REAL WORLD RESEARCH

Analysis on Clinical Characteristics and Combination Medications of Elemene Injection in the Treatment of Esophageal Cancer in Real World Research

SHI Pu-wen (史卜文)[1], ZHAO Xiao-xiao (赵晓晓)[1], XIE Yan-ming (谢雁鸣)[1], YU Xiao-kang (余小康)[2]

1. Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing 100700, China
2. School of Statistics, Renmin University of China, Beijing 100872, China
Correspondence to: XIE Yan-ming, E-mail: ktzu2018@163.com
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ABSTRACT **Objective:** To explore the clinical characteristics of Elemene Injection in the treatment of patients with esophageal cancer. **Methods:** A total of 310 patients diagnosed with esophageal cancer from the Hoptital Information System (HIS) of 21 hospitals across the country were selected in the study, and these patients all had been treated with Elemene Injection. In this study, the clinical general medication record information, diagnosis scheme information, general treatment information and combined medications information were analyzed by frequency statistics and association rules. **Results:** Elemene Injection was used most in patients aged 46-65 (177 cases, 57.10%); male patients were more than female. Among the main diagnoses of the most seasons and solar terms in hospitalization, the top three diagnoses were esophageal malignant tumor, malignant tumor, and hypertension. In terms of combination medication, the combination of western medicine blood substitutes and perfusion fluids, general nutritional drugs, vitamins, antibacterial drugs, and immune-promoting drugs were the main ones; the combination of traditional Chinese medicine was mainly anti-tumor drugs (48.71%). In addition, among the combination medications, the highest frequency of Elemene Injection combined with western medicine and traditional Chinese medicine were Xiaoaiping Injection (消癌平注射液) and ascorbic acid. **Conclusion:** The main susceptible people of esophageal cancer was middle-aged around 46-65, and there were more male patients than female; through the first diagnosis of western medicine, it can be found that in addition to patients suffering from esophageal cancer or other cancers, patients with high blood pressure, heart disease, and diabetes could use Elemene Injection. Therefore, when receiving such patients, attention should be paid to checking whether the patient had such diseases. At the same time, when using Elemene Injection, it's necessary to pay attention to certain combined medications to avoid adverse reactions.

KEYWORDS Real world research; Combination medications; Elemene Injeciton; Esophageal cancer patients; Clinical characteristics

Esophageal cancer is a malignant tumor that occurs in the epithelial tissue of the esophagus,[1] accounting for 2% of all malignant tumors. Esophageal cancer is classified into early, middle, and advanced stages; the usual treatment methods include surgery, chemotherapy, and drug therapy. The diet of esophageal cancer is mainly is nutritious and easy-to-digest foods. The etiology is related to chronic nitrosamine stimulation, inflammation and trauma, genetic factors and the content of trace elements in drinking water, food and vegetables. The occurrence of esophageal cancer is related to long-term smoking and drinking liquor, long-term eating hot food, hard food and poor chewing.[2] The incidence of esophageal cancer has obvious family clustering phenomenon, which is related to the

susceptibility of the population and environmental. In high-incidence areas of esophageal cancer, it is common for families with esophageal cancer patients to appear for 3 or more consecutive generations.[3]

Elemene emulsion is extracted from *Cur cuma wenyujin*, a ginger plant. It can reduce the mitosis of tumor cells, induce cell apoptosis, and inhibit the growth of tumor cells. According to pharmacological experiments, intraperitoneal injection of elemene emulsion significantly inhibited the synthesis of DNA, RNA and protein in tumor cells. The drug can also directly act on the cell membrane to rupture tumor cells, change and enhance the immunogenicity of tumor cells, and induce and promote the immune response of the body to tumor cells. Clinically, it is mainly used for adjuvant treatment of gastric cancer, bowel cancer, lung cancer and other tumors, and it also has a certain effect on some advanced tumors patients with pleural and ascites.

MATERIALS AND METHODS

Data Source

Based on the large-scale database constructed by the Institute of Clinical Basic Research of China Academy of Chinese Medical Sciences, the research data comes from the Hospital Information System (HIS) database and Laboratory Information Management System (LIS) inpatient information of 21 hospitals across the country, with a total of 310 patients. The data analysis of this study mainly revolves around diagnostic information, medication information, medical advice information and laboratory examination information, etc.[4]

Data Standardization and Normalization

As different clinical hospitals have different data rules, classification standards and management methods recorded in the study, the data is standardized for easy analysis. For the standardization of western medicine diagnosis, according to the international classification of diseases (ICD-10) coding, and the standardization of Traditional Chinese Medicine (TCM) syndromes according to the national standard *Classification and Codes of TCM Diseases and Syndromes*,[5] the mixed, missing and irrelevant information has been removed before analysis.[6]

Data Inclusion and Exclusion Criteria

Inclusion criteria: for patients diagnosed with "esophageal cancer" and "esophageal tumor" in the HIS system, Elemene Injection was used in the patient's medical order. Exclusion criteria: exclude items with combined medications as solvents, including 5% glucose injection, sodium chloride injection, and glucose and sodium chloride injection. The items where the combined medications are potassium chloride and vitamins are eliminated.

Data Statistical Analysis Method

Use SAS(9.2) statistical software to carry out descriptive analysis based on frequency and rate of patient's general information, diagnosis information, and medication information, and use Excel 2016 to assist mapping. At the same time, use SPSS, based on Apriori algorithm to carry out association analysis on the characteristics of combined medications in medical orders.[7]

RESULTS

General Characteristics of the Patients

Sex and age

Among the 310 cases who used Elemene Injection, 262 were male patients, accounting for 84.52%, and 48 were female patients, accounting for 15.48%. There were more males patients than females. The oldest patient was 85 years old and the patients were with an average age of 62.552 years; according to age breakdown statistics, 46-65 years old was the most, 177 cases, accounting for 57.10%, followed by 66-85 years old, 120 cases, accounting for 38.71% (Table 1).

The patient's department, condition and method of hospitalization

Among the 310 cases with esophageal cancer, thoracic surgery was the most in hospitalization, with a total of 183 cases, accounting for 59.03%, followed by the radiotherapy center, with 59 cases, 19.03%, and the tumor diagnosis and treatment center, with 23 cases, 7.42%. Most hospitalized were in general form, with 285 cases, accounting for 91.94%. Most of them were admitted as outpatients,

Table 1. Basic information

Item	Frequency	Percentage (%)
Sex		
Male	262	84.52
Female	48	15.48
Age		
19-45	13	4.19
46-65	177	57.10
66-85	120	38.71
Hospitalization		
Thoracic Surgery	183	59.03
Radiotherapy Center	59	19.03
Cancer Center	23	7.42
Department of TCM	19	6.13
Internal Medicine Clinical Department	9	2.90
Radiology	4	1.29
Other	3	0.97
Gastroenterology	3	0.97
Department of Interventional Medicine	2	0.65
Clinical Department of Surgery	2	0.65
Cadre Ward	1	0.32
Respiratory Medicine	1	0.32

with 305 cases, accounting for 98.39%.

Analysis of the relationship between seasons, solar terms and patients' hospitalization

Among the 310 cases with esophageal cancer, 85 cases were admitted in spring and summer, each accounting for 27.42%, followed by winter, 75 cases, accounting for 24.19% (Table 1); among the hospitalized cases of solar terms, Lixia (Summer begins) solar terms were the most hospitalized cases, 24 cases, accounting for 7.74%, followed by Yushui (The rains), 23 cases, accounting for 7.42%, and Xiazhi (Summer solstice), 20 cases, accounting for 6.45% (Figure 1).

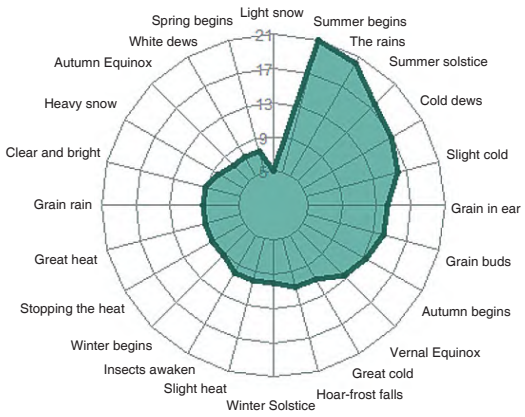

Figure 1. Radar chart of hospitalization in solar terms

Analysis of Western Medicine Diagnosis and TCM Symptoms of Patients Using Elemene Injection Based on the Diagnostic Information Sheet

First Western medical diagnosis

According to the diagnosis of the first Western medicine, among the top 6 diagnosed diseases, malignant tumors were the most, accounting for 38.24%, followed by hypertension, accounting for 3.42% (Table 2).

TCM syndrome

After excluding the difficult classification, the syndrome types were ranked as deficiency of both qi and yin, spleen-stomach disharmony, and phlegm-heat obstructing lung. Syndrome of deficiency of both qi and yin was the most, 4 cases, accounting for 18.18%; followed by spleen-stomach disharmony, phlegm-heat obstructing the lung, 1 case each, accounting for 4.55% (Table 2).

Table 2. Diagnostic information

No.	Western medicine diagnosis	Frequency	Percentage (%)	TCM Syndrome	Frequency	Percentage (%)
1	Malignant Tumor of Esophagus	782	34.77	Other	16	72.73
2	Malignant Tumor	78	3.47	Deficiency of Both qi and yin	4	18.18
3	Hypertension	77	3.42	Spleen-Stomach Disharmony	1	4.55
4	Diabetes	35	1.56	Phlegm-Heat Obstructing the Lung	1	4.55
5	Coronary Heart Disease	27	1.20			
6	Esophageal Tumor	24	1.07			
7	Lung Infection	23	1.02			
8	Lung Malignant Tumor	21	0.93			
9	Liver Malignant Tumor	18	0.80			
10	Mediastinal Lymphatic Tuberculosis	17	0.76			

Analysis of Combined Medications in Patients with Esophageal Cancer

Combining a single drug

Among the 310 cases with useful medicine records, a total of 369 types of western medicines and 120 types of traditional Chinese medicines had been used in combination. The top 10 varieties and types of traditional Chinese medicine and Western medicine were extracted respectively. The top 3 commonly used western medicines were general nutrition drugs (4.00%), vitamins (3.82%), insulin for injection and their similar drugs (3.37%); the top 3 traditional Chinese medicines were Xiaoaiping injection (7.39%), Brucea javanica oil emulsion injection (6.19%), compound Kushen injection (5.57%) (Table 3). The top 3 commonly used in combination of western medicines were blood substitutes and perfusion solutions (33.29%), general nutrition drugs (5.97%), and vitamins (5.42%); the top 3 traditional Chinese medicines are anti-tumor drugs (48.71%), tumor adjuvant medication (8.46%), phlegm, antitussive and anti-asthmatic agents (8.11%) (Table 3).

Association rules of traditional Chinese medicine and Western medicine drug combination

To analyze the combination of traditional Chinese medicine and western medicines, the top 10 drug varieties with the highest combination probability were selected for analysis. The support degree aims to reflect the probability of A and B appearing at the same time in the association rule. According to the support degree, the most common combination of one type of traditional Chinese medicine combined with one type of western medicine was Xiaoaiping injection + ascorbic acid, followed by brucea javanica oil emulsion injection + thymosin and Brucea javanica oil emulsion injection + heparins (Table 4). The most common combination of one type of traditional Chinese medicine combined with two types of western medicine was human serum albumin microspheres + pethidine + Shenfu injection, followed by pethidine + hydroxyethyl starch + Shenfu injection and contrast agent + lentinan + Shenfu injection (Table 5).

Web analysis of association rules for combination drugs

In order to show the actual situation of the combined application of Elemene Injection with a variety of traditional Chinese medicines and western medicines more intuitively and clearly, SPSS Clementine software was used to perform an association analysis on the combined traditional Chinese medicines and western medicines using Suxiao Jiuxin Pills. The green circle represents traditional Chinese medicine, and the red circle represents western medicine. When the frequency of Elemene Injection combined with Chinese and western medicine is ⩾39.68%, it is indicated by a thick line. When the frequency of Elemene Injection combined with Chinese and western medicine is ⩽17.74%, it is indicated by a dotted line. When the frequency was between the two, it is indicated by a thin solid line. That is, if two points are connected by a thick line, they are easier to use together. On the contrary, if two points are connected by a thin line, they are more difficult to use together. As the

Table 3. Medication information

No.	Western medicine		Traditional Chinese medicine	
	Medicine type	Frequency [case (%)]	Medicine type	Frequency [case (%)]
1	General Nutrition Medicine	1973 (4.00)	Xiaoaiping Injection	235 (7.39)
2	Vitamins	1880 (3.82)	Brucea Javanica Oil Emulsion Injection	197 (6.19)
3	Insulin for Injection and Similar Drugs	1660 (3.37)	Compound Kushen Injection	177 (5.57)
4	Ambroxol (Meso cough)	1225 (2.49)	Shenfu Injection	144 (4.53)
5	Ascorbic Acid	1021 (2.07)	Shenqi Fuzheng Injection	67 (2.11)
6	Furosemide	1006 (2.04)	Kangfuxin Liquid	67 (2.11)
7	Amino Acids	973 (1.97)	Huachansu Injection	65 (2.04)
8	Calcium Gluconate	851 (1.73)	Ganmao Qingre Granules	56 (1.76)
9	Thymosin	810 (1.64)	Simotang Oral Liquid	55 (1.73)
10	Dexamethasone	794 (1.61)	Tumor Adjuvant Medication	52 (1.64)

Table 4. Name association rules for one type of TCM combined with one type of Western medicine

One Type of TCM=>One Type of Western Medicine	Rule Support (%)	Confidence (%)	Lift
{Xiaoaiping Injection} => {Ascorbic Acid}	21.290323	82.500000	1.304847
{Brucea Javanica Oil Emulsion Injection} => {Hymosin}	20.967742	83.333330	1.201550
{Brucea Javanica Oil Emulsion Injection} => {Heparins}	20.322581	80.769230	1.148553
{Shenfu Injection} => {Insulin for Injection and Similar Drugs}	18.387097	96.610170	1.711380
{Shenfu Injection} => {Ambroxol (Meso Cough)}	18.387097	96.610170	1.654649
{Shenfu Injection} => {Lidocaine}	18.387097	96.610170	1.610169
{Shenfu Injection} => {Ascorbic Acid}	18.387097	96.610170	1.528018
{Shenfu Injection} => {Thymosin}	18.387097	96.610170	1.392984
{Shenfu Injection} => {Thrombin}	18.064516	94.915250	1.974747
{Shenfu Injection} => {General Nutrition Medicine}	18.064516	94.915250	1.827561
{Shenfu Injection} => {Furosemide}	18.064516	94.915250	1.508909

Table 5. One type of TCM combined with two type of Western medicine

No.	Two Types of Western Medicine Combined with One Type of TCM	Rule Support (%)	Confidence (%)	Lift
1	{Human Serum Albumin Microspheres, Pethidine} => {Shenfu Injection}	10.322581	82.051280	4.311169
2	{Pethidine, Hydroxyethyl Starch} => {Shenfu Injection}	9.032258	80.000000	4.203390
3	{Contrast Agent, Lentinan} => {Shenfu Injection}	5.483871	80.952380	4.253430
4	{Thrombin, Lentinan} => {Shenfu Injection}	5.483871	85.000000	4.466102
5	{Gentamicin, Lentinan} => {Shenfu Injection}	5.483871	85.000000	4.466102
6	{General Nutrition Medicine, Lentinan} => {Shenfu Injection}	5.483871	80.952380	4.253430
7	{Ambroxol (Meso Cough), Lentinan} => {Shenfu Injection}	5.483871	80.952380	4.253430
8	{Lidocaine, Lentinan} => {Shenfu Injection}	5.483871	85.000000	4.466102
9	{Vitamins, Lentinan} => {Shenfu Injection}	5.483871	80.952380	4.253430
10	{Heparins, Lentinan} => {Shenfu Injection}	5.483871	80.952380	4.253430

distribution of the combined medications shown in the figure, Elemene Injection was commonly used with heparins, thymosin, dexamethasone, vitamins, ascorbic acid, furosemide, lidocaine, ambroxol (mexo cough), solvents and thinners, including perfusion solution, amino acids, insulin for injection and similar drugs, general nutrition medicine, fat emulsion, gentamicin, pantoprazole, thrombin, contrast agent (Figure 2).

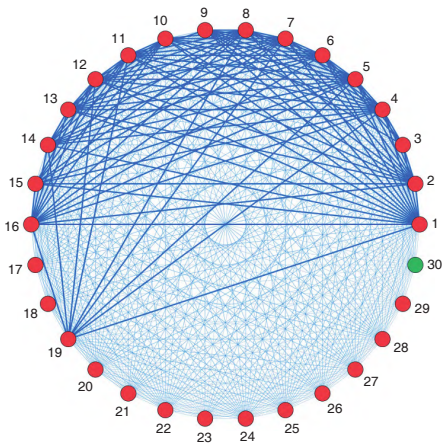

Figure 2. Name association of elemene injection combined medications Web

Note：1. Heparins, 2. Thymosin, 3. Dexamethasone, 4. Vitamins, 5. Ascorbic Acid, 6. Furosemide, 7. Lidocaine, 8. Ambroxol (Meso cough), 9. Solvents and Thinners, including Perfusion Solution, 10. Amino Acids, 11. Insulin for Injection and Similar Drugs, 12. General Nutrition Medicine, 13. Fat milk, 14. Gentamicin, 15. Pantoprazole, 16. Thrombin, 17. Glycerin, 18. Recombinant Human Interleukin, 19. Contrast Agent, 20. naproxen, 21. Tropisetron, 22. Cefminox, 23. Metoclopramide, 24. Magnesium Sulfate, 25. Fentanyl, 26. Omeprazole, 27. Mosapride, 28. Human Serum Albumin Microspheres, 29. Cimetidine, 30. Xiaoaiping Injection

DISCUSSION

Basic Information Characteristics of Patients with Esophageal Cancer Using Elemene Injection

From the statistical results, the number of male patients with esophageal cancer who used Elemene Injection was significantly more than that of female patients. The age ranged from 46 to 65 years old, followed by 66 to 85 years old, and most of them were middle-aged male patients. Most of these

patients had the habit of smoking and drinking. Studies have shown that smoking and drinking can increase the risk of esophageal cancer, up to 132% and 123%.[8] A number of studies have confirmed the close relationship between smoking and drinking and esophageal cancer.[9-12] Another study showed that the risky dietary factors of esophageal cancer are also related to the preference for spicy food, heavy oil, heavy salt, and pickled foods.[13] In addition to the diagnosis of malignant tumors, it was found in the first diagnosis of western medicine that the top diagnoses are hypertension, coronary heart disease, etc. The cause of this type of cardiovascular and cerebrovascular diseases was also closely related to lifestyle and diet. In 2015, the analysis of tumor prevalence published in the *Chinese Journal of Oncology* showed that the incidence rate and mortality rate of esophageal cancer have reached sixth and fourth places in China.[14] Therefore, it is very necessary to popularize the relevant prevention knowledge of esophageal cancer. It is necessary to closely monitor and actively prevent people who are susceptible to esophageal cancer. Early screening, early diagnosis, and early treatment of such patients can reduce the incidence of the disease.

Hospitalization Characteristics of Patients Using Shengmai Injection

The department distribution, format, cost and length of hospitalization

From the perspective of departments of hospitalization, the distribution is relatively concentrated. The top 3 are thoracic surgery, radiotherapy center, and tumor diagnosis and treatment center, suggesting that the majority of inpatients using Elemene Injection are tumor patients. A large amount of data in the real world showed that the drug has been widely used in clinical practice.

The first Western medicine diagnosis and TCM syndromes of hospitalization

Among the patients with the first western medicine diagnosis of hospitalization, the top 6 diseases using Elemene Injection were esophageal (shiguan) malignant tumor, esophageal (shidao) malignant tumor, malignant tumor, hypertension, coronary heart disease, and diabetes. Malignant tumors of the esophagus (shiguan) were the most, accounting for 30.9%, followed by malignant tumors of the esophagus (shidao) , accounting for 3.87%. As we all know, malignant tumors have become the biggest killer of diseases, and esophageal cancer is also one of the high incidence cancers according to research findings with the occurrence closely related to diet and living habits.[15]

As for TCM syndromes, the syndromes types are deficiency of both qi and yin, spleen-stomach disharmony, and phlegm-heat obstructing lung. These symptoms are mostly caused by poor emotions, dietary irregularities, impermanence in daily life, etc. Deficiency of healthy qi and dysfunction of qi would cause qi deficiency, qi stagnation, blood deficiency, blood stasis, phlegm stasis, yin deficiency, and yang deficiency; and cancer is a wasting disease that consumes qi and injures yin, so the deficiency of both qi and yin is the most common syndrome of esophageal cancer with the symptoms including fatigue, lack of energy and laziness. Elemene is a substance extracted from Radix Curcumae. According to TCM, Radix curcumae belongs to the liver meridian, heart meridian and lung meridian, and has the function of activating blood and relieving pain, promoting qi and relieving depression, clearing the heart and cooling blood, normalizing function of gallbladder and curing jaundice.[16] It can also smooth qi, clear heat and remove dampness, and protect cancer. Coronary heart disease belongs to "chest impediment" in TCM with the main symptoms of qi stagnation and blood stasis. The clinical symptoms are mainly chest pain which can be relieved by Yujin to activate blood circulation and promote qi.

The relationship between patients' hospitalization using Elemene Injection and seasons and solar terms

This study found that more patients were admitted to the hospital around the *yushui* (The rains) to *xiazhi* (Summer solstice), which is basically consistent with the incidence of disease in spring and summer. During this period of time, due to the warmer weather, more and more people began to gather for eating and drinking wine, eat pickled, smoked, fried, spicy and salty food even

overeat. According to existing studies, these dietary habits are the risk factors for esophageal cancer.[17] Cardiovascular and cerebrovascular diseases mostly occur in winter and spring, and the solar terms are *yushui* (The rains), *xiaohan* (Slight cold) and *hanlu* (Cold dews) which explain that solar terms and seasonal changes are inseparable reasons for diseases. According to the theory of TCM, man corresponds to nature. *Huangdi's Internal Classic* <<黄帝内经>> says "yin and yang are the foundation of all things". "The beginning, ending, and progress of things in the universe have natural principles. If human beings reluctantly change the natural principles when dealing with problems, diseases or troubles will occur". Under normal conditions of the human body, disease changes are closely related to seasonal climate changes,[18] and they all have certain laws. The changing characteristics of solar terms and seasons have a certain impact on the disease, and the occurrence and progress of the disease itself also has certain laws. According to the combination of past research and the real-world data of this research, the relationship between dietary habits and seasonal solar terms and diseases can be found. Therefore, combining diseases with seasonal solar terms and dietary habits plays an important role in the prevention and health care of esophageal cancer.

Analysis of Combined Medications of Elemene Injection

Epidemiological studies have found that esophageal cancer is one of the main "killers" that threaten the health of Chinese residents. The incidence of esophageal cancer is closely related to dietary and living habits. In TCM, the disease belongs to the categories of "cancer", "abdominal mass" and "accumulation-gathering". The pathogenesis of the disease is mainly due to the imbalance of yin and yang, seven-affect binding depression, and the damage of the viscera, leading to stagnation of qi and blood stasis, which will become "abdominal mass" and "accumulation-gathering" for a long time. *General Treatise on the Cause and Symptoms of Diseases* says: "When the viscera are affected by evil, but they fail to form an accumulation-gathering at the beginning. And they remain stagnant, finally will become". The treatment in TCM for Zhang Jingyue's *Complete Works of Jingyue* says: "Anyone who cures accumulation-gathering have only four methods called attack, disperse, dissipate and supplement". Therefore, it is necessary to pay attention to TCM syndrome differentiation when combining drugs. According to the analysis of combined medications of Elemene Injection, western medicine blood substitutes and perfusion fluid are used most frequently. Studies have shown that blood substitutes have a good oxygen-carrying function and play an auxiliary role in the treatment of tumors.[19] Anti-tumor drugs appear most frequently in the combination of TCM. The anti-tumor drugs include Xiaoaiping injection, Brucea javanica oil emulsion, compound bitter injection, and Shenqi Fuzheng Injection. In Elemene Injection combined with one type of TCM and one type of western medicine, the top two are Xiaoaiping injection with ascorbic acid and brucea javanica oil emulsion injection with thymosin. Esophageal cancer is a wasting disease, so in addition to anti-cancer treatment, patients also need to enhance immunity.

Limitation

The data of this study was from the electronic medical records of 21 hospitals, which truly reflected the clinical medication regimen in the treatment of esophageal cancer, reflected the main characteristics of clinical medication of Elemene Injection for the treatment of esophageal cancer. The dosage and course of treatment of the drug basically complied with the instructions. However, it was a retrospective study, and the safety should to be confirmed by more evidence such as centralized monitoring with hospitals and spontaneous reporting systems.[20] The effectiveness also needs further research in RCT trials.

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