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RESEARCH ARTICLE

Impact of Cardiorenal Anaemia Syndrome on Clinical Features in Elderly Outpatients with Chronic Heart Failure: A Japanese Community Hospital Experience

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ABSTRACT

Background: **Cardiorenal anaemia syndrome (CRAS) has been reported to be associated with all-cause mortality and cardiovascular events in outpatients with heart failure (HF).**

Objective: **To evaluate the clinical situation of CRAS including NYHA class and care status in elderly outpatients with HF.**

Methods: **A total of 41 elderly (>65 years) outpatients with HF attending our hospital were analysed retrospectively and cross-sectionally. Clinical variables included lifestyle diseases, atrial fibrillation, valvular heart disease, HFpEF, chronic kidney disease (CKD), cardiac function (LVEF, E/e', LADI, BNP), anaemia (Hb, Fe/TIBC (%), ferritin), medications (diuretics, MRA, ACEI/ARB, β-blockers, SGLT2i, ARNI, tolvaptan), NYHA class (I/II/III/IV). The nursing variables analysed were Japanese nursing certification class, which assesses active daily living (ADL), instrumental ADL, cognitive function, mental function, physical function, communication, and need for support/care (from least to most intensive, independence 0/support(S)1/S2/care(C)1/C2/C3/C4/C5) and frailty. Subjects were divided into two groups (CRAS+ group and CRAS− group) according to the presence of CRAS, defined as HF associated with CKD (eGFR < 60 mL/min/1.73 m^2) and anaemia (Hb < 13 g/dL, men and Hb < 12 g/dL, women). All variables were compared between the two groups.**

Results: **Mean age was 83.7 ± 7.1 years (67∼100). Female gender was 63.4% (26/41). The incidence of HFpEF was 33/41 (80.5%). The incidence of CRAS was 53.7% (22/41). The incidence of lifestyle diseases was not different between the two groups. Cardiac function was not significantly different between the two groups (CRAS+ vs. CRAS−): LVEF (59.1 ± 8.3 vs. 61.3 ± 7.2); E/e (15.1 ± 5.8 vs. 15.0 ± 7.0); LAVI (50.6 ± 16.6 vs. 54.3 ± 30.9); BNP (347.0 ± 234.4 vs. 291.3 ± 197.0). Hb was significantly lower in the CRAS+ group than in the CRAS group (10.4 ± 1.4 vs. 13.4 ± 1.7, P < 0.0001). Fe/TIBC and ferritin were not significantly different between the two groups. Regarding medications, tolvaptan tended to be used more frequently in the CRAS+ group than in the CRSA− group (4/22 vs. 0/18, P = 0.111). The other drugs were used with similar frequency. Meanwhile, the NYHA class tended to be higher in the CRAS+ group than in the CRAS− group: NYHA (8/9/5/0 vs. 8/11/0/0, P = 0.082). Nursing class showed more intensive care in the CRAS+ group than in the CRAS− group (4/3/3/2/4/1/3/2 vs. 11/0/6/1/0/1/0/0, P = 0.021).**

Conclusions: **The association of CRAS with HF was associated with more intensive support/care status but not with cardiac function/BNP and other factors. Prevention and active treatment of CRAS may improve the independence of elderly outpatients with HF.**

Keywords: Anaemia, cardiorenal syndrome, iron deficiency, nursing care.

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1. Introduction

In an ageing society, the prevalence of heart failure (HF) is increasing and the term 'heart failure pandemic' has been coined [1], [2]. The rate of new cases of HF increases with age [3]. Elderly patients with HF are often associated with organ dysfunction other than the heart, such as renal and vascular dysfunction. Cardiorenal syndrome also increases in older people with HF due to the effects of ageing and treatment with diuretics, which also reduce renal function [4]. In addition, when anaemia is complicated, cardiorenal anaemia syndrome (CRAS) occurs and HF, chronic kidney disease (CKD) and anaemia may interact to form a negative spiral and be one of the risk factors for worsening prognosis [5], [6]. Anaemia worsens prognosis when it is complicated by CKD, and HF also worsens and becomes resistant to treatment through the association of anaemia [7]. CRAS has been reported to be associated with a cardiovascular event [8] and mortality [5], [6], [9], [10]. On the other hand, in recent years, the concept of frailty has taken hold and new problems such as skeletal muscle disorders, nutritional disorders, decreased independence and caregiving in HF patients have attracted attention [11]. Therefore, intervention for elderly HF patients is an urgent issue not only for medical care but also for multiprofessional and multidisciplinary responses [2]. The aim of this study was to evaluate the clinical characteristics of elderly HF patients from the perspective of the presence or absence of complications of CRAS, including the status of long-term care.

2. Methods

The study involved a group of chronic HF patients aged 65 years and older who were attending our outpatient clinic as of September 1, 2023. We specifically included patients with stable HF status in the outpatient setting, while excluding those who had been hospitalized in the last 6 months. The comorbidities observed in the study comprised lifestyle-related diseases such as hypertension, diabetes mellitus (DM), and dyslipidemia, as well as HF, CKD, and anaemia. The study evaluated several factors, including CRAS, cerebrovascular disease (CVD), dementia, New York Heart Association (NYHA) class, frailty, and nursing class, to determine self-reliance level. Cases of advanced or end-stage cancer were not included in the study. Blood biochemical data from the most recent time point were generally used, with intermediate values from the last three times being adopted in cases of high fluctuations. Additionally, the use of drugs for HF at the beginning of the analysis was examined. The following are definitions of various medical terms:

- *Hypertension* is characterized by a systolic blood pressure of 140 mmHg or higher and/or a diastolic blood pressure of 90 mmHg or higher, or by the use of antihypertensive medication.
- *Dyslipidemia* is characterized by a total cholesterol level of over 220 mg/dL and/or a triglyceride level of over 150 mg/dL and/or an HDL cholesterol level of less than 40 mg/dL, or by the use of therapeutic medication.
- Regarding *diabetes mellitus*, a fasting blood sugar (FBS) level of 126 mg/dL or higher, occasional blood glucose level of 200 mg/dL or higher, or an oral glucose tolerance test 2-hour value of 200 mg/dL or higher recorded on two different measurement days, or FBS level of 126 mg/dL or higher and HbA_{1C} level of 6.5% or higher recorded on the same day when typical symptoms of DM are recognized, indicate the presence of the disease.
- *Chronic kidney disease (CKD)* can be indicated by an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m^2.
- *Anaemia* can be indicated by a hemoglobin (Hb) level of less than 12 g/dL in females and less than 13 g/dL in males.
- *The CRAS syndrome* is comprised of heart failure, CKD, and anaemia.
- *Nursing care accreditation degree classification* is a classification system for nursing care accreditation.
- *HF* refers to cardiac dysfunction with typical symptoms and is classified into HF with reduced ejection fraction (HFrEF) [12], [13] (left ventricular ejection fraction (LVEF) $< 40\%$), HFmrEF ($40 \leq$ LVEF $< 50\%$), or HF with preserved ejection fraction (HFpEF) (LVEF $\geq 50\%$ and E/e' > 14 and left atrial volume index (LAVI) > 34).
- *Frailty* was defined according to the cardiovascular health (CHS) criteria, which encompass deficits in five areas: low weight, physical inactivity, exhaustion, weakness, and slowness [14].

The classification and contents of long-term care certification are presented in Table I [15]. Long-term care certification is judged on a 7-point scale for a 1 to 2 scale support requirement and a 1 to 5 scale for long-term care requirement. In this study, an eight-point scale was used to assess also independence. Moreover, the eight aforementioned classes are classified into three categories: independence, support requirement, and long-term care requirement.

Japan has a long-term care certification system that assesses and certifies the level of care needed for individuals who require assistance in their daily lives, such as the elderly and people with disabilities. The purpose of this system is to assess the level of care objectively needed for each individual and support the use of appropriate services and welfare systems. Long-term care certification is primarily based on the long-term care insurance system of local governments. During the certification process, a specialist will carefully evaluate the user's unique situation and determine the appropriate level of support required. This will enable the specialist to provide personalized support that meets the individual's specific needs.

The study took into account comorbidities such as cardiovascular disease and dementia.

It was found that untreated advanced cancers or orthopedic diseases did not have an impact on independence.

TABLE I: Classification of Japanese Nursing Care Certification Class (Referred to as Kaigo Nintei in Japanese)

Independence	The individual is capable of carrying out fundamental daily activities, such as walking and standing up independently, as well as more complex tasks, such as taking medication orally and using the telephone.
0	
Support	A condition in which an individual can perform basic daily activities independently but requires assistance with instrumental activities of daily living to prevent the need for long-term care.
1	
2	The condition is classified into two categories based on the degree of instrumental activities of daily living. The level of support required increases from 1 to 2.
Care	A condition where an individual faces difficulty in performing basic daily activities independently and requires nursing care. It is categorized into five levels based on the degree of activities of daily living and instrumental activities of daily living. The level of care required increases gradually from level 1 to level 5.
1	
2	
3	
4	
5	

2.1. Statistical Analysis

A comparison of continuous variables between the two groups was conducted using an unpaired t-test when the data were normally distributed, and a Mann-Whitney U test when the data were not normally distributed. To compare the proportions between the two groups, the χ^2 test or, if necessary, the Fisher test was used. The analysis was carried out using JMP 10.0.2 (A Business Unit of SAS Campus Drive Cary, NC). A P-value of < 0.05 was considered to be statistically significant.

It is worth noting that all patients provided written informed consent for the use of their data and publication in this journal. The authors have disclosed that there are no conflicts of interest related to this study.

3. Results

Table II presents the clinical characteristics of the study participants, including their mean age of 83.7 ± 7.1 years (range: 67–100), with 63.4% (26/41) being female. The study found that 80.5% (33/41) of participants had HF with preserved ejection fraction (HFpEF), 90.2% (37/41) had cardiorenal syndrome, and 53.7% (22/41) had CRAS. Additionally, 6 cases of CVD were present, including 4 cases of cerebral infarction, 1 case of lacunar infarction, and 1 case of both lacunar and cerebral infarction. Lastly, only 1 case was diagnosed with dementia.

The study found that there were no significant differences in the comparison of variables between the CRAS+ group and CRAS− group with regard to age and the incidence of lifestyle diseases.

Additionally, cardiac function (LVEF, E/e', LAVI) and brain natriuretic peptide (BNP) (347.0 ± 234.4 vs. 291.3 ± 197.0) were not significantly different between the two groups. However, it was observed that the CRAS+ group had a significantly lower Hb level compared to the CRAS− group (10.4 ± 1.4 vs. 13.4 ± 1.7, $P < 0.0001$). Fe/total iron binding capacity (TIBC) (%) and ferritin levels were similar between the two groups. It is worth noting that NYHA class tended to be higher in the CRAS+ group than in the CRAS− group: (I/II/III/IV: 8/9/5/0 vs. 8/11/0/0, $P = 0.082$). Additionally, the nursing class showed a higher level of intensive care in the CRAS+ group compared to the CRAS− group. There was a significant difference between the two groups in the three categories of independence, support requirement, and long-term care requirement (I/S/C: 4/6/12 vs. 11/6/2, $P = 0.006$) (Fig. 1). It is worth noting that the CRAS group showed a more intensive care level in nursing class.

In terms of medical treatment (Table III), tolvaptan tended to be used more frequently in the CRAS+ group than in the CRSA− group (4/22 vs. 0/18, $P = 0.111$), while the other drugs were used with similar frequency.

The comparison of ratios between the CVD+ group and the CVD− group for 8 and 3 nursing class groups did not reveal any significant differences (Table IV).

4. Discussion

In this study, it was observed that there was no significant difference in renal function or cardiac function between the group with CRAS and the group without CRAS in the elderly HF. However, there was a significant difference in the classification of long-term care requirements, which can be considered as a comprehensive indicator of decreased independence. It was noted that the proportion of patients certified as requiring support or long-term care was higher in the CRAS group. In this study, it was found that a significant proportion of elderly patients experienced cardiorenal syndrome, which was complicated by renal dysfunction. The study also suggests that the superimposition of anaemia may have a negative impact on the independence of these patients.

It is worth noting that CRAS is often observed in HF patients and is an independent predictor of all-cause mortality [16]. Therefore, it is important to identify CRAS and consider modifying any reversible factors. The reason for the lack of difference in BNP, cardiac function, and kidney function between the groups with and without CRAS is currently unknown. However, it is interesting that the need for long-term care appears to increase in the CRAS group. Based on our analysis, we believe that the effect of anaemia is particularly significant in cardiorenal syndrome [4]. Regarding the association between anaemia and independence in HF patients, Kitano *et al*. found a relationship between the Barthel index and mortality. Additionally, in the study, Hb levels were lower in the group below 85 compared to the group above 85 in the Barthel index in the Basel index [17]. It is speculated that preventing and treating anaemia could be important in reducing the number of elderly HF patients who require long-term care. Prevention of anaemia may benefit from prompt response to bleeding disorders, necessary and appropriate management of renal anemia [18], and careful examination for the existence of chronic inflammatory diseases [19].

Iron deficiency is associated with anaemia, renal dysfunction, and a lower quality of life, as well as reduced exercise capacity and a worse prognosis for patients with worsening HF in CRAS via a common pathway [20]. In elderly adults with advanced HF and CRAS with mild

TABLE II: Baseline Clinical Characteristics, Cardiac Function, and Laboratory Data

	Overall (N = 41)	CRAS (+) (N = 22)	CRAS (−) (N = 19)	P-value
Clinical Valuables:				
Age (years)	83.7 ± 7.1 (67~100)	85.4 ± 7.0	81.7 ± 6.9	0.099
Sex (Male/Female)	15/26	10/12	5/14	0.330
Height (cm)	151.9 ± 9.9	152.1 ± 10.8	151.8 ± 9.1	0.923
Weight (kg)	51.1 ± 13.6	48.4 ± 13.0	54.2 ± 14.0	0.178
Hypertension	31/41 (75.6%)	16/22 (%)	15/19 (%)	0.644
Diabetes mellitus	19/41 (46.3%)	12/22 (54.6%)	7/19 (36.8%)	0.257
Dyslipidemia	26/41 (63.4%)	16/22 (72.7%)	10/19 (52.6%)	0.183
CKD	37/41 (90.2%)	22/22 (100%)	15/19 (79.0%)	0.0383
Anaemia	25/41 (61.0%)	22/22 (100%)	3/19 (15.8%)	<0.0001
Atrial fibrillation (N = 15)	15/41 (36.6%)	6/22 (27.3%)	9/19 (47.4%)	0.183
Ischemic heart disease	13/41 (31.7%)	9/22 (40.9%)	4/19 (21.1%)	0.200
Valvular disease	10/41 (24.4%)	7/22 (24.4%)	3/19 (15.8%)	0.292
NYHA (1/2/3/4)	16/20/5/0	8/9/5/0	8/11/0/0	0.082
Frail	30/41 (73.2%)	18/22 (81.8%)	12/19 (63.2%)	0.290
Cerebrovascular disease	6 (14.6%)	4 (18.2%)	2 (10.5%)	0.668
Nursing care level (I/S1/S2/C1/C2/C3/C4/C5)	15/3/9/3/4/2/3/2	4/3/3/2/4/1/3/2	11/0/6/1/0/1/0/0	0.021
Cardiac Function:				
HFpEF	33/41 (80.5%)	17/22 (77.3%)	16/19 (84.2%)	0.703
LVEF (%)	60.1 ± 7.1	59.1 ± 8.3	61.3 ± 7.2	0.376
E/e'	15.1 ± 6.2 (N = 36)	15.1 ± 5.8 (N = 21)	15.1 ± 7.0 (N = 15)	0.993
LAVI (mL/m^2)	52,1 ± 23.4 (N = 33)	50.6 ± 16.6 (N = 19)	54.3 ± 30.9 (N = 14)	0.661
Laboratory data:				
Hemoglobin (g/L)	11.8 ± 2.1	10.4 ± 1.7	13.4 ± 1.7	<0.0001
Creatinine (mg/dL)	1.13 ± 0.37	1.20 ± 0.42	1.04 ± 0.28	0.162
eGFR (mL/min/1.73 m^2)	43.2 ± 13.1	41.8 ± 12.6	44.9 ± 13.9	0.464
Fe (μg/dL)	73.5 ± 34.2 (N = 31)	61.9 ± 29.0 (n = 16)	82.7 ± 38.1 (n = 15)	0.096
TIBC (μg/dL)	298.0 ± 73.2 (n = 30)	297.6 ± 86.0 (n = 16)	305.8 ± 61.0 (n = 14)	0.768
Fe×100/TIBC (%)	26.3 ± 12.9 (N = 30)	23.3 ± 15.1 (n = 16)	28.4 ± 10.5 (n = 14)	0.298
Ferritin (ng/mL)	141.2 ± 336.2 (N = 31)	162.3 ± 454.8 (n = 16)	109.6 ± 110.3 (n = 15)	0.666
BNP (pg/mL)	321.2 ± 217.0	347.0 ± 234.4	291.3 ± 197.0	0.420

Abbreviations: CRAS, cardiorenal anemia syndrome; CKD, chronic kidney disease; NYHA, New York Heart Association; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; eGFR, estimated glomerular filtration rate; TIBC, total iron binding capacity; BNP, brain natriuretic peptide.

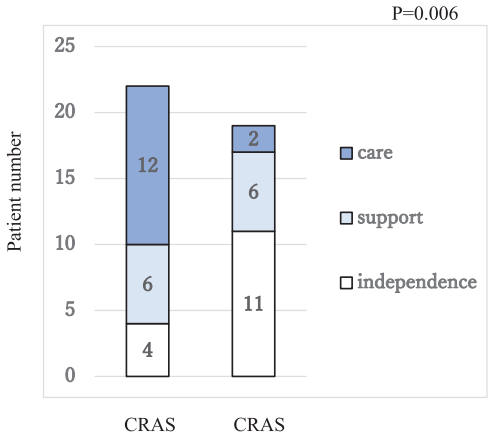

Fig. 1. Comparison of care requirement classification between groups with and without cardiorenal anaemia syndrome.
Abbreviation: CRAS, cardiorenal anaemia syndrome.

to moderate renal impairment, long-term intravenous (IV) iron in combination with recombinant human erythropoietin increased Hb and lowered N-terminal pro-BNP, leading to improved cardiovascular hospitalization and functional capacity [18]. Furthermore, there have been several reports demonstrating the effectiveness of administering IV ferric carboxymaltose, regardless of the presence or absence of anaemia [21], [22]. Trials involving symptomatic HF patients with iron deficiency have shown improvement in NYHA functional class, fatigue score, quality of life, and 6-minute walk test through the use of IV iron [23]–[25]. Additionally, the impact on myocardial mitochondria has also been noted [26]. It is important to note that the target patients in these studies had HFrEF as their type of cardiac dysfunction. Meanwhile, 80.5% of our patients had HFpEF, for which the benefits of IV iron have not been clarified. Therefore, previous studies may not be applicable to our target patients. Additionally, most patients in our study had ferritin levels below 100, and many were iron deficient. As a result, it may not be appropriate to apply the guidelines of the European Society of Cardiology [27], [28] to Japan, as the extent to which iron parameters should be improved needs to be studied in Japan in the future. Therefore, no cases of IV iron preparation were found in our study, which revealed that elderly HF had a high ratio of HFpEF, reaching 80.5%. This suggests that elderly HF and CRAS face challenges related to HFpEF. The prevention and treatment of HFpEF is undoubtedly important. However, the evidence for effective treatments is currently limited. While angiotensin receptor-neprilysin inhibitors (ARNIs) [29] and sodium-glucose cotransporter-2 inhibitors (SGLT2is)

TABLE III: Medical Treatments

Medical treatment	Overall (N = 41)	CRA syndrome (+) (N = 22)	CRA syndrome (−) (N = 19)	P-value
Loop diuretics	25/41 (61.0%)	14/22 (63.6%)	11/19 (57.9%)	0.707
Spironolactone	20/41 (48.8%)	9/22 (40.9%)	11/19 (57.9%)	0.278
Tolvaptan	4/41 (9.8%)	4/22 (18.2%)	0/19 (0%)	0.111
ACEI/ARB	23/41 (56.1%)	11/22 (50.0%)	12/19 (63.2%)	0.392
β blocker	25/41 (61.0%)	12/22 (54.6%)	13/19 (68.4%)	0.363
SGLT2i	19/41 (46.3%)	10/22 (45.5%)	9/19 (47.4%)	0.903
ARNI	5/41 (12.2%)	4/22 (18.2%)	1/19 (5.3%)	0.350
Statin	22/41 (53.7%)	11/22 (50.0%)	11/19 (57.9%)	0.613

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockade; SGLT2i, sodium-glucose cotransporterr-2 inhibitor; ARNI, angiotensin receptor-neprilysin inhibitor.

TABLE IV: Relationship between Cerebrovascular Disease and Care Grade

	Cerebrovascular disease + (N = 6)	Cerebrovascular disease – (N = 35)	P-value
Independence/S1/S2/C1/C2/C3/C4/C5	1/1/2/0/1/0/0/1	14/2/7/3/3/2/3/1	0.571
Independence/Support/Care	1/3/2	14/9/12	0.407

Abbreviations: S, support; C, care.

[30] have been reported to be effective, their use in our study was not yet sufficient. In the future, it is desirable to actively use ARNI in conjunction with other basic drugs for HF. However, the problem of tolerability in the elderly should be carefully considered. ARNI has been reported to be effective in improving anaemia in CRAS [31].

Patients with HF often have comorbidities other than HF, and the type and number of comorbidities cumulatively affect exercise capacity and functional status [32]. Comobidities other than heart failure (HF) is common in elderly patients with HF, which can lead to a decline in functional status. Therefore, coordination between nursing and medical care is essential to manage these comorbidities. This study assessed the decline in frailty as a factor associated with decreased independence, but it did not evaluate mental or cognitive function [33]. By using the level of certified care required as a variable, which is a comprehensive expression of reduced independence, it was possible to stratify elderly patients with HF into those with and without CRAS. A history of cerebrovascular disease (CVD) is an important consideration when determining the level of care required. However, in this study, we included six cases and found no statistically significant difference in the incidence of CVD between groups with or without CRAS. Furthermore, there was no significant difference in the level of care required between patients with or without CVD (Table IV).

The treatment of CRAS should be based on various factors, including the patient's iron status, classification of heart and kidney disease, and predictors of deterioration of clinical status such as eGFR, LVEF, and Hb levels. Although a multidisciplinary approach is necessary when considering treatments with medical therapy, guidelines are limited [34]. Furthermore, a basic baseline assessment of anaemia should be conducted in all patients with HF [35], and regular assessments are recommended for anaemia in CKD. To evaluate possible reasons for anaemia and rule out definite iron deficiency, it is suggested that a complete blood cell count, absolute reticulocyte count, serum ferritin levels, serum transferrin saturation, and serum vitamin B_{12} and folate levels should be measured [36]. In cases of anaemia with CKD caused by erythropoietin stimulating agents (ESA) and serum iron deficiency, the primary treatment is IV iron and (ESA). However, for anaemia with HF, only IV iron is recommended, and ESA is not advised [35]. Managing CRAS in patients with CKD and HF can be challenging for healthcare professionals as some symptoms may persist even when following the recommended guidelines [34].

5. Conclusion

Elderly HFs with CRAS had a high degree of care requirement according to the nursing care certification classification. Independence in HF in the elderly is affected not only by HF and cardiac function, but also by complicated diseases such as anaemia, so attention should be taken during the patient treatment and care.

5.1. Limitations

The study has some limitations that should be taken into consideration. It is important to acknowledge these limitations in order to fully understand the implications of the study's findings. Firstly, due to the small sample size, it may be necessary to include more cases in future studies. Secondly, as a cross-sectional study, long-term follow-up to monitor the impact on prognosis is necessary. Thirdly, the analysis of cardiac function by echocardiography only recorded E/e' by the septal. Fourthly, not all patients were tested for dementia, which prevented it from being included as a predicting factor of CRAS. Fifthly, variables regarding iron deficiency were not tested in all subjects. Finally, it was observed that there was no statistically significant difference in the presence or absence of CVD, which may affect independence and the level of required care. However, further investigation is necessary to increase the number of cases.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

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