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Malnutrition, renal dysfunction and left ventricular hypertrophy synergistically increase the long-term incidence of cardiovascular events.

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Malnutrition, renal dysfunction, and left ventricular hypertrophy synergistically increase the long-term incidence of cardiovascular events

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Short title: Synergistic impact of Malnutrition, CKD, and LVH

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Abstract

Although malnutrition indicates unfavorable prognoses in some clinical settings, the synergistic impact of nutritional indices, renal dysfunction, and left ventricular hypertrophy (LVH) on cardiovascular events is unknown. Among 338 patients aged 40–80 years who underwent echocardiographic evaluation between 2003 and 2005, 161 followed up for >7 years were recruited. Malnutrition was defined as a geriatric nutritional risk index (GNRI) ≤ 96. Mean age was 63.5 ± 9.2 years; mean estimated glomerular filtration rate (eGFR) was 72.9 ± 18.7 mL/min/1.73m^2; mean left ventricular mass index was 114 ± 33 g/m^2; and mean GNRI was 100.4 ± 6.0. Among the patients, 25% (n=40) had an eGFR <60 mL/min/1.73m^2, 29% (n=46) chronic kidney disease (CKD), and 37% (n=59) LVH. During the follow-up period (median: 96 months), cardiovascular events were recorded in 15 patients (9%). Kaplan-Meier curves showed a significantly higher incidence in patients with eGFR <60 mL/min/1.73m^2 (log rank P=0.007), GNRI ≤ 96 (P=0.003), or LVH (P=0.010). In Cox regression analysis, eGFR, LVH, and GNRI were independent determinants of cardiovascular events after adjusting for age, gender, and hypertension. Furthermore, the combination of the presence of LVH and lower GNRI was significantly associated with higher rates of cardiovascular events not only in all patients but in patients with CKD. In conclusion, malnutrition, low eGFR, and LVH were independent determinants of cardiovascular events; they synergistically increased rates of these events in the long term. It is extremely important to evaluate and manage the progression of LVH and improve nutritional status even in non-dialysis patients.

Key words: nutritional status, renal function, left ventricular hypertrophy,

1 cardiovascular diseases

2

Introduction

Chronic kidney disease (CKD) is one of the most important risk factors for cardiovascular events worldwide.[1, 2] Left ventricular hypertrophy (LVH) is common, and a strong predictor of cardiovascular events in patients with CKD.[3, 4] LVH is also known to be preventable or even reversible by controlling blood pressure and volume in patients with CKD.[5, 6] Malnutrition has been identified as an independent risk factor for cardiovascular events in dialysis patients.[7] A recent study revealed higher all-cause (including cardiovascular diseases) mortality rates in predialysis patients with CKD with malnutrition.[8] The geriatric nutritional risk index (GNRI) is a simple, well-established nutritional assessment tool for both elderly individuals[9] and hemo- and peritoneal dialysis patients.[10, 11] It is based on only three objective parameters: body weight, height, and serum albumin level. We recently reported that the cut-off value of GNRI for predicting all-cause and cardiovascular mortality is 96 in hemodialysis patients.[12] However, this assessment has not yet been applied to non-dialysis patients.

Malnutrition and LVH have already been shown to be associated with cardiovascular events in patients with CKD, but the synergistic impact of malnutrition, low estimated glomerular filtration rate (eGFR), and LVH on cardiovascular events in a long-term follow-up is still unknown. Therefore, we investigated the associations between GNRI, eGFR, LVH, and cardiovascular events during a follow-up period of >7 years.

Methods

Participants

We enrolled 338 patients aged 40 to 80 who underwent echocardiographic evaluation between June 2003 and May 2005. After excluding patients who were on hemodialysis, had comorbidities with malignancies or infectious diseases, or were followed for <7 years, 161 patients (male, n = 82; female, n = 79; mean age, 63.5 ± 9.2 years) were enrolled. Age, gender, lipid parameters, and conventional cardiovascular risk factors were also recorded. This study was performed in strict accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the Ethical Scientific Committee of Asahikawa Medical University. All study participants provided written informed consent.

Data collection

Body mass index (BMI) was calculated by dividing weight by height squared (m^2). We calculated GNRI using serum albumin values, weight, and ideal body weight. GNRI was calculated as reported by Yamada et al.[10]: GNRI = [14.89 x albumin (g/dL)] + [41.7 x (weight / ideal body weight)]. Note that body weight/ideal body weight was >1 when a subject's body weight exceeded their ideal body weight. Ideal body weight was calculated using height and a BMI of 22, which is reportedly associated with the lowest morbidity rate in the Asian population.[13] Hypertension was defined as systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 mmHg, or current use of anti-hypertensive agents. Diabetes was defined as one of the following: fasting blood sugar ≥ 126 mg/dL, non-fasting blood sugar ≥ 200 mg/dL, glycosylated hemoglobin ≥ 6.5%, or current use of insulin or oral hypoglycemic agents. Dyslipidemia was defined

as a total cholesterol level ≥ 220 mg/dL, high-density lipoprotein cholesterol level <40 mg/dL for men, <50 mg/dL for women, triglyceride level ≥ 150 mg/dL, or medication with anti-hyperlipidemic agents. Proteinuria was defined as 1+ or more on dipstick test.

Echocardiographic evaluation

Standard echocardiographic measurements were obtained from the left parasternal and apical views according to the recommendations of the American Society of Echocardiography[14] using an ALOKA alpha 10 ultrasound system (Aloka, Japan). The left ventricular (LV) end-diastolic diameter, LV end-systolic diameter, left atrial diameter (LAD), interventricular septum thickness, and posterior wall thickness were determined using standard echocardiographic 2D measurements. LV mass (LVM) was determined using the 2D area-length formula. LVMs were indexed to the body surface area as the LVM index (LVMI). LVH was defined as a LVMI ≥ 125 g/m^2 for men and ≥ 110 g/m^2 for women.[15] The ejection fraction was calculated using the modified Simpson method. Transmitral inflow was recorded using pulsed wave Doppler recordings at the mitral valve leaflet tips in the apical 3-chamber view. The peak early diastolic filling velocity (E), peak late diastolic filling velocity (A), E/A ratio, and deceleration time of the E wave were measured. The tissue Doppler imaging program was set to the pulsed wave Doppler mode, and sample volumes were positioned at the septal corner of the mitral annulus.[16] We then measured the early diastolic mitral inflow velocity and calculated the ratio of E over e' (E/e') to represent LV filling pressure.[17]

Follow-up

Follow-up data were retrieved from clinical records and/or death certificates by personnel blinded to the anthropometric, body composition, and laboratory assessments. Heart failure was defined as admission as a result of new or worsening heart failure with New York Heart Association (NYHA) class greater than or equal to II. The follow-up began on the date of enrollment and finished at death from any cause or March 31, 2014 - whichever came first.

Statistical analysis

Results are expressed as means ± standard deviations. Baseline characteristics between the cardiovascular event and cardiovascular event-free groups were compared using the chi-square test and the Mann-Whitney U test as appropriate. The relationships between eGFR, echocardiographic function, and malnutrition at the time of enrollment were analyzed using univariate linear regression analysis. Uni- and multivariate linear regression analyses and Cox proportional hazards models were performed to determine the correlation and independent variables for cardiovascular events. The impact of GNRI, eGFR, and LVH on cardiovascular events, including acute coronary syndrome, heart failure, stroke, aortic dissection, and aortic rupture were analyzed using Kaplan-Meier curves and log-rank tests. P-values <0.05 were considered statistically significant. All data were analyzed using SPSS ver. 19.0 Windows (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics

Table 1 shows the baseline characteristics of all patients who did or did not develop cardiovascular events during a follow-up period of a median of 96.0 ± 15.6 months. The mean age of the 161 patients at baseline was 63.5 ± 9.2 years, 51% were male, 68% had hypertension, 24% had diabetes, and 45% had dyslipidemia. Mean eGFR was 72.9 ± 18.7 mL/min/1.73m^2. Mean serum albumin level was 4.0 ± 0.3 mg/dL and mean GNRI 100.4 ± 6.0. Among the patients, 25% (n = 40) had an eGFR <60 mL/min/1.73m^2 (G3a, n = 29; G3b, n = 9; and G4, n = 2), 9% (n = 15) had proteinuria, 29% (n=46) had CKD, and 37% (n = 59) had LVH. The patients with nephrotic syndrome were not included.

During the follow-up period, 15 (9.3%) patients experienced cardiovascular events (acute coronary syndrome, n = 7; heart failure, n = 4; stroke, n = 2; aortic dissection, n = 1; and aortic rupture, n = 1). Sex, BMI, hemoglobin level, and the prevalence of hypertension, diabetes, and dyslipidemia did not significantly differ between the two groups. Patients who developed cardiovascular events were significantly older, had lower eGFR, serum albumin levels, e' and GNRI, and higher LVMI. The use of diuretics, angiotensin II receptor blockers, and angiotensin converting enzyme inhibitors was significantly higher in patients who developed cardiovascular events.

Correlations between eGFR, LVMI, and GNRI

Univariate correlations between eGFR, LVMI, GNRI, and various parameters at baseline are listed in Table 2. eGFR correlated significantly and negatively with age,

the prevalence of proteinuria, LAD, and LVMI, and positively with e', serum albumin level, and GNRI in univariate linear regression analysis. LVMI correlated significantly and negatively with eGFR and e', and positively with the prevalence of proteinuria, LAD, and E/e'. In contrast, GNRI correlated significantly and positively with BMI, hemoglobin level, serum albumin level, and eGFR. GNRI did not correlate with LAD, LVMI, and LV end-diastolic diameter, suggesting that GNRI occurred irrespective of volume overload.

Follow-up data

Univariate correlations between the incidence of cardiovascular events and various parameters are listed in Table 3. Cardiovascular events were significantly and positively associated with age, the prevalence of proteinuria, LAD, E/e', and LVMI, and negatively with eGFR, serum albumin level, and GNRI in univariate linear regression analysis. Next, we analyzed independent determinants of cardiovascular events using multivariate linear regression analyses, the results of which are presented in Table 4. LVMI was positively associated, whereas eGFR and GNRI level were negatively associated, with cardiovascular events. Furthermore, we investigated the independent variables for cardiovascular events using Cox proportional hazards models. Age (hazard ratio 1.121, 95% CI 1.013–1.241), eGFR (hazard ratio 0.961, 95% CI 0.928–0.995), GNRI (hazard ratio 0.886, 95% CI 0.807–0.973), and LVMI (hazard ratio 1.017, 95% CI 1.002–1.033) were significantly associated with cardiovascular events after adjusting for sex, hemoglobin level, and the prevalence of hypertension and diabetes (Table 5), suggesting that malnutrition is an independent predictor of cardiovascular events, even in non-dialysis patients.

Next, we examined the impact of malnutrition, low eGFR, and LVH on

cardiovascular events using Kaplan-Meyer curves. We stratified by the presence or absence of malnutrition defined as GNRI ≤ 96 based on our previous report [12]. As shown in Figure 1, lower GNRI (Figure 1A), lower eGFR (Figure 1B), and the presence of LVH (Figure 1C) were significantly associated with higher rates of cardiovascular events. The presence of proteinuria (Figure 1D) and higher LAD (Figure 1E) were also associated with higher rates of cardiovascular events. The prevalence of hypertension was not significantly associated with cardiovascular events (Figure 1F).

We further examined the synergistic impact of malnutrition, low eGFR, and LVH on cardiovascular events. The combination of lower eGFR and the presence of LVH was significantly associated with higher rates of cardiovascular events (P = 0.003; Figure 2A). The combination of lower eGFR and lower GNRI was also significantly associated with higher rates of cardiovascular events (P < 0.001; Figure 2B). Furthermore, the combination of the presence of LVH and lower GNRI was significantly associated with higher rates of cardiovascular events not only in all patients (P < 0.001; Figure 2C) but also in patients with CKD (n=46, P = 0.014; Supplementary Figure S1), suggesting that malnutrition, renal dysfunction, and LVH have a synergistic impact on the incidence of cardiovascular events, even in non-dialysis patients.

Finally, we verified the possibility that the proteinuria might decrease the serum level of albumin which consists of the formula of GNRI in independent of malnutrition. However, there are no significant differences between the severity of dipstick proteinuria, serum albumin (Figure 3A) and GNRI (Figure 3B), suggesting that the proteinuria did not affect the nutritional status in this study.

Discussion

To the best of our knowledge, this study is the first to describe that: (1) malnutrition, low eGFR, and LVH are all independent predictors of cardiovascular events and have a synergistic impact on cardiovascular events in non-dialysis patients who were followed up for >7 years; (2) a cutoff value of GNRI of ≤96 is useful for predicting cardiovascular events, even in non-dialysis patients.

This study demonstrated that eGFR was significantly and positively associated with GNRI, which is useful for predicting cardiovascular events. GNRI was originally used to predict malnutrition-related complications and mortality in elderly hospitalized patients, and the defined cutoff values according to weight loss and albumin concentrations were: GNRI <82, major nutrition-related risk; 82 to <92, moderate nutrition-related risk; 92 to ≤98, low nutrition-related risk; >98, no risk.[9] Several studies in hemodialysis patients have reported that the GNRI cutoff value is around 90 to 91.[10] Additionally, GNRI was also reported to be helpful for predicting death due to cardiovascular events or re-hospitalization in patients with chronic heart failure.[18, 19] However, most recently, we have reported that the cut-off value of GNRI for predicting all-cause and cardiovascular mortality is 96 in hemodialysis patients.[12] In this study, we clearly showed that a cutoff value of GNRI of ≤ 96 is useful for predicting cardiovascular events, even in non-dialysis patients.

GNRI uses body weight to assess nutritional status. Furthermore, body weight is affected by fluid status, which may lead to underestimation of nutritional status in patients with CKD or chronic heart failure. In this study, however, we showed that GNRI was not associated with LAD, LVMI, or LV end-diastolic diameter, suggesting that GNRI was an independent predictor of cardiovascular events independent of

volume overload. Although the proteinuria might decrease the serum level of albumin which consists of the formula of GNRI, we clearly showed that the levels of proteinuria were not associated with serum albumin and GNRI, suggesting that the proteinuria did not affect the nutritional status in this study. On the other hand, the use of diuretics at baseline was significantly more prevalent in patients who developed cardiovascular events in this study. Several studies have revealed that loop diuretic use is associated with increased mortality risk in chronic heart failure patients because it increases the activity of the renin-angiotensin-aldosterone system.[20] Diuretics may also induce hypokalemia,[21] thus promoting cardiac arrhythmias and sudden death.

Our sub-analysis for the effects of LVH and GNRI on cardiovascular events only in patients with CKD revealed consistent results that the combination of the presence of LVH and lower GNRI was significantly associated with higher rates of cardiovascular events. Although it has been revealed that age, systolic blood pressure, LVM, and left atrial size are related to the incidence of atrial fibrillation,[22, 23] there is the possibility that these factors might mediate the association between CKD and atrial fibrillation incidence observed in several previous studies,[24, 25] because GFR generally decreases with age, and pressure and volume load augmented by renal dysfunction directly increase arterial stiffness, LVM, and left atrial size.[26, 27] Most recently, it has been reported that subclinical nephrosclerosis is linked to LVH independent of classical atherogenic factors.[28] Furthermore, it is well known that a strong correlation exists between the three significant separate clinical entities of malnutrition, inflammation, and atherosclerosis, which coexist in patients with end-stage renal disease and are collectively known as malnutrition-inflammation-atherosclerosis (MIA) syndrome,[7] suggesting that chronic inflammation might affect the cardiovascular events in this study.

Our study had several limitations. First, it is a retrospective observational study and a relatively small sample size in a single center and thus suffers from all drawbacks of such a study including selecting bias. Second, we did not check the control of blood pressure during the observational period, thus, although baseline blood pressures were not associated with cardiovascular events in our study, we cannot assess the actual impact of hypertension which is a major risk factor for cardiovascular events. Third, we did not check the prevalence of atrial fibrillation and smoking thus we could not conclude that there was an interaction between these factors and the incidence of cardiovascular events. Further and larger prospective studies are needed to determine the synergistic impact of malnutrition and LVH in patients with CKD.

In conclusion, this study clearly demonstrated that malnutrition, low eGFR, and LVH are independent determinants of cardiovascular events and synergistically increase the rates of these events in the long term. It is extremely important to evaluate and manage the progression of LVH, as well as to improve the nutritional status even in non-dialysis patients.

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Disclosures

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Figure legends

Figure 1.

Kaplan-Meier curves for cardiovascular events according to (A) geriatric nutritional risk index (GNRI) ≤96 or >96, (B) estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or ≥60 mL/min/1.73 m^2, (C) the presence or absence of left ventricular hypertrophy (LVH), (D) the presence or absence of proteinuria, (E) left atrial diameter (LAD) <40 mm or ≥40 mm, and (F) the presence or absence of hypertension. Lower GNRI (A), lower eGFR (B), and the presence of LVH (C), proteinuria (D), and higher LAD (E) were associated with higher rates of cardiovascular events, but the prevalence of hypertension was not significantly associated with cardiovascular events (F).

Figure 2.

Kaplan-Meier curves for cardiovascular events according to (A) the combination of lower or higher eGFR (<60 or ≥60 mL/min/1.73 m^2, respectively) and the presence or absence of LVH; (B) the combination of lower or higher eGFR and lower or higher GNRI (≤96 or >96, respectively); or (C) the combination of the presence or absence of LVH and lower or higher GNRI.

Figure 3.

Scatter dot plots of the levels of serum albumin (A) and GNRI (B) according to the severity of dipstick proteinuria. Error bars represent the means ± standard deviations for each group. There are no significant differences between each group both in serum albumin (A) and GNRI (B).

Figure 1

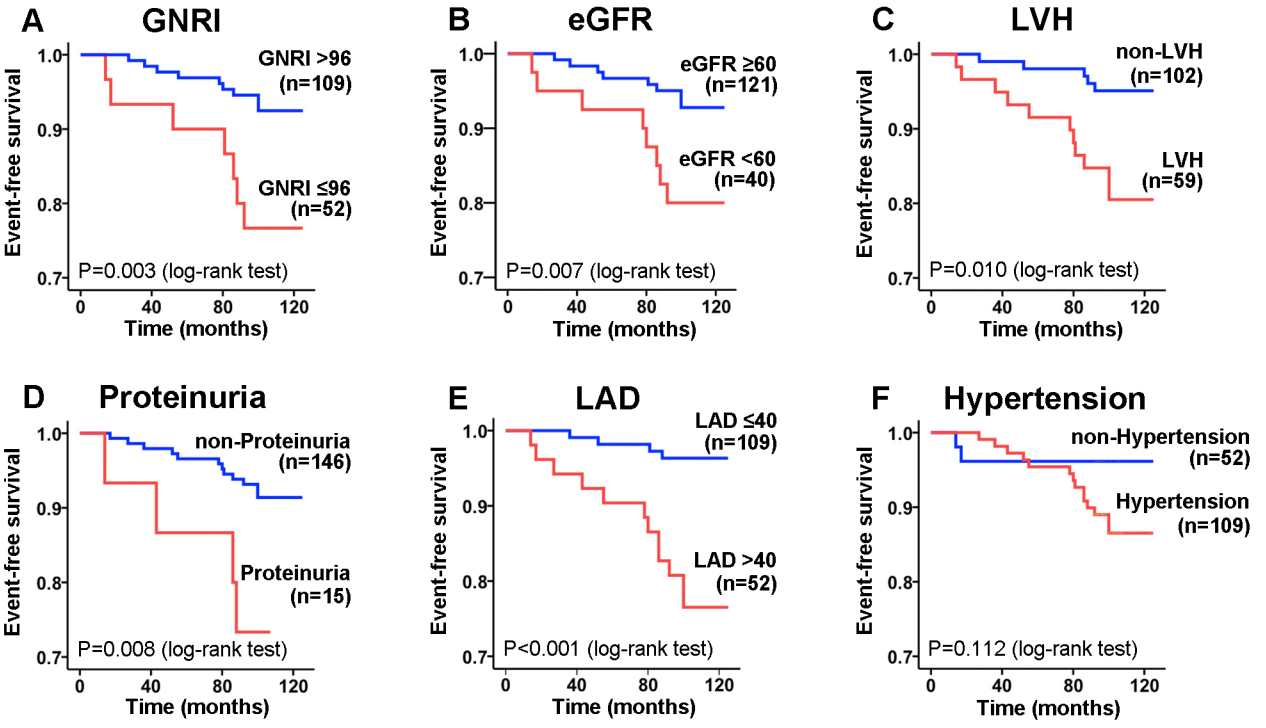

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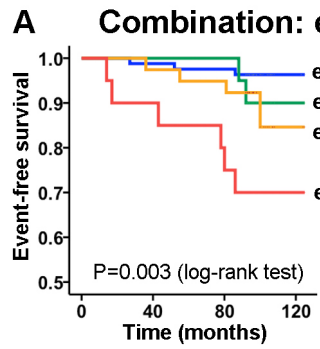
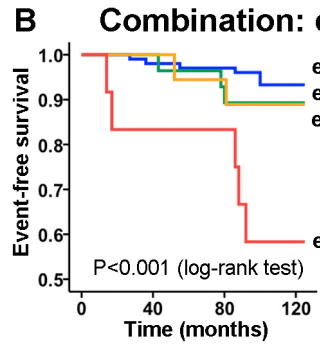
Figure 2





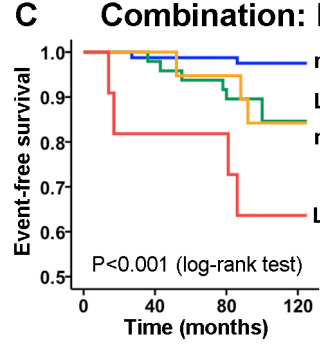


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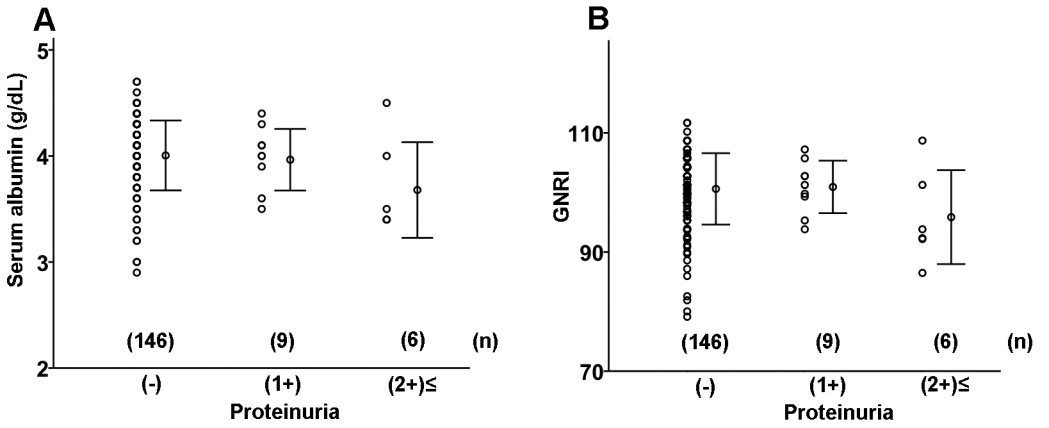
Figure 3



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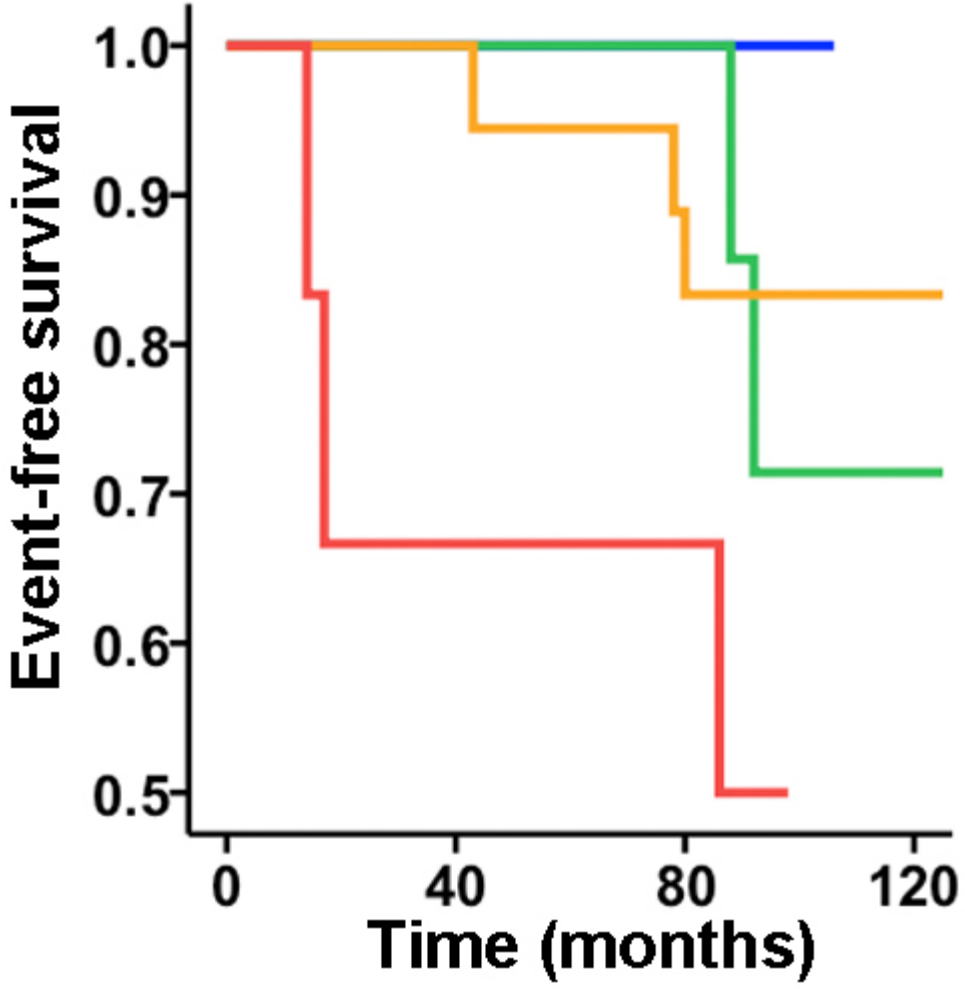
Supplementary Figure S1

Combination: LVH and GNRI in patients with CKD



non-LVH and GNRI >96 (n=15)

LVH and GNRI >96 (n=18)

non-LVH and GNRI ≤96 (n=7)

LVH and GNRI ≤96 (n=6)

P=0.014 (log-rank test)

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