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Utility of post-operative modified Glasgow Prognostic Score in localized renal cell carcinoma

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MBBS
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An abstract of
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Abstract

Utility of post-operative modified Glasgow Prognostic Score in localized renal cell carcinoma

By

Ninad Salastekar

Objective: To assess post-operative modified Glasgow Prognostic Score (mGPS) as an independent predictor of relapse-free survival (RFS) and cancer-specific survival (CSS) after nephrectomy in patients with localized renal cell carcinoma.

Methods: Patients with clinically localized (T1-T3N0M0) clear cell RCC were followed prospectively following potentially curative nephrectomy. Patient age, sex, race, tumor stage, grade and size, presence of necrosis, and both pre- and post-operative mGPS scores were considered as potential predictors of RFS and CSS. Patients were assigned 0, 1 or 2 mGPS points based on plasma levels of C - reactive protein (CRP) and serum albumin. Unadjusted and multivariable Cox regression analyses examined the association of various patient, disease and mGPS-related characteristics with RFS and CSS.

Results: Of the 509 patients in this study, 16% experienced disease recurrence or metastatic spread and 8% patients died due to RCC. Post-operative mGPS scores of of 0, 1 and 2 were observed in 76%, 7% and 17% of patients with relapse, and in 74%, 5% and 21% of patients who died of RCC, respectively. In the multivariable analysis, male gender, tumor stage, grade, and post-operative (but not pre-operative) mGPS served as independent predictors of RFS. Similarly, tumor stage, grade, and post-operative (but not pre-operative) mGPS served as independent predictors of CSS.

Conclusion: Post-operative mGPS is a stronger predictor of relapse and cancer-specific mortality than the corresponding pre-operative score, in patients with surgically removed localized RCC. Clinicians may consider using post-operative mGPS to improve risk-stratification of RCC patients, especially with localized disease. This information may assist clinical decisions regarding patient counseling, post-operative surveillance, or adjuvant therapy.

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Table of Contents

Introduction

Based on the 2014 projections, renal cell carcinoma (RCC) is expected to represent approximately 4% of the new cancer cases in the United States [1]. An estimated 13,860 deaths will occur in 2014 due to RCC [1]. Approximately 70% cases of RCC present as localized disease of which nearly one third develop metastases following potentially curative nephrectomy [2, 3]. Without treatment, the overall survival in patients who develop metastatic disease is less than 10% [2-5]. However, there has been an increase in the cancer-specific survival in the era of immunotherapy and targeted therapy [6, 7]. It is important to identify cases that are at a higher risk of developing relapse or metastases as well as those at a higher risk of dying due to cancer, after a potentially curative surgery. This information may then be used to offer better surveillance and potentially more effective adjuvant therapy, and to identify targets for clinical trials.

Risk stratification of RCC cases is traditionally based on patient characteristics, pathological criteria such as tumor stage and grade, and recently, markers of systemic inflammatory response [2, 5, 8-15]. Recently, one of the markers of systemic inflammation, C-reactive protein (CRP), has been investigated as an independent predictor of survival in patients suffering from a number of cancers including RCC [4, 12, 14, 16, 17]. CRP, an acute phase reactant, is produced in response to RCC-secreted interleukin- 6 (IL-6). Although much of CRP is produced in the liver, a substantial amount is contributed by the tumor itself [18]. Increased pre-operative level of CRP has been consistently associated with poor outcomes in patients suffering from various malignancies including RCC [12, 14, 16, 17, 19]. Decreased

level of albumin, in part in response to systemic inflammation, also has proven prognostic significance in cancer [20-23].

The modified Glasgow Prognostic Score (mGPS), a scoring system which combines pre-operative CRP and albumin levels, was shown to be an independent predictor of survival in patients suffering from a number of cancers [24-26]. According to this scoring system, patients are assigned a score of 0 if their pre-operative plasma CRP level is ≤10 mg/L regardless of the albumin level, a score of 1, for CRP >10 mg/L and serum albumin ≥3.5 g/dL, and a score of 2, if their CRP level is above 10 mg/L in presence of hypoalbuminemia (<3.5 g/dL).

Previously, pre-operative mGPS has been shown to be an independent predictor of RFS and CSS in patients with localized as well as metastatic RCC [24, 25]. We recently reported that patients with a higher post-operative CRP level have poorer outcome even after controlling for pre-operative CRP levels [13]. We sought to extend these observations by comparing the utility of the mGPS calculated post-operatively versus that based on pre-operative CRP and albumin levels,. We hypothesized that post-operative mGPS would be an independent predictor of relapse-free survival (RFS) and cancer specific survival (CSS) in these patients.

Methods

Patients

Patients with clear cell RCC treated with potentially curative nephrectomy were included in this prospective cohort study. Patients were identified using prospectively maintained Emory University nephrectomy database. Eligibility criteria for the study included age of 18 years or

older, clear cell histology of the primary neoplasm and negative surgical margins after removal of the macroscopic tumor. Patients with T4 disease and clinically evident nodal disease or distant metastasis on cross-sectional imaging of chest, abdomen and pelvis were excluded from the study.

Clinical and Laboratory Assessment

Pathological staging was done using the 1997 TNM renal tumor classification [27]. Initial assessment was based on 6 stages (T1a, T1b, T2, T3a, T3b and T3c). Due to very few events (relapses or deaths) in some of these categories, the analyses were based on three broader groups - T1, T2 and T3. Tumors were classified according to the Fuhrman criteria into grades 1 through 4 [9]. For the purpose of the present analyses, grades 1 and 2 were combined into a single group.

CRP and albumin levels were assessed pre- and post-operatively. Pre-operative mGPS was calculated using CRP and albumin levels measured within one month before the surgery. The first laboratory measurement of CRP and albumin between 15 and 90 days in the post-operative period was used for inclusion in the postoperative mGPS. We did not use measures within two weeks of the operation because those tend to reflect acute reaction to surgery. The limit of detection of the assay for CRP was 0.2 mg/L. The modified Glasgow Prognostic Score (mGPS) was calculated using the same criteria for both pre- and post-operative mGPS [19, 24]. Patients with post-operative CRP level less than or equal to 10 mg/L were given a score of 0, regardless of serum albumin level. Patients with post-operative CRP level greater than 10 mg/L and post-operative albumin level greater than or equal to 3.5 g/dL were given a score of 1. Patients with post-operative CRP level greater than 10 mg/L and post-operative albumin level less than 3.5 g/dL were given a score of 2.

Outcome Measures

The outcome measures for this study were RFS and CSS after potentially curative nephrectomy. Relapse/metastases were diagnosed radiologically using computerized tomography and magnetic resonance imaging at routine follow-up visits. Mortality was assessed using multiple sources including patient medical records, Social Security Death Index, death certificates and National Death Index. All outcomes were ascertained during 60 months of follow up.

Statistical Analysis

Survival analysis was carried out using the Cox Proportional Hazards (PH) model. All demographic and clinic-pathological variables were categorized. The validity of the proportional hazards assumption was assessed using log-log survival curves and goodness of fit test for each covariate. Unadjusted analyses were performed to identify predictors of RFS and CSS at a two-sided significance level of □ =0.05. The variables identified as significant determinants of the outcome in the unadjusted analyses were included in a multivariate Cox PH model and the final model was derived using a backward selection procedure in which a variable was removed from the model if the p value for that variable was greater than 0.10.

Models were examined for collinearity and interaction. Significance in multivariate analyses was assessed at two-sided □ -error of 0.05. Hazard Ratios (HR) with 95% confidence interval (CI) were obtained for all significant predictors. All analyses were carried out using SAS® 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Demographic and Clinical Characteristics

A total of 509 patients were eligible for inclusion in the study. The mean age of the study population was 59 years. Among all patients 62% were males and 79% were non-Hispanic whites. With respect to tumor stage, 67%, 9% and 24% of patients presented with T1, T2 and T3 disease, respectively (Tables 1 and 2). In terms of Fuhrman nuclear grade criteria, 3% of tumors were grade 1, 47% were grade 2, 43% were grade 3 and 7% were grade 4. At the end of the study period, 17% of the patients had relapse/metastasis and 8% died due to cancer. The distributions of various patient, and disease related characteristics across pre- and post-operative mGPS scores are shown in Tables 1 and 2 respectively. The overall distribution of post-operative mGPS in the study was 84%, 5% and 11% for a score of 0, 1, and 2, respectively. The corresponding percentages for pre-operative mGPS were 85%, 5% and 10% respectively. Figures 1 and 2 present the Kaplan-Meier survival curves for RFS and CSS respectively, categorized by the post-operative mGPS. The RFS curves for patients with scores of 1 and 2 were significantly different from that of patients with score 0 (p-values of 0.012 and 0.003, respectively). While the CSS for patients with a score of 2 was significantly different from those with a score of 0 (p-value <0.001), patients with a score of 1 and 0 had similar CSS (p-value= 0.057).

Analysis of RFS predictors

Crude analyses identified age ($\geq$ 65 vs. $<$65 years), sex, both pre- and post-operative mGPS, stage and grade, and presence of tumor necrosis as significant predictors of RFS at $p<0.05$

(Table 3). After multivariate analyses using backward elimination, only sex, post-operative mGPS , tumor stage and nuclear grade were identified as significant independent predictors of RFS. Patients with post-operative mGPS of 2 had a statistically significant 2.64- fold decrease (95% CI 1.38-5.03) in RFS rate compared to those with post-operative mGPS of 0 after controlling for sex, tumor stage and grade. The difference in RFS rate between patients with post-operative mGPS of 1 and 0 was less pronounced and not statistically significant (HR=1.90; 95% CI; 0.80-4.48). Men had almost 4 times worse RFS compared to women (HR=3.77; 95% CI 2.00-7.12). Relative to patients with T1 RCC, those with T3 tumor stage had a 4-fold decrease in RFS (HR=4.11; 95% CI 2.29-7.37). Grades 3 and 4 were associated with 1.7 and 8-fold higher rates of recurrence, respectively, compared to Grades 1 or 2 (reference category). .

Analysis of CSS predictors

In the unadjusted models, both pre- and post-operative mGPS, tumor stage and grade, and presence of tumor necrosis were all significant predictors of CSS (Table 4). In the multivariable analyses, the variables retained in the final Cox PH model included only post-operative mGPS, tumor stage and grade. Compared to post-operative mGPS of 0 the HRs (95% CIs) for scores and 1 and 2 were 0.68 (0.15-2.99) and 2.38 (1.04-5.46), respectively. Patients with T3 tumor stage had a 4-fold decrease in CSS compared to those with T1. The corresponding HR estimates were 3.59 (95% CI 1.20-10.71) for grade 3 and 14.69 (95% CI 4.25-45.29) for grade 4 relative to grade 1 or 2 disease.

Discussion

Systemic inflammatory response plays a pivotal role in carcinogenesis, cancer progression, and development of metastasis [28-30]. Measures of systemic inflammation can be used in

monitoring response to cancer therapy [28]. Recent studies have shown the association between cachexia and systemic inflammatory response as measured by levels of CRP [31, 32]. Elevated pre-operative level of CRP and incorporation of pre-operative CRP into a prognostic score have been previously shown to predict survival of RCC patients [2, 3, 13, 24, 25, 33]. The post-operative CRP levels have also been linked to RCC prognosis; however, to-date no studies compared the relative utility of pre- and post-operative mGPS. The present analyses were conducted to determine which of the two measures, or perhaps both, serve as independent predictors of RFS and CSS in RCC patients. .

The findings of this study indicate that nephrectomy-treated RCC patients with a higher mGPS score, calculated using post-operative levels of CRP and albumin, are more likely to experience a relapse or die from the disease. Previous studies by Lamb et al and Ramsey et al have reported that patients with a higher pre-operative mGPS have a worse prognosis in RCC [24, 25]. However, these studies did not consider post-operative mGPS as a predictor of survival. In the current study, when both pre- and post- operative mGPS were included in the predictive model only post-operative score remained as an independent predictor along with other disease characteristics such as tumor stage and grade.

Increased serum levels of IL-6, an interleukin with pro-inflammatory, immune-modulatory and growth factor function, are found in RCC patients due to active production of this cytokine by the renal tumor cells [34-37]. IL-6 in turn stimulates the production of CRP from hepatic cells and this acute phase protein synthesis is enhanced in the presence of tumor necrosis factor – alpha and interferon- gamma [38]. It has also been suggested that production of CRP by the renal tumor cells themselves also contributes to the increased serum CRP levels in RCC [18]. In metastatic RCC, the post-operative level of CRP is

expected to remain high following nephrectomy due to the continued secretion of cytokines from the remaining tumor cells. By contrast, in localized RCC, the removal of the tumor is expected to eliminate the source of cytokine production, unless the disease is under-staged. Increased post-operative level of CRP and decreased post-operative albumin level (i.e., higher post-operative mGPS) might indicate the presence of micro- metastases, undetectable clinically or on cross-sectional imaging at the time of nephrectomy. Micro-metastases have been associated with increased risk of relapse and poor outcomes in a number of cancers including breast, colorectal and non-small cell lung cancer [39-42]. Thus, higher post-operative mGPS should be viewed as a reason for concern that warrants increased surveillance for possible relapse.

To our knowledge, the current study is the first to assess post-operative mGPS as an independent predictor of RFS and CSS in RCC patients. Clinically, patients may be divided into two risk categories: those at a high risk of relapse/ disease-specific death (post-operative mGPS=2) and those at a low risk (post-operative mGPS<2). Such risk stratification might help with appropriate counseling for decision-making regarding survival as well as adjuvant therapy. It can help identify potential subjects for immunotherapy and targeted therapy clinical trials. Also, the high risk group may be targeted for the development of novel markers of micro-metastases to better understand and predict poor outcomes.

The potential clinical utility of these results notwithstanding, their interpretation warrants caution due to several limitations. This study included only clear cell RCC, and cannot be extrapolated to other histologic types. Although the present study cohort was relatively large, all patients were recruited from a single center, and the external validity of our findings to RCC cases in other setting and other socio-demographic groups remains unknown. These

observations underscore the need for replication and external validation of the results presented here.

Conclusion

The findings of this study demonstrate that systemic inflammatory response in the post-operative period serves as an independent predictor of survival in patients with localized RCC. Clinicians may consider the inclusion of post-operative mGPS in addition to, or instead of pre-operative mGPS to the routine follow-up of kidney cancer patients. If these results are confirmed, the inclusion of post-operative mGPS in prognostic assessment may assist clinical decisions regarding patient counseling, post-operative surveillance, and initiation of adjuvant therapy.

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Tables and Figures

Table 1: Distribution of demographic and clinic-pathological factors across levels of pre-operative mGPS score

	Pre-operative mGPS score			
	0	**1**	**2**	**Overall**
	N (%)	N (%)	N (%)	N (%)
Age				
< 65 years	287 (87)	14 (4)	29 (9)	330 (65)
≥ 65 years	146 (82)	10 (6)	23 (13)	179 (35)
Males	271 (86)	13 (4)	33 (10)	317 (62)
Non-Hispanic whites	297 (86)	16 (5)	34 (10)	347 (79)
Relapse	58 (69)	5 (6)	21 (25)	84 (16)
Cancer Specific deaths	28 (67)	2 (5)	12 (28)	42 (8)
Tumor size				
< 5 cm^3	95 (90)	5 (5)	6 (6)	106 (21)
≥ 5 cm^3	338 (84)	19 (5)	46 (11)	403 (79)
T classification				
T1	308 (91)	15 (4)	17 (5)	340 (67)
T2	38 (83)	2 (4)	6 (13)	46 (9)
T3	85 (71)	7 (6)	28 (23)	120 (24)
Fuhrman grade				
1 or 2	233 (92)	7 (3)	14 (5)	254 (50)
3	178 (82)	16 (7)	24 (11)	218 (43)
4	21 (58)	1 (3)	14 (39)	36 (7)
Necrosis present	81 (69)	12 (10)	25 (21)	118 (23)

Table 2: Distribution of demographic and clinic-pathological factors across levels of post-operative mGPS score

	Post-operative mGPS score			
	0	**1**	**2**	**Overall**
	N (%)	N (%)	N (%)	N (%)
Age				
< 65 years	277 (84)	19 (6)	34 (10)	330 (65)
≥ 65 years	149 (83)	9 (5)	21 (12)	179 (35)
Males	264 (83)	17(5)	36 (11)	317 (62)
Non-Hispanic Whites	291 (84)	22 (6)	34 (10)	347 (79)
Relapse	64 (76)	6 (7)	14(17)	84 (16)
Cancer Specific deaths	31 (74)	2 (5)	9 (21)	42 (8)
Tumor size				
< 5 cm^3	95 (90)	6 (6)	5 (5)	106 (21)
≥ 5 cm^3	331 (82)	22 (5)	50 (12)	403 (79)
T classification				
T1	290 (85)	18 (5)	32 (10)	340 (67)
T2	33 (72)	4 (9)	9 (19)	46 (9)
T3	100 (83)	6 (5)	14 (12)	120 (24)
Fuhrman grade				
1 or 2	216 (85)	12 (5)	26 (10)	254 (50)
3	183 (84)	14 (6)	21 (10)	218 (43)
4	26 (72)	2 (6)	8 (22)	36 (7)
Necrosis present	94 (80)	11 (9)	13 (11)	118 (23)

Table 3: Unadjusted and multivariate survival analysis assessing predictors of Relapse-Free Survival (RFS) in RCC, (n=509)

	Unadjusted analysis		Multivariate analysis	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age *(≥ 65 vs. <65 years)*	1.61 (1.00-2.58)	0.049		
Sex *(Males vs Females)*	2.63 (1.46-4.73)	0.001	3.77 (2.00-7.12)	<0.001
Race *(White vs Other)*	1.22 (0.60-2.48)	0.582		
Pre-operative mGPS				
0	1 (reference)			
1	2.00 (0.79-5.01)	0.144		
2	4.04 (2.34-6.99)	<0.001		
Post-operative mGPS				
0	1 (reference)		1 (reference)	
1	2.03 (0.87-4.74)	0.101	1.90 (0.80-4.48)	0.143
2	2.53 (1.34-4.77)	0.004	2.64 (1.38-5.03)	0.003
Tumor size *(≥ 5 vs. <5 cm^3)*	1.50 (0.76-2.92)	0.239		
Tumor stage				
T1	1 (reference)		1 (reference)	
T2	2.44 (1.05-5.68)	0.039	1.80 (0.76-4.26)	0.167
T3	6.17 (3.67-10.37)	<0.001	4.11 (2.29-7.37)	<0.001
Fuhrman grade				
1 or 2	1 (reference)		1 (reference)	
3	2.84 (1.53-5.27)	0.001	1.73 (0.90-3.35)	0.025
4	15.27 (7.69-30.32)	<0.001	8.19 (3.74-17.91)	<0.001
Necrosis Present	3.40 (2.12-5.46)	<0.001		

Table 4: Unadjusted and multivariate survival analysis assessing predictors of Cancer Specific Survival (CSS) in RCC, (n=509)

	Unadjusted analysis		Multivariate analysis	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age *(≥ 65 vs. <65 years)*	1.78 (0.96-3.28)	0.066		
Sex *(Males vs Females)*	2.03 (0.99-4.13)	0.052		
Race *(White vs Other)*	0.63 (0.29-1.39)	0.255		
Pre-operative mGPS				
0	1 (reference)			
1	1.38 (0.33-5.81)	0.660		
2	4.40 (2.22-8.75)	<0.001		
Post-operative mGPS				
0	1 (reference)		1 (reference)	
1	1.38 (0.33-5.79)	0.659	0.69 (0.16-2.95)	0.617
2	3.84 (1.80-8.19)	<0.001	2.27 (1.03-5.02)	0.042
Tumor size *(≥ 5 vs. <5 cm^3)*	1.12 (0.50-2.54)	<0.777		
Tumor stage				
T1	1 (reference)		1 (reference)	
T2	4.01 (1.46-11.04)	0.007	2.53 (0.88-7.23)	0.084
T3	8.19 (3.91-17.14)	<0.001	4.05 (1.84-8.95)	<0.001
Fuhrman grade				
1/2	1 (reference)		1 (reference)	
3	5.24 (1.80-15.28)	0.002	3.59 (1.20-10.71)	0.022
4	33.13 (11.05-99.28)	<0.001	14.69 (4.25-45.29)	<0.001
Necrosis *(Present)*	3.51 (1.90-6.49)	<0.001		

Figure Legends

Figure 1: Kaplan Meier curves of relapse-free survival after nephrectomy in patients with localized RCC, categorized by post-operative modified Glasgow Prognostic Score (mGPS)

Figure 2: Kaplan Meier curves of cancer-specific survival after nephrectomy in patients with localized RCC, categorized by post-operative modified Glasgow Prognostic Score (mGPS)

Figure 1

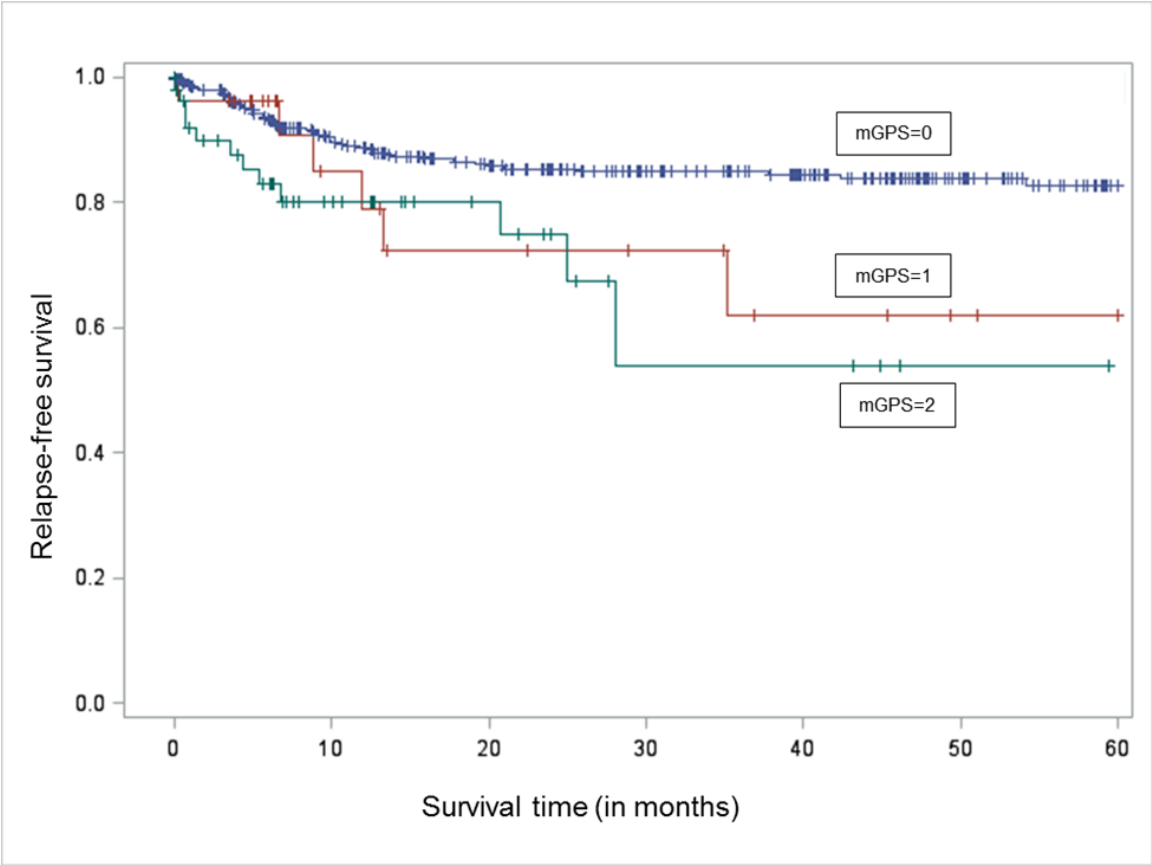
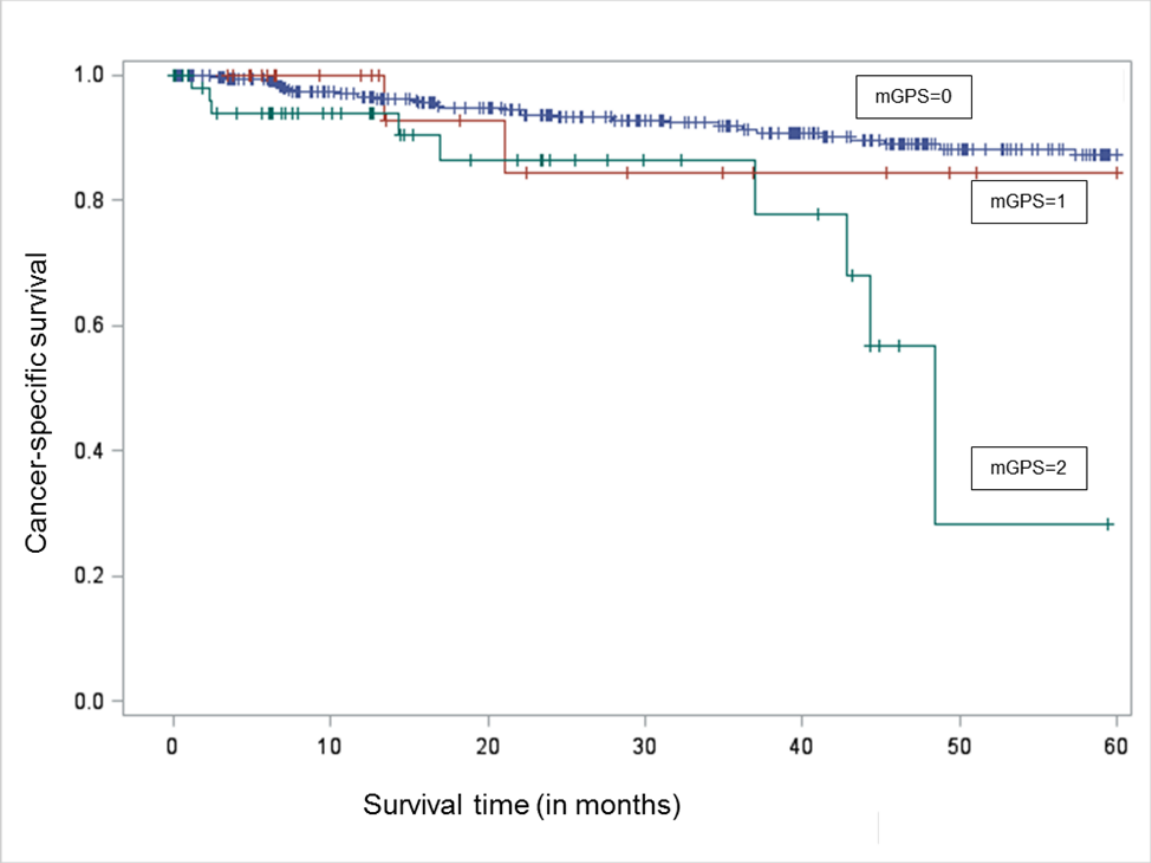

1.0
0.8
0.6
0.4
0.2
0.0
Relapse-free survival
0
10
20
30
40
50
60
Survival time (in months)
mGPS=0
mGPS=1
mGPS=2

Figure 2


1.0
0.8
0.6
0.4
0.2
0.0
Cancer-specific survival
0
10
20
30
40
50
60
Survival time (in months)
mGPS=0
mGPS=1
mGPS=2