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Original Article

Predictive value of albumin combined with neutrophil-to-lymphocyte ratio for efficacy and safety profiles in patients with pancreatic ductal adenocarcinoma receiving liposomal irinotecan plus 5-fluorouracil and leucovorin

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Abstract: Liposomal irinotecan plus 5-fluorouracil and leucovorin (nal-IRI + 5-FU/LV) treatment has demonstrated survival benefits but noticeable side effects in patients with pancreatic ductal adenocarcinoma (PDAC) that is refractory to gemcitabine-based therapy. This study aimed to explore whether combining albumin with the neutrophil-to-lymphocyte ratio (NLR), herein known as the albumin and neutrophil-to-lymphocyte ratio score (ANS), could be utilized as a simple tool to predict survival and safety profiles in such patient groups. We retrospectively enrolled 434 consecutive PDAC patients treated with nal-IRI + 5-FU/LV between 2018 and 2020 at nine medical centers in Taiwan. Patients were divided into three groups: ANS 0 (high albumin and low NLR), ANS 1 (low albumin or high NLR), and ANS 2 (low albumin and high NLR), for comparison. The median overall survival times for the ANS 0, 1, and 2 groups were 8.7 months (95% confidence interval (CI), 7.0-10.3 months), 5.2 months (95% CI, 4.3-6.0 months), and 2.6 months (95% CI, 1.9-3.3 months), respectively. The ANS was found to be an independent variable for overall survival and time-to-treatment failure in multivariate analyses. Patients in the ANS 2 group had significantly higher incidences of grade 3 or higher treatment-related adverse events than those in the other two groups. The present study showed that the ANS was an independent prognosticator in PDAC patients receiving nal-IRI + 5-FU/LV therapy. The ANS can be a simple predictor of survival outcome and safety profiles in PDAC patients treated with nal-IRI + 5-FU/LV.

Keywords: Albumin, liposomal irinotecan, neutrophil-to-lymphocyte ratio, pancreatic cancer, prognosis

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the 14th most common cancer and the 7th leading cause of cancer-related deaths worldwide in 2020 [1]. Gemcitabine-based chemotherapy has been the standard first-line treatment for patients with unresectable or metastatic PDAC over the past two decades [2, 3]. Until recently, the pivotal NAPOLI-1 study established the clinical efficacy of liposomal irinotecan plus 5-fluorouracil and leucovorin (nal-IRI + 5-FU/LV) as the newest treatment of choice in patients with PDAC refractory to gemcitabine-based therapy [4]. The median survival time increased from 4.2 months in patients who received only 5-FU/LV to 6.1 months in those who received nal-IRI + 5-FU/LV [4]. However, 48% of the patients in the nal-IRI + 5-FU/LV arm of the NAPOLI-1 trial experienced severe treatment-related adverse events, which contributed to a significantly higher dose reduction rate (33% vs. 4%) in the nal-IRI + 5-FU/LV arm than in the 5-FU/LV arm [4]. The benefit of increased survival time in patients receiving nal-IRI + 5-FU/LV might come at the cost of higher toxicity profiles.

To identify which patients might benefit the most in terms of increased probability of survival resulting from treatment with nal-IRI + 5-FU/LV, Chen et al. constructed a prognostic nomogram based on a post-hoc analysis of the NAPOLI-1 study using eight clinical variables, including: nal-IRI + 5-FU/LV treatment, performance status, neutrophil-to-lymphocyte ratio (NLR), albumin, carbohydrate antigen 19-9 (CA19-9), stage IV disease at diagnosis, body mass index (BMI), and presence of liver metastasis after nal-IRI + 5-FU/LV treatment [5]. However, this model was not utilized in clinical practice due to a lack of validation outside the clinical trial setting and relatively complex calculations. Additionally, this nomogram was constructed to predict only the survival outcome of the patient, while the model lacked the ability to predict treatment-relative toxicity. As the nal-IRI + 5-FU/LV regimen causes noticeable side effects, a concise and straightforward model is necessary to identify patients vulnerable to treatment-related adverse events who might benefit from improved survival.

Albumin is a surrogate indicator for nutrition, as a lower albumin level indicates malnourishment and is associated with poor tolerance to antitumor treatments [6, 7]. A higher NLR indicates an increased systemic inflammatory response through the induction of cytotoxic cell death of lymphocytes or elevated neutrophil counts, which may decrease the cytolytic activity of natural killer cells [8, 9]. Therefore, a higher NLR has been consistently associated with poor treatment outcomes in patients with pancreatic cancer [10, 11]. Our previous study reported that albumin and NLR both were poor prognosticators in mPDAC patients treated with nal-IRI + 5-FU/LV [12]. While albumin and NLR values are both easily evaluated in clinical practice, an increasing number of studies have demonstrated that combining albumin and the NLR, as the albumin-NLR score (ANS), accurately predicted survival outcome and postoperative complications in patients with pancreatic cancer [13] and gastric cancer [14]. Whether or not the ANS may be used in the prediction of treatment outcomes in PDAC patients undergoing chemotherapy is unclear as of yet. While the nal-IRI + 5-FU/LV regimen has demonstrated improved survival benefits with noticeable side effects in clinical trials [4, 5], the present study hypothesized that the ANS was a simple predictive and prognostic tool for predicting survival and safety profiles in patients with PDAC treated with nal-IRI + 5-FU/LV.

Methods

Patient selection

Based on the NAPOLI-1 study [4], the combination regimen of nal-IRI + 5-FU/LV was reimbursed for PDAC patients in Taiwan by the National Health Insurance in August 2018. We retrospectively reviewed the medical records of 677 consecutive patients who received nal-IRI + 5-FU/LV for the treatment of PDAC between August 2018 and November 2020 at nine medical centers in Taiwan. All patients were pathologically or cytologically confirmed to have PDAC. Patients received nal-IRI + 5-FU/LV (nal-IRI 80 mg/m^2 administered intravenously over 90 minutes, followed by leucovorin 400 mg/m^2 administered intravenously over 30 minutes and 5-fluorouracil 2400 mg/m^2 administered over 46 hours every 2 weeks) according to the NAPOLI-1 study [4]. A total of 243 patients, whose pretreatment albumin and

NLR data were not available within 7 days before the initiation of the nal-IRI + 5-FU/LV treatment were excluded from our analysis; therefore, a total of 434 patients were enrolled in the present study.

Data collection

The patients' demographic and clinicopathological data at the onset of treatment with nal-IRI + 5-FU/LV were obtained. Laboratory data were obtained within seven days of the first cycle of treatment with nal-IRI + 5-FU/LV. An NLR value less or higher than the median was assigned to 0 and 1 point, respectively, whereas an albumin value higher or less than the median was assigned to 0 and 1 point, respectively [13]. The median albumin value in the present study was 3.7 g/dL, and the NLR was 4.2. Accordingly, patients with both albumin ≥ 3.7 g/dL and NLR < 4.2 were allocated a score of 0, patients with either albumin < 3.7 g/dL or NLR ≥ 4.2 were allocated a score of 1, and patients with both albumin < 3.7 g/dL and NLR ≥ 4.2 were allocated a score of 2. Patients were assigned to one of the following groups based on their score: ANS 0, 1, and 2 respectively.

Imaging studies with computed tomography scan or magnetic resonance imaging were performed during regular follow-ups every 8-12 weeks, or when clinically indicated during chemotherapy. Tumor response was evaluated through imaging studies according to the Response Evaluation Criteria for Solid Tumors (RECIST) 1.1. Patients who required early termination of treatment or who died before imaging studies were performed were determined to have experienced disease progression. All enrolled patients were monitored through December 31, 2020, or until death.

Statistical analysis

Basic patient demographic data were summarized as frequency (%) for categorical variables and as median with interquartile range (IQR) or range for continuous variables. Differences in tumor response between the three ANS groups were compared using the chi-squared (χ^2) test. Time-to-treatment failure (TTF) was defined as the time from the initiation of nal-IRI + 5-FU/LV treatment to the date of treatment discontinuation for any reason. Overall survival (OS) was defined as the time between the initiation of nal-IRI + 5-FU/LV treatment and death from any cause. TTF and OS were calculated using the Kaplan-Meier method. Log-rank tests were used to determine statistically significant differences among survival curves. All clinicopathological variables were evaluated using univariate Cox regression analysis to ascertain the impact of each variable on TTF and OS. All variables in the univariate analysis with *p*-values < 0.10 were further analyzed using multivariate analysis. To compare the performance of the model, the linear chi-square test, the -2 log likelihood, and the c-index were used. In general, higher linear chi-squared and lower -2 log likelihood values indicate a more accurate model, and a higher c-index value indicates increased discriminative ability of the model. SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. All statistical assessments were 2-sided and a *p*-value of < 0.05 was considered the threshold for statistical significance.

Results

The basic characteristics of the 434 patients included in the present study are presented in **Table 1**. The median age was 63 years (range, 27-89 years), and 52% of the participants were men. A total of 8 patients (1.7%) received nal-IRI + 5-FU/LV as the first-line treatment for metastatic PDAC, while 250 (57.6%) received it as the second-line, and 176 (40.6%) as the third-line. The most common first-line chemotherapeutic agents were gemcitabine (99.1%), titanium silicate (TS)-1 (53.7%), platinum (38.0%), 5-fluouracil (20.0%), and irinotecan (15.4%). ANSs were assigned as follows: 137 (31.6%) patients had a score of 0, 154 (35.5%) had a score of 1, and 143 (32.9%) had a score of 2. No statistical differences were observed among the three ANS groups in terms of age, sex, primary tumor location, site of metastases, prior treatment line for metastatic disease, pretreatment CA19-9 levels, median dose intensity of nal-IRI, and time from first-line treatment to nal-IRI therapy. The median dose intensity of nal-IRI during the first six treatment cycles was 82% (IQR,

Table 1. Patients' basic characteristics

Variable	Category	Entire cohort (n = 434)	ANS 0 (n = 137)	ANS 1 (n = 154)	ANS 2 (n = 143)	*P* value
Age, years	Median (range)	63 (27-89)	62 (27-81)	63 (23-86)	64 (34-89)	0.11[a]
Sex, n (%)	Male	226 (52.1)	65 (47.4)	78 (50.6)	83 (58.0)	0.19[b]
	Female	208 (47.9)	72 (52.6)	76 (49.4)	60 (42.0)	
Body mass index, kg/m^2	Median (range)	20.7 (12.4-39.0)	21.3 (13.0-36.1)	21.1 (12.4-39.0)	19.9 (13.9-30.8)	0.015[a]
ECOG performance, n (%)	0	106 (24.4)	39 (28.5)	39 (25.3)	28 (19.6)	<0.001[b]
	1	205 (47.2)	77 (56.2)	72 (46.8)	56 (39.2)	
	2	97 (22.4)	18 (13.1)	35 (22.7)	44 (30.8)	
	3	26 (6.0)	3 (2.2)	8 (5.2)	15 (10.5)	
Primary tumor location, n (%)	Head	237 (54.6)	68 (49.6)	81 (52.6)	88 (61.5)	0.34[b]
	Body	98 (22.6)	32 (23.4)	38 (24.7)	28 (22.6)	
	Tail	85 (19.6)	34 (24.8)	29 (18.8)	22 (15.4)	
	Overlapping	14 (3.2)	3 (3.3)	6 (3.9)	5 (3.5)	
Site of metastases prior to nal-IRI treatment, n (%)	Liver	295 (68.0)	94 (68.6)	103 (66.9)	98 (68.5)	0.94[b]
	Peritoneum	144 (33.2)	42 (30.7)	55 (35.7)	47 (32.9)	0.36[b]
	Distant lymph nodes	123 (28.3)	43 (31.4)	41 (26.6)	39 (27.3)	0.63[b]
	Lung	81 (18.7)	23 (16.8)	24 (15.6)	34 (23.8)	0.15[b]
	Bone	36 (8.3)	9 (6.6)	13 (8.4)	14 (9.8)	0.62[b]
	Others	32 (7.4)	10 (7.3)	12 (7.8)	10 (7.0)	0.97[b]
Prior pancreatectomy, n (%)	Yes	151 (34.8)	45 (32.8)	53 (34.4)	53 (37.1)	0.62[b]
CA19-9 prior to nal-IRI treatment, ug/mL	Median (IQR)	1354 (95-6242)	1265 (87-5410)	1077 (42-6917)	1190 (57-6705)	0.11[a]
Prior treatment line for metastatic disease, n (%)	Median (range)	1 (0-7)	1 (0-7)	1 (0-4)	1 (0-5)	0.08[a]
	0	8 (1.7)	4 (2.9)	3 (1.9)	1 (0.7)	
	1	250 (57.6)	89 (65.0)	83 (53.9)	78 (54.5)	
	2	131 (30.2)	34 (24.8)	51 (33.1)	46 (32.2)	
	3	30 (6.9)	7 (5.1)	14 (9.1)	9 (6.3)	
	≥ 4	15 (3.5)	3 (2.1)	3 (1.9)	9 (6.3)	
Time from first-line treatment to nal-IRI treatment, months	Median (range)	7.2 (0-93.8)	8.4 (0-93.8)	7.4 (0-55.1)	6.2 (0-43.7)	0.40[a]
NLR	Median (IQR)	4.2 (2.5-6.9)	2.3 (1.0-2.6)	4.2 (3.1-7.3)	7.4 (4.8-11.1)	<0.001[a]
Albumin	Median (IQR)	3.7 (3.2-4.0)	4.1 (3.9-4.5)	3.7 (2.6-4.3)	3.1 (2.3-3.2)	<0.001[a]
Prior gemcitabine treatment, n (%)	Yes	430 (99.1)	136 (99.3)	153 (99.4)	141 (98.6)	0.99[b]
Prior TS-1 treatment, n (%)	Yes	233 (53.7)	70 (51.1)	82 (53.2)	81 (56.6)	0.64[b]
Prior platinum treatment, n (%)	Yes	165 (38.0)	51 (37.2)	58 (37.7)	56 (39.2)	0.94[b]
Prior 5-fluouracil treatment, n (%)	Yes	87 (20.0)	26 (19.0)	30 (19.5)	31 (21.7)	0.83[b]
Prior irinotecan treatment, n (%)	Yes	67 (15.4)	19 (13.9)	22 (14.3)	26 (18.2)	0.54[b]
Median dose intensity of nal-IRI during the first six treatment cycles	Median (IRQ)	82% (56%-92%)	82% (52%-92%)	82% (48%-91%)	77% (44%-86%)	0.07

ECOG, Eastern Cooperative Oncology Group; Nal-IRI, nanoliposomal irinotecan; CA19-9, carbohydrate antigen 19-9; IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio. [a]Mann-Whitney U test, [b]Chi-square test.

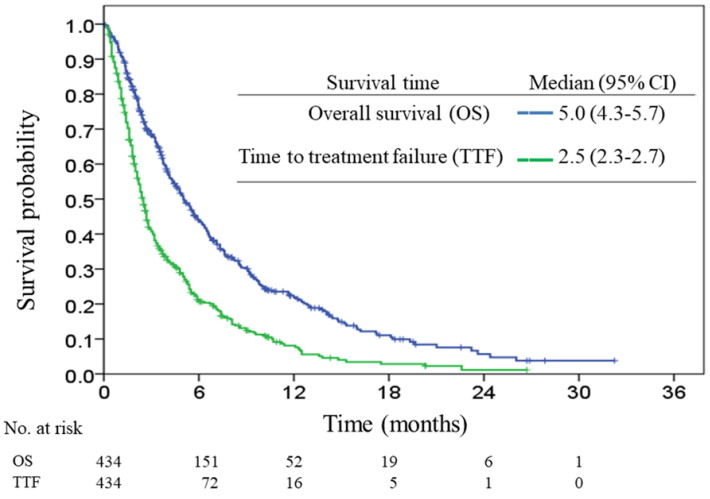

Figure 1. Overall survival and time-to-treatment failure curves.

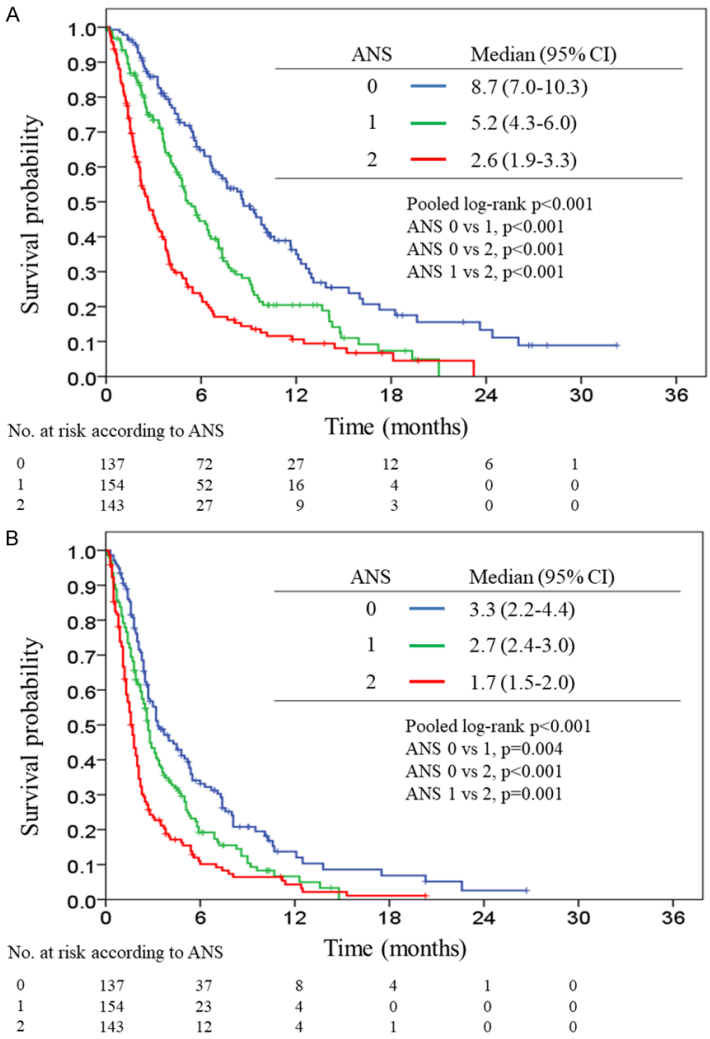

Figure 2. Kaplan-Meier estimates of overall survival (A) and time-to-treatment failure (B) among three ANS groups. ANS, albumin and neutrophil-to-lymphocyte ratio score.

52-92%), 82% (IQR, 48-91%), and 77% (IQR, 44-86%) among patients in the ANS 0, 1, and 2 groups, respectively (p = 0.07 for within-group comparison). Patients in the ANS 2 group had a lower BMI and poorer Eastern Cooperative Oncology Group (ECOG) performance status at baseline than those in the other two groups.

By the end of the follow-up period of the present study, 322 (74.2%) of the 434 patients had died. The median OS and TTF were 5.0 months (95% confidence interval (CI), 4.3-5.7 months) and 2.5 months (95% CI, 2.3-2.7 months), respectively (**Figure 1**). The median OS times for ANS groups 0, 1, and 2 were 8.7 months (95% CI, 7.0-10.3 months), 5.2 months (95% CI, 4.3-6.0 months), and 2.6 months (95% CI, 1.9-3.3 months), respectively (**Figure 2A**). The median TTF was 3.3 months (95% CI, 2.2-4.4 months), 2.7 months (95% CI, 2.4-3.0 months), and 1.7 months (95% CI, 1.5-2.0 months), respectively (**Figure 2B**). There were statistically significant differences in OS and TTF between the three groups (all p-values < 0.01). **Table 2** presents univariate and multivariate analyses for OS. Multivariate analysis showed that poor Eastern Cooperative Oncology Group (ECOG) performance, the presence of liver metastases, CA19-9 levels higher than the median value, albumin < 3.7 g/dL, NLR ≥ 4.2, and first-line treatment with TS-1 were the independent prognostic variables for OS.

The crude hazard ratios (HRs) for OS were 1.67 (95% CI, 1.25-2.21; p < 0.001) and 2.88 (95% CI, 2.18-3.81; P < 0.001) when comparing the patients in the ANS 1 and ANS 2 groups with those in the ANS 0 group (**Figure 3A**). After adjusting for ECOG performance, status of liver metastases, CA19-9, and first

Table 2. Univariate and multivariate analyses for overall survival

Variable	Category	Univariate analysis			Multivariate analysis		
		HR	95% CI	p	Adjusted HR	95% CI	p
Sex	Female vs. male	0.78	0.62-0.97	0.027	0.83	0.65-1.04	0.11
Age, years	< 65 vs. ≥ 65	1.37	1.10-1.71	0.005	1.24	0.97-1.57	0.08
Body mass index, kg/m^2	> 21.1 vs. ≤ 21.1	0.78	0.63-0.97	0.023	0.85	0.67-1.08	0.19
ECOG performance	2-3 vs. 0~1	2.56	2.01-3.25	< 0.001	1.99	1.53-2.58	< 0.001
Primary tumor location	Head	Reference			Reference		
	Body	1.28	0.98-1.67	0.065	1.18	0.88-1.57	0.27
	Tail	1.12	0.84-1.51	0.45	1.13	0.82-1.55	0.47
	Overlapping	1.83	1.02-3.30	0.043	1.72	0.94-3.14	0.08
Previous pancreatectomy	Yes vs. no	0.57	0.45-0.73	< 0.001	0.80	0.62-1.04	0.09
Presence of liver metastases	Yes vs. no	1.53	1.21-1.95	0.001	1.84	1.40-2.40	< 0.001
Presence of peritoneum metastases	Yes vs. no	1.37	1.09-1.73	0.007	1.11	0.86-1.43	0.43
Presence of distant lymph nodes metastases	Yes vs. no	1.04	0.82-1.32	0.72			
Presence of lung metastases	Yes vs. no	1.41	1.07-1.86	0.014	1.29	0.96-1.72	0.09
Presence of bone metastases	Yes vs. no	1.29	0.86-1.92	0.22			
Presence of other metastases	Yes vs. no	0.90	0.59-1.36	0.61			
CA19-9, ug/ml	< 1354 (median)	Reference			Reference		
	≥ 1354	1.63	1.30-2.05	< 0.001	1.28	1.01-1.63	0.046
Albumin, gm/dL	≥ 3.7	Reference			Reference		
	< 3.7	2.04	1.63-2.55	< 0.001			
Neutrophil-to-lymphocyte ratio	< 4.2	Reference					
	≥ 4.2	1.90	1.52-2.37	< 0.001			
ANS	0	Reference					
	1	1.67	1.25-2.21	< 0.001	1.64	1.15-2.34	0.006
	2	2.88	2.18-3.81	< 0.001	2.68	1.61-4.47	< 0.001
Time interval from first-line treatment to nal-IRI treatment, months	< 7.2 (median) vs. ≥ 7.2	1.08	0.86-1.34	0.53			
Prior line of chemotherapy for metastatic disease	2-3 vs. 0~1	1.21	0.97-1.51	0.10			
Prior irinotecan treatment	yes vs. no	1.75	1.29-2.37	< 0.001	1.34	0.86-2.09	0.20
Prior TS-1 treatment	yes vs. no	1.30	1.04-1.62	0.022	1.39	1.09-1.78	0.007
Prior platinum treatment	yes vs. no	1.16	0.92-1.45	0.21			
Prior 5-fluouracil treatment	yes vs. no	1.37	1.04-1.80	0.026	1.17	0.77-1.76	0.46

ECOG, Eastern Cooperative Oncology Group; CA19-9, carbohydrate antigen 19-9; Nal-IRI, nanoliposomal irinotecan; HR, hazard ratio; CI, confidence interval; ANS, albumin and neutrophil-to-lymphocyte ratio score.

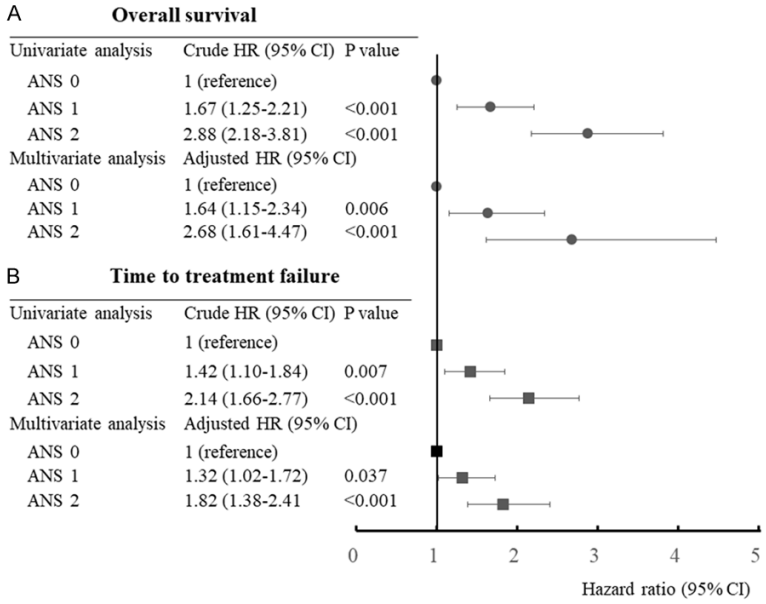

Figure 3. Hazard ratio for overall survival (A) and time-to-treatment failure (B) in patients with different ANS groups; ANS, albumin and neutrophil-to-lymphocyte ratio score.

Table 3. Performance of Albumin, NLR, and ANS in predicting survival outcomes

Variable	-2 log likelihood*	Chi-square**	C-index (95% CI)***
Albumin	544.2	39.5	0.60 (0.55-0.66)
NLR	530.1	31.9	0.63 (0.58-0.69)
ANS	525.1	55.9	0.66 (0.61-0.71)

NRL, neutrophil-to-lymphocyte ratio; ANS, albumin-NLR score; CI, confidence interval. *A lower -2 log likelihood value indicates a smaller difference within the model and is an indicator of better homogeneity. **A higher chi-square value of linear trend indicates a better discriminatory ability and gradient monotonicity of the model. ***A higher c-index means a better discriminatory ability of the model.

line treatment with TS-1, patients in the ANS 1 and ANS 2 groups had 1.64-fold (95% CI, 1.15-2.34; p = 0.006) and 2.68-fold (95% CI, 1.61-4.47; P < 0.001) increases in likelihood of overall mortality compared to those in the ANS 0 group. Regarding TTF, the crude HRs were 1.42 (95% CI, 1.10-1.84; P = 0.007) and 2.14 (95% CI, 1.66-2.77; P < 0.001) when comparing the patients in the ANS 1 and ANS 2 groups with those in the ANS 0 group, respectively (**Figure 3B**). After adjusting the aforementioned variables, the adjusted HRs when comparing patients in the ANS 1 and ANS 2 groups with those in the ANS 0 group were 1.32 (95% CI, 1.02-1.72; P = 0.037) and 1.82 (95% CI, 1.38-2.41; P < 0.001) times more than those in the ANS 0 group, respectively. **Table 3** shows the survival prediction performance for ANS, albumin, and NRL. The ANS had the highest predicting power and discrimination ability in terms of having the lowest -2 log likelihood value (525.1 for ANS vs. 544.2 for albumin and 530.1 for NLR), highest chi-square value (55.9 for ANS vs. 39.5 for albumin and 31.9 for NLR), and highest c-index (0.66 for ANS vs. 0.60 for albumin and 0.63 for NLR).

When evaluating the tumor response to nal-IRI + 5-FU/LV treatment, 44 (7.6%), 113 (26.0%), and 288 (66.4%) patients showed partial response, stable disease, and progressive disease, respectively. Patients in the ANS 0 group experienced a higher rate of partial response (12.4%) and stable disease (32.8%) than those in the ANS 1 (5.2% vs. 27.9%, respectively) and ANS 2 groups (5.6% vs. 17.5%, respectively) (**Figure 4**). There was a statistically significant difference in tumor response between the three ANS groups (P = 0.001).

Major (grade 3 or higher) adverse events are shown in **Table 4**. The most common treatment-related adverse events were anemia (22.6%), neutropenia (21.0%), and hypokalemia (17.7%). Patients in the ANS 2 group had significantly higher incidences of grade 3 or higher anemia, thrombocytopenia, and hypokalemia than those in the other two groups.

Discussion

The present study demonstrated that albumin level and NLR were independent prognostic factors in predicting survival outcomes in patients with PDAC who were treated with nal-IRI + 5-FU/LV. Additionally, the results of the present study showed that the ANS, the combined evaluation of albumin and NLR, demonstrated better prognostic accuracy than that of

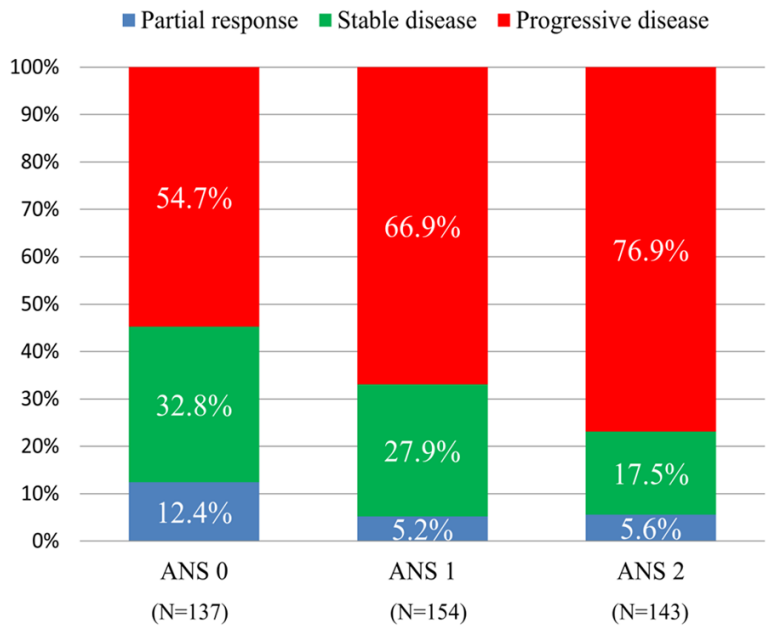

Figure 4. Best tumor responses to nal-IRI + 5-FU/LV treatment in patients from different ANS groups; ANS: albumin and neutrophil-to-lymphocyte ratio score; nal-IRI + 5-FU/LV: liposomal irinotecan plus 5-fluorouracil and leucovorin.

albumin or NLR alone. PDAC patients with a high ANS, that is, a lower albumin level combined with a higher NLR, were more likely to have a poor prognosis. Moreover, patients with a higher ANS were also found to have lower treatment response rates and higher incidences of grade 3 or 4 treatment-related adverse events than those with a lower ANS. The results of the present study provide a novel finding for using the pretreatment ANS as a simple prognosticator for survival outcome and safety profiles in patients with PDAC treated with nal-IRI + 5-FU/LV.

In the present study, the ANS was used to distribute the cohort into three groups with similar patient numbers, and a distinct survival benefit between the groups. The results of the present study suggested that the ANS might assist clinicians in survival discrimination and in determining appropriate treatment goals. Patients in the ANS 0 (higher albumin and lower NLR) group achieved a median survival of 8.7 months and a 45% disease control rate in contrast to a median survival of 2.6 months and a 23% disease control rate in patients in the ANS 2 group, although both groups received nal-IRI + 5-FU/LV treatment. To put the prognostic and predictive value of the ANS into context, the patients who received 5-FU/LV alone in the NAPOLI-1 trial had a longer median OS compared to patients with higher a ANS in the present study who received nal-IRI + 5-FU/LV (4.2 vs. 2.6 months, respectively) [4]. On the other hand, the patients in the present study with a low ANS had a longer median survival (8.7 months as opposed to 6.1 months) compared to those from the NAPOLI-1 study who also received nal-IRI + 5-FU/LV. These results indicated the benefit of nal-IRI in patients with a low ANS. In contrast, alternative treatment with 5 FU/LV alone or best supportive care for patients with ANS 2 may be considered because of the limited treatment efficacy and higher toxicity profiles from the addition of nal-IRI in subsequent chemotherapy.

Several inflammation-based biomarkers, including the NLR [15, 16], C-reactive protein [17], the Glasgow Prognostic Score [18], platelet-to-lymphocyte ratio [19], and prognostic nutrition index [20], have been evaluated as prognostic factors in PDAC patients. However, information regarding the ability of these biomarkers to predict OS in pancreatic cancer is inconsistent and varies widely due to heterogeneous treatment modalities [21]. Albumin and NLR have been shown to be independent prognostic factors in a post-hoc analysis of the NAPOLI-1 trial [5], whereas the other inflammation-based biomarkers have inadequate data with which to assess their prognostic value in PDAC patients receiving nal-IRI + 5-FU/LV therapy. Therefore, it is reasonable to construct a prognostic model for PDAC patients receiving nal-IRI + 5-FU/LV based on the combination of albumin and NLR. Furthermore, the results of the present study showed the improved performance of ANS in predicting OS as compared to using albumin or NLR alone. While both albumin and NLR are easily evaluated, ANS may be widely applied to all patients with PDAC upon initiating nal-IRI + 5-FU/LV therapy.

The prognostic role of pretreatment albumin and NLR has been well documented for various cancers [13-21]. However, few studies have

Table 4. Treatment-related toxicity according to ANS

Variable	Entire cohort N = 434 n (%)	ANS 0 N = 137 n (%)	ANS 1 N = 154 n (%)	ANS 2 N = 143 n (%)	*p*-value*
Hematological toxicity					
Anemia	98 (22.6)	16 (11.7)	32 (20.8)	50 (35.0)	< 0.001
Neutropenia	91 (21.0)	24 (17.5)	32 (20.8)	35 (24.5)	0.36
Thrombocytopenia	35 (8.1)	5 (3.6)	11 (7.1)	19 (13.3)	0.011
Febrile neutropenia	17 (3.9)	8 (5.8)	4 (2.6)	5 (3.5)	0.35
Non-hematological toxicity					
Hypokalemia	77 (17.7)	19 (13.9)	23 (14.9)	35 (24.5)	0.035
Elevation of total bilirubin	39 (9.0)	8 (5.8)	13 (8.4)	18 (12.6)	0.14
Vomiting	21 (4.8)	4 (2.9)	8 (5.2)	9 (6.3)	0.41
Diarrhea	18 (4.1)	3 (2.2)	7 (4.5)	8 (5.6)	0.34
Elevation of AST	18 (4.1)	4 (2.9)	6 (3.9)	8 (5.6)	0.52
Non-neutropenic infection	13 (3.0)	2 (1.5)	6 (3.9)	5 (3.5)	0.44
Elevation of ALT	11 (2.5)	2 (1.5)	5 (3.2)	4 (2.8)	0.61
Fatigue	7 (1.6)	0	4 (2.6)	3 (2.1)	0.18

ALT, alanine aminotransferase; AST, aspartate aminotransferase. **p*-value for linear trend among the three ANS groups.

explored the association between albumin level and NLR with adverse events of anticancer therapy. Hypoalbuminemia indicates a malnourished status that leads to decreased treatment tolerance and increased post-treatment complications [22]. Recent studies have reported that the NLR is highly indicative of postoperative complications in pancreatic cancer patients after pancreaticoduodenectomy [23]. As described in previous reports, the results of the present study showed that the ANS was significantly associated with treatment-related adverse events in patients with PDAC. Patients with a higher ANS were found to have a higher incidence of severe adverse events; therefore, the results of the present study suggested that clinicians may be able to use the ANS to identify vulnerable patients who might have high incidence of treatment-related adverse events while receiving nal-IRI + 5-FU/LV therapy.

The OS of 5.0 months in the present cohort was comparable to published real-world data [24-26], but it was lower than that of the nal-IRI + 5-FU/LV arm (6.1 months) of the NAPOLI-1 study [4]. Furthermore, the objective tumor response rate (7.6%) in the present cohort was lower than that in the NAPOLI-1 study (16%) [4]. Differences in demographic characteristics between the two cohorts may potentially lead to variations in survival outcomes because poor ECOG performance and the presence of liver metastases are both independent negative prognosticators for OS, and later-line chemotherapy upon nal-IRI treatment had a trend for shorter OS in the univariate analysis in our study. In the present cohort, we had more cases with an ECOG performance of 2 or 3 (28%), whereas only < 10% of the NAPOLI-1 study had a Karnofsky performance status score of 50-70 [4]. Patients in the present study had a higher percentage of liver metastases (68%) than those in the NAPOLI-1 study (64%) [4]. Furthermore, 41% of the patients in the present cohort received nal-IRI + 5 FU/LV as a third-line or later chemotherapy option, compared to 34% of the patients in the NAPOLI-1 study [4]. In addition, survival discrepancy between our cohort and NAPOLI-1 cohort reflected the difference between clinical trial efficacy and real-word effectiveness [27]. Before the availability of nal-IRI in Taiwan, we previously reported that the median OS was 4.2 months in PDAC patients who received second line therapy [28, 29]. Despite the innate demographic differences and clinical trial setting between our cohort and NAPOLI-1 study, this study showed that survival outcomes of patients with PDAC in Taiwan have improved since the approval of nal-IRI + 5-FU/LV reimbursement. The present study is the first to demonstrate the predictive value of the ANS on efficacy and safety profiles in PDAC patients who received palliative chemotherapy with nal-IRI + 5-FU/LV.

This study was strengthened by the inclusion of a large number of patients from nine medical centers across Taiwan. However, some limitations merit further discussion. First, selection bias did exist, due to the retrospective design of the study. Second, the ANS was developed based on PDAC patients treated with nal-IRI + 5-FU/LV therapy in the present study; whether its applicability would be generalized in PDAC patients receiving chemotherapy with other chemotherapeutic regimens remains uncertain. Therefore, the performance of the ANS as observed in the present study needs external validation for confirming its ability to predict the survival outcome and safety profiles of various antitumor treatments. Third, all patients underwent UGT1A1 genotype testing, and those homozygous for the UGT1A1*28 allele reduced the initial nal-IRI dose by 20 mg/m^2 in the NAPOLI-1 study [4]. However, the UGT1A1 genotype test is not routinely performed in Taiwan. The precise incidence of UGT1A1 polymorphism and its relationship with side effects among the three ANS groups in our study is unknown. Finally, the cut-off value as a prognostic factor for albumin was 4 g/dL and NLR was 5 in the post-hoc analysis of the NAPOLI-1 study [5]. We arbitrarily allocated the median value of albumin and NLR as cut-off values in the present study because it is easier to use in clinical practice and allowed the division of the patients into three groups with relatively equal patient numbers. There is currently no consensus on the optimal cut-off value of albumin and NLR used as the prognostic factor in patients with PDAC. Further studies are necessary to reach a consensus on the optimal albumin and NLR cut-off values for prognoses in patients with PDAC. In addition, the performance of the ANS, as observed in the present study, requires external validation to confirm its ability to predict patient's treatment efficacy and tolerance of various antitumor treatments.

Conclusions

The results of the present study showed that the ANS, the evaluation of both albumin and NLR, demonstrated better prognostic accuracy than albumin or NLR alone in PDAC patients receiving nal-IRI + 5-FU/LV therapy. Patients with a higher ANS were found to have poorer survival outcomes, lower tumor response rates, and higher incidences of severe treatment-related adverse events than those with a lower ANS. The ANS may therefore be widely used as a simple prognosticator for survival outcome and safety profiles in PDAC patients treated with nal-IRI + 5-FU/LV.

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Informed consent requirements were waived because of the retrospective nature of the analysis, and all data were de-identified as well as encrypted.

Disclosure of conflict of interest

Author Sz-Chi Chiu was employed by the company PharmaEngine, Inc. The remaining authors declare that there is no conflict of interest.

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