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SHORT REPORT

Prognostic factors in patients with metastatic or recurrent pancreatic cancer treated with first-line *nab*-paclitaxel plus gemcitabine: implication of inflammation-based scores

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Summary

Background *Nab*-paclitaxel plus gemcitabine (AG) is standard first-line chemotherapy for patients with metastatic pancreatic cancer (mPC). However, prognostic factors for patients with mPC treated with AG, are largely unknown. We retrospectively identified prognostic factors, including inflammation-based prognostic scores, in patients with mPC, and recurrent pancreatic cancer treated with AG as first-line treatment. *Method* A total of 203 patients with histologically-confirmed recurrent or metastatic pancreatic cancer who were treated with first-line AG in Asan Medical Center, Seoul, Korea, between February 2016 and December 2016 were included in this analysis. As inflammation-based scores, baseline neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and modified Glasgow prognostic scores (mGPS) were tested. *Result* Median age was 62 years and 116 patients (57%) were male. With median follow-up duration of 21.5 months, median progression-free survival (PFS) was 7.1 (95% CI 6.2–7.9) months, and overall survival (OS) was 15.1 (95% CI 12.6–17.6) months. In the multivariate analysis, PFS was significantly associated with liver metastasis (HR 1.43), distant lymph node metastasis (HR 1.48), and elevated CA19–9 (HR 1.56). In multivariate analysis for OS, elevated CA19–9 (HR 1.75), liver metastasis (HR 1.76), distant lymph node metastasis (HR 1.41), and high mGPS (mGPS ≥1 vs.0: HR 1.64) were independent prognostic factors. NLR and PLR were not significantly associated with PFS and OS. *Conclusion* Among the inflammation based prognostic scores, mGPS was a reliable prognostic indicator that could stratify survival outcomes in patients with recurrent or mPC who received AG as first-line chemotherapy.

Keywords Pancreatic cancer · Chemotherapy · *nab*-paclitaxel · Gemcitabine · Prognostic factor · Neutrophil-lymphocyte ratio · Platelet-lymphocyte ratio · Glasgow prognostic scores

Introduction

Pancreatic cancer remains a fatal disease, with a global 5-year survival rate less than 10% [1], and the fifth leading cause of cancer-related mortalities in Korea [2]. Although surgery is the only curative treatment for localized disease, less than 20% of patients are fit for resection at the time of diagnosis.

For patients with unresectable or metastatic pancreatic cancer, systemic chemotherapy is the mainstay treatment. *Nab*-paclitaxel plus gemcitabine (AG) is one of standard first-line systemic chemotherapy regimens for patients with mPC based on the significantly improved efficacy outcomes compared to gemcitabine monotherapy in the MPACT trial [3–5].

Prognostic factors of patients with mPC have been investigated, but most previous studies were based on a heterogeneous patient population, or patients treated with

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old chemotherapies [6, 7]. Although a recent post-hoc analysis of the MPACT trial showed that performance status, the presence of liver metastases, age, number of metastatic sites, and number of chemotherapy cycles might be prognostic factors for patients with mPC treated with AG [8], further studies are needed to define novel prognostic factors for these patients.

Inflammation-based prognostic scores such as neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and the modified Glasgow prognostic score (mGPS) have been evaluated as prognostic factors for several types of cancers [9–11]. It is therefore worthy to identify the potential implications of inflammation-based prognostic markers in patients with mPC treated with AG.

Here, we retrospectively performed a prognostic factor analysis in patients with recurrent or metastatic pancreatic cancer who received first-line AG to evaluate the prognostic relevance of NLR, PLR and mGPS.

Methods

Patients

A total of consecutive 203 patients with histologically-confirmed recurrent or initially metastatic pancreatic cancer received first-line AG in Asan Medical Center, Seoul, Korea, between February 2016 and December 2016, and were included in this analysis. Patients with locally advanced pancreatic cancer were excluded in this study. The following data were collected from their electronic medical records: age, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS), disease status at presentation, number of metastatic sites, sites of metastases, baseline carbohydrate antigen 19–9 (CA19–9), primary pancreatic tumor location, number of chemotherapy cycles, neutrophil counts, lymphocyte counts, platelet counts, serum albumin levels, and serum C-reactive protein (CRP) levels. This study was approved by the Institutional Review Board of Asan Medical Center.

Inflammation-based prognostic scores

In this study, NLR, PLR, and mGPS were evaluated as inflammation-based prognostic scores. NLR and PLR were defined as the absolute count of neutrophil and platelets divided by the absolute count of lymphocytes, respectively. For NLR and PLR, patients were classified by median values. For mGPS, patients were graded based on the presence or absence of elevated CRP (>10 mg/L) and hypoalbuminemia (<3.5 g/L) levels. A mGPS score of 0 indicated that none of these factors were present, mGPS 1 indicated elevated CRP, and mGPS 2 indicated that both factors were present [12].

Table 1 Baseline patient characteristics

Variable	No. (%) ($N = 203$)
Age	
Median years (range), y	62 (36–82)
≤ 65 y	126 (62.1%)
>65 y	77 (37.9%)
Sex	
Male	116 (57.1%)
Disease status at presentation	
Initially metastatic	148 (72.9%)
Recurrent	55 (27.1%)
ECOG	
0 or 1	195 (96.1%)
≥2	8 (3.9%)
Number of metastatic sites	
0 or 1	122 (60.1%)
≥2	81 (39.9%)
Site(s) of metastases	
Liver	113 (55.7%)
Peritoneum	70 (34.5%)
Lung	38 (18.7%)
Bone	9 (4.4%)
Lymph node	73 (36.0%)
mGPS	
0	137 (67.5%)
1	19 (9.3%)
2	47 (23.2%)
Neutrophil to lymphocyte ratio	
Median	2.3
<Median	106 (52.2%)
≥Median	97 (47.8%)
Platelet to lymphocyte ratio	
Median	142.3
<Median	97 (47.8%)
≥Median	106 (52.2%)
CA 19–9 level	
Median	280.0 U/mL
≤ WNL (0–37 U/mL)	55 (27.1%)
> UNL (>37 U/mL)	148 (72.9%)
Pancreatic primary tumor location	
Head	83 (40.9%)
Body	36 (17.7%)
Tail	51 (25.1%)
Multi-centric	33 (16.3%)

ECOG Eastern Cooperative Oncology Group score, *mGPS* modified Glasgow Prognostic Score, *UNL* upper normal limit, *WNL* Within normal limit, *CA19–9* carbohydrate antigen 19–9

Treatment and response assessments

All patients were treated with AG, which is a 30-min intravenous infusion of nab-paclitaxel at a dose of 125 mg/m^2 followed by gemcitabine at a dose of 1000 mg/m^2 on days 1, 8, and 15, every 4 weeks, as described in the MPACT trial [3]. Tumor-response was evaluated every 8 weeks using computed tomography and graded according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Statistical analyses

Overall survival (OS) was defined as the time from the initiation of chemotherapy until the date of death from any cause. Progression-free survival (PFS) was defined as the time from the initiation of chemotherapy until the date of disease progression, or death from any cause, whichever occurred first. Survival curves were estimated by the Kaplan-Meier method. Univariate and multivariate analyses using the Cox proportional hazard regression model were performed to find prognostic factors. In the multivariate analysis, variables showing potential association in the univariate analysis ($p < 0.1$) as well as universal factors such as age and gender were included. A two-sided $p < 0.05$ was regarded as statistically significant. All statistical analyses were performed using SPSS version 23.0 (IBM Corp, Armonk, NY, USA).

Results

Baseline characteristics

The baseline characteristics of patients are summarized in Table 1. The median age was 62 years (range, 36–82), and 116 patients (57.1%) were male. Most patients (96.1%) had ECOG PS ≤ 1 and 148 patients (72.9%) had metastatic disease at the time of diagnosis. The most common metastatic site was the liver ($n = 113$; 55.7%), followed by lymph nodes ($n = 73$; 36.0%), and peritoneum ($n = 70$; 34.5%). Baseline CA 19–9 levels were elevated in ($n = 148$; 72.9%) patients.

Efficacy outcomes with AG

Complete response was achieved in 3 (1.5%), and partial response was achieved in 57 (28.1%) patients, indicating an overall response rate (ORR) of 29.6%. With the median follow-up duration of 21.5 months [95% confidence interval (CI), 19.2–23.8] in surviving patients, the median PFS was 7.1 months [95% CI, 6.2–7.9] and median OS was 15.1 months [95% CI, 12.6–17.6].

Inflammation-based prognostic scores

The median values of NLR and PLR were 2.3 and 142.3, respectively. Sixty-six patients (32.5%) had mGPS ≥1

Table 2 Clinicopathologic features for inflammation-based prognostic scores

	mGPS			NLR			PLR		
	0 ($n = 137$)	≥1 ($n = 66$)	*P* value	<2.3 ($n = 102$)	≥2.3 ($n = 101$)	*P* value	<142.3 ($n = 102$)	≥142.3 ($n = 101$)	*P* value
Age			0.99			0.34			0.21
≤65	85 (62.1%)	41 (62.1%)		60 (58.8%)	66 (65.3%)		59 (57.8%)	67 (66.3%)	
>65	52 (37.9%)	25 (37.9%)		42 (41.2%)	35 (34.7%)		43 (42.2%)	34 (33.7%)	
Sex			0.02			0.35			0.94
Male	71 (51.9%)	45 (68.2%)		47 (46.1%)	40 (39.6%)		44 (43.1%)	43 (42.6%)	
Female	66 (48.1%)	21 (31.8%)		55 (53.9%)	61 (60.4%)		58 (56.9%)	58 (57.4%)	
Disease status at AG			0.003			0.003			0.17
Recurrent	91 (66.5%)	57 (86.4%)		37 (36.2%)	18 (17.9%)		32 (31.3%)	23 (22.8%)	
Initially metastatic	46 (33.5%)	9 (13.6%)		65 (63.8%)	83 (82.1%)		70 (68.7%)	78 (77.2%)	
ECOG PS			0.02			0.50			0.17
0 or 1	135 (98.5%)	60 (90.9%)		99 (97.1%)	96 (95.0%)		100 (98.0%)	95 (94.1%)	
≥2	2 (1.5%)	6 (9.1%)		3 (2.9%)	5 (5.0%)		2 (2.0%)	6 (5.9%)	
Number of metastatic sites			0.02			0.10			0.93
0 or 1	90 (65.6%)	32 (48.4%)		67 (65.7%)	55 (54.5%)		61 (59.8%)	61 (60.4%)	
≥2	47 (34.4%)	34 (51.6%)		35 (34.3%)	46 (45.5%)		41 (40.2%)	40 (39.6%)	
Primary pancreatic tumor site			0.04			0.94			0.83
Body/tail/multicentric	62 (45.2%)	40 (60.6%)		51 (50.0%)	51 (50.5%)		52 (50.9%)	50 (49.5%)	
Head	75 (54.8%)	26 (39.4%)		51 (50.0%)	50 (49.5%)		50 (49.1%)	51 (50.5%)	
Baseline CA 19–9			0.77			0.17			0.91
Normal	38 (27.7%)	17 (25.8%)		32 (31.4%)	23 (22.8%)		28 (27.5%)	27 (26.7%)	
Elevated	99 (72.3%)	49 (74.2%)		70 (68.6%)	78 (77.2%)		74 (72.5%)	74 (73.3%)	

mGPS modified Glasgow prognostic score, *NLR* neutrophil-lymphocyte ratio, *PLR* platelet-lymphocyte ratio, *ECOG PS* Eastern Cooperative Oncology Group performance status

Table 3 Univariate and multivariate analysis for Overall survival (OS) and Progression-free survival (PFS)

Variables	OS			PFS		
	Median, months (95% CI)	HR (95% CI)	*P* value	Median, months (95% CI)	HR (95% CI)	*P* value
Univariate analysis						
Age						
≤65	15.1 (12.3–17.9)	Reference		7.4 (6.2–8.6)	Reference	
>65	15.5 (11.1–19.8)	0.83 (0.59–1.16)	0.28	6.9 (5.7–8.1)	0.90 (0.65–1.24)	0.52
Sex						
Male	15.5 (12.6–18.4)	Reference		7.3 (6.5–8.1)	Reference	
Female	14.2 (10.8–17.6)	1.15 (0.83–1.60)	0.42	6.4 (4.6–8.2)	1.12 (0.82–1.52)	0.49
Disease status at presentation						
Recurrent	18.0 (16.5–19.5)	Reference		7.9 (5.9–9.9)	Reference	
Initially metastatic	12.9 (11.2–14.6)	1.54 (1.04–2.28)	0.03	6.7 (5.7–7.7)	1.36 (0.96–1.93)	0.08
ECOG PS						
0 or 1	15.1 (12.9–17.4)	Reference		7.2 (6.2–8.2)	Reference	
≥2	7.6 (3.6–11.6)	1.63 (0.78–3.34)	0.18	2.7 (1.3–4.1)	2.20 (1.07–4.49)	0.03
Presence of liver metastases						
No	17.4 (13.7–21.1)	Reference		9.1 (6.5–9.7)	Reference	
Yes	12.4 (8.5–16.3)	1.86 (1.33–2.61)	<0.001	6.3 (5.4–7.3)	1.60 (1.17–2.20)	0.003
Presence of distant LN metastases						
No	17.1 (14.9–19.4)	Reference		7.6 (6.4–8.9)	Reference	
Yes	12.4 (9.6–15.2)	1.32 (0.95–1.85)	0.10	6.3 (5.6>–7.0)	1.35 (0.97–1.85)	0.07
Elevated CA 19-9 level						
Normal	19.3 (12.4–26.2)	Reference		7.6 (6.4–8.9)	Reference	
Elevated	13.4 (10.9–15.9)	1.98 (1.32–2.96)	0.001	6.3 (5.6–7.0)	1.72 (1.19–2.47)	0.004
mGPS						
0	17.4 (15.3–19.5)	Reference		7.9 (6.9–8.9)	Reference	
≥1	10.3 (8.9–11.7)	1.60 (1.14–2.24)	0.007	5.9 (5.3–6.6)	1.37 (0.98-1.90)	0.06
NLR						
<median (2.3)	16.8 (14.6–18.9)	Reference		7.6 (6.1-9.2)	Reference	
≥median (2.3)	12.9 (10.4–15.4)	1.31 (0.94–1.82)	0.11	6.5 (5.4-7.6)	1.07 (0.79-1.46)	0.65
PLR						
<median (142.3)	16.0 (12.7-19.3)	Reference		8.0 (7.0–9.0)	Reference	
≥median (142.3)	14.0 (11.4-16.6)	1.13 (0.81-1.57)	0.47	6.1 (5.0–7.2)	1.26 (0.93–1.72)	0.13
Multivariate analysis						
ECOG PS						
0 or 1				7.2 (6.2-8.2)	Reference	
≥2				2.7 (1.3-4.1)	2.09 (1.01-4.36)	0.05
Presence of liver metastasis						
No	17.4 (13.7–21.1)	Reference		9.1 (6.5–9.7)	Reference	
Yes	12.4 (8.5–16.3)	1.76(1.25–2.49)	0.001	6.3 (5.4–7.3)	1.43 (1.03–1.98)	0.03
Presence of distant LN metastasis						
No	17.1 (14.9–19.4)	Reference		7.6 (6.4–8.9)	Reference	
Yes	12.4 (9.6–15.2)	1.41(1.01–1.97)	0.04	6.3 (5.6–7.0)	1.48 (1.07–2.05)	0.02
Elevated CA 19-9 level						
Normal	19.3 (12.4–26.2)	Reference		7.6 (6.4–8.9)	Reference	
Elevated	13.4 (10.9–15.9)	1.75(1.16–2.64)	0.008	6.3 (5.6–7.0)	1.56 (1.07–2.28)	0.02
mGPS						
0	17.4 (15.3–19.5)	Reference				
≥1	10.3 (8.9–11.7)	1.64(1.16–2.30)	0.005			

HR hazard ratio, *CI* confidence interval, *mGPS* modified Glasgow prognostic score, *ECOG PS* Eastern Cooperative Oncology Group performance status

(Table 1). High NLR (≥median) was significantly associated with metastatic disease at the time of diagnosis (Table 2). PLR did not show any significant relationship with clinical characteristics. High mGPS (≥1) was significantly associated with female gender, metastatic disease at presentation, poor ECOG PS (≥2), more metastatic sites (≥2), and a primary pancreas head tumor.

Prognostic factor analysis

Univariate analyses of each clinicopathologic factor for the association with OS and PFS are summarized in Table 3. mGPS was significantly associated with OS (mGPS 0, median 17.4 months [95% CI 15.3–19.5]; mGPS 1, 10.1 months [95% CI 6.1–14.1]; mGPS 2, 11.1 months [95% CI 7.7–14.5], $p =$

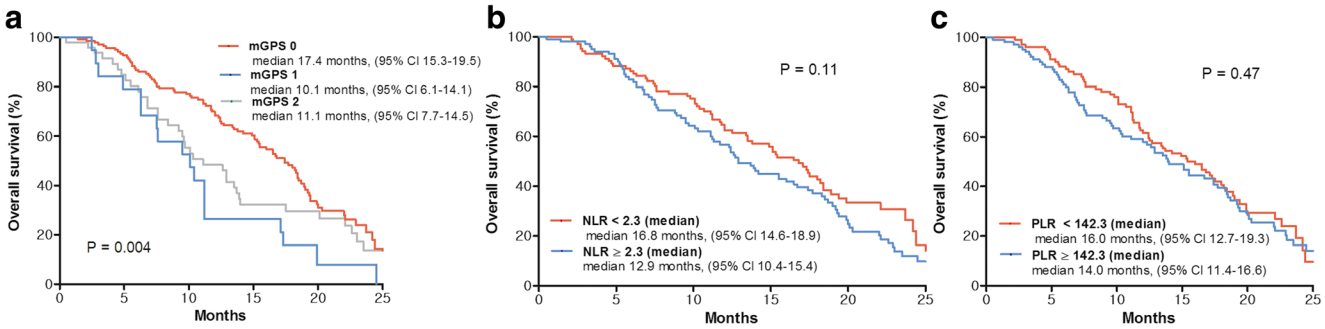

Fig. 1 Overall survival according to inflammation-based scores. mGPS **a**, NLR **b**, and PLR **c**, *mGPS* = modified Glasgow prognostic score, *NLR* = neutrophil-lymphocyte ratio, *PLR* = Platelet-lymphocyte ratio

0.004; Fig. 1a). However, neither NLR nor PLR were associated with OS (<median vs ≥ median, $p = 0.11$ and $p = 0.47$, respectively; Fig. 1b-c).

In the multivariate analysis for OS (Table 3), liver metastases (HR 1.76, 95% CI 1.25–2.49, $p = 0.001$), distant lymph node metastases (HR 1.41, 95% CI 1.01–1.97, $p = 0.04$), elevated baseline CA19–9 (HR 1.75 95% CI 1.16–2.64, $p = 0.008$), and high mGPS (1–2 vs 0, HR 1.64 95% CI 1.16–2.30, $p = 0.005$; Table 3) were independent prognostic factors for poorer OS.

The median PFS did not differ according to the mGPS ($p = 0.17$), NLR ($p = 0.65$) and PLR ($p = 0.13$) (Fig. 2). Although patients with mGPS 1–2 seemed to have poorer PFS than those with mGPS 0, the difference was not statistically significant ($p = 0.06$; Fig. 3). In the multivariate analysis (Table 3), poorer PFS was significantly associated with the presence of liver metastases (HR 1.43, 95% CI 1.03–1.98, $p = 0.03$), the presence of distant lymph node metastases (HR 1.48, 95% CI 1.07–2.05, $p = 0.02$), and elevated baseline CA19–9 (HR 1.56, 95% CI 1.07–2.28, p = 0.02).

Discussion

The survival outcomes of cancer patients depend not only on tumor characteristics, but also on host-related factors. In particular, the cancer-associated inflammatory response is a crucial host-related factor. Cancer-associated inflammation may be a key indicator of cancer initiation and progression by release of pro-inflammatory cytokines around tumor cells [13], and several inflammation-based indicators including mGPS, NLR, and PLR may assess cancer-associated inflammation with prognostic impact. The current study investigated the prognostic relevance of mGPS, NLR, and PLR in patients with recurrent or mPC, treated with first-line AG.

In our study, high mGPS scores were significantly associated with poorer OS in patients with recurrent or metastatic pancreatic cancer who received AG as first line chemotherapy. Although our results are in line with previous reports of patients with operable or advanced pancreatic cancer [14–18], those studies included a heterogeneous patient population (in terms of tumor stage) and used old chemotherapeutic agents. Considering that the prognosis of metastatic pancreatic cancer largely depends on chemotherapeutic activity, our study strengthens the argument that mGPS is an independent prognostic factor for patients with metastatic pancreatic cancer, treated with standard first-line AG. Although high mGPS was marginally related with poorer PFS, the difference was not statistically significant. Our study indicates that mGPS may be a prognostic factor for metastatic pancreatic cancer, not a predictive factor for the efficacy of first-line AG.

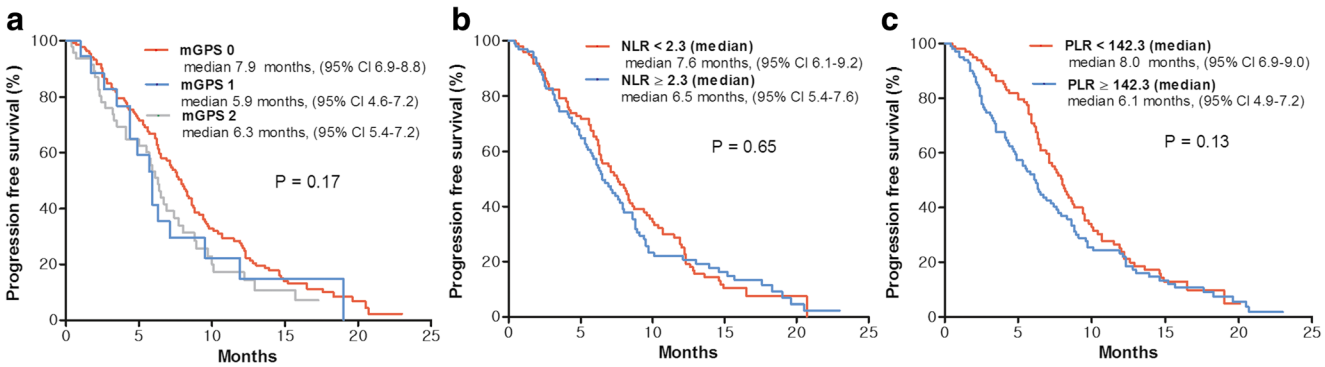

Fig. 2 Progression-free survival according to inflammation-based scores. mGPS **a**, NLR **b**, and PLR **c**, *mGPS* = modified Glasgow prognostic score, *NLR* = neutrophil-lymphocyte ratio, *PLR* = Platelet-lymphocyte ratio

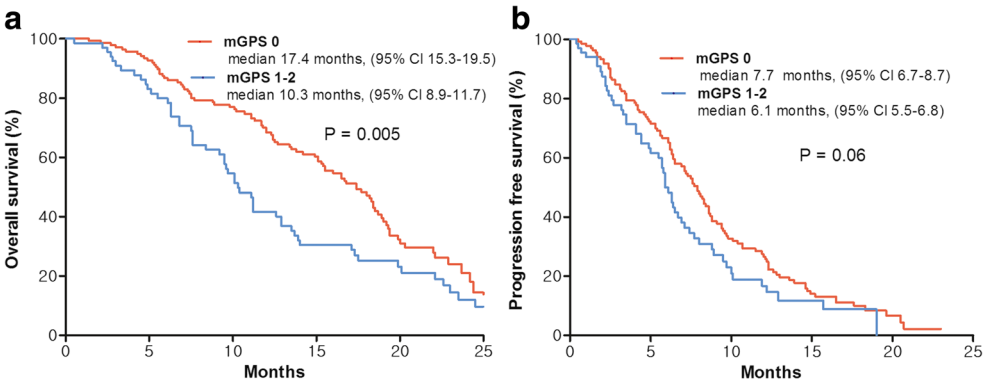

Fig. 3 Survival outcomes according to the mGPS (score 0 *vs.* 1–2). Overall survival (**a**) and Progression-free survival (**b**), *mGPS* = modified Glasgow prognostic score

The mGPS consists of CRP and albumin. In our study, however, survival outcomes did not differ between patients with mGPS 1 (elevated CRP but normal serum albumin levels) and mGPS 2 (elevated CRP levels and hypoalbuminemia). These results suggest that CRP may have bigger role in predicting prognosis in patients with metastatic pancreatic cancer, compared to serum albumin levels, and this is consistent with recent data obtained while examining patients with biliary tract cancer [19]. Previous studies also showed that CRP has significant relationship with clinical outcomes in patients with pancreatic cancer [20, 21].

In our patient cohort, NLR and PLR were not associated with either PFS or OS, and these results are in contrast with the results of a previous study which suggested that NLR and PLR may be the prognostic factor in patients with advanced pancreatic cancer [22]. Differences in baseline patient characteristics, disease stage, and chemotherapeutic agents may produce discrepancies in the prognostic relevance of NLR and PLR between previous study and ours. Further evaluations in other homogeneous patient cohorts are needed to validate the current findings.

Despite recent studies investigating the implication of inflammation-based scores, there is no strong preclinical or clinical evidence to support their relevance to the management of pancreatic cancer, as most studies including ours were based on the retrospective cohorts. Although CRP was used as a stratification factor in a randomized phase III trial of ruxolitinib, based on its ability to predict outcomes in a randomized phase II trial, that trial was stopped because of negative results after the interim analysis [23]. Further investigations are needed to determine which inflammation-based scores characterize preclinical or clinical aspects of pancreatic cancer. These efforts may be important if we are to incorporate these markers in the design of future clinical trials of novel agents and optimize daily practice for patients with pancreatic cancer.

In the current study, liver metastases, distant lymph node metastases, and elevated baseline CA19–9 were independent prognostic factors in patients with recurrent or metastatic pancreatic cancer who received first-line AG. In the post-hoc analysis for patients enrolled in the MPACT trial [24], a randomized phase III trial comparing AG vs gemcitabine monotherapy for metastatic pancreatic cancer, age, NLR (<5 vs >5), Karnofsky performance status scale score, and presence of liver metastases were significantly associated with OS in 861 patients who received AG or gemcitabine monotherapy. Interestingly, there was no difference in survival outcomes of patients treated with AG according to baseline CA 19–9 levels, while elevated CA 19–9 levels were significantly associated with poorer OS in patients treated with gemcitabine monotherapy [24]. Discrepancies in baseline patient characteristics (4% with ECOG PS 2 or greater in our cohort vs 7.5% in the MPACT trial) and the selected analyzed variables might have resulted in these differences in terms of significant prognostic factors.

The current study has several caveats. As ours was a retrospective study, the variables we analyzed were also collected retrospectively by medical chart review, which might have caused unintended bias. Despite of these limitations, our study was based on the one of largest real-world metastatic pancreatic cancer patient cohort receiving first-line AG.

In conclusion, mGPS was an independent prognostic factor in patients with recurrent or metastatic pancreatic cancer treated with first-line AG, while NLR and PLR did not show a significant relationship. Metastasis in liver and distant lymph nodes, and elevated CA 19–9 levels were also poor prognostic factors. Further investigations are needed to reveal the implication of these markers in the management of patients with pancreatic cancer.

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Compliance with ethical standards

Conflicts of interest The authors have no conflicts of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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