Hemoglobin Variability as Risk Factor of Left Ventricle Dilation in Chronic Kidney Disease Patient on Routine Hemodialysis

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ABSTRACT

Background: Several patients with chronic kidney disease (CKD) undergoing routine hemodialysis (HD) have abnormalities of left ventricle (LV) morphology with feature LV dilation due to volume overload and chronic ischemia, which has high risk of mayor adverse cardiovascular event. Anemia causes LV dilation through high output state mechanism. Anemia management in CKD patients causes hemoglobin (Hb) fluctuations or hemoglobin variability (Hb-Var) which is thought to cause LV dilation through relative repetitive ischemia mechanisms. Research linking Hb-Var as risk factor for LV dilation has never been done.
Method: Matched case-control study was carried out by taking echocardiographic data of CKD patients undergoing routine HD in HD Unit Dr. Sardjito hospital. The LV diameter is divided into samples with LV (+) dilated profile as a case group, and LV (-) dilated as a control group. Matching was done on variables of age, gender and HD frequency. The Hb-Var parameter was calculated by the residual SD method based on the Hb value in the last 6 months. Fisher-Exact hypothesis test was used to assess the relationship between Hb-Var and LV dilation, while the logistic regression test was used for multivariate testing.
Result: Total of 79 subjects entered in this study, there were 23 subjects of case groups and 28 subjects of control group after matching and adjusting the control formula. The proportion of high Hb-Var in the group with dilated LV (+) and dilated LV (-) were 21.7% and 17.9%, respectively. The Fisher-Exact test shows that there is no relationship between Hb-Var and LV dilation, with OR 1.28 (95% CI 0.32-5.10). Logistic regression test shows that there are no variables that affect independently of LV dilation.
Summary: CKD patients undergoing routine HD with high Hb-Var profiles do not have a higher risk of LV dilation than patients with low Hb-Var profiles.

Keywords: hemoglobin variability; left ventricle dilation; chronic kidney disease, hemodialysis

INTISARI

Latar Belakang: Sebagian pasien penyakit ginjal kronik (PGK) yang menjalani hemodialisis (HD) rutin memiliki abnormalitas morfologi ventrikel kiri (VKi) berupa dilatasi VKi oleh karena *volume overload* dan iskemia kronik, yang memiliki risiko tinggi kejadian kardiovaskular mayor. Anemia menyebabkan dilatasi VKi melalui mekanisme *high output state*. Manajemen anemia pada pasien PGK menyebabkan fluktuasi hemoglobin (Hb) atau variablitas hemoglobin (Var-Hb) yang diduga menyebabkan dilatasi VKi melalui mekanisme iskemia repetitif relatif. Penelitian yang menghubungkan Var-Hb sebagai faktor risiko dilatasi VKi belum pernah dilakukan.

Metode Penelitian: Studi *matched* kasus-kontrol dilakukan dengan mengambil data ekokardiografi pasien PGK yang menjalani HD rutin di Unit HD RSUP Dr. Sardjito. Diameter VKi dibagi menjadi sampel dengan profil dilatasi VKi (+) sebagai kelompok kasus, dan dilatasi VKi (-) sebagai kelompok kontrol. *Matching* dilakukan pada variabel usia, jenis kelamin dan frekuensi HD. Parameter Var-Hb dihitung dengan metode residual SD berdasarkan nilai Hb dalam 6 bulan terakhir. Uji hipotesis *Fisher-Exact* dipakai untuk menilai hubungan antara Var-Hb dan dilatasi VKi, sedangkan uji regresi logistik dipakai untuk uji multivariat.

Hasil: Sebanyak 79 subjek yang masuk dalam penelitian ini, terdapat 23 subjek kelompok kasus dan 28 subjek kelompok kontrol setelah proses *matching* dan penyesuaian rumus kontrol. Proporsi Var-Hb tinggi pada kelompok dengan dilatasi VKi (+) dan dilatasi VKi (-) masing-masing 21,7% dan 17,9%. Uji *Fisher-Exact* menunjukkan tidak terdapat hubungan antara Var-Hb dengan dilatasi VKi, dengan OR 1,28 (IK 95% 0,32-5,10). Uji regresi logistik menunjukkan tidak terdapat variabel yang mempengaruhi secara independen terhadap dilatasi VKi.

Simpulan: Pasien PGK yang menjalani HD rutin dengan profil Var-Hb tinggi tidak memiliki risiko lebih tinggi untuk terjadi dilatasi VKi dibandingkan pasien dengan profil Var-Hb rendah.

INTRODUCTION

Patients with chronic kidney disease (CKD) who have undergone chronic hemodialysis (HD) have cardiac structural abnormalities in the form of asymmetric hypertrophy, eccentric remodeling and geometric distortion.[1] Left ventricular (LV) morphology changes in CKD patients undergoing routine HD are thought to be the cause of more than 80 % of this population die from cardiovascular causes, namely arrhythmia or sudden cardiac death (SCD).[2] Correction of traditional and non-traditional risk factors is crucial because cardiorenal syndrome (CRS) type IV includes chronic cardiovascular processes in CKD.[3,4]

Anemia is the most common complication in CKD, in addition to non-traditional risk factors, which have an adverse effect on quality of life, and increase morbidity and mortality.[3,5] Anemia causes high output state conditions characterized by increased venous return, arterial vasodilation and increased sympathetic activity, causing volume overload. Volume overload status will cause myocardial remodeling in the form of addition of heart muscle mass in series or eccentric hypertrophy, which is characterized by LV dilation and left ventricular hypertrophy (LVH).[3]

Full range of therapeutic modalities used in anemia management is not always beneficial, because too high Hb values have been known to cause poor cardiovascular consequences.[6] National Kidney Foundation Dialysis Outcome Quality Initiative (NKF-DOQI) suggests that hemoglobin levels should be maintained between 11- 12 g / dl in CKD patients.[7]

In fact, it is not easy to maintain Hb levels in a narrow range, so that Hb levels show fluctuating values based on laboratory measurements every month in CKD patients, which is called hemoglobin variability (Hb-Var). Changing Hb levels are expected to accelerate LV remodeling process more rapidly.[8] Relative ischemia and recurrent hypoxia due to conditions of anemia in CKD cause signal activation of

myocardial cell growth, which has an impact on LV hypertrophy and dilation.[9]

One specific parameter to assess the effect of Hb-Var is the LV diameter. The ability of LV diameter as a component of SCD risk stratification can help in the management of primary prevention of SCD.[10] Most common causes of LV dilation are ischemic heart disease, other etiologies include severe organic heart valve disease, congenital heart disease, cardiomyopathy, and chronic hypertension.[11,12] Based on above theory, Hb-Var which has an ischemic effect on the myocardium has a LV dilatation effect in CKD patients. Research linking Hb-Var to CKD patients undergoing routine HD with LV dilated has never been done.

METHODS

This study is an analytic observational using paired case-control design to looking for the LV dilation risk factors in CKD patients undergoing routine HD. The case group in this study were patients with LVdilated (+) profile, and as a control group were patients with LV dilated (-) profiles.

Matching characteristics between case and control groups included a combination of age variables (paired with subject groups within 5 years), gender (men with men, women and women), and HD frequency (2 times/week). The study was conducted in HD room and Echocardiography room of the Dr. General Hospital Sardjito Yogyakarta from December 2017 to April 2018. Inclusion criteria consist of stage 5 CKD patients undergoing routine HD, willing to be a research subject and signed an informed consent, there is a serial Hb examination every month in the last 6 months. Exclusion criteria consist of echocardiographic features that are difficult to assess, history of atherosclerotic ischemic heart disease, history of congenital heart disease, history of severe organic heart valve disease, history of cardiomyopathy heart disease, history of primary erythrocyte formation disorders, and a history of malignancy.

Research subjects were collected by looking data registers in the HD room. When the subject underwent routine HD at HD Unit of Dr. SardjitoHospital, the subject was asked about his willingness to participate in this study by signing an informed consent. After agreement, the patient's data is then tracked to see the basic characteristics, comorbidities, laboratory results, and therapeutic history through medical records and interviews.

Laboratory data include Hb levels, blood urea nitrogen (BUN), creatinine, albumin, and iron status. Laboratory blood sampling is carried out every month after the HD procedure, in accordance with the routine procedure at HD unit Sardjito hospital. Hb value is taken from laboratory examination in the past 6 months.

The six Hb values are calculatedbased on formula :

Hb-Var

$$\sqrt{\frac{(\bar{x}-x_1)+(\bar{x}-x_2)+(\bar{x}-x_3)+(\bar{x}-x_4)+(\bar{x}-x_5)+(\bar{x}-x_6)}{5}},$$

where $\bar{x}$ is the Hb mean in the last 6 months, and x_i is the Hb level in the month-*i*, then the result are classified into the high Hb-Var group (≥1 g/dl) or low (<1 g/dl).

Echocardiographic data was taken at the Echocardiography examination room of the Sardjito hospital. Transthoracal echocardiography (TTE) is performed after an HD procedure in less than 24 hours post HD procedure. All patients underwent TTE examination with a VIVID 7 device (General Electric, USA). Left ventricle diameter measurement uses M-mode method by placing the cursor perpendicular to the mitral tip, calculated from anterior basal border to posterior basal border of endocardium. Calculation of LV diameter is performed intraobserverly and interobservered by 2 expert examiners, offline from a workstation computer using Echopac (General Electric) software which is blind to clinical datasubject. Left vetricle diameter values that have been validated are classified into groups with LV dilated profiles and non-LV dilated based on American Society Cardiology criteria.

Collecting data were analyzed statistically with IBM SPSS Statistics 23

program. Basic characteristics data are presented based on matching results from variables that can be controlled through the t-test. Other variables that are examined included in the basic characteristics data, carried out a comparative test with t-test and normality test with Kolmogorov-Smirnov.

Hemoglobin variability hypothesis testing as a risk factor for LV dilation is performed using a 2x2 table with Chi-square analysis if the expected <5 is a maximum of 20% of the cell count, or Fisher's Exact if the Chi-square condition is not met. Bivariate analysis was conducted to determine the strength of the confounding variable relationship with LV dilation. P values <0.25 indicate that these variables are eligible to be included in multivariate analysis. Multivariate analysis was performed to determine independent risk factors associated with LV dilation. The results of this analysis are reported as an OR with a value of p <0.05 indicating that the variable is a risk factor of LV dilation.

RESULTS

This research was conducted by taking an affordable population of CKD patients undergoing routine HD in HD Unit of Dr. Sardjito hospital. One hundred twenty eight patients who had routine HD schedules were given information to participate as subjects in this study.

After exclusion, there were 79 subjects left which would then be divided into case groups and controls based on whether or not LV was dilated. A total of 51 subjects consisting of 23 case subjects and 28 control subjects (figure 1).

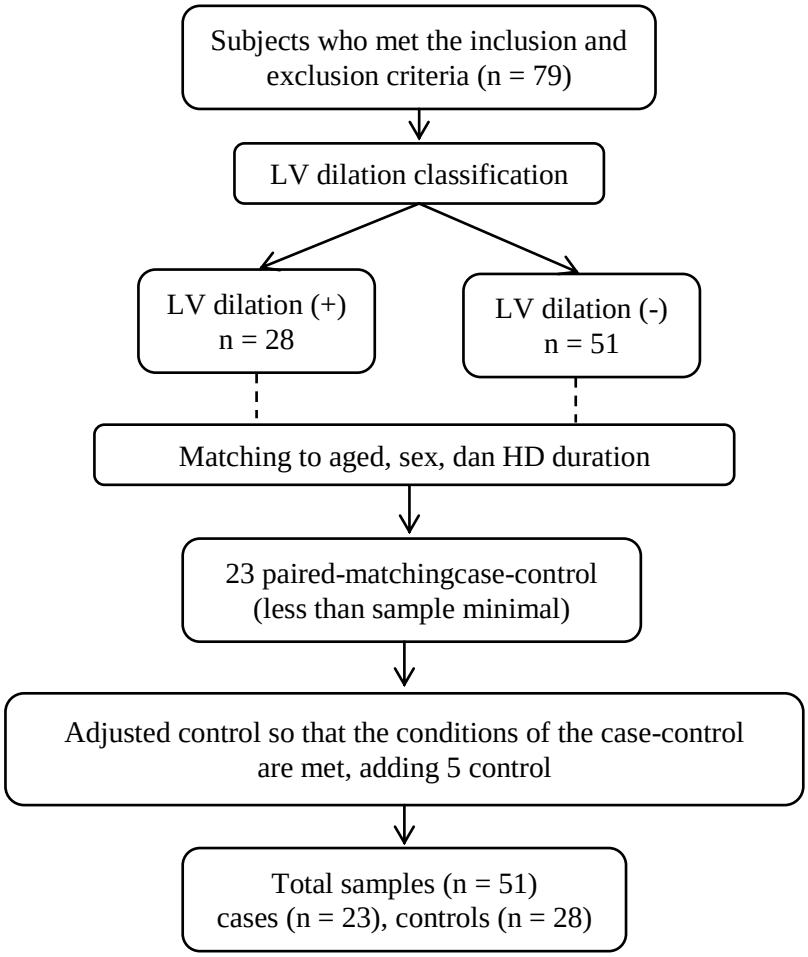

Figure 1. Subject selection scheme with matching method

Most CKD patients who underwent routine HD showed a history of hypertension, with one third of the total population having comorbid diabetes mellitus. Anemic status of this population shows that Hb levels are always below normal values with mean Hb levels in the last 6 months and maximum Hb in case and control groups are 9.2/10.3 g/dl and 9.2/10.9 g/dl, respectively. Median Hb-Var in the case and control groups showed values of 0.77 g/dl and 0.78 g/dl, with high Hb-Var values ranging from 15-20%. Profile of LV geometry in the LV dilation (+) group showed concentric hypertrophy of 73.9% and eccentric hypertrophy of 26.1%, while the LV dilation (-) group showed 39.3% normal geometry, 50% concentric hypertrophy, and 10.7% eccentric hypertrophy. Most CKD patients undergoing routine HD use angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB), and calcium channel blockers (CCB), with only a few using β-blockers (table 1).

Table1. Baseline characteristics of CKD patients undergoing routine HD based on LV dilation (+) and LV dilation (-) classification

Characteristics	LV dilation (+) (n = 23 / 45%)	LV dilation (-) (n = 28 / 55%)	p value
Sex, men (%)	13 (56.5)	16 (57.1)	0.97*
Age (mean ± SD)	50.0±14.4	51.5±13.4	0.72*
HD frequency, times/week (mean±SD)	2.0±0.0	2.0±0.0	1.00*
Body surface area, m^2 (mean±SD)	1.58±0.18	1.60±0.21	0.61
HD duration, month (median; IQR)	48; 60	36; 81	0.66
Hypertension (%)	22 (95.7)	24 (85.7)	0.24
Diabetes mellitus (%)	8 (34.8)	10 (35.7)	0.95
Laboratoryparameters			
BUN, mg/dl (median; IQR)	57.0; 19.7	53.2; 23.1	0.34
Creatinine, mg/dl (mean±SD)	10.6±27.2	9.7±8.3	0.41
Albumin, g/dl (median; IQR)	4.0 ; 0.6	3.9 ; 0.4	0.46
Hemoglobin (last 6 month)			
Mean, g/dl (mean ± SD)	9.2±1.0	9.2±1.4	0.13
Minimum, g/dl (mean ± SD)	8.3±1.4	8.9±1.6	0.21
Maximum, g/dl (mean ± SD)	10.3±1.3	10.9±1.5	0.12
Hb-Var, g/dl (median; IQR)	0.77; 0.53	0.78; 0.32	0.17
Hb-Var, high (%)	5 (21.7)	5 (17.9)	0.73
Hematocrit, % (mean ± SD)	27.5±4.0	28.2±3.8	0.15
TTE parameters			
LVIDd, mm (median; IQR)	54.0; 6.0	46.0; 5.0	<0.001
Men, mm (mean ± SD)	55.0; 6.0	47.5; 4.0	
Women, mm (mean ± SD)	51.5; 4.0	44.5; 4.0	
LVEF (mean ± SD)	56.0±15.0	69.0±10.0	<0.001
LV geometry			0.002
Normal (%)	0	11 (39.3)	
Concentric hypertrophy (%)	17 (73.9)	14 (50.0)	
Eccentric hypertrophy (%)	6 (26.1)	3 (10.7)	
Drugs			
ACE-I or ARB (%)	22 (95.7)	20 (71.4)	0.03
CCB (%)	19 (82.6)	20 (71.4)	0.35
β-blocker (%)	3 (13.0)	1 (3.6)	0.22

*) Matching variable.

EF: ejection fraction; IQR: interquartile range; LVIDd: left ventricle internal diameter at diastole; SD: standard deviation

Table 2. Hypothesis test Hb-Varas risk factor for LV dilation

	LV dilation (+)	LV dilation (-)	Total	OR (95%CI)
High Hb-Var	5 (21.7%)	5 (17.9%)	10	1.28 (0.32-5.10) p=0.50
Low Hb-Var	18 (78.3%)	23 (82.1%)	41	
Total	23	28	51	

Table 3. Multivariateanalysis of risk factors for LV dilation

Variables	OR (95% CI)	p
Hb-Var	0.86 (0.17-4.33)	0.86
Body surface area	0.17 (0.01-8.16)	0.37
HD duration	1.00 (0.98-1.01)	0.94
Hypertension	<0.01 (<0.01)	0.99
Diabeter mellitus	0.5 (0.12-2.14)	0.35
Albumin	1.39 (0.38-5.00)	0.62
Hb mean	0.94 (0.46-1.92)	0.86
ACE-I / ARB	<0.01 (<0.01)	0.99
CCB	0.51 (0.06-4.37)	0.54
β-blocker	5.10 (0.38-68.09)	0.22

This study uses a case-control design, so Chi-square analysis is used with the calculation of OR. Fisher-Exact test showed p=0.5, so it was concluded that Hb-Var was not a risk factor for LV dilation both clinically and statistically, in CKD patients undergoing routine HD with OR 1.28 (0.32-5.10) (table 2). Multivariate test with logistic regression showed that all variables suspected of risk factors did not significantly influence LV dilation (table 3).

DISCUSSION

This study using a case-control design to assess effect of Hb-Var cause LV dilation in CKD patients, especially those undergoing routine HD. The advantage of the case-control method is that the characteristics of the subjects in both case and control populations can be equated so that the expected output proportion is the same, and is very useful in the population of CKD patients undergoing routine HD with many comorbidities and risk factors that influence LV dilation. The second advantage is the case-control design is suitable to detect rare cases or risk factors, which in this study is Hb-Var which has a complex pathophysiology and dominance of the influence of other risk factors.

The third advantage is the statistical output of case-control designs in the form of OR that have better statistical and clinical value than the risk of prevalence in cross-sectional designs, even though they are inferior to relative risk (RR). The method of selecting samples with matching in this study is conducted on variables that can be controlled, namely HD frequency, age and sex with an acceptable limit of agreement of 0.672, so that the matching is expected to be appropriate.

More than 90% patients in this study had comorbid hypertension. Hypertension is the most common complication in CKD, and its prevalence increases with increasing age and severity of disease.[13] Thirty five percents patients in this study subject had a diabetes mellitus (DM) profile. The prevalence of the most common causes of CKD is DM, hypertension nephopathy, glomerulo nephritis, and other causes such as stones, nephrotic syndrome.[14] Diabetes mellitus is a traditional risk factor for CKD that has a role in CKD progression through a mechanism of deteriorating

kidney function and influencing traditional risk factors and another non-traditional.[15]

The anemia profile in this study showed mean 9.2 g/dl and maximum 10.7 g/dl in the last 6 months, indicating an complication of CKD in the form of anemia which has not yet received optimal management so that the Hb value is maintained at the level of 11-12 g/dl as recommended NKF-DOQI. Management of anemia in CKD patients, especially those undergoing routine HD based on the consensus of the Indonesian Nephrology Association, requires correction of the overall cause of anemia before starting erythropoietin stimulating agent (ESA) therapy.[16] Some condition to be considered related to correction of anemia include infection, iron status, and malnutrition. The risk of ESA hypo response will increase if these factors are not corrected.[17–19]

Mean Hb-Var obtained value 0.7 g/dl with a high category 19.8%. Hemoglobin variability is associated with successful of anemia therapy.[20] The smaller Hb-Var value, anemia management is close to optimal. In this study, high levels of Hb-Var were still found, most likely related to provision of less optimal anemia therapy. Hb-Var can be influenced by many factors, not only condition of anemia itself along with the treatment of anemia, other comorbidities such as infections and bleeding complications, HD and hospitalization.[21,22] Blood samples procedure can also affect measured Hb levels, both taken before and after the HD procedure. In this study, examination of Hb levels was carried out after the HD procedure in accordance with the local hospital policy, thus causing the status to underestimate the anemia profile due to the ultrafiltration process.[23]

Median of LVIDd subjects in this study were 50 mm, with mean EF is 63%. More than 50% of subjects gave LV geometrical feature in form of concentric hypertrophy, the remainder was eccentric hypertrophy and little with normal geometry. Combination of pressure-volume overload in CKD undergoing routine HD will cause a progressive increase in myocardium, so addition of left ventricle mass index (LVMI) is more visible than the addition of relative wall thickness (RWT).[5] If mechanism of volume overload is more dominant, then feature of eccentric hypertrophy will be more visible. Combination of pressure-volume overload is a complex pathophysiological process, so that changes in LV geometry can vary with the characteristics of asymmetric hypertrophy and LV distortion.[2]

Hemodialysis pattern in Indonesia usually uses the rules 2 times a week with a duration of 4 hours, due to local insurance policies. This pattern is below the standard HD conventional pattern. This may be a factor that contributes to volume overload, thus increasing number of CKD patients undergoing routine HD with eccentric hypertrophy profiles.

Most CKD patients undergoing routine HD get antiremodeling therapy inACE-I or ARB, sometimes combined with CCB dihydropiridin type.This combination is useful for reducing LV maladaptivity due to excessive remodeling, by reducing blood pressure which plays a role in the pressure overload mechanism.[24] Use of ACE-I and/or ARB is also known to have a mass regression effect of LV and interstitial collagen deposits, and the effect will increase when combined with CCB.[25] The use of β-blockers in the subjects in this study is still small, which may be caused by non-optimal prescribing. Class-β-blocker drugs are known to inhibit LV remodeling through sympathetic nervous system suppression, which is a modulation of LV remodeling process.[26] Combination of the use of ACE-I and β-blockers is also known to reduce hospital admission in CKD patients.[4]

Hypothesis testing shows that Hb-Var does not affect LV dilation, soanalysis of confounding variables is needed to find risk factors for VKi dilation. The first Hb-Var study states high Hb-Var is associated with mortality,[8] but the Hb-Var study after this stated that Hb-Var was not associated with mortality. This is due to relative repetitive ischemic theory occurs due to high Hb-Var which is covered by many comorbidities in CKD patients undergoing routine HD, one of which is the degree of anemia, which has a much greater effect on increasing mortality.[21,27,28] Subsequent

research tried to determine the effect of Hb-Var on the heart which is a specific organ affected by relative repetitive ischemia due to changes in Hb levels using LVMI parameters.[29] The result is an increase in LVMI in 1 year in the group with baseline anemia. Increased LVMI can also be caused by CKD progression, especially combination of volume-pressure overload processes caused by various comorbidities and CKD complications, especially those undergoing routine HD. LVMI is also not a specific parameter of LV remodeling due to ischemic processes compared to LV diameter.

Multivariate tests of risk factors for LV dilation show there are no variables that influence independently of LV dilation. This may be due to several variables not included in risk factor analysis. Most common cause of LV dilation in CKD populations undergoing routine HD is volume overload, and remainder including ischemic heart disease both coronary and non-coronary etiology, organic heart valve disorders, dilated, hypertrophic or arrhythmia-induced cardiomyopathy.[5,30] Risk factors related to volume overload that were not analyzed in this study were Kt/V because of difficulties in medical recordsdocumentation. The theory of HD-induced ischemia is difficult to interpret as a measurable variable. There are no quantitative methods of measuring uremic toxins such as p-cresol and indoxyl sulfate. Identification of imaging degree of ischemia in heart muscle is only based on the examination of TTE that has high subjectivity and cannot detect severity of myocardial lesions, while examination of coronary angiography, nuclear, and cardiac magnetic resonance is not routinely performed in CKD patients undergoing routine HD.[31] Some of factors mentioned above, which affect volume status of body fluids and ischemia that play a role in the LV remodeling process, which in this study were not included as confounding dilated LV.

Limitation

Limitations of this study are number of variables play a role in pathophysiology that affect process of ischemia and volume overload in CKD undergoing routine HD, but in this study no analysis was carried out, causing no significant variables cause LV dilation in this study, because there is no modality that can measure these variables, or examination modality has never been carried out in this population. Second, comorbid variables of hypertension and DM, as well as the variables of drug use did not include duration of diagnosis and duration of treatment due to limitations in data collection.

CONCLUSION

CKD patients undergoing routine HD with high Hb-Var profiles do not have a higher risk of LV dilation than patients with low Hb-Var profiles.

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