

Original Article

Could neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and mean platelet volume serve as potential biomarkers for detection of resectable pancreas ca?

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Abstract: Introduction: Pancreatic cancer (PAC) is the fourth leading cause of cancer death in man and women. The aim of this study was to investigate the prognostic significance of three systemic inflammation-based factors, preoperative neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and mean platelet volume (MPV) in patients undergoing PAC surgery. Materials and methods: A total of 41 stage 1 and stage 2 PAC patients and 43 age-matched and sex-matched healthy participants, who were diagnosed as healthy, were included in the study. Preoperative data including MPV, NLR, and PLR were recorded. Results: NLR, PLR, and MPV were significantly higher in preoperative stage 1 and stage 2 PAC patients compared with age-matched and sex matched healthy participants (5.51 vs 2.5, $P=0.002$; 180 vs 134, $P=0.017$; 9.2 vs 2.5 fl, $P=0.004$). The results of ROC analysis suggested 2.94 as the cutoff value for NLR [area under the curve (AUC): 0.705, $P=0.002$; sensitivity: 65%, specificity: 72%], 144.9 as the cutoff value for PLR (AUC: 0.684, $P=0.01$ sensitivity: 62%, specificity: 76%), and 8.7 fl as the cutoff value of MPV (AUC: 0.693, $p=0.006$; sensitivity: 64%, specificity: 73%). Conclusion: Our results suggest that NLR, PLR and MPV may be used as easily available additional biomarkers for PAC in screening general population.

Keywords: Pancreatic cancer, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, mean platelet volume

Introduction

Many molecular markers have been proposed for the early diagnosis of pancreatic cancer (PAC), but most are not ready to be included as part of the routine diagnostic algorithm because they still lack sensitivity, specificity or reproducibility. CA19-9 is the most widely used serum-based marker for the diagnosis and follow-up of pancreatic cancer. The sensitivity and specificity vary, ranging from 70% to 90% and 68% to 91%, respectively [1]. However, Ca19-9 lacks sensitivity for early or small-diameter pancreatic cancers. Poorly differentiated pancreatic cancers also appear to produce less Ca19-9 than either moderately or well differentiated cancers [2]. Another limitation is that CA19-9 can also be elevated in benign inflammatory and cholestatic diseases of the pancreaticobiliary tract [2].

For more than 3 decades, information on neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), mean platelet volume (MPV) has been widely available to health care practitioners, as part of the data provided in the full blood count. Elevated NLR has reportedly been associated with poor survival following resection or chemotherapy in variety of cancer [3-5]. In colorectal cancer, an increasing number of studies have reported an association between elevated NLR (> 5) and poor prognosis [5].

The role of new tumor marker PLR has been defined recently in prognosis of PAC. This is based on the fact that PAC causes thrombosis and lymphocytopenia [6]. Platelet activation is a link in the pathophysiology of diseases prone to thrombosis and inflammation. Lymphocytopenia occurs due to systemic inflammation

Table 1. Hematological results of the patients and controls

	PAC	Control	P Value
Neutrophil	6092±4212	3944±1219	0.002
PLT	230±84	244±64	0.39
MPV	9.21±1.2	8.5±0.82	0.004
NLR	5.51±7.3	2.5±1.1	0.002
PLR	180±103	135±65	0.017

Abbreviations: PLT, Platelet; MPV, Mean platelet volume; NLR, Neutrophil/lymphocyte ratio; PLR, Platelet/lymphocyte ratio; PAC, Pancreatic Cancer.

caused by cancers that release a number of inhibitory immunologic mediators [7].

The diagnostic value of platelet size has recently been shown to be elevated in neoplastic disorders particularly in gastric cancer [8]. Moreover, it has been determined that platelet size has a predictive value for bone marrow metastasis in patients with solid tumors [9]. Numerous platelet markers, including MPV, have been investigated in connection with both thrombosis and inflammation [10, 11].

The aim of this study was to investigate the prognostic significance of three systemic inflammation-based factors, preoperative NLR, PLR and MPV in patients undergoing stage 1 and stage 2 PAC surgery.

Material and methods

We conducted the study in the dates covering December 2010 to November 2013 by medical records of patients with stage 1 and stage 2 PAC who examined at Ankara Dış Kapı Education and Research Hospital. Patients with coexistent hematological disorders, renal disease, chronic infection, coronary artery or cerebrovascular disease, and other types of cancers were excluded from the study. We also excluded the patients who had received preoperative chemoradiotherapy and those with postoperative infections including wound infections. The staging of PAC was performed according to the tumor-nodes-metastases (TNM) classification, in accordance with the American Joint Committee on Cancer recommendations. According to the 7th edition of American Joint Committee on Cancer recommendations, unresectable stage 3 and stage 4 pancreatic cancers excluded from this study. In total, 41 stage 1 and stage 2 PAC patients and 43 age-matched and sex-matched healthy participants, who were

diagnosed as healthy, were included in the study. Preoperative and postoperative data including MPV, NLR, and PLR were recorded. Preoperative data were obtained from medical records in the week before the operation. CBCs of ethylenediaminetetraacetic acid-treated (EDTA) blood were measured using Siemens Healthcare Diagnostic Item ADVIA 2120i (Siemens Healthcare, Malvern, Pennsylvania, USA), and blood samples were analyzed within 1 h after vein puncture.

Statistical analysis

SPSS statistical analyze software (SPSS 16.0, Chicago, Illinois, USA) was used for statistical analyses. Data were expressed as mean ± SD. An independent t-test was used to compare the parameters of preoperative PAC patients and controls. The χ^2 -test was used to compare the categorical variables. The paired sample test was used to compare the variables. Receiver operating characteristic (ROC) curve analysis was carried out to identify optimal cutoff values of NLR, PLR, and MPV. A *P*-value cutoff less than 0.05 was considered statistically significant.

Results

A total of 41 patients with PAC and a control group of 43 healthy participants were enrolled in this study. There was no statistical difference between the groups in age and sex. Independent of TNM stage, NLR, PLR, and MPV were significantly higher in preoperative PAC patients compared with age-matched and sex matched healthy participants (5.51 vs 2.5, *P*=0.002; 180 vs 134, *P*=0.017; 9.2 vs 2.5 fl, *P*=0.004; **Table 1**). We further investigated NLR, PLR, and MPV according to TNM stage. There was no statistically significant difference between NLR, PLR, and MPV on stage 1 and stage 2 pancreatic cancers. The results of ROC analysis suggested 2.94 as the cutoff value for NLR [area under the curve (AUC): 0.705, *P*=0.002; sensitivity: 65%, specificity: 72%], 144.9 as the cutoff value for PLR (AUC: 0.684, *P*=0.01 sensitivity: 62%, specificity: 76%), and 8.7 fl as the cutoff value of MPV (AUC: 0.693, *P*=0.006; sensitivity: 64%, specificity: 73%; **Figure 1**).

Discussion

Pancreatic adenocarcinoma (PAC) is a devastating disease with an extremely poor progn-

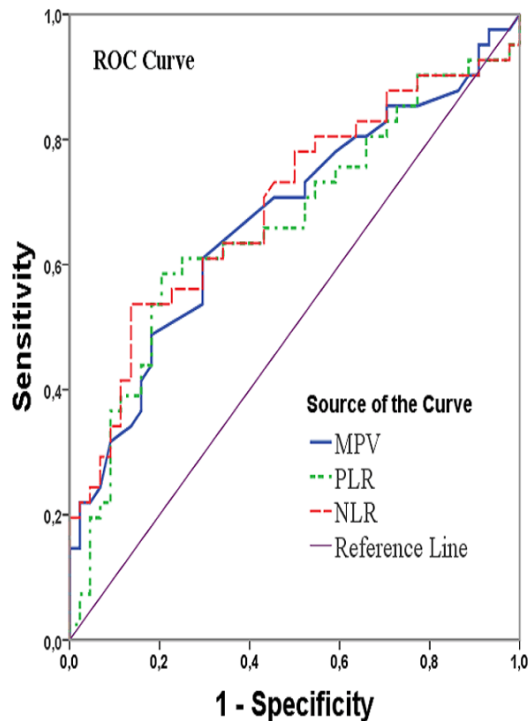


Figure 1. Receiver operating characteristic curves NLR, PLR and MPV for predicting stage 1 and stage 2 pancreatic cancer. Abbreviations: MPV, Mean platelet volume; NLR, Neutrophil/lymphocyte ratio; PLR, Platelet/lymphocyte ratio.

sis and prompt diagnostic evaluation is vital when PAC is suspected. The diagnostic role of CA19-9 as a test for the detection of pancreatic malignancy remains poorly defined, because, as in other diagnostic modalities, the utility of CA19-9 has several confounding limitations [1]. After inflammatory processes have emerged as key mediators of pancreatic cancer development and progression, many inflammatory pathways have been identified in recent years [12, 13]. Unfortunately, except Ca19-9, a novel diagnostic marker was not developed using inflammatory process of pancreatic malignancy, that platelet and lymphocyte related markers are well known to be increased ongoing inflammation process. To the best of our knowledge, this is the first novel study to investigate MPV, NLR and PLR as other diagnostic and monitoring markers for PAC.

In the development and progression of cancer, inflammation is a crucial and essential process [14, 15]. Persistence of the inflammatory process within the tumor leads to an increase in the proliferation of tumor cells, angiogenesis,

and the inhibition of apoptosis. Several reports have suggested that markers of systemic inflammation including cytokines, C-reactive protein, NLR, and PLR may provide useful information on the prognosis of colorectal gastrointestinal cancer [16, 17]. Thus, pathogenesis of PAC appears to be an inflammation-driven malignancy, as well as colorectal gastrointestinal cancer. Usually, cancer cells are a source of inflammatory cytokines and growth factors. Interleukin-6 (IL-6) is an inflammatory cytokine that can cause carcinogenesis through several signal pathways involved in carcinogenesis, as well as metastasis of a variety of malignancies, including PAC [18].

It has been shown that PAC patients have higher levels of IL-6 compared with a healthy control group [18]. We acknowledged that IL-6 is released from leukocytes and is also able to activate the production of IL-6 by tumor cells through the IL-6 receptor [19]. Besides their role in homeostasis, platelets and leucocytes take part in the pathophysiology of tumor angiogenesis. Platelets are known to be the major transporter of vascular endothelial growth factor, which is the target for antiangiogenic therapies [20]. Vascular endothelial growth factor accelerates the formation of blood vessels in the tumor and facilitates infiltration and spread to adjacent tissues, which in turn promotes the formation of metastases [20]. Solid tumors such as renal, gastric, and colon malignancies produce IL-6, which induces the proliferation and differentiation of megakaryocyte progenitors through specific receptors [21-23]. This process causes platelet activation and aggregation. Platelet size has been shown to reflect changes in the level of platelet stimulation and the rate of platelet production [24].

Increased MPV value, an indicator of platelet volume, points the presence of a subpopulation of young, metabolically and enzymatically more active platelets taking part in the process of homeostasis [25]. We speculate that increased MPV in a patient group newly diagnosed with PAC may be a reflection of ongoing inflammation, and it can be related to increased levels of cytokines, particularly IL-6. Thus, we suggest that MPV could be used for detection for PAC.

NLR and PLR are two representative indices of systemic inflammation. It has been shown that

a preoperative NLR of greater than 4 or 5 is associated with a poor outcome in gastric cancer, non-small-cell lung cancer, and ovarian cancer [26-28]. Neutrophils and leukocytes play a crucial role in the host systemic inflammatory response. A nonspecific systemic inflammatory response due to a tumor leads to an increase in the levels of circulating neutrophils and an elevated NLR, all of which are clearly demonstrated in our study.

Lymphocytes play a key role in cytotoxic cell death and the production of cytokines that inhibit proliferation and metastatic spread of tumor cells [29, 30]. In contrast, neutrophils have a protumor effect by being the primary source of circulating angiogenesis-regulating chemokines, growth factors, and proteases [31]. Elevated neutrophil levels may result in an increase in angiogenesis, which promotes development and progression of the neoplasm [31]. Therefore, NLR can be considered as the balance between protumor inflammatory status and antitumor immune status. At present, there is little information on the relevance of these prognostic markers to both diagnosis and monitoring of PAC. Our results demonstrate that newly diagnosed PAC patients have significantly higher NLR and PLR compared with the healthy control group.

We have some limitations to our study. First, our study has a single-center design and a retrospective nature of data acquisition. Second, the high NLR, PLR, and MPV that were observed in our study group of newly diagnosed PAC patients may be a reflection of a nonspecific inflammatory response due to PAC. Hence, any inflammatory or malignant process can lead to an increase in these parameters. In practice, these markers, if used alone, may have a low positive predictive value in screening an asymptomatic population. Therefore, prospective studies with inflammatory marker screening as IL-6, TNF on a larger number of asymptomatic patients are needed to compare the performance of NLR, PLR, and MPV with that of other diagnostic and monitoring tests to confirm their diagnostic utility. Despite these limitations, we think our findings are still important.

Conclusion

Our results suggest that patients with stage I and stage II disease have higher levels of these

parameters than controls. Thus, patients with high NLR, PLR, and MPV with suspicious symptoms and/or signs of PAC are candidates for early evaluation, which can prevent delay in the diagnosis of PAC.

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Disclosure of conflict of interest

None.

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