134.2 ± 23.9	142.8 ± 22.2	0.1014
Mean Hb (g/dL)	12.6 ± 2.0	10.7 ± 2.1	**0.0002**
CKD stage Ⅴ	11%	89%	
Mean SBP (mmHg)	131.2 ± 16.0	146.0 ± 19.8	**< 0.0001**
Mean Hb (g/dL)	9.5 ± 1.3	9.0 ± 1.4	**0.0139**

Data are shown as mean ± SD.
LVH: left ventricular hypertrophy, BP: blood pressure

Table 4 Stepwise linear regression analysis of factors associated with LVMI

	p value	r value	F value
SBP	<0.0001	0.741	**36.74**
u-Pro/Cr	<0.0001	2.036	0.254
Alb	0.0045	-3.295	1.546
s-Cre	<0.0001	4.882	2.413
Hb	<0.0001	-7.808	**64.55**
EPO	<0.0001	0.001	1.829
Pi	<0.0001	8.214	0.169
Fe	0.0005	-0.190	1.068

SBP:systolic BP, u-Pro/Cr:urine protein/urine creatinine ratio, Alb:albumin, s-Cre:serum concentration of creatinine, Hb:hemoglobin, EPO: dose of erythropoietin /month, Pi:phosphorus, Fe: serum concentration of Fe

Legends for figures

Figure 1. Correlation between systolic blood pressure (SBP) and left ventricular mass index (LVMI)
SBP was directly correlated with LVMI (r=0.314, p＜0.0001).

Figure 2. Correlation between level of hemoglobin (Hb) and left ventricular mass index (LVMI)
Level of Hb was inversely correlated with LVMI (r=-0.372, p＜0.0001).

Figure 3. Comparison of left ventricular mass index (LVMI) among CKD stages
LVMI in stages IV and V was significantly higher than that in stages I and II (p＜0.001).