Composite Biomarkers for Assessing Frailty Status in Stable Older Adults With Cardiovascular Disease

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Background: The relationship between frailty status and laboratory measurements in cardiovascular disease (CVD) remains unclear. We investigated which laboratory measurements indicated frailty in stable older CVD patients.

Methods and Results: One-hundred thirty-eight stable older CVD patients were evaluated by laboratory measurements, with frailty assessed using the Kihon Checklist (KCL). Laboratory measurements were compared between frail and non-frail groups. Across the entire cohort, mean age was 81.7 years, mean left ventricular ejection fraction was 57.8%, and mean plasma B-type natriuretic peptide was 182 pg/mL. KCL scores were used to divide patients into non-frail (n=43; KCL <8) and frail (n=95; KCL ≥8) groups. Serum iron was significantly lower in the frail than non-frail group (mean [±SD] 61.2±30.3 vs. 89.5±26.1 μg/dL, respectively; P<0.001). Blood urea nitrogen (BUN; 27.3±16.5 vs. 19.7±8.2 mg/dL; P=0.013) and C-reactive protein (CRP; 1.05±1.99 vs. 0.15±0.21 mg/dL; P=0.004) were significantly higher in the frail than non-frail group. Multivariate analysis revealed that serum iron, CRP, and BUN were significant independent predictors of frailty (β=-0.069, 0.917, and 0.086, respectively).

Conclusions: Frailty status was significantly associated with iron, CRP, and BUN in stable older CVD patients. Composite biomarkers (inflammation, iron deficiency, and renal perfusion) may be useful for assessing frailty in these patients.

Key Words: Biomarker; Cardiovascular disease; Frailty; Inflammation; Older adult

Frailty is an important concept in geriatric medicine, and understanding its etiology has become a fundamental aspiration of many researchers in the field of aging. Frailty is an aging-associated syndrome that produces subclinical dysfunction across multiple organ systems, leading to increased risk of mortality. Between 25% and 50% of patients with cardiovascular disease (CVD) are frail. Moreover, according to a systematic review, the prevalence of frailty in heart failure (HF) ranges from 18% to 54%. The development of frailty is linked to various conditions, such as chronic inflammation and changes in the immune and endocrine systems, and includes multiple deranged pathways that require further elucidation. However, the importance of general laboratory measurements in assessing frailty in older adults with CVD remains unclear. Therefore, the aim of this study was to evaluate which laboratory measurements indicate frailty in stable older adults with CVD.

Biomarkers identified through the implementation of multivariate strategies may be used to support the detection of frailty. The progression of these biomarkers can be tracked over time or in response to interventions, and reveals the onset of complications, such as mobility disability, at a very early stage. Therefore, there is an increasing need to identify and validate robust biomarkers for frailty. Inflammation, as indicated, for example, by serum concentrations of C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α, has been implicated in the pathogenesis of both frailty and HF, although the pathophysiology of both disorders is complex and includes multiple deranged pathways that require further elucidation. However, the importance of general laboratory measurements in assessing frailty in older adults with CVD remains unclear. Therefore, the aim of this study was to evaluate which laboratory measurements indicate frailty in stable older adults with CVD.
Methods

Study Population
We conducted a cross-sectional study of patients who were admitted to the Cardiology Department of the National Center of Geriatrics and Gerontology, Japan, between August 2016 and December 2019. The study population consisted of 138 patients with CVD who were at least 65 years old and were able to perform cardiopulmonary exercise testing, undergo laboratory measurements, echocardiography, and a physical function evaluation, and complete questionnaires. These assessments were performed after the patients had been medically stabilized.

The inclusion criteria were structural heart disease consisting of coronary artery disease (having experienced angina pectoris or myocardial infarction, with or without a history of revascularization procedures), symptomatic HF (including conditions such as non-ischemic cardiomyopathy, ischemia, tachycardia, bradycardia, valvular disease, and hypertension), and others (see below). Non-ischemic cardiomyopathies were defined as ventricular myocardial abnormalities in the absence of coronary artery disease or valvular, pericardial, or congenital heart disease. Tachycardia and bradycardia included atrial, supraventricular, and ventricular arrhythmias, sick sinus syndrome, and atrioventricular block in the absence of structural heart disease. Valvular heart disease was diagnosed on the basis of hemodynamic or echocardiographic findings or a history of valvular or congenital cardiac surgery. Hypertension was defined as a systolic blood pressure $\geq 140$ mmHg, diastolic blood pressure $\geq 90$ mmHg, or a history of treatment for hypertension. Included in the “others” category were aortic disease, peripheral artery disease, and other vascular diseases. HF was defined as pulmonary venous congestion or edema on chest X-ray plus any symptoms (e.g., dyspnea, ankle swelling, peripheral edema, or fatigue).

Exclusion criteria were severe respiratory dysfunction (those receiving long-term oxygen therapy for respiratory disease), liver dysfunction (Child-Pugh Class C), stroke, renal dysfunction (albuminuria and glomerular filtration rate category G5), malignant tumors carrying a prognosis of $<1$ year, difficulty walking 10 m even with a walking aid, a Mini-Mental State Examination score $<18$, and living in a nursing care facility before admission.

Only patients who were stable after admission were enrolled in the study (Figure 1). Of the 228 patients with unscheduled hospital admission due to progressing cardiovascular disease to the Cardiology Department of the National Center of Geriatrics and Gerontology, Japan, between August 2016 and December 2019, 138 were included in the present study. CPX, cardiopulmonary exercise.

Figure 1. Study flowchart for the present analysis. Of the 228 patients with an unscheduled admission due to progressing cardiovascular disease to the Cardiology Department of the National Center of Geriatrics and Gerontology, Japan, between August 2016 and December 2019, 138 were included in the present study. CPX, cardiopulmonary exercise.
Composite Biomarkers of Frailty in Geriatric CVD

Rank and Pearson’s correlation coefficients were used to assess the relationships between KCL score and laboratory measurements. Multivariate linear regression analyses were used to identify factors that were independently associated with KCL score; the multivariate model included all baseline variables that had a significant correlation with KCL score in the Pearson’s correlation. All analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Two-sided P<0.05 was considered statistically significant.

Results

Patient Characteristics

Baseline clinical characteristics of the patients are presented in Table 1. In all, 138 consecutive older adult patients with CVD (78 (57%) men; mean age 81.7±6.6 years) were enrolled in the study. At the time of enrollment, all patients were stable and on optimal pharmacological therapy according to current guidelines for the treatment of CVD.17,18 The median plasma B-type natri-
Blood urea nitrogen (BUN) was significantly higher in the frail than non-frail group (27.3±16.5 vs. 19.7±8.2 mg/dL, respectively; P=0.013), as was serum CRP (1.05±1.99 vs. 0.15±0.21 mg/dL, respectively; P=0.004).

Correlations Between Biomarkers and Frailty

The KCL score was significantly associated with hemoglobin, albumin, BUN, iron, CRP, eGFR, and BNP in the Spearman’s rank and Pearson’s correlation analyses (Table 3). We then analyzed these significantly associated parameters for KCL score in multivariate analyses and found that serum iron and CRP concentrations and BUN were significant independent predictors of frailty (β=−0.069, 0.917, and 0.086, respectively; Table 3).

Discussion

The main aim of the present study was to elucidate the relationship between general biomarkers and frailty in older adults with CVD. Here, we report for the first time that serum iron and CRP and BUN concentrations are strongly associated with the presence of frailty in older adults with CVD. Frail patients scored significantly more poorly than non-frail patients on these items related to nutrition, inflammation, and protein catabolism. However, the frail group had people on a gradual scale from mild to severe frailty. In fact, the KCL scoring system runs from 0 to 25 points. Therefore, we thought it may be more important data-wise to correlate the baseline characteristics with the KCL score. Furthermore, we wanted to show which laboratory data contributed to the KCL scores. Among the blood biomarkers, iron, CRP, and BUN were regulatory factors independent of the deterioration of KCL in older adults with CVD.

Iron

Aging-related comorbidities are an emerging problem in patients with CVD. Among them, iron deficiency is an important therapeutic target regardless of the concomitant hemoglobin level. A recent study confirmed the relationship between reduced iron concentration and the occurrence of frailty syndrome. Iron deficiency affects up to 50% of CVD patients, and its association with poor quality of life, impaired exercise tolerance, and increased mortality rates has been widely established. Current European Society of Cardiology Guidelines for CVD recommend a diagnostic workup for iron deficiency in all CVD patients. Iron deficiency has detrimental effects in patients with coronary artery disease, HF, or pulmonary hypertension, and possibly in patients undergoing cardiac surgery. Perturbations of iron metabolism resulting in changes in iron status are observed in a variety of age-related medical conditions, including kidney disease, cancer, CVD, and neurodegenerative diseases.

**BUN**

The kidneys play an important role in the initiation and progression of CVD, and approximately one-third of patients with CVD show some degree of renal dysfunction. BUN is an independent predictor of long-term mortality in older, medically stable veterans. Elevated BUN may reflect poor global health status, rather than solely being an indicator of the severity of acute illness or unstable chronic disease.

Silverberg et al first described the term “cardiorenal
Anemia syndrome. This term has been widely used in recent years, now that we understand the importance of the associations among HF, renal failure, and anemia. High BUN has a negative effect on patient survival and reflects the extent of catabolism. In the acute phase of a critically ill patient, this catabolism may be beneficial, providing amino acids for hepatic gluconeogenesis and for the synthesis of proteins involved in immune functions, but persistent hypercatabolism in critically ill patients results in decreased immune function, which leads to increased mortality. In addition, Kameda et al reported that metabolite profiles efficiently distinguish frailty from nonfrailty. Oxidative stress resulting from diminished antioxidant levels could be a key vulnerability for the pathogenesis of frailty, exacerbating illnesses related to human aging. Therefore, BUN is considered an integral marker of tissue necrosis, protein catabolism, and renal perfusion.

**CRP**

In older adults, there is a significant association between elevated levels of high-sensitivity CRP and the development of HF. In addition, aging has been associated with an increase in inflammatory biomarkers. Increased serum CRP concentrations are positively associated with increased severity of frailty in people aged >75 years, and increasing frailty is also associated with increasing TNF-α and IL-6 levels. Here, we chose to perform only those standard laboratory measurements that are used for health insurance purposes, so we did not check TNF-α and IL-6 levels. However, even in the absence of clinical signs, CRP may be useful in detecting frailty in older adult patients with CVD.

**BNP**

In patients with chronic HF, the BNP concentration provides powerful prognostic information regarding survival and deterioration of functional status. In the Valsartan Heart Failure Trial, patients with the greatest rise in BNP concentrations despite therapy had the highest rates of morbidity and mortality. Notably, in the present study we found that serum iron and CRP concentrations and BUN were superior to BNP concentrations for the diagnosis of frailty in older adults with stable CVD. Ninety-one per cent of our 138 patients were admitted because of

| Table 2. Comparisons of Non-Frail and Frail Groups |
|-----------------|-----------------|-----------------|-----------------|
|                | Non-frail group (KCL <8; n=43) | Frail group (KCL ≥8; n=95) | P value |
| Age (years)    | 79.1±7.6        | 83.1±6.1        | 0.019    |
| Sex (male/female) | 25/18          | 53/42           | 0.724    |
| BMI (kg/m²)    | 24.1±3.6        | 21.0±3.3        | 0.001    |
| Diuretics      | 17 (39)         | 61 (64)         | 0.056    |
| Tolvaptan      | 9 (22)          | 22 (23)         | 0.878    |
| ACE-I/ARBs      | 22 (52)         | 41 (43)         | 0.539    |
| β-blockers      | 9 (22)          | 30 (32)         | 0.877    |
| Spironolactone  | 9 (22)          | 22 (23)         | 0.878    |
| Anticoagulants  | 17 (39)         | 36 (38)         | 0.948    |

Clinical data

|                | Non-frail group (KCL <8; n=43) | Frail group (KCL ≥8; n=95) | P value |
|----------------|-----------------|-----------------|-----------------|
| LVEF (%)       | 62.1±9.4        | 55.7±15.9       | 0.082    |
| E/e'           | 15.1±7.2        | 16.1±6.7        | 0.534    |
| LAD (mm)       | 40.7±8.3        | 39.1±6.0        | 0.402    |
| WBC (mm³)      | 57.3±16.3       | 59±22.4         | 0.741    |
| Hb (g/dL)      | 13.3±1.9        | 11.5±1.9        | 0.001    |
| Pt (g/dL)      | 20.4±5.1        | 20.1±7.3        | 0.87     |
| TP (g/dL)      | 7.2±0.5         | 6.7±0.6         | 0.547    |
| Albumin (g/dL) | 4.0±0.3         | 3.6±0.6         | <0.001   |
| AST (IU/L)     | 22±4.3          | 23.5±18.2       | 0.705    |
| ALT (IU/L)     | 21.7±11.2       | 20.7±40.3       | 0.906    |
| LDH (IU/L)     | 205.1±35        | 204.5±58.5      | 0.963    |
| BUN (mg/dL)    | 19.7±8.2        | 27.3±16.5       | 0.013    |
| Cr (mg/dL)     | 0.9±0.2         | 1.3±0.7         | 0.004    |
| TC (mg/dL)     | 186±32          | 173±37          | 0.164    |
| TG (mg/dL)     | 127.2±58.9      | 119.3±67.8      | 0.637    |
| Fe (μg/dL)     | 89.5±26.1       | 61.2±30.3       | <0.001   |
| CRP (mg/dL)    | 0.15±0.21       | 1.05±1.99       | 0.004    |
| HbA1c (%)      | 6.1±0.4         | 6.2±0.8         | 0.602    |
| BNP (pg/mL)    | 123.4±143.6     | 221.9±194.6     | 0.038    |
| eGFR (mL/min/1.73m²) | 56.4±14.1  | 47.7±23         | 0.101    |

Unless indicated otherwise, data are given as the mean±SD or n (%). ALT, aspartate aminotransferase; AST, alanine aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; E/e', ratio of early transmitral flow velocity to early diastolic mitral annular velocity; Fe, iron; LAD, left atrial dimension; LDH, lactate dehydrogenase; Plt, platelets; TG, triglycerides; WBC, white blood cell count. Other abbreviations as in Table 1.
worsening HF. Even in patients in a stable condition after medical treatment, BNP is supposed to indicate disease severity or prognosis in HF. However, although BNP was significantly correlated with KCL, it was not a significant independent predictor of frailty according to the KCL in older adult patients with CVD. In assessing frailty, we need to pay attention to the evaluation of laboratory items other than powerful conventional prognostic markers, such as BNP, in the elderly CVD population.

Frailty and CVD

Frailty is a multidimensional syndrome based on an aggregate susceptibility to adverse health outcomes due to age- and disease-related deficits that accumulate across multiple domains. It is also associated with mortality. Several tools have been developed for assessing frailty, but there is no international standard measurement. The KCL, a self-administered questionnaire, is considered useful for frailty screening in older adult populations. KCL scores are significantly correlated with Fried’s frailty phenotype values.

The mean age of the patients in this study was 81.7 years, and many were frail (68.5% had KCL scores ≥8). The mean BNP concentration once the patients had been stabilized after appropriate medical therapy during admission was 182pg/mL. In addition, the frail CVD patients were significantly older and had a significantly lower body mass index than those who were not frail, in accordance with the general concept of frailty. However, echocardiogram parameters, such as LVEF and left arterial dimension, did not differ between the 2 groups. In the case of LVEF, this finding is not surprising given that approximately half of all patients with HF have preserved ejection fraction. This population likely well represents those patients currently admitted to Japanese hospitals with worsening CVD: the numbers of older adults with CVD are likely increasing because of the recent decline in the birthrate and aging of the population. Therefore, our study focused on evaluating the clinical usefulness of common biomarkers for detecting frailty as determined by the KCL in the increasing Japanese population of stable older adult patients with CVD.

One of the reasons why composite biomarkers are useful for assessing frailty is multimorbidity, which is common in older adults. The strong association of multimorbidity with age is well recognized, but, because of the variations mentioned above, further research is needed to develop accurate composite markers that take these multimorbidities into account.

Clinical Implications

Laboratory measurements are commonly evaluated in daily practice because they are inexpensive, repeatable, and non-invasive tests. In the present study, we did not include specialized items relevant to frailty, such as IL-6 and TNF-α, in the laboratory measurements because we wanted to test only those biomarkers used in general assessments. To the best of our knowledge, the present study is the first to have investigated the ability of these standard laboratory measurements to detect frailty in older adults with stable CVD. The primary goals of CVD therapy are to improve quality of life and extend survival. The recognition of frailty within the medical community has created the need for diagnostic tests to determine when a patient’s physical ability has deteriorated.

Study Limitations

The present study was a single-center study with a small sample size. Moreover, we did not assess repeated measures over time or follow the incidence of cardiac events in the enrolled patients. We did not check ferritin levels, which are associated with iron levels. Nor did we check IL-6 and TNF-α levels, which are also related to frailty. We also did not assess changes in the trajectory of exercise capacity or frailty due to medical intervention or cardiac rehabilitation.

Table 3. Correlation and Multivariate Linear Regression Analyses for KCL Scores

| Laboratory measurement | Spearman | Pearson | Multivariate |
|------------------------|----------|---------|-------------|
|                        | ρ        | r       | β (95% CI)  |
| WBC                    | -0.020   | -0.079  | 0.514       |
| Hb                     | -0.337   | -0.317  | 0.008       |
| Fli                    | -0.163   | -0.053  | 0.661       |
| Albumin                | -0.435   | -0.461  | <0.001      |
| AST                    | -0.151   | -0.089  | 0.464       |
| ALT                    | -0.162   | -0.036  | 0.766       |
| LDH                    | -0.077   | -0.055  | 0.649       |
| BUN                    | 0.256    | 0.351   | 0.003       |
| Cr                     | 0.211    | 0.245   | 0.041       |
| TC                     | -0.176   | -0.144  | 0.236       |
| LDL-C                  | -0.214   | -0.191  | 0.121       |
| TG                     | -0.237   | -0.190  | 0.045       |
| Fe                     | -0.435   | -0.441  | <0.001      |
| CRP                    | 0.428    | 0.431   | 0.001       |
| eGFR                   | -0.321   | -0.280  | 0.041       |
| HbA1c                  | 0.007    | 0.114   | 0.350       |
| BNP                    | 0.334    | 0.291   | 0.015       |

ρ, Spearman’s rank correlation coefficient; r, Pearson’s correlation coefficient; β, multiple regression coefficient; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol. Other abbreviations as in Tables 1, 2.
Conclusions
Frailty status was significantly associated with serum iron and CRP concentrations and BUN in stable older adults with CVD. Composite biomarkers for inflammation, iron deficiency, and renal perfusion may be useful for assessing frailty in stable older adults with CVD.

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T.M. is a member of Circulation Reports’ Editorial Team. The remaining authors have no conflicts of interest to disclose.

Author Contributions
A.H., A.S., I.K., T.M., and H.A. supervised the research and prepared the text. K.H. and K.S. evaluated frailty. A.H., K.N., M.K., N.S., and A.S. evaluated patients. All authors reviewed the text and agree with the paper’s publication.

IRB Information
This study was approved by the Ethics and Conflict of Interest Committee of the National Center for Geriatric and Gerontology (Reference no. 1272).

References
1. Ferrucci L, Mahallati A, Simonick EM. Frailty and the foolishness of Eos. J Gerontol A Biol Sci Med Sci 2006; 61: 260–261.
2. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Grotti J, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56 M146–M156.
3. Aihara J. Frailty in patients with cardiovascular disease: Why, when, and how to measure. Circ Cardiovasc Risk Rep 2011; 5: 467–472.
4. Jha SR, Ha HS, Hickman LD, Hannu M, Davidson PM, Macdonald PS, et al. Frailty in advanced heart failure: A systematic review. Heart Fail Rev 2015; 20: 553–560.
5. Denfeld QE, Winters-Stone K, Mudd JO, Gelow JM, Burdi S, Lee CS. The prevalence of frailty in heart failure: A systematic review and meta-analysis. Int J Cardiol 2017; 236: 283–289.
6. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013; 381: 752–762.
7. Walston J, Hadley EC, Ferrucci L, Guralnik JM, Newman AB, Studenski SA, et al. Research agenda for frailty in older adults: Toward a better understanding of physiology and etiology: Summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. J Am Geriatr Soc 2006; 54: 991–1001.
8. Kulmala J, Nykanen I, Hartikainen S. Frailty as a predictor of all-cause mortality in older men and women. Geriatr Gerontol Int 2014; 14: 899–905.
9. Uchikado Y, Ikeda Y, Ohishi M. Current understanding of the role of frailty in cardiovascular disease. Circ J 2020; 84: 1903–1908.
10. Ailt SR, Lo P, Villanueva JE, Joshi Y, Emmanuel S, Macdonald PS. Prevention and reversal of frailty in heart failure: A systematic review. Circ J 2021; 86: 14–22.
11. Satake S, Shimada H, Yamada M, Kim H, Yoshida H, Gondo Y, et al. Prevalence of frailty among community-dwellers and outpatients in Japan as defined by the Japanese version of the Cardiovascular Health Study criteria. Geriatr Gerontol Int 2017; 17: 2629–2634.
12. Saedi AA, Feehan J, Phu S, Duque G. Current and emerging biomarkers of frailty in the elderly. Clin Interv Aging 2019; 14: 389–398.
13. de Boer RA, Naylor M, deFilippi CR, Enserro D, Bhambhani V, Kizer JR, et al. Association of cardiovascular biomarkers with incident heart failure with preserved and reduced ejection fraction. JAMA Cardiol 2018; 3: 215–224.
14. Satake S, Senda K, Hong XJ, Miura H, Endo H, Sakurai T, et al. Validity of the Kihon Checklist for assessing frailty status. Geriatri Gerontol Int 2016; 16: 709–715.
15. Sewo Sampaio PY, Sampaio RA, Yamada M, Arai H. Systematic review of the Kihon Checklist: Is it a reliable assessment of frailty? Geriatri Gerontol Int 2016; 16: 893–902.
16. Arai H, Satake S. English translation of the Kihon Checklist. Geriatri Gerontol Int 2015; 15: 518–519.
17. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, et al. Clinical practice update on heart failure 2019: Pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019; 21: 1169–1186.
18. Arnett DK, Blumenthal RS, Albert MA, Burzoner AB, Goldberg ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019; 74: 1376–1414.
19. Waeber AA, Jennings A, Fairweather-Tait SJ. Iron status in the elderly: A review of recent evidence. Mech Ageing Dev 2018; 175: 55–73.
20. Zawadzki B, Mazur G, Butrym A. Iron dysregulation and frailty syndrome. J Clin Med 2021; 10: 5596.
21. Fitzsimons S, Dougherty RN. Iron deficiency in patients with heart failure. Eur J Heart Cardiovasc Pharmacother 2015; 1: 58–64.
22. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC): Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129–2200.
23. von Haeling S, Jankowska EA, van Veldhuisen DJ, Ponikowski P, Anker SD. Iron deficiency and cardiovascular disease. Nat Rev Cardiol 2015; 12: 659–669.
24. Major RW, Cheng MRI, Grant RA, Shantikumar S, Xu G, Oozercarly I, et al. Cardiovascular disease risk factors in chronic kidney disease: A systematic review and meta-analysis. PLoS One 2018; 13: e0192935.
25. Sullivan DH, Sullivan SC, Bopp MM, Roberson PK, Lensing SY. BUN as an independent predictor of post-hospital-discharge mortality among older veterans. J Nutr Health Aging 2018; 22: 759–765.
26. Silveberg D, Wexler D, Blum M, Wollman Y, Iaina A. The cardio-renal anemia syndrome: Does it exist? Nephrol Dial Transplant 2003; 18(Suppl 8): vii7–viii12.
27. Beier K, Eppannapally S, Bazick HS, Chang D, Mahadevappa K, Gibbons FK, et al. Elevation of blood urea nitrogen is predictive of long-term mortality in critically ill patients independent of “normal” creatinine. J Am Soc Nephrol 2007; 18: 398–406.
28. Kameda M, Teruya T, Yanagida M, Kondoh H. Frailty markers comprise blood metabolites involved in antioxidation, cognition, and mobility. Proc Natl Acad Sci USA 2020; 117: 9483–9489.
29. Araujo JP, Lourenco P, Azvedo A, Frioes F, Rocha-Goncalves F, Ferreira A, et al. Prognostic value of high-sensitivity C-reactive protein in heart failure: A systematic review. J Card Fail 2009; 15: 256–266.
30. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzmiller DW, et al. Predictors of congestive heart failure in the elderly: The Cardiovascular Health Study. J Am Coll Cardiol 2000; 35: 1628–1637.
31. Vatic M, von Haehling S, Ebner N. Inflammatory biomarkers of frailty. Exp Gerontol 2020; 133: 110858.
32. Hubbard RE, O’Malony MS, Savva GM, Calver BL, Woodhouse KW. Inflammation and frailty measures in older people. J Cell Mol Med 2009; 13: 3103–3109.
33. Maisel A, Hollander JE, Guss D, McCullough P, Nowak R, Green G, et al. Primary results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT). A multicenter study of Betapine natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. J Am Coll Cardiol 2004; 44: 1328–1333.
34. Anand IS, Fisher LD, Chiang YT, Latini R, Masson S, Maggioni AP, et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). Circulation 2003; 107: 1278–1283.
35. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004; 59: 255–263.

36. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005; 173: 489–495.

37. Lupón J, Gonzalez B, Santaeugenia S, Altimir S, Urrutia A, Mas D, et al. Prognostic implication of frailty and depressive symptoms in an outpatient population with heart failure. *Rev Esp Cardiol* 2008; 61: 835–842.

38. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004; 43: 317–327.