

# Research progress of hematological indicators related to the prognosis of Small-cell lung cancer that can be easily ignored in clinical work

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**Abstract:** Lung cancer has the highest incidence and mortality in the world. Small-cell lung cancer (SCLC) accounts for about 15% of the total lung cancer, which belongs to neuroendocrine tumor, and among the patients, there are about 1/3 belong to the Limited Stage (LS). Chemotherapy combined with radiotherapy is the standard treatment for patients with LS-SCLC patients. However, SCLC is extremely aggressive and prone to early distant metastasis, and most of the patients are already in the Extensive Stage (ES) when they start seeking treatment. The prognosis of ES-SCLC patients is very poor, and its treatment has made little progress in recent decades. Therefore, sensitive and accurate indicators are needed to evaluate the prognosis of patients before starting treatment. Many studies have used hematology indexes at the initial diagnosis to predict the prognosis of SCLC patients, it involves liver function, routine blood coagulation and routine blood tests, including lactate dehydrogenase, fibrinogen, D-dimer, the ratio of neutrophils to lymphocytes(NLR), the ratio of platelets to lymphocytes(PLR), etc., which can play a role in the clinical work to indicate the treatment node.

**Keywords:** SCLC, prognosis, lactate dehydrogenase, fibrinogen, D-dimer, NLR, PLR

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## 1. Introduction

According to pathological types, Lung Cancer can be divided into Non-small-cell lung cancer (NSCLC) and Small-cell lung cancer (SCLC), of which SCLC patients account for about 15%[1]. Its characteristics include short time of tumor multiplication, rapid growth, strong invasion ability and high degree of malignancy, resulting in poor prognosis of SCLC patients[1,2]. During the treatment of SCLC patients, about 30% to 40% of the patients showed Limited Stage (LS) at the initial diagnosis, and about 60% of the patients were initially diagnosed as Extended Stage (ES)[3-6]. SCLC is highly sensitive to radiotherapy and chemotherapy, but due to the high degree of malignancy of SCLC, most patients will develop clinical drug resistance within a few months after first-line treatment, leading to disease progression[7,8]. It has been found that the median survival time of LS-SCLC patients is about 15-24 months. The median survival of ES-SCLC patients was about 8-10 months[3,6]. The 5-year survival rate of LS-SCLC patients was about 15%-25%, and that of ES-SCLC patients was less than 5%[9,10]. Therefore, before treatment, sensitive and accurate indicators are needed to evaluate the prognosis and guide clinical treatment.

Some histological and immunohistochemical markers have been used to monitor the therapeutic response of SCLC patients, including Thyroid

Transcription Factor-1 (TTF-1, positive in more than 85% of SCLC patients), Cytokeratin 7, Chromosome 3 Deletion, Leu-7, Chromaffin A, Synaptophysin, Myc Amplification and p53 Mutation (about 75%)[11]. These tests, which are expensive, aggravate patient's financial burden. At present, many studies have used hematological indicators to predict the prognosis of patients with SCLC cancer. Tumor markers such as Carcinoembryonic Antigen (CEA), Neuron-Specific Enolase (NSE) and Gastrin-Releasing Peptide precursor (Pro GRP) are widely used in clinical work, which will not be described here. However, Clinical indicators such as lactate dehydrogenase (LDH)[12-14], fibrinogen (Fib)[15], D-dimer (D-D)[15,16] the ratio of neutrophils to lymphocytes (NLR) and the ratio of platelets to lymphocytes (PLR)(17,18) also have certain guiding value for the prognosis of SCLC patients, which have been neglected due to their lack of extensive application. These examinations are convenient, fast, cheap, relatively harmless to human body, which can play the role of prompt treatment node in clinical work. In this paper, the research progress of these neglected SCLC hematological indicators is summarized as follows.

## 2. Lactate Dehydrogenase

Studies have shown that higher lactate dehydrogenase (LDH) levels in patients with SCLC

are associated with a shorter survival period, while normal baseline serum LDH levels are significantly associated with a better survival rate. Hsieh et al. found that serum LDH levels before treatment were not only a predictor of treatment response in ES-SCLC patients, but also an independent prognostic indicator. In the patients with ES-SCLC, the effective rate of treatment in the group with increased LDH level was lower than that in the normal group (39% vs 79%,  $P = 0.002$ ); in the patients with LS-SCLC, the level of LDH had no effect on the treatment[19]. According to the retrospective analysis of 999 Chinese patients with SCLC, Hong et al. found that serum LDH level could be an independent prognostic factor for Overall Survival (OS) and Progression-free Survival (PFS) in Chinese patients with SCLC.(13) The study of Anami et al. found that among those patients with SCLC brain metastasis receiving brain radiotherapy, the increase of LDH level was an independent predictor of the decrease of survival rate[20]. Bernhardt et al. found that for patients with LS-SCLC, the increase of LDH before chemotherapy and radiotherapy is an independent prognostic factor for OS shortening[21].

LDH is composed of two subunits A and B encoded by two different genes LDH-A and LDH-B. LDH-A is identified as the direct target gene of c-Myc oncogene transcription factor[22-24], LDH has five isoenzymes (LDH1-LDH5), which are widely expressed in different tissues and can be detected in serum. In the process of glycolysis and gluconeogenesis, LDH catalyzes the mutual transformation of pyruvate and lactic acid and plays a key role. Its activity and content are of great significance to glucose metabolism. Warburg effect links LDH with tumor metabolism, which shows that under the condition of sufficient oxygen, cancer cells can rely on anaerobic respiration to convert glucose into lactate, and LDH is the key enzyme in this process. The use of glucose metabolites can not only generate energy, but also promote cell growth and replication[25-28]. Clinical studies have confirmed that increased glycolysis can promote the progression of malignant tumors[29].

Hypoxia Inducible Factor-1 (HIF-1) plays a role in regulating energy stability in the Warburg effect[30,31]. HIF-1 is a heterodimer transcription factor consisting of two subunits, HIF-1a and HIF-1b[31]. Tumor cells proliferate rapidly and require a large amount of energy supply. The tumor is often in a chronic hypoxic environment, which will activate HIF-1. At the same time, glycolysis will increase the production rate of pyruvate and lactic acid, which will interfere with HIF-1 Regulatory degradation, which allows HIF-1 to accumulate not only under anaerobic conditions, but also under aerobic conditions[32,33]. HIF-1 directly enhances glycolysis by increasing the transcription of glycolytic enzyme genes, stimulates the expression of

glycolytic enzymes, and activates Pyruvate Dehydrogenase Kinase-1 (PDK-1) to directly inhibit mitochondrial function to drive cells Metabolism shifts to glycolysis[34,35]. Subsequently, the accumulation of glycolytic metabolites may promote the further activation of HIF-1 and enhance the stability of HIF-1, thus forming a positive feedback in the process of energy generation[36]. HIF-1 also up-regulates Vascular Endothelial Growth Factor (VEGF), a key regulator linking glycolysis and angiogenesis[37,38]. Under the regulation of VEGF and HIF-1, the rapid growth of tumor cells can make the tumor continue to develop.

Therefore, LDH inhibitors can inhibit the progress of tumor. LDH is a therapeutic target for tumor energy metabolism and can also be used as a marker of tumor burden in patients with advanced cancer. Measuring LDH levels can help monitor cancer treatment[39-42]. as well as SCLC patients, similar reports have been found in Colon cancer, Nasopharyngeal carcinoma, Breast cancer, Prostate cancer, Germ cell carcinoma and melanoma[43-51].

### 3. Fibrinogen and D-dimer

Fan et al. found that the level of fibrinogen was negatively correlated with the prognosis of patients with SCLC (HR 1.505, 95% CI 1.018-2.226;  $P = 0.041$ ). The increase of fibrinogen level led to the shortening of survival period of patients with ES-SCLC (7m vs.12m;  $P = 0.004$ ). The increase of plasma fibrinogen was an independent factor of poor prognosis of patients with SCLC[52]. Zhu et al. pointed out that no matter which disease stage SCLC patients are in, PFS and OS of patients with high level of fibrinogen or D-dimer before and after chemotherapy are worse than those with low level of fibrinogen or D-dimer. After two cycles of chemotherapy, the levels of fibrinogen and D-dimer are predictors of chemotherapy response and prognosis of SCLC patients[15]. Chen et al. found a similar conclusion that the increase of plasma D-dimer level before chemotherapy was related to the shortening of PFS and OS in patients with SCLC (PFS: 6.2m vs. 9.6m,  $P < 0.001$ ; OS: 15.7m vs. 24.4m,  $P < 0.001$ ). After two cycles of chemotherapy, the survival rate of patients with high D-dimer level was significantly lower than that of patients with low D-dimer level, suggesting that D-dimer level may be a potential predictor of treatment response in SCLC patients[16]. Antoniou et al. found that there was a certain relationship between the chemotherapy effect and the level of plasma D-dimer in SCLC patients. The level of D-dimer decreased in patients with good treatment effect, while the level of D-dimer increased in patients with disease progression[53]. A similar conclusion was reported by GE et al[54].

Fibrinogen is one of the common components in extracellular matrix. It is a kind of protein with coagulation function. It can dissolve in water and is mainly synthesized by liver. It is the most abundant coagulation factor in plasma and plays an important role in the process of coagulation and thrombosis. Thrombin is the key enzyme in the process of blood coagulation. The monomer protein produced by thrombin by removing fibrin A and B in fibrinogen is called fibrin, which is the final product of blood coagulation. Specific degradation products produced by fibrin activation and hydrolysis are called fibrin degradation products, which can promote angiogenesis. D-dimer is the simplest fibrin degradation product and is a sensitive marker in the process of fibrinolysis[55-57].

Fibrinogen mainly supports and protects tumor cells. Fibrinogen is used to connect tumor cells to the extracellular matrix, can also bind growth factors (such as VEGF and FGF-2) to promote angiogenesis, and is associated with adhesion, proliferation, and migration of tumor cells[58-60]. Tumor cells can induce increased expression of fibrinogen related products (including cross-linked fibrin and fibrin degradation products), which can be deposited around tumor cells, enhance the interaction between tumor cells and platelets, and promote thrombin formation[60-62]. Cross-linked fibrin plays a stabilizing role in the migration and metastasis of tumor cells[62]. When tumor cells metastasize from the primary site to a distant location, platelets - fibrin aggregates form around them, which can protect tumor cells from the attack of the immune system[63]. When tumor cells transfer to distant organs, plasma and platelets play a cooperative role in forming micro thrombus, attaching and stabilizing tumor cells[64]. Through the study of normal mice and mice without fibrinogen, it was found that the probability of lung metastasis was reduced when tumor cells were injected into mice without fibrinogen, and it was proved that the lack of fibrinogen would reduce the invasiveness of tumor cells in both hematogenous and lymphatic metastasis[62,65].

D-dimer is associated with tumor angiogenesis. D-dimer is related to VEGF, the most important angiogenic factor, and thrombin and other enzymes that promote angiogenesis during coagulation[66]. The elevated plasma d-dimer level reflects the abnormal activation of the coagulation-fibrinolytic system. After the activation of the coagulation-fibrinolytic system, the expression of Tissue Factors (TFs) in tumor cells increases, activating thrombin, and accompanying TNF- $\alpha$  and IL-1 $\beta$  secretion of inflammatory factors, and promote the activation of the coagulation system[67-70]. Plasminogen activators, especially urokinase-type plasminogen (uPA), promote tumor

invasion and metastasis by degrading the extracellular matrix and hydrolyzing local proteins[71]. The abnormal activation of coagulation-fibrinolytic system accelerates the growth, invasion and metastasis of tumor cells. It has been reported that D-dimer levels are significantly increased in patients with metastatic disease, and its level can reflect the treatment effect and prognosis of lung cancer patients[53,72,73].

Therefore, plasma fibrinogen and D-dimer levels reflect the relationship between coagulation activation and tumor cells, and this relationship can predict the clinical prognosis of patients with SCLC. The results showed that the level of plasma fibrinogen and D-dimer increased, which had a predictive significance for the poor treatment effect and short survival period of SCLC patients. Similar studies have been performed not only in SCLC patients but also in other cancer types. The serum fibrinogen concentration in tumor patients is related to tumor stage and size, and those with high concentrations have a poor prognosis. Hyperfibrinemia is related to the prognosis of colorectal cancer, cervical cancer, ovarian cancer, esophageal cancer, pancreatic adenocarcinoma and other malignant tumors. The prognosis of patients with high fibrinogen is poor[55,74-79].

#### **4. the ratio of neutrophils to lymphocytes (NLR) and the ratio of platelets to lymphocytes (PLR)**

Wang et al. found that NLR showed independent prognostic significance in patients with SCLC. The median OS (18.0m vs. 31.0m,  $P = 0.01$ ) and PFS (9.3m vs. 13.0m,  $P = 0.006$ ) of high NLR group are shorter. NLR may be helpful to monitor disease progress and adjust treatment plan[17]. By calculating the cutoff value, Deng et al. found that patients with  $NLR \geq 2.65$  were significantly associated with poor PFS and OS, and were independent risk factors for PFS (HR = 1.38; 95% CI 1.04 – 1.83;  $P = 0.027$ ) and OS (HR = 1.35; 95% CI 1.02 – 1.79;  $P = 0.039$ ). High PLR was associated with poor PFS, but it was not an independent prognostic factor for PFS and OS[18]. Kasmann et al. found that the survival rate was improved when NLR levels were low in patients with LS-SCLC through univariate analysis ( $p = 0.063$ ; HR 2.19 [95% CI 0.96–5.06]), but multivariate analysis found that there was no improvement in overall survival ( $p = 0.03$ ; HR 2.05 [95% CI 1.06–3.95]), and NLR was an independent prognostic factor affecting overall survival.(80) According to Kaplan Meier analysis, Shen et al. found that patients with high PLR had worse PFS than those with low PLR ( $P < 0.001$ )[81].

Virchow first observed leukocytes in tumors in the 19th century and found a link between inflammatory

cells and tumors. With the development of research, it is found that inflammatory cells play an important role in the occurrence, development and metastasis of tumors[82]. NLR and PLR are markers of systemic inflammation. NLR is the ratio of neutrophils to lymphocytes. PLR is the ratio of platelets to lymphocytes. Lymphocyte is the smallest white blood cell, which is produced by lymphoid organs. It mainly exists in the circulating lymph of lymphatic vessels. It is an important cell component of immune response function of the body and the main executor of almost all immune functions of the lymphoid system. Platelet is small pieces of cytoplasm that is separated from the cytoplasm of mature megakaryocytes in the bone marrow and is vital for the body's hemostatic function. Neutrophil is the most abundant cell in the blood with phagocytosis function, and the cell is rich in bactericidal substances such as lysosomal enzymes.

The relationship between tumors and inflammation lies in the activation of common transcription factors, of which Nuclear Factor- $\kappa$ B (NF- $\kappa$ B) and Transcription Signal Transducer-3(TST-3) are common transcription factors. NF- $\kappa$ B is activated in the inflammatory environment and can also be activated by carcinogens. Activated NF- $\kappa$ B can increase the expression of genes encoding inflammatory cytokines, and also help cell survival, proliferation and angiogenesis, and promote tumor development[83]. TST-3 is active in many immune cells and tumor cells, and plays an important role in cell cycle progression and apoptosis protection[83]. Therefore, transcription factors such as NF -  $\kappa$  B and TST-3 represent the intersection of tumor and inflammation.

As a kind of inflammatory cells, neutrophils affect the occurrence and development of tumors. When the neutrophil rises, it means that the inflammatory response is enhanced, which can promote the release of inflammatory mediators (such as Interleukin-1, Interleukin-6), stimulate the secretion of VEGF, increase the bioavailability and biological activity of VEGF, and mediate tumor angiogenesis[82,84,85]. Neutrophils can also inhibit the activity of lymphocytes and natural killer cells, destroy the immune response, reduce the anti-tumor response of the body, and promote the growth, proliferation, invasion and metastasis of tumor cells[85,86]. Lymphocyte is an important executor of immune response, which has been proved to play a significant role in anti-tumor immunity[87,88]. The target cells of lymphocytes are mainly T lymphocytes and natural killer cells, which can produce cytokines to recognize and clear tumor cells, inhibit tumor cell proliferation and induce cell death[89,90]. Among them, Ts cells, a kind of T cells are the main effector cells against tumors, which kill tumor cells by releasing perforin and granzymes to promote apoptosis[91]. Platelet is an

important source of cytokines. After activation, it can secrete many kinds of bioactive factors, such as Transforming Growth Factor -  $\beta$  (TGF -  $\beta$ ), Epidermal Growth Factor (EGF), to stimulate tumor cell proliferation and promote tumor angiogenesis[92,93]. Some studies have shown that platelets can also promote the formation of tumor extracellular matrix, maintain the stability of tumor cells, and increase the invasiveness of tumor cells[63]. In the circulatory system, tumor cells and platelets interact. Platelets can provide a procoagulant surface to promote the expansion of tumor-related coagulation, and enclose tumor cells within it. It protects tumor cells from the effects of immune responses and prevents them from being cleared, which will promote tumor cell growth and metastasis[93-95].

NLR and PLR represent the balance between inflammatory cells. Once the balance is broken, it indicates that the anti-tumor immune inflammatory response of the body is unbalanced, the anti-tumor immune function of the body is weakened, and there is no effective immune response to the tumor, leading to the invasion and development of the tumor[96,97]. NLR and PLR are not only independent factors of poor prognosis in patients with SCLC, but also higher ratio indicates poor prognosis[18]. and it has been proved that they could affect the prognosis of many kinds of malignant tumors. NLR can affect the prognosis of metastatic melanoma, esophageal cancer, colorectal cancer, pancreatic cancer, prostate cancer, diffuse large B-cell lymphoma and non-small cell lung cancer[98-104]. And PLR has been proved to be related to the prognosis of breast cancer, nasopharyngeal carcinoma and NSCLC[105-107].

## 5. Discussion

Small-cell lung cancer accounts for about 15% of the total number of lung cancer, which is characterized by rapid growth, strong invasiveness and high degree of malignancy. These characteristics cause SCLC patients to be prone to distant metastasis at an early stage and have a poor prognosis. The median survival time of patients with LS-SCLC is about 15-24 months; that of patients with ED-SCLC is about 8-10 months. Sensitive and accurate indicators are needed to evaluate the prognosis of the disease and guide clinical treatment. By reviewing the relevant literature, we found that some hematological indexes before treatment of small cell lung cancer can be used to predict the prognosis of the disease. Increased LDH, increased fibrinogen and d-dimer, and increased NLR and PLR all suggest poor prognosis of small cell lung cancer, which can be personalized survival prediction, prompt treatment nodes in clinical work, and timely modification of treatment regimen.

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## Availability of data and materials

Data sharing is not applicable to this article because there is no data generated or analyzed in this article.

## Authors' contributions

Haocheng Wang conceived and wrote this manuscript. Ya Dong and Dongfeng Shan performed the investigation. Xue Yang and Qi Qi reviewed and edited the manuscript. Zhuang Yu supervised the study and provided financial support.

## Ethics approval and consent to participate

Not applicable.

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## Competing interests

The authors declare that they have no competing interests.

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