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ORIGINAL RESEARCH ARTICLE

The inflammation-based modified Glasgow prognostic score is associated with survival in stable heart failure patients

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Abstract

Aims The progression of heart failure is presumably dependent on the individual inflammatory host response. The combination of the inflammatory markers, albumin, and C-reactive protein, termed modified Glasgow prognostic score (mGPS), has been derived from cancer patients and validated in multiple cohorts. This study aimed to investigate the impact of the easily available mGPS on survival of stable patients with heart failure with reduced ejection fraction (HFrEF).

Methods and results Patients with stable HFrEF undergoing routine ambulatory care between January 2011 and November 2017 have been identified from a prospective registry at the Medical University of Vienna. Comorbidities, laboratory data as well as the nutritional risk index at baseline were assessed. All-cause mortality was defined as the primary study end point. The mGPS was calculated, and its association with heart failure severity and impact on overall survival were determined. Data were analysed for a total of 443 patients. The mGPS was 0 for 352 (80%), 1 for 76 (17%), and 2 for 14 (3%) patients, respectively. Elevation of mGPS was associated with worsening of routine laboratory parameters linked to prognosis, especially NT-proBNP [median 1830 pg/mL (IQR 764–3455) vs. 4484 pg/mL (IQR 1565–8003) vs. 6343 pg/mL (IQR 3750–15401) for mGPS 0, 1, and 2, respectively; $P < 0.001$] and nutritional risk index. In the Cox regression analysis, the increase of mGPS was associated with adverse outcome in the univariate analysis [crude hazard ratio 3.00 (95% CI 2.14–4.21), $P < 0.001$] and after adjustment for multiple covariates as age, gender, body mass index, and glomerular filtration rate as well as heart failure severity reflected by NT-proBNP and New York Heart Association class [adj. hazard ratio 1.87 (95% CI 1.19–2.93), $P = 0.006$].

Conclusions Enhanced inflammation and nutritional depletion are more common in advanced heart failure. The inflammation-based score mGPS predicts survival in HFrEF patients independently of NT-proBNP emphasizing the significance of the individual pro-inflammatory response on prognosis.

Keywords mGPS; Glasgow prognostic score; Heart failure

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Introduction

The prognosis of patients with heart failure with reduced ejection fraction (HFrEF) remains poor despite continuous development in pharmacological and device therapy among patient management.[1] The association of inflammation and heart failure has long been recognized and acknowledged by the cytokine hypothesis.[2] Elevated inflammatory markers have been found in HFrEF correlating with disease severity and prognosis.[3–5] Whether elevated inflammatory mediators are solely a marker of disease severity or play a direct role in heart failure remains to be proven; however, there is

evidence emerging that inflammation may trigger the development and progression of heart failure.[6–8]

Similar to heart failure, cancer is also a systemic disease, sharing activated inflammatory response and functional and nutritional decline with disease progression as a pathophysiologic hallmark. The inflammation-based prognostic score termed modified Glasgow prognostic score (mGPS), combining C-reactive protein (CRP) and albumin, is the currently the most validated inflammatory-based risk score in cancer, acknowledging the central role of inflammation and related nutritional decline in malignant diseases.[9] The mGPS is simple to measure, easily available, and well standardized. The clinical utility of mGPS in other diseases than cancer has not been investigated yet. There has been merely one report on acute decompensated heart failure patients confirming the usefulness of the mGPS for the prediction of prognosis.[10] No data exist on outpatient stable patients with chronic HFrEF.

The aim of this study was to evaluate the relationship of the inflammation-based mGPS with heart failure severity and nutritional status along with its predictive value on all-cause mortality in stable chronic HFrEF patients.

Methods

Study population

Patients with the diagnosis of HFrEF presenting to the heart failure outpatient clinic at the Vienna General Hospital, a university-affiliated tertiary centre, were enrolled between January 2011 and November 2017 from a prospective registry. Inclusion criteria were the diagnosis of chronic stable HFrEF, an age >18 years, and complete routine laboratory data for the respective visit. For each patient data from the earliest visit at the outpatient ward, documented within the registry and fulfilling inclusion criteria, has been obtained. HFrEF was defined as a left ventricular ejection fraction $<35\%$, and the presence of heart failure symptoms and/or signs, according to current guidelines.[11] Comorbidities, such as hypertension or diabetes mellitus, and medical therapy were recorded. Patients were controlled as clinically appropriate. Written, informed consent was obtained from all study participants. The study protocol complies with the Declaration of Helsinki and was approved by the local ethics committee of the Medical University of Vienna.

Laboratory analysis and nutritional parameters

Venous blood samples were drawn and routinely available laboratory parameters including NT-proBNP, high-sensitivity CRP, and albumin were analysed according to local laboratory standard procedures. The glomerular filtration rate was estimated using the Cockcroft-Gault equation [estimated glomerular filtration rate (eGFR)]. To assess the nutritional status, body mass index (BMI) was calculated as kg/m^2 and the nutritional risk index (NRI) as 1.5 × serum albumin [g/L] + current body weight/ideal body weight [kg].

Modified Glasgow prognostic score

The mGPS was assessed as previously defined.[9] Briefly, patients without abnormalities in CRP and albumin levels, that is, CRP ≤ 10 mg/L and albumin ≥ 35 g/L, were classified to a score of 0. In case of elevated CRP without hypoalbuminemia, that is, CRP >10 mg/L and albumin ≥ 35 g/L, 1 point was allocated. If both parameters were altered, that is, CRP >10 mg/L and albumin <35 g/L, patients received 2 points.

Study end point

All-cause mortality was defined as the primary study end point, and data were obtained from the Austrian Central Office of Civil Registration.

Statistical analysis

Continuous parameters were presented as median and interquartile range (IQR) and categorical data as counts and percentages. For comparisons between the patient groups with different mGPS, the Kruskal–Wallis test and the Mann–Whitney *U*-test as well as the χ^2 test were used. Correlations between two variables were assessed by calculation of the Spearman Rho correlation coefficient to evaluate the effect of mGPS on all-cause mortality; Cox proportional hazard regression analysis was performed. Additionally, the association of usual clinical and laboratory parameters with all-cause mortality was assessed. To account for potential confounding effects and to estimate the association of mGPS with mortality, multivariate Cox regression analysis was calculated including clinical confounders as well as parameters reflecting heart failure severity, that is, NT-proBNP and New York Heart Association (NYHA) class. NT-proBNP was entered in a logarithmic form. Results are presented as hazard ratios (HRs) per IQR. The probabilities of events over time were presented as Kaplan–Meier curves. Groups were compared by the means of the log-rank test. For all tests *P* values lower than 0.05 were considered to be statistically significant. The statistical analysis was carried out with the SPSS® 24.0 software system (IBM Corp, New York, NY, USA).

Results

Baseline characteristics

A total of 443 patients were included in the study. The detailed baseline characteristics of the study population are displayed in *Table 1*. The median age of the study population was 64 years (IQR 53–72), and 73% of the patients were male. The median BMI was 26.6 kg/m^2 (IQR 23.8–30.2). Median NT-proBNP levels were 2053 pg/mL (IQR 842–4345) with most patients presenting in the NYHA classes II (40%) and III (37%). 83.9% of patients had still moderately or severely depressed left ventricular ejection fraction despite already established heart failure (HF) medication. Patients received well-titrated dosages of guideline recommended heart failure therapy.

Association between mGPS, NRI, and heart failure severity

The mGPS score was 0 for 352 (80%), 1 for 76 (17%), and 2 for 14 (3%) patients, respectively. Age, gender, BMI, comorbidities, and heart failure medication were comparable between the three groups. Comparisons of the routine laboratory parameters are displayed in *Table 1*. Besides worse levels of markers associated with inflammation as albumin and CRP, also haemoglobin levels and kidney function are known to be associated with outcome in heart failure and were significantly altered in patients with progressing mGPS. The median NRI was 131 (IQR 124–137). NRI correlated inversely with NT-proBNP levels [rs = -0.32, $P < 0.001$] and was continuously decreasing with increasing NYHA class [137 (IQR 130–141) vs. 132 (IQR 125–137) vs. 127 (IQR 120–135), $P < 0.001$ for NYHA I vs. II vs. III, respectively]. The association of the mGPS groups and heart failure severity reflected by NYHA class and NT-proBNP levels is displayed in *Figure 1*. Increasing mGPS was characterized by worse NYHA class and increasing levels of NT-proBNP [$P = 0.029$ for NYHA class and $P < 0.001$ for NT-proBNP].

Survival analysis

During a median follow-up of 21 months (IQR 10–28), 75 of 443 patients (16.9%) died. Regarding the cause of death, there was no difference in the distribution of the mGPS between patients dying from cardiac (progression of heart failure/myocardial ischaemia or arrhythmia) and noncardiac (cancer-related, renal failure, sepsis, or stroke) reasons. *Table 2* shows the association of common clinical variables, laboratory parameters, and NRI with survival. Increasing mGPS was associated with worse outcome in the univariate analysis [crude HR 3.00 (95% CI 2.14–4.21), $P < 0.001$], after adjustment for age and NT-proBNP [adj. HR 2.08 (95% CI 1.38–3.12), $P < 0.001$] and after adjustment for multiple covariates as age, gender, BMI, and eGFR as well as heart failure severity reflected by NT-proBNP and NYHA class [adj. HR 1.87 (95% CI 1.19–2.93), $P = 0.006$]. Relative to mGPS of 0 hazard ratios for all-cause mortality were 3.66 (95% CI 2.25–5.94), $P < 0.001$ for mGPS 1 and 2.76 (95% CI 1.79–4.27), $P < 0.001$ for mGPS 2. Kaplan–Meier curves shown in *Figure 2* confirmed the high discriminatory power of mGPS on survival with a 3 years estimate of 84.1%, 52.8%, and 44.2% for the respective mGPS groups with 0, 1, and 2 points ($P < 0.001$ between all groups, log-rank test).

Discussion

This is the first study investigating the impact of a simple inflammation-based risk score on overall survival in stable HFrEF patients. Elevation of mGPS was accompanied by increasing heart failure severity, assessed by NT-proBNP and NYHA class, as well as worsening of kidney and liver functional parameters. An increase in mGPS was significantly associated with enhanced mortality, independently of age and NT-proBNP, with a 3.0-fold to 3.5-fold risk increase for a lethal outcome in 3 years for patients with mGPS >0. Patients with elevated mGPS also showed an impairment in their nutritional status, reflected by the NRI score, emphasizing the interrelationship between inflammation and nutritional depletion in HFrEF and their impact on prognosis.

During the last decades, it became apparent that apart from recognized mechanisms acknowledged as the haemodynamic and neurohumoral hypothesis of the heart failure, inflammation may play a similarly significant role in the pathogenesis and progression of the disease, which led to the elaboration of the cytokine hypothesis.[2,12,13] Elevated inflammatory markers have been found in HFrEF correlating with disease severity and prognosis.[3–5] The causality between heart failure and the pro-inflammatory state is not evident. Either inflammation is a direct cause of HF and then its role in the pathogenesis and progression of HFrEF has important therapeutic implications,[14] or, if inflammation is predominantly a marker of the disease, it may help identify patients benefiting from intensified therapeutic regimens. There is evidence however that an elevated inflammatory state is not only a marker of disease severity but also may trigger the development and progression of heart failure. To begin with, heart failure may develop on the basis of comorbidities associated with low-grade chronic inflammation as obesity, diabetes, and predisposing substrates as endothelial dysfunction or atherosclerosis.[13] Patients with dilated cardiomyopathy have a detectable viral genome in >60% of cases,[6] and nearly half of patients with dilated cardiomyopathy show cardiac T-cell infiltrates indicating an underlying chronic inflammatory

Table 1 Baseline characteristics of the total cohort of chronic stable heart failure with reduced ejection fraction patients (n = 443) and according to mGPS groups

	Total study population (n = 443)	mGPS 0 (n = 352)	mGPS 1 (n = 76)	mGPS 2 (n = 14)	P value
Age, years (IQR)	64 (53–72)	64 (53–72)	62 (53–71)	71 (54–76)	0.524
Male sex, n (%)	325 (73.4%)	253 (71.9%)	59 (77.6%)	13 (92.9%)	0.139
BMI, kg/m^2 (IQR)	26.6 (23.8–30.2)	26.5 (24.0–30.1)	27.7 (22.2–31.7)	24.0 (21.9–28.0)	0.132
NRI, – (IQR)	131 (124–137)	133 (126–138)[b,c]	126 (120–132)[b,d]	117 (110–119)[c,d]	<0.001
Systolic BP, mmHg (IQR)	130 (114–146)	130 (117–147)[b,c]	119 (103–140)[b]	110 (90–142)[c]	<0.001
Diastolic BP, mmHg (IQR)	80 (70–89)	80 (70–90)	80 (70–82)	73 (64–90)	0.014
Heart rate, bpm (IQR)	71 (62–80)	70 (61–79)[b]	75 (67–89)[b]	70 (62–81)	0.004
Comorbidities					
Diabetes mellitus, n (%)	134 (30.2%)	105 (29.8%)	22 (28.9%)	7 (50.0%)	0.229
Arterial hypertension, n (%)	158 (35.7%)	132 (37.5%)	24 (31.6%)	2 (14.3%)	0.177
Ischaemic aetiology of HF, n (%)	208 (47.0%)	159 (45.2%)	43 (56.6%)	6 (42.9%)	0.096
Atrial fibrillation, n (%)	103 (23.3%)	80 (22.7%)	20 (26.3%)	3 (21.4%)	0.781
NYHA functional class					0.029
NYHA I, n (%)	68 (15.3%)	61 (17.3%)	7 (9.2%)	0 (0.0%)	
NYHA II, n (%)	178 (40.2%)	150 (42.6%)	25 (32.9%)	3 (21.4%)	
NYHA III, n (%)	164 (37.0%)	118 (33.5%)[b,c]	37 (48.7%)[b]	9 (64.3%)[c]	
NYHA III+/IV, n (%)	9 (2.0%)	7 (2.0%)	1 (1.3%)	1 (7.1%)	
Laboratory parameters					
Creatinine, mg/dL (IQR)	1.44 (0.96–1.56)	1.31 (0.94–1.46)[b]	1.91 (1.12–2.04)[b]	2.21 (1.01–2.41)	<0.001
eGFR, mL/min/1.73m^2 (IQR)	70.5 (48.1–95.5)	73.3 (51.3–98.2)[b]	58.7 (37.8–84.7)[b]	47.4 (40.2–86.1)	0.003
BUN, mg/dL (IQR)	27.8(16.2–32.9)	26.3 (15.9–30.8)[b]	34.0 (18.3–48.7)[b]	34.1 (19.6–42.3)	0.019
Sodium, mmol/L (IQR)	140 (138–142)	140 (138–141)	139 (137–142)	141 (137–143)	0.264
Haemoglobin, g/dL (IQR)	13.25 (12.10–14.60)	13.51 (12.30–14.70)[b,c]	12.30 (10.75–13.80)[b]	11.56 (10.80–12.20)[c]	<0.001
Platelet count, G/L (IQR)	225 (178–261)	220 (176–257)[c]	244 (182–266)	266 (212–317)[c]	0.031
Leucocytes, G/L (IQR)	8.14 (6.33–9.06)	8.08 (6.38–8.84)	8.54 (6.01–9.67)	7.35 (6.10–9.35)	0.741
Bilirubin, mg/dL (IQR)	0.73 (0.41–0.89)	0.71 (0.41–0.86)	0.85 (0.41–0.98)	0.63 (0.31–0.58)	0.112
Cholinesterase, kU/L (IQR)	6.99 (5.58–8.35)	7.33 (5.91–8.55)[b,c]	5.81 (4.18–6.91)[b,d]	4.42 (3.66–5.35)[c,d]	<0.001
Gamma-GT, U/L (IQR)	50 (27–105)	45 (24–95)[b,c]	76 (41–127)[b]	106 (64–301)[c]	<0.001
LDH, U/L (IQR)	213 (174–230)	207 (172–225)[b]	240 (187–259)[b]	224 (188–242)	0.001
CK, U/L (IQR)	80 (57–117)	82 (60–119)	72 (48–108)	78 (58–169)	0.109
HbA1c, % (IQR)	6.62 (5.70–7.00)	6.71 (5.80–7.00)	6.18 (5.25–6.80)	6.24 (5.50–6.90)	0.292
AST, U/L (IQR)	28 (20–30)	27 (20–30)	30 (21–32)	33 (21–40)	0.299
ALT, U/L (IQR)	28 (17–32)	28 (17–32)	25 (16–32)	38 (17–44)	0.267
Total cholesterol, mg/dL (IQR)	171 (138–201)	173(143–202)[c]	166 (121–196)	138 (121–149)[c]	0.003
Triglycerides, mg/dL (IQR)	114 (84–157)	117 (85–163)	106 (81–141)	97 (68–136)	0.061
NT-proBNP, pg/mL (IQR)	2053 (842–4345)	1830 (764–3455)[b,c]	4484 (1565–8003)[b]	6343 (3750–15 401)[c]	<0.001
Albumin, g/L (IQR)	43.3 (40.3–45.7)	44.1 (42.0–46.0)[b,c]	39.4 (36.5–42.1)[b,d]	33.2 (30.8–34.0)[c,d]	<0.001
hsCRP, mg/dL (IQR)	0.36 (0.16–0.74)	0.27 (0.14–0.51)[b,c]	1.59 (1.11–2.46)[b,d]	2.64 (1.47–5.26)[c,d]	<0.001
Echocardiographic characteristics (n = 330)					
LVEF (≥moderately reduced), n (%)	277/330 (83.9%)	223/263 (84.8%)	47/56 (83.9%)	7/11 (63.6%)	0.194
LVEF, % (IQR)	31 (24–38)	32 (23–39)	28 (23–35)	29 (28–46)	0.479
Left ventricular end-diastolic diameter, mm (IQR)	55 (43–64)	55 (43–64)	56 (43–66)	57 (43–61)	0.951
Left atrial diameter, mm (IQR)	60 (48–68)	60 (48–68)	61 (49–69)	61 (55–68)	0.932

(*Continues*)

Table 1 (continued)

	Total study population (n = 443)	mGPS 0 (n = 352)	mGPS 1 (n = 76)	mGPS 2 (n = 14)	P value
Right ventricular function, (≥moderate), *n* (%)	103/330 (31.2%)	79/263 (30.0%)	20/56 (35.7%)	4/11 (36.4%)	0.711
Right ventricular end-diastolic diameter, mm (IQR)	36 (27–42)	36 (27–42)	34 (26–42)	35 (27–41)	0.912
Right atrial diameter, mm (IQR)	57 (45–65)	57 (45–65)	60 (46–64)	55.5 (50–62)	0.933
Mitral regurgitation (≥moderate), *n* (%)	177/330 (53.6%)	137/263 (52.1%)	35/56 (62.5)	5/11 (45.5%)	0.360
Tricuspid regurgitation (≥moderate), *n* (%)	146/330 (44.2%)	112/263 (42.6%)	29/56 (51.8)	5/11 (45.5%)	0.502
Medication					
RAS blockade, *n* (%)	414 (93.5%)	337 (95.7%)	64 (84.2%)	13 (92.9%)	0.158
Max. recommended dose ≥50%, *n* (%)	294/414 (71.0%)	246/337 (73.0%)[b,c]	42/64 (65.6%)[b]	6/13 (46.2%)[c]	0.008
Beta blockers, *n* (%)	413 (93.2%)	333 (94.6%)	66 (86.8%)	14 (100%)	0.529
Max. recommended dose ≥50%, *n* (%)	332/413 (80.4%)	269/333 (80.8%)	50/66 (75.7%)	13/14 (92.9%)	0.385
MRA, *n* (%)	318 (71.8%)	259 (73.6%)	50 (65.8%)	9 (64.3%)	0.478
Max. recommended dose ≥50%, *n* (%)	301/318 (94.7%)	245/259 (94.6%)	47/50 (94.0%)	9 (64.3%)	0.759
Loop diuretics, *n* (%)	210 (47.4%)	162 (46.0%)	39 (51.3%)	9 (64.3%)	0.172
Ivabradin, *n* (%)	16 (3.6%)	10 (2.8%)[c]	4 (5.3%)	2 (14.3%)[c]	0.065

Comparisons between groups were assessed by the Kruskal–Wallis and Mann–Whitney *U*-test for continuous variables and by the χ^2 test for categorical data.
[a]ALT, alanine transaminase; AST, asparate transanminase; BMI, body mass index; BP, blood pressure; bpm, beats per minute; BUN, blood urea nitrogen; CK, creatine kinase; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; hsCRP, high-sensitive C-reactive protein; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; mGPS, modified Glasgow prognostic score; MRA, mineralcorticoid receptor antagonist; NRI, nutritional risk index; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; RAS, renin–angiotensin system
[b]For comparison between the mGPS 0 and 1.
[c]For comparison between the mGPS 0 and 2.
[d]For comparison between the mGPS 1 and 2.

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Figure 1 Association between the inflammatory score mGPS and heart failure severity reflected by (A) New York Heart Association (NYHA) classification and (B) NT-proBNP levels. Comparison between groups was conducted by (A) the χ^2 test and (B) the Kruskal–Wallis test.

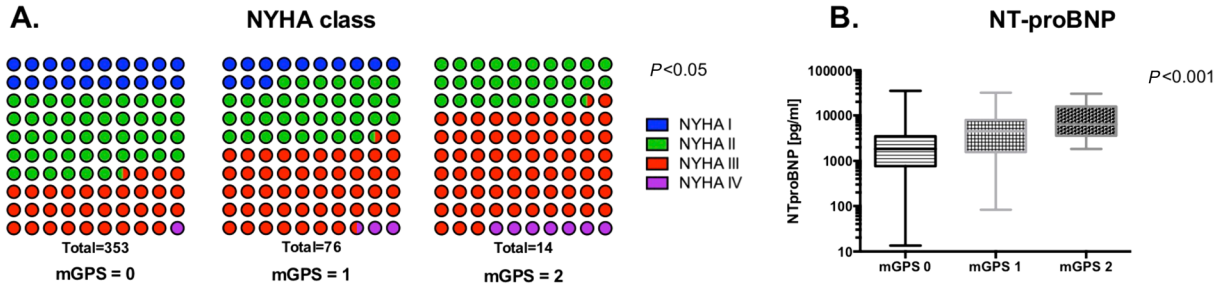
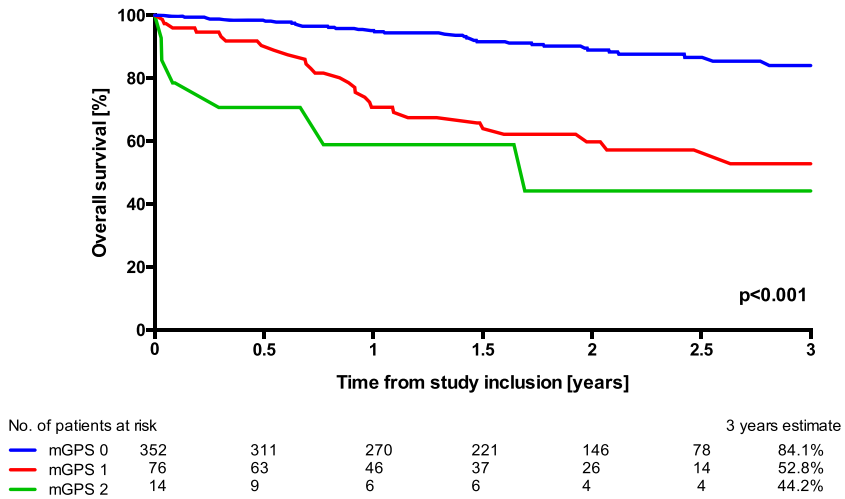


Table 2 Association of laboratory parameters with outcome in stable chronic heart failure with reduced ejection fraction patients, univariate and multivariate analysis

Variable	IQR	Crude HR (95% CI)	*P* value	ROC	Adj. HR[b] (95% CI)	*P* value
Age (years)	19	1.81 (1.26–2.61)	0.001	0.650	—	—
eGFR (mL/min/1.73m^2)	47.4	0.46 (0.31–0.67)	<0.001	0.703	—	—
NT-proBNP (pg/mL)	3502	1.40 (1.28–1.54)	<0.001	0.768	1.37 (1.22–1.53)	<0.001
LVEF (%)	14	0.91 (0.57–1.48)	0.680	0.540	0.84 (0.53–1.32)	0.451
NRI, –	13	0.62 (0.45–0.86)	0.004	0.597	0.61 (0.42–0.88)	0.008
Systolic RR (mmHg)	32	0.58 (0.41–0.82)	0.002	0.615	0.65 (0.46–0.93)	0.017
BMI (kg/m^2)	6.4	0.89 (0.67–1.19)	0.431	0.532	1.03 (0.74–1.42)	0.881
GGT (U/L)	78	1.17 (1.07–1.27)	<0.001	0.670	1.13 (1.03–1.24)	0.012
Haemoglobin (g/dL)	2.5	0.53 (0.39–0.72)	<0.001	0.652	0.62 (0.44–0.88)	0.007
Sodium (mmol/L)	4	0.75 (0.57–0.99)	0.045	0.573	0.81 (0.63–1.05)	0.107
Albumin (g/L)	5.40	0.50 (0.39–0.64)	<0.001	0.650	0.55 (0.43–0.74)	<0.001
hsCRP (mg/dL)	0.58	1.14 (1.08–1.19)	<0.001	0.700	1.11 (1.06–1.17)	<0.001

[a]BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; IQR, interquartile range; HR, hazard ratio; hsCRP, high-sensitive C-reactive protein; LVEF, left ventricular ejection fraction; NRI, nutritional risk index; NT-proBNP, N-terminal pro B-type natriuretic peptide; ROC, receiver operating characteristic.
[b]Adjusted for age, gender, eGFR.

Figure 2 Kaplan–Meier analysis of overall survival in stable heart failure with reduced ejection fraction patients according to the modified Glasgow prognostic score (mGPS). Groups were compared by the log-rank-test.



process.[7] Also, patients with a chronic immune disorder as rheumatoid arthritis show an increased risk for developing heart failure, and importantly, this risk is similar for ischaemic and nonischaemic aetiologies.[8] Consequently, inflammation has been targeted with anti-inflammatory therapies as corticosteroids, statins, or TNF-α blockade, however, without a significant clinical breakthrough.[15–18] This has been attributed to the complexity of the inflammatory response and the limited understanding of the balance of immune mediated injury and repair as well as its temporo-spatial behaviour.[12] The inflammatory hypothesis has recently also been tested for atherothrombosis in coronary heart disease, one of the most frequent reasons for heart failure, in the CANTOS trial.[19] Inhibition of the interleukin-1β pathway by 150 mg canakinumab in patients with mildly elevated CRP led to a lower risk of recurrent cardiovascular events independent of lipid-level lowering and, interestingly, also reduced cancer mortality.[19] For HF patients, the substance was related to a dose-dependent reduction in HF hospitalization and the composite end point of HF hospitalization and mortality.[20] The results inspire further investigations in the immunotherapy field for cardiovascular diseases.

Similar to heart failure, cancer is also a systemic disease sharing activated inflammatory response and nutritional and functional decline as a pathophysiologic hallmark. Chronic or dysregulated inflammation is associated with an increased risk of cancer and immune response in established malignant disease is a double-edged sword.[21] Interestingly, elevated pro-inflammatory markers in cancer correlate with elevated levels of cardiovascular markers even in patients without established cardiac disease.[22] Moreover, there is a hint that heart failure may predispose for the development of malignant disease,[23] although this was challenged by a more recent analysis.[24] This interplay may be based on systemic inflammation induced by one disease triggering the other. CRP and albumin are acute phase proteins synthesized by the liver, and secretion and serum levels are influenced by pro-inflammatory cytokines.[25] Elevated CRP levels were associated with a 2.8-fold increased risk for the development of congestive heart failure in the Framingham study.[3] CRP is known to be increased in chronic heart failure, and serum concentrations are related to functional limitation and prognosis, however, interestingly, not to the severity of LV dysfunction measured by ejection fraction.[26] Hypoalbuminemia is common in HFrEF patients and more prevalent with increasing age and disease severity and is independently associated with an increased risk of death.[27] Hypoalbuminemia is mainly caused by malnutrition, inflammation, and cachexia but also other factors as haemodilution, liver dysfunction, or nephrotic syndrome. There is clinical evidence that low albumin levels facilitate the onset of pulmonary oedema.[28] Albumin is discussed as a potentially modifiable risk factor in many cardiovascular diseases; however, it is unknown whether hypoalbuminemic HFrEF patients benefit from nutritional interventions or albumin administration.[29] Liver dysfunction and HFrEF often coexist may it due to shared risk factors or cardiohepatic interactions.[30] HFrEF itself may aggravate liver dysfunction owed to impaired haemodynamics resulting in chronic liver hypoxia and congestion that affects prognosis negatively and complicates management.[30] Increased liver biomarkers as well as hypalbuminaemia are associated with worse outcome in HFrEF.[31]

The inflammation-based prognostic score mGPS combining CRP and albumin is simple to measure, easily available, and well standardized. The mGPS is currently the most validated risk score in cancer patients.[9] The mGPS has additional prognostic information in various cancer scenarios independent from tumour site and for both operable and inoperable disease states.[9] Although the role of inflammation has similarly been recognized in heart failure, inflammatory scores have not been integrated into HFrEF risk assessment. There was merely one report on the impact of the GPS on the prognosis in acutely decompensated heart failure patients showing a significant association between elevated scores and mortality. No data on chronic stable HFrEF patients can be revealed in the literature.

This study showed that the mGPS score is associated with heart failure severity reflected by NT-proBNP levels and NYHA stages, and other routine laboratory markers related to prognosis, particularly liver biomarkers as GGT and BChE. Moreover, mGPS is an independent predictor for all-over survival bearing additional information on top of NT-proBNP. By that, we confirm the relationship between a more activated chronic inflammatory state and worse prognosis in heart failure and report the successful implementation of the cancer-cohort-derived mGPS risk score to a cohort with stable HFrEF patients. This represents the first description of the performance of a purely inflammation-based risk score in this population. Moreover, this is one of the first reports on the significance of the mGPS for risk stratification in patient cohorts with a systemic disease other than cancer. As in cancer patients, the prognosis of HFrEF patients with an elevated mGPS is very poor, with an almost 3.0-fold to 3.5-fold probability for a lethal outcome within 3 years compared with patients with mGPS at 0. These patients may be offered multimodal therapy to delay worsening their quality of life and death.

The compensatory mechanisms accompanying heart failure cause an imbalance in anabolic/catabolic processes resulting in a loss of appetite, malabsorption, increased lipolysis, muscle wasting, and cardiac cachexia. Malnutrition in patients with heart failure is often underestimated, despite its association with poor outcome.[32] Simple malnutrition scores as the NRI are more closely related to outcome than BMI solely.[32] The NRI has been shown to be a valuable tool for risk prediction early identifying HFrEF patients with nutritional depletion prior to cardiac cachexia.[33] There is good evidence that mGPS is reliably associated with weight and muscle loss

and poor performance suggesting that the score could well define the cachexia syndrome in cancer patients.[9] Similarly, our data have shown that an increase in mGPS is associated with a worsening in NRI confirming the close relationship between inflammation and nutritional decline in HFrEF.

In conclusion, this study has shown the clinical utility of the simple and objective inflammation-based score in HFrEF patients emphasizing the important role of the individual inflammatory response to HF. An activated inflammatory state appears to be characteristic for a more advanced disease. The mGPS may help clinicians to identify HFrEF patients with worse prognosis with urgent need for intensified therapy and/or alternate treatment options.

Limitations

The intention of this study is not to add another predictive risk score with superior performance compared with other available scores but to build the basis for common concepts of different diseases, that is, cancer and heart failure. This manuscript also does not compare the performance of the mGPS with other parameters or claims its superiority but aims to apply the concept of inflammatory state developed in cancer on heart failure. Whether the predictive value of mGPS is superior to its components might be tested in bigger cohorts. The mGPS might be a worthy supplement to multifactorial evaluations, however, similar to cancer, mGPS based management algorithms were not tested. One limitation of this study is that it has been conducted in a single centre. Laboratory measurements have been assessed only at a single time point and studies with serial measurements throughout disease progression might provide additional insights. Moreover, the additional determination of nonroutine inflammatory and nutritional markers may provide a better understanding of the interrelationship of heart failure, inflammation, and cachexia and their association with prognosis. A small number of patients in the highest mGPS group may be countered by the inclusion of patients with more advanced disease or decompensated heart failure.

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Conflict of interest

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References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 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.
2. Seta Y, Shan K, Bozkurt B, Oral H, Mann DL. Basic mechanisms in heart failure: the cytokine hypothesis. *J Card Fail* 1996; **2**: 243–249.
3. Vasan RS, Sullivan LM, Roubenoff R, Dinarello CA, Harris T, Benjamin EJ, Sawyer DB, Levy D, Wilson PWF, D'Agostino RB. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation* 2003; **107**: 1486–1491.
4. Kaya Z, Leib C, Katus HA. Autoantibodies in heart failure and cardiac dysfunction. *Circ Res* 2012; **110**: 145–158.
5. Holthoff HP, Zeibig S, Jahns-Boivin V, Bauer J, Lohse MJ, Kääb S, Clauss S, Jahns R, Schlipp A, Münch G, Ungerer M. Detection of anti-beta1-AR autoantibodies in heart failure by a cell-based competition ELISA. *Circ Res* 2012; **111**: 675–684.
6. Kuhl U, Pauschinger M, Noutsias M, Seeberg B, Bock T, Lassner D, Poller W, Kandolf R, Schultheiss HP. High prevalence of viral genomes and multiple viral infections in the myocardium of adults with "idiopathic" left ventricular dysfunction. *Circulation* 2005; **111**: 887–893.
7. Kuhl U, Noutsias M, Seeberg B, Schultheiss HP. Immunohistological evidence for a chronic intramyocardial inflammatory process in dilated cardiomyopathy. *Heart* 1996; **75**: 295–300.
8. Mantel A, Holmqvist M, Andersson DC, Lund LH, Askling J. Association between rheumatoid arthritis and risk of ischemic and nonischemic heart failure. *J Am Coll Cardiol* 2017; **69**: 1275–1285.
9. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. *Cancer Treat Rev* 2013; **39**: 534–540.
10. Namiuchi S, Sugie T, Saji K, Takii T, Suda A, Kato A. The systemic inflammation-based Glasgow Prognostic Score as a prognostic factor in patients with acute heart failure. *J Cardiovasc Med (Hagerstown)* 2015; **16**: 409–415.
11. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M. 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 J Heart Fail* 2016; **18**: 891–975.
12. Dick SA, Epelman S. Chronic heart failure and inflammation: what do we really know? *Circ Res* 2016; **119**: 159–176.
13. Van Linthout S, Tschope C. Inflammation—cause or consequence of heart failure or both? *Curr Heart Fail Rep* 2017; **14**: 251–265.
14. Heymans S, Hirsch E, Anker SD, Aukrust P, Balligand JL, Cohen-Tervaert JW, Drexler H, Filippatos G, Felix SB, Gullestad L, Hilfiker-Kleiner D, Janssens S, Latini R, Neubauer G, Paulus WJ, Pieske B, Ponikowski P, Schroen B, Schultheiss HP, Tschöpe C, van Bilsen M, Zannad F, McMurray J, Shah AM. Inflammation as a therapeutic target in heart failure? A scientific statement from the Translational Research Committee of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2009; **11**: 119–129.
15. Kjekshus J, Apetrei E, Barrios V, Bohm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007; **357**: 2248–2261.
16. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **372**: 1231–1239.
17. Chen HS, Wang W, Wu SN, Liu JP. Corticosteroids for viral myocarditis. *Cochrane Database Syst Rev* 2013; **10**: CD004471.
18. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, Djian J, Drexler H, Feldman A, Kober L, Krum H. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation* 2004; **109**: 1594–1602.
19. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ, CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017; **377**: 1119–1131.
20. Everett BM, Cornel JH, Lainscak M, Anker SD, Abbate A, Thuren T, Libby P, Glynn RJ, Ridker PM. Anti-inflammatory therapy with canakinumab for the prevention of hospitalization for heart failure. *Circulation* 2019; **139**: 1289–1299.
21. Crusz SM, Balkwill FR. Inflammation and cancer: advances and new agents. *Nat Rev Clin Oncol* 2015; **12**: 584–596.
22. Pavo N, Raderer M, Hulsmann M, Neuhold S, Adlbrecht C, Strunk G, Goliasch G, Gisslinger H, Steger GG, Hejna M, Köstler W. Cardiovascular biomarkers in patients with cancer and their association with all-cause mortality. *Heart* 2015; **101**: 1874–1880.
23. Hasin T, Gerber Y, McNallan SM, Weston SA, Kushwaha SS, Nelson TJ, Cerhan JR, Roger VL. Patients with heart failure have an increased risk of incident cancer. *J Am Coll Cardiol* 2013; **62**: 881–886.
24. Selvaraj S, Bhatt DL, Claggett B, Djousse L, Shah SJ, Chen J, Imran TF, Qazi S, Sesso HD, Gaziano JM, Schrag D. Lack of association between heart failure and incident cancer. *J Am Coll Cardiol* 2018; **71**: 1501–1510.
25. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol* 2014; **15**: e493–e503.
26. Windram JD, Loh PH, Rigby AS, Hanning I, Clark AL, Cleland JG. Relationship of high-sensitivity C-reactive protein to prognosis and other prognostic markers in outpatients with heart failure. *Am Heart J* 2007; **153**: 1048–1055.
27. Horwich TB, Kalantar-Zadeh K, MacLellan RW, Fonarow GC. Albumin levels predict survival in patients with systolic heart failure. *Am Heart J* 2008; **155**: 883–889.
28. Arques S, Ambrosi P. Human serum albumin in the clinical syndrome of heart failure. *J Card Fail* 2011; **17**: 451–458.
29. Arques S. Human serum albumin in cardiovascular diseases. *Eur J Intern Med* 2018; **52**: 8–12.
30. Xanthopoulos A, Starling RC, Kitai T, Triposkiadis F. Heart failure and liver disease: cardiohepatic interactions. *JACC Heart Fail* 2019; **7**: 87–97.
31. Allen LA, Felker GM, Pocock S, McMurray JJ, Pfeffer MA, Swedberg K, Wang D, Yusuf S, Michelson EL, Granger CB, CHARM Investigators. Liver function abnormalities and outcome in patients with chronic heart failure: data from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. *Eur J Heart Fail* 2009; **11**: 170–177.
32. Sze S, Pellicori P, Kazmi S, Rigby A, Cleland JGF, Wong K, Clark AL. Prevalence and prognostic significance of malnutrition using 3 scoring systems among outpatients with heart failure: a comparison with body mass index. *JACC Heart Fail* 2018; **6**: 476–486.
33. Gouya G, Voithofer P, Neuhold S, Storka A, Vila G, Pacher R, Wolzt M, Hülsmann M. Association of nutritional risk index with metabolic biomarkers, appetite-regulatory hormones and inflammatory biomarkers and outcome in patients with chronic heart failure. *Int J Clin Pract* 2014; **68**: 1293–1300.