

Data Mining-Driven: Identification of Potential Traditional Chinese Medicine Categories Targeting Vasculogenic Mimicry in Esophageal Cancer

Yunqin Wang¹, Yu Wang¹, Qian Zhang³, Ruoshui Xia¹, Yanqing Liu^{1,2}, Jue Chen^{1,2*}

¹Affiliated Hospital of Yangzhou University, No. 368 Hanjiang Middle Road, Hanjiang District, Yangzhou 225001, Jiangsu, China

²Medicine Department of Yangzhou University, No. 136 Jiangyang Middle Road, Yangzhou 225001, Jiangsu, China

³Radiation Therapy Department of Zhongshan Hospital, Fudan University, No. 180 Fenglin Road, Xuhui District, Shanghai 200032, China

*Corresponding author: Jue Chen, 1019924551@qq.com

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Abstract: *Background:* Vasculogenic mimicry refers to a specialized tumor microvasculature independently formed by tumor cells, which facilitates the recurrence, metastasis, and therapeutic resistance in esophageal cancer. Within the framework of traditional Chinese medicine (TCM) theory, there is currently no clear conceptual classification or diagnostic-therapeutic principles for this phenomenon. *Objective:* To explore traditional Chinese medicine (TCM) herbs and syndrome factors related to the treatment of vasculogenic mimicry in esophageal cancer, and to provide a reference for clarifying the TCM clinical syndromes of vasculogenic mimicry in esophageal cancer. *Methods:* Based on public databases such as TCMSP, CNKI, and PubMed, TCM herbs related to esophageal cancer, clinical medications, and herbs inhibiting vasculogenic mimicry were retrieved. The herbs collected from multiple databases were standardized, collated, and cross-analyzed, and core herbs were screened for further analysis. *Results:* Among the public databases, herbs inhibiting vasculogenic mimicry and commonly used clinical herbs for esophageal cancer were mainly of the blood-activating and stasis-resolving type (Huoxue Huayu). In contrast, esophageal cancer-related herbs in the TCMSP database were mainly of the heat-clearing and toxin-resolving type (Qingre Jiedu). A total of 22 TCM herbs related to vasculogenic mimicry in esophageal cancer were identified, mainly blood-activating and stasis-resolving herbs, involving three syndrome factors: “blood stasis (Xueyu), Qi deficiency (Qixu), and Qi stagnation (Qizhi).” *Conclusion:* Vasculogenic mimicry can promote the progression of esophageal cancer, and blood-activating and stasis-resolving herbs may improve the prognosis of patients with esophageal cancer.

Keywords: Esophageal cancer; Vasculogenic mimicry; Recurrence and metastasis; Traditional Chinese medicine

Online publication: October 13, 2025

1. Introduction

Esophageal cancer is a common malignant tumor of the upper gastrointestinal tract in most economically underdeveloped countries and regions, including China, and surgical resection is the standard treatment except for cervical esophageal cancer ^[1]. Although postoperative adjuvant therapy as a supplement to surgical resection has improved the prognosis of some patients outside the T1N0 stage, a considerable proportion of patients still have regional lymph node recurrence and distant organ metastasis. This phenomenon suggests that current postoperative adjuvant treatment strategies do not cover some prognostic risk factors that have not yet been clearly defined. In previous studies, our research group found that the presence of vasculogenic mimicry (VM) had a certain adverse effect on the survival of esophageal cancer, and found that positive VM would affect the effect of postoperative adjuvant treatment. VM is a kind of highly aggressive tumor cells that remodel into vascular-like channels to provide nutrients to itself ^[2]. The formation of VM realizes the exchange of substances between the local microenvironment, including tumor cells, and the outside world, leading to tumor recurrence and distant metastasis. Therefore, intervening in VM is a potential strategy to reduce the risk of postoperative recurrence progression in patients with esophageal cancer with such pathological structures. However, Western medicine has limitations in inhibiting VM, and the intervention effect is not good, so it is necessary to combine traditional Chinese medicine (TCM) methods to form a systematic treatment strategy.

There is no clearly defined corresponding TCM pattern for vasculogenic mimicry in esophageal cancer. In view of the complex mechanism of VM and insufficient conventional treatment intervention, the use of drugs can be guided under the overall view of traditional Chinese medicine and the core idea of syndrome differentiation and treatment. Therefore, the potential TCM pattern can be inferred through the medication used for esophageal cancer related to VM. Previous studies have shown that extracts of Chinese herbs, such as those categorized as activating blood circulation and resolving stasis, can inhibit VM-related processes. Since there are few traditional Chinese medicine studies on esophageal cancer VM, this study plans to explore effective traditional Chinese herbs targeting VM and summarize the rules, and provide theoretical support for the comprehensive treatment of relevant patients through inferring patterns from medicines.

2. Methods

2.1. Literature search

PubMed, the China National Knowledge Infrastructure (hereinafter referred to as CNKI), the Wan fang Data Knowledge Platform (hereinafter referred to as Wan fang data), and VIP Chinese Science and Technology Journal Database (hereinafter referred to as VIP) were searched for Chinese herbal monomers or active ingredients that have been experimentally verified to inhibit vasculogenic mimicry. The keywords in PubMed were “Vasculogenic Mimicry” and “Herbs or Chinese Medicine or Chinese Traditional drug”. The search keywords of CNKI, Wanfang, and VIP were “Vasculogenic Mimicry” and “traditional Chinese medicine or formula, or prescription.”

CNKI, Wanfang data, and VIP searched for effective prescription studies for the clinical treatment of esophageal cancer, and the search keywords were “esophageal cancer” and “traditional Chinese medicine or formulas or prescriptions or empirical formulas “. The search time range was from 2014 to 2024, and the search fields included keywords, abstracts, subjects, titles, and titles.

2.2. Data analysis

Statistical analysis of the clinical data extracted from the literature was performed using Excel 2019 software.

2.3. Inclusion and exclusion criteria

2.3.1. Inclusion criteria

- (1) The disease described in the literature is esophageal cancer/esophageal squamous cell carcinoma;
- (2) The literature content confirms that the Chinese herb/formula related to vasculogenic mimicry is effective through experimental validation (in vivo or in vitro);
- (3) The literature format is research-based/clinical;
- (4) Studies on clinical formulas related to esophageal cancer must be published between 2014 and 2024.

2.3.2. Exclusion criteria

- (1) Non-esophageal cancer diseases documented in the literature;
- (2) The literature format is a review type;
- (3) Duplicate literature (different articles write the same professor's experience and integrate it into one article);
- (4) The full text of the literature is not available.

2.3.3. Flow chart

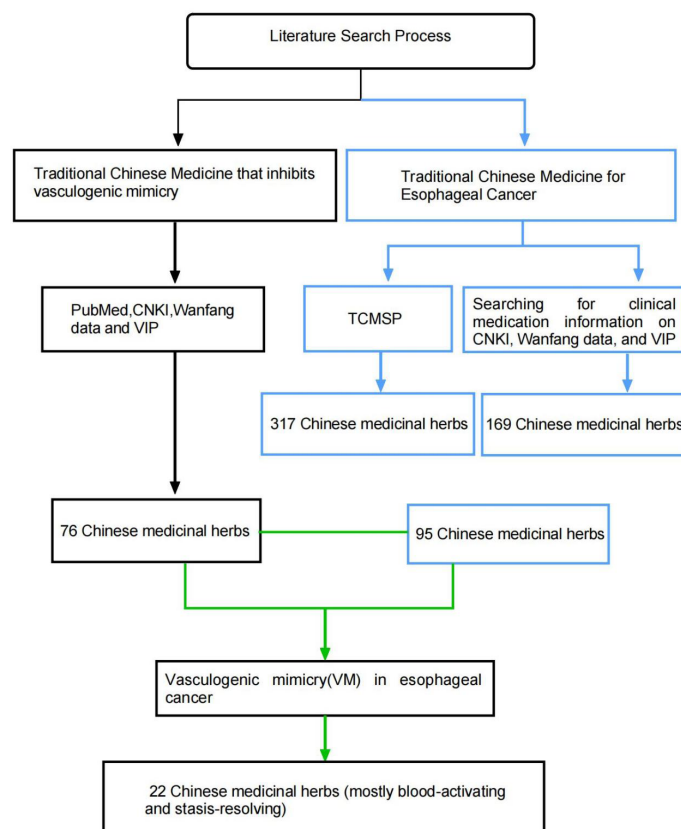


Figure 1. Flowchart of the literature selection process.

3. Results

3.1. The categories of traditional Chinese medicines related to inhibiting vascular mimicry are mainly blood-activating and stasis-resolving medicines

Traditional Chinese medicines that have been experimentally verified to effectively inhibit vascular mimicry were retrieved from PubMed, CNKI, and other databases. These included traditional Chinese medicine extracts curcumin, berberine, artemisinin, etc.; traditional Chinese herb pairs like *Astragalus membranaceus* (Huangqi) - *Atractylodes macrocephala* (Baizhu), *Panax ginseng* (Renshen), *Astragalus membranaceus* (Huangqi), and *Hedyotis diffusa* - *Scutellaria barbata* (Banzhilian) etc., as well as effective prescriptions such as anti-cancer prescriptions and spleen-strengthening and phlegm-reducing prescriptions. A total of 76 Chinese medicines were ultimately included. To explore whether these VM-inhibiting medicines share common patterns, the study analyzed the efficacy of the 76 Chinese medicines. The results revealed that the VM-inhibiting medicines primarily belong to the category of blood-activating and stasis-resolving medicines, with cold property and bitter taste (Figure 2).

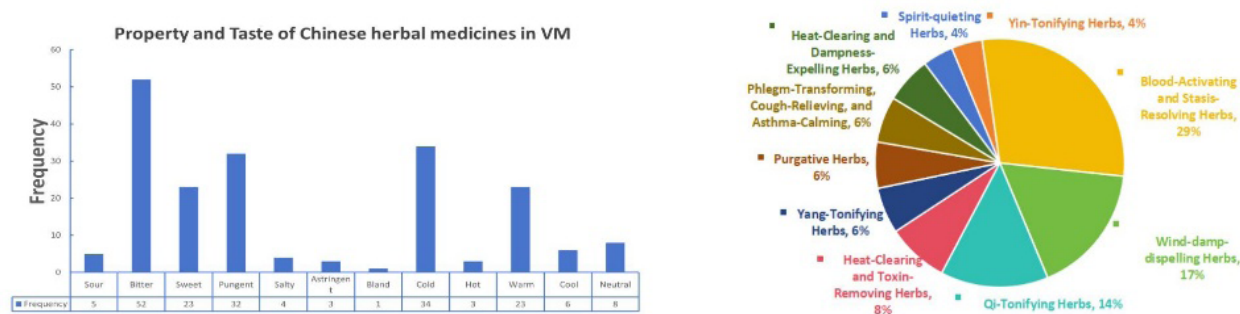


Figure 2. Literature search frequency map of property, taste and efficacy distribution of traditional Chinese medicine inhibiting VM.

3.2. Clinically effective Chinese medicines for esophageal cancer are primarily blood-activating and stasis-resolving medicines and Qi-regulating medicines

In order to understand the clinical use of traditional Chinese medicine in the clinical treatment of esophageal cancer, we collected and sorted out the effective prescriptions for the treatment of esophageal cancer in clinical practice, and searched the relevant prescriptions for the treatment of esophageal cancer from 2014 to 2024 in relevant databases. The prescriptions were primarily derived from the commonly used clinical prescriptions of renowned professors and scholars who have made significant contributions to anti-tumor therapy with Traditional Chinese Medicine, such as Huang Jinming, Pan Minqiu, Hua Baojin, Wang Xixing, Zheng Yuling, Xiong Jibo, Liu Yanqing, Li Zhigang, and Qi Lei. Ultimately, 51 clinically effective prescriptions were integrated, including a total of 752 flavors of traditional Chinese medicine. After cleaning the data, standardizing the names of the Chinese medicines, and removing duplicates, 187 flavors of traditional Chinese medicine were obtained after sorting. The analysis using Excel revealed that *Pinellia ternata* (Banxia), *Poria cocos* (Fuling), *Atractylodes macrocephala* (Baizhu), *Glycyrrhiza uralensis* (Gancao), *Citri Reticulatae Pericarpium* (Chenpi), *Astragalus membranaceus* (Huangqi), *Curcuma aromatica* (Yujin), *Angelica sinensis* (Danggui), *Curcuma zedoaria* (Ezhu), and *Amomum villosum* Lour (Sharen) were among the most frequently used medicines in the treatment of esophageal malignancies (Figure 3).

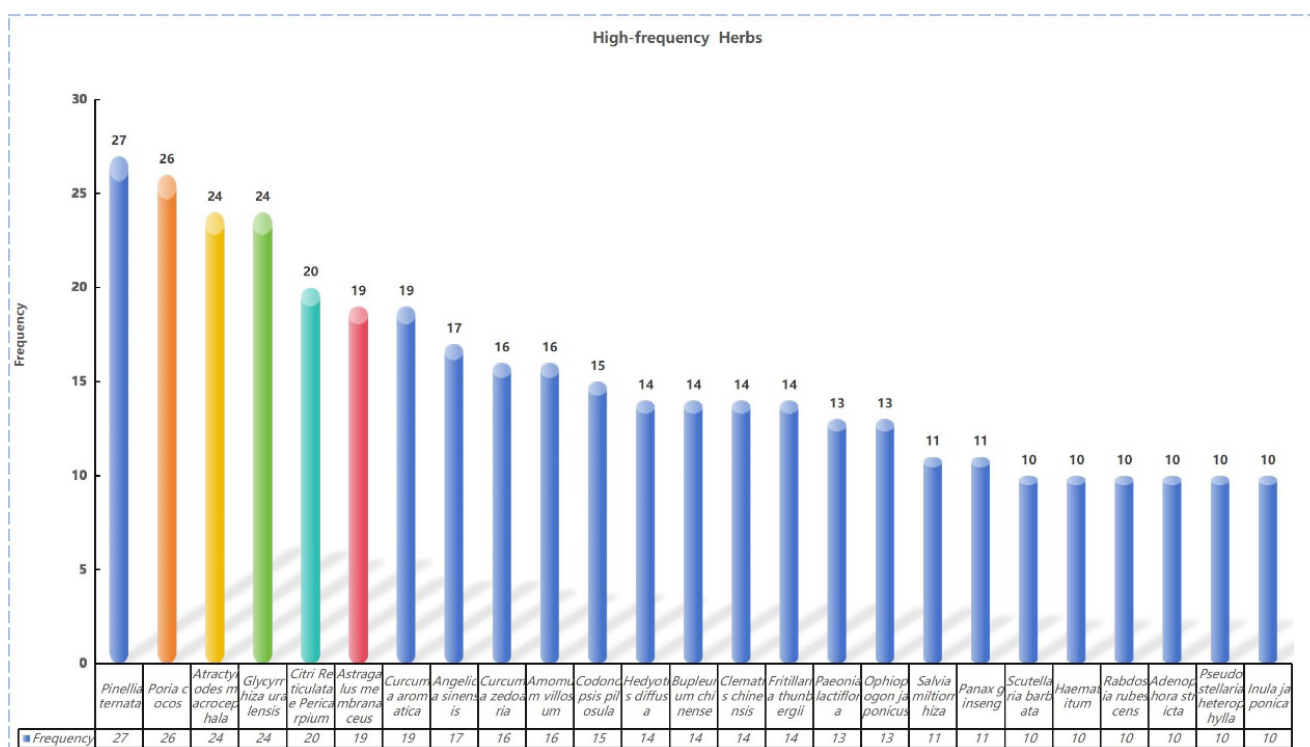


Figure 3. Frequency bar chart of commonly used Chinese herbal medicines in clinical practice (defined as commonly used Chinese herbal medicines with an application frequency of ≥ 10 times).

The above 187 Chinese medicines were standardized, and 18 were excluded, resulting in the final inclusion of 169 medicines. The analysis of 169 flavors of traditional Chinese medicine revealed that the primary efficacies of Chinese medicines used clinically to treat esophageal cancer are Blood-Activating and Stasis-Resolving medicines and Qi-Regulating medicines. The majority are bitter in taste, predominantly cold in property, and enter the Liver Meridian (Figure 4).

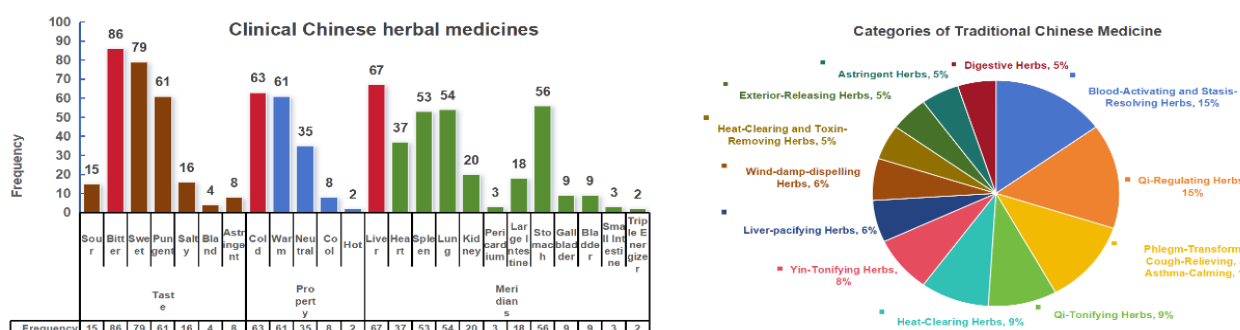


Figure 4. Literature search for the distribution frequency chart of traditional Chinese medicine in clinical use of esophageal cancer.

3.3. Chinese medicines inhibiting esophageal cancer vasculogenic mimicry are primarily blood-activating and stasis-resolving medicines

The study first intersected the Chinese medicines for esophageal cancer from two different sources—the TCMSP database and clinical data—ultimately obtaining 95 overlapping medicines, among which Blood-Activating and Stasis-Resolving medicines accounted for the highest proportion (Figure 5).



Figure 5. Efficacy of esophageal cancer-TCMSP and clinical TCM concentrated drugs.

In order to more accurately screen for Chinese medicines related to vasculogenic mimicry of esophageal cancer, the VM-related medicines were overlapped with the core medicines for esophageal cancer, resulting in an intersection of 22 medicines (Table 1). Statistical results revealed that among these medicines, 11 have the pattern element of blood stasis, accounting for 50% of this subset. The results showed that the corresponding effects of traditional Chinese medicine for esophageal cancer VM were mainly to promote blood circulation and reduce stasis, and the related TCM syndromes were mainly “blood stasis, Qi deficiency, and Qi stagnation”.

Table 1. 22 flavors of Chinese medicine properties, taste, return to meridians, efficacy, and TCM syndrome table

No.	Chinese Medicine	Taste	Propert	Meridians	Efficacy	TCM Pattern Elements
1	<i>Sophora flavescens</i>	Bitter	Cold	Heart, liver , Stomach, Large Intestine , Bladder Meridians	Heat-Clearing and Dampness-Expelling Herbs	Heat, Toxicity, Dampness
2	<i>Scleromitrium diffusum</i>	Bitter,Sweet	Cold	Stomach, Large Intestine, Small Intestine Meridians	Heat-Clearing and Toxin- Removing Herbs	Toxicity, Dampness, Blood stasis
3	<i>Polygonum cuspidatum</i>	Bitter	Cold	Liver, Gallbladder, Lung meridians	Dampness-Percolating and Diuresis-Promoting Herbs	Dampness, Phlegm, Blood stasis
4	<i>Coicis semen</i>	Sweet,bland	Cool	Spleen, Stomach, lung meridians	Dampness-Percolating and Diuresis-Promoting Herbs	Heat, Toxicity, Dampness
5	<i>Bupleurum chinense</i>	Bitter,Pungent	Cold	Liver and Gallbladder meridians	Exterior-Releasing Herbs	Qi stagnation, Qi deficiency
6	<i>Salvia miltiorrhiza</i>	Bitter	Cool	Heart, pericardium, liver meridian	Blood-Activating and Stasis- Resolving Herbs	Blood stasis, Heat
7	<i>Panax notoginseng</i>	Sweet,Bitter	Warm	Liver, Stomach Meridians	Blood-Activating and Stasis- Resolving Herbs	Blood stasis, Qi stagnation
8	<i>Curcuma aromatica</i>	Pungent,Bitter	Cold	Liver, Gallbladder, Heart meridians	Blood-Activating and Stasis- Resolving Herbs	Blood stasis, Dampness, Heat
9	<i>Sparganium stoloniferum</i>	Pungent,Bitter	Neutral	Liver and Spleen meridians	Blood-Activating and Stasis- Resolving Herbs	Blood stasis, Qi stagnation, Food accumulation
10	<i>Carthamus tinctorius</i>	Pungent	Warm	Heart, liver meridians	Blood-Activating and Stasis- Resolving Herbs	Blood stasis
11	<i>Ligusticum chuanxiong</i>	Pungent	Warm	Liver, Gallbladder, Pericardium Meridians	Blood-Activating and Stasis- Resolving Herbs	Blood stasis, Qi stagnation,Wind- Dampness
12	<i>Curcuma phaeocaulis</i>	Pungent,Bitter	Warm	Liver and Spleen meridians	Blood-Activating and Stasis- Resolving Herbs	Blood stasis, Qi stagnation, Food accumulation
13	<i>Commiphora molmo</i>	Pungent,Bitter	Neutral	Heart, Liver, Spleen meridians	Blood-Activating and Stasis- Resolving Herbs	Blood stasis
14	<i>Trichosanthes fructus</i>	Sweet,Bitter	Cold	Lung, Stomach, Large Intestine meridians	Phlegm-Transforming, Cough-Relieving, and Asthma-Calming Herbs	Phlegm, Heat
15	<i>Magnolia officinalis</i>	Bitter,Pungent	Warm	Spleen, Stomach, Lung, Large Intestine Meridians	Dampness-resolving Herbs	Phlegm, Dampness, Qi Stagnation, Food accumulation
16	<i>Rheum palmatum</i>	Bitter	Cold	Spleen, Stomach, Large Intestine, Liver, Pericardium meridians	Purgative Herbs	Heat, Toxicity, Blood stasis
17	<i>Paeonia lactiflora</i>	Bitter,sour	Cold	Liver and Spleen meridians	Blood-Enriching Herbs	Blood deficiency, Yin deficiency, Qi deficiency
18	<i>Atractylodes macrocephala</i>	Sweet,Bitter	Warm	Spleen, Stomach meridians	Qi-tonifying herbs	Qi deficiency, Phlegm, Dampness
19	<i>Panax quinquefolius</i>	Sweet,Bitter	Cool	Heart, lung, kidney meridians	Qi-tonifying herbs	Qi deficiency, Yin deficiency, Heat
20	<i>Astragalus membranaceus</i>	Sweet	Warm	Spleen, Lung meridians	Qi-tonifying herbs	Qi deficiency, Toxicity
21	<i>Panax ginseng</i>	Sweet,Bitter	Neutral	Lung, Spleen, Heart meridians	Qi-tonifying herbs	Qi deficiency
22	<i>Pseudostellaria heterophylla</i>	Sweet,Bitter	Neutral	Spleen, Lung meridians	Qi-tonifying herbs	Qi deficiency, Yin deficiency

4. Discussion

Through data mining, this study found that the proportion of traditional Chinese medicines for the treatment of esophageal cancer—whether from public databases or clinical experience—Blood-Activating and Stasis-Resolving medicines accounted for a higher proportion than other categories, involving the three pattern elements of “blood stasis, Qi deficiency, and Qi stagnation,” which is consistent with the core pathogenesis of esophageal cancer. Esophageal cancer belongs to the category of “dysphagia-occlusion syndrome” in traditional Chinese medicine, and the core pathogenesis is Qi stagnation, blood stasis, and phlegm coagulation intertwined in the esophagus, of which blood stasis runs through the disease, particularly in the advanced and late stages. Emotional disturbances and dietary irregularities can lead to Qi stagnation transforming into fire, which scorches fluids to form phlegm, phlegm and stasis, then bind together to form lumps^[3]. Blood stasis is not only a pathological product, but also hinders the flow of Qi and blood, leading to a deficiency of both Qi and blood and exacerbating stasis, thus forming a vicious cycle. The “Theory of the Origins of Diseases” also emphasizes the core role of Qi stagnation and blood stasis. Modern research has confirmed that patients with esophageal cancer often exhibit a hypercoagulable state and microcirculatory disorders. Blood-activating and Stasis-resolving Chinese medicines (e.g., *Pruni semen* (Taoren), *Carthamus tinctorius* (Honghua), *Radix paeoniae rubra* (Chishao), *Curcuma rhizoma* (Ezhu), etc.) can improve microcirculation, reduce blood viscosity, inhibit tumor proliferation, alleviate the toxic side effects of radiotherapy and chemotherapy, promote drug penetration, and enhance the sensitivity of radiotherapy and chemotherapy^[4–9]. Their combined use can significantly reduce tumor size and relieve obstruction^[10]. For esophageal cancer with the blood stasis pattern, Xuefu Zhuyu Decoction is often used as the basis, like *Semen impatientis* (Jixingzi) and *Herba artemisiae anomalae* (Liu Jinu), and other blood-breaking and stasis-removing drugs are used to relieve menstruation and pain^[11]. The combination of spleen-fortifying and stasis-dispelling Chinese medicines with concurrent radiotherapy and chemotherapy can reduce the incidence of radiation esophagitis and myelosuppression and improve the quality of life, and the mechanism may be related to the regulation of the immune microenvironment and the inhibition of inflammation^[12].

Radix notoginseng powder (San Qi Fen) combined with *Bletilla striata* powder (Baiji Fen) can control ulcerative bleeding and pain^[13]. Pharmacological studies have shown that the active ingredients of traditional Chinese medicine (such as tanshinone and curcumin) can induce apoptosis, inhibit proliferation, and angiogenesis by regulating signaling pathways such as PI3K/AKT and NF- κ B^[14,15]; Cantharidin exhibits significant toxicity to esophageal cancer cells^[16]; and *Spatholobi Caulis* (Jixueteng) can increase the CD4+/CD8+ ratio and enhance immunity^[17]. The treatment of blood circulation and blood stasis reduction embodies the idea of “tonifying by unblocking,” and the application requires treatment based on pattern differentiation, avoiding excessive use of stasis-breaking medicines that may consume qi, especially for those who are deficient in righteous Qi after surgery. It is appropriate to match qi-tonifying medicines to “remove stasis without harming righteousness.” Western medicine believes that VM is one of the culprits of its progression, and the effect of conventional postoperative adjuvant therapy is limited. Traditional Chinese medicine believes that the post-operative state is primarily a deficiency of both Qi and blood combined with residual static blood and the generation of phlegm-dampness, with “stasis, phlegm, and deficiency” running through the whole process^[18].

In previous studies, it was found that VM-positive patients have a higher likelihood of recurrence and metastasis than VM-negative patients, and stage II-III ESCC VM-positive patients derived minimal clinical benefit from postoperative adjuvant therapy. There was also no significant difference in efficacy between the three adjuvant treatment modalities. This may be related to the complex formation mechanism of VM; hypoxia

is a perfect inducer of VM formation, and tumor hypoxia activates HIF-1 α , upregulates the expression of genes such as VEGF and MMP-9, and promotes extracellular matrix (ECM) degradation and lumen formation^[19]. In addition to the activation of HIF-1 α promoting the formation of vascular-like structures in tumor cells, the plasticity of tumor cells themselves is enhanced under hypoxic conditions, which also endows tumor cells with endothelial cell-like characteristics^[20]. Changes in cellular properties make intercellular connections loose, and new connections between variant tumor cells and other tumor cells are required to form vascular-like channels composed of vascular endothelial cells to support tumor growth and metastasis^[21]. The hypoxic microenvironment promotes tumor cell metabolic reprogramming. Mitochondria are key sites of cellular metabolism. After the aerobic metabolic pathway is inhibited, it cannot meet the normal growth and reproduction of tumor cells, which will induce the Warburg effect, resulting in an increase in anaerobic glycolytic capacity and lactate accumulation in tumor cells^[22,23]. The above process is merely one part of the complex mechanism involved in the formation of VM, so studying drugs and related strategies to inhibit esophageal cancer VM from a modern medical perspective is challenging.

VM is a pathological phenomenon of highly aggressive tumors, and although there is no direct correspondence theory in traditional Chinese medicine, studies suggest that it is related to the concept of “diseased collaterals”^[24]. However, the author believes that vasculogenic mimicry is related to the diseased collaterals, but the concept of vascular mimicry cannot be simplistically equated with the disease network in general; rather, it should belong to a refined type of diseased collateral, namely, “toxic collaterals.” Toxic collaterals are a specific type of diseased collateral proposed based on the theory of diseased collaterals and the theory of “cancer toxin.” They refer to the pathological collaterals generated by cancer toxin, serving to extract essence and nutrients for the tumor and facilitate its metastasis and spread. Pathogenic collaterals are the product of pathological changes in the collaterals and are the basic pathogenesis of diseases^[25]. Toxic collaterals belong to the category of diseased collaterals, but they specifically refer to the hyperactive form created by the action of cancer toxin on the local collateral system. The formation of VM is thought to be the result of the accumulation of cancer toxin, which manifests as abnormal hyperactivity of the collateral pathways, accelerating tumor spread and nutrient supply. Therefore, VM can be regarded as a toxic collateral formed by cancer toxin acting on the collaterals, which is a specific manifestation of the diseased network in the tumor.

At present, cancer treatment has entered an era of multidisciplinary collaboration, and the combination of traditional Chinese and Western medicine forms a synergistic effect through complementary mechanisms. This integration is reflected not only at the technical level, but also in the innovation of treatment concepts - from allopathic therapy to homeostasis reconstruction. Academician Tong Xiaolin innovatively proposed the theory of “state-target syndrome differentiation”, which translates macroscopic theories into microscopic applications. This approach takes the disease as the reference, the state as the basis, and symptoms as targets, proposing specific disease target prescriptions/target drugs^[26]. However, due to the lack of research on VM in esophageal cancer and the corresponding symptoms and indicators have not been clearly reported. Therefore, we attempted to use data mining to identify traditional Chinese medicines targeting VM in esophageal cancer, reverse infer the symptoms/indicators corresponding to the disease, and then deduce the symptoms from the target medicines, and ultimately summarize the possible syndrome patterns corresponding to VM in esophageal cancer. This aims to maximize the potential and advantages of traditional Chinese medicine in the treatment of VM in esophageal cancer. However, this study still has certain limitations; the above research results have not been further experimentally and clinically verified. In the future, it will screen relevant genes and targeted drugs for in-depth research, effectively

transform the research results, and better serve clinical practice.

5. Conclusion

The corresponding traditional Chinese medicine syndrome pattern of vascular mimicry in esophageal cancer may be blood stasis and Qi deficiency, and blood-activating and stasis-reducing drugs are expected to improve the prognosis of esophageal cancer patients with VM-positive.

Funding

National Natural Science Foundation of China (Project No.: 82474597); Key Project of Jiangsu Traditional Chinese Medicine Science and Technology Development (Project No.: ZD202330); Major Project of Natural Science Research in Jiangsu Universities (Project No.: 22KJA360009); Graduate Innovation Project of Jiangsu Province (Project No.: KYCX25-4103)

Disclosure statement

The authors declare no conflict of interest.

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