MEDS Chinese Medicine (2024)
Clausius Scientific Press, Canada

DOI: 10.23977/medcm.2024.060414
ISSN 2616-1753 Vol. 6 Num. 4

# *Research Progress on Traditional Chinese Medicine in the Treatment of Cancer-Related Fever*

**Juan Huang[1,a], Chenguang Yang[2,b,*]**

*[1]Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China*
*[2]Shaanxi Provincial Hospital of Traditional Chinese Medicine, Xi'an, Shaanxi, 710068, China*
*[a]1835355710@qq.com, [b]18383808618@163.com*
*[*]Corresponding author*

***Keywords:*** Cancer-Related Fever, Traditional Chinese Medicine, Syndromes

***Abstract:*** With the development of economy, the change of modern people's life style, the increase of social pressure and the long-term effect of unhealthy behavior habits, the incidence of tumor is increasing year by year. According to statistics, about 2 / 3 of cancer patients have fever during the course of the disease, of which about 40 % are cancerous fever. Western medicine treatment is mostly symptomatic treatment with non-steroidal drugs, which can quickly reduce fever, but it is easy to repeat, and long-term use leads to gastrointestinal damage, skin reaction, liver and kidney function damage, etc. Traditional Chinese medicine has a unique advantage in the treatment of cancerous fever. Through the observation, auscultation and palpation, individualized Chinese medicine decoction treatment is given on the basis of dialectics, combined with acupuncture, acupoint application, cupping and other comprehensive treatment, which can achieve good antipyretic effect, improve symptoms and low incidence of adverse reactions. The purpose of this paper is to summarize the latest progress of traditional Chinese medicine in the treatment of cancerous fever, in order to provide some reference for practical medication.

## 1. Overview

Cancer-related fever is a non-infectious fever that occurs in patients with malignant tumors, either directly related to the tumor or caused by tumor treatment. Cancer-related fever often manifests as recurrent fever in the afternoon and at night, with body temperature mostly below 38.5 ℃, although some patients may experience high fever. It is a paraneoplastic syndrome characterized by fever that persists despite the exclusion of infection and ineffectiveness of antibiotic treatment. About 70% of cancer patients experience fever, with causes including infectious, tumor-related, postoperative, drug-induced, and others, as detailed in figure 1. Statistics from 2013 to 2022 indicate that the main causes of fever of unknown origin include infectious, autoimmune, and tumor-related diseases. Among these, tumor-related fever accounts for 7.9% of fevers of unknown origin [1]. Common tumors associated with cancer-related fever include Hodgkin lymphoma, non-Hodgkin lymphoma, soft tissue sarcoma, acute or chronic leukemia, and renal cell carcinoma [2]. Western medical treatments for cancer-related fever often have limitations, as patients may experience side effects such as nausea, vomiting, and liver or kidney toxicity during

treatment, with a short duration of efficacy. Traditional Chinese medicine (TCM) treatment can avoid the drawbacks of using non-steroidal anti-inflammatory drugs, such as excessive sweating damaging yin, low rate of temperature rebound after stopping medication, and lower incidence of adverse reactions. By summarizing and analyzing relevant literature from both domestic and international sources, this article aims to outline the latest advancements in TCM treatment for cancer-related fever, with the hope of providing insights for clinical management of this condition.

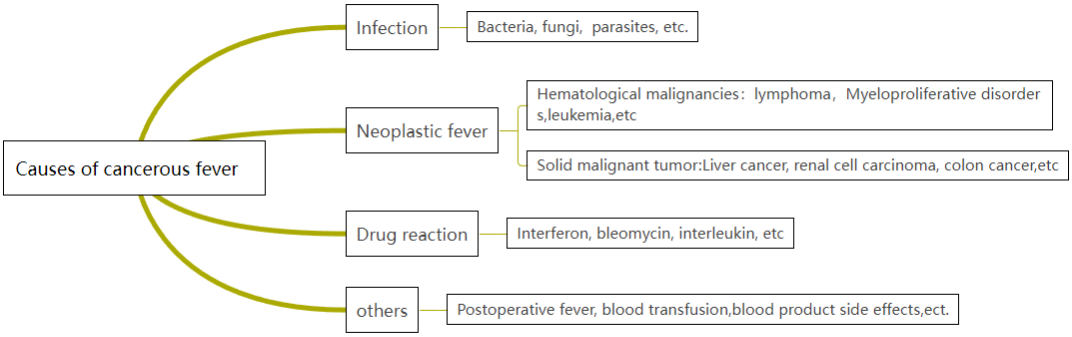


Figure 1: Causes of cancerous fever

## 2. Modern Medical Research on Cancer-Related Fever

The pathological mechanism of tumor-related fever is currently unclear, but it is thought to be related to tumor necrosis, factor release, and neurogenic mechanisms. Products released by tumor cells can activate certain inflammatory cells to produce pyrogens, which act on the hypothalamic temperature regulation center, leading to an elevated set point for body temperature and resulting in fever. These pyrogens include tumor necrosis factor-alpha, interleukin-1, interleukin-6, and interferon, among others [3]. In patients with brain metastases, tumor-related fever is neurogenic, and its mechanism may involve brain tissue damage and the activation of phospholipase A2, which acts on the hypothalamic temperature regulation center through the cyclooxygenase pathway [4]. The incidence of cancer-related fever is higher in patients with liver metastases, possibly related to metabolic changes that produce high levels of pyrogenic bile salts [5].

Diagnosis:

Body temperature exceeds 37.8 ℃ at least once daily;

Fever persists for more than 2 weeks;

Physical examination, laboratory tests, and imaging studies lack evidence of infection;

Empirical antibiotic treatment for at least 7 days still results in fever;

Normal body temperature is maintained during treatment with naproxen, and fever is promptly and completely resolved with the naproxen test, while excluding infectious fever, drug-induced fever, allergic reactions, transfusion reactions, etc [6].

## 3. Research on Cancer-Related Fever in Traditional Chinese Medicine (TCM)

Cancer-related fever falls under the TCM category of "internal injury fever." There is currently no unified understanding in academia regarding the etiology and pathogenesis of cancer-related fever. Professor Wang Xixing [7], based on the theory of Yin fire, believes that it is caused by spleen and stomach qi deficiency, dysfunction of the ascending and descending mechanisms of the middle jiao, and liver dysfunction leading to excessive movement of fire, resulting in cancer-related fever.Xu Bowen and others [8] believe that the tumor obstructs the flow of qi, causing stagnation

and closure of yang qi, which leads to the generation of pathogenic heat and results in fever. Professor Jia Yingjie [9] identifies the pathogenesis as deep-seated toxicity, excessive pathogenic factors harming yin, and deficiency fire rising, thus the method of supporting the righteous and detoxifying should be consistently applied. The author believes that due to various factors such as emotion, diet, daily life, external evil, congenital endowment and anti-tumor treatment, carcinogenic fever is mostly caused by deficiency in origin and excess in superficiality. The specific syndromes are shown in figure 2. The pathogenesis is basically deficiency of healthy qi and excessive toxicity, so the method of strengthening healthy qi and detoxification should run through.

## 4. Treatment

### 4.1. Traditional Chinese Medicine Decoction Treatment

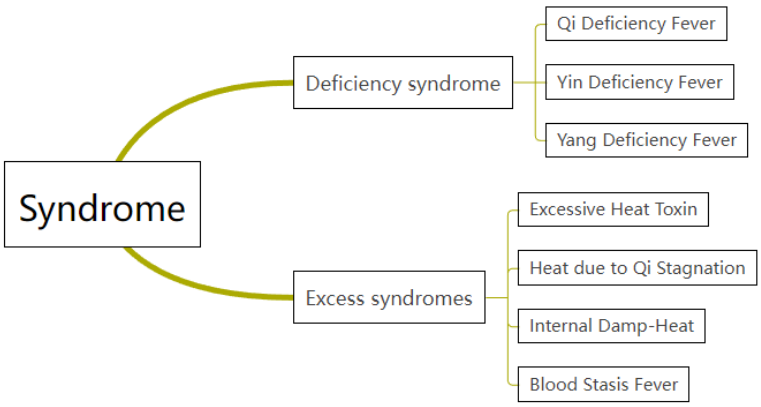


Figure 2: Syndrome

#### 4.1.1. Deficiency Syndrome

Qi Deficiency Fever: The "Treatise on the Origins and Symptoms of Various Diseases" states: "Fever due to deficiency is caused by insufficient yin qi and excess yang qi, leading to internal and external heat, not due to external pathogenic factors." The spleen and stomach are the source of qi and blood production and are responsible for transportation and transformation. When qi is deficient, the essence cannot be generated and cannot nourish the whole body. Li Dongyuan proposed in "On the Spleen and Stomach" that "fire cannot coexist with original qi; one prevails while the other is diminished." When original qi is insufficient, yin fire becomes excessive, and deficiency yang rises, causing fever. The treatment should focus on tonifying the middle and benefiting qi, and gently eliminating heat. Wang Cui and Ma Yan's [10]experiments found that the effective rate of treating cancer-related fever with the "Buzhong Yiqi Decoction" was higher than that of indomethacin (90% compared to 67.5%, $P<0.05$), and the patients' symptoms improved significantly. Liu Jinna's [11] network pharmacology analysis found that the "Buzhong Yiqi Decoction" can prevent and treat qi deficiency fever through multiple core targets such as TNF, AKT1, IL-6, and various pathways including the TNF signaling pathway, Toll-like receptor signaling pathway, NOD-like receptor signaling pathway, and HIF-1 signaling pathway.

Yin Deficiency Fever: Yin deficiency fever develops from qi deficiency fever, where prolonged illness causes an imbalance of qi, blood, yin, and yang in the body. Additionally, treatments such as chemotherapy, targeted therapy, and immunotherapy further deplete the body's fluids. The treatment principle is to nourish yin and clear heat. Zhao Bo's [12]experiment found that the

efficacy of Qinghao Bieqia Decoction in treating cancer-related fever was higher than that of ibuprofen sustained-release capsules (90.59% compared to 77.65%, P<0.05), and it could reduce white blood cell levels and improve patients' quality of life. Tan Qin and others[13], through network pharmacology analysis, found that Qinghao Bieqia Decoction may exert its therapeutic effects on cancer-related fever by acting on targets such as VEGFA, CASP3, AKT1, MMP9, TNF, HIF1A, EGF, TP53, PTGS2, IL6, thereby regulating pathways like TNF, IL-17, and PI3K-Akt.

Yang Deficiency Fever: Qi deficiency further develops into yang deficiency, leading to fever due to floating and deficient yang. The treatment principle is often "to assist yang and benefit qi." Liu Ruichun[14] included 70 patients with yang deficiency type cancer-related fever; the treatment group received modified Zaizao Powder orally, while the control group received indomethacin suppositories. The results showed that the treatment group had better antipyretic effects and symptom improvement than the control group.

### 4.1.2. Excess syndromes

Excessive Heat Toxin: In cancer patients, the accumulation of cancer toxins over time obstructs the flow of qi, leading to damp-heat and stasis toxins accumulating in the body, which then transforms into heat. Additionally, treatments such as chemotherapy, targeted therapy, and immunotherapy can cause imbalances in qi, blood, yin, and yang, resulting in fever due to stagnation. The treatment principle is to clear heat and detoxify. Fan Rui[15] found that the total effective rate of the treatment group using a combination of modified Wumei Xiaodu Decoction and indomethacin suppositories for treating cancer-related fever was 96.7%, significantly higher than the control group's 60%, with a statistically significant difference (P<0.05). Shen Ling and others[16] discovered that the short-term and long-term effective rates of Qingre Jiedu Decoction for treating cancer-related fever were both higher than those of enteric-coated indomethacin tablets, and it could also improve immune system function.

Heat due to Qi Stagnation: Professor Liu Huaimin believes that the unfavorable opening and closing of the Shaoyang is the pathological basis for cancer-related fever[17]. The "Suwen: Theory of Yin and Yang Separation and Combination" states: "Therefore, the separation and combination of the three Yangs is such that Taiyang is for opening, Yangming is for closing, and Shaoyang is the pivot." Shaoyang plays a key role in promoting, unblocking, elevating, and communicating between the internal and external, which is crucial for the movement and transformation of Qi. Patients often experience significant psychological stress, with liver Qi stagnation, and the tumor mass obstructs the local and systemic Qi flow, leading to disordered Qi rising and falling, resulting in fever. Treatment focuses on harmonizing Shaoyang and regulating Qi. Clinical observations by Xiao Xin found that the effectiveness of Xiao Chai Hu Decoction in treating cancer-related fever was higher than that of conventional drug treatments (oral ibuprofen, intravenous lornoxicam, etc.) (92.5% compared to 70%, P<0.05), and it can improve patient symptoms and control inflammatory responses[18].

Internal Damp-Heat: Liu Wansu believes that damp-heat is closely related to tumor formation. Cancer toxins obstruct Qi flow and the transformation of water and fluids, leading to damp-heat, which further obstructs Qi flow, causing tumor fever and prolonged illness. Treatment focuses on clearing heat and transforming dampness. Zhang Lirong, through comparative clinical observations of Sanren Decoction, Sanren Decoction combined with diclofenac sodium rectal administration, and diclofenac sodium rectal administration for treating cancer-related fever, found effectiveness rates of 78.38%, 82.05%, and 54.76%, respectively, indicating the effectiveness of Sanren Decoction in treating cancer-related fever[19].

Blood Stasis Fever: Ye Tianshi believes that "long illness enters the collaterals," and "the meridians govern Qi, while the collaterals enter the blood." Cancer patients with prolonged illness

experience obstruction of the meridians, presenting symptoms such as fixed masses, stabbing pain, and a dark tongue. Treatment focuses on invigorating blood and resolving stasis.Zhang Jie and others[20] conducted a clinical observation comparing Xuefu Zhuyu Decoction with non-steroidal anti-inflammatory drugs for treating cancer-related fever, finding that the cooling effect and KPS scores of Xuefu Zhuyu Decoction were both higher than those of the control group.

## 4.2. Other Treatments

### 4.2.1. Traditional Chinese Medicine (TCM) Patent Medicine

Commonly used traditional Chinese medicines for treating cancer-related fever include Xinhuang tablets, Angong Niuhuang pills, Xihuang pills, and Xuebijing injection. Jiang Jin[21] included 40 patients with cancer-related fever, with the experimental group receiving Xinhuang tablets and the observation group receiving indomethacin suppositories for rectal administration. After treatment, the SAS and SDS scores in the experimental group were lower than those in the observation group and before treatment ($P<0.05$), while the levels of immunoglobulin and quality of life scores were higher than those in the observation group ($P<0.05$). The overall incidence of adverse reactions was lower in the experimental group than in the observation group ($P<0.05$). Zhang Xiaoqing and others[22] included 48 patients with cancer-related fever, finding that the experimental group (Angong Niuhuang pills) had better tolerance compared to the control group (indomethacin suppositories), with lower recurrence and adverse reaction rates ($P<0.05$). Yu Ting and others[23] included 80 patients with cancer-related fever, with the treatment group receiving Xihuang pills and the control group receiving sustained-release sodium ibuprofen. The total effective rate in the treatment group was higher than that in the control group, and both KPS and WHOQOL-BREF scores were higher in the treatment group than in the control group ($P<0.05$).Lin Hao and others[24] included 66 patients with cancer-related fever. The treatment group received Xuebijing injection combined with enteric-coated indomethacin tablets, while the control group received only enteric-coated indomethacin tablets. The total effective rates for the two groups were 84.8% and 63.6%, respectively. The treatment group significantly reduced the levels of TNF-α in the body and increased the levels of IL-10.

### 4.2.2. External Treatment Methods

External treatment methods for cancer-related fever are also widely used in traditional Chinese medicine (TCM) clinical practice, improving patient prognosis. Li Le and others[25] included 70 patients with fever due to leukemia. The control group used conventional cooling methods, while the observation group used oral traditional Chinese medicine combined with bloodletting and cupping at the Dazhui acupoint. The total effective rate in the observation group was 97.14%, higher than the control group (82.86%), with a statistically significant difference ($P<0.05$). Liu Yanying[26] included 60 patients with cancer-related fever, where the experimental group received a self-made cooling blood paste applied to acupoints, while the control group used conventional Western medicine. The results showed that the experimental group had a significantly greater decrease in body temperature and symptom scores compared to the control group, effectively alleviating fever and improving patients' quality of life ($P<0.05$). Zhang Ningjing[27] included 86 patients with cancer-related fever, finding that the total effective rates for the control group (acetaminophen tablets) and the experimental group (TCM syndrome differentiation acupuncture) were 90.70% and 69.77%, respectively, with the improvement rate in quality of life in the experimental group significantly higher than that in the control group ($P<0.05$). Chen Xiang and others [28] used acupuncture to treat cancer-related fever and found that selecting acupoints such as

Hegu, Siguang, Quchi, and Zusanli based on syndrome differentiation had good antipyretic effects.

## 5. Conclusions

In recent years, with the increase in the incidence and detection rates of cancer, the number of patients experiencing cancer-related fever has also risen. Although researchers and clinicians have further studied and explored this issue, the pathophysiological mechanisms remain unclear, and there are many difficulties in diagnosis. Western medicine primarily treats this condition with non-steroidal anti-inflammatory drugs, which carry risks of gastrointestinal reactions and liver and kidney damage with long-term use. Traditional Chinese Medicine (TCM) has unique advantages in treating cancer-related fever, employing individualized herbal treatments based on syndrome differentiation, along with comprehensive therapies such as acupoint application, acupuncture, and enemas. These methods have shown good results in terms of fever reduction, symptom improvement, and enhancing patients' quality of life. However, there is currently no clear classification of symptoms or standardized prescriptions, and various practitioners have diverse diagnostic approaches, lacking a certain level of standardization. Therefore, we should summarize the experiences and case studies of practitioners, compile treatment experiences, and conduct multi-faceted validation, ultimately transforming this into a set of standardized TCM protocols for treating cancer-related fever to guide clinical practice.

## References


*[1] Kang S, Zheng R. Distribution of the causes of fever of unknown origin in China, 2013-2022. J Transl Int Med. 2024, 12(3): 299-307. Published 2024 Jul 27. doi:10.2478/jtim-2024-0008*

*[2] Pasikhova Y, Ludlow S, Baluch A. Fever in Patients with Cancer. Cancer Control. 2017, 24(2): 193-197. doi:10.1177/107327481702400212*

*[3] Deng P B, Jiang J, Hu C P, et al. Tumor-related cytokine release syndrome in a treatment-naïve patient with lung adenocarcinoma: A case report[J]. World J Clin Cases, 2022, 10(5): 1580-1585.*

*[4] Shi N, Xing C, Chang X, et al. Pancreatic carcinoma masked as fever of unknown origin: A case report and comprehensive review of literature[J]. Medicine, 2016, 95(35): e4643.*

*[5] Johnson M. Neoplastic fever[J]. Palliat Med. 1996, 10(3): 217-224. doi:10.1177/026921639601000306*

*[6] Wang Lyuyu, Peng Ling. The pathogenesis, diagnosis and treatment of tumor fever [J]. Tumor prevention and treatment, 2024, 37 (08): 705-712.*

*[7] Shi Zhiyao, Fang Zhiyong, Guo Yuxi, et al. Experience of TCM master Wang Xixing in treating cancerous fever based on yin fire theory [J].Journal of Guangzhou University of Traditional Chinese Medicine, 2024,41(08): 2169-2174. DOI: 10.13359 / j.cnki.gzxbtcm.2024.08.033.*

*[8] Xu Bowen, Zhao Weizhe, Li Jie, et al. Based on the theory of ' Fuyang ', there must be Fuyang ', the method of ascending yang and dispersing fire is used to treat cancerous fever [J]. Global Chinese Medicine, 2021, 14 (01): 132-134.*

*[9] Zhang Chang, Mou Ruiyu, Li Xiaojiang. Professor Jia Yingjie's clinical experience in the treatment of lung cancer fever [J]. Tianjin Traditional Chinese Medicine, 2022, 39 (05): 566-569.*

*[10] Wang Cui, Ma Yan. Observation on the curative effect of Buzhong Yiqi Decoction in the treatment of cancerous fever [J]. Electronic Journal of Clinical Medical Literature, 2019, 6 (05): 155. DOI: 10.16281 / j.cnki.jocml. 2019. 05. 137.*

*[11] Liu Jinna. To explore the mechanism of Buzhong Yiqi Decoction in the treatment of qi deficiency fever syndrome based on network pharmacology [J]. Hebei Medicine, 2022, 44 (23): 3564-3568.*

*[12] Zhao Bo. Observation on the clinical effect of Qinghao Biejia Decoction in the treatment of cancerous fever [J]. Journal of Clinical Rational Drug Use, 2019, 12 (07): 7-8 + 10. DOI : 10.15887 / j.cnki.13-1389 / r.2019.07.004.*

*[13] Tan Qin, Huang Liming, Xiao Xue, et al. Analysis of the mechanism of action of Qinghao Biejia Decoction in the treatment of cancerous fever based on network pharmacology [J].Clinical rational drug use, 2024, 17 (11) : 6-10 + 181.DOI : 10.15887 / j.cnki.13-1389 / r.2024.11.002.*

*[14] Liu Ruichun. Clinical observation of Modified Zaizao Powder in the treatment of cancerous fever (Yang deficiency fever syndrome) [D]. Changchun University of Traditional Chinese Medicine, 2019. DOI: 10.26980 / d.cnki.gcczc. 2019. 000157.*

*[15] Fan Rui. Clinical study on Jiawei Wuwei Xiaodu Decoction in the treatment of cancerous fever of lung cancer with blood stasis and toxin syndrome [D]. Yunnan University of Traditional Chinese Medicine, 2018.*
*[16] Shen Ling, Han Guangcheng. Study on the efficacy of Qingre Jiedu Decoction in the treatment of cancerous fever in elderly patients with lung cancer [J].Chinese prescription drugs, 2021, 19 (06): 129-130.*
*[17] Jie Ruizheng, Liu Huaimin. Analysis of the treatment of cancerous fever based on the theory of ' Shaoyang as the pivot ' [J].Traditional Chinese medicine research, 2022, 35 (09): 5-7.*
*[18] Xiao Xin. The clinical effect of Xiaochaihu Decoction in the treatment of cancerous fever [J].Journal of Clinical Rational Drug Use, 2022, 15 (14): 44-47. DOI: 10.15887 / j.cnki.13-1389 / r.2022.14.013.*
*[19] Zhang Lirong. Clinical study of Sanren Decoction in the treatment of damp-heat cancer fever [D].Fujian University of Traditional Chinese Medicine, 2021.DOI : 10.27021*
*[20] Zhang Jie, Li Jianbo, Zhang Li. Clinical observation of Xuefu Zhuyu Decoction in the treatment of cancerous fever [J].Chinese Pharmacists, 2018, 21 (01): 112-114.*
*[21] Jiang Jin. Efficacy analysis of Xinhuang Tablets in the treatment of cancerous fever of malignant tumor [J].Northern Pharmacy, 2021, 18 (11): 132-134.*
*[22] Zhang Xiaoqing, Dai Xingbin, Yue Yinzi. Observation on the efficacy and safety of Angong Niuhuang Pill in the treatment of cancerous fever [J].Hunan Journal of Traditional Chinese Medicine, 2013, 29 (09) : 69-70.DOI : 10.16808 / j.cnki.issn1003-7705.2013.09.033.*
*[23] Yu Ting, Su Yongfeng, Wang Yaqi, et al. Clinical Efficacy of Xihuang Pills on Cancer Fever in Patients with Advanced Malignant Tumors [J].Chinese Contemporary Medicine, 2023,30 (32) : 77-80.*
*[24] Lin Hao, Wu Danhong, Yang Ailian, et al. Application and efficacy of Xuebijing injection in cancerous fever [J]. Strait Pharmacy, 2021, 33 (07): 170-171.*
*[25] Li Le, Wang Xue, Zhao Xinru. Application effect of oral administration of traditional Chinese medicine combined with Dazhui acupoint bloodletting and cupping nursing in cancer fever of leukemia patients [J].Chinese contemporary medicine, 2022,29 (12) : 186-188.*
*[26] Liu Yanying.Clinical study on acupoint application of self-made Liangxiao ointment to inhibit cancerous fever [J].World 's latest medical information abstract, 2017,17 (33) : 109-110.*
*[27] Zhang Yujing.Effectiveness of acupuncture in the treatment of advanced cancer-related fever [J]. Shenzhen Journal of Integrated Traditional Chinese and Western Medicine, 2021, 31 (01): 47-49. DOI: 10.16458 / j.cnki.1007-0893.2021.01.01.021*
*[28] Chen Xiang, Wu Hao, Meng Shan, et al. TCM syndrome differentiation and progress of acupuncture in the treatment of cancerous fever [J]. The world's latest medical information digest, 2018, 18 (65): 145. DOI : 10.19613 / j.cnki.1671-3141.2018.65.110*