Chapter 3

Neutrophil/Lymphocyte Ratio, Platelet/Lymphocyte Ratio, and Mean Platelet Volume for Detection of Resectable Pancreas Cancer

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Additional information is available at the end of the chapter

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Abstract

Several biomarkers have been preferred for the early diagnosis of pancreatic adenocancer (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. However, CA19-9 lacks sensitivity for early or small-diameter pancreatic cancers. 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. However, these biomarkers have more than used in the routine. The present chapter shares the prognostic significance of the hematological parameters in the light of our own findings and recent studies in the literature.

Keywords: NLR, PLR, MPV, resectable pancreas cancer, biomarker

1. Introduction

Pancreatic adenocarcinoma is a devastating disease with an extremely poor prognosis and prompt diagnostic evaluation is vital when PAC is suspected. CA19-9 is the most widely used serum-based marker for the diagnosis and follow-up of pancreatic cancer [1]. 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. The sensitivity and specificity of CA19-9 vary, ranging from 70 to 90% and 68 to 91%, respectively. 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. Another limitation is that CA19-9 can also be elevated in benign inflammatory and cholestatic diseases of the pancreaticobiliary tract [2, 3].

After inflammatory processes have emerged as key mediators of pancreatic cancer development and progression, many inflammatory pathways have been identified in recent years. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and mean platelet volume (MPV) are the most used in the literature [4–6]. Elevated NLR has reportedly been associated with poor survival following resection or chemotherapy in a variety of cancer. In colorectal cancer, an increasing number of studies have reported an association between elevated NLR and poor prognosis [7]. The first study done by us, including a total of 41 resectable PAC patients and 43 age-matched and sex-matched healthy participants [8]. 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) (**Table 1**). Our results suggested that NLR, PLR and MPV might be used as easily available additional biomarkers for PAC in screening general population (**Figure 1**).

The role of new tumor marker PLR has been defined recently in the prognosis of PAC [9]. Miglani et al. reported that PLR has been at least as good as CA 19-9 as diagnostic marker to differentiate between malignant and inflammatory head mass of pancreas. This is based on the fact that PAC causes thrombosis and lymphocytopenia. Platelet activation is a link in the pathophysiology of diseases prone to thrombosis and inflammation. Lymphocytopenia occurs due to systemic inflammation caused by cancers that release a number of inhibitory immunologic mediators [10]. The diagnostic value of platelet size has recently been shown to be elevated in neoplastic disorders particularly in gastric cancer. Moreover, it has been determined that platelet size has a predictive value for bone marrow metastasis in patients with solid tumors [11]. Numerous platelet markers, including MPV, have been investigated in connection with both thrombosis and inflammation.

	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

Table 1. Hematological results of the patients and controls.

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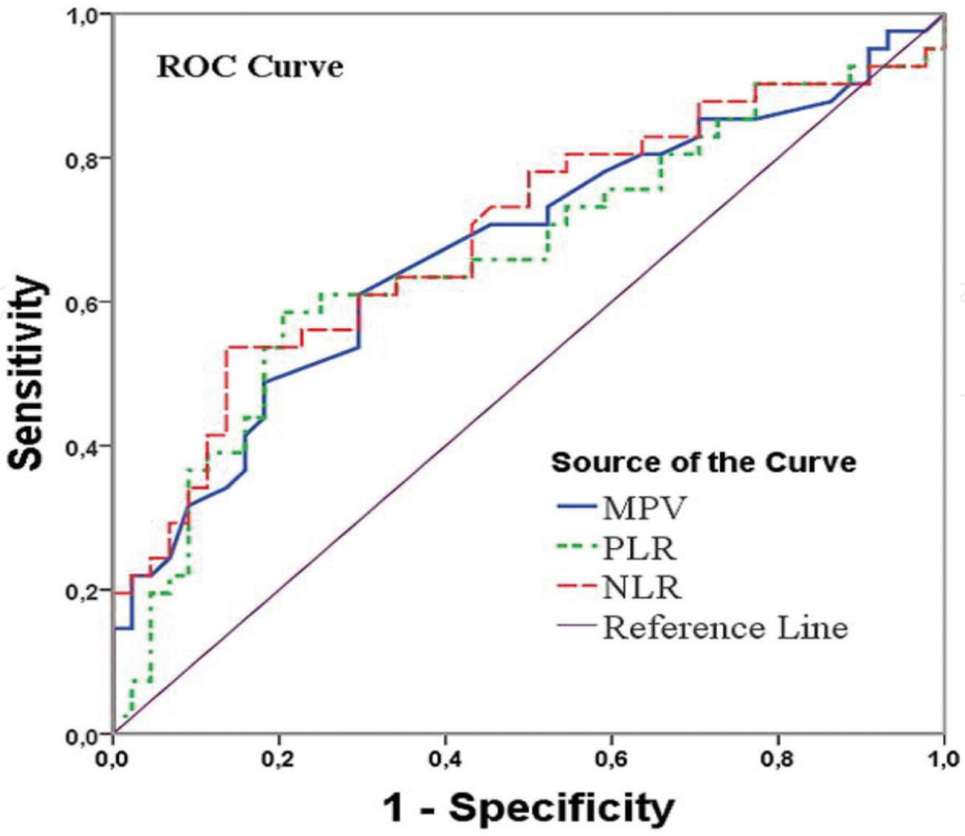

Figure 1. Receiver operating characteristic curves NLR, PLR and MPV for predicting stage 1 and stage 2 pancreatic cancer. Abbreviations: MPV: mean platelet volume; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio.

2. Inflammation and PAC

In the development and progression of cancer, inflammation is a crucial and essential process [12]. Persistence of the inflammatory process within the tumor leads to an increase in the proliferation of tumor cells, angiogenesis, and the inhibition of apoptosis [13, 14]. 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 [15, 16]. 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 [17].

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. Besides their role in homeostasis, platelets and leucocytes take part in the pathophysiology of tumor angiogenesis [19]. Platelets are known to be the major transporter of vascular endothelial growth factor, which is the target for antiangiogenic therapies. 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. 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.

According to the literature, lymphocytes play a key role in cytotoxic cell death and the production of cytokines that inhibit proliferation and metastatic spread of tumor cells. In contrast, neutrophils have a protumor effect by being the primary source of circulating angiogenesis-regulating chemokines, growth factors, and proteases [4]. Elevated neutrophil levels may result in an increase in angiogenesis, which promotes development and progression of the neoplasm [6]. 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. Similarly as being in our experience, newly diagnosed PAC patients have high NLR and PLR values than healthy human.

3. Diagnostic weakness and missing points

Even with decades passed, measurement of this parameter is still not standardized, as it can easily be obtained with electronic meters. This is a major flaw because many pre-analytical and analytical variables can affect platelet size. The pre-analytical variables include vascular occlusion method, the correctness of the filling of the vial and the mixing of the sample, the type of anticoagulant, the storage temperature and the duration of the analysis. Any inflammatory or malignant process can lead to an increase in these parameters [21].

In practice, these markers, if used alone, may have a low positive predictive value in screening an asymptomatic population. Getting in touch with EDTA, *ethylene diamine tetra acetic acid*, the most common anticoagulant used in laboratory practice, effects the platelet morphology and leads to swelling and an increase in volumes. The differences in the methodology of platelet counting with different automated analytics are most like to be major analytical variable for the measurement [22].

The poor standardization of the number of physiological variables affecting platelet size and the poor standardization of this parameter makes it very unlikely that small differences in this parameter, defined by clinical trials in various clinical conditions, could be used for clinical purposes. In the future, better methodological standardization and more personalized reference intervals may make them as a reliable parameter for differential diagnosis and prognostic identification in daily clinical practice, but there is a need for well-designed clinical trials to confirm this hypothesis [23].

4. Diagnostic efficiency and strengths

Certainly, the most important advantage is their cost-efficiency. In routine analyzes of PAC, several parameters have been being used at high cost. These parameters have so low cost

which cannot be easily overlooked. Additionally, 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 of PAC instead of CA19-9. 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. NLR and PLR are two representative indices of systemic inflammation [24]. 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. 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 also clearly demonstrated in our study.

5. Conclusion

As in our results and the literature, the patients with PAC have higher levels of these biomarkers than healthy people. 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. 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.

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