



ORIGINAL ARTICLE



Modified Glasgow Prognostic Score is a novel predictor of clinical outcome in heart failure with preserved ejection fraction

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ABSTRACT

Objectives. Although the modified Glasgow Prognostic Score (mGPS) has been reported to have prognostic value in patients with various cancers, the association between mGPS and prognosis in patients with heart diseases have not been well studied. The aim of this study was to evaluate the predictive value of mGPS in outcomes of patients with heart failure and preserved ejection fraction (HFpEF). **Design.** We prospectively followed consecutive adult patients with HFpEF admitted to the cardiology outpatient unit. Echocardiographic and laboratory data were recorded at enrolment. mGPS was scored as 0, 1, or 2 based on C-reactive protein (CRP) and albumin levels. Patients with both elevated CRP (>1 mg/dL) and hypoalbuminemia (<3.5 g/dL) are given mGPS of 2, patients with serum CRP ≤ 1 g/dL with or without hypoalbuminemia received scores of 0. Patients with only elevated CRP levels received mGPS of 1. The primary composite endpoint of the study was all-cause mortality or heart failure hospitalization through one year. **Results.** A total of 315 HFpEF outpatients were included, and 42 (13.3%) reached the primary endpoint at one year of follow-up. Compared to patients without mortality or heart failure-related hospitalization, patients who reached the primary endpoint during follow-up were older, were more likely be symptomatic, had higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) and mGPS levels at study entry. Multivariate analysis showed that both NT-proBNP and mGPS were independent predictors of primary composite endpoint. Combining NT-proBNP with mGPS improved its prognostic value with an increase of area under the receiver operating characteristic curve from 0.759 to 0.822 ($p = .001$). **Conclusion.** This is the first study which demonstrates that mGPS is a predictor of outcomes in patients with HFpEF.

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is an increasingly prevalent form of heart failure (HF), and associated with poorer quality of life, higher hospitalization rates, increased mortality and high medical expenditure [1]. Patients with HFpEF have very high rates of 5-year mortality (75–76%) and rehospitalization (82–86%) rates, which are similar to the patients with HF and reduced ejection fraction (HFrEF) [2]. Since patients with HFpEF tend to be older and have a high co-morbidity burden such as coronary artery disease, chronic obstructive pulmonary disease, diabetes, and chronic renal disease malnutrition is expected to be a common problem in patients with HFpEF [3,4]. Although malnutrition has been shown to be associated with adverse outcomes in patients with HFrEF [5,6], the significance of biomarkers of malnutrition or nutritional risk assessment tools have not been well studied in HFpEF patients. Serum albumin is often used as a marker of malnutrition, and recent studies have shown that hypoalbuminemia predicts hospitalization and survival in patients with HFpEF [7,8]. However, previous data showed that the level of serum albumin can be affected by many factors like

hepatic or renal dysfunction, presence of inflammation or infection, and fluid status [9]. To overcome the limitation of albumin, several objective nutritional indexes have been developed and assessed in HF patients [10].

The Glasgow Prognostic Score (GPS) is an inflammation-based marker composed of serum elevation of C-reactive protein (CRP) and decrease in albumin concentration [11]. The GPS ranges from 0 to 2: patients with both an elevated CRP and decreased albumin are assigned a score of 2, whereas those with either an elevated CRP or decreased albumin alone are assigned a score of 1. Patients with a normal CRP concentration and albumin level are assigned a score of 0. The modified GPS (mGPS) score is also based on serum albumin and CRP concentrations [12]. The main difference between the GPS and the mGPS is that the mGPS defines hypoalbuminemic patients without elevated CRP as having low risk (mGPS = 0). Although GPS was originally proposed to assess the risk in cancer patients undergoing surgery [12], it has been effectively used for predicting the outcome in other diseases like idiopathic pulmonary fibrosis [13], systemic lupus erythematosus [14], and inflammatory bowel diseases [15]. However, the importance of the

assessment of immunonutritional status using mGPS in patients with HFpEF remains unclear.

Therefore, the aim of this study was to evaluate the predictive value of mGPS for all-cause mortality or heart failure-related hospitalizations in patients with HFpEF who were admitted to the cardiology outpatient units.

Methods

This study is a single center, prospective and observational study included only patients aged 18 years or older and conducted in Turkey. The study was initiated in 31 March 2018, and the last patient was enrolled in 20 May 2018.

Study patients

Patients were defined as HFpEF according to current European Society of Cardiology guidelines [1]; patients with a left ventricular ejection fraction (LVEF) $\geq 50\%$, who had at least one sign and symptom of heart failure, who had elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (>125 pg/mL) and at least one additional echocardiographic criterion including relevant structural heart disease or diastolic dysfunction were included. Patients with an LVEF $<50\%$; patients with significant chronic pulmonary disease; patients with primary severe heart valve disease or with any history of surgically corrected heart valves; patients with myocardial infarction, stroke, or coronary artery bypass graft surgery in the past 90 days; percutaneous coronary intervention or pacemaker implantation in the past 30 days; heart transplant recipients; known infiltrative, hypertrophic or congenital heart diseases; and pregnant patients were excluded from the study. Patients were also excluded due to chronic or infectious disease or due to taking immunosuppressive drugs for disease control that may influence the status of mGPS.

Data were collected during index admission to outpatient cardiology unit and outpatient visits were arranged after the first visit, and clinical status was ascertained *via* telephone interview for patients not attending the outpatient clinical visits.

All patients were prospectively followed up for 12 months or until death. The study was approved by local institutional review board and written informed consent was obtained from all patients.

Data collection and study endpoints

All of the consecutive outpatients with HFpEF underwent comprehensive clinical evaluation, electrocardiography, and 2D transthoracic echocardiography. Patient demographic characteristics, comorbid conditions, and all medications were noted. Blood samples were obtained at admission to the outpatient clinic to measure routine laboratory variables including NT-proBNP, albumin and CRP levels. According to definition of mGPS (0, 1, and 2), patients were classified into three groups; patients with both elevated CRP (>1 mg/dL) and hypoalbuminemia (<3.5 g/dL) were allocated a

score of 2; patients with only CRP >1 mg/dL were allocated a score of 1; and patients with neither of these abnormalities were allocated a score of 0. Patients were followed by telephone call every 3 months up to 12 months regarding potential hospitalizations and mortality until study closure. This information was used for the primary composite endpoint of all-cause mortality and heart failure hospitalization at 12 months. The study protocol was approved by the ethics committee of Mugla University and a written informed consent was obtained from all patients.

Statistical analysis

Baseline continuous variables were presented as mean \pm standard deviations (SD) or median with the first and fourth quartile (Q1–Q4); depending on the distribution of the data. The categorical variables are expressed in frequencies and percentages. The continuous variables were compared using the *t*-test or the Mann–Whitney *U*-test, as appropriate. Univariate analysis was performed for continuous variables and Chi-square test or Fisher's exact test was applied for categorical variables. Multivariate analysis using stepwise logistic regression model tested variables that were significant ($p < .05$) in the univariate analysis to determine independent predictors of all-cause mortality and heart failure hospitalizations. Univariate and multivariate logistic regression analyses were also applied to determine crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the relationship between NT-proBNP and mGPS, and primary endpoints. To evaluate the discriminatory ability of the mGPS, receiver operating characteristics (ROC) curves were generated, and the areas under the curve (AUC) were measured and compared. The NT-proBNP and mGPS + NT-proBNP were further tested for prognostic value in predicting outcome by logistic regression analysis, and their effectiveness was assessed using AUC. The added predictive ability of the mGPS was also assessed by the difference in C-statistics of models before and after NT-proBNP inclusion. For all tests, a *p*-value $< .05$ was considered statistically significant. Analyses were performed with the statistical package SPSS 24.0 (SPSS Inc, Chicago, IL).

Results

Three hundred and fifteen patients were included in the study. The 12-month outcomes (mortality, causes of death and hospitalizations) of the study patients are detailed in Table 1. All-cause mortality rate was 4.8%, and heart failure-related hospitalization rate was 9.5% at 1 year. Combined incidences of death or hospitalization for heart failure at 1 year were 13.3%.

Demographic, clinical, and laboratory characteristics of patients on admission who reached the endpoint relative to the rest of the cohort are shown in Table 2. These patients were older, were more likely be symptomatic (had higher NYHA functional class, were more likely to have crepitant rales, and orthopnea), and had higher prevalence of coronary artery disease at presentation to the outpatient clinics.

Patients with events had lower body mass index and albumin, but higher CRP and NT-proBNP levels than those without events. There were no significant differences between the groups with respect to left ventricular ejection fraction and prevalence of atrial fibrillation. Patients with higher mGPS on admission levels at study entry were more likely to reach the combined primary endpoint than the patients with lower mGPS levels.

Predicting clinical outcome

On univariate analyses, older age, higher New York Heart Association class, higher NT-proBNP, CRP, and mGPS but lower albumin levels at admission were significantly associated with primary outcome. However, after adjusting for other potential confounding factors, multivariate analyses showed that only age (OR: 2.53, 95% CI 1.01–4.87, $p < .01$), New York Heart Association class III/IV (OR: 1.32, 95% CI 0.52–3.33, $p = .042$), NT-proBNP >371 pg/mL (OR: 3.18, 95% CI 1.12–6.15, $p < .01$), mGPS 1 (OR: 2.42, 95% CI 1.35–4.87, $p = .015$), mGPS 2 (OR: 3.84, 95% CI 2.09–5.51, $p < .01$) at admission were independently associated with the primary outcome (Table 3). After adjustment for other co-variables, mGPS remained a significant prognostic factor

Table 1. Outcomes at 1 year.

Outcome	Number of patients
All cause death	15 patients
Cardiovascular death	7 patients
Non-cardiovascular death	6 patients
Unknown	2 patients
HF hospitalization	30 patients
All-cause death or HF hospitalization ^a	42 patients

HF: heart failure.

^aReflects the first event of each type during the study; totals may not match because some patients had both events during the study period.

($p < .001$). Receiver operating characteristic curve analysis revealed that combination of mGPS with NT-proBNP was found to improve prognostic value of NT-proBNP with an increase of AUC from 0.759 to 0.822 ($p = .001$) (Figure 1). The addition of the variable elevated mGPS to the NT-proBNP model resulted in significant increase in C-statistics, which ranged from 0.705 to 0.785 ($p = .032$).

Discussion

To our knowledge, this is the first study to evaluate the predictive value of mGPS in HFpEF patients and demonstrated that mGPS was an independent predictor of death or heart failure-related hospitalization among ambulatory patients with HFpEF. Patients with higher mGPS, measured at outpatient clinics, were at higher 1-year risk of hospitalization due to HF or all-cause mortality. Moreover, combination of

Table 3. Multivariate analysis for the prediction of primary composite endpoint of all-cause death and hospitalization for heart failure at 12 months.

	Odds ratio	95% CI	<i>p</i>
Age (per 1 year)			
Unadjusted	2.53	1.01–4.87	$< .01$
Adjusted ^a	1.87	1.21–4.56	.01
NYHA functional class III/IV			
Unadjusted	1.32	0.52–3.33	.042
Adjusted ^a	1.21	0.75–2.45	.045
NT-proBNP >371 pg/mL (median)			
Unadjusted	3.18	1.12–6.15	$< .01$
Adjusted ^a	2.12	1.05–5.25	.030
Modified Glasgow Prognostic Score			
Unadjusted	2.51	1.19–5.46	.005
Adjusted ^a	1.75	1.28–1.96	.006

Abbreviations as in Table 2.

^aAdjusted for age, sex, New York Heart Association class, coronary artery disease, hypertension, diabetes, chronic kidney disease, anemia, atrial fibrillation, and N-terminal pro B-type natriuretic peptide.

Table 2. Characteristics of patients who reached and did not reach the primary outcome.

	Without events (<i>n</i> = 273)	With events (<i>n</i> = 42)	<i>p</i> value
Gender (female)	148 (54.2)	22 (52.3)	.424
Age, years	67 (58–78)	70 (66–81)	$< .001$
Body mass index, kg/m ²	29 (26–36)	27 (24–32)	.007
Smoking	56 (20.5)	8 (19.1)	.254
NYHA III/IV symptoms	60 (21.9)	20 (47.6)	$< .001$
Orthopnea	62 (22.7)	18 (42.8)	.001
Pulmonary crepitations	57 (20.9)	15 (35.7)	.007
Comorbidities			
Hypertension	194 (71.1)	31 (73.8)	.325
Diabetes mellitus	70 (25.6)	11 (26.2)	.125
Chronic kidney disease	23 (8.4)	3 (7.1)	.425
Coronary artery disease	60 (21.9)	13 (30.9)	.001
Cerebrovascular disease	15 (5.4)	2 (4.7)	.332
Chronic obstructive pulmonary disease	36 (13.2)	5 (11.9)	.562
Laboratory data			
NT-proBNP, pg/ml	311.8 (152–810)	625 (222–1645)	$< .001$
Fasting blood glucose, mg/dl	98 (93–139)	104 (94–135)	.085
Serum creatinine, mg/dl	0.82 (0.7–1.0)	0.83 (0.7–1.0)	.585
Hemoglobin, g/dl	12.8 (11.9–14.3)	12.9 (11.7–14.5)	.675
Albumin (g/dl)	3.7 ± 0.65	3.2 ± 0.52	$< .001$
C-reactive protein (mg/dL)	2.2 ± 3.1	4.5 ± 5.4	$< .001$
Modified Glasgow Prognostic Score			
0	165 (60.4)	22 (52.4)	
1	95 (34.8)	14 (33.3)	$< .001$
2	13 (4.8)	6 (14.3)	

Data are presented as median with the first and the third quartile (Q1–Q4) or number (%).

NYHA: New York Heart Association; NT-proBNP: N-terminal pro B-type natriuretic peptide.

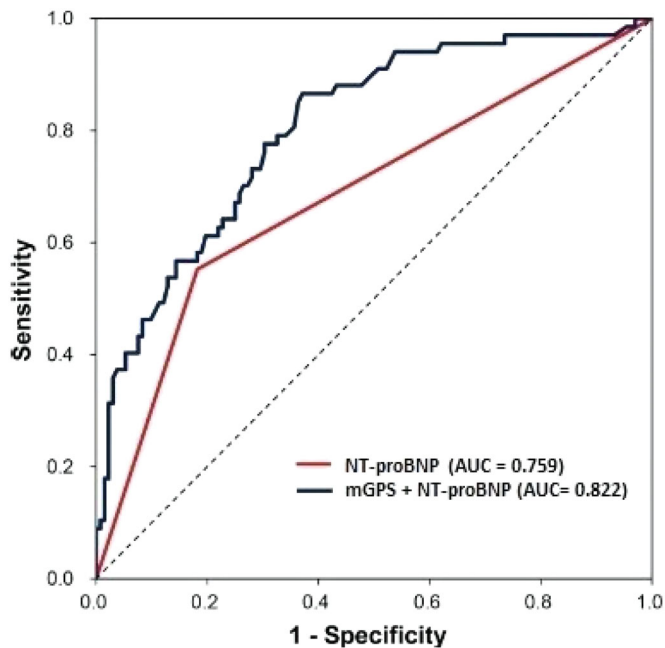


Figure 1. Receiver operating characteristic curves for mGPS and mGPS + NT-proBNP in the prediction of mortality or heart failure-related hospitalizations in ambulatory patients with HFpEF. The area under the receiver operating characteristic curve (AUC) for NT-proBNP was 0.759, and AUC for mGPS + NT-proBNP was 0.822 ($p = .001$).

mGPS and NT-proBNP enhanced the prognostic value in the form of a better AUC and increased C-statistics.

Several studies have reported the utility of prognostic risk scores [16], biomarkers [17], and nutritional indices [18] for predicting prognosis in patients with HF [16–18]. However, most of previous HF outcome prediction models compiled data from HFpEF patients or inpatients with HFpEF who were then tracked after hospital discharge and the prognostic value of these tools in more heterogeneous ambulatory HFpEF cohorts had not been well established.

Indices such as mGPS, prognostic nutritional index (PNI), controlling nutritional status (CONUT) score, and geriatric nutritional risk index (GNRI) are objective tools assessing the immunonutritional condition of patients with various diseases [19]. Immunonutritional status has also emerged as an important risk factor in HF patients [20]. Yoshihisa et al. investigated the predictive value of PNI, GNRI, and CONUT score for mortality in patients with HFpEF and found that each index was an independent predictor of all-cause mortality [20].

Prognostic significance of immunonutritional indexes have also been examined in a few studies in patients with HFpEF [21–23]. In an observational study, the significance of PNI was investigated in 1673 patients hospitalized for acute HF and 52% of the patients had HFpEF [21]. Patients were divided into 3 groups according to PNI tertiles; PNI; >44.8 , 44.8 to >39.3 , and ≤ 39.3 . A higher PNI tertile was related to better survival free from all-cause mortality and patients with a PNI ≤ 39.3 had worst prognosis [21]. The prognostic value of GNRI in HFpEF patients was evaluated in two different studies [22,23]. Kinugasa et al. retrospectively examined the clinical significance of admission GNRI in 152 elderly patients who were hospitalized with HFpEF

[22] and found that patients in the low-GNRI group had higher natriuretic peptide levels compared to those in the high-GNRI group and lower GNRI at presentation was an independent predictor of mortality in elderly HFpEF patients [22]. In another retrospective study, Nishi et al. analyzed the data of 110 elderly hospitalized HFpEF patients and revealed that HFpEF patients with a low GNRI at discharge had an increased risk of all-cause death compared with patients in the high GNRI group [23]. They also showed that adding the GNRI to the logBNP increased the predictive value for all-cause death whereas the addition of serum albumin or the body mass index to the logBNP did not significantly increase the AUC for all-cause death [23].

Glasgow Prognostic Score and mGPS have been used for predicting the prognosis of patients with cancer [11]. However, the association between GPS and prognosis in HF patients has been studied only in one study [24]. In this retrospective, single center, and observational study, efficacy of the GPS was investigated for predicting the prognoses of 336 patients with acute decompensated HF [24]. The mean LVEF of the study population was 45%, and only 36% of the patients had a LVEF $\geq 50\%$. The results of this study showed that GPS was predictive of the outcomes of patients with HF, but the authors did not analyze the results separately in patients with HFpEF and HFrEF [24].

The increased inflammatory response and malnutrition are common in HFpEF. Since the mGPS reflects both the inflammatory and the nutritional status, it is assumed to be a predictor of outcomes in HFpEF in our study. The prognostic value of mGPS was compared with NT-proBNP which is a well-known predictor of adverse outcomes in patients with HFpEF [25]. Our results suggest that the addition of mGPS to NT-proBNP provided incremental prognostic value, and patients with HFpEF who had concomitant elevations of NT-proBNP and mGPS were at particularly high risk for 1-year composite outcome of death and HF hospitalization. The current study also suggests that, mGPS could act as a tool to offer early identification of adverse events in patients with HFpEF.

Study limitations

This study was performed at single center, and our results may not be relevant to all patients with HFpEF. Our study was limited to outpatient cardiology units, and hospitalized HFpEF patients were not included in this study. We evaluated mGPS and NT-proBNP at a single time point and we did not assess the changes in these markers. Finally, residual and unmeasured confounding affecting the findings in our study cannot be ruled out. Further prospective studies are needed to determine the causal relationship as well as the diagnostic and prognostic value of mGPS in HFpEF and the potential role as a therapeutic target.

Conclusions

The results of this pilot study suggests that screening of immunonutritional status using mGPS at outpatient clinics

may be helpful in predicting the prognosis of HFpEF patients and mGPS-guided management strategy may help adopting early nutritional interventions to patients at high risk of developing complications. As the estimation of the mGPS is inexpensive and easy in daily clinical practice, we suggest that the mGPS could be calculated routinely in patients with HFpEF.

Disclosure statement

The authors declare that they have no conflict of interest.

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