Serum Albumin Levels Predict Clinical Outcomes in chronic kidney disease (CKD) Patients Undergoing Cardiac Resynchronization Therapy

Tomohiro Uchikawa, Masayuki Shimano, Yasuya Inden and Toyoaki Murohara

Abstract

Objective  A low level of serum albumin is common in chronic kidney disease (CKD) patients with heart failure (HF). Cardiac resynchronization therapy (CRT), a novel therapeutic option, improves cardiac performance in patients with severe HF. In addition, CKD has recently been found to be associated with outcomes after CRT; however, the associations of the serum albumin levels with adverse events and the long-term prognosis in CKD patients who have undergone CRT are unknown. In this study, we investigated whether the albumin levels can be used to predict mortality rate and incidence of cardiovascular events in CKD patients treated with CRT.

Methods  A retrospective chart review was conducted in 102 consecutive CKD patients receiving a CRT device for the treatment of advanced HF. The long-term outcomes following device implantation were assessed according to the albumin levels.

Results  During a median follow-up of 2.6 years, 34 patients (33.3%) died and 66 patients (64.7%) experienced cardiovascular events. A Kaplan-Meier survival analysis revealed that the CKD patients with decreased albumin levels exhibited significantly higher rates of all-cause mortality and cardiovascular events, including hospitalization for progressive HF, than the CKD patients without hypoalbuminemia. Importantly, a multivariate Cox regression analysis of confounding factors showed a low serum albumin level to independently predict all-cause death and cardiovascular events.

Conclusion  Hypoalbuminemia independently predicts cardiac morbidity and mortality in CKD patients receiving CRT. Assessing the albumin levels provides valuable information regarding the long-term prognosis in CKD patients who undergo CRT.

Key words: albumin, cardiac resynchronization therapy, biomarker

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Introduction

Hypoalbuminemia is a common finding in patients with heart failure (HF) (1-3). The condition becomes more prevalent with increasing age (4, 5) and in the presence of chronic kidney disease (CKD) (6, 7). Hypoalbuminemia has emerged as an independent predictor of HF within the last two decades, especially in elderly and CKD patients (3, 4, 8), and facilitates the development of pulmonary edema based on the presence of a low plasma protein concentration and Staring’s law (9, 10). In addition, CKD constitutes the primary pathophysiological mechanism underlying the development of hypoalbuminemia in HF patients (7, 11).

Cardiac resynchronization therapy (CRT) has been established as a novel therapeutic option for treating patients with advanced HF (12-14). Several studies have shown that CRT decreases the rates of mortality and hospital admission (15, 16). Nevertheless, approximately one-third of patients do not respond to CRT (17-20). Recently, the presence of CKD in patients receiving CRT has been reported to be...
associated with an increased risk of mortality and cardiovascular events (21-25), while approximately two-thirds of patients hospitalized for HF experience renal failure (26, 27). However, little is known regarding which CKD patients will have the best outcomes after CRT based on pre-implant assessments, as the echocardiographic measurement of dyssynchrony, which we believe to be the most important predictor, has completely failed to select patients for CRT (18, 28). This is because other factors, such as the cardiac contractile function, lead position and systemic conditions, are ignored when the investigation is focused on electromechanical dyssynchrony. Therefore, it is clinically valuable to identify pre-implant characteristics that predict good outcomes in CKD patients who undergo CRT.

Given the aforementioned background, we hypothesized that the presence of hypoalbuminemia is a predictive factor of the risk of illness and death in CKD patients who have undergone CRT. In the present study, we investigated whether low albumin levels could be used to predict the long-term prognosis after CRT in CKD patients.

Materials and Methods

Study population

We conducted a retrospective chart review of 161 consecutive patients with HF who underwent CRT at Nagoya University Hospital between January 2005 and December 2011. The patients were selected according to the following selection criteria for CRT provided by the Japanese Circulation Society: (1) the presence of severe HF despite the administration of optimized medical therapy; (2) left ventricular (LV) systolic dysfunction with an LV ejection fraction (LVEF) of <35%; and (3) a QRS duration of >120 ms. We excluded 56 non-CKD patients and three patients who required recent revascularization within six months of the study period. All subjects provided their written informed consent.

Laboratory measurements

Fasting blood samples were obtained from every patient. After each patient rested for 10 minutes in the supine position, vital signs were recorded and 35 mL of blood was collected from the antecubital vein. The serum high-sensitivity C-reactive protein levels were measured at SRL Inc. (Tokyo, Japan), a commercial clinical testing laboratory.

Echocardiography

Two-dimensional echocardiography was performed by two experienced sonographers using the Vivid 7 Dimension/Pro System (GE Healthcare, Buckinghamshire, UK) before CRT device implantation. The images were recorded using a 3.5-MHz transducer in a cine-loop format and digitally stored for an offline analysis. The LV end-diastolic diameter (LVEDD) and LV end-diastolic volume (LVEDV) were measured as recommended by the American Society of Echocardiography. The LVEF was calculated using the modified Simpson’s rule. The degree of septal-to-posterior wall motion delay (SPWMD) was assessed as a parameter of dyssynchrony.

Follow-up and assessment of cardiac events

All patients underwent regular follow-up through outpatient clinical visits (typically every two months) or device interrogation (typically every six months). Cardiovascular events, including myocardial infarction, acute coronary syndrome, cerebral infarction and hospitalization for exacerbation of HF, were assessed by cardiologists from Nagoya University Hospital. The cause of death was ascertained by reviewing the patient’s clinical records.

Statistical analysis

All data are expressed as the mean ± standard deviation. Univariate and multivariate Cox regression analyses were performed to control for potentially confounding echocardiographic, demographic and clinical variables. Freedom from death and cardiovascular events was determined according to a Kaplan-Meier analysis using the log-rank test. A level of p<.05 was considered to indicate statistical significance. All analyses were performed using the SPSS software package (version 18.0; SAS Institute Inc., Cary, USA).

Results

Baseline characteristics

The baseline characteristics of the study subjects are shown in Table 1. The albumin levels ranged from 27 to 45 g/L (median, 38 g/L; reference range, 40-50 g/L in our hospital laboratory). Hypoalbuminemia was defined as a serum albumin level of <38 g/L. The mean age of the CRT recipients in this study was 69.8±9.3 years, and 68.6% of the men were predominantly classified as having a New York Heart Association (NYHA) functional class III or IV status with a wide QRS duration (163±28 ms). The mean body mass index was 22.3±4.1 kg/m². The etiology of HF in 34.3% of the patients was ischemic heart disease. Coronary angiography was performed in all patients before implantation of the CRT device, and the patients underwent revascularization if needed and if possible. Five patients (4.9%) had atrial fibrillation. Eight patients (7.8%) had previously implanted pacing devices. The baseline pharmacological treatment of all patients consisted of beta blockers, angiotensin-converting enzymes or angiotensin receptor antagonists, an Aldactone blocker and diuretics, unless one of the medications was contraindicated or not tolerated. Baseline laboratory data and echocardiograms were obtained one day before CRT device implantation. The data showed decreased estimated glomerular filtration rates (eGFR, 39.1±13.5 mL·min⁻¹·1.73 m⁻²); normal biochemical levels of total cholesterol (174.7±37.9 mg/dL) and triglycerides (129.5±88.0 mg/dL) and elevated neurohormonal levels of brain natriuretic peptide (BNP,
546.0±767.6 pg/mL) and atrial natriuretic peptide (ANP, 242.9±334.7 pg/mL) in the CKD patients before CRT device implantation. All patients had severe LV dysfunction (mean LVEF, 27.4 %±8.6 %) with extensive dilatation (LVEDD, 68.6±8.3 mm; LVEDV, 211±76 mL).

**Clinical outcomes of the patients during follow-up**

The mean follow-up duration was 2.61±2.06 years, and 34 (33.3%) patients died. In three patients, the cause of death was non-cardiac-related (cancer: two patients, and traumatic accident: one patient). A total of 66 (64.7%) patients were hospitalized for cardiovascular events, including the exacerbation of HF following CRT device implantation.

**Prediction of the prognosis after CRT**

We first performed a Kaplan-Meier survival analysis of two groups of CKD patients classified according to the serum albumin levels. The results showed that the patients with decreased albumin levels had significantly higher all-cause mortality (Figure A) than those with elevated albumin levels. Subsequently, we performed a univariate Cox regression analysis to examine the correlations between conventional risk factors, including the albumin level and the long-term prognosis (all-cause mortality), after CRT. Statistically significant differences in the serum albumin and ANP levels were noted before CRT device implantation (Table 2). However, we found no significant differences in the serum BNP levels, age, echocardiographic parameters (LVEDD, LVEDV, LVEF and SPWMD) or upgrading of pre-existing pacing devices (Table 2). Of note, only the basal albumin level (p <.05) before CRT device implantation was found to be an independent predictor of all-cause mortality in the multivariate Cox regression model after controlling for the ANP levels (Table 2).

The Kaplan-Meier survival analysis revealed that the patients with lower albumin levels had significantly higher combined end points (death or hospitalization for cardiovascular events, including deterioration) than those with higher albumin levels (Figure B). Moreover, the serum albumin levels and eGFR values were associated with the combined primary end points (Table 3). However, the logBNP, hemoglobin and echocardiography dyssynchrony parameters did not predict cardiac morbidity (Table 3), and the number of subjects evaluated in this study may be too small to give the results statistical meaning. In the multivariate Cox regression model devised after controlling for predictive values in the univariate analysis, the basal albumin levels before CRT de-
Table 2. Predictors of All-cause Death in the CKD Patients

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
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<th>Multivariate</th>
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<tr>
<td></td>
<td>HR</td>
<td>CI (HR)</td>
<td>p value</td>
<td>HR</td>
<td>CI (HR)</td>
<td>p value</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.328</td>
<td>0.124-0.866</td>
<td>0.024</td>
<td>0.316</td>
<td>0.110-0.988</td>
<td>0.048</td>
</tr>
<tr>
<td>Age</td>
<td>0.994</td>
<td>0.966-1.023</td>
<td>0.701</td>
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<tr>
<td>IHD</td>
<td>1.205</td>
<td>0.592-2.450</td>
<td>0.607</td>
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<tr>
<td>BMI</td>
<td>1.033</td>
<td>0.944-1.131</td>
<td>0.477</td>
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<tr>
<td>eGFR</td>
<td>0.981</td>
<td>0.957-1.006</td>
<td>0.139</td>
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<tr>
<td>hsCRP</td>
<td>1.105</td>
<td>0.977-1.250</td>
<td>0.111</td>
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<tr>
<td>Sodium</td>
<td>0.973</td>
<td>0.878-1.078</td>
<td>0.602</td>
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<tr>
<td>Hemoglobin</td>
<td>0.990</td>
<td>0.822-1.220</td>
<td>0.990</td>
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<tr>
<td>Log BNP</td>
<td>2.120</td>
<td>0.835-5.382</td>
<td>0.114</td>
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<tr>
<td>Log ANP</td>
<td>4.115</td>
<td>1.416-11.961</td>
<td>0.009</td>
<td>2.602</td>
<td>0.833-8.131</td>
<td>0.100</td>
</tr>
<tr>
<td>LVEDD</td>
<td>1.022</td>
<td>0.963-1.085</td>
<td>0.465</td>
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<tr>
<td>LVEDV</td>
<td>1.001</td>
<td>0.995-1.007</td>
<td>0.744</td>
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<tr>
<td>LVEF</td>
<td>0.995</td>
<td>0.944-1.049</td>
<td>0.848</td>
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<tr>
<td>SPWMD (ms)</td>
<td>0.997</td>
<td>0.991-1.003</td>
<td>0.310</td>
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<tr>
<td>QRS width</td>
<td>1.007</td>
<td>0.994-1.019</td>
<td>0.309</td>
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</table>

The values are presented as 95% confidence intervals (CIs). HR indicates the hazard ratio. The abbreviations are summarized in Table 1.

Table 3. Predictors of the Combined Primary End Points (Death or Cardiovascular Events) in the CKD Patients

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
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<th></th>
<th>Multivariate</th>
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<tr>
<td></td>
<td>HR</td>
<td>CI (HR)</td>
<td>p value</td>
<td>HR</td>
<td>CI (HR)</td>
<td>p value</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.470</td>
<td>0.258-0.857</td>
<td>0.014</td>
<td>0.553</td>
<td>0.347-0.998</td>
<td>0.047</td>
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<td>Age</td>
<td>0.985</td>
<td>0.963-1.008</td>
<td>0.190</td>
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<tr>
<td>IHD</td>
<td>0.862</td>
<td>0.520-1.430</td>
<td>0.565</td>
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<tr>
<td>BMI</td>
<td>1.003</td>
<td>0.942-1.067</td>
<td>0.935</td>
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<tr>
<td>eGFR</td>
<td>0.975</td>
<td>0.957-0.993</td>
<td>0.006</td>
<td>0.980</td>
<td>0.962-0.998</td>
<td>0.033</td>
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<tr>
<td>hsCRP</td>
<td>1.012</td>
<td>0.902-1.136</td>
<td>0.836</td>
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</tr>
<tr>
<td>Sodium</td>
<td>0.951</td>
<td>0.889-1.017</td>
<td>0.140</td>
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<tr>
<td>Hemoglobin</td>
<td>0.902</td>
<td>0.806-1.010</td>
<td>0.074</td>
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<tr>
<td>Log BNP</td>
<td>1.826</td>
<td>0.983-3.390</td>
<td>0.057</td>
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<tr>
<td>Log ANP</td>
<td>1.483</td>
<td>0.846-2.597</td>
<td>0.169</td>
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<tr>
<td>LVEDD</td>
<td>1.030</td>
<td>0.996-1.065</td>
<td>0.088</td>
<td></td>
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<tr>
<td>LVEDV</td>
<td>1.002</td>
<td>0.999-1.005</td>
<td>0.283</td>
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<tr>
<td>LVEF</td>
<td>0.972</td>
<td>0.931-1.014</td>
<td>0.190</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPWMD (ms)</td>
<td>0.997</td>
<td>0.992-1.001</td>
<td>0.054</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS width (ms)</td>
<td>1.003</td>
<td>0.993-1.014</td>
<td>0.538</td>
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</table>

The values are presented as 95% confidence intervals (CIs). HR indicates the hazard ratio. The abbreviations are summarized in Table 1.

Discussion

This study demonstrated for the first time that the serum albumin levels measured before CRT device implantation independently predict morbidity and mortality in CKD patients receiving CRT. Moreover, the association between the albumin levels and mortality is superior to that observed between the serum ANP levels and mortality. Consequently, measuring the serum albumin levels potentially provides risk stratification in CKD patients undergoing CRT.

Recently, we focused considerable attention on HF as a systemic syndrome characterized by multifactorial interactions between cardiac circulatory failure, organ injury and the development of neurohormonal and biochemical disorders (29). HF is primarily related to coexisting systolic and diastolic abnormalities; however, the progression of cardiac dysfunction causes several extracardiac pathologies. The well-established contribution of anemia and renal insufficiency to the worsening of HF and risk stratification illustrates this pathophysiological perspective (30-32). These findings are consistent with the prognoses of HF observed in CRT recipients (21, 24). Meanwhile, hypoalbuminemia occurs in one-third of patients with HF (33) and is thought to result primarily from malnutrition, inflammation and cachexia (34). With regard to inflammation, the hsCRP level is the most widely used predictor of worse clinical outcomes (35); however, this practice is not consistent with our data. One possible explanation for this discrepancy is the difference between CRT responders and non-responders, meaning that improvements in the cardiac function after CRT decrease the hsCRP levels in CRT responders (36). Therefore, the hsCRP levels did not predict worse outcomes after CRT in this study.
with malnutrition, is a 65-kDa protein that accounts for >50% of the total plasma protein concentration (37). In healthy individuals, the liver synthesizes and releases 10-15 g of albumin into the vascular space each day. Approximately 40% of the total albumin content is maintained in the vascular space and constantly exchanged between the plasma and interstitium (38). In addition, albumin synthesis is regulated by several stimuli, such as nutrient intake, insulin and oncotic pressure (37, 39-41). Serum albumin catabolism has not been well characterized, although it is thought to occur in all tissues, especially the skin, muscles and liver (42, 43). Moreover, severe HF can induce failure of other organs and induce substantial neurohumoral and biochemical disturbances through a vicious circle of disease progression. Consequently, hypoalbuminemia may result from HF, for instance, as part of wasting syndrome. In this study, we showed that hypoalbuminemia is a surrogate marker of worse HF outcomes after CRT.

Cardio-renal syndrome, a form of renal dysfunction associated with congestive heart failure, confers a worse prognosis independent of the LVEF (44). Unsurprisingly, severe CKD is associated with worse outcomes after device therapy (45-48). Based on current knowledge regarding the involved biventricular pacing mechanisms, patients with beneficial CRT outcomes typically exhibit impairment of electro-mechanical ventricular dyssynchrony leading to reverse remodeling (49-51). Nevertheless, the Predictors of Response to CRT (PROSPECT) study suggested that echocardiographic and tissue Doppler parameters may have limited predictive accuracy (18). In contrast, the creatinine-based equations used to estimate the GFR predict good long-term clinical outcomes after CRT (21, 25), although their precision when applied to CKD patients receiving CRT is unclear. In the present study, we showed that the serum albumin levels at baseline independently predict all-cause mortality and cardiovascular event-related hospitalization in CKD patients receiving CRT after controlling for eGFR. These data suggest that measuring the serum albumin levels before CRT device implantation provides useful information regarding morbidity and mortality in CKD patients undergoing CRT.

However, our study has limitations similar to those of any single-center observational study. In addition, we have no data regarding targeted nutritional support, anti-inflammatory interventions or albumin administration. Furthermore, the basal albumin levels were not found to be associated with mortality or cardiovascular events in the non-CKD patients who underwent CRT because the number of subjects was too low to allow for a statistically meaningful evaluation. Future large clinical trials and further research in this area are warranted to confirm the usefulness of measuring the albumin level in this setting.

Taken together, our observations suggest that the albumin levels predict cardiac morbidity and mortality in CKD patients receiving CRT. Measuring the level of serum albumin provides useful information regarding the long-term prognosis after CRT. Further careful assessments should be considered for attentive follow-up, although the assessment of the albumin level is independent of the selection of treatment using CRT.

Conclusion

In CKD patients with HF, the albumin level is therefore considered to have a strong value for predicting the rates of mortality and cardiovascular events after CRT device implantation.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

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