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Inflammatory cytokines as diagnostic biomarkers in esophagus cancer

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Abstract

One of the most important types of proteins related to inflammation is cytokines which are considered potential biomarkers of esophageal cancer. In this way, these biomarkers, in conjunction with imaging techniques, may prove practical in the diagnosis and monitoring of therapy for various malignancies, such as esophageal cancer. Remarkably, in this article, the importance of cytokines is demonstrated to declare its practical applications on the dysregulation of cytokines in esophagus cancer and their clinical and pathological implications in diagnosis and also therapy. It has been confirmed that twenty-two cytokines exhibit abnormal levels in patients with esophageal cancer. Correspondingly, MIF is related to the regulation of growth processes, and IL-1*β*, IL-6, and IL-8 are related directly to regulation in the transcription process. IL-1β and IL-6 stimulate the production of proinflammatory cytokines. Additional research is crucial to determine the biological significance of cytokines in esophageal cancer, including their potential for early diagnosis, pre- and post-operative prognosis, and monitoring the response to chemotherapy and radiotherapy in cancer patients.

Keywords: Inflammatory cytokines, Diagnostic biomarkers, Esophagus cancer, Mechanism

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Introduction

Esophageal cancer is one of the most common cancers worldwide and the eighth leading cause of cancer (1). Esophageal squamous cell carcinoma (ESCC) is the most common histological type of esophageal cancer (1, 2). This cancer is usually found in the advanced stages of the disease and local or distant metastases appear (2, 3).

For this reason, the prognosis and survival prognosis of patients with ESCC is poor. In ESCC, the lack of serosa and the abundance of submucosal lymphatic structures favor disease spread during the disease (3). For that reason, most ESCC patients have micrometastases that are not visible at the tumor site at diagnosis. Tumor resection is an important method of treatment for ESCC. Therefore, radiotherapy and chemotherapy are complementary treatment methods (4).

Advances in clinical observations involving imaging techniques such as endoscopy, computed tomography (CT), magnetic resonance imaging, and positron emission tomography are useful for detecting esophageal dysplasia or neoplasms. These methods are very accurate in determining how to treat cancer. However, in some cases, the cancer is said to have advanced at the time of surgery, and in most cases treatment is straightforward. The two biggest risk factors for ESCC are smoking and alcohol consumption (5).

These include a variety of chemical carcinogens that stimulate inflammatory responses, induce oxidative stress parameters, disrupt genetics, alter enzyme activity, and induce angiogenesis (5). In recent years, it has been shown that the oncogenic transformation of cells is indicated at the molecular level, among others, by changes in the expression of proteins (6, 7).

This protein may be a marker for the early progression of esophageal cancer. New biomarkers close to imaging techniques may help in the diagnosis and treatment of patients with ESCC. It is important to identify biomarkers using simple and non-invasive methods. Several studies were performed using enzyme-linked immunosorbent assay (ELISA), Western blot (WB), immunohistochemistry (IHC), proteomic s, and airway mass and found a reduction in serum and tumor tissue protein levels. in ESCC patients. Studies on the relationships between protein alterations and clinical and pathological parameters may reveal the role of these molecules as ESCC biomarkers (7-9).

Biological Role of Cytokines and Growth Factors

Cytokines belong to a group of soluble proteins of low molecular weight. They act as mediators between cells, establish cell growth processes, and participate in differentiation, migration, and apoptosis (10, 11). Various types of specialized cells of the innate and adaptive immune system secrete it. Cytokines affect various cellular functions through specific receptors. It plays an important role in immunity, inflammation, repair, tissue homeostasis, and hematopoiesis (11). Cytokines are characterized by pleiotropy, reduction, synergism, and antagonism (12, 13).

The group of cytokines currently includes many elements with different origins and functions. Therefore, it isn't easy to classify these peptides. In composition, it includes interleukins (IL), interferons (IFN), chemokines (IL-8), and growth factors such as transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), and epidermal growth factor.

In practice, cytokines are both proinflammatory (eg IL-1, IL-6, IL-8, IL-18, IFN-γ, TNF-α, TNF-β and FasL) and anti-inflammatory factors (eg IL- 4, IL-10, and TGF-β). (11, 13, 14). Many inflammatory cytokines have been implicated in various mechanisms leading to cancer (14, 15). It is well known that the process of malignant transformation is closely related to abnormal responses in cytokine expression (13, 15). Cytokines also play an important role in stimulating tumorigenic angiogenesis and inducing metastasis (13).

Cytokines in SCC of Esophagus

The tumor microenvironment contains not only cancer cells but also fibroblasts, endothelial cells, immune cells, and cytokines, which play an important role in the regulation of this type of cell communication (14, 16-18). Under certain conditions, in the early stages of cancer development, endogenous cytokines can stimulate host immune responses against tumor cells. However, current data suggest that many of these factors contribute to poor prognosis and contribute to

tumor growth, progression, metastasis, and clinical resistance (11, 12). For these reasons, changes in the ESCC microenvironment may have important implications for cancer development. Like other malignant tumors, esophageal cancer cells secrete several disease-causing factors to suppress the host's defenses (8, 9).

The cytokine network of ESCC is rich in proinflammatory cytokines, growth factors, and chemokines. In this study, I demonstrated that 22 cytokines are associated with clinical and pathological symptoms and survival rates of ESCC**.** The main cytokines associated with ESCC are VEGF-A, VEGF-C, VEGF-D, bFGF, HGF, MIF, TGF-β, IL-6, IL-8 and FasL, and midkine, IL-18, PDGF-BB, CTGF and CXCL12 (19, 20).

High expression of VEGF family members, including HGF and bFGF, was observed ESCC tumor tissues, suggesting their potential role in the processes of tumor growth, angiogenesis, and metastasis (21, 22). In addition, VEGF-A, C, D, IL-8, IL-6, IL-18, TGF-β, HGF, FasL, PDGF-BB, and midkine members influence tumor progression, lymph node metastasis, and distant metastasis. parameters (20, 23). The functions of ESCC-derived cytokines are shown in **Table 1**. MIF is associated with the regulation of growth processes, and IL-1β, IL-6, and IL-8 are associated according to the transfer law. IL-1β and IL-6 are stimulators of proinflammatory cytokine production. FasL induces apoptosis of activated lymphocytes in the host's immune system, thereby causing cancer (24, 25).

Transforming growth factor beta (TGF-β) plays a dual role in tumor development. In the early stages of cancer, these cytokines act as tumor suppressors, but later they promote tumor invasion by stimulating extracellular matrix formation, tumor growth, angiogenesis, and abolishing military blockade (26).

Although most cytokines are known to play a role in cancer growth and metastasis, other cytokines such as IL-2, IL-12, IL-23, IL-27, and IFN-γ exert anticancer responses through various molecular mechanisms (27).

Table 1. Cellular role of ESCC-associated cytokines.

Function	Cytokine
Immune suppression	TGF-β
Growth regulation	MIF
Transcription regulation	• IL-1β • IL-6 • IL-8
• **Inflammatory** • **cytokines secretion**	• IL-1β • IL-6
Apoptosis negative regulation	FasL
• **Host immune stimulation** • **(Th1 response)**	• IL-2 • IFN-γ • IL-12 • IL-18
Angiogenesis stimulation	• VEGF-A • VEGF-C • VEGF-D • IL-8 • HGF • bFGF • PDGF-BB MIF
Metastasis induction	• VEGF-A • VEGF-C • VEGF-D • bFGF • HGF • midkine

Cytokines as a marker for the presence of ESCC

Histologic changes in the development of ESCC include mild to malignant epithelial dysplasia, localized carcinoma, and invasive carcinoma (2). The pathogenesis of esophageal cancer is still unclear. Molecular studies have shown that genetic changes, as well as alcohol consumption and smoking, are responsible for pathological changes in the squamous epithelium of the esophagus (2, 28, 29). Early detection of this type of cancer is the most effective way to treat patients with ESCC.

Therefore, there is a need to find changes in cytokine levels related to tumorigenesis. In this review, 22 cytokines showed different levels in ESCC patients. Among these peptides, 20 showed higher levels, and only IL-2 and IFN-γ showed lower levels were reported (25, 30). IHC studies showed higher expression of selected cytokines in esophageal cancer tissue compared to normal tissue (20).

This suggests that the regulation of these peptides is involved in growth and progression. on tumor expression of VEGF-A, VEGF-C, TGF-β, IL-1β, IL-6, HGF, CTGF, CXCL12, FAS-L, a-FGF, bFGF, IGFBP7, IGF-II, midkine and MIF . Research has shown the relationship between cytokine production and cancer (21, 31-34).

However, the biological function of these cytokines in tumor cells and the tumor microenvironment is different. On the other hand, the expression of cytokines in tumor cells promotes tumor growth and stimulates oncogenic transformation; on the other hand, the production of these peptides in the immune cells of the tumor microenvironment can also contribute to the antitumor immune response (35). Most studies analyzed cytokine expression in esophageal tissue samples using the IHC method. However, these researchers examined the expression of cytokines in tumor tissues in both early and advanced TNM stages of cancer. There are no studies analyzing cytokine expression only in early stage ESCC. The lack of this type of study is due to the high invasiveness of ESCC and therefore to the small group of patients with early-stage cancer. Serum cytokines are positively correlated with tumor stage, angiogenesis, and metastasis. The biological significance of circulating cytokines in esophageal cancer is currently unknown. One of the hypotheses indicates that high serum levels of some cytokines can be associated with apoptosis induced by activated lymphocytes, which facilitates tumor cell progression and metastasis. This deactivation of host immune surveillance may be important for circulating cancer cells in the blood and lymph nodes (25).

Several ELISA studies, including ours, have shown significantly higher levels of VEGF-A, VEGF-C, VEGF-D, TGF-β, IL-6, IL-8, IL-12, IL-18, PDGF- BB, HGF, FasL, MIF and midkine levels in the serum of ESCC patients (23, 33, 36-38). The relationship between serum concentrations of VEGF-A, VEGF-C, VEGF-D, IL-12, IL-18, PDGF-BB, HGF, FasL, and midkine and cancer stage was shown (25, 39-41). Analysis of IFN-γ and IL-2 showed that the serum levels of these factors were significantly reduced in patients with ESCC (20).

Both cytokines are important inducers of Th1-related inflammatory responses and inhibit cancer development (13, 20). Based on the IHC and ELISA studies, we think that VEGF-A, VEGF-C, and HGF are useful biomarkers for the clinical diagnosis of the presence of ESCC, but they may not be useful for the early detection of esophageal cancer (30, 33, 35, 42-44). Serum levels of VEGF-A, VEGF-C, VEGF-D, and TGF-β were found to be increased in ESCC patients and significantly decreased after surgical treatment (23). Serum analysis of these cytokines may help monitor treatment efficacy in patients with ESCC **(Figure 1).**

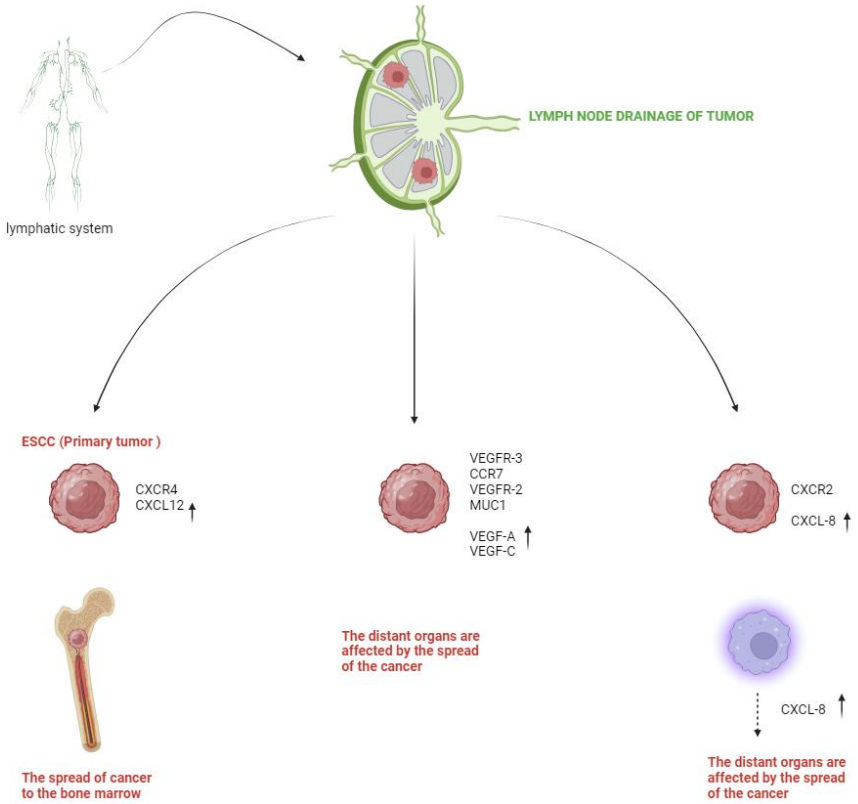

Figure 1. The impact of chemokines and cytokines on a rise and metastasis of tumors. Elevated expression of the CXCL12/CXCR4 axis in primary tumor cells and/or ECSCs augments p-ERK-1/2 activation and amplifies the capacity of these cells to infiltrate and spread to lymph nodes and bone marrow. Primary tumor cells produce a high quantity of powerful angiogenic (VEGF-A) and lymphangiogenic (VEGF-C) factors, which initiates a malignant process. Through the CXCR2 receptor expressed in primary tumor cells, increased amounts of CXCL-8 released by TAMs or primary tumor cells phosphorylate the AKT and ERK1/2 signaling pathways.

Cytokines as anxiogenic factors

The angiogenic process is important for tumor growth and progression in ESCC (45-47). Growing cancers require an extensive network of blood vessels to deliver oxygen and nutrients. The formation of new blood vessels allows cancer cells to circulate and metastasize at a distance. The formation of new capillaries requires several sequential steps, which are mediated and controlled by a variety of angiogenic factors, such as angiogenic enzymes, adhesion molecules, endothelium-specific receptors, angiogenic cytokines, chemokines, and growth factors (48, 49). Angiogenic factors can act directly on vascular endothelial cells to stimulate their activity, differentiation, growth, and migration. The following cytokines are involved in ESCC: members of the VEGF family, bFGF, and IL-8 (49). Based on the factors mentioned above, it appears that members of the VEGF family play an important role in this process. VEGF-A (also known as VEGF) plays a role in tumor angiogenesis and tumor growth. This growth factor protects endothelial cells from apoptosis and plays an important role in maintaining the balance of the circulatory system (19, 49). In clinical studies, VEGF-A is significantly associated with tumor progression, especially local metastasis to lymph nodes. Two studies have shown that overexpression of VEGF-A is associated with the formation of new ligaments (19). Most researchers have suggested that VEGF-C and VEGF-D are involved in the development of new lymphatic vessels. The significant relationship between VEGF-C protein expression, serum concentration, and the presence of lymph node metastases was shown in 10 articles. In eight articles, the authors showed the relationship between VEGF-C and the depth of tumor invasion (35). Two studies showed a significant correlation between serum or tissue VEGF-D levels and lymph node

metastasis (50). In this paper, the authors also showed the relationship between VEGF-D and cancer stage. The present results show that the cytokines that form the VEGF family play an important role in lymphangiogenesis as a specific marker of malignancy. Another angiogenic factor, bFGF, also has a prognostic effect on ESCC angiogenesis. Han et al. (51) IHC studies showed that bFGF expression was significantly associated with microangiogenesis primary tumor progression and lymph node metastasis. There is also a second group of cytokines that induce the production of angiogenic cytokines. These include IL-1β, IL-6, IL-8, MIF, HGF, PDGF-BB, and TGF-β. IL-1β, IL-6, and IL-8 are important for the induction of signaling pathways involved in the production of angiogenic cytokines. They contribute to the development of cancer, tumor growth, and metastasis (38). MIF can induce angiogenic factors such as VEGF-A and IL-8 in tumors, but not in normal epithelial cells. High expression of this cytokine correlates with lymph node status, tumor differentiation, microvascular tissue, and survival in ESCC patients and is positively correlated with VEGF-A expression (43). Studies of tumor tissue and serum have shown that HGF levels are associated with cancer stages and the metastatic process. The study by Ren et al. (43) also showed that HGF stimulated the expression of VEGF-A, IL-8, and PDGF. Another factor that plays an important role in tumor development is TGF-β. A study by Deng et al (52). Demonstrated that the TGF-β signaling pathway is perturbed in ESCC and can promote tumor invasion, metastasis, and patient survival. Also, connective tissue growth factor (CTGF) is one of the proteins involved in the TGF-β signaling pathway and plays an important role in the activation of angiogenesis and tumor growth. In another nine studies, increased levels of cytokines such as IL-12, IL-18, PDGF-BB, midkine, FasL, and IGF-II were associated with tumor invasion, lymph node metastasis, and higher TNM stage ESCC in patients . reported that the chemokine CXCL12 is overexpressed in ESCC and that expression is associated with lymph node metastasis (53).

Cytokines as Markers of Distant Metastasis

Angiogenesis has been linked to metastasis, which is a major cause of cancer death (54). Also, biological factors associated with metastasis are often involved earlier in the processes of cell adhesion and angiogenesis (8). Neoplastic cells that can acquire the ability to invade and metastasize leave primary tumors and colonize new tissue in the host. Tumor cells use different motility mechanisms for their transformation and migration. Biochemical mediators such as cytokines are involved in these complex processes. Seven cytokines were associated with ESCC metastasis. Three studies showed that overexpression of VEGF-A and VEGF-C may play an important role in the distant migration of cancer cells while circulating levels of VEGF-A and VEGF-C were significantly increased in patients with distant metastases in five cases. Studies of these results confirmed that VEGF-A and especially VEGF-C are potent factors in ESCC metastasis processes by inducing lymphatic angihyperplasia. Kleespies et al. suggest that high serum levels of these cytokines may promote the growth of micrometastases in distant body sites (36). An immunohistochemical study by Imsumran et al. showed that high expression of IGF-II in ESCC tumor tissue correlated with lymph node involvement and metastasis. Findings described by Krzystek-Korpacka et al.(55) showed that serum levels of IL-8 and PDGF-BB were associated with local and distant metastases. Serum HGF levels were also positively correlated with VEGF-A and IL-8 and associated with distant metastasis. Serum FasL concentration was significantly higher in ESCC patients with distant metastases, supporting the hypothesis that FasL can induce apoptosis of activated lymphocytes, weaken the host immune system, and facilitate tumor metastasis (43). In this way, the existence and regulation of antitumor immunity in esophagus cancer is illustrated in **Figure 2.**

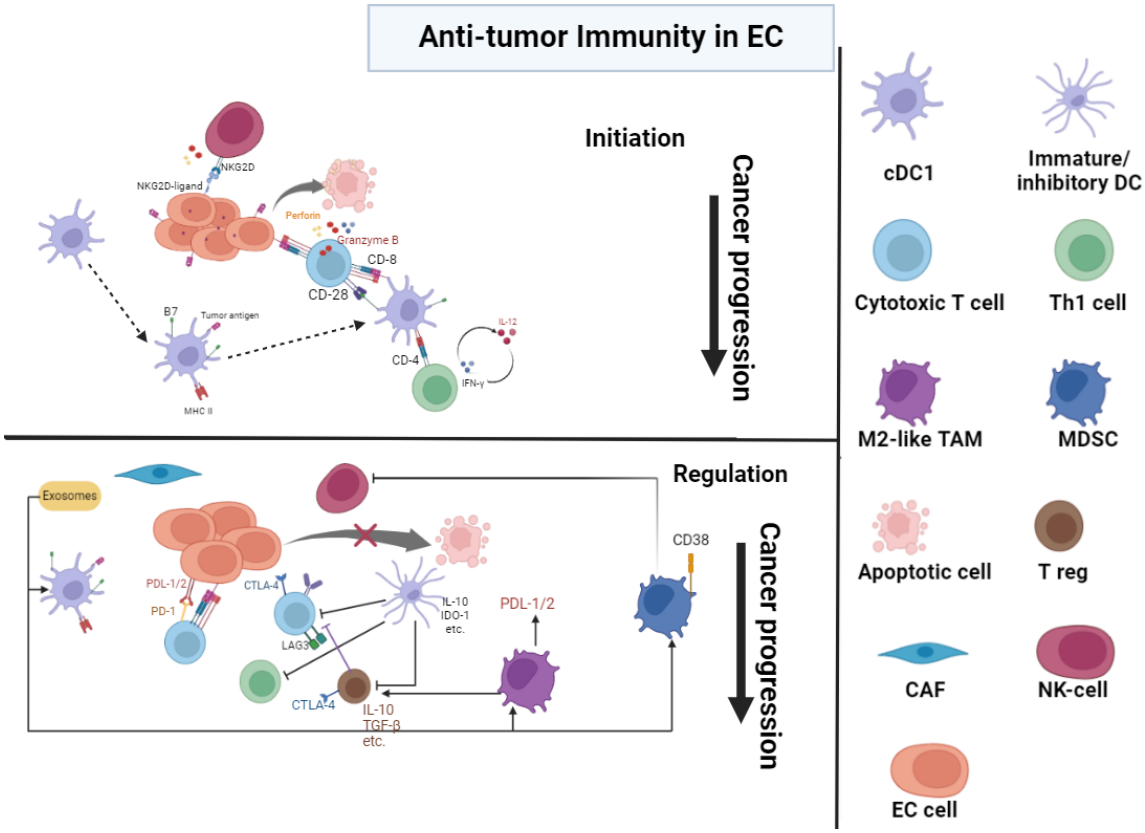

Figure 2. The initiation and regulation of EC antitumor immunity. Particularly in the early stages of EC, EC cells can trigger an antitumor immune response and contain a large number of tumor antigens.

miRNAs

MiRNAs are highly conserved, non-coding single-stranded small RNA molecules encoded by endogenous genes and about 20–24 nucleotides in length (56). They can participate in the regulation of several biological functions, including cell differentiation, apoptosis, proliferation, and metabolism by regulating the expression of target genes (57). In 2002, Calin et al found that miRNAs are downregulated in chronic B lymphocytic leukemia, the first report of a link between miRNAs and tumors. Currently, miRNAs are thought to mediate post-transcriptional regulation of gene expression mainly through both target mRNA degradation and inhibition of protein translation (58). More and more studies have shown that different miRNAs play different roles in promoting cancer or tumor suppression, and those aberrantly expressed miRNAs can unbalance the expression of oncogenic or suppressive genes in the body, ultimately leading to the formation of tumors (59). MiRNAs not only have abnormal expression in tumor tissues but also have specific expression in patient serum. Recent studies have shown that tumor-derived miRNAs are resistant to endogenous ribonuclease activity, so they can be present in a stable form in human serum. In addition, serum miRNA expression levels are reproducible and consistent between individuals, making them ideal candidates for blood diagnostic screening. Because Zhang et al (60). serum miRNA levels in ESCC patients were first reported in 2010, several studies have investigated the differential expression of circulating miRNAs and their potential applications in ESCC (61). Thus, miRNA markers found in circulation may play a role in enabling the early diagnosis of ESCC. Until now, more and more studies have confirmed that c-miRNA can be used as a new serum molecular marker for the early diagnosis of ESCC. Most studies focused on candidate miRNAs selected from previous ESCC tissue analysis, while other investigators used high-throughput technology to analyze miRNAs in discovery sample datasets and then performed qRT-PCR on an independent validation dataset to determine tissue diagnostic value. candidate miRNAs (62). From 33 manuscripts, a total of 43 different types of miRNAs were investigated in the serum of ESCC patients. In

these studies, the sensitivity, specificity, and AUC of miRNAs for the diagnosis of ESCC were 55.3-96.9%, 47.4-100%, and 0.590-0.951, respectively. Among the most studied individual miRNAs in ESCC are known miRNAs such as miR-21, miR-223, miR-375, miR-25, and miR-100 (63).It analyzed the diagnostic value of miR-21 and found that it has good sensitivity and specificity for ESCC, which are 71.0% and 96.9%, respectively. However, the number of ESCC patients included in the study was small, and the lack of miR-21 validation studies limits clinical expansion. This study reports the analysis of a test and validation panel of serum miRNAs that may be potential diagnostic biomarkers for ESCC. The combination of a test cohort and a validation cohort significantly improved the reliability of diagnostic accuracy compared to many previous studies without a validation cohort. For example, the serum level of miR-1322 gave an area under the curve of the receiver operating characteristic (ROC) of 0.847 (95% CI: 0.795-0.890), which was used to discriminate between ESCC and healthy controls in the experimental group. Similar results were obtained in the valid group (area under the ROC curve: 0.845; 95% CI: 0.780-0.897) (64). They showed that the seven miRNA profile can be used as a biomarker of ESCC and, more importantly, that it has the potential to predict early ESCC. The study found that a panel of seven miRNAs was a more sensitive marker for ESCC than the conventional biomarker carcinoembryonic antigen. created a diagnostic model of serum miRNAs in 566 ESCC patients and 4965 control patients, the largest study to date to design ESCC diagnostic models. This article used two independent cohorts to study the diagnostic model consisting of miR-8073, miR-6820-5p, miR-6794-5p, miR-3196, miR-744-5p, and miR-6799-5p. The sensitivities/specificities were 100%/98.0% and 96.0%/98.0%, respectively, with similar diagnostic values in early ESCC (64). In addition, Li et al (61) reviewed 18 publications and investigated 39 different types of miRNAs in EC patients. The authors report relatively high sensitivity and specificity of combined and individual miRNA markers, indicating some value in diagnostic application. The results showed that single miRNAs did not show statistically significantly better accuracy than multiple miRNA panels, which is contrary to some previous studies (61). Since only two studies reported in this article compared multi-miRNA panels, this finding may not be sufficient to support such a conclusion. Many studies have shown that circulating miRNAs in serum have potential clinical use as early tumor diagnostic markers, but more clinical data and mechanistic studies are needed. Our current knowledge about miRNAs can be boiled down to this, first, the transcription of a single miRNA may require the simultaneous regulation of multiple miRNAs. On the other hand, a single miRNA can be involved in the simultaneous regulation of the expression of several mRNAs (65). Second, processing and detection methods for serum circulating miRNA have yet to be standardized, and the selection of internal parameters requires further verification and standardization. Finally, most studies on serum circulating miRNAs in early tumor diagnosis include small-sample, single-center studies, while large-sample, multicenter, prospective clinical trials are needed.

Long non-coding RNAs

Long non-coding RNAs (lncRNAs) are non-coding RNAs longer than 200 bases that lack an open reading frame and therefore lack protein-coding capacity (66). LncRNAs regulate gene expression at different levels. LncRNAs regulate gene expression and act differently than miRNAs, which not only affect protein post-translational regulation but also act in multiple ways that affect gene transcriptional activity and protein degradation (67, 68). A large body of evidence indicates that lncRNAs have cancer-promoting or cancer-preventing effects by influencing tumor cell proliferation, invasion, metastasis, differentiation, apoptosis, and genomic stability (69). HOX-transcribed RNA (HOTAIR) is the first long noncoding RNA with transregulatory effects in primary and metastatic breast cancer. In addition, some studies found that HOTAIR is also highly expressed in ESCC tissues, and the expression level is inversely correlated with differentiation grade and positively correlated with TNM stage (70). Previous studies on lncRNAs have mainly focused on cancer tissues. (71). In recent years, researchers have studied the expression levels of lncRNAs in the serum or plasma of cancer patients, and many studies have shown that lncRNAs can also exist in other body fluids, including serum, plasma, and other body fluids. Not sure. Furthermore, a study by Arita et al confirmed that lncRNAs remain in circulating blood under certain conditions (72).

Recently, several laboratories have proposed different serum or plasma lncRNAs that can be used for early diagnosis and monitoring of the severity of ESCC. Wang et al (73) qRT-PCR analysis revealed elevated levels of HOTAIR in the serum of ESCC patients. However, further investigation is needed to determine the sensitivity and specificity of this finding, as initial data suggests a specificity of 56.0%. Furthermore, serum levels of HOTAIR decrease after ESCC surgery. These results suggest that serum lncRNA-HOTAIR may be a molecular marker for ESCC. Several studies have shown that lncRNAs tested individually or in combination have similar or superior diagnostic performance to traditional cancer biomarkers. The levels of three lncRNAs, POU3F3, HNF1A-AS1, and SPRY4-IT1, in the plasma of patients with ESCC, were significantly higher than those of normal controls, in plasma POU3F3 show a very strong correlation (area under the curve 0.842), sensitivity 72.8%, specificity 89.4%) (74). In 147 ESCC and 123 healthy controls, plasma POU3F3 and squamous cell carcinoma antigen (SCCA) were found to have good detection and improved diagnostic performance (area under the curve 0.926, sensitivity 85.7%, specificity 81.4%). 80.8% of patients with early ESCC were detected, suggesting that the combination of POU3F3 and SCCA may be useful for early detection of ESCC (74). Circulating lncRNAs are thought to be stable in blood because of encapsulation in microvesicles or exosomes (72). A better understanding of the transport of lncRNAs within and between cells and the basic biology of cell-derived lipid vesicles may help to develop biomarkers for the detection of human diseases in circulating lncRNAs. In addition, the detection of biomolecular markers in peripheral blood has the advantage of a simple and minimally invasive surgery. Therefore, finding new lncRNAs as diagnostic molecular markers in blood circulation is expected to be a hot scientific topic in the field of biomarker research. To introduce circulating lncRNAs into clinical practice, further research and improvements on the standardization of sample preparation methods, the control of endogenous lncRNAs in body fluids, and the combination of extraction methods should be performed. Criteria for evaluating lncRNA quality and reliability of qPCR results should be accurate and reliable while minimizing selectivity (71). Most of the current studies were designed with small samples and have no real clinical application. Therefore, it is necessary to expand the sample size and combine multicenter clinical validation studies to develop lncRNA detection kits to detect markers in blood to improve the efficiency of early detection and subsequent investigation of the function of lncRNAs in tumors.

Conclusion

The article showed that certain cytokines play a role in the aggressive nature of ESCC and are associated with primary tumor progression, lymphatic and distant metastases, and patient outcomes. VEGF family members appear to play an important role as early markers of ESCC. In addition, HGF and bFGF may serve as specific prognostic markers for ESCC. Changes in levels of angiogenic cytokines and growth factors, such as VEGF-A, VEGF-C, TGF-β, and HGF, and microvascular assessment can be used to indicate lymphangiogenesis and distant metastasis in patients with ESCC. Cytokines play an important role in tumor growth, angiogenesis, and metastasis, but their role in ESCC is not fully understood. Further studies are needed to confirm the biological significance of cytokines in ESCC and their utility for early diagnosis, staging, and response monitoring of chemotherapy and radiotherapy cancer patients. Among all proteins related to inflammation, cytokines play an important role in cancer development and progression and may be implicated as possible biological markers of esophageal cancer.

Author contribution

ATMH designed the statistical analysis and wrote the paper.

Conflict of interest

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