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## **Original** Article

# The application of the Glasgow prognostic score to predict the survival in patients with metastatic pancreatic carcinoma

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# ABSTRACT

**Objectives:** Thither is a more pressing effort to think about chemotherapy (CTx) in second-line and beyond in patients with metastatic pancreatic cancer (mPC). The current work aimed to evaluate the value of the Glasgow prognostic score (GPS) and modified Glasgow prognostic score (mGPS) to predict the survival in patients receiving second-line CTx protocol.

**Material and Methods:** We retrospectively reviewed the patients' medical files with mPC who received second-line CTx protocol between September 2013 and December 2017. The GPS/mGPS graded from 0 to 2 based on C-reactive protein and serum albumin.

**Results:** One hundred and sixty-nine patients with mPC were eligible. Survival of patients with Score 0 (GPS/mGPS) was better than that of Score 1 (GPS/mGPS) or Score 2 (GPS/mGPS), which was statistically significant (P < 0.001). Of 78 patients who died, only 16 patients belonged to Score 0 (GPS/mGPS), compared to 30 patients belonged to Score 1 (GPS/mGPS) and 32 patients belonged to Score 2 (GPS/mGPS). Univariate analysis showed that high GPS/mGPS (P < 0.000) as well as poor Eastern Cooperative Oncology Group Performance Status (P < 0.000) and metastasis either to the liver (P < 0.01) or lung (P < 0.04) were linked with worse prognosis. A statistically significant association was detected between the two scores. Cohen's Kappa coefficient ( $\kappa$ ) was 0.9, SD = 0.03; 95% CI (0.787–0.922; P < 0.001).

**Conclusion:** Our data suggested that GPS/mGPS is an easy and applicable index that may be used in daily practice and may help in the prognostic stratification of mPC patients to avert overtreatment in frail patients and raise the best supportive treatment concept.

Keywords: Metastatic pancreatic cancer, Glasgow prognostic score, Modified Glasgow prognostic score

# INTRODUCTION

In the year 2018, a projected 55.440 cases will be diagnosed and about 43,330 deaths from pancreatic cancer (PC) in the United States. By 2030, PC is expected to be the second cause of cancer-related death after lung cancer. More than 80% of patients presenting beyond the curative surgery at the time of diagnosis, this may be linked to non-specific clinical manifestations. A stage for stage, PC is linked with the lowest survival and poor outcome of most cancer subtypes. In the metastatic setting, the 5-year survival is approximately 3%.<sup>[1,2]</sup> Historically, more than 50% of patients were not appropriate for the second-line chemotherapy (CTx) protocol after disease progression. Therefore, it is critical to define the patients who may take maximum benefit from CTx and avoid unneeded treatment in frail patients.

Glasgow prognostic score (GPS) defined by combining serum albumin level and C-reactive protein (CRP), is an inflammatory, simple and applicable score that may reflect a host inflammatory response and has been described to have a prognostic implication in various types of cancer<sup>[3-5]</sup> such as non-small cell lung,<sup>[6]</sup> liver cancer,<sup>[7]</sup> oesophageal cancer<sup>[8]</sup> and colorectal cancer.<sup>[9]</sup> However, there are conflicting data regarding the value of isolated hypoalbuminaemia on survival; therefore, modified Glasgow prognostic score (mGPS) had been initiated.<sup>[10,11]</sup>

Despite many studies referring to the relation between GPS/ mGPS and prognosis of PC,<sup>[12]</sup> their roles in metastasis

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settings receiving second-line CTx protocol had not been fully assessed.

Despite, the progress in palliative care management, still, CTx applied to a subset of patients without survival benefit or improvement in the quality of life.<sup>[13]</sup> Accurate estimation of survival helps to avoid inappropriate treatment and to prevent unneeded toxicity.

Hence, the present work aimed to assess the predictive value of GPS/mGPS in mPC receiving second-line CTx protocol. We supposed that GPS/mGPS may be useful for physicians in predicting the survival of patients with mPC receiving second-line CTx protocol.

# MATERIAL AND METHODS

A retrospective study included 169 eligible patients with mPC who were diagnosed and treated in the Medical Oncology Department, Faculty of Medicine, Zagazig University, Egypt, from September 2013 to December 2017. The inclusion criteria were aged  $\geq 18$  years old, pathologically confirmed ductal PC, radiological and/or pathological evidence of metastasis, progressed after first-line CTx protocol and measurable disease.

All required laboratory investigations of CRP, serum albumin level and CA19.9 were reviewed from the patients' medical files before delivering the planned CTx protocol. The score of GPS/mGPS ranged from 0 to 2.<sup>[14]</sup> [Table 1] illustrates the scoring and description. The correlation of GPS/mGPS with clinicopathologic features was evaluated. The minimum follow-up period was 3 months or till death.

## Statistical analysis

Continuous variables were shown as the mean  $\pm$  SD and median (range) and the categorical variables were shown as a figure (percentage). Percentage of categorical variables was compared using Pearson's Chi-square test or Fisher's exact test when appropriate. Overall survival (OS) was calculated as the time interval from GPS/mGPS assessment until the last follow-up or death. These time-to-event distributions were calculated using

Table 1: Glasgow and items.	modified Glasgow prognostic scoring and
Score	Criteria
*GPS	
GPS 2	Increased CRP <sup>‡</sup> and hypoalbuminaemia <sup>d</sup>
GPS 1	Increased CRP or hypoalbuminaemia
GPS 0	Normal both albumin level and CRP
<sup>†</sup> mGPS	
mGPS 2	Increased CRP and hypoalbuminaemia
mGPS 1	Increased CRP
mGPS 0	Normal CRP

\*GPS: Glasgow prognostic scoring, <sup>†</sup>mGPS: modified Glasgow prognostic scoring, <sup>‡</sup>Increased CRP, C-reactive protein >10 mg/l, <sup>d</sup>hypoalbuminaemia, serum albumin <3.5 g/l the method of the Kaplan-Meier plot and compared using a two-sided exact log-rank test. Univariate Cox regression was applied to calculate hazard ratios and their corresponding Wald 95% confidence interval (CI). Inter-ratter agreement between GPS and mGPS was analysed using McNemar and Kappa (K) statistics. The agreement was obtained if the McNemar was not significant and the Kappa statistic was significant, the criteria to qualify for the strength of the agreement were as follows: K < 0.2: Poor; K 0.21-0.40: Fair; K 0.41-0.60: Moderate; K 0.61-0.80: Good and K 0.81-1.00: Very good. The strength of relationship between GPS and mGPS was determined by computing the Kendall tau correlation coefficient, (+) sign was an indicator for a direct relationship and the (-) sign was an indicator for an inverse relationship, also values near 1 were an indicator for strong relationship and values near 0 were an indicator for weak relationship. All tests were two-sided. P < 0.05 was considered statistically significant. All statistics were performed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) and MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium).

# RESULTS

## Characteristics of the patients in GPS group

One hundred and sixty-nine patients with mPC were eligible and included in the final analysis with 60.9% was male and 64.5% were ≥60 years old. The Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 0, I and II in 38.5%, 20% and 32.5% of the cases, respectively. The bulk of patients had histologically Grades II and III (58% and 25.4%, respectively). The upper limit of normal was 37 U/mL for CA19.9 and the median was 697 U/mL (range, 19-7896 U/mL). The pre-treatment evaluation revealed that GPS-0, GPS-1 and GPS-2 were 67 (39.6%), 55 (32.5%) and 47 (27.8%) compared with 83 (49.1%), 39 (23.1%) and 47 (27.8%) of mGPS- 0, GPS-1 and GPS-2, respectively. Gemcitabine, FOLFOX (oxaliplatin and 5-FU), capecitabine and FOLFIRI (irinotecan and 5-FU) were the most commonly used second-line CTx protocol (38.5%, 32%, 18.9% and 10.7%, respectively) [Table 2]. The median follow-up period was 74 days (ranging from 19 to 132) and the mean  $\pm$  SD was 71.7  $\pm$  28.6.

## GPS, clinicopathologic features and survival outcome

There was a statistically significant correlation included ECOG PS (P < 0.001), liver metastasis (P < 0.001), lung metastasis (P < 0.001) and peritoneal metastasis (P = 0.07) (trend to be significant). Of 78 patients who died, only 16 patients (23.9%) belonged to the GPS-0, compared to 30 patients (54.5%) belonged to GPS-1 and 32 patients (68.1%) belonged to the GPS-2. The distribution of GPS and clinicopathologic features is illustrated in [Table 2].

The median survival time was 37 days (range: 34–39) for GPS 2 and 74 days (range: 67–80) for GPS 1, while NR in GPS 0 [P < 0.001; Figure 1].

	*GPS-0 ( <i>n</i> =67)	GPS-1 ( <i>n</i> =55)	GPS-2 ( <i>n</i> =47)	P-value
Age				
<60 years	28 (46.7%)	17 (28.3%)	15 (20%)	0.4
≥60 years	39 (35.8%)	38 (34.9%)	32 (29.4%)	
Sex				
Male	44 (42.7%)	32 (31.1%)	27 (26.2%)	0.6
Female	23 (34.8%)	23 (34.8%)	20 (30.3%)	
ECOG PS				
0	54 (83.1%)	11 (16.9%)	0 (0.0%)	< 0.001
1	12 (24.5%)	35 (71.4%)	2 (4.1%)	
2	1 (1.8%)	9 (16.4%)	45 (81.8%)	
Grade				
I	17 (60.7%)	7 (25%)	4 (14.3%)	0.1
II	37 (37.8%)	32 (32.7%)	29 (29.6%)	
III	13 (30.2%)	16 (37.2%)	14 (32.6%)	
CA19.9			()	
Normal	9 (30%)	13 (43.3%)	8 (26.7%)	0.3
Elevated	58 (41.7%)	42 (30.2%)	39 (28.1%)	
Liver metastasis				
No	41 (65.1%)	12 (19%)	10 (15.9%)	< 0.001
Yes	26 (24.5%)	43 (40.6%)	37 (34.9%)	
Lung metastasis				
No	54 (44.6%)	45 (37.2%)	22 (18.2%)	< 0.001
Yes	13 (27.1%)	10 (20.8%)	25 (52.1%)	101001
Peritoneal metastasis				
No	27 (31.4%)	33 (38.4%)	26 (30.2%)	0.07
Yes	40 (84.2%)	22 (26.5%)	21 (25.3%)	0107
Bone metastasis		22 (2010 /0)	21 (2010 /0)	
No	62 (40%)	50 (32.3)	43 (27.7)	0.5
Yes	5 (35.7%)	5 (35.7%)	4 (28.6%)	0.0
Treatment protocol	0 (000 /0)		1 (2010/0)	
Gemcitabine	25 (38.5%)	20 (30.8%)	20 (30.8%)	0.9
Capecitabine	14 (43.8)	10 (31.2%)	8 (25%)	017
<sup>§</sup> FOLFOX	21 (38.9%)	20 (37%)	13 (24.1%)	
FOLFIRI	7 (38.9%)	5 (27.8%)	6 (33.3%)	
Mortality	, (00.970)	2 (27.070)	0 (00.070)	
Alive	51 (76.1%)	25 (45.5%)	15 (31.9%)	< 0.001
Died	16 (23.9%)	30 (54.5%)	32 (68.1%)	<0.001

<sup>s</sup>FOLFOX: Oxaliplatin, leucovorin, 5-FU, <sup>II</sup>FOLFIRI: Irinotecan, leucovorin, 5-FU. *P*<0.05 was considered statistically significant

#### mGPS, clinicopathologic features and survival outcome

The relation between mGPS and clinicopathologic characteristics is illustrated in [Table 3]. Similarly, a statistically significant correlation was identified with ECOG PS (P < 0.001), liver metastasis (P < 0.001), lung metastasis (P < 0.001) and and peritoneal metastasis (P = 0.06) (trend to be significant) considering the mortality numbers, it was equal between GPS and mGPS.

The median survival time was 37 days (range: 34–39) for mGPS-2 and 66 days (range: 62–69) for mGPS-1, while NR in mGPS-0 [P < 0.001; Figure 2].

Regarding the type of second-line CTx, there was a statistically insignificant correlation with GPS/mGPS (P = 6 and 0.9, respectively).

#### At univariate analysis

GPS (score 0 vs. 1–2) {95% CI, 3.6–13.0; P < 0.000}; mGPS (score 0 vs. 1–2) {95% CI, 20.8–1175.0; P < 0.000}; ECOG PS (PS 0 vs. 1–2) {95% CI, 12.9–107.6; P < 0.000}; liver metastasis (no vs. yes) {95% CI, 1.1–2.9; P < 0.01} and lung metastasis (no vs. yes) {95% CI, 1.01–2.7; P < 0.04} showed a statistically significant association with the OS. Other clinicopathological

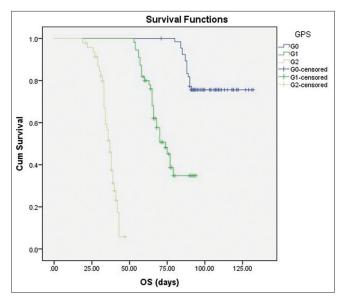


Figure 1: The patients' survival according to GPS 0, 1 and 2. (P < 0.001).

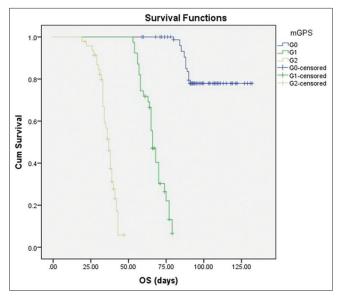


Figure 2: The patients' survival according to mGPS 0, 1 and 2. (P<0.001).

characteristics included the type of CTx protocol showed no significant association with the OS.

#### The relationship between GPS and mGPS

A statistically significant association was detected between two scores (P < 0.001). Cohen's kappa coefficient ( $\kappa$ ) was 0.9, SD = 0.03; 95% CI (0.787–0.922; P < 0.001).

### DISCUSSION

At present, systemic treatment for mPC is defined mainly by patients' performance status and disease stage. Nevertheless, surgery is the primary curative treatment in the localised stage, only when the metastasis and/or advanced disease are confirmed, the treatment aimed to palliate. Despite the advancement in diagnostic methods and novel therapeutic approaches, the mortality and morbidity rate of mPC is still eminent. Therefore, it is valuable to research to define new indicators that help in predicting survival outcome for patients with mPC.

Consequently, many inflammatory scores had been suggested for pointing to the survival outcome in various malignant tumours in routine clinical usage.<sup>[15]</sup> GPS, mGPS, CRP, systematic inflammatory index, platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio are examples of valid inflammatory scores.<sup>[16-18]</sup>

The role of GPS/GPS which contains both albumin and CRP reflects both nutritional status and systemic inflammatory response.<sup>[19-21]</sup>

In the present study, a high GPS/mGPS was statistically significantly associated with poor survival outcomes in patients receiving second-line CTx protocol. Survival of patients with Score 0 was better than that of Score 1 and/ or 2 (P < 0.001). Of 78 patients who died, only 16 patients belonged to Score 0 (GPS/mGPS), compared to 30 patients who belonged to Score 1 (GPS/mGPS) and 32 patients belonged to Score 2 (GPS/mGPS). Those results were in agreement with other previous data.

A retrospective study that included 807 patients with PC indicated that the OS was statistically significantly better for the mGPS-0 compared with the mGPS-1 (15.9 vs. 5.8 months, respectively), the authors concluded that the mGPS is an independent predictive factor, particularly for advanced/metastatic setting.<sup>[10]</sup>

Similarly, Chen *et al.* presented an abstract in ESMO 2018 about the predictive value of mGPS in patients with mPC treated with liposomal irinotecan with fluorouracil and leucovorin (NAPOLI-1 study). *Post hoc* analysis was matched with the data of the prognostic role of mGPS in survival estimation. Furthermore, the median OS was statistically significantly improved in patients with mGPS-0 compared with patients with mGPS-2 and/or mGPS-1.<sup>[22]</sup>

The same results were obtained by Glen *et al.* when evaluated GPS on 187 patients with inoperable PC.<sup>[23]</sup> Moreover, Shimoda *et al.* analysed the survival rate of 83 patients with advanced/mPC treated in the second Department of Surgery, Dokkyo Medical University, Mibu, Japan, by CTx either single or combined. They observed that ECOG PS, CA19.9 and GPS were independent prognostic factors.<sup>[24]</sup>

A comparable study by Sinn *et al.*<sup>[25]</sup> on 208 patients with advanced PC who received second-line CTx protocol reported that serum CA19.9 and PS were associated with OS. These results are similar to what was shown in our study. The same results reported by Kasuga *et al.*<sup>[26]</sup> on 61 patients with advanced PC and gemcitabine refractory in second-line CTx protocol.

The prognostic value of CA19.9 and PS has been confirmed in previous meta-analysis and systemic review in the same setting.<sup>[27,28]</sup> However, the prognostic value of CA19.9 was

	*mGPS-0 ( <i>n</i> =83)	mGPS-1 ( <i>n</i> =39)	mGPS-2 ( <i>n</i> =47)	P value
Age				
<60 years	33 (55%)	12 (20%)	15 (25%)	0.5
≥60 years	50 (45.9%)	27 (24.8%)	32 (29.4%)	
Sex				
Male	55 (53.4%)	21 (20.4%)	27 (26.2%)	0.4
Female	28 (42.8%)	18 (27.3)	20 (30.3%)	
<sup>†</sup> ECOG PS				
0	46 (98.5%)	1 (1.5%)	0 (0.0%)	< 0.001
1	16 (32.7%)	31 (63.3%)	2 (4.1%)	
2	3 (5.5%)	7 (12.7%)	45 (81.8%)	
Grade				
Ι	19 (67.9%)	5 (17.9%)	4 (14.3%)	0.3
II	46 (46.9%)	23 (23.5%)	29 (29.6%)	
III	18 (41.9%)	11 (25.6%)	14 (32.6%)	
*CA19.9		· · · · ·	× ,	
Normal	14 (46.7%)	8 (26.7%)	8 (26.7%)	0.9
Elevated	69 (49.6%)	31 (22.3%)	39 (28.1%)	
Liver metastasis				
No	45 (71.4%)	8 (12.7%)	10 (15.9%)	< 0.001
Yes	38 (35.8%)	31 (29.2%)	37 (34.9%)	
Lung metastasis				
No	66 (54.5%)	33 (27.3%)	22 (18.2%)	< 0.001
Yes	17 (35.4%)	6 (12.5%)	25 (52.1%)	
Peritoneal metastasis				
No	38 (44.2%)	22 (25.6%)	26 (30.2%)	0.06
Yes	45 (54.2%)	17 (20.5%)	21 (25.3%)	
Bone metastasis				
No	75 (48.4%)	34 (23.9%)	43 (27.7%)	0.7
Yes	8 (57.1%)	2 (14.3%)	4 (28.6%)	
Treatment protocol				
Gemcitabine	31 (47.7%)	14 (21.5%)	20 (30.8%)	0.6
Capecitabine	15 (46.9%)	9 (28.1%)	8 (20.5%)	
<sup>§</sup> FOLFOX	26 (48.1%)	15 (27.8%)	13 (24.1%)	
FOLFIRI	83 (49.1%)	39 (23.1%)	47 (27.8%)	
Mortality	. /	· /	· /	
Alive	67 (80.7%)	9 (23.1%)	15 (31.9%)	< 0.001
Died	16 (19.3%)	30 (76.9%)	32 (68.1%)	

<sup>s</sup>FOLFOX: Oxaliplatin, leucovorin, 5-FU, <sup>II</sup>FOLFIRI: Irinotecan, leucovorin, 5-FU. *P*<0.05 was considered statistically significant

not confirmed in our study (P = 0.3). The controversy in the results may be related to differences in sample size, lifestyle, diet, or genetics.

Growing evidence demonstrated the link between tumour microenvironments and the inflammatory response. The released cytokines influence tumour behavior, including tumour growth, angiogenesis and even therapeutic resistance.<sup>[29]</sup> The molecular basis implying the link between GPS/mGPS and poor mPC outcome is still vague. A possible explanation is that the nutritional and immune status of the patients was represented by these scores. CRP and serum albumin (a component of GPS/mGPS) are acute-phase proteins produced by hepatocytes.<sup>[30]</sup>

CRP level is controlled by several cytokines such as transforming growth factor-B, tumour necrosis factor (NF), interleukin (IL)-1 and IL-2. Data showed the association between IL-1 and IL2 levels and survival outcome in PC. In addition, CRP is associated with tumour-infiltrating lymphocytes.<sup>[31,32]</sup>

Furthermore, many studies had demonstrated that CRP is an independent prognostic factor in different malignant tumours.<sup>[33-35]</sup>

Thus, the investigators proposed that inhibition of IL-1 may induce tumour growth arrest by antagonising IL-1-induced NF- $\kappa$ B activity.<sup>[36,37]</sup>

The serum albumin level is used as a surrogate marker of nutritional status and liver function. Hypoalbuminaemia

is associated with poor survival outcomes in many types of cancers including PC.<sup>[8,38-42]</sup>

According to the guidelines for the management of mPC, the use of second-line CTx is highly recommended after failure of first-line CTx. However, the value of palliative CTx in those subgroups of patients keeps controversial and the determination of therapy remains a matter of argument.<sup>[43,44]</sup> When we decided palliative CTx, quality of life and therapy-related toxicity are of great importance. In this setting, the prognostic factors may aid the physician in choosing the proper protocol for proper patients.

## CONCLUSION

GPS/mGPS is an easy and applicable index that may be used in daily practice and may help in the prognostic stratification of mPC patients to avoid overtreatment in frail patients regardless of the type of second-line CTx protocol.

#### Declaration of patient consent

Patients' consent not required as patients' identity is not disclosed or compromised.

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Nil.

#### **Conflicts of interest**

There are no conflicts of interest.

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