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**Original Paper**

# Impact of Cardiorenal Anemia Syndrome on Short- and Long-Term Clinical Outcomes in Patients Hospitalized with Heart Failure

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**Key Words**
Anemia · Renal failure · Heart failure · Prognosis

**Abstract**
***Background:*** Dysfunctional interplay between the heart and kidneys may lead to the development of anemia. The aim of this study was to evaluate the impact of cardiorenal anemia syndrome (CRAS) on short- and long-term outcomes among patients hospitalized with heart failure (HF). ***Methods:*** We enrolled 303 patients hospitalized with HF. We divided the patients into two groups: a CRAS group (n = 64) and a non-CRAS group (n = 239). We defined CRAS as HF accompanied by (1) an estimated glomerular filtration rate <60 ml/min/1.73 $m^2$ calculated by the Modification of Diet in Renal Disease at admission and (2) a hemoglobin level <12 g/dl for females and <13 g/dl for males at admission. The primary outcome was a composite of cardiac death, non-fatal myocardial infarction and rehospitalization for HF. ***Results:*** During a median follow-up period of 25.6 months (range 0.1–35.3 months), the patients with CRAS had a significantly increased risk for the primary outcome (27.5 vs. 10.7%, p < 0.001) compared with the patients in the non-CRAS group. Using Cox proportional hazard analyses, the hazard ratio (HR) for the presence of CRAS was found to be 1.874 (95% confidence interval [CI] 1.011–3.475, p = 0.046); HRs were also computed for the presence of diabetes mel-

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litus (HR = 2.241, 95% CI 1.221–4.112, p = 0.009), New York Heart Association class III or IV HF (HR = 2.948, 95% CI 1.206–7.205, p = 0.018) and the use of intravenous loop diuretics (HR = 2.286, 95% CI 0.926–5.641, p = 0.073). ***Conclusions:*** Renal dysfunction and anemia are a fatal combination and are associated with poor prognosis in patients with HF.



## Introduction

Heart failure (HF) is a systemic disease that involves organs and tissues in addition to the heart and vasculature [1]. Between 25 and 50% of patients with HF are affected by kidney disease to at least some extent [2, 3]. Anemia has also frequently been observed as a comorbidity of HF, but its clinical significance has largely been neglected, except when it has been deemed life-threatening [4, 5]. Both renal dysfunction and anemia have been studied extensively in HF, and they are known risk factors for increased morbidity and mortality in patients with HF [6, 7].

Cardiorenal anemia syndrome (CRAS), which occurs in approximately 20% of all patients hospitalized for HF, can be considered a pathological triangle in which the primary failing organ, either the heart or kidney, leads to dysfunction of the other, and the dysfunctional interplay between these organs may lead to the development of anemia [8]. Anemia, renal insufficiency and HF exacerbate each other in what has been described as a 'vicious cycle of deterioration' that leads to poor outcomes, including faster progression to end-stage renal disease and further progression of chronic HF [9, 10].

Although both renal dysfunction and anemia have been extensively studied in HF, only a few studies have thoroughly examined their reciprocal relationship in HF [11, 12]. The aim of this study was to evaluate the impact of CRAS on short- and long-term outcomes of patients hospitalized with HF.

## Methods

*Study Population*

We enrolled 303 consecutive patients with HF (New York Heart Association [NYHA] class II–IV) admitted to Seoul St. Mary's Hospital of The Catholic University of Korea between July 2005 and October 2007. We divided the patients into two groups: a CRAS group (n = 64) and a non-CRAS group (n = 239). CRAS was defined as established HF combined with (1) an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 $m^2$ calculated by the Modification of Diet in Renal Disease at admission and (2) a hemoglobin (Hb) level of <13 g/dl for males and <12 g/dl for females at admission [12]. In this study, we excluded patients who had active bleeding in the gastrointestinal tract or other solid organs, acute or chronic infections or inflammatory diseases, and malignancies, including hematologic malignancies and those affecting solid organs. Patients who received renal replacement therapy, such as hemodialysis, peritoneal dialysis and renal transplantation, were also excluded from this study.

Clinical data were obtained from a comprehensive review of subjects' medical records using established criteria for hypertension, diabetes mellitus, hyperlipidemia and myocardial infarction.

*Clinical Outcomes*

Patients were followed up for a median of 25.6 months (range 0.1–35.3 months) and were monitored on a regular basis. The clinical outcome of interest in our study was a composite of cardiac death, non-fatal myocardial infarction and rehospitalization for HF, which was defined according to the Framingham criteria [1].

*Statistical Analysis*

Continuous variables are presented as means ± standard deviations and categorical variables as numbers and percentages. Group comparisons were performed using Student's t test or Mann-Whitney

**Table 1.** Baseline patient characteristics according to the presence of CRAS

| | All (n = 303) | CRAS (n = 61) | Non-CRAS (n = 242) | p value |
|---|---|---|---|---|
| Demographics | | | | |
| Age, years | 68.3±13.8 | 75.7±11.8 | 66.4±13.6 | <0.001 |
| Male | 147 (48.5%) | 24 (39.3%) | 123 (50.2%) | 0.109 |
| Body mass index | 23.7±3.2 | 13.4±3.4 | 23.8±3.1 | 0.396 |
| Comorbidity | | | | |
| Hypertension | 176 (59.3%) | 40 (69.0%) | 136 (56.9%) | 0.094 |
| Diabetes mellitus | 97 (32.7%) | 29 (50.0%) | 68 (28.5%) | 0.002 |
| Hyperlipidemia | 78 (25.4%) | 11 (18.0%) | 67 (27.6%) | 0.247 |
| Current smoking | 80 (27.0%) | 8 (13.8%) | 72 (30.3%) | 0.011 |
| Atrial fibrillation | 61 (20.1%) | 7 (11.5%) | 54 (22.3%) | 0.059 |
| Prior myocardial infarction | 36 (11.9%) | 10 (25.6%) | 26 (12.6%) | 0.035 |
| Cerebrovascular accident | 25 (8.3%) | 9 (15.5%) | 16 (6.7%) | 0.030 |
| Cause of HF | | | | 0.354 |
| Ischemic | 156 (51.5%) | 26 (42.6%) | 130 (53.7%) | |
| Valvular | 21 (6.9%) | 5 (8.1%) | 16 (6.6%) | |
| Arrhythmia | 37 (12.2%) | 5 (8.1%) | 32 (13.2%) | |
| Dilated cardiomyopathy | 89 (29.4%) | 25 (40.9%) | 64 (26.4%) | |
| NYHA functional class | | | | 0.003 |
| II | 130 (42.9%) | 18 (29.5%) | 112 (46.3%) | |
| III | 151 (49.8%) | 34 (55.7%) | 117 (48.3%) | |
| IV | 22 (7.3%) | 9 (14.8%) | 13 (5.4%) | |
| Laboratory findings | | | | |
| Hb, g/dl | 12.7±2.1 | 10.4±1.3 | 13.3±1.9 | <0.001 |
| Hct, % | 36.9±5.7 | 31.4±3.8 | 38.3±5.2 | <0.001 |
| Mean corpuscular volume, fl | 90.7±6.6 | 89.6±8.1 | 90.9±6.1 | 0.215 |
| Creatinine, mg/dl | 1.12±0.57 | 1.80±0.85 | 0.96±0.28 | <0.001 |
| eGFR, ml/min/1.73 $m^2$ | 70.6±26.0 | 38.8±13.1 | 78.7±21.9 | <0.001 |
| Albuminuria | 58 (20.9%) | 19 (35.8%) | 39 (17.4%) | 0.003 |
| Total cholesterol, mg/dl | 173.2±45.1 | 162.7±48.3 | 178.1±44.1 | 0.175 |
| Triglycerides, mg/dl | 123.1±86.3 | 120.2±108.3 | 127.3±78.2 | 0.725 |
| HDL-C, mg/dl | 41.4±14.3 | 42.1±13.4 | 40.0±14.2 | 0.674 |
| hsCRP, mg/dl | 2.56±4.69 | 3.31±5.32 | 2.35±4.61 | 0.243 |
| NT-proBNP, pg/ml | 5,167.5±8,137.7 | 13,236.8±12,425.3 | 3,133.5±4,887.7 | <0.001[a] |
| Echocardiography | | | | |
| LVEF, % | 48.9±14.6 | 46.0±13.8 | 49.7±14.7 | 0.081 |
| LVEDD, mm | 53.8±8.8 | 53.4±8.7 | 53.8±8.9 | 0.785 |
| LVESD, mm | 37.7±11.2 | 38.2±11.9 | 37.6±11.1 | 0.751 |
| Left atrial dimension, mm | 42.9±10.9 | 44.1±8.2 | 42.6±11.5 | 0.362 |
| Intravenous loop diuretics | 170 (56.1%) | 53 (86.8%) | 117 (48.3%) | <0.001 |
| Discharge medication | | | | |
| ACEI/ARB | 183 (62.0%) | 34 (58.6%) | 149 (62.9%) | 0.550 |
| Beta-blocker | 151 (51.4%) | 36 (62.1%) | 115 (48.7%) | 0.069 |
| Calcium channel blocker | 67 (22.9%) | 15 (25.9%) | 52 (22.1%) | 0.544 |
| Diuretic | 184 (60.7%) | 52 (85.2%) | 132 (54.5%) | <0.001 |

Figures are mean ± standard deviation or n (%).

ACEI/ARB = Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; HDL-C = high-density lipoprotein cholesterol; hsCRP = highly sensitive C-reactive protein; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension.

[a] Statistical significance test was done by Mann-Whitney U test. Normality test was performed by Shapiro-Wilk test.

**Table 2.** Independent predictors of CRAS in patients with HF based on univariate and multivariate logistic regression analyses

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | p value | OR | 95% CI | p value |
| Age ≥65 years | 3.368 | 1.671–6.788 | 0.001 | 1.559 | 0.618–3.932 | 0.347 |
| Male gender | 0.628 | 0.654–1.112 | 0.110 | | | |
| Body mass index ≥25 | 0.755 | 0.389–1.466 | 0.407 | | | |
| Hypertension | 1.683 | 0.912–3.105 | 0.096 | | | |
| Diabetes mellitus | 2.515 | 1.399–4.520 | 0.002 | 1.951 | 0.891–4.272 | 0.095 |
| Current smoking | 0.369 | 0.166–0.818 | 0.014 | 0.320 | 0.107–0.957 | 0.042 |
| NYHA III or IV | 2.058 | 1.123–3.771 | 0.019 | 2.434 | 0.702–8.441 | 0.161 |
| NT-proBNP ≥3rd tertile | 13.554 | 6.240–29.437 | <0.001 | 7.453 | 2.813–19.746 | <0.001 |
| Albuminuria | 2.651 | 1.371–5.124 | 0.004 | 1.398 | 0.572–3.418 | 0.462 |
| LVEF ≤35% | 1.148 | 0.575–2.293 | 0.696 | | | |
| Intravenous loop diuretics | 4.815 | 2.271–10.208 | <0.001 | 4.923 | 1.615–15.003 | 0.005 |
| ACEI/ARB | 0.756 | 0.413–1.385 | 0.366 | | | |
| Beta-blocker | 1.846 | 1.007–3.384 | 0.070 | | | |
| Calcium channel blocker | 1.285 | 0.653–2.529 | 0.467 | | | |

ACEI/ARB = Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; OR = odds ratio.

U test as appropriate, and the $\chi^2$ test was used for frequency variables. Analysis of variance was used in comparing eGFR and Hb according to NYHA class and Hb according to eGFR. We divided all patients into two groups according to the presence of CRAS and then compared the incidences of specific clinical outcomes between these groups using Kaplan-Meier survival curves. Using Cox proportional hazards univariate and multivariate analyses, we calculated the odds ratios for the associations between prespecified risk factors, including CRAS, and the primary clinical outcome. Covariates found to be statistically significant in the univariate analysis ($p < 0.1$) were considered candidate variables for the multivariate models. Statistical analyses were performed with SPSS version 15.0 (SPSS Inc., Chicago, Ill., USA). For all analyses, a p value <0.05 was considered statistically significant.

## Results

*Baseline Characteristics*

Table 1 shows the baseline characteristics of the 303 patients with HF who were enrolled in this study (mean age 68.3 ± 13.8 years, males 147 [48.5%]) according to the presence of CRAS. The patients with CRAS were older and more frequently diabetic, had HF of a more advanced NYHA class, had higher plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), had more frequent albuminuria and were more likely to be prescribed intravenous and oral diuretics compared with the non-CRAS group. The patients with CRAS have significantly lower Hb and hematocrit (Hct), but there was no significant different in mean corpuscular volume. Figure 1 shows the interplay between renal dysfunction and anemia in the patients with HF who were enrolled in this study. Hb levels and eGFRs were positively correlated in HF patients (fig. 1c), and both of these measures gradually decreased as the NYHA functional class increased (fig. 1a, b).

*Predictors of CRAS*

In the univariate and multivariate logistic regression analyses, age ≥65 years, presence of diabetes mellitus, NT-proBNP levels ≥3rd tertile and use of intravenous diuretics were

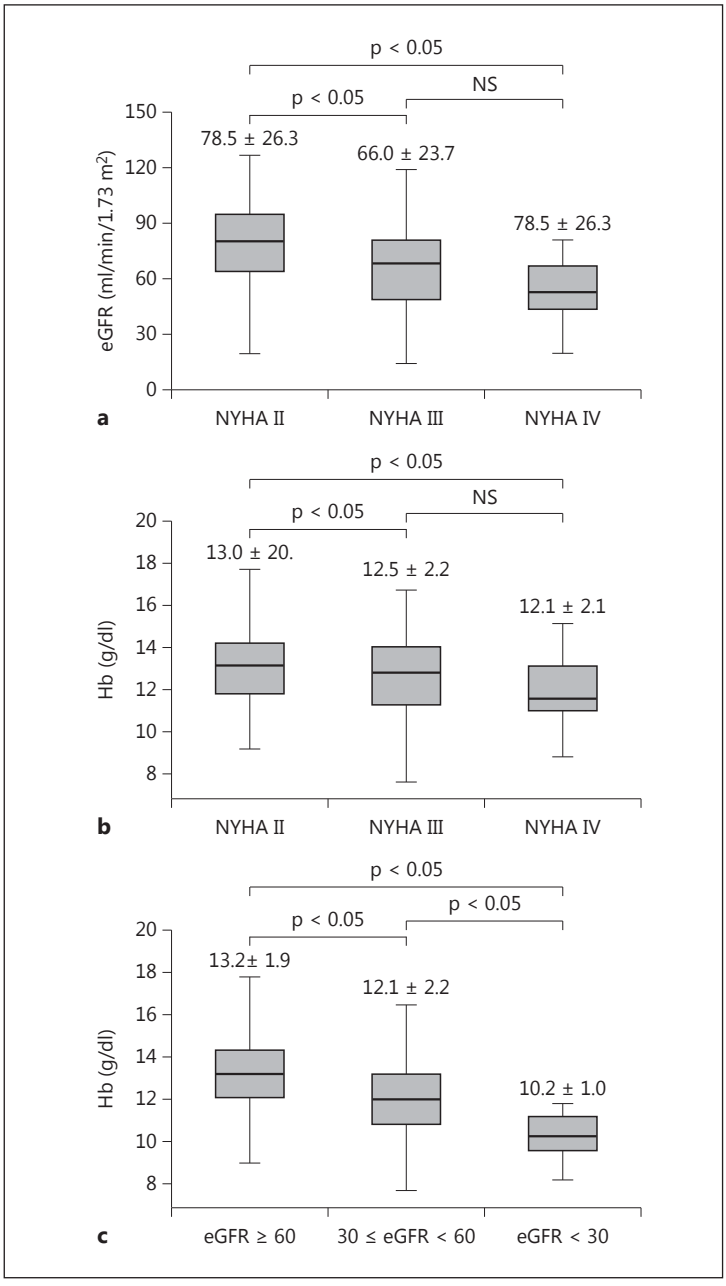


**Fig. 1.** Interplay between renal dysfunction and anemia in patients with HF. Hb levels and eGFRs were positively correlated in HF patients (**c**), and both of these measures gradually decreased as the NYHA functional class increased (**a**, **b**). NS = Not significant.

independent predictors of the presence of CRAS. However, hypertension, NYHA class III or IV HF, left ventricular ejection fraction (LVEF) <35% and use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers or calcium channel blockers were not associated with the development of CRAS (table 2).

*Clinical Outcomes in CRAS*

During a median follow-up period of 25.6 months (range 0.1–35.3 months), the primary composite outcome occurred in 44 (14.5%) patients as follows: cardiac death in 13 (4.3%) patients, non-fatal myocardial infarction in 22 (7.3%) patients and rehospitalization for HF in 27 (8.9%) patients. The patients with CRAS had a significantly increased risk for the primary composite outcome (34.4 vs. 11.2%, p < 0.001) as well as for renal replacement therapy (6.5

**Table 3.** Clinical outcomes in CRAS

| | All (n = 303) | CRAS (n = 61) | Non-CRAS (n = 242) | p value |
|---|---|---|---|---|
| Cardiac death | 13 (4.3%) | 7 (10.1%) | 6 (2.6%) | 0.017 |
| Non-fatal myocardial infarction | 22 (7.3%) | 8 (13.1%) | 16 (6.6%) | 0.093 |
| Rehospitalization for HF | 27 (8.9%) | 16 (26.2%) | 18 (7.4%) | <0.001 |
| Renal replacement therapy | 6 (2.0%) | 4 (6.5%) | 2 (0.8%) | 0.001 |
| Primary composite outcome | 44 (14.5%) | 21 (34.4%) | 27 (11.2%) | <0.001 |

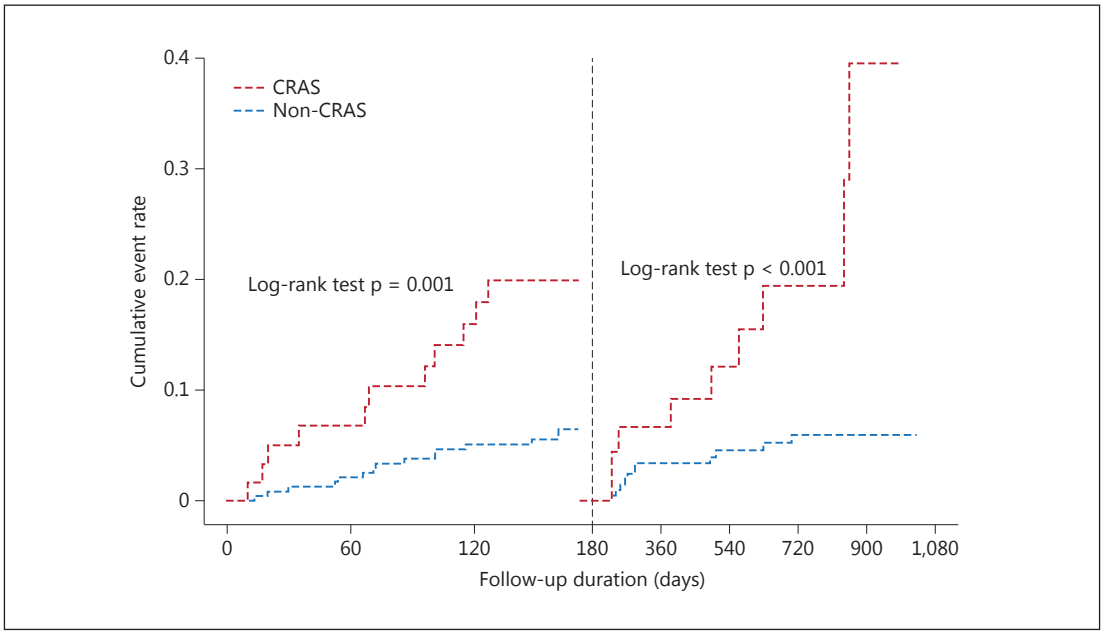


**Fig. 2.** Landmark analysis of the cumulative incidence of clinical outcomes (cardiac death, non-fatal myocardial infarction and rehospitalization for HF) in patients with and without CRAS.

vs. 0.8%, p = 0.001) compared with the patients in the non-CRAS group (table 3). A landmark analysis at 6 months showed that the patients with CRAS had poor prognoses at both the short- and long-term clinical follow-ups (fig. 2). Using univariate and multivariate Cox hazard regression analyses, the hazard ratio (HR) for the presence of CRAS was found to be 2.326 (95% confidence interval [CI] 1.102–4.909, p = 0.027); HRs were also computed for the presence of diabetes mellitus (HR = 2.513, 95% CI 1.331–4.747, p = 0.005), NYHA class III or IV HF (HR = 2.883, 95% CI 1.207–6.887, p = 0.017) and the use of intravenous loop diuretics (HR = 1.608, 95% CI 0.669–3.862, p = 0.288) (table 4).

## Discussion

The major finding of the present study was that the development of CRAS was associated with older age, the presence of diabetes mellitus, higher NT-proBNP levels and the use of intravenous diuretics. The presence of CRAS, together with diabetes mellitus, NYHA functional class

**Table 4.** Independent predictors of primary composite outcome in patients with CRAS based on Cox proportional hazard analysis

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p value | HR | 95% CI | p value |
| Age ≥65 years | 1.840 | 0.957–3.536 | 0.067 | 1.286 | 0.635–2.606 | 0.484 |
| Male gender | 0.637 | 0.355–1.142 | 0.130 | | | |
| Hypertension | 1.378 | 0.756–2.520 | 0.297 | | | |
| Diabetes mellitus | 2.782 | 1.565–4.946 | <0.001 | 2.513 | 1.331–4.747 | 0.005 |
| Current smoking | 0.570 | 0.266–1.219 | 0.147 | | | |
| NYHA III or IV | 4.658 | 2.172–9.991 | <0.001 | 2.883 | 1.207–6.887 | 0.017 |
| NT-proBNP ≥3rd tertile | 2.830 | 1.395–5.742 | 0.004 | 0.963 | 0.294–3.161 | 0.951 |
| Albuminuria | 2.644 | 1.452–4.814 | 0.001 | 1.674 | 0.876–3.199 | 0.119 |
| LVEF <35% | 1.860 | 0.980–3.533 | 0.058 | | | |
| Intravenous loop diuretics | 3.262 | 1.577–6.748 | 0.001 | 3.978 | 1.323–11.963 | 0.014 |
| Discharge medication | | | | | | |
| ACEI/ARB | 1.657 | 0.872–3.151 | 0.123 | | | |
| Beta-blocker | 0.893 | 0.498–1.602 | 0.705 | | | |
| Calcium channel blocker | 0.833 | 0.400–1.733 | 0.624 | | | |
| Diuretic | 2.703 | 1.363–5.361 | 0.004 | 1.368 | 0.433–4.323 | 0.593 |
| Presence of CRAS | 3.625 | 2.047–6.421 | <0.001 | 2.326 | 1.102–4.909 | 0.027 |

ACEI/ARB = Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

III or IV HF and the use of intravenous loop diuretics, is a predictor of poor short- and long-term clinical outcomes in patients with HF. These findings suggest that renal dysfunction and anemia are a fatal combination in HF and lead to poor prognoses in patients with HF.

*Predictors of CRAS*

The development of CRAS is multifactorial and can be caused by dysfunctional interplay between the heart and kidneys, which can lead to the development of anemia. Indeed, it is well known that heart disease has several negative effects on kidney function and vice versa. Anemia is also a frequent comorbidity that has a medically significant impact in patients already suffering from both chronic kidney disease and chronic HF; its prevalence in patients with cardiorenal syndrome has been observed to be between 39 and 45%.

Although the pathophysiology of CRAS is at least partially understood, limited data are available to provide guidance on the diagnosis of CRAS and the risk factors associated with CRAS in patients with HF. A recent observational study showed that the prevalence of CRAS was 18.7% and that advanced age, lower body mass index, presence of diabetes mellitus, ischemic etiology, lower LVEF and lack of treatment with renin-angiotensin system inhibitors were independently associated with CRAS [12]. In this study, the incidence of CRAS was 20.1%, and the independent risk factors for CRAS were age ≥65 years, presence of diabetes mellitus, NT-proBNP levels in the upper tertile and use of intravenous loop diuretics; however, the presence of CRAS was not related to body mass index, LVEF or use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. These findings suggest that the severity of volume overloading and subsequent achievement of euvolemia using intravenous loop diuretics may affect the development of CRAS. Indeed, the efficacy of loop diuretics declines with repeated exposure [13] and high doses of loop diuretics may have harmful effects, including activation of the renin-angiotensin system and the sympathetic nervous system, electrolyte disturbances and worsening of cardiac and renal function [14–17].

Therefore, intravenous loop diuretics should be used with caution despite their essential role in the current treatment of patients with acute decompensated HF [18].

*Clinical Outcomes in CRAS*

Both renal dysfunction and anemia have been studied extensively in HF; they are known risk factors for increased morbidity and mortality. In a study of elderly congestive HF patients in the Medicare population [19], the 2-year survival rate was 74% among patients with congestive HF, 65% among those with congestive HF and anemia, 62% among those with congestive HF and renal dysfunction, and 54% among those with all three conditions. Data from the Studies of Left Ventricular Dysfunction (SOLVD) trial [20] suggest that anemia and renal dysfunction act synergistically to multiply mortality risk. Go et al. [11] observed that lower HB levels and decreased renal function independently increased the risks of death and hospitalization in HF, and the relative risk of death associated with lower Hb levels was notably higher in the presence of better kidney function. Our data show that the presence of CRAS contributed to poor short- and long-term prognoses in patients with HF. During a median follow-up period of 25.6 months, the patients with CRAS had a two-fold increase in the adjusted risk of the primary outcome compared with the patients without CRAS. The available data and our findings suggest that renal dysfunction and anemia represent a continuum of disease progression in HF and that the development of these comorbidities should be viewed as a critical step in the progression of the disease toward death rather than solely as comorbidities.

Administration of loop diuretics to patients with HF has been shown to activate the renin-angiotensin-aldosterone system and the sympathetic nervous system, both of which are known to play a fundamental role in the progression of HF [14, 15]. In addition, the use of loop diuretics may also lead to electrolyte imbalances that may exacerbate cardiac arrhythmias and increase the risk of sudden cardiac death [16, 17]. Clinically, several observational data have suggested that diuretics use may be associated with worse outcomes in patients with HF [21, 22]. Most recently, analyses of the data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) study demonstrated a nearly linear relationship between loop diuretic dose and mortality over a 6-month follow-up period in patients hospitalized with advanced HF [22]. Consistent with these findings, our data also showed that the use of intravenous loop diuretics was an independent risk factor for the primary outcome as well as for the presence of CRAS. Indeed, substantial questions remain regarding how to best use diuretics to treat volume overload in patients with HF, given that diuretics are an essential component of current treatment strategies for patients with acute decompensated HF [23]. Non-pharmacological approaches, such as ultrafiltration, may be an effective alternative therapy in high-risk patients with CRAS [24]. Therefore, it is important to recognize and diagnose CRAS when it is present and to identify effective management strategies in HF patients with CRAS.

*Study Limitations*

First, this study was not a prospective randomized trial, and despite covariate adjustments, other measured and unmeasured factors may have influenced the outcomes. Second, in the present study, Hb concentrations on admission were examined, and these levels may not accurately reflect Hb levels after discharge or changes in Hb levels over time. We also did not attempt to identify the etiology or assess the treatment or maintenance of anemia during the follow-up period. Third, no data were available on the infusion strategies (bolus vs. continuous) or doses (low vs. high) of intravenous loop diuretics administered during hospitalization. However, a recent prospective, randomized study in patients with acute decompensated HF found no significant difference in the change in renal function or in clinical outcomes between infusion strategies and doses [23].

## Conclusions

The development of CRAS was associated with older age, presence of diabetes mellitus, higher NT-proBNP levels and use of intravenous diuretics. The presence of CRAS, together with diabetes mellitus, NYHA functional class III or IV HF and use of intravenous loop diuretics, was associated with poor short- and long-term clinical outcomes in patients with HF. These findings suggest that renal dysfunction and anemia are a fatal combination and contribute to poor prognosis in patients with HF.

## Statement of Ethics

All subjects provided written informed consent to participate in the study. The institutional review board of Seoul St. Mary's Hospital of The Catholic University of Korea approved the study protocol.

## Disclosure Statement

The authors have no conflicts of interest to declare.

## References

1 Kannel WB: Epidemiology and prevention of cardiac failure: Framingham Study insights. Eur Heart J 1987; 8(suppl F):23–26.
2 Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ: Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation 2000;102:203–210.
3 Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, Krumholz HM: Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol 2006;47:1987–1996.
4 Hamaguchi S, Tsuchihashi-Makaya M, Kinugawa S, Yokota T, Takeshita A, Yokoshiki H, Tsutsui H; JCARE-CARD Investigators: Anemia is an independent predictor of long-term adverse outcomes in patients hospitalized with heart failure in Japan. A report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circ J 2009;73:1901–1908.
5 von Haehling S, Schefold JC, Hodoscek LM, Doehner W, Mannaa M, Anker SD, Lainscak M: Anaemia is an independent predictor of death in patients hospitalized for acute heart failure. Clin Res Cardiol 2010;99:107–113.
6 Ronco C, Haapio M, House AA, Anavekar N, Bellomo R: Cardiorenal syndrome. J Am Coll Cardiol 2008;52: 1527–1539.
7 Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, van der Meer P: Anemia and mortality in heart failure patients: a systematic review and meta-analysis. J Am Coll Cardiol 2008; 52:818–827.
8 Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, Brosh D, Laniado S, Schwartz D, Yachnin T, Shapira I, Gavish D, Baruch R, Koifman B, Kaplan C, Steinbruch S, Iaina A: The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol 2000;35:1737–1744.
9 Kazory A, Ross EA: Anemia: the point of convergence or divergence for kidney disease and heart failure? J Am Coll Cardiol 2009;53:639–647.
10 von Haehling S, Anker SD: Cardio-renal anemia syndrome. Contrib Nephrol 2011;171:266–273.
11 Go AS, Yang J, Ackerson LM, Lepper K, Robbins S, Massie BM, Shlipak MG: Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure: the Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study. Circulation 2006;113:2713–2723.
12 Scrutinio D, Passantino A, Santoro D, Catanzaro R: The cardiorenal anaemia syndrome in systolic heart failure: prevalence, clinical correlates, and long-term survival. Eur J Heart Fail 2011;13:61–67.
13 Ellison DH: Diuretic therapy and resistance in congestive heart failure. Cardiology 2001;96:132–143.
14 Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN: Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. Ann Intern Med 1985;103:1–6.
15 Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P: Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. Br Heart J 1987;57:17–22.

16 Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ: Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. Circulation 1999;100:1311–1315.
17 Klein L, O'Connor CM, Leimberger JD, Gattis-Stough W, Piña IL, Felker GM, Adams KF Jr, Califf RM, Gheorghiade M; OPTIME-CHF Investigators: Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. Circulation 2005;111:2454–2460.
18 Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Wang Y, Young JB, Krumholz HM: Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. Am Heart J 2004;147:331–338.
19 Herzog CA, Muster HA, Li S, Collins AJ: Impact of congestive heart failure, chronic kidney disease, and anemia on survival in the Medicare population. J Card Fail 2004;10:467–472.
20 Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, Sarnak MJ: Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol 2001;38:955–962.
21 Philbin EF, Cotto M, Rocco TA, Jenkins PL: Association between diuretic use, clinical response, and death in acute heart failure. Am J Cardiol 1997;80:519–522.
22 Hasselblad V, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, Adams KF Jr: Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. Eur J Heart Fail 2007;9:1064–1069.
23 Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM: Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797–805.
24 Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, Jaski BE, Fang JC, Feller ED, Haas GJ, Anderson AS, Schollmeyer MP, Sobotka PA; UNLOAD Trial Investigators: Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol 2007;49:675–683.