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Systemic inflammation-based Glasgow Prognostic Score as a prognostic indicator in chronic heart failure

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ABSTRACT

Background: The Glasgow Prognostic Score (GPS), based on C-reactive protein and serum albumin concentrations provides useful prognostic information for patients with cancer or acute decompensated heart failure (HF). Herein, we aimed to evaluate the relationship between the GPS and long-term prognosis in patients with chronic HF.

Methods: In this large multicentre prospective observational study, part of the Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study, we analysed the relationship between mortality and the GPS in 6,480 patients with chronic HF (mean age, 68 ± 13 years; 69 % male). Patients with elevated C-reactive protein levels (>1.0 mg/dL) and hypoalbuminaemia (<3.5 g/dL) received a GPS of 2; those with either received a GPS of 1, and those with neither received a GPS of 0.

Results: During median follow-up of 9.62 years, 2,564 patients (39.6 %) died. Increased GPS was associated with a significantly higher mortality risk in Kaplan–Meier analysis (log-rank $P < 0.0001$). This trend was consistent across sex, age, New York Heart Association class, HF stage and type, and cancer history. Adjusted Cox proportional hazards analysis showed the following hazard ratios for all-cause death, relative to a GPS of 0, 1.27 (95 % confidence interval, 1.13–1.44; $P < 0.0001$) for a GPS of 1 and 1.83 (95 % confidence interval, 1.45–2.32; $P < 0.0001$) for a GPS of 2. This increased risk was independent of B-type natriuretic peptide levels.

Conclusions: The GPS, which reflects systemic inflammation status, is a useful predictor of long-term prognosis in patients with chronic HF.

1. Introduction

Heart failure (HF) affects more than 23 million people worldwide and is a major and growing public health issue in most developed countries [1]. Although advances in the treatment of chronic HF have been made, mortality rates remain high [2], increasing the importance of prognostic assessment. N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels are widely used to predict prognosis in patients with chronic HF [3,4]. Albumin [5,6] and C-reactive protein (CRP) [7] levels have also been reported to predict prognosis of patients with HF, even though these markers are not directly related to heart disease.

The Glasgow Prognostic Score (GPS) consisting of CRP and serum albumin concentrations is a valuable prognostic tool in patients with cancer [8]. This score is simple to calculate, routinely available, and predicts cancer prognosis independently of tumour stage and conventional scoring systems [9]. We previously applied the GPS to cardiovascular diseases, demonstrating that it is a useful tool for predicting the prognosis of hospitalized patients with acute decompensated HF [10]. Similar results have been reported in patients with chronic HF [11–13], although these studies involved relatively small patient cohorts.

Therefore, in the present study, we examined the relationship between the GPS and prognosis in patients with chronic HF in our Chronic

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Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study, one of the largest multicentre prospective observational studies on patients with chronic HF [14].

2. Methods

2.1. Study Setting and population

The CHART-2 Study is a hospital-based prospective observational study with 24 hospitals across the six prefectures in Japan [14]. Between October 2006 and March 2010, 10,209 consecutive patients with HF were registered, of whom 5,333 were in stage B and 4,876 were in stage C/D. Patients who were asymptomatic but had structural heart disease and/or impaired left ventricular function were categorized as being in stage B. Stage C was defined as current or past symptoms of HF associated with underlying structural heart disease, and stage D was defined as refractory HF in which specialized and advanced treatment strategies were indicated. HF was diagnosed according to the criteria of the Framingham Heart Study [15]. Comprehensive patient data, including medical history, laboratory results, and echocardiographic findings, were recorded in a computerized database at enrolment. The clinical research coordinators conducted annual follow-ups through medical record reviews, surveys, and telephone interviews [14]. The investigation conforms with the principles outlined in the Declaration of Helsinki, and the protocol was approved by the institutional review board of each participating institution. All participants provided written informed consent.

2.2. Study protocol

To investigate the relationship between the GPS and patient prognosis, we excluded 3,729 patients with missing data in CRP and/or serum albumin concentrations, resulting in a final study population of 6,480 patients. Various patient characteristics, including age, sex, body mass index (BMI), patient status, comorbidities, and laboratory data were analysed. Patients with elevated CRP levels (>1.0 mg/dL) and hypoalbuminaemia (<3.5 g/dL) received a GPS of 2, those with either elevated CRP levels or hypoalbuminaemia received a GPS of 1, and those with CRP levels of $\leq$ 1.0 mg/dL and albumin levels of $\geq$ 3.5 g/dL received a GPS of 0 (Table 1). Patients were classified into three groups based on the three possible scores (0, 1, and 2). The study outcome was all-cause mortality. Patients with left ventricular ejection fraction (LVEF) $\leq$ 40 %, 41–49 %, and $\geq$ 50 % were classified as having HF with reduced LVEF (HFrEF), HF with mildly reduced LVEF (HFmrEF), and HF with preserved LVEF (HFpEF), respectively. The Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) provides a very useful mortality score for patients with chronic HF derived from a large international database [16]. The MAGGIC score also predicts one-year mortality with good accuracy in patients with HF in Japanese population [17]. To investigate the incremental value of the GPS, a combined score was calculated by weighting the MAGGIC score and GPS using the regression coefficient and compared with the MAGGIC score alone in terms of 1-, 2-, and 3-year mortality. Duration of HF was not assessed in this study and was substituted by a history of hospitalization for HF.

Table 1
Glasgow Prognostic Score.

C-reactive protein/albumin levels	Glasgow Prognostic Score
C-reactive protein $\leq$ 1.0 mg/dL and serum albumin $\geq$ 3.5 g/dL	0
C-reactive protein > 1.0 mg/dL	1
Serum albumin < 3.5 g/dL	1
C-reactive protein > 1.0 mg/dL and serum albumin < 3.5 g/dL	2

2.3. Statistical methods

Continuous data are presented as means ± standard deviations (SDs) or as medians and interquartile ranges and were compared using the Student's t-tests. Categorical data are presented as percentages and were compared using the chi-squared tests. Kaplan–Meier estimates were compared using log-rank tests to evaluate the relationship between the GPS and risk of all-cause death. Univariate Cox proportional hazards analysis was used to examine the relative risk of all-cause mortality in the groups with a GPS of 1 or 2 compared with the group with a GPS of 0, stratified by sex, age, New York Heart Association (NYHA) class, stage of HF, type of HF, and history of cancer. Age stratification was achieved by dividing patients into four age quartiles. Additionally, we constructed three Cox proportional hazards regression models: an unadjusted model, an age- and sex-adjusted model, and a fully adjusted model. The fully adjusted model included the GPS and 13 variables considered to influence mortality: age, sex, BMI, NYHA class, stage of HF, presence of diabetes mellitus, presence of hypertension, history of cancer, haemoglobin level (g/dL), estimated glomerular filtration rate (eGFR) (mL/min/1.73 m2), grade of proteinuria, B-type natriuretic peptide level (BNP) level (pg/mL), and LVEF (%). To assess the potential impact of missing GPS values, patients with missing CRP or serum albumin data were classified as a separate GPS-missing group; Kaplan–Meier and Cox proportional hazards analyses were performed on this group.

Receiver operating characteristic (ROC) curve analysis of the MAGGIC score and the combined score consisting of the MAGGIC score and GPS was performed to compare the prognostic accuracy of both scores with respect to mortality. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were applied to examine the added value of the GPS over the MAGGIC score. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using JMP software version 17.2.0 (SAS Institute, Cary, NC, USA) and R software (https://www.r-project.org/). Data were a minimum of 90 % complete for all variables examined. The most common missing covariates were BNP level (n = 617, 9.5 % missing) and LVEF (n = 281, 4.3 % missing). In the multivariable models, missing data was handled with complete case analysis, and multiple imputation method was not performed.

3. Results

3.1. Patient characteristics

In this study, we retrospectively analysed 6,480 patients with a mean age of 68 ± 13 years, of whom 69 % were male. In terms of the GPS, 84.6 % (n = 5,479), 12.9 % (n = 838), and 2.5 % (n = 163) of patients had scores of 0, 1, and 2, respectively. Table 2 presents the baseline patient characteristics according to the GPS. As compared with patients with a GPS of 0, those with a GPS of 1 or 2 were older, had more severe disease according to NYHA class and HF stage, and were more likely to have diabetes mellitus and a history of cancer. Additionally, BMI decreased as the GPS increased. Table 3 shows patient status, echocardiographic data, laboratory findings, and medication use according to the GPS. As the GPS increased, blood pressure and haemoglobin levels decreased, whereas blood urea nitrogen, creatinine, and BNP levels increased.

3.2. Mortality and Kaplan–Meier analysis

During the follow-up period (mean ± SD, 8.28 ± 3.92 years; median [interquartile range], 9.62 [4.93–11.6] years), 2,564 patients (39.6 %) died. The annual mortality rate was 39.5 per 1,000 individuals overall and 35.4, 61.4, and 69.5 in the GPS 0, 1, and 2 groups, respectively. Kaplan–Meier analysis (Fig. 1) showed that the risk of death significantly increased with increasing GPS (log-rank $P < 0.0001$). Patients with a history of cancer had a higher mortality rate than those without

Table 2
Patient characteristics.

	GPS 0 (n = 5,479)	GPS 1 (n = 838)	GPS 2 (n = 163)	P
Age (years)	67 ± 12	71 ± 13	72 ± 14	<0.0001
Male	3,787 (69.1 %)	562 (67.1 %)	108 (66.3 %)	0.38
Body mass index (kg/m^2)	23.9 ± 4.3	22.6 ± 4.8	21.5 ± 5.6	<0.0001
NYHA class				<0.0001
I	2,848/5,460 (52.2 %)	319/832 (38.3 %)	62/162 (38.3 %)	
II	2,279/5,460 (41.7 %)	398/832 (47.8 %)	74/162 (45.7 %)	
III	311/5,460 (5.7 %)	103/832 (12.4 %)	22/162 (13.6 %)	
IV	22/5,460 (0.4 %)	12/832 (1.4 %)	4/162 (2.5 %)	
Stage of heart failure				<0.0001
B	2,900 (52.9 %)	337 (40.2 %)	68 (41.7 %)	
C	2,522 (46.0 %)	478 (57.0 %)	88 (54.0 %)	
D	57 (1.0 %)	23 (2.7 %)	7 (4.3 %)	
Diabetes mellitus	1,899 (34.7 %)	324 (38.7 %)	64 (39.3 %)	0.044
Dyslipidaemia	4,631 (84.5 %)	688 (82.1 %)	133 (81.6 %)	0.14
Hypertension	4,959 (90.5 %)	763 (91.1 %)	141 (86.5 %)	0.19
Ischemic heart disease	2,938 (53.6 %)	454 (54.2 %)	97 (59.5 %)	0.32
Chronic atrial fibrillation	1,024 (18.7 %)	170 (20.3 %)	36 (22.1 %)	0.32
History of cancer	776 (14.2 %)	160 (19.1 %)	36 (22.1 %)	<0.0001

Data are expressed as mean ± standard deviation or number (percentage). GPS, Glasgow Prognostic Score; NYHA, New York Heart Association

Table 3
Patient status, laboratory findings, and medications.

	GPS 0 (n = 5,479)	GPS 1 (n = 838)	GPS 2 (n = 163)	P
Systolic blood pressure (mmHg)	129 ± 19	127 ± 21	123 ± 20	<0.0001
Diastolic blood pressure (mmHg)	74 ± 12	72 ± 13	69 ± 12	<0.0001
Heart rate (bpm)	71 ± 14	73 ± 15	75 ± 16	<0.0001
LVEF (%)	61 ± 14	59 ± 15	57 ± 16	<0.0001
LVDd (mm)	50 ± 8	51 ± 9	50 ± 10	0.49
LVDs (mm)	34 ± 10	35 ± 10	35 ± 12	0.020
Type of heart failure				<0.0001
HFrEF	530/5,255 (10.1 %)	107/790 (13.5 %)	28/154 (18.2 %)	
HFmrEF	515/5,255 (9.8 %)	110/790 (13.9 %)	16/154 (10.4 %)	
HFpEF	4,210/5,255 (80.1 %)	573/790 (72.5 %)	110/154 (71.4 %)	
Haemoglobin (g/dL)	13.5 ± 1.8	12.1 ± 2.1	11.4 ± 1.9	<0.0001
Blood urea nitrogen (mg/dL)	17.7 ± 7.9	21.6 ± 13.3	21.6 ± 18.4	<0.0001
Creatinine (mg/dL)	0.8 [0.7, 1.0]	0.9 [0.7, 1.2]	0.9 [0.7, 1.2]	<0.0001
eGFR (mL/min/1.73 m^2)	65.1 ± 20.0	57.0 ± 24.5	61.8 ± 30.2	<0.0001
Albumin (g/dL)	4.2 ± 0.3	3.5 ± 0.5	3.0 ± 0.4	<0.0001
C-reactive protein (mg/dL)	0.1 [0.1, 0.2]	0.65 [0.2, 1.6]	1.9 [1.5, 3.2]	<0.0001
BNP (pg/mL)	62.7 [25.5, 155.6]	139.1 [50.5, 349.1]	177.0 [77.6, 308.0]	<0.0001
Medication				
ACEI/ARB	69.2 %	69.3 %	68.1 %	0.95
Beta-blockers	40.8 %	43.2 %	40.5 %	0.40
MRA	14.7 %	18.7 %	12.3 %	0.0055
Loop diuretics	27.6 %	42.8 %	36.8 %	<0.0001
Statin	43.2 %	34.4 %	35.0 %	<0.0001
Antiplatelets	60.6 %	60.4 %	60.1 %	0.98
Oral anticoagulants	28.3 %	28.5 %	28.8 %	0.98

Data are expressed as mean ± standard deviation, median [interquartile range], or number (percentage). GPS, Glasgow Prognostic Score; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; HFrEF, heart failure with reduced left ventricular ejection fraction; HFmrEF, heart failure with mildly reduced left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonist.

cancer. However, regardless of cancer history, the risk of death increased as the GPS increased (Supplementary Fig. 1). Kaplan–Meier analysis showed that the survival curve of the GPS-missing group closely overlapped with that of the group with a GPS of 0 (Supplementary Fig. 2.

Figs. 2 and 3 show the results of univariate Cox proportional hazards analyses for all-cause mortality, comparing the groups with a GPS of 1 or 2 with the group with a GPS of 0. The risk of mortality was higher in the group with a GPS of 1 than in the group with a GPS of 0 and was still higher in the group with a GPS of 2, irrespective of sex or age. Among patients with NYHA class I–III HF, the mortality risk was higher in the groups with a GPS of 1 or 2 than in the group with a GPS of 0. In patients with NYHA class IV, the mortality risk tended to be higher in the group with a GPS of 1 and was higher in the group with a GPS of 2 than in the group with a GPS of 0. Similar trends were observed for HF stage, HF type, and cancer history, although the mortality risk in the group with a GPS of 2 and HFmrEF did not reach statistical significance.

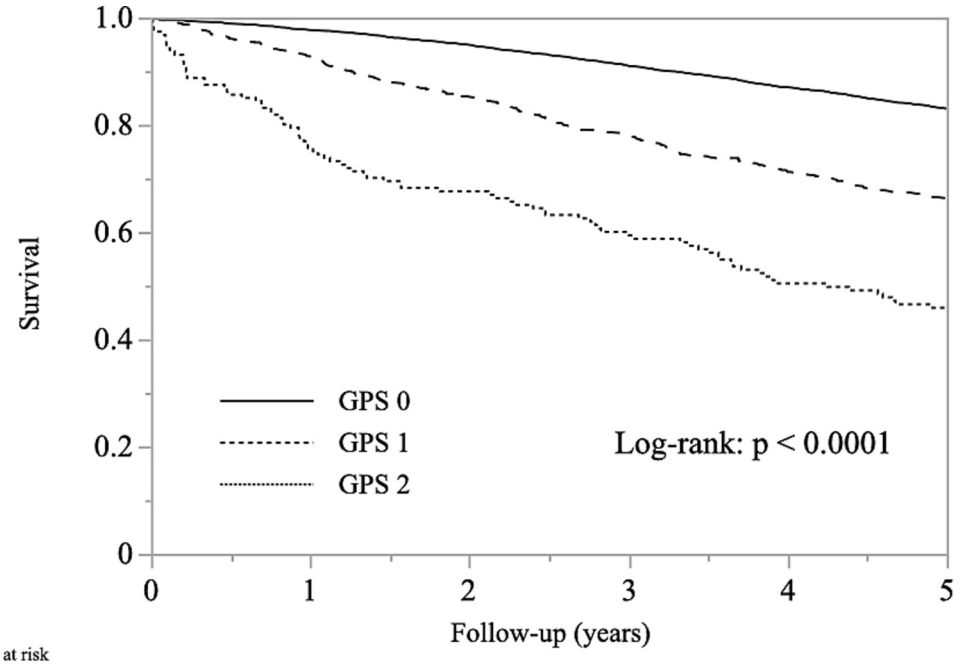
3.3. Cox proportional hazards models

Table 4 summarizes the results of the Cox proportional hazards models for all-cause mortality. In the unadjusted model, hazard ratios for all-cause death were 2.15 (95 % confidence interval [CI] 1.95–2.37; P < 0.0001) for a GPS of 1 and 3.21 (95 % CI 2.65–3.89; P < 0.0001) for a GPS of 2, compared with a GPS of 0. In the age- and sex-adjusted model, hazard ratios were 1.90 (95 % CI 1.71–2.10; P < 0.0001) for a GPS of 1 and 2.94 (95 % CI 2.42–3.56; P < 0.0001) for a GPS of 2, compared with a GPS of 0. In the fully adjusted model, the hazard ratios for all-cause death were 1.27 (95 % CI 1.13–1.44; P < 0.0001) for a GPS of 1 and 1.83 (95 % CI 1.45–2.32; P < 0.0001) for a GPS of 2, compared with a GPS of 0, indicating significantly greater mortality risks.

In the unadjusted model, no significant difference in mortality risk was found between the GPS-missing group and the group with a GPS of 0 (Supplementary Table 1). However, in the age- and sex- adjusted model, the GPS-missing group had a significantly lower hazard ratio than that of the group with a GPS of 0. In the fully adjusted model, this difference was no longer significant. These results suggest that factors beyond age and sex, such as HF severity and comorbidities, contributed to the differences observed in the age- and sex- adjusted model.

3.4. Discrimination and reclassification of the incremental value of the GPS

The areas under the ROC curves (AUCs) for the MAGGIC and composite scores were 0.776 and 0.804 for 1-year mortality, 0.782 and 0.799 for 2-year mortality, and 0.775 and 0.785 for 3-year mortality, respectively, with the AUC for composite score being significantly larger at all time points (P = 0.00054, 0.0012, and 0.015, respectively) (Supplementary Fig. 3). The NRIs for the MAGGIC score versus combined score were 0.609 (P < 0.0001), 0.254 (P < 0.0001), and 0.038 (P = 0.32) and the IDIs were 0.033 (P < 0.0001), 0.027 (P < 0.0001), and 0.017 (P = 0.0002) for 1-, 2-, and 3-year mortality, respectively. The AUC, NRI, and IDI results suggested that the GPS significantly improved the prognostic prediction ability of the MAGGIC score for 1- and 2-year



Number at risk

GPS 0	5479	5315	5103	4822	4535	4268
GPS 1	838	770	694	621	550	500
GPS 2	163	124	109	95	80	72

Fig. 1. Kaplan–Meier curves for all-cause death in patients with a GPS of 0, 1, and 2. GPS, Glasgow Prognostic Score.

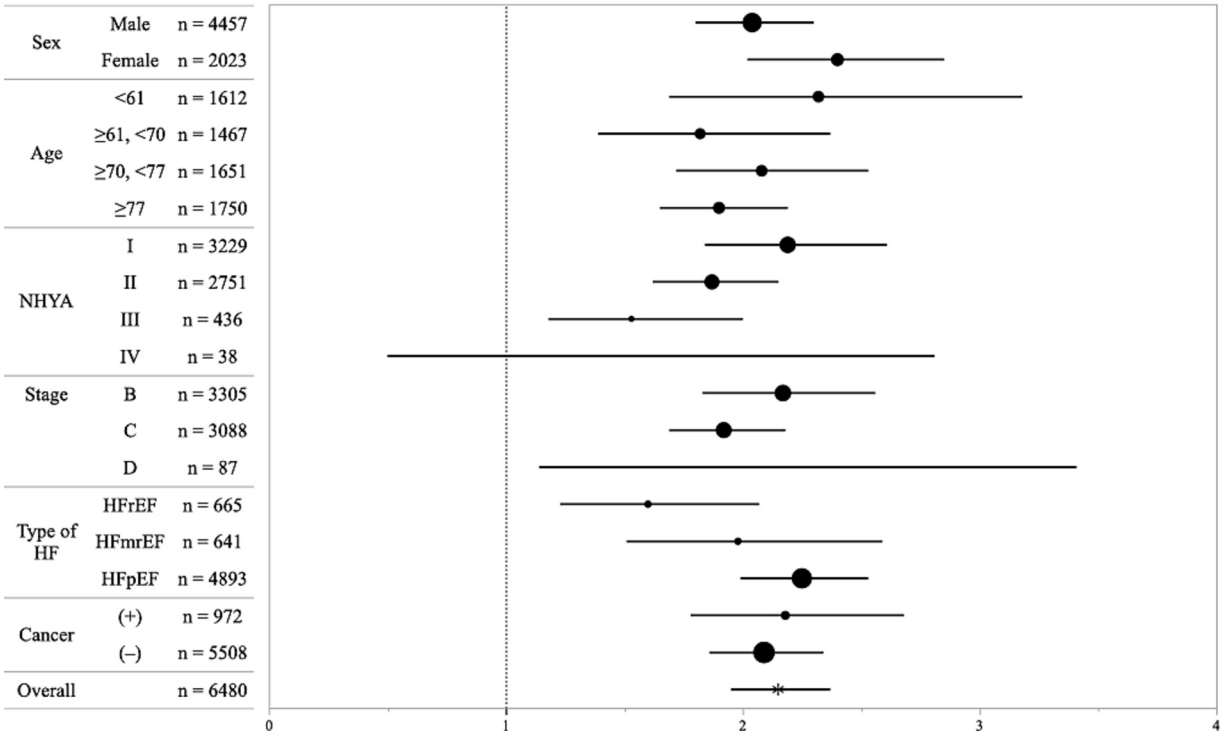


Fig. 2. Forest plot showing the risks for all-cause death of patients with a GPS of 1 relative to those with a GPS of 0. GPS, Glasgow Prognostic Score; NYHA, New York Heart Association; HF, heart failure; HFrEF, heart failure with reduced left ventricular ejection fraction; HFmrEF, heart failure with mildly reduced left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction.

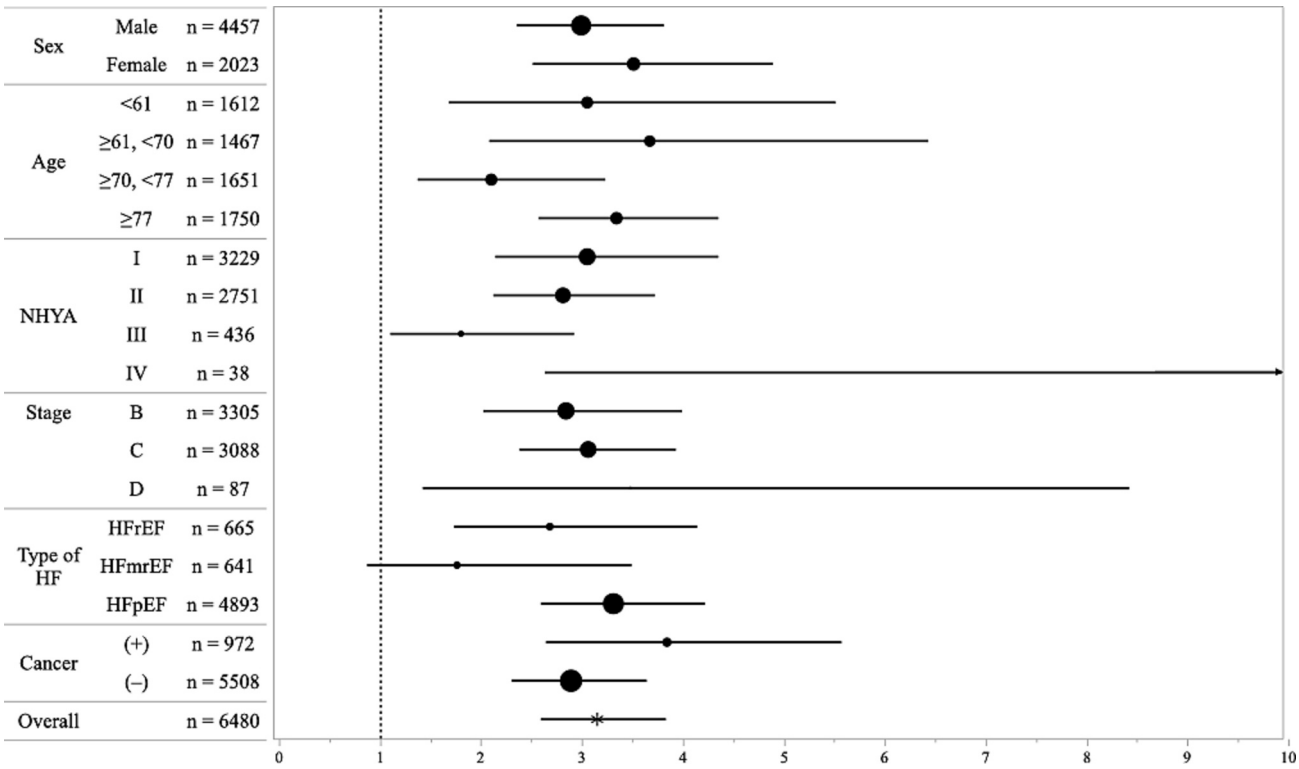


Fig. 3. Forest plot showing the risks for all-cause death of patients with a GPS of 2 relative to those with a GPS of 0. In patients with NYHA IV, the hazard ratio is 10.1, with a 95% CI of 2.69–38.3. The upper limit of the CI has been set to 10 in this figure to improve readability. CI, confidence interval; GPS, Glasgow Prognostic Score; NYHA, New York Heart Association; HF, heart failure; HFrEF, heart failure with reduced left ventricular ejection fraction; HFmrEF, heart failure with mildly reduced left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction.

Table 4
Cox proportional hazard models for all-cause death.

Model	Hazard ratio	95 % confidence interval	P-value
Unadjusted			
GPS 0	1.0 (reference)		
GPS 1	2.15	1.95–2.37	<0.0001
GPS 2	3.21	2.65–3.89	<0.0001
Age- and sex-adjusted			
GPS 0	1.0 (reference)		
GPS 1	1.90	1.71–2.10	<0.0001
GPS 2	2.94	2.42–3.56	<0.0001
Fully adjusted			
GPS 0	1.0 (reference)		
GPS 1	1.27	1.13–1.44	<0.0001
GPS 2	1.83	1.45–2.32	<0.0001

The fully adjusted model is adjusted for age, sex, body mass index, New York Heart Association class, stage of heart failure, diabetes mellitus, hypertension, history of cancer, haemoglobin level, estimated glomerular filtration rate, grade of proteinuria, B-type natriuretic peptide level, and left ventricular ejection fraction. GPS, Glasgow Prognostic Score.

mortality.

4. Discussion

The major finding of the present study was that a higher GPS was associated with an increased mortality risk in patients with chronic HF, suggesting that the GPS is a useful predictor of prognosis in patients with chronic HF.

4.1. Effectiveness of the GPS in predicting outcomes in patients with chronic HF

The GPS has been used extensively to predict prognosis in patients with cancer. Notably, the prognostic value of the GPS is independent of tumour stage or conventional scoring systems, and it is based on easily measurable and routine components. The modified GPS (mGPS), which uses cut-off values of > 0.5 mg/dL for CRP and < 3.5 g/dL for albumin, has also been shown to effectively predict survival in patients with cancer and those with HF. Despite their primary use in cancer, these scores are considered to have equivalent value as systemic inflammation-based prognostic scores [8].

We previously demonstrated that the GPS also has a predictive value for outcomes in patients with acute decompensated HF, independent of more directly cardiac-related factors such as previous HF hospitalizations, oedema at admission, and BNP levels [10]. In outpatient settings, the prognostic value of the mGPS has been studied in patients with chronic HF, with a focus on HFrEF [11] and HFpEF [12]. However, these studies involved relatively small sample sizes of 443 and 315 patients, respectively, with limited numbers of patients (14 and 19, respectively) exhibiting a GPS of 2, and a small number of events.

The present study, which included patients enrolled in CHART-2, one of the largest multicentre prospective observational studies of chronic HF, confirmed the predictive value of the GPS. Our cohort included 6,480 patients with a GPS, 163 of whom had a GPS of 2, and revealed that the GPS was a significant prognostic factor for HF outcomes independent of BNP levels. These results were consistent across various subcategories including sex, age, NYHA class, HF stage, HF type, and cancer history. Furthermore, although a history of cancer in particular should have a significant effect on the GPS, this is the first time that the usefulness of the GPS has been demonstrated in patients with chronic HF, regardless of a history of cancer. A higher proportion of patients with a history of cancer had an elevated GPS; however, the relationship

between the GPS and mortality remained consistent in patients with and without a history of cancer. This underscores the utility of the GPS as a simple and widely applicable predictive tool and highlights the importance of a holistic approach in patients with chronic HF, considering both cardiac and non-cardiac factors. The GPS is composed of inflammatory indicators, CRP and serum albumin levels, which are not included in established chronic HF mortality scores such as the MAGGIC score. This study demonstrated that GPS may provide additional prognostic value beyond that of the MAGGIC score and improve its predictive accuracy. Combining the GPS with established scores may enable clinicians to better stratify risk and personalise treatment strategies for patients with chronic HF.

4.2. Role of systemic inflammation in HF prognosis

Albumin [5,6], CRP [7], and their combination in the GPS [10–13] have been recognized as valuable predictors of HF. Hypoalbuminaemia, which is common in patients with HF, often results from malnutrition, inflammation, or cachexia. It is associated with an increased transcapillary escape rate [18], which exacerbates HF symptoms due to congestion.

Systemic inflammation is a key factor in the development and progression of HF. Elevated levels of tumour necrosis factor [19] and interleukin (IL)-6 [20] have been observed in advanced HF and are independently associated with increased mortality. Additionally, IL-1β inhibitors have been shown to reduce HF-related hospitalizations and mortality in a dose-dependent manner [21] and improve exercise capacity [22] in patients with chronic HF. These findings underscore the critical role of systemic inflammation in HF progression.

Patients with chronic HF often experience disease-related malnutrition and inflammation, as observed in cancer, chronic obstructive pulmonary disease, inflammatory bowel disease, chronic kidney disease, and other end-stage organ diseases [23]. Recent evidence has revealed that malnutrition and inflammation significantly reduce survival rates in patients with HF, partly through protein-energy wasting, a mechanism common to various chronic diseases [24]. The interaction between inflammation and malnutrition results in a vicious cycle that critically affects the long-term prognosis of patients with chronic HF. To improve the prognosis of patients with a GPS of 1 or 2, improving and maintaining the general condition of patients is crucial. Strategies such as optimising nutritional status, implementing active rehabilitation to preserve or increase exercise tolerance, and ensuring comprehensive HF management are essential. These supportive interventions could contribute to improved outcomes in this high-risk population.

This study showed that the GPS improved the prognostic value of the MAGGIC score, which does not include the inflammatory indicators albumin and CRP, and these results may reinforce the idea that inflammation influences the prognosis of patients with chronic HF. However, although this observational study demonstrates an association between the GPS and prognosis in patients with chronic HF, it cannot establish a causal relationship. To confirm whether the GPS directly influences prognosis and to determine its potential role in guiding treatment strategies, future randomised controlled trials are needed. These studies should investigate whether interventions aimed at reducing systemic inflammation, such as inflammatory cytokine targeting, can lower the GPS and, more importantly, whether a reduction in the GPS translates into improved clinical outcomes in patients with chronic HF. These trials could help establish the GPS not only as a prognostic marker but also as a modifiable therapeutic target.

4.3. Study limitations

This study has some limitations. First, as all the patients were Japanese and the proportion of patients with HFpEF was higher than that in other studies on HF, caution should be exercised when generalizing the results to other populations. Second, as the CHART-2 Study began in 2006, we were unable to assess the influence of recently identified biomarkers such as NT-proBNP or newly available medications such as sodium-glucose cotransporter 2 inhibitors or angiotensin receptor-neprilysin inhibitors. Third, this analysis used baseline data and did not consider changes in the GPS over time. Fourth, the history of cancer included both previous and current cases, which may have different prognostic implications. The lack of data regarding cancer activity and stage is a further limitation, as these factors could influence both the GPS and patient outcomes. Fifth, both serum albumin and CRP levels were not examined at the time of registration in one-third of cases. Compared to patients with a GPS (n = 6,480), patients in the GPS-missing group (n = 3,729) had a mean age one year greater, and there were 2.3 % more males, 12 % more patients with NYHA class 2, 3.4 % more patients in stage B, and 2.1 % fewer patients with HFrEF in this group. The prognostic value of the GPS could not be analysed for the excluded cases (Supplementary Tables 2 and 3). However, Kaplan–Meier and Cox proportional hazards analyses of patients with missing GPS values indicated that the exclusion of patients with missing GPS values was unlikely to introduce significant bias. Sixth, it is possible that the patient group included cases of elevated CRP levels due to acute infection, which may not have been interpreted accurately.

5. Conclusions

The present study with a large number of patients with chronic HF from the CHART-2 Study showed that a GPS of 1 or 2 was associated with an increased risk of mortality compared with a GPS of 0, independent of BNP levels. The GPS, based on CRP and serum albumin concentrations, can therefore effectively predict the long-term prognosis of patients with chronic HF.

CRediT authorship contribution statement

Shigeto Namiuchi: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kotaro Nochioka:** Writing – review & editing, Investigation, Data curation. **Ryoichi Ushigome:** Investigation, Data curation. **Shinichiro Sunamura:** Investigation, Data curation. **Atsushi Tanita:** Investigation, Data curation. **Tsuyoshi Ogata:** Investigation, Data curation. **Kazuki Noda:** Investigation, Data curation. **Toru Takii:** Investigation, Data curation. **Hiroaki Shimokawa:** Writing – review & editing, Supervision, Funding acquisition. **Satoshi Yasuda:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2025.101660.

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