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Review Article

Prognostic Value of Evaluating Platelet Role, Count and Indices in Laboratory Diagnosis of Different Types of Solid Malignancies

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Abstract

Platelets are associated with the processes that aid in tumour growth and progression. Platelet Count (PLT) and platelet indices like Mean Platelet Volume (MPV), Platelet Large Cell Ratio (P-LCR), Plateletcrit (PCT) and Platelet Distribution Width (PDW) are markers that are linked with platelet activities in cancer. This review involves the evaluation of PLT, MPV and PCT in different cancers. Platelets actions should be always monitored during several diseases, as their potential exceeds the classical function in preventing bleeding. Vast roles of platelets were discovered in several biological functions. Therefore, studying their indices can be effective in the diagnosis of several disorders including cancer.

Key words: Platelet count, mean platelet volume, plateletcrit, cancer, PLT, MPV and PCT

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INTRODUCTION

Cancer has become known to be a key risk of mortality and morbidity and liability to the world development and health systems. Recent studies in untreated cancer patients have reported several abnormal conditions including dysregulation in thyroid functions, vitamin D deficiency in both the study group and COVID-19 patients and have detected different levels of platelets between COVID-19 patients living at different altitude¹⁻⁴. More than 200 types are known so far that affect humans. Despite significant improvements in cancer therapy strategies over the previous decades, cancer yet stands enormous challenges in the health services providers. In the united states of America, cancer is one of the highest causes of death among the population^{5,6}.

Platelets, perform a major role in thrombosis and primary hemostasis. In clinical laboratories, platelets related parameters are called "platelet indices" and includes PCT, PDW, PCT and MPV. MPV is related to the average platelet volume within the blood, however, PDW shows heterogeneity concerning platelet volume. It should be noted here that PCT (indicates platelet mass per unit of volume) can be calculated from MPV and PC. In several diseases like diabetes mellitus, preeclampsia, Myocardial Infarction (MI) and different types of cancers it has been observed that platelet count and platelet indices are altered. In several pathophysiological conditions like Alzheimer's disease, Huntington's disease, Parkinson's disease, Amyotrophic lateral sclerosis and multiple sclerosis specific platelet alteration has been reported. Recent studies have detected different levels of platelet between COVID-19 patients living at different altitude⁴.

Platelets: also called thrombocytes are originate from the megakaryocytes. They are performing different cellular functions and have been linked to the processes that promote cancer and metastasis. It has been reported that platelets by secreting various cytokines and growth factors promote tumour-related mechanisms like angiogenesis, growth, invasion and metastasis directly or indirectly. Some of the reports claim that thrombocytosis promotes tumour metastasis. It should be noted here that platelet indices are routinely carried out. Measurement of platelet indices has emerged as the common procedure in cancers and includes MPV, PCT and PDW (measures variability in platelet sizes) and P-LCR (measures abnormal platelet counts). Studies in recent years have suggested the use of PLT and their indices as inflammatory markers in human cancers, cerebrovascular, cardiovascular and thromboembolic and inflammatory diseases⁵. Low cost, high reproducibility and high applicability of platelet related parameters like PLT and platelet indices

have rendered them suitable concerning usability. Platelet indices and the count has emerged as novel inflammatory markers in different types of cancers⁷⁻⁹.

Platelets role in several biological functions in the body has been studied. Following any abnormal response that affects their homeostasis, they start to release stored molecules that participate in the human immune system. Moreover, other synthesized molecules are also released which affect the immune system and surveillance. When an injury occurs or infection invades the bloodstream, platelets is one of the early responders to this trigger¹⁰. The release of cytokines and chemokines increase at this site of the immune response and platelets have several cytokines and chemokines receptors expressed on their surface which leads to an increase in the count of platelets at this site and affect the surrounding immune cells to promote inflammation¹⁰. Pattern recognition receptors are expressed on platelets surface that interacts directly with pathogen-associated molecules patterns triggering an immune response^{11,12}. Platelets are an essential part of the blood and are available intravascularly, however, due to the previously mentioned properties and functions, they can attract several cells upon response. This can also induce the maturation of many lymphocytes, neutrophils, dendritic cells and macrophages^{13,14}. Specifically affecting both neutrophils and macrophages the famous phagocytic cells via their microparticles released after their activation^{15,16}.

CD154 is expressed on the platelets and studies identified their vital role in adaptive immune system response¹⁷. T-cells play an important immune response especially against cancerous cells and these cells perform a better function in platelet enriched area^{18,19}. CD40-L is expressed on the platelets and their role expands to affect most of the immune cells including T-cells, B-cells and natural killer cells²⁰⁻²².

Cancer mortality is expected to reach 20 M in the next few years. The biggest risk factor associated with this rise in mortality rate with cancer, is due to the late diagnosis, few preventive methods and treatment does not begin usually at early stages. Numerous research has recommended the use of platelet count from 60 years ago as an inflammatory marker for the diagnosis of several diseases including cancer⁶⁻⁹. Tumour growth and metastasis are associated with the abnormal change in platelet count and functions^{9,22}. Mean Platelet Volume (MPV), was detected to expand in several solid tumours including head and neck, colon cancer, gastric cancer, cervical cancer, lung cancer²³⁻²⁷. The effect of platelet inhibitors was effective to counter cancer comorbidities, also, aspirin was effective to improve survival in head and neck cancer patients²⁸.

The present review aimed to determine the importance of platelet measurement in the clinical laboratory in several types of cancer including breast cancer, uterine cancer, cervical cancer, endometrial cancer, thyroid cancer, colon cancer, ovarian cancer, Head and Neck Squamous Cell Carcinomas (HNSCC) cancer, lung cancer, bladder cancer, liver cancer and skin cancer.

Breast cancer: It is the most widespread type of cancer among women globally²⁹. With current advances in promoting health education and awareness, diagnosis, therapy and disease prevention, breast cancer become a controllable type of cancer. A study has reported that diagnosis of breast cancer early is effective in the survival rate among women³⁰. Platelet clinical measurements were involved with a breast cancer diagnosis. The MPV reduce rapidly in breast cancer patients with liver metastasis³¹. Patients with poor prognosis have suffered from expansion in Platelet count^{32,33}. Aggregation was reported among platelet due to the direct effect of breast cancer cells³⁴.

Lung cancer: With the increase in pollution and smoking lung cancer has increased in the recent century. Diagnosis and treatment have appeared as a major objective in malignancy investigation due to the boost mortality and morbidity³⁵. Clinical diagnosis of platelet indices has emerged to be essential in lung cancer. It has been reported among lung cancer patients that high level of Platelet Distribution Width (PDW), low Plateletcrit (PCT) and low MPV²⁴.

Endometrial cancer: Endometrial cancer has emerged as one of the essential gynaecological tumours among women population worldwide with more than 70000 fatalities and the addition of more than a quarter-million new cases annually³⁶. Type I is identified as less aggressive and with quick diagnosis promote good prognosis and high survival rate after treatment³⁷.

The highly aggressive type II is poorly differentiated and is correlated with myometrial invasion, extrauterine proliferate and have a poor prognosis with a low survival rate following treatment^{38,39}. Alterations in inflammatory cells have been correlated to endometrial cancer⁴⁰.

Cervical cancer: Cervical cancer is a popular type of gynaecological cancer, also, it is very common globally among developed and developing countries⁴¹. In 2018, more than half a million cases and more than 300 thousand death occurred due to cervical cancer alone^{29,41}. Platelet counts were studied

by several studies in cervical cancer patients and they have reported inconsistent results, a study reported the count to expand while another has reported contrast findings⁴²⁻⁴⁵. These reported results indicate an essential in-depth study should be performed to identify the role of platelet and their measurements in cervical cancer.

Colon cancer: Colon cancer is considered to be a popular type of preventable solid malignancies⁴⁶. Extensive screening in developed countries has dropped the mortality rate, incidence of colon cancer has also dropped widely. A study has reported MPV has increased and is considered an inflammatory marker in colon cancer patients⁴⁷.

Ovarian cancer: This cancer is estimated to affect about 2% of women globally⁴⁸. World Health Organization (WHO) reported that an increase in cases of ovarian cancer global incidence will be 300 thousand and the rate of mortality will be 200 thousand women in the current decade⁴⁹.

Unlike cervical cancer, no approach or national programs have been widely available for general screening for ovarian cancer. A study has reported higher PLT in ovarian cancer patients⁵⁰.

HNSCC: This tumour is an exceedingly heterogeneous cancer affecting more than a million patients annually worldwide⁵¹. HNSCC is in the nasopharynx, oral cavity, oropharynx, larynx and hypopharynx. Current advancements in cancer therapy methods are anticipated to result in better results for HNSCC patients. In one of the studies, it has been reported that MPV cannot be treated as a useful biomarker in HNSCC patients⁵². However, further studies should be performed for evaluating the role of platelets indices in this type of tumour.

Bladder cancer: Bladder cancer is frequently found in women and is also 4th the most common cancer form in men. Annually, around 400 thousand men and women are diagnosed with bladder cancer globally⁵¹. The disease affects men than women, the reported ratio according to WHO is 3:1 and the elderly people are affected more⁵³. Despite the innovations in cancer therapy, bladder cancer therapy remained unaffected for more than 30 years.

Decline level of PDW has been linked as an indicator of bladder cancer and with advanced cancer stages and therefore has been reported to be a potential biomarker⁵⁴.

Thyroid cancer: Thyroid cancer is a widespread form of endocrine cancer, 2% of total diagnosed cancers worldwide

is for this type of cancer^{55,56}. In 2018, thyroid cancer was associated with about half a million cases and more than 40 thousand mortality rates globally. An expansion in PCT levels and decline in PDW has been described in papillary thyroid cancer patients compared to controls healthy people⁵⁷.

Liver cancer: Liver cancer has ranked 6th concerning incidence and 4th concerning mortality among all cancers worldwide. In 2018, a total of around 800 thousand cases and 750 thousand deaths have been linked to liver cancer⁵¹. Thrombocytopenia and high MPV values have been linked with successful outcomes in Hepatocellular Carcinoma (HCC) patients with advanced-stage⁵⁸⁻⁶⁰.

Skin cancer: Skin cancer is also a popular form of cancer worldwide, this cancer is divided into malignant melanoma and non-melanoma skin cancer⁵⁵. The incidence of skin cancer has been growing according to several studies due to several factors^{56,61}. The preponderance of skin cancers expands locally and later invade nearby cells and tissues. Most skin cancer incidents recover wells, however, the rapid increase in incidence.

CONCLUSION

The classical role of platelet in preventing bleeding is widely recognized. Many receptors are expressed on the surface of these cells which are involved in the regulation and manipulation of many physiological functions. Platelet count and indices are essential in routine clinical laboratory tests but their interpretations can mean more than a number. These cells roles in the innate immune system were identified through several kinds of literature, phagocytic cells, inflammatory markers and antimicrobial functions. The role of platelets has become clear in recent years. Malignancy depends mainly on angiogenesis and the progression to reach other organs. Tumour cells lines have been found to recruit platelet in their side to promote their angiogenic properties. Platelets activation markers released in several types of cancer were higher than normal controls. Immunostaining methods have detected chemoattraction of platelets to cancer sites. Galectins are proteins that function as carbohydrate-bindings sites, this protein has several functions specifically in inflammation and immune response. Moreover, this protein has a function in cells adhesion molecules and is involved in angiogenic and interaction between platelets and cancer cells. Platelet count and indices have emerged as new markers of inflammation in cancer and can be easily analyzed in the new

haematology analyzers. An alteration in the values of PLT, MPV and PCT was observed in the current study suggesting an important link in the platelet count/indices and cancer development. The data obtained in the current study need to be re-validated in the larger population.

SIGNIFICANCE STATEMENT

Platelets have a well-known role in the coagulation system and the pathogenesis of inflammation. Platelet number and indices have emerged as new markers of inflammation in different types of cancers. This study reviewed platelet number and indices in cancers like breast cancer, cervical cancer, endometrial cancer, colon cancer ovarian cancer, HNSCC, uterine cancer, lung cancer, bladder cancer, thyroid cancer, liver cancer and skin cancer. The findings obtained will be quite helpful for the cancer researchers to carry out the larger cohort of the cancer population. Future studies should focus on anaemia; a recent study has detected a high prevalence of anaemia among cancer patients at diagnosis`.

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