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Editorial

Platelet-to-lymphocyte ratio and CA19-9 are simple and informative prognostic factors in patients with resected pancreatic cancer

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We read with great interest the paper "Combined preoperative platelet-to-lymphocyte ratio and serum carbohydrate antigen 19-9 level as a prognostic factor in patients with resected pancreatic cancer" published in *Hepatobiliary & Pancreatic Diseases International* [1]. The authors reviewed the oncological outcomes of 103 patients with pancreaticoduodenectomy, distal pancreatectomy or total pancreatectomy for pancreatic ductal adenocarcinoma (PDAC). They correlated the overall (OS) and disease specific survival (DSS) of these patients with platelet-to-lymphocyte ratio (PLR) and carbohydrate antigen 19-9 (CA19-9) level which were measured within one month prior to surgery. The authors used cutoff values of 129.1 for PLR and 74.0 U/mL for CA19-9. The worst prognosis was found for patients with high PLR and high CA19-9 (five-year OS = 11.9%, DSS = 16.8%). An intermediate survival for patients with either one of the two factors was decreased (five-year OS = 31.9% and DSS = 36.4%), and the best prognosis for patients with low PLR and low CA19-9 (five-year OS = 44.0% and DSS = 47.7%).

Incidence of pancreatic cancer is continuously increasing globally with a 33.6% increase between 1990 and 2016; 19.7% of this increase is due to the increase of aged population, 12.4% due to population growth, and 1.5% due to change in incidence rate [2]. Despite significant improvements of the surgical techniques, intensive care, adjuvant and neoadjuvant chemoradiotherapy regimen and imaging, pancreatic cancer continues to be one of the most lethal human malignancies [3–6]. There are significant efforts in the fundamental and clinical research to find genetic and epigenetic biomarkers with increased accuracy to guide therapy in patients with PDAC [7,8]. CA19-9 and PLR are easily accessible, informative, and seem to correlate with prognosis in patients with surgical resection for pancreatic cancer.

CA19-9, also termed as sialyl Lewis-a (sLea), is the most commonly used and largely studied serum tumor marker for diagnosis and post-therapy surveillance in patients with pancreatic cancer [9]. It is expressed on the surface of the cancer cells. CA19-9 is accumulating during carcinogenesis due to epigenetic silencing of the gene for 2–6 sialyl transferase [10]. The CA19-9 was reported to be also useful in predicting prognosis in patients with pancreatic cancer [11]. Hata et al. analyzed 269 resected patients with PDAC and revealed that lymph node metastasis ($P < 0.0001$) and postoperative CA19-9 > 37 U/mL ($P < 0.0001$) were independent predictors of poor survival. Patients with higher postoperative CA19-9 levels had a higher rate of microscopically positive resection margins, hepatic and peritoneal recurrences [12]. Postoperative CA19-9 level seems to be a better prognostic factor than its preoperative measurement, and radical surgery should be offered irrespective of its initial value [12]. Hayasaki et al. analyzed 307 patients undergoing surgical resection after neoadjuvant chemoradiotherapy [13]. They found that DSS was significantly poorer in resectable patients with pretreatment CA19-9 > 500 U/mL, and that CA19-9 was not associated with DSS in resected patients with borderline resectable or locally advanced disease [13].

The inflammation represents a crossroad between intrinsic factors (genome stability genes, oncogenes, tumor suppressors) and local microenvironment (immune factors and stromal tissue) contributing to carcinogenesis and cancer progression [14–16]. Very refined prognostic biomarkers, such as IL-2, IL-6, IL-10, vascular endothelial growth factor (VEGF) and transforming growth factor (TGF), are investigated in scientific research [17,18]. However, important information about systemic inflammation, to help decision making in daily clinical practice can be obtained from routine blood samples (PLR, neutrophil-to-lymphocyte ratio [NLR], C-reactive protein) [1,19]. A meta-analysis of 34 studies including 7105 patients with pancreatic cancer revealed that high PLR and NLR were defined as values from 150 to 200, and 2 to 5, respectively [20]. They found a significant correlation between high PLR (HR = 1.143, 95% CI: 1.037 to 1.259) and NLR (HR = 1.737, 95% CI: 1.502 to 2.009) and poor survival. Both parameters had no prognostic role in patients who underwent chemoradiotherapy [20]. Song et al. conducted a meta-analysis of 8 studies including 1904 patients with pancreatic cancer [21], and found that the PLR was

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Table 1
Studies which investigated the prognostic factors in patients with pancreatic cancer.

Studies	No. of patients	Investigated predictor factors (cutoff value)	Oncological outcome	Results
Shirai et al. [22]	107, PDAC, stage I–III	PLR (143)	OS	Univariate analysis HR = 1.22; 95%CI = 1.00–2.47
Tao et al. [23]	159, PDAC, all resected	PLR (130.96) CA19-9 (39 U/mL) NLR (2.12)	LN metastasis	Multivariate analysis PLR: HR = 1.852; 95%CI = 0.832–4.123; $P = 0.131$ CA19-9: HR = 2.738; 95%CI = 1.151–6.515; $P = 0.023$ NLR: HR = 2.588; 95%CI = 1.246–5.376; $P = 0.011$
Asari et al. [24]	37, PDAC, stage I-III	PLR (225)	OS	Multivariate analysis HR = 3.05; 95%CI = 1.21–7.71
Bhatti et al. [25]	84, PDAC, stage I-III	PLR (100-200)	OS	Univariate analysis HR = 0.98; 95%CI = 0.89–1.07
Kim et al. [26]	302 PDAC, all advanced, under chemotherapy, none resected	PLR (180) CA19-9 (1000 U/mL) NLR (3.8) CRP-albumin ratio (3.85)	OS	Multivariate analysis PLR: HR = 1.345; 95%CI = 1.048–1.726 CA19-9: HR = 1.373; 95%CI = 1.066–1.768 NLR: HR = 1.712; 95%CI = 1.326–2.211 CRP-albumin ratio: HR = 1.454; 95%CI = 1.106–1.911
			PFS	Multivariate analysis PLR: non-significant NLR: HR = 1.837; 95%CI = 1.432–2.356 CA19-9: HR = 1.326; 95%CI = 1.039–1.694 CRP-albumin ratio: HR = 1.48; 95%CI = 1.166–1.878
Feng et al. [27]	214 patients with advanced pancreatic cancer, stage 3 and 4 disease	PLR (124.6) NLR (2.8) WBC (5.8 x10^9/L) Granulocyte count (3.7 x 10^9/L)	OS	Multivariate analysis PLR: HR = 1.078; 95%CI = 0.752–1.546; $P = 0.68$ NLR: HR = 1.435; 95%CI = 0.913–2.257; $P = 0.11$ WBC: HR = 1.808; 95%CI = 1.055–3.096; $P = 0.03$ Granulocyte count: HR = 7.346; 95%CI = 1.275–42.321
Gao et al. [28]	122 inoperable pancreatic cancer	PLR (142.14) NLR (3.81)	OS	Univariate PLR: OR = 0.922; 95%CI = 0.641–1.325; $P = 0,660$ NLR: OR = 1.007; 95%CI = 0.701–1.448; $P = 0.969$ Multivariate analysis: non-significant
Song et al. [29]	59 metastatic pancreatic cancers	CA19-9 (626 U/mL) NLR (3.75)	OS	Multivariate analysis CA19-9: HR = 2.22; 95%CI = 1.240-3.976; $P = 0.007$ NLR: HR = 3.698; 95%CI = 2.044–6.692; $P < 0.001$
Lee et al. [30]	82 patients with advanced disease, receiving gemcitabine and erlotinib	PLR (150) NLR (5) CA19-9 (1000 U/mL) CRP–albumin ratio (0.5)	OS	Univariate analysis PLR: HR = 1.43; 95%CI = 0.79-2.60; $P = 0.24$ CA19-9: HR = 1.45; 95%CI = 0.79-2.66; $P = 0.22$ Multivariate analysis NLR: HR = 2.76; 95%CI = 1.33-5.75; $P = 0.007$ CRP–albumin ratio: HR = 1.60; 95%CI = 0.84–3.04; $P = 0.151$
			PFS	Univariate analysis PLR: HR = 1.22; 95%CI = 0.73–2.02; $P = 0.448$ CA19-9: HR = 1.33; 95%CI = 0.81–2.21; $P = 0.264$ NLR: HR = 1.80; 95%CI = 1.04–3.19; $P = 0.049$ CRP–albumin ratio: HR = 1.72; 95%CI = 1.07–2.80; $P = 0.047$

PDAC: pancreatic ductal adenocarcinoma; PLR: platelet-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; LN: lymph node; HR: hazard ratio; 95% CI: 95% confidence interval; LRR: local recurrence rate; OS: overall survival; PFS: progression free survival; DFS: disease free survival; DSS: disease specific survival; OR: odds ratio; WBC: white blood cells.

associated with decreased OS (HR = 1.22, 95% CI: 1.04 to 1.43, $P = 0.02$), especially in Asian studies, patients with metastatic disease and for values of PLR over 150. We summarized other studies investigating the prognostic factors in patients with pancreatic cancer (Table 1).

In conclusion, CA19-9 and platelet-to-lymphocyte ratio are easily accessible, informative, and correlate with prognosis in patients with surgical resection for pancreatic cancer. However, studies investigating these biomarkers present a significant heterogeneity, and should be validated by prospectively collected data.

Contributors

NI wrote the first draft of the article, performed acquisition of the data, analyzed and interpreted the data. BM analyzed and interpreted the data, revised the manuscript for important intellectual content. HS, EHA and ME analyzed and interpreted the data. All authors approved the final version of the manuscript. NI is the guarantor.

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