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The prognostic value of mean platelet volume in cancer patients

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Abstract

Basic hematological indices, such as platelets count (PLT), platelet distribution width (PDW), mean platelet volume (MPV), and plateletcrit (PCT), are readily accessible and commonly tested indicators. As platelets play a significant role in many physiological and pathological pathways, the abnormalities in these indices inference about irregularities within the organism, such as homeostatic disorders or inflammation. Recent studies revealed a significant impact of MPV on the course and prediction in different types of neoplasms. This review summarizes the most important studies on the impact of MPV levels on outcome and prognosis in different types of cancer conducted in recent years. MPV levels have a significant impact on the length of progression-free survival (PFS) and overall survival (OS) in many types of solid tumors, such as colorectal carcinoma, gastric cancer, pancreatic cancer, esophageal cancer, non-small cell lung cancer, breast cancer, and thyroid cancer. They also affect the prognosis in some lymphoproliferative diseases, such as diffuse large B-cell lymphoma, acute lymphoblastic leukemia, or primary and secondary myelofibrosis.

Keywords:
mean platelet volume, platelets, prognosis, neoplasms

Introduction

Basic hematological indices, such as platelets count (PLT), platelet distribution width (PDW), mean platelet volume (MPV), and plateletcrit (PCT), are readily accessible and commonly tested indicators. As platelets play a significant role in many physiological and pathological pathways, the abnormalities in these indices inference with homeostatic disorders or inflammation. As for oncological process, the deviation from the norm in platelet parameters was first described in 1872, when Leopold Riess observed increased number of thrombocytes in patients with carcinoma [1]. In the next years, these findings were confirmed and complemented. The abnormalities in platelet indices turned out not only to be a marker of the neoplastic process but also to correlate with the severity of the disease. There are many studies confirming the correlation between the PLT and the survival time in cancer. Increased amount of thrombocytes was described to have a negative impact in common cancer entities including breast, lung, colon, esophageal, gastric, renal transitional cell, endometrial and ovarian cancers, as well as melanoma and glioblastoma [2–7]

Therefore, other platelet indices, including MPV, were considered as potential prognosis-affecting factors. MPV is a machine-calculated measurement of the average size of platelets found in the blood. It reflects the platelet production in bone marrow or platelet destruction problems [8]. Recent studies revealed a significant impact of MPV on the course and prediction in different types of neoplasms. This is particularly interesting in the context of the potential use of a relatively cheap, high reproducible, and high applicable laboratory test, such as complete blood count, as a prognostic factor in patients with cancer. The following work summarizes the current knowledge about the prognostic value of MPV in different types of cancer, as well as in prediction of post-chemotherapy complications.

Prognostic value of MPV in solid tumors

Recent studies show a correlation between MPV values and the prognosis in gastrointestinal tumors. In colorectal carcinoma, the MPV level is significantly higher than in patients with colorectal adenoma or healthy participants. There is a significant correlation between MPV and vascular invasion [9]. Furthermore, in patients with metastatic colorectal cancer, the MPV level is significantly higher compared to those with no metastasis. Interestingly, patients with lower levels of MPV have a better response to bevacizumab-combined chemotherapy [10]. The platelet indices were also evaluated as a potential biomarker for colorectal carcinoma; however, MPV showed no significant correlation with cancer antigens, such as carcinoembryonic antigen (CEA) or Ca19.9. In this matter, PLT seems to be more useful, while the results suggested that combined detection of PCT and CEA performs better than the detection of CEA alone [9].

Likewise, elevated levels of MPV are observed in gastric cancer patients. The study of Kilincalp et al. [11] revealed significantly higher MPV levels in preoperative patients compared with healthy subjects (8.31 vs. 7.85 fL; *p*: 0.007). Surgical tumor resection resulted in a significant

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decrease of MPV levels. The authors suggest that MPV may be used in the diagnosis of gastric cancer patients, independently of the clinical stage. The other study showed that in patients with this type of neoplasm, a low baseline MPV level is correlated with reduced number of metastases [12]. Interestingly, this study also proved the link between MPV level and the effectiveness of chemotherapy. Patients characterized by the lower baseline level of MPV had a better response to chemotherapy. Also individuals whose MPV level decreased after first-line chemotherapy had improved response, compared to those remaining in the high MPV-level group. The influence of MPV on the prognosis was also significant. The median overall survival (OS) of the high MPV level group was 9 months, whereas for the low MPV-level group – 15.5 months ($p < 0.001$). Progression-free survival (PFS) was respectively 3 and 6 months ($p < 0.001$). In conclusion, the authors suggested that MPV may be used in the prediction of chemotherapy response and the follow-up of gastric cancer.

The MPV value helps in differential diagnosis of nonfunctional pancreatic neuroendocrine tumors (PNET) from pancreatic adenocarcinomas. The preoperative median MPV levels are significantly lower in patients with PNET (median = 7.8 fL) than in patients with pancreatic adenocarcinomas (8.6 fL, $p = 0.014$) [13]. Furthermore, the high level of MPV corresponds to the worse course of the disease in pancreatic cancer. Study of Lembeck et al. [14] showed that patients with high MPV were more likely to have high-grade G3/4 tumors ($p = 0.004$). Moreover, they had lower average PLT, higher average bilirubin levels, and higher CRP levels. In multivariable analysis, the adverse association between large platelets and a higher risk-of-death prevailed in metastatic stage IV patients, but not in patients with early/locally advanced disease [14]. Furthermore, in patients with pancreatic ductal adenocarcinoma (PDAC), a large platelet volume is associated with high-grade G3/4 tumors ($p = 0.004$) and worse OS in patients with metastatic disease in univariable analysis ($p = 0.005$). Multivariable analysis of metastatic PDAC patients showed the adverse association between large platelets and a higher risk-of-death prevailed ($p = 0.02$) [14].

In the other paper, Zhang et al. [15] identified that prolonged prothrombin time (PT), high fibrinogen (FBG), and high MPV were independent prognostic factors for poor OS in advanced pancreatic cancer (PT > 11.3 s, $p = 0.009$; FBG > 2.5 g/L, $p = 0.011$; MPV > 12.2 fL, $p = 0.005$). They performed univariate and multivariate analysis of 320 patients using Cox proportional hazards regression, respectively. In addition, they proposed a novel scoring system based on PT, FBG, and MPV to predict the prognosis of patients with advanced pancreatic cancer (prognostic value in both stage III ($p < 0.001$) and stage IV ($p = 0.036$) patients), which might be used to evaluate the prognosis of patients with advanced pancreatic cancer.

Otherwise, opposite dependence occurs in the case of esophageal cancer. Survival analysis revealed that both the disease-free survival (DFS) and OS in the higher MPV group (MPV > 7.4 fL) are significantly longer than those in the low MPV group (DFS $p < 0.001$; OS $p = 0.003$). In addition, MPV has been identified as an independent poor prognostic factor for OS [16].

Reduced MPV is associated with shorter survival in other cancer as well. Studies by two independent research groups show that in renal cancer, worse prognosis is associated with the presence of low MPV levels [17, 18]. Yun et al. [17] revealed that lower MPV was associated with poorer prognosis histology types, more advanced T classification, worse Urinary Incontinence Severity Score (UISS), and Mayo clinic stage, size, grade, and necrosis score (SSIGN) category. Moreover, patients with low MPV levels had worse 5-year OS (50.8% vs. 75.9%) than those with high MPV levels ($p < 0.001$). The study of Seles et al. [18] confirmed the results on a larger group of patients. Further, the study showed that small platelet volume was associated with large tumors ($p = 0.043$), sarcomatoid components ($p < 0.0001$), histologic tumor necrosis ($p = 0.044$), and vascular invasion ($p = 0.022$). Decreased MPV was associated with an increased risk of death-from-renal cell carcinoma (RCC), while, the 10-year cumulative incidence of death-from-RCC was 13.1% in patients with low MPV levels and 6.2% in opposite group. A similar correlation exists in other cancer of the urinary system. In muscle-invasive bladder cancer decreased MPV level had a significantly shorter 5-year OS than patients with MPV > 9.1 fL (68.1% vs. 83.1%, $p = 0.007$) [19].

Evaluation of various hematological indices in patients with advanced non-small cell lung cancer (NSCLC) showed that MPV was significantly decreased in the NSCLC group compared with the control group. However, the PLT was significantly increased in the NSCLC group. Consequently, the MPV/PLT ratio was also decreased in the NSCLC group and it influenced OS, which was significantly shorter in the group with a low MPV/PC ratio (10.3 months vs. 14.5 months, $p = 0.0245$). Multivariate analysis confirmed that a low MPV/PC ratio was an independent unfavorable predictive factor for OS [20]. Furthermore, in locally advanced (stage IIIA/B) inoperable NSCLC MPV, as well as PLT and ECOG performance score were found as the most significant independent factors affecting survival ($p < 0.001$, $p = 0.008$, and, $p = 0.034$, respectively) [21]. Whereas, in epidermal growth factor receptor (EGFR) mutant lung adenocarcinoma, the MPV level not only influence prognosis but also predict the outcome of EGFR tyrosine kinase inhibitor (TKI) therapy. In this type of cancer, high MPV was significantly associated with shorter PFS – 8.2 months in contrast to 14.7 months in low MPV-level group ($p = 0.0137$). Interestingly, MPV was significantly increased in patients with smoking history. The EGFR–TKI therapy influenced MPV level. That parameter was decreased in group of patients after treatment, and the mean difference between pretreatment and posttreatment was 0.51 (95% confidence interval [CI] 0.38 ± 0.63, $p < 0.001$, paired *t*-test) [22].

Likewise, in patients with invasive breast cancer, pretreatment MPV levels were significantly higher than in healthy controls (8.65 fL vs. 8.34 fL, $p = 0.002$). Moreover, high MPV levels significantly correlated with clinicopathologic parameters, such as distant metastasis ($p = 0.039$), primary tumor size ($p = 0.042$), and the tumor-node-metastasis (TNM) stages ($p = 0.035$). Patients with MPV > 8.45 fL had significantly shorter OS compared to group with lower MPV level. The multivariate Cox proportional hazard models survival analysis demonstrated that MPV level was significant independent prognostic factors ($p = 0.035$, hazard ratio [HR] 1.86, 95% CI = 1.06–3.25) [23].

The diagnostic role of MPV in thyroid cancer has been confirmed in several researches. Baldane et al. [24] showed that preoperative

MPV levels in patients with papillary thyroid carcinoma were found to be significantly higher in comparison with benign goiter patients and healthy controls (8.05 fL vs. 7.57 fL/7.36 fL, $p = 0.001$). After surgical treatment of carcinoma, a significant decrease in MPV levels was seen. It decreased to 7.60 fL ($p = 0.005$), so the postoperative MPV levels of patients and healthy controls were comparable. The same association was confirmed by other studies, which showed that MPV was significantly higher in the group of patients with thyroid cancer than in the benign group [25, 26]. However, the prognostic role of MPV in this type of cancer has not yet been established.

Prognostic value of MPV in lymphoproliferative diseases

MPV seems to be significant prognostic factor not only in solid tumors but also in lymphoproliferative diseases. The prediction in these kinds of neoplasms is difficult and frequently require complicated analysis, including immunological, biochemical, and cytogenetic parameters.

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), accounting for 25% of all NHL cases in adults. In most cases, it presents an aggressive clinical course. The International Prognostic Index (IPI) score is used for prognosis; however, in significant percentage of cases, the course is unfavorable despite the low-risk index. Meanwhile, recent studies proved that in DLBCL patients receiving R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, low MPV level is related to worse outcome. According to the study of Zhou et al. [27], the 2-year PFS rate is significantly longer in patients with MPV >9.1 fL compared to group with lower MPV level (84.0% vs. 60.6%, $p = 0.003$). Moreover, the 2-years OS rate in those groups was 87.9% and 70.4%, respectively ($p = 0.03$). Univariate Cox regression analysis showed that low MPV (<9.1 fL) was independent prognostic factors for OS ($p = 0.038$) and PFS ($p = 0.008$). Multivariate analysis that included all the parameters having a p value of <0.05 in the univariate analysis revealed that low MPV was independently associated with shorter OS (HR =0.588, 95% CI = 0.322–0.876, $p = 0.045$) and PFS (HR = 0.456, 95% CI = 0.251–0.829, $p = 0.010$) [27]. Decreased MPV is also associated with the risk of venous thromboembolism (VTE) and increased mortality in patients treated for DLBCL. VTE is a frequent complication in patients with cancer and is associated with increased morbidity and mortality. The study of Rupa-Matysek et al. [28] showed that pre-chemotherapy MPV values were reduced in the patients with DLBC who developed VTE compared with those who did not. In univariate analysis, MPV ≤10th percentile was associated with VTE occurrence, in contrast to age, male gender, platelet count, Ki-67 index, DLBCL subclassification, advanced stage presence of constitutional symptoms, high and high-intermediate IPI, and VTE risk. Whereas, patients with MPV >10th percentile had statistically significantly longer VTE-free survival than patients with lower MPV. Moreover, an estimated 3.5-year survival was 78% in patients without VTE occurrence and 55% in those who developed VTE and the probability of survival was higher in the patients with pre-chemotherapy high MPV compared with those with lower MPV ($p = 0.0021$) [28].

In patients diagnosed with Hodgkin lymphoma (HL), pre-chemotherapy MPV value cannot be used as a predictive marker for response. However, like in DLBCL, it may represent a useful prognostic marker for a significant VTE risk especially when incorporated into VTE risk assessment models. The study on patients with diagnosed HL proved that pre-chemotherapy values of MPV were significantly lower in the patients who developed VTE during follow-up (median 6.9 fL) in comparison to the patients without VTE (median 7.2 fL, $p = 0.034$). Patients with baseline MPV 6.8 fL or below more often developed VTE compared to patients with higher MPV values (19% vs. 5.5%, $p = 0.0244$). Of the HL patients, in both the univariate and multivariate models, the patients with baseline low MPV levels had an above twofold increased risk of VTE development [29].

There are also reports about the prognostic role of platelet parameters in acute lymphoblastic leukemia (ALL) in pediatric patients [30, 31]. ALL is the most common type of cancer-affecting children, unfortunately, approximately 10% of young patients never achieve complete remission [32, 33]. In the study of Huang et al. [30], PLT, MPV, and PCT levels were found to be lower in the ALL group than in the normal and ALL complete remission induced groups ($p < 0.05$). Although in other research, the MPV was larger in patients with leukemia (mean ± SD: 8.615 ± 1.59 fL) than in controls group (mean ± SD: 8.355 ± 1.11 fL) at diagnosis, but it was statistically not significant between the two groups ($p = 0.36$). Authors suggested that the cause of this was probably dysplastic platelets in the leukemia group [31].

The clinical and prognostic significance of MPV was reported also in patients with primary (PMF) and secondary myelofibrosis (SMF). In these diseases, elevated MPV was associated with worse clinical outcome, including lower platelets ($p = 0.016$), higher white blood cells ($p = 0.015$), higher percentage of circulatory blasts ($p = 0.009$), higher lactate dehydrogenase ($p = 0.011$), larger spleen size ($p = 0.014$), and higher Dynamic International Prognostic Score (DIPS) category ($p = 0.027$). Higher MPV was univariately associated with inferior OS in the whole cohort (HR = 3.82, $p = 0.006$) [34].

Conclusions

This review summarizes the most important studies on the impact of MPV levels on outcome and prognosis in different types of cancer conducted in recent years. In summary, MPV levels have a significant impact on the length of PFS and OS in many types of solid tumors, and also affect the prognosis in some lymphoproliferative diseases. However, the effect is not unitary and depends on the type of cancer. Moreover, MPV cutoff has not been fully validated so far, and standardization is essential to properly use MPV in clinical practice. Further studies are necessary to consider the use of affordable and accessible laboratory test such as MPV level as a prognostic factor. Moreover, the MPV cutoff level has not been fully validated so far and standardization is a major need.

Authors' contributions/Wkład autorów

MM, JK, KG – writing and discussion of manuscript

Conflict of interest/Konflikt interesu

Authors declare no conflict of interest.

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Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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