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Modified Glasgow Prognostıc Score May Be Useful to Predict Major Adverse Cardiac Events in Heart Failure Patients Undergone Cardiac Resynchronization Treatment

Modifiye Glasgow Prognostik Skoru Kardiyak Resenkronizasyon Tedavisi Uygulanan Hastalarda Majör Advers Kardiyak Olayları Öngörmede Yararlı Olabilir

ABSTRACT

Objective: Whether modified Glasgow prognostic score predicts prognosis in patients with cardiac resynchronization therapy with defibrillation is unknown. Our aim was to investigate the association of modified Glasgow prognostic score with death and hospitalization in cardiac resynchronization therapy with defibrillation patients.

Materials and Methods: A total of 306 heart failure with reduced ejection fraction patients who underwent cardiac resynchronization therapy with defibrillation implantation were categorized into 3 groups based on their modified Glasgow prognostic score categorical levels. C-reactive protein >10 mg/L or albumin <35 g/L was assigned 1 point each and the patients were classified into 0, 1, and 2 points, respectively. Remodeling was determined according to the clinical event and myocardial remodeling criteria. Major adverse cardiac events were defined as mortality and/or hospitalization for heart failure.

Results: Age, New York Heart Association functional class, modified Glasgow prognostic score prior to cardiac resynchronization therapy with defibrillation, sodium levels, and left atrial diameter were higher in the major adverse cardiac events(+) group. Age, left atrial diameter, and higher modified Glasgow prognostic score were found to be predictors of heart failure hospitalization/death in multivariable penalized Cox regression analysis. Besides, patients with lower modified Glasgow prognostic score showed better reverse left ventricular remodeling demonstrated by increase in left ventricle ejection fraction and decline in left ventricle end systolic volume.

Conclusion: Modified Glasgow prognostic score prior to cardiac resynchronization therapy with defibrillation can be used as a predictor of long-term heart failure hospitalization and death in addition to age and left atrial diameter. These results can guide the patient selection for cardiac resynchronization therapy with defibrillation therapy and highlight the importance of nutritional status.

Keywords: Modified Glasgow prognostic score, long-term prognosis, cardiac resynchronization therapy, heart failure with reduced EF, nutritional treatment

ÖZET

Amaç: Modifiye Glasgow prognostik skor (mGPS)'un kardiyak resenkronizasyon tedavisi ile defibrilasyon (KRT-D) hastalarında prognozu öngördüğünü gösteren herhangi bir çalışma yoktur. Amacımız KRT-D hastalarında mGPS ile ölüm ve hastaneye yatış arasındaki ilişkiyi araştırmaktı.

Yöntemler: KRT-D implantasyonu yapılan toplam 306 düşük ejeksiyon fraksiyonlu kalp yetersizliği (DEF-KY) hastası, önceki çalışmalar baz alınarak mGPS seviyelerine göre kategorik olarak üç gruba ayrıldı. C-reaktif protein(CRP) >10 mg/L veya albümin <35 g/L olması durumlarının her biri 1 puan olarak kabul edildi ve hastalar sırasıyla 0, 1 ve 2 puan alanlar olarak gruplandırıldı. Remodelling, klinik olay ve miyokardiyal yeniden şekillenme kriterlerine göre belirlendi. Majör advers kardiyak olaylar (MACE), mortalite ve/veya kalp yetersizliğine bağlı hastane yatışı olarak kaydedildi.

Bulgular: Hastaların yaşı, New York Heart Association (NYHA) fonksiyonel sınıfı, KRT-D öncesi mGPS, sodyum seviyeleri ve sol atriyum çapı (SoAÇ); MACE izlenen grupta daha yüksekti. Çok değişkenli Cox regresyon analizinde yaş, SoAÇ ve yüksek mGPS; kalp yetersizliğine bağlı hastane yatışı/ölüm için öngördürücüler olarak tespit edildi. Ayrıca, daha düşük mGPS'li hastalarda,

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sol ventrikül ejeksiyon fraksiyonunda (SVEF) iyileşme ve sol ventrikül sistol sonu hacminde (SoV-ESV) azalma olarak ifade edilen olumlu tersine sol ventrikül yeniden şekillenmesi izlendi.

Sonuç: MGPS, yaş ve SoAÇ'a ek olarak kalp yetersizliği nedeniyle hastane yatış ve ölümün öngördürücüsü olarak kullanılabilir. Bu sonuçlar, KRT-D tedavisi için hasta seçimine rehberlik edebilir ve beslenmenin önemini vurgulayabilir.

Anahtar Kelimeler: Modifiye Glasgow prognostik skoru, uzun vadeli prognoz, kardiyak resenkronizasyon tedavisi, düşük ejeksiyon fraksiyonlu kalp yetersizliği, beslenme tedavisi

Elevated inflammatory markers and malnutrition have been found to be correlated with disease severity and prognosis in heart failure with reduced ejection fraction (HFrEF),[1-3] and there is evidence emerging that inflammation may trigger both the development and progression of heart failure (HF).[4]

Serum albumin, often used as a marker of malnutrition, can be affected by many factors like hepatic or renal dysfunction, presence of inflammation or infection, and fluid status.[5] To overcome this limitation of albumin to be used in HF, several objective nutritional indexes have been developed and assessed for HF patients.[6] Hayıroğlu et al[7] assessed that serum albumin is a predictor of long-term mortality in patients with dual-chamber permanent pacemakers. In addition, Çinier et al[8] showed that prognostic nutritional index predicts long-term mortality in HFrEF patients with implantable cardioverter-defibrillator. One of these indexes, the Glasgow prognostic score (GPS), is an inflammation-based index composed of serum elevation of C-reactive protein (CRP) and decrease in albumin concentration.[9] Although this index is currently the most validated inflammatory-based risk score in cancer, it has been effectively used for predicting the outcome in other diseases like idiopathic pulmonary fibrosis[10] and inflammatory bowel diseases.[11] It was also demonstrated that the inflammation-based modified Glasgow prognostic score (mGPS) is associated with survival in acute decompensated HF and in stable HF patients.[12,13] The main difference between the GPS and the mGPS is that the mGPS defines hypoalbuminemic patients without elevated CRP as low risk.

Cardiac resynchronization therapy (CRT) is an important non-pharmacological therapy in end-stage HF. Even though many patients meet the inclusion criteria for CRT implantation, approximately 30% of them do not respond to resynchronization treatment. Prevention of the incidence of nonresponse is a pivotal step in improving the overall efficacy of CRT treatment.[14]

Modified Glasgow prognostic score and CONUT score together were associated with in-hospital mortality among elderly patients with acute HF in comparison of nutritional risk indexes.[15] Until now, CONUT, the only studied nutrition index in CRT, has been suggested to be an independent risk factor of death/HF and was negatively correlated with left ventricle (LV) reverse remodeling.[16] The aim of this study was to analyze nutritional and inflammation status using mGPS in symptomatic HF patients receiving CRT and its association with response to CRT in terms of structural reverse remodeling and long-term events (hospitalization for HF and/or death).

Materials and Methods

Study Population

This study was designed as a single-center, retrospective cohort study from prospectively collected and conducted data at the Cardiology Clinic of Samsun Research and Training Hospital. After the exclusion of 28 patients, a total of 306 consecutive patients with a CRT-defibrillator (CRT-D) device compatible with standard clinical indications were recorded between February 14, 2016, and April 15, 2020. All patients who met the following criteria were accepted as CRT candidates: New York Heart Association (NYHA) functional class II, III, or ambulatory IV despite receiving HF treatment for at least 3 months, with ischemic or nonischemic cardiomyopathy, decreased left ventricle ejection fraction (LVEF) (<35%) and prolonged QRS duration (>130 msn) with branch block (LBBB). Patients who did not have CRP and albumin values at admission, patients who had chronic and infectious diseases at the time of implantation, and patients who did not tolerate the maximal doses of pharmacological therapy were excluded from the study. The maximum tolerated dose is defined according to clinical trials which tested increasing doses on different groups until the highest dose with acceptable side effects are encountered.

Basal features of the study participants were collected as follows: age, gender, NYHA functional class, atrial fibrillation, ischemic heart disease, pharmacological therapy, demographic characteristics, comorbid conditions, QRS duration, and echocardiographic parameters; corresponding left ventricle end-diastolic volume (LVEDV), left ventricle end-systolic volume (LVESV), LVEF, and left atrial diameter (LAD) and medications received. The follow-up (FU) visits were every 6 month or 1-year intervals for a maximum of 50 months in our Pacemaker and Arrhythmia Clinic. Repeat electrocardiograms, echocardiograms, and interrogation of previous medications and clinical improvement were recorded. C-reactive protein and albumin levels were measured from the routine blood samples obtained at admission in the outpatient clinic. The study was conducted in accordance with the general principles stated in the Declaration of Helsinki. Written informed consent of all patients was taken and the local research ethics committee reviewed the study protocol (approval number 2021/8/16).

Remodeling and Study Endpoint

In contemporary era, remodeling can be evaluated by checking criteria of myocardial remodeling and criteria for the composite endpoints.[14] The clinical event criteria means cardiac function index such as NHYA classification and occurrence of all-cause mortality and HF hospitalization.[17] Myocardial remodeling

criteria indicates mainly left ventricle end systolic volume index calculated by echocardiography in most clinical trials.[18]

Fifteen percent regression in LVESV and improvement of LVEF of more than 5% were signs of reverse remodeling. Reverse remodeling was strongly correlated with mortality and HF hospitalizations and corresponded well-defined criteria to assess response to CRT. Medical database research concerning potential hospitalizations and mortality was carried on until study endpoints were reached. This information was used for recording major adverse cardiac events (MACEs) data. Major adverse cardiac events was defined as all-cause mortality and/or HF hospitalization during study period.

Modified Glasgow Prognostic Score

By discrimination of mGPS (0, 1, and 2) according to malnutrition degree as shown in previous HF studies,[13,19] patients were categorized into 3 groups: in simple terms, if both parameters consisting of CRP >10 mg/L and albumin <35 g/L were changed, score summed up to 2 points; in case of raised CRP without hypoalbuminemia, that is, CRP >10 mg/L and albumin ≥35 g/L, 1 point was assigned; patients with neither of these abnormalities in CRP or albumin levels, that is, CRP ≤10 mg/L and albumin ≥35 g/L, were assigned a score of 0.

Statistical Analysis

We performed statistical analyses using coxphf, ggplot, l, and survminer packages in R (version 4.0.1; The R Project for Statistical Computing, Vienna, Austria). Categorical variables were expressed as numbers and percentages of patients. Continuous variables were expressed as mean ± SD or if there was a non-normal distribution we used median 25-75 quartiles (IQR). Histogram and Shapiro–Wilks test were used to determine the distribution of continuous variables. Continuous variables were compared using Student's *t*-test (normally distributed data) and Mann–Whitney *U* test (non-normally distributed continuous data and ranked data) as appropriate. Categorical variables were compared using Chi-square or Fisher's exact tests.

Primer Outcome: Time to death or HF hospitalization.

Secondary Outcome: CRT response.

Regression Modeling: Association of different variables of death/HF hospitalizations was examined with penalized maximum likelihood estimation Cox proportional hazard regression method to reduce the overfitting risk.[20] Unlike maximizing the log likelihood in traditional Cox proportional hazard regression method, maximizing the penalized log likelihood was applied in penalized Cox regression. The results were represented as hazard ratio (HR) with 95% CIs. The screened variables in univariable analysis were age, atrial fibrillation, ischemic etiology, left atrial diameter, gender, and mGPS. Variables in multivariable Cox regression analysis were chosen according to univariable screening results, literature, and our focused variable.[21]

Survival curves with rates were constructed using the Kaplan–Meier method and mGPS groups were compared with the Log-Rank test. We also searched proportionality of Cox regression model with Schoenfeld residuals, which assess proportionality graphically. Adjusted hazard ratio plots were constructed for age. In addition, 3-dimensional (3D) plot was constructed for predicted probability of death or hospitalization which was adjusted with age and mGPS. A 2-tailed *P* value <0.05 was set as statistically significant.

Results

Baseline Characteristics

Patients in the higher mGPS group had lower serum albumin and hemoglobin levels ($P=0.001$), LVEF FU ($P=0.001$), ΔLVEF ($P=0.002$), ΔLVESV ($P=0.001$) compared to the lower mGPS group. The following were higher among patients with higher mGPS versus lower mGPS: age ($P=0.017$), ischemic etiology ($P=0.012$), CRP ($P=0.001$), LVESV FU ($P=0.001$), and LAD FU ($P=0.006$). The mean FU time was 28 ± 15 months.

The nutritional status of patients was defined based on mGPS before CRT implantation. Cardiac resynchronization therapy candidates were categorized into normal nutritional status (128 patients; 41.8%), mild malnutrition (99 patients; 32.3%), and moderate-severe malnutrition (79 patients; 25.8%). The basal features of the patients concerning mGPS are listed in Table 1. As mGPS increased, the patients were older, had lower serum hemoglobin, and had higher creatinine levels. In higher mGPS, there was a higher percentage of ischemic etiology. New York Heart Association functional class, body mass index (BMI), width of the QRS, and medical treatment (angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta-blockers, and mineralocorticoid receptor antagonist) were similar among 3 groups.

Structural Remodeling

Regular check-up displayed the prominent reverse LV remodeling in patients with lower mGPS. A substantial (>15%) LVESV decline and LVEF (>5%) rise was found in 111 (87.2%) and in 101 (78.8%) of patients with normal nutritional status, in 51 (51.5%) and in 66 (66.6%) of patients with mild malnutrition, in 23 (29.1%) and in 43 (54.4%) of patients with moderate-to-severe malnutrition, respectively (Table 1). Also mean ΔLAD during FU was lower among the higher mGPS groups (Table 1).

Mortality/Heart Failure Admissions

Table 2 summarizes the basal features and clinical response of the study population according to MACE. Age, NHYA class, mGPS prior to CRT, sodium levels, and LAD differed significantly between groups. Because of the limited number of study population, univariable and multivariable penalized Cox proportional hazard model analyses were used to reveal the association of variables with HF/death.

Our multivariable Cox regression analysis demonstrated that age and LAD were independent predictors of HF/death during the study period. Higher mGPS was also associated with an increased risk of HF/death during long-term FU. The nutritional status prior to CRT defined by mGPS was determined as an independent predictor of cardiovascular events in univariate and multivariate analysis at FU (Tables 3 and 4).

The fine-gray competing risk regression analysis depicted mGPS (1.44, 95% CI 1.10-1.87, $P=0.02$) (Table 5).

As demonstrated in Kaplan–Meier analysis, long-term cumulative probability free of HF/death was statistically significant between mGPS 0-1 and mGPS 2 groups ($P=0.0071$) (Figure 1). Figure 2

Table 1. Baseline Characteristics, Reverse Remodeling, and Clinical Response According to mGPS

Variable	mGPS 0 (n=128)	mGPS 1 (n=99)	mGPS 2 (n=79)	*P*
Age (years)	66.2 ± 10.2	68.2 ± 10.1	72.6 ± 9.5	**0.017**
Male, n (%)	85 (67.1)	53 (53.7)	46 (59.3)	0.221
NYHA class, n (%)				0.101
II	48 (37.2)	26 (26.5)	10 (12.6)	
III	74 (57.4)	63 (64.3)	58 (73.5)	
IV	7 (5.4)	9 (9.2)	11 (13.9)	
Ischemic etiology, n (%)	36 (28.2)	39 (39.4)	42 (53.1)	**0.012**
DM, n (%)	30 (23.5)	31 (31.3)	27 (34.3)	0.244
BMI	28.9 ± 4.7	28.3 ± 4.5	27.8 ± 4.1	0.639
CRP (mg/L)	4.2 ± 2.1	7.8 ± 4.0	12.8 ± 4.9	**0.001**
Albumin (g/L)	4.2 ± 0.2	3.8 ± 0.4	3.6 ± 0.2	**0.001**
Creatinine (mg/dL)	1.01 ±0.43	1.02 ± 0.36	1.32± 0.48	**0.003**
Sodium (mmol/L)	137.8 ± 2.6	136.9 ± 3.1	136.1 ± 3.6	0.013
Hemoglobin (g/dL)	13.57 ± 1.64	12.91 ± 1.81	12.21 ±1.97	**0.001**
AF, n (%)	37 (29.4)	34 (34.3)	32 (40.6)	0.314
QRS width (ms)	161 ± 24	163.2 ± 17.4	161.5 ± 18.8	0.427
LVESV (mL)	157 ± 33	159 ± 37	174 ± 49	0.117
LVEF (%)	27.4 ± 5.4	27.2 ± 6.1	25.2 ± 7.2	0.213
LAD (mm)	48.1 ± 6.2	49.4 ± 7.3	51.5 ± 8.1	0.058
ACEI/ARB, n (%)	117 (91.8)	83 (83.6)	62 (79.3)	0.147
BB, n (%)	118 (92.6)	85 (86.2)	67 (85.1)	0.407
MRA, n (%)	54 (42.4)	49 (49.4)	39 (49.3)	0.338
LVEF FU (%)	40.5 ± 10.1	37.6 ± 8.6	33.4 ± 7.2	**0.001**
ΔLVEF (%)	13.1 ± 7.5	10.4 ±6.6	8.1 ± 5.1	**0.002**
ΔLVEF > 5%, n (%)	101 (78.8)	66 (66.6)	43 (54.4)	**0.039**
LVESV FU	110.8 ± 32.8	118.7 ± 36.7	140.1 ± 48.1	**0.001**
Δ LVESV (mL)	47.1 ± 13.1	40.5 ± 15.5	28.7 ± 18.2	**0.001**
ΔLVESV > 15%, n (%)	111 (87.2)	51 (51.5)	23 (29.1)	**0.001**
LAD FU (mm)	46.7 ± 4.9	48.8 ± 6.2	50.5 ± 7.1	**0.006**
ΔLAD FU	1.3 ± 4.8	1.1 ± 3.2	0.8 ± 2.4	**0.018**
Clinical response, n (%)	79 (62.3)	39 (57.6)	43 (53.8)	0.318
Clinical response, n (%)				0.0391
Worse	0	3 (3.1)	5 (6.3)	
No change	49 (37.6)	38 (38.4)	31 (39.2)	
Improvement 1 class	66 (51.7)	47(47.4)	35 (44.3)	
Improvement 2 class	13 (10.5)	10 (10.1)	8 (10.2)	

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; AF, atrial fibrillation; BB, beta-blockers; BMI, body mass index; DM, diabetes mellitus; FU, Follow-up; LAD, left atrium diameter; LVEF, left ventricle ejection fraction; LVESV, left ventricular end systolic volume; mGPS, modified Glasgow prognostic score, MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; Δ, changes.
Comparisons between groups were assessed by the ANOVA for continuous variables and by the χ^2 test for categorical data.
Values are presented as number (%), mean ± SD.
Statistically significant *P* values are shown in boldface.

shows 3D predicted probability of MACE based on patient age and mGPS. For example, 80 years age and mGPS_2 predicted the probability of MACE by 65% until 50 months, when adjusted with LA diameter, etiology, rhythm, sodium, and female gender; however, with 80 years age and mGPS_0_1, the predicted probability of MACE was 50% until 50 months according to regression analysis. Figure 3 depicts the difference between an observed covariate value and what you might have expected based on all those at risk at that time, until 50 months. The model holds assumptions. During FU, 50 (16.3%) patients died from underlying disease: 22 (7.1%) cardiac (14 sudden death with 9 CİED shocks, 8 pump failure), 7 (2.2%) tumor, 6 (1.9%) stroke, 10 (3.2%) cardiovascular, and 5 (1.6%) infection.

Discussion

Our study has demonstrated that pre-implantation values of mGPS—an indicator of nutrition inflammation index—predict long-term prognosis in patients who underwent CRT implantation. Modified Glasgow prognostic score was significantly associated with mortality, hospitalization, and CRT response in patients with advanced HF at a mean 28 ± 15 months FU. Our study is the first to show that mGPS determines the long-term outcomes and clinical and echocardiographic response in CRT candidates.

Inflammatory cytokines can reflect the severity of HF as well as accelerate its progression.[22] Increased CRP levels have been shown to increase the development of congestive HF in Framingham study by 2.8 times.[23] C reactive protein increases in chronic HF and is associated with functional limitation and prognosis.[24] Occurrence of hypoalbuminemia due to decreased synthesis of albumin in liver is a determinant of poor results.[25] Proinflammatory cytokines such as CRP and albumin can contribute to the destruction process encompassing loss of appetite and higher energy expenditure by influencing the levels of adipocytokines.[26]

Çinier et al[27] demonstrated that elevated CRP/albumin ratio increased all-cause mortality in patients with HFrEF and ICD. Because mGPS is associated with weight, muscle loss, and low performance, it is the most valid risk score for cachexia in

Table 2. Baseline Characteristics and Clinical Response According to Primary Outcome

Variable	MACE(-) (n=189)	MACE(+) (n=117)	*P*
Age (years)	66.7 ± 10.1	72.8 ± 10.7	**0.001**
Male, n (%)	119 (63)	71 (60.7)	0.743
NYHA class, n (%)			**0.001**
II	82 (43.3)	22 (19.2)	
III	92 (48.8)	70 (60.3)	
IV	15 (7.9)	25 (20.5)	
mGPS prior CRT, n (%)			**0.001**
mGPS 1	96 (50.8)	31 (26.9)	
mGPS 2	61 (32.5)	39 (33.3)	
mGPS 3	32 (16.7)	47 (39.7)	
Ischemic, n (%)	60 (31.7)	52 (44.9)	0.059
DM, n (%)	46 (24.4)	39 (33.3)	0.166
BMI	28.6 ± 4.6	28.1 ± 4.4	0.441
Creatinine (mg/dL)	1.03 ± 0.36	1.13 ± 0.52	0.189
Sodium (mmol/L)	137.6 ± 3.1	136.3 ± 2.7	**0.001**
Hemoglobin (g/dL)	12.74 ±1.86	12.63 ±1.92	0.781
AF, n (%)	64 (33.9)	50 (42.9)	0.234
QRS width (ms)	162.5 ± 14.3	166.5± 22.5	0.278
LVESV (mL)	157.6 ±36.5	167.4±40.7	0.101
LVEF (%)	26.1±5.9	27.5±6.1	0.143
LAD (mm)	47.9±6.4	51.3±7.0	**0.001**
ACEI/ARB, n (%)	160(85)	101 (85.9)	0.866
BB, n (%)	168(89)	102 (87.3)	0.737
MRA, n (%)	105(55.9)	54 (46.0)	0.204
Clinical response, n (%)			0.077
Worse	11 (5.5)	12 (10.3)	
No change	59 (31.5)	51 (44.9)	
Improvement 1 class	81 (42.5)	36 (32.1)	
Improvement 2 class	38 (20.5)	18 (12.8)	

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; AF, atrial fibrillation; BB, beta-blockers; BMI, body mass index; DM, diabetes mellitus; LAD, left atrium diameter; LVEF, left ventricle ejection fraction; LVESV, left ventricular end systolic volume; mGPS, modified Glasgow prognostic score, MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.
Comparisons between groups were assessed by the Student's *t* test for continuous variables and by the χ^2 test for categorical data.
Values are presented as number (%), mean ± SD.
Statistically significant *P* values are shown in boldface.

Table 3. Penalized Univariate Cox Proportional Hazards Model for Death/HF Hospitalizations in Patients with CRT

Variable	Crude HR, 95% CI	*P*
Age	1.026 (1.003-1.050)	0.025
AF	1.093 (0.707-1.690)	0.689
Ischemic etiology	1.372 (0.893-2.107)	0.152
LAD	1.050 (1.018-1.084)	0.002
Male	0.941 (0.609-1.452)	0.782
mGPS		
0-1 reference	1.0	–
2	1.872 (1.172-2.991)	0.009
Sodium	0.971 (0.905-1.043)	0.422

Penalize maximum likelihood cox regression.
Abbreviations: AF, atrial fibrillation; HR, hazard ratio; LAD, left atrium diameter; mGPS, modified Glasgow prognostic score.
Statistically significant *P* values are shown in boldface.

Table 4. Penalized Multivariate Cox Proportional Hazards Model for Death/HF Hospitalizations in Patients with CRT

Variable	Adjusted HR, 95% CI	*P*
Age	1.020 (1.001-1.045)	**0.041**
AF	1.096 (0.688-1.727)	0.695
Ischemic etiology	1.352 (0.866-2.093)	0.181
LAD	1.049 (1.017-1.083)	**0.002**
Male	0.928 (0.597-1.459)	0.743
mGPS		
0-1 reference	1.0	–
2	1.772 (1.072-2.815)	**0.026**
Sodium	0.974 (0.903-1.052)	0.514

Abbreviations: AF, atrial fibrillation; HR, hazard ratio; LAD, left atrium diameter; mGPS, modified Glasgow prognostic score.

Table 5. Adjusted Hazard Model for the Sub-Distribution (Fine-Gray)

Variable	HR, 95% CI	*P*
Age	1.02 (0.99-1.06)	0.12
AF	1.41 (0.71-2.82)	0.34
Ischemic etiology	1.15 (0.57-2.33)	0.22
LAD	1.04 (1.00-1.08)	0.03
Gender (male reference)	0.95 (0.49-1.85)	0.88
mGPS, 2 vs. 0, 1	1.44 (1.10-1.87)	0.02
Sodium	0.95 (0.85-1.07)	0.35

Abbreviations: AF, atrial fibrillation; HR, hazard ratio; LAD, left atrium diameter; mGPS, modified Glasgow prognostic score.
Fine-gray sub-distribution hazard comparing (alive) with died cardiovascular reason accounting for died non-cardiovascular.

cancer patients.[9] The association of mGPS with cardiac cachexia has been studied in several studies involving HF patients. It has been conducted that GPS determines the 3-year prognosis in a population of 336 patients with acute decompensated HF.[12] Hazard ratios of GPS 1 and GPS 2 were 1.97 and 3.4, respectively, compared to GPS 0 independent from brain natriuretic peptide (BNP). Cho et al[13] have claimed that mGPS is associated with 6-year survival in stable HF patients. Compared to mGPS 0, mGPS 1 and mGPS 2 increased mortality 2.76 times and 3.66 times, respectively. Modified Glasgow prognostic score has also

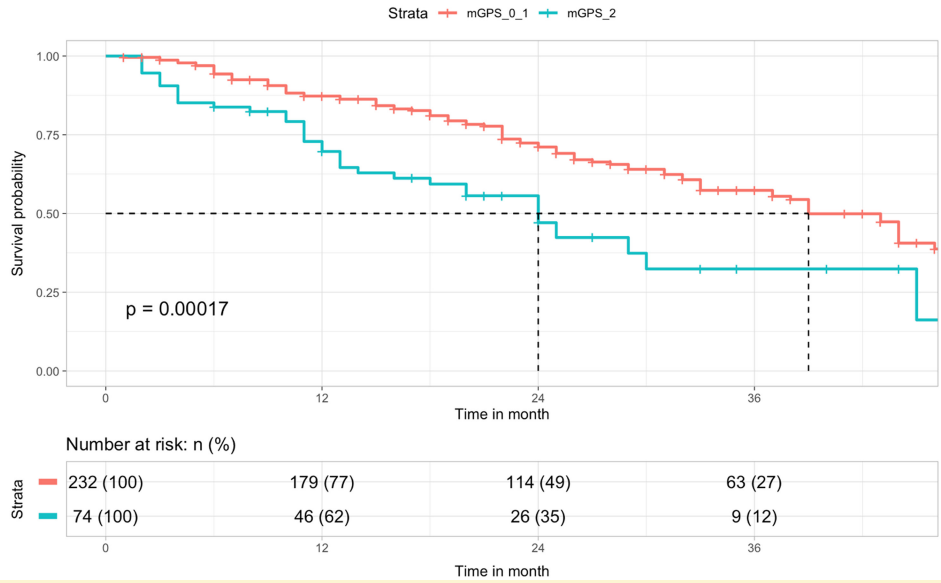


Figure 1. Kaplan–Meier analysis of death/heart failure (HF) free survival of cardiac resynchronization therapy (CRT) implanted reduced ejection fraction patients according to modified Glasgow prognostic score (mGPS). Groups were stratified by the log-rank test.

been proposed to predict the 1-year clinical outcomes in HF with preserved ejection fraction.[19] Modified Glasgow prognostic scores 1 and 2 were observed to increase mortality and/or HF hospitalization 2.42 times and 3.84 times, respectively, when mGPS 0 was accepted as the reference value. In concordance with these studies, we found that higher mGPS was associated with non-response and poor prognosis in HF patients who underwent CRT device implantation.

Age, LV end-diastolic diameter, male gender, presence of atrial fibrillation, serum BNP, and creatinine levels were the significant negative pre-implantation predictors and QRS width was the positive pre-implantation predictor of a 10-year survival in a cohort of 877 patients who underwent CRT in a study by Patel et al[21] In another study by Stankovic et al.[28] age, functional class, and ischemic etiology were found to be positive pre-implant predictors of 3-year mortality in a population of 500 patients. It was recognized that the number of predictors of mortality and hospitalization lowered as the number of patients and mean age reduced. In the study in which the CONUT index was investigated as the nutritional index, it was observed that some other

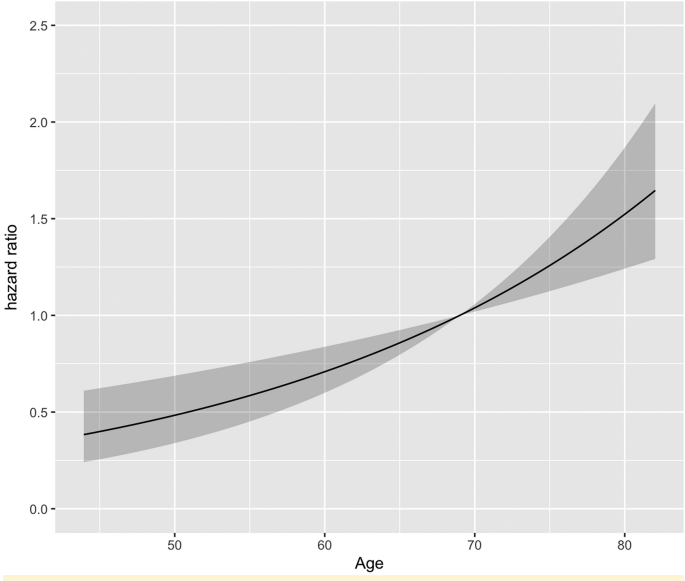
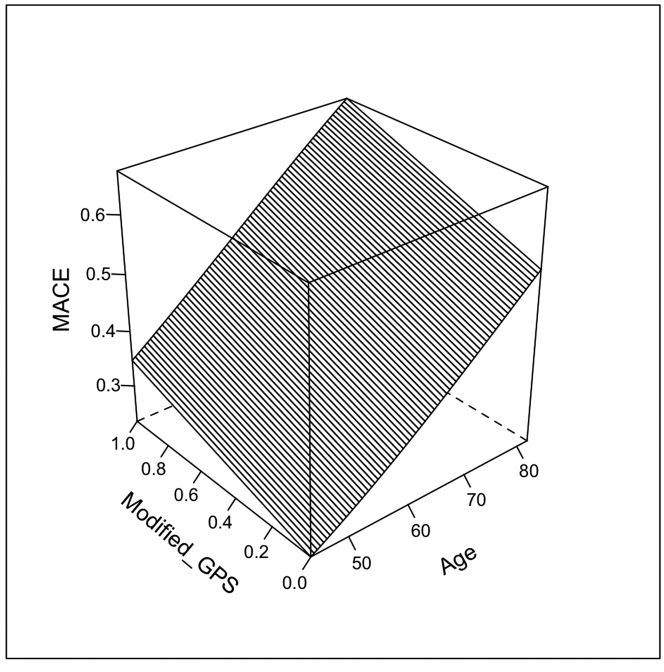


Figure 2. Three-dimensional predicted probability of major adverse cardiac event (MACE) based on patient age and modified Glasgow prognostic score (mGPS).



Adjusted to: La_diameter=49 ischemic_etiology=0 ritm_af=0 Sodium=137 Gender=0

Figure 3. The Schoenfeld residuals.

variables were also associated with mortality and HF hospitalization because the number of patients and average age in this study were higher than ours. Moreover, other variables with significant positive predictive value for death/HF were age, gender, sodium level, and LAD in CONUT CRT study.

After summarizing similar studies highlighting CRT response, the interpretation of our study data analysis has reached some conflicting results. Despite BMI values and percentage of DM were similar between study groups based on either mGPS or MACE, they could not be used to estimate cardiac cachexia. At first sight, patients with higher mGPS had higher creatinine levels, percentage of ischemic etiology, age, and lower hemoglobin levels. These differences could be attributed to the fragile nature of disease progression expressed as immunomalnutrition index. In addition, more prevalent ischemic etiology suggests that inflammation contributes to the course of the disease. The smaller number of our patients and the low average age might have exhibited the variables that might have a significant relationship with mortality and HF to be less pronounced. Cardiac resynchronization therapy-pacemaker (CRT-P) patients were not included in our study because most of the patients who underwent CRT-P implantation have an expected life expectancy of less than a year, which might have affected our study results creating a more heterogeneous group. This fact may explain that the mortality rate was lower when compared to previous studies. In our study, we obtained the result that mGPS 2 increased mortality and HF 1.77 times compared to mGPS 0 and mGPS 1. Furthermore, age and LAD were the other variables that significantly predicted mortality and HF. Although gender and sodium differed significantly when the groups were separated according to the presence of MACE, this significance was not preserved in multivariate Cox regression analysis. The age above 70 showed a steeper slope on the hazard ratio plot graphic. Another interesting point of our study was that the LA diameter was a significant predictor in penalized multivariate Cox regression analysis independent of the presence of atrial fibrillation. By virtue of mGPS which is a simultaneous indicator of nutrition and inflammation, contains fewer parameters, it is easier to calculate, faster, and feasible compared to other prognostic nutritional scores, and it can predict long-term results as a more practical method in such patients. Time-varying β coefficient of mGPS exposed that its effect gradually decreases over time. Therefore, our study analysis noticed that repeated measurements gave more accurate results in predicting long-term results and mGPS improvement after CRT rather than a single measurement.

Limitations

First limitation of this study was the relatively small number of patients who were registered in a single center. Second limitation was that CRT-P patients were not allocated in the study. Third limitation was the lack of data about N-terminal pro-B-type natriuretic peptide levels. Another limitation was that the rise in CRP levels could be secondary to infectious diseases. Additionally, the dynamicity of mGPS which allowed changes in daily measurements might also interfere with the results. As a result, single mGPS measurement might be unable to show relationship between mGPS and adverse events and nutritional improvement after CRT in a longer period. Large-scale prospective studies should be carried out to better define the association between mGPS and CRT response, pathophysiological mechanisms, and clinical outcomes.

In conclusion, our study has shown that mGPS as an indicator of immunomalnutrition can be useful in detecting LV reverse remodeling, non-response, and patient selection for CRT and may be an additional prognostic risk factor. Moreover, age and LAD were the other positive pre-implant predictors of mortality/HF in CRT patients. It may also be concluded that mGPS-based nutritional interventions may aid to prevent long-term adverse events in CRT candidates.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of University of Health Sciences, Samsun Training and Research Hospital, (Approval No: GOKA/ Date:2021/8/16).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.E., U.A.; Design – M.Y., O.C.Y.; Supervision – İ.Ş., U.A.; Materials – M.U., M.Y.; Data Collection and/or Processing – M.U., O.O.Ş., A.K.; Analysis and/or Interpretation – A.K. İ.Ş.; Literature Review – Ö.Ç., O.Ş.; Writing – G.E. U.A.; Critical Review – A.K., U.A.

Declaration of Interests: The authors declare that they have no competing interest.

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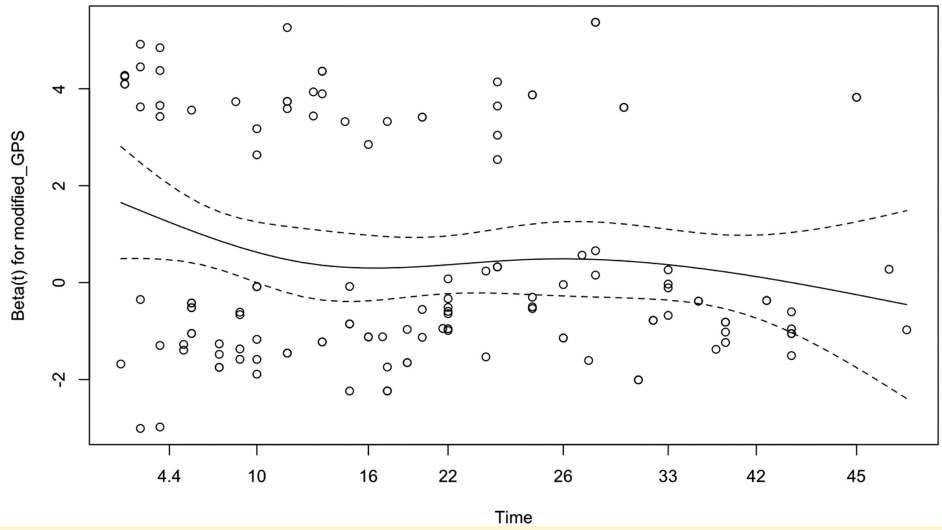

Supplementary Figure S1. Hazard ratio plots of MACE according to patient age.