Prognostic Value of Reduced Left Ventricular Ejection Fraction at Start of Hemodialysis Therapy on Cardiovascular and All-Cause Mortality in End-Stage Renal Disease Patients

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Background and objectives: Cardiac failure is directly affected by left ventricular (LV) dysfunction, and particularly LV systolic dysfunction is strongly associated with survival in ESRD patients. The aim of this study was to determine the prognostic value of reduced LV ejection fraction (LVEF) measured at the time of initiation of hemodialysis (HD) in incident HD patients.

Design, setting, participants, & measurements: 1254 consecutive ESRD patients who electively started HD therapy were screened by echocardiography within 1 month after its inception. They were divided into five groups according to LVEF levels with a decrease of 0.1 each and were followed up for up to 7 years. Survival was examined with the Kaplan-Meier method and compared using the log-rank test.

Results: Among the 1254 patients, LVEF levels >0.6, 0.5 to 0.6, 0.4 to 0.5, 0.3 to 0.4, and <0.3 were seen in 842 (67.1%), 247 (19.7%), 107 (8.5%), 41 (3.3%), and 17 (1.4%) patients, respectively. On Kaplan-Meier analysis, 7-year event-free rates from cardiovascular death were 84.2, 83.7, 73.6, 59.4, and 30.9% in order of groups with decreasing LVEF of 0.1 each, respectively. Seven-year event-free rates from all-cause death were 69.2, 61.7, 57.1, 45.9, and 23.1% in the respective groups. Even after adjustment for other risk factors, decreasing LVEF was a strong independent predictor for cardiovascular death.

Conclusions: Reduced LVEF on starting HD therapy could stratify risk of cardiovascular and all-cause mortality in ESRD patients. Screening by echocardiography at start of HD therapy might be recommended to predict prognosis in patients with ESRD.


Cardiovascular disease is a major complication in patients on maintenance hemodialysis (HD) and accounts for one half of the causes of their deaths (1–5). Moreover, in this population, cardiac dysfunction is common (6) and is related to a higher incidence of mortality and hospitalization (7). Left ventricular (LV) dysfunction directly affects cardiac failure, particularly, and is strongly associated with a poor survival in patients with ESRD with constant body-fluid overload status (8).

Routine assessment of LV ejection fraction (EF) has been recommended in patients with heart failure (9). Curtis and co-workers showed that lower LVEF was associated with a linear increase in mortality in nearly 8000 non-HD patients with stable heart failure (10). Analysis of patients on maintenance HD by ultrasonic-echocardiography (UCG) has been recommended for risk stratification (11). Zoccali et al. revealed an association between reduced LVEF and increased adverse events in 254 asymptomatic HD patients in their cohort study (12). However, the association between LV systolic dysfunction at the beginning of HD therapy and the prognosis remains unclear in such patients. We hypothesized that LVEF might predict their prognosis after initiating HD therapy. Thus, we assessed the potential prognostic value of reduced LVEF detected by UCG at the beginning of HD therapy in ESRD patients in this study.

Materials and Methods

Study Population

This study consisted of 1254 consecutive ESRD patients who began HD therapy between November 2000 and August 2007. UCG was prospectively performed on a nondialysis day within 1 month after beginning HD therapy. The patients were followed up for up to 7 years.

Blood data were analyzed from fasting blood samples obtained between 7:00 and 8:00 a.m. on the next day of HD when UCG was performed. The primary endpoint was cardiovascular death caused by heart failure, myocardial infarction, arrhythmia, sudden death, and other cardiac deaths. The secondary endpoint was all-cause death. Data
for endpoints were obtained from hospital charts and through telephone interviews with patients conducted by trained reviewers blinded to the UCG analysis. In this study, cases of unwitnessed death were counted as sudden deaths. Diabetes was defined as a history or presence of diabetes and/or a fasting plasma glucose concentration >126 mg/dl and/or having a fasting plasma glucose concentration >126 mg/dl or a glycosylated hemoglobin (HbA1c) concentration >6.5%. Hypertension was defined as having systolic BP >160 mmHg and/or diastolic BP >90 mmHg or undergoing antihypertensive treatment. Dyslipidemia was defined as having total cholesterol levels >220 mg/dl or taking lipid-lowering therapy. Smoking habit was defined as currently smoking or having discontinued cigarette use within 6 months before starting HD.

The study protocol conformed to the guidelines of the ethics committee of our institution and was conducted in accordance with the Declaration of Helsinki. The physicians obtained written informed consent from each patient.

Echocardiography

According to the recommendations of the American Society of Echocardiography, UCG was performed on a nondialysis day. UCG recordings were evaluated by two expert physicians blinded to other clinical information. LVEF was measured using modified Simpson method (13). The measurements from two technicians were averaged. Patients were divided into five groups according to their LVEF levels: patients with LVEF ≥0.6, 0.5 to 0.6, 0.4 to 0.5, 0.3 to 0.4, and <0.3, respectively. LVEF <0.5 was considered as LV systolic dysfunction (14,15).

The intraobserver variabilities of LVEF in UCG were well correlated (r = 0.939, P < 0.001). The mean difference was 0.002 ± 0.04.

Statistical Analyses

SPSS was used for statistical analyses. All values are expressed as mean ± SD or incidences (%). Differences among the groups were evaluated by unpaired t test for continuous variables and by χ² test for categorical variables. Differences in event-free survival among the groups were examined with Kaplan-Meier method and compared using a log-rank test.

Hazard ratios (HR) and 95% confidence intervals (CIs) were calculated for each factor by a Cox univariate analysis. Covariates including established risk factors (age, gender, body mass index [BMI], diabetes, hypertension, dyslipidemia, smoking status, serum albumin levels, serum C-reactive protein [CRP] levels, and LV mass index) and LVEF were assessed by Cox multivariable regression analysis to determine significant predictors for the endpoint. In addition, estimates of the Harrell C index of the Cox models and its 95% CIs were calculated in a baseline model with established risk factors and a second enriched model containing the baseline established risk factors plus LVEF (16,17). In addition, likelihood-ratio tests were performed to evaluate whether the model with established risk factors improved after the addition of LVEF, as Harrell described (18). A value of P < 0.05 was considered statistically significant.

Results

The median duration of follow-up was 4.2 years (SD 2.4). Among 1254 enrolled patients, 828 (66.0%) were males. The mean age was 62 ± 14 years. Diabetes was seen in 564 patients (45.0%). The mean BMI was 21.0 ± 3.2 kg/m². LV systolic dysfunction with LVEF <0.5 was observed in 165 (13.2%) ESRD patients at the beginning of HD therapy.

Table 1 shows baseline characteristics stratified by LVEF values: group 1 consisted of subjects with LVEF ≥0.6 (n = 842); group 2, LVEF ≥0.5 and <0.6 (n = 247); group 3, LVEF ≥0.4 and <0.5 (n = 107); group 4, LVEF ≥0.3 and <0.4 (n = 41); group 5, LVEF <0.3 (n = 17). Gender (P = 0.016), age (P = 0.013), incidence of diabetes (P = 0.010), hypertension (P = 0.0008), and LV mass index (P < 0.0001) were significantly different among the groups.

A total of 317 patients (25.3%) died during the follow-up period (Table 2). Among them, 99 (7.9% of total patients) of these deaths were cardiovascular deaths. Figure 1 shows Kaplan-Meier curves for the primary endpoint. The cardiovascular deaths significantly increased when the LVEF levels decreased. The 7-year event-free rates from cardiovascular deaths were 84.2, 83.7, 73.6, 59.4, and 30.9% in groups 1, 2, 3, 4, and 5, respectively. According to the secondary endpoint, survival rates significantly decreased as the LVEF levels decreased. The 7-year event-free rates from all-cause

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics among groups according to LVEF levels</th>
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<td>Entire Cohort</td>
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<tr>
<td>Male</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Diabetes</td>
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<td>CRP (mg/l)</td>
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<td>LVMI (g/m²)</td>
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LVMI, left ventricular mass index. Values are given as mean ± SD or percentage.
death were 69.2, 61.7, 57.1, 45.9, and 23.1% in groups 1, 2, 3, 4, and 5, respectively (Figure 2).

Table 2 shows the proportion of cause of death among the groups according to LVEF levels. The lower the LVEF, the more frequent the cardiovascular deaths. Especially, in group 5, cardiovascular death accounted for 70% of total deaths.

Table 3 and Table 4 show the results of Cox hazard analysis to determine the predictive value for cardiovascular mortality and all-cause mortality. As LVEF decreased, the risks of cardiovascular death and all-cause death increased, even after multivariate analysis. These data suggested that LV systolic dysfunction was a strong and independent predictor of cardiovascular death and all-cause death. For cardiovascular mortality, the age, diabetes, and serum CRP levels were also independent predictors (age: HR 1.03, 95% CI 1.01 to 1.05, \( P = 0.0041 \); diabetes: HR 2.36, 95% CI 1.45 to 3.87, \( P = 0.0006 \); serum CRP levels: HR 1.01, 95% CI 1.01 to 1.02, \( P = 0.0002 \)). As to all-cause mortality, other independent predictors were age, male gender, diabetes, BMI, serum albumin levels, and serum CRP levels (age: HR 1.05, 95% CI 1.03 to 1.06, \( P < 0.0001 \); male: HR 1.60, 95% CI 1.08 to 2.38, \( P = 0.019 \); diabetes: HR 1.85, 95% CI 1.30 to 2.64, \( P = 0.0007 \); BMI: HR 0.86, 95% CI 0.80 to 0.92, \( P < 0.0001 \); serum albumin levels: HR 0.62, 95% CI 0.43 to 0.90, \( P = 0.012 \); serum CRP levels: HR 1.01, 95% CI 1.01 to 1.02, \( P < 0.0001 \).

Table 5 shows the results of the Harrell C index calculations for Cox regression analysis predicting cardiovascular mortality and all-cause mortality in a baseline model with established risk factors and a model with established risk factors plus LVEF. The Harrell C index increased significantly when LVEF was added to a model with established risk factors in prediction of both cardiovascular mortality and all-cause mortality (0.789 versus 0.750, \( P = 0.0049 \); 0.768 versus 0.751, \( P = 0.001 \), respectively).

When we divided patients into quartiles according to LVEF, the first quartile (Q1), second quartile (Q2), third quartile (Q3), and fourth quartile (Q4) included patients with LVEF \(<0.559\), 0.559 to 0.614, 0.614 to 0.653, and \(\geq 0.653\), respectively. The 7-year event-free rates from cardiovascular death were 81.7% in Q1, 92.0% in Q2, 93.8% in Q3, and 87.6% in Q4 by Kaplan-Meier survival rate (\( P < 0.0001 \)). As to all-cause death, the 7-year event-free rates were 57.0% in Q1, 71.8% in Q2, 75.8% in Q3, and 67.7% in Q4 (\( P = 0.0015 \)).

We performed logistic regression analysis to assess the association of clinical characteristics and other UCG variables with LVEF \(<0.5\). Diabetes, asynergic wall motion, and mitral regurgitation were independently associated with LVEF \(<0.5\) (diabetes: OR 1.48, 95% CI 1.02 to 2.13, \( P = 0.038 \); asynergic wall

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**Table 2. Proportion of mortality among the groups according to LVEF levels**

<table>
<thead>
<tr>
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<th>(\geq 0.6) ((n = 842))</th>
<th>0.6 to 0.5 ((n = 247))</th>
<th>0.5 to 0.4 ((n = 107))</th>
<th>0.4 to 0.3 ((n = 41))</th>
<th>&lt;0.3 ((n = 17))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall death, (N(%))</td>
<td>186 (22.1)</td>
<td>70 (28.3)</td>
<td>33 (30.8)</td>
<td>16 (39.0)</td>
<td>12 (70.6)</td>
</tr>
<tr>
<td>Cardiovascular death, (N(%))</td>
<td>48 (5.7)</td>
<td>21 (8.5)</td>
<td>13 (12.1)</td>
<td>9 (21.9)</td>
<td>8 (47.1)</td>
</tr>
<tr>
<td>Noncardiovascular death, (N(%))</td>
<td>138 (16.4)</td>
<td>49 (19.8)</td>
<td>20 (18.7)</td>
<td>7 (17.1)</td>
<td>4 (23.5)</td>
</tr>
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Proportion of cause of death

Cardiovascular (%) | 25.8 | 30.0 | 39.3 | 56.2 | 66.7
heart failure (%) | 9.7 | 14.3 | 24.2 | 18.8 | 41.7
myocardial infarction (%) | 7.5 | 4.3 | 3.0 | 12.5 | 8.3
sudden death (%) | 4.8 | 2.9 | 6.1 | 6.3 | 8.3
arrhythmia (%) | 1.1 | 7.1 | 3.0 | 12.5 | 8.3
other cardiovascular (%) | 2.7 | 1.4 | 3.0 | 6.3 | 0.0
Noncardiovascular (%) | 74.2 | 70.0 | 60.7 | 43.8 | 33.3
**Discussion**

The main finding of this study is that the reduced LVEF at the start of HD strongly predicts poor survival for both cardiovascular and all-cause mortality. Severe LV systolic dysfunction (LVEF <0.3) had a ninefold higher risk for cardiovascular death and a fourfold higher risk for all-cause death even after adjustment for other risk factors. Besides, even mild LV systolic dysfunction significantly worsened a survival rate in HD patients. Furthermore, more than one tenth of patients had LVEF levels <0.5 when starting HD therapy. One strength of this study is that the sample size is relatively large; enrolled HD patients numbered 1254. In addition, we calculated the Harrell C index to determine model discrimination and showed that a combination of established risk factors and LVEF significantly increased the C index to predict both cardiovascular and all-cause mortality, compared with a combination of established risk factors only.

So far, many studies have attempted to investigate whether there is a causal relationship between the reduced LVEF and
mortality (10,12,19–23); however, the results have been inconsistent. Of those studies, Curtis and co-workers showed that lower LVEF is associated with a linear increment in mortality in outpatients with stable heart failure. Furthermore, even after adjustment for other risk factors, LVEF <35% is an independent predictor in a large cohort study recruiting nearly 8000 patients with stable heart failure (10). However, the study consisted of a limited number of patients with chronic kidney disease. On the other hand, Zoccali and co-workers enrolled 250 asymptomatic HD patients with mean duration of HD for 40 months and assessed the prognostic value of LV systolic function prospectively (12). They showed that if the LVEF decreases by 1%, the risk of fatal and nonfatal cardiovascular events independently increase by 1.04-fold on multivariate analysis in patients on hemodialysis. They suggested repeating UCG after 1.5 years might be useful for risk stratification. However, few reports have examined the potential association between the value of LVEF at the beginning of HD therapy and the prognosis in patients with ESRD. Only one report has shown that such populations are associated with lower cardiac functions upon starting therapy for ESRD, resulting in a poor prognosis (24). We consider the point when starting HD therapy to be very important because predictors for future cardiovascular events are clinically relevant. The present findings may, thus, be of great significance from the viewpoint of risk stratification in ESRD patients at the beginning of HD.

Another important finding in this study is that even mild LV systolic dysfunction significantly worsened the prognosis in ESRD patients. Pre-existing systemic arteriosclerosis and constant fluid overload in patients with ESRD might play an important additional role in poor survival. It is well known that microvascular disease and macrovascular disease, cardiac fibrosis, and sympathetic hyperactivity are associated with cardiovascular death including sudden death in patients on HD (25,26). These factors may also be related to structural cardiac abnormalities such as asynergic wall motion and mitral regurgitation. These multifactorial pathologic conditions might result in lower LVEF and a worse prognosis especially in patients with LV systolic dysfunction.

In agreement with previous studies, diabetes and serum CRP levels were associated with adverse clinical outcomes in this study. Diabetes has been well known as a risk factor for ischemic heart disease, reduced cardiac functions, and cardiac events (27,28). Serum CRP levels also reflect vascular wall inflammation and predict adverse cardiac events (29–31). In addition, BMI and serum albumin levels were inversely related to all-cause mortality (32,33). These factors might be related to MIA syndrome, which indicates malnutrition, inflammation, and atherosclerosis. These risk factors should also be considered in managing patients on HD.

Limitations
This study has several limitations. First, this study had a single-center design. Larger multicenter studies are warranted to corroborate our findings. Second, we did not evaluate LV diastolic function. Third, all enrolled patients in the study were Japanese. A report showed that 5-year survival rates in overall patients on HD were 54% in Japan, 48% in Europe, and 40% in the United States, respectively (34). These differences should be considered to interrupt the results. Fourth, we have no data on other variables related to dialysis therapy such as access or urea clearance \times time normalized by total body water. Finally, precise medical treatment and therapeutic intervention were not evaluated in this study. These data may be very clinically important. We did not have data on the efficacies of medications to prevent adverse events. Further investigations are warranted in this regard.

Conclusions
LVEF at inception of dialysis appears to be a strong prognostic marker for CV and all-cause death. Knowledge of LVEF improved discrimination of a prognostic model incorporating known cardiovascular risk factors and may be a useful adjunct in assessing the mortality risk in incident dialysis patients.

Acknowledgments
The authors thank Dr. Shonen Yoshida (Division of Clinical Research, Nagoya Kyoritsu Hospital) for valuable suggestions on this manuscript. We also thank Mr. Koichi Ibuki and Mr. Ryueki Kanda (Division of Clinical Laboratory, Nagoya Kyoritsu Hospital) for their technical support.

Disclosures
None.

References

Kjøller-Hansen L, Steffensen R, Grande P: Beneficial effects of ramipril on left ventricular end-diastolic and end-systolic volume indexes after uncomplicated invasive revascularization are associated with a reduction in cardiac events in patients with moderately impaired left ventricular function and no clinical heart failure. J Am Coll Cardiol 42: 736–742, 2003


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