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

Running title: Risk factors for LVMI in CKD patients

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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 $194 \times Cr^{-1.094} \times Age^{-0.287} \times (0.739 \text{ if female})$ (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 II and V, and Hb was significantly lower in patients with LVH in stages IV and 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 IV and V in nondiabetic 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 Bsm1 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 euvoletic 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/1.73m²), 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 IV and 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


### Table 1 Patient characteristics in each CKD stage

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<th>III</th>
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<td>538</td>
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<td>66</td>
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<td>Age</td>
<td>48.0±19.3*</td>
<td>52.4±17.2†</td>
<td>61.0±14.8</td>
<td>61.4±15.2</td>
<td>61.7±14.2</td>
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<td>Primary kidney disease (%)</td>
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Data are shown as mean ± SD, or number of patients.

* $p < 0.0001$ stage I vs II, IV, V. † $p < 0.0001$ stage II vs III, IV, V
Table 2  Clinical parameters in each CKD stage

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<td>s-Cre (mg/dL)</td>
<td>0.6±0.1</td>
<td>1.1±2.5</td>
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<td>LVMI (g/m²)</td>
<td>53.7±17.5</td>
<td>53.0±16.2</td>
<td>61.6±18.9</td>
<td>66.4±19.4*</td>
<td>75.3±24.5*</td>
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<td>Systolic BP (mmHg)</td>
<td>128.1±20.1</td>
<td>131.8±22.5</td>
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<td>141.3±24.7*</td>
<td>144.5±20.1*</td>
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<td>Hemoglobin (g/dL)</td>
<td>13.9±1.8</td>
<td>13.9±1.8</td>
<td>12.6±2.0†</td>
<td>11.1±2.3†</td>
<td>9.0±1.4†</td>
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<td>u-Pro/u-Cre (g/g Cr)</td>
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<td>1.2±3.4</td>
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<td>3.4±3.6</td>
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<tr>
<td>Albumin (g/dL)</td>
<td>4.4±1.5</td>
<td>4.3±3.6</td>
<td>3.5±0.8‡</td>
<td>3.5±0.7‡</td>
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<td>Phosphorus (mg/dL)</td>
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<td>3.6±0.5</td>
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<td>3.9±0.8</td>
<td>5.1±1.1§</td>
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<td>iPTh (pg/mL)</td>
<td>77.3±95.4</td>
<td>61.5±61.5</td>
<td>56.7±27.7</td>
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<td>250.7±159.5§</td>
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<td>Fe (µg/dL)</td>
<td>100.8±47.3</td>
<td>87.8±44.1</td>
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<td>68.2±27.7</td>
<td>63.5±34.2**</td>
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<td>Erythropoietin (IU/month)</td>
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<td>0</td>
<td>146±926</td>
<td>2849±6296</td>
<td>15970±10929**</td>
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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.
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<td>I</td>
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<td>Mean Hb (g/dL)</td>
<td>13.7 ± 1.9</td>
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<td>II</td>
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<td>III</td>
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<td>Mean SBP (mmHg)</td>
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<td>Mean Hb (g/dL)</td>
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<td>V</td>
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<td>Mean Hb (g/dL)</td>
<td>9.5 ± 1.3</td>
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Data are shown as mean ± SD.
LVH: left ventricular hypertrophy, BP: blood pressure
Table 4  Stepwise linear regression analysis of factors associated with LVMI

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<td>Fe</td>
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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 ($p<0.001$).