REVIEW

# Platelets: The Emerging Clinical Diagnostics and Therapy Selection of Cancer Liquid Biopsies

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**Abstract:** Due to the inherent molecular heterogeneity of metastatic tumours and the dynamic evolution ability of tumour genomes, tumour tissues obtained through biopsy and other methods cannot capture all of the features of tumour genomes. A new diagnostic concept called "liquid biopsy" has received widespread attention in recent years. Liquid biopsy has changed the clinical practice of oncology and is widely used to guide targeted drug utilization, monitor disease progression and track drug resistance. The latest research subject in liquid biopsy is platelets. Platelets originate from multifunctional haematopoietic stem cells in the bone marrow haematopoietic system. They are small cells from the cytoplasm of bone marrow megakaryocytes. Their main physiological functions are to participate in the processes of physiological haemostasis and coagulation. Tumour cells transfer biomolecules (such as RNA) to platelets through direct contact and release of exosomes, which changes the platelet precursor RNA. Under the stimulation of tumour cells and the tumour microenvironment, platelet precursor mRNA is spliced into mature RNA and converted into functional protein to respond to external stimuli, forming tumour-educated platelets (TEPs). The detection of TEPs in the peripheral blood of patients is expected to be used in clinical tumour diagnosis. This emerging liquid biopsy method can replace and supplement the current tumour detection methods. Further research on the role of platelets in tumour diagnosis will help provide a novel theoretical basis for clinical tumour diagnosis.

**Keywords:** liquid biopsy, platelet, diagnosis, RNA, noninvasive

## Introduction

Over the years, through the unremitting efforts of the majority of medical personnel, great progress has been made in the treatment of various tumours (including surgical resection, concurrent radiotherapy, chemotherapy, and immunotherapy), but most are limited to treating early tumours.[1] The treatment of moderate and advanced cancers is still facing great difficulties, so the early diagnosis of tumours is particularly important. The early clinical symptoms of most tumours are not typical, and routine physical examinations, including imaging, endoscopy and disease examinations, cannot accurately detect malignancies.[2] Therefore, there is an urgent need for a more accurate, efficient and convenient examination method to diagnose early tumours and closely monitor dynamic changes in the tumours after treatment.

With the continuously elucidated mechanisms of tumour occurrence, drug resistance, and tumour microenvironment regulation, liquid biopsy will be increasingly widely utilized in the clinical field. Liquid biopsy provides an important basis

for early diagnosis and screening, efficacy monitoring, prognostic evaluation and drug guidance. Liquid biopsy, including circulating tumour cells, circulating tumour DNA, microribonucleic acid, extracellular vesicles, exosomes, and TEPs in the peripheral blood of tumour patients, has reached the demand of tumour screening and early diagnosis by a non-invasive method.[3,4] Platelets, known for their haemostatic effects, also play a significant role in the growth and development of tumours.[5] Under the stimulation of various stimulating factors, platelets in an ordinary resting state release their intracellular granular material, and then the granule protein is integrated into the endothelium of its plasma membrane, which is called platelet activation. Platelet activation is the initiation process that mediates inflammation and tumour-related functions.[6–8] When platelet surface receptors are activated, specific precursor mRNA splicing will occur, resulting in a unique mRNA expression profile that can be used for tumour diagnosis and prognosis. This review will illustrate and reveal the latest progress of platelets in tumour liquid biopsy in recent years.

## The Vital Role of Platelet Count in Tumour Detection

Platelets have two major physiological properties: adhesion and aggregation.[9] More precisely, fibrinogen is the major ligand for platelet $\alpha IIB\beta 3$ integrin during platelet aggregation.[10] The aggregation of platelets can promote the release of numerous factors that play an important role in the study of coagulation. Platelets are not only involved in haemostasis but also act as regulatory factors within the immune system.[11,12] In patients with malignant tumours, there will be changes in systemic platelet activation. The most prominent characteristic is platelet count elevation, which induces a high coagulation status and finally results in the formation of thrombi and fibrinogen increases.[13] In addition, multiple reports have demonstrated that in patients with prostate cancer accompanied by diffuse intravascular coagulation disorders, their platelet and fibrinogen levels are increased sharply.[14,15] The increase in platelets is beneficial for the activation of tumour cells; therefore, the platelet count may be one of the markers of tumour progression. Beili Wang and colleagues found that the platelet count may be a potential biomarker for predicting the prognosis of patients with hepatitis B virus-related hepatocellular carcinoma treated with catheter arterial chemoembolization.[16] The study of Oh SE et al

also found that platelet count may be a cost-effective biomarker for screening and monitoring poor prognosis of gastric cancer patients who have undergone radical surgery.[17] Zheng RR and colleagues found that the combination of platelet count and International Federation of Obstetrics and Gynaecology (FIGO) staging improved the predictive performance of FIGO staging and provided additional risk stratification for patients with operable cervical cancer.[18] Väyrynen JP and colleagues found that high platelet counts are associated with systemic inflammation in colorectal cancer (CRC).[19] However, this study was unable to prove a statistically significant correlation between platelet count, aspirin use and tumour infiltrating immune cell density. The study by Midorikawa Y and colleagues also found that thrombocytopaenia predicts a poor prognosis for patients with liver cirrhosis and liver cancer, while thrombocytopaenia predicts a poor prognosis for patients without cirrhosis.[19] In brief, the relevant studies are listed in Table 1.[16–39]

## Research Progress on the Mean Platelet Volume (MPV) in Malignant Tumours

Platelets play an important role in the coagulation process. Simultaneously, changes within various indicators in platelets directly or indirectly reflect the characteristics of inflammation. One of the often-overlooked indicators is mean platelet volume (MPV).[40] It is generally believed that MPV directly reflects the average volume of platelets and indirectly reflects the rate of platelet production. There is a clear range of MPV in normal humans, and its detection and evaluation are mostly used for diseases such as blood diseases.[41,42] In the latest research, scientists found that abnormalities in MPV may indicate the occurrence of certain diseases before the platelet count and clinical symptoms become abnormal.[43] More precisely, MPV has a significant correlation with the occurrence and development of inflammation, and the increase in tissue penetration caused by inflammation is a key factor in the escalation of platelet volume.[44] For example, studies have shown that in gastric cancer, liver cancer, lung cancer, and endometrial cancer, increased MPV can be used as a tumour biomarker. The related data are listed in Table 2.[22,23,27,28,45–75.] Differentiating benign and malignant thyroid nodules is a breakthrough point in clinical diagnosis. The study of Sit M found that an increase in MPV can be regarded as an auxiliary diagnostic tool to distinguish malignant and benign

**Table 1** Summary of the Correlation of Platelet Count with Tumor

| Disease Model/Patient Type | Comments | Ref. |
|---|---|---|
| Hepatocellular carcinoma (HCC) | Platelet count may be a potential biomarker for predicting the prognosis of patients with hepatitis B virus-related hepatocellular carcinoma treated with catheter arterial chemoembolization. | Wang B et al,[15] |
| HCC | Platelet count was better than indocyanine green (ICG) R15 level in predicting the occurrence of liver failure (PHLF) in patients with HCC with preserved liver function. | Tomimaru Y et al,[20] |
| HCC | Decreased platelet cell count and higher MPV are associated with better prognosis in patients with advanced HCC. | Scheiner B et al,[21] |
| Liver cancer | Decrease in the number of platelets indicates a poor prognosis for patients with liver cirrhosis and liver cancer, while an increase in platelet count indicates a poor prognosis for patients without cirrhosis. | Midorikawa Y et al,[19] |
| Gastric cancer | Platelet count may be a cost-effective biomarker for screening and monitoring poor prognosis of gastric cancer patients who have undergone radical surgery. | Oh SE et al,[16] |
| Lung cancer | Increased platelet count and decreased MPV were the poor prognosis of lung cancer patients, and platelet count was also associated with bone, soft tissue, lymph node metastasis and malignant pleural effusion. | Ohuchi M et al,[22] |
| Lung adenocarcinoma (ADC) | Even if the platelet count is within the reference range, elevated platelet counts were significantly associated with high lymph node metastasis rates in patients with ADC. | Qu CH et al,[23] |
| Non-small cell lung cancer (NSCLC) | Platelet count could predict the prognosis of patients with NSCLC treated with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). | Xu L et al,[24] |
| Cervical cancer | The combination of platelet count and International Federation of Obstetrics and Gynecology (FIGO) staging improves the predictive performance of FIGO staging and provides additional risk stratification for patients with operable cervical cancer. | Zheng RR et al,[17] |
| Head and neck squamous cell carcinoma (HNSCC) | Univariate analysis showed that platelet count was significantly correlated with the survival rate of patients with HNSCC. However, in multivariate analysis, platelet count lost its prognostic ability. | Pardo L et al,[25] |
| Colorectal cancer (CRC) | MPV/platelet count may be helpful in the diagnosis of CRC. | Wu YY et al,[26] |
| CRC | Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and mean platelet volume (MPV) may be useful markers for the diagnosis and early recognition of different stages of CRC. | Stojkovic Lalosevic M et al,[27] |
| CRC | High platelet counts were associated with systemic inflammation of CRC. However, this study was unable to prove a statistically significant correlation between platelet count, aspirin use and tumor infiltrating immune cell density. | Väyrynen JP et al,[18] |
| Rectal cancer | The mortality of rectal cancer patients with high platelet counts before surgery is higher than that of rectal cancer patients with low platelet levels. Research results suggest that preoperative platelet count can be used as an important indicator for predicting the prognosis of rectal cancer, but its prognostic value for colon cancer needs to be further clarified. | Chen LL et al,[28] |
| Rectal cancer | In locally advanced rectal cancer, elevated platelet count before neoadjuvant radiotherapy and chemotherapy is a sign of poor prognosis. | Belluco C et al,[29] |
| Ovarian cancer | In multivariate analysis, age, CA125 and thrombocytosis independently predicted the presence of ovarian malignancies. | Watrowski R et al,[30] |

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**Table 1** (Continued).

| Disease Model/Patient Type | Comments | Ref. |
|---|---|---|
| Ovarian cancer | Mean platelet volume (MPV), neutrophil to lymphocyte ratio (NLR) and platelet count in the detection of malignant ovarian tumors have been evaluated as useful new markers. | Yilmaz E et al,[31] |
| Epithelial ovarian cancer (EOC) | Platelet count can be used as a biomarker to monitor EOC recurrence and predict treatment response. | Hu Q et al,[32] |
| Prostate cancer | The results of the study indicate that performance status (PS) and platelet count are independent prognostic factors for evaluating disease-specific survival (DSS) in patients with metastatic prostate cancer receiving endocrine therapy. | Shimodaira K et al,[33] |
| Diffuse large B-cell lymphoma (DLBCL) | Platelet count and albumin level are useful prognostic factors, and their combined use can even predict the survival of elderly patients with DLBCL. | Ochi Y et al,[34] |
| Acute myeloid leukemia (AML) | Platelet count can predict the survival rate of patients with moderate-risk AML. | Zhang Y et al,[35] |
| AML | The platelet count before treatment has predictive value for the prognosis of patients with non-M3 AML. | Zhang Q et al,[36] |
| Breast cancer | Platelets have important predictive value for the prognosis of patients with ipsilateral supraclavicular lymph node metastasis (ISLN) in breast cancer patients, indicating that platelet counts can be used to distinguish high-risk patients and thus obtain clinical benefits. | Liu S et al,[37] |
| T-cell lymphoma | The results of the study prove that the decrease in the number of platelets is an independent prognostic factor for the survival of patients with peripheral T-cell lymphoma. | Choi M et al,[38] |

thyroid nodules.[49] Yin JB and colleagues retrospectively collected clinical pathological data of most patients with pancreatic cancer (PC) and assessed the relationship between MPV levels and clinical parameters.[50] Survival analysis revealed that the increase in MPV was not related to the location, size, or CA19-9 of the tumour. However, elevated MPV is associated with poor survival in PC patients with concurrent liver metastases. Gallbladder cancer (GBC) represents the most common biliary malignancy. Due to the lack of typical symptoms, GBC is often detected at an advanced stage when the tumour cannot be removed or has metastasized. Therefore, there is an urgent need to identify new markers for the early detection of GBC in patients. Zhang X and colleagues found that the decrease in MPV and the increase in platelet distribution width (PDW) were independently related to GBC. This finding shows that MPV and PDW are available parameters for the early detection of GBC.[52]

## Activated Platelets Can Participate in Tumour Formation and Progression

Platelet activation promotes the initiation of the coagulation cascade and constitutes an important risk factor for thrombosis. Platelets activated by tumour cells further promote cancer progression through key processes such as angiogenesis and metastasis.[76,77] Platelet activity can be inferred by platelet volume indices (PVIs), which include PDW, MPV, platelet distribution width-to-platelet count ratio (PDW/P), and mean platelet volume-to-platelet count ratio.[78] The specific adhesion molecule P-selectin expressed on the surface of activated platelets can also promote the aggregation of neutrophils. After activation of platelets, arachidonic acid derivatives, thromboxane, platelet factor 4 (PF4) and other inflammatory mediators can be released to expand the inflammatory response.[79] Thromboxane A2 (TXA2) is a product with strong physiological activity generated during the metabolism of arachidonic acid and has a strong platelet activation effect. The increased activity of TXA2 in tumour patients may indicate the presence of platelet activation in patients and play a certain role in tumour occurrence, development and metastasis. As the inhibitory effect of aspirin on TXA2 plays a role in the prevention of cancer, it is important to explore the production of TXA2 in platelets.[80] After aggregation, platelets become part of the thrombus, especially the microthrombus in disseminated intravascular coagulation (DIC). Platelets and platelet-related markers, such as the platelet-to-lymphocyte ratio, are significant

**Table 2** Summary of Correlation of Mean Platelet Volume (MPV) with Tumor

| Disease Model/Patient Type | Comments | Ref. |
|---|---|---|
| CRC | MPV may be useful markers in diagnostic and early recognition of different stages of CRC; additionally, combined all with neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have stronger diagnostic efficacy. | Stojkovic Lalosevic M et al,[27] |
| CRC | MPV/PC may be helpful in the diagnosis of CRC. | Wu YY et al,[26] |
| CRC | Serum MPV or platelet distribution width (PDW) content may be used as a predictor of postoperative sepsis in patients with CRC. | Li XT et al,[44] |
| CRC | Elevated MPV might act as a marker of prognosis and therapeutic target for CRC. | Li N et al,[45] |
| metastatic colorectal cancer (mCRC) | The baseline MPV level may act as a predictive factor for survival in mCRC patients undergoing standard chemotherapy. | Chang J et al,[46] |
| Colon cancer (CC) | Increased MPV and decreased platelet distribution width (PDW) appear to be poor prognostic factors in the early stages of, especially in CC patients with stage III disease. | Sakin A et al,[47] |
| Malignant thyroid nodule | MPV can be regarded as an auxiliary diagnostic tool to distinguish malignant and benign thyroid nodules. | Sit M et al,[48] |
| Pancreatic cancer (PC) | MPV elevated is associated with poor survival in PC patients with concurrent liver metastases. | Yin JB et al,[49] |
| Pancreatic ductal adenocarcinoma (PDAC) | MPV independently predicts poor survival in PDAC patients with Type 2 diabetes mellitus (T2DM). | Yin JB et al,[50] |
| Gallbladder cancer (GBC) | MPV and PDW are available parameters for early detection of GBC. | Zhang X et al,[51] |
| Hepatocellular carcinoma (HCC) | Lower MPV is a risk indicator of HCC patients survival outcomes after liver transplantation (LT). | Zhang AB et al,[52] |
| HCC | Thrombocytopenia and higher MPV are associated with better outcome in patients with advanced HCC. | Scheiner B et al,[21] |
| Osteosarcoma | The high preoperative MPV/plateletcrit ratio may serve as an independent prognostic factor for a favorable prognosis in male osteosarcoma patients. | Gou B et al,[53] |
| Esophageal cancer | Reduced MPV is associated with worse survival outcome in esophageal cancer. | Shen W et al,[54] |
| Esophageal squamous cell carcinoma (ESCC) | Decreased MPV and mean platelet volume/platelet count ratio (MPR) are significantly associated with locally advanced ESCC. These may help the screening and risk stratification of locally advanced ESCC. | Sun SY et al,[55] |
| ESCC | COP-MPV is a promising predictor for postoperative survival in ESCC patients. | Zhang F et al,[56] |
| Lung cancer | Increased platelet count and decreased MPV are the poor prognosis of lung cancer patients, and platelet count is also associated with bone, soft tissue, lymph node metastasis and malignant pleural effusion. | Ohuchi M et al,[22] |
| Non-small cell lung cancer (NSCLC) | MPV may represent one of the easiest measuring tools as an independent prognostic marker for survival in locally advanced NSCLC. | Sakin A et al,[57] |
| NSCLC | The increased MPV level may be used as a prognostic biomarker to estimate for poor overall survival in patients with NSCLC. | Omar M et al,[58] |
| Diffuse large B-cell lymphoma (DLBCL) | Low baseline MPV is an independent prognostic marker of poor outcome in patients with DLBCL. | Zhou S et al,[59] |

(*Continued*)

**Table 2** (Continued).

| Disease Model/Patient Type | Comments | Ref. |
|---|---|---|
| DLBCL | The pre-chemotherapy MPV value is a cheap and available parameter that may be a useful prognostic marker for a significant risk of venous thromboembolism (VTE) and inferior survival rates in patients with DLBCL. | Rupa-Matysek J et al,[60] |
| Multiple myeloma (MM) | The low MPV is correlated with poor prognosis in patients with MM and may serve as an important indicator for disease progression and prognosis of patients with MM. | Gao P et al,[61] |
| MM | The low MPV predicted an unfavorable prognosis in patients with MM. | Zhuang Q et al,[62] |
| Renal cell carcinoma (RCC) | Reduced MPV is identified as an independent predictor of adverse clinical outcome in RCC. | Yun ZY et al,[63] |
| Clear cell renal cell carcinoma (ccRCC) | The mean platelet volume-to-lymphocyte ratio (MPVLR) is an easily obtainable prognostic marker for overall survival in nonmetastatic ccRCC patients treated with nephrectomy. | Życzkowski M et al,[64] |
| Invasive breast cancer (IBC) | High pre-treatment MPV level in IBC patients was a potential predictive factor. | Gu M et al,[65] |
| BC | The combination of preoperative D-Dimer and MPV improves the predictive power of postoperative deep venous thrombosis risk in BC patients. | Cui LN et al,[66] |
| Breast cancer with bone metastases | MPV can be used to predict the development of isolated bone metastases patients with breast cancer. | Tanriverdi O et al,[67] |
| Primary malignant bone tumor | MPV and MPV/PLT ratios can be used as a diagnostic support parameter in primary malignant bone tumors, but have no prognostic value. | Sökmen FC et al,[68] |
| Oral squamous cell carcinoma (OSCC) | Count of platelet (COP) -MPV score is a simple and a more effective prognostic factor than other considered factors in predicting the prognosis of OSCC patients. | Park JW et al,[69] |
| Resectable gastric cancer | MPV measurement can provide important diagnostic and prognostic results in patients with resectable gastric cancer. | Shen XM et al,[70] |
| Prostate cancer | The combined use of prostate specific antigen (PSA), MPV, and platelet distribution width (PDW) may be clinically useful in distinguishing between prostate cancer (PCa) and benign prostate hyperplasia (BPH). | Fu S et al,[71] |
| Laryngeal squamous cell carcinoma (LSCC) | Preoperative hyperfibrinogenemia, increased MPV and NLR were associated with reduced prognosis in patients with LSCC. | Sheng X et al,[72] |
| Ovarian cancer | Combinations of the markers red cell distribution width (RDW), MPV, and CA125 may improve the differential diagnosis of ovarian cancer and benign ovarian cancers. | Qin YY et al,[73] |
| Differentiated thyroid carcinoma (DTC) | Their findings suggest that neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and MPV changes indicate systemic inflammation that occurs after radioiodine (RAI) therapy because of thyroid remnant tissue ablation. | Demir Y et al,[74] |

prognostic factors in patients with breast cancer.[81,82] Beili Wang and colleagues conducted a prospective study of 191 hepatocellular carcinoma (HCC) patients and 99 healthy subjects.[83] Flow cytometry was used to evaluate the platelet activation state by two platelet markers, PAC-1 and CD62p. The patients who received transcatheter arterial chemoembolization (TACE) or resection treatment were monitored for ≥6 months. The results demonstrated that the positive percentage of the platelet activation molecule PAC-1 is a new indicator for diagnosing and predicting the

prognosis of HCC surgery. Furthermore, cancer patients generally present a hypercoagulable state. In addition, coagulation and inflammation play an important role in the pathophysiology of haematological malignancies. Elmoamly S and colleagues measured inflammatory markers in a group of 171 patients with haematological malignancies.[84] The results indicated that the platelet activation marker von Willebrand Factor (vWF) was statistically related with the mortality of lymphoproliferative diseases, implying that vWF could be used as

a prognostic marker. In addition, Shi L et al found that the platelet activation index is a potential marker for predicting gemcitabine/cisplatin (GP) resistance in the treatment of advanced and metastatic non-small cell lung cancer (NSCLC).[85] In short, the data have shown that activated platelets have the potential to be tumour biomarkers.

## TEPs May Facilitate Blood-Based Tumour Diagnosis

Circulating platelets interact with tumour cells during their life cycle to obtain tumour-related biomolecules; additionally, they can continuously ingest and enrich circulating free proteins, nucleic acids, vesicles and particles.[86] There are two main sources of protein in the cytoplasm: one is inherited from its precursor megakaryocytes, such as platelet factor 4; the other is taken from the blood, such as P-selectin, Fibrinogen, etc.; and some proteins have both sources at the same time, such as platelet factor V. After platelets are educated, their proteome and RNA expression profile undergo significant changes, so they are called "tumour-educated platelets".[87] In the process of tumour development, tumours "educate" platelets, leading to changes in their mRNA expression profiles and phenotypes. Therefore, TEP mRNA profiles have the potential to diagnose cancer and be used as biomarkers with the following advantages: 1) platelets do not contain nuclei, so genomic DNA does not interfere with them; 2) platelets are easy to collect, separate and analyse and are easy to standardize in general clinical laboratories; 3) the TEP RNA profile reflects the pathological process of cancer cells, which may provide better sensitivity for the early detection of cancer cells.[88,89]

The research results of Liu L et al showed that compared with healthy donors, the platelet mRNA set MAX, MTURN and HLA-B of lung cancer patients and early-stage lung cancer patients were significantly upregulated.[90] These findings suggest that the platelet mRNA set MAX, MTURN and HLA-B can facilitate blood-based lung cancer diagnosis and chemotherapy response prediction. Currently, there are no molecular biomarkers for the early detection of non-small cell lung cancer (NSCLC). However, excitingly, Shan Xing and colleagues used RNA-seq to analyse platelet RNA isolated from the blood of 9 NSCLC patients (stage I and II) and 8 healthy controls.[91] The results demonstrated that TEP ITGA2B is a promising marker to improve the identification of patients with stage I NSCLC and differentiate malignant

from benign lung nodules. Dong X et al used low-speed centrifugation to separate platelets from plasma and performed quantitative polymerase chain reaction (qPCR) to detect small nucleolar RNA SNORD55.[92] The results showed that, compared with healthy controls, SNORD55 in the TEP of NSCLC patients was significantly lower, especially in early-stage patients. Importantly, they verified that TEP SNORD55 can be used as a promising biomarker for NSCLC. Chang-Liang Luo et al found that EGFRvIII RNA is present in both TEP RNA and plasma, but EGFR intracellular mutations cannot be detected in TEP DNA isolated from NSCLC.[93] These data also indicate that TEP is a promising source for NSCLC diagnosis and companion diagnosis.

Yang L et al used RNA sequencing to identify gene expression signatures in platelets from colorectal cancer patients and healthy volunteers.[94] Then, they verified the selected biomarkers using PCR. The results demonstrated that TIMP1 mRNA in platelets is a potential independent diagnostic biomarker for colorectal cancer, and platelets could carry RNA to colorectal cancer cells, promoting the development of colorectal cancer. Even rare malignant tumours, such as sarcomas, are a heterogeneous group caused by interstitial tissue. The recurrence rate is extremely high, and there is no method for early detection through blood-based biomarkers. Therefore, the development of blood-based liquid biopsy as a biomarker for disease recurrence monitoring would be an important step. Recently, it has been shown that TEPs have specific spliced RNA characteristics. Kimberley M. Heinhuis and colleagues tested and sequenced platelet RNA from isolated sarcoma patients (active disease), pre-sarcoma patients (≥3 years of cancer-free) and 65 healthy donors.[95] These results indicate that liquid biopsy based on TEP RNA may be helpful for the diagnosis of sarcoma.

TEPs can participate in the systemic and local reactions of tumour growth, thereby changing the tumour RNA profile. Myron G et al confirmed the diagnostic potential of TEPs by sequencing the mRNA of 283 platelet samples.[96] Among the six different tumour types, namely, non-small cell lung cancer, colorectal cancer, glioblastoma, pancreatic cancer, breast cancer and hepatobiliary cancer, the location of the primary tumour was correctly identified with 71% accuracy. In addition, the use of alternative TEP mRNA profiles can accurately distinguish between MET- or HER2-positive and mutant KRAS, EGFR or PIK3CA tumours. Their findings indicate that platelets provide a valuable platform for pan-cancer,

multiple types of cancer and companion diagnosis. Sidra Asghar and colleagues found that the expression of AKT and PI3K mRNA in platelets can be used as diagnostic markers for early HCC.[97] Nik Sol et al developed the digital SWARM algorithm to improve the monitoring of glioblastoma progression and demonstrated that the TEP tumour score of a single glioblastoma patient represents tumour behaviour and can be used to distinguish false positive progress from real progress.[98] Finally, the combination of the TEP score and MRI analysis can enhance the detection and clinical management of patients with false-positive glioblastoma progression.

Cancer diagnosis based on tissue biopsy has limitations because the tumour tissue is in the process of continuous development and the heterogeneity is extremely high. The current research aims to examine whether TEP may be a potential all-in-one source for blood-based cancer diagnosis to overcome the limitations of conventional cancer biopsy. Lele Liu et al also identified a platelet mRNA set: MAX, MTURN and HLA-B can achieve blood-based lung cancer diagnosis and chemotherapy response prediction.[99] Chitrita Goswami et al also proposed 11 types of platelet genes (CD79B, CSDE1, IL-32, ITGA2B, LUC7L, NDUFAB1, RBM6, SKAP2, SS18L2, TRAF3IP3 and ZNF195), providing reliable and economically viable platelet-based classification between NSCLC and healthy samples.[100] MicroRNAs (miRNAs) are small noncoding RNA molecules that contain approximately 18–24 nucleotides. miRNAs can regulate cell development, differentiation, the cell cycle and apoptosis. Hui Wang et al found that the expression levels of TEP miR-34c-3p and miR-18a-5p in nasopharyngeal carcinoma were upregulated, which has important clinical significance for the diagnosis of nasopharyngeal carcinoma.[101] The results of this study also suggest that TEP miRNAs can be used as a new type of NPC diagnostic liquid biopsy.

## Discussion

When a tumour occurs, some trace substances contained in platelets change. If the activated platelet response is not controlled when tissue or vascular endothelial cells are damaged, the matrix releases several mediators, such as prostanoids, growth factors, angiogenic factors, cytokines, chemokines and platelet microparticles. The proliferation of mesenchymal cells, including leukocytes and fibroblasts, not only increases the concentration of cytokines and inflammatory substances in the matrix microenvironment but also contributes to the development of chronic inflammatory

reactions, which are conducive to the formation of tumours.[102,103] For example, platelets can store, synthesize and release numerous angiogenic regulators to promote angiogenesis in tumours. In addition, platelets can adhere to endothelial cells through tumour cells, help tumour cells penetrate the vascular endothelium, enter the blood circulation, and form distant metastases. Due to the large number of particles in platelets, the release of the contents of the particles can promote the growth of tumour cells and resistance to radiotherapy and chemotherapy.[104]

Extracellular vesicles derived from platelets can also be used for liquid biopsy by using differential centrifugation, kit methods, ultrafiltration, gel filtration chromatography and other methods for the diagnosis and identification of tumour liquid biopsy, which can be applied to precision treatment. Therefore, the function of extracellular vesicles and extraction methods are also future research directions. In the studies above, not only was the number of platelets in cancer patients significantly higher than that in healthy subjects, but this number was also related to cancer progression. Abnormally elevated protein, RNA and other trace substances in the platelet granular organelles of cancer patients promote tumour occurrence, proliferation and metastasis.[105] In addition, there is evidence that platelets can help tumour cells escape the immune system by directly masking the surface antigens of tumour cells, leading to tumour occurrence and development.[106,107] However, liquid biopsy projects that use TEP as a molecular marker still have some limitations. One is the difficulty in the pre-analysis stage. For blood-based biomarker research, the delay between blood sampling and analysis must be as short as possible; all patients should be tested under the same conditions as much as possible to develop better comparative study; sampling must use buffer to regulate TEPs, so that the target biomarker in the study can be well preserved. Second, in patients with very small tumours or not visible on chest imaging, the low number of biomarkers in the TEPs requires high-sensitivity detection technology. The third is to detect cancer-specific biomarkers. Although encouraging results have been achieved so far, the pre-analysis processing and specific analysis steps have not been standardized, which is also an obstacle to the deployment of liquid biopsy for early cancer diagnosis in clinical practice. Further research on tumour-related platelets and their mechanisms will provide broad prospects for the early diagnosis and clinical prevention and treatment of tumours.

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# Disclosure

There are no conflicts of interest to declare.

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