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

Negoi, Ionut; Beuran, Mircea; Hostiuc, Sorin; El-Hussuna, Alaa; de-Madaria, Enrique

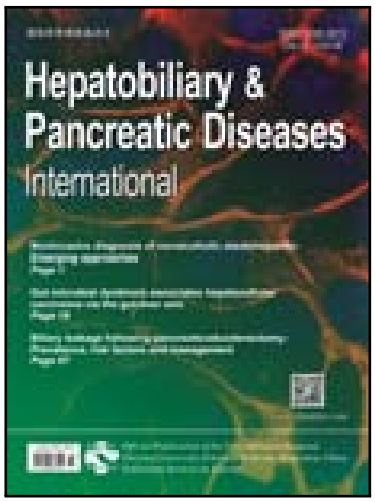
*Published in:*
Hepatobiliary & pancreatic diseases international : HBPD INT

*DOI (link to publication from Publisher):*
10.1016/j.hbpd.2019.03.011



*Publication date:*
2019

*Document Version*
Accepted author manuscript, peer reviewed version




# Platelet-to-lymphocyte ratio and CA 19-9 are simple and informative prognostic factors in patients with resected pancreatic cancer

Ionut Negoi , Mircea Beuran , Sorin Hostiuc , Thomas Pinkney , Alaa El-Hussuna , Enrique de-Madaria

PII: S1499-3872(19)30072-4
DOI: https://doi.org/10.1016/j.hbpd.2019.03.011
Reference: HBPD 158

To appear in: *Hepatobiliary & Pancreatic Diseases International*

Received date: 18 February 2018
Accepted date: 26 March 2019

Please cite this article as: Ionut Negoi , Mircea Beuran , Sorin Hostiuc , Thomas Pinkney , Alaa El-Hussuna , Enrique de-Madaria , Platelet-to-lymphocyte ratio and CA 19-9 are simple and informative prognostic factors in patients with resected pancreatic cancer, *Hepatobiliary & Pancreatic Diseases International* (2019), doi: https://doi.org/10.1016/j.hbpd.2019.03.011

**Editorial**

# Platelet-to-lymphocyte ratio and CA 19-9 are simple and informative prognostic factors in patients with resected pancreatic cancer

**Ionut Negoi[1,2,*], Mircea Beuran[1,2], Sorin Hostiuc[1,3], Thomas Pinkney[4], Alaa El-Hussuna[5], Enrique de-Madaria[6]**

(Negoi I, Beuran M, Hostiuc S, Pinkney T, El-Hussuna A, de-Madaria E)

[1] *Carol Davila University of Medicine and Pharmacy Bucharest, Romania*

[2] *Department of General Surgery, Emergency Hospital of Bucharest, Romania*

[3] *Department of Legal Medicine and Bioethics, National Institute of Legal Medicine Mina Minovici, Romania*

[4] *Academic Department of Surgery, University of Birmingham, Birmingham, UK*

[5]*Department of Surgery, Aalborg University Hospital, Hobrovej 18-22, 9000, Aalborg, Denmark*

[6]*Servicio de Aparato Digestivo, Unidad de Patología Pancreática, Gastroenterology Department, Pancreatic Unit, Hospital General Universitario de Alicante, Alicante, Spain*

*Bucharest, Romania*

*** Corresponding Author**: Ionut Negoi, Carol Davila University of Medicine and Pharmacy Bucharest, Romania (E-mail address: negoiionut@gmail.com)

**Received: 18 February 2018**

**Accepted: 26 March 2019**

**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, PT, EHA and ME analyzed and interpreted the data. All authors approved the final version of the manuscript. NI is the guarantor.

**Funding:** None.

**Ethical approval:** Not needed.

**Competing interest:** No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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 (CA 19-9) 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 CA 19-9. The worst prognosis was found for patients with high PLR and high CA 19-9 (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 CA 19-9 (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]. CA 19-9 and PLR are easily accessible, informative, and seem to correlate with prognosis in patients with surgical resection for pancreatic cancer.

CA 19-9, 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. CA 19-9 is accumulating during carcinogenesis due to epigenetic silencing of the gene for 2-6 sialyl transferase [10]. The CA 19-9 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 CA 19-9 > 37 U/mL ($P$<0.0001) were independent predictors of poor survival. Patients with higher postoperative CA 19-9 levels had a higher rate of microscopically positive resection margins, hepatic and peritoneal recurrences [12]. Postoperative CA 19-9 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 CA 19-9 > 500 U/mL, and that CA 19-9 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 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.

In conclusion, CA 19-9 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.

## References

1 Sakamoto T, Saito H, Amisaki M, Tokuyasu N, Honjo S, Fujiwara Y. Combined preoperative platelet-to-lymphocyte ratio and serum carbohydrate antigen 19-9 level as a prognostic factor in patients with resected pancreatic cancer. Hepatobiliary Pancreat Dis Int 2019. Articles in press.

2 Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Akinyemiju TF, Al Lami FH, Alam T, Alizadeh-Navaei R, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2016: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2018;4:1553-1568.

3 Negoi I, Beuran M, Hostiuc S, Negoi RI, Inoue Y. Surgical Anatomy of the Superior Mesenteric Vessels Related to Pancreaticoduodenectomy: a Systematic Review and Meta-Analysis. J Gastrointest Surg 2018;22:802-817.

4 Negoi I, Beuran M, Hostiuc S, Negoi RI, Inoue Y. Surgical Anatomy of the

Superior Mesenteric Vessels Related to Colon and Pancreatic Surgery: A Systematic Review and Meta-Analysis. Sci Rep 2018;8:4184.

5 Negoi I, Hostiuc S, Runcanu A, Negoi RI, Beuran M. Superior mesenteric artery first approach versus standard pancreaticoduodenectomy: a systematic review and meta-analysis. Hepatobiliary Pancreat Dis Int 2017;16:127-138.

6 Beuran M, Negoi I, Paun S, Ion AD, Bleotu C, Negoi RI, et al. The epithelial to mesenchymal transition in pancreatic cancer: A systematic review. Pancreatology 2015;15:217-225.

7 Negoi I, Hostiuc S, Sartelli M, Negoi RI, Beuran M. MicroRNA-21 as a prognostic biomarker in patients with pancreatic cancer - A systematic review and meta-analysis. Am J Surg 2017;214:515-524.

8 Loosen SH, Neumann UP, Trautwein C, Roderburg C, Luedde T. Current and future biomarkers for pancreatic adenocarcinoma. Tumour Biol 2017;39:1010428317692231.

9 Scarà S, Bottoni P, Scatena R. CA 19-9: Biochemical and Clinical Aspects. Adv Exp Med Biol 2015;867:247-260.

10 Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. J Gastrointest Oncol 2012;3:105-119.

11 Dong Q, Yang XH, Zhang Y, Jing W, Zheng LQ, Liu YP, et al. Elevated serum CA19-9 level is a promising predictor for poor prognosis in patients with resectable pancreatic ductal adenocarcinoma: a pilot study. World J Surg Oncol 2014;12:171.

12 Hata S, Sakamoto Y, Yamamoto Y, Nara S, Esaki M, Shimada K, et al. Prognostic impact of postoperative serum CA 19-9 levels in patients with resectable pancreatic cancer. Ann Surg Oncol 2012;19:636-641.

13 Hayasaki A, Isaji S, Kishiwada M, Fujii T, Iizawa Y, Kato H, et al. Survival Analysis in Patients with Pancreatic Ductal Adenocarcinoma Undergoing Chemoradiotherapy Followed by Surgery According to the International Consensus on the 2017 Definition of Borderline Resectable Cancer. Cancers

(Basel) 2018;10.

14 Munn LL. Cancer and inflammation. Wiley Interdiscip Rev Syst Biol Med 2017;9.

15 Padoan A, Plebani M, Basso D. Inflammation and Pancreatic Cancer: Focus on Metabolism, Cytokines, and Immunity. Int J Mol Sci 2019;20.

16 Coussens LM, Zitvogel L, Palucka AK. Neutralizing tumor-promoting chronic inflammation: a magic bullet? Science 2013;339:286-291.

17 Yako YY, Brand M, Smith M, Kruger D. Inflammatory cytokines and angiogenic factors as potential biomarkers in South African pancreatic ductal adenocarcinoma patients: A preliminary report. Pancreatology 2017;17:438-444.

18 Yako YY, Kruger D, Smith M, Brand M. Cytokines as Biomarkers of Pancreatic Ductal Adenocarcinoma: A Systematic Review. PLoS One 2016;11:e0154016.

19 Fujiwara Y, Haruki K, Shiba H, Hamura R, Horiuchi T, et al. C-Reactive Protein-based Prognostic Measures Are Superior at Predicting Survival Compared with Peripheral Blood Cell Count-based Ones in Patients After Curative Resection for Pancreatic Cancer. Anticancer Res 2018;38:6491-6499.

20 Oh D, Pyo JS, Son BK. Prognostic Roles of Inflammatory Markers in Pancreatic Cancer: Comparison between the Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio. Gastroenterol Res Pract 2018;2018:9745601.

21 Song W, Tian C, Wang K, Zhang RJ, Zou SB. Preoperative platelet lymphocyte ratio as independent predictors of prognosis in pancreatic cancer: A systematic review and meta-analysis. PLoS One 2017;12:e0178762.