



Medical decision support system for cancer treatment in precision medicine in developing countries

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ABSTRACT

In many developing countries and regions, there are medical problems such as dense populations, lack of medical resources, and shortage of doctors, making it impossible to provide patients with more convenient full-cycle services. Non-small cell lung cancer is a malignant tumor with the highest morbidity and mortality in the world. Research on the auxiliary treatment of intelligent systems is helpful in understanding and evaluate the disease. The system can help doctors provide patients with effective drug treatments and personalized medical services by actively learning the experience of outstanding experts. According to expert knowledge, through quantitative efficacy scores and specific analysis of evaluation indicators, based on the efficacy evaluation matrix and the extraction of key features of patients and drugs, a predictive model of drug efficacy evaluation for adjuvant therapy is established. The model divides into latent feature extraction and curative effect collaborative prediction modules. In the feature extraction module, adding noise to the original data in model training process helps reduce the impact of the sparseness of the patient's medication data. By considering the uncertainty of experts in drug efficacy evaluation modeling, based on probability analysis and efficacy prediction, the proposed method demonstrates the potential options in the face of hesitating choices. According to the predicted efficacy score, candidate drugs are selected to assist doctors in disease analysis and secondary diagnosis. Experiments have shown that drug efficacy prediction methods can provide adjuvant treatments for diseases and quantify the therapeutic effects of targeted drugs. The efficacy information and detection information of patient-drug pairs are helpful to improve decision-making ability, and the proposed medical decision support system framework is superior to other deep learning methods. By adding data, the performance can be significantly improved.

1. Introduction

Cancer is a worldwide issue of concern today, and lung cancer has become the first killer of cancer in the world. According to statistics, there are approximately 2.0939 million new cases of lung cancer and 1.761 million deaths each year, which is a malignant tumor with the highest incidence (11.6%) and mortality (18.4%) in the world (Organization, 2018). Among the 27 cancers counted, lung cancer has the highest mortality rate. The five-year survival rate of lung cancer in most countries is less than 18%. Among them, 80% of patients with non-small cell lung cancer have reached an advanced stage at the time of diagnosis. On average, more than 6000 people die from cancer every day, and nearly five people die from cancer every minute (Malmir et al., 2017). Among the burden of disease, lung cancer has ranked second after

cardiovascular disease (Chen, Sun et al., 2018; Deluche et al., 2015).

Most developing countries are distributed in Asia and Africa. Asia accounts for almost 60 percent of the world's population, almost half of all new cases, and more than half of all deaths occur in Asia (Freddie et al., 2018). Fig. 1 shows the population, cancer incidence, and mortality in each region. It can be seen that morbidity and mortality are highest in Asia. Moreover, cancer death rates in Asia and Africa (57.3% and 7.3%) are higher than their incidence rates (48.4% and 5.8%) (Organization, 2018). The burden of cancer is gradually shifting to developing countries. In many developing countries, because of their large populations, limited economic and technological levels, many developing regions are not performing well in cancer treatment. The poor cancer prognosis results in high mortality rates for cancer patients (Cordero et al., 2020; Seera and Lim, 2014). In addition, due to cultural

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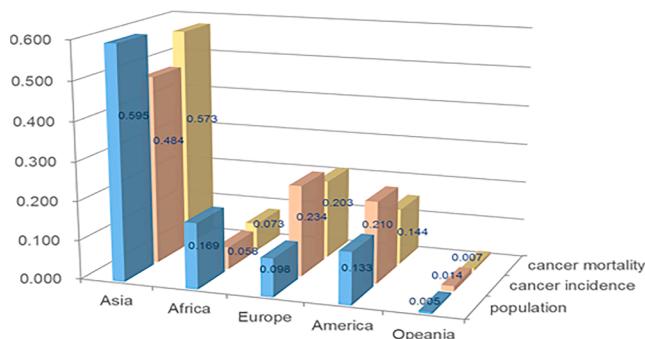


Fig. 1. Proportion of population, cancer incidence and cancer mortality in all continents.

and environmental differences worldwide, individual living habits are also an essential factor in cancer. Lung cancer is common cancer among men in East Asia, with the highest incidence among men. Such is due to the high smoking rate of men in East Asia, the large population, and inadequate medical resources (Zhou et al., 2020). Compared with developed countries, people's awareness of prevention and treatment in developing regions is relevant weak. Cancer patients in developing areas have limited opportunity for timely diagnosis and treatment. Many patients are diagnosed with advanced cancer the first time when they see a doctor.

China's cancer incidence and mortality rank first in the world. For a hundred new cancer patients every in the world, Chinese account for 21% (Malmir et al., 2017). Lung cancer has become the most lethal cancer in China. Treatment methods for lung cancer are usually divided into surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy. However, the cost of immunotherapy treatment and research is unaffordable. Many developing countries could not have enough technology and economic capacity to make immunotherapy treatment ubiquitous. There are nearly 1.4 billion people in China, and the average number of doctors per thousand people is only 2.16. There is some gap between the number of professional doctors and that of developed countries. The proportion of ICU beds in total beds in medical institutions is about 5%-6%, which is far below the developed countries' level (Chen, Sun et al., 2018). China has a large number of smokers, and most of them are men. According to statistics, the number of new lung cancer patients each year is up to about 750,000, with an average of 40 people per 100,000 (Freddie et al., 2018; Wu, Tan, Chen, Zhao, 2018b).

Among them, 85% of lung cancer patients are non-small cell lung cancer. China's currently existing doctors and equipment are challenging to meet patients' needs, and the per capita medical and health resources are distinctly behind the world average (Chen, Sun et al., 2018). Furthermore, hospitals' geographical distribution is extremely uneven, with 60% of the population in the Midwest but only 21% of hospitals. Medical resources are mainly distributed in developed cities and hospitals. There is only one professional doctor per 1000 people in rural areas, and where services are only 1/8 of the total. This situation has caused most people to flock to the city for medical treatment, and medical services are in short supply. On average, doctors need to diagnose nearly 200 people every day to meet demand, which is a workload that is far beyond heavy. The time that a doctor can spend on a patient is short, and it is difficult to provide research services for individual patients. Traditional treatment methods such as chemotherapy have severe damage, although effectively, which has led to difficulties for many patients to receive timely treatment or side effects of treatment, leading to a large number of medical disputes.

In China, chemotherapy is still the first-line treatment of advanced NSCLC, and it is commonly used in patients with advanced cancer (Sharifi et al., 2017). However, in destroying the proliferation of cancer cells, chemotherapy also destroys the growth and reproduction of healthy cells. The side effects of destroying processes on a human's body

are unusually large and unbearable for patients. Moreover, its efficacy has reached a bottleneck (McGarry and McDonald, 2018; Wu et al., 2019). Therefore, targeted therapy has broken the bottleneck of the treatment of advanced NSCLC. It has become an adjuvant therapy method after surgery, which is only effective for targeted cancer cells and has fewer side effects on healthy cells than chemotherapy. Over the past few decades, targeted drugs have made good progress in inhibiting cancer development in some cancer patients. Targeted therapy mainly targets specific targets to suppress the development of cancer. In recent years, new drugs have been continuously developed, but they have been vulnerable. Due to the therapeutic effect of drug-targeted specific targets that often lasts for a short time, tumor cells can still generate drug resistance through functional redundancy and activation of the signal pathway. As a result of the complexity of the tumor, poor drug resistance will lead to limited efficacy. In this series of biological processes that cause disease, some processes can become redundant, and interference with drugs of a single molecular target is robust. It can be considered that targeted therapy as the primary treatment for cancer also has a limitation. Researchers predict the combination of drugs that is suitable for patients by studying drug combination therapies adapted to patients to overcome this bottleneck. It also responded to "precision medicine" currently advocated (Wei and Denny, 2015). Besides, it has been found that more drugs can act on complex disease processes to play a crucial role in the treatment process. Combination therapy may be more effective than disease alone in treating disease (Kourou et al., 2014; Masood et al., 2018).

Some researchers have proposed that one goal of precision medicine is to develop a treatment plan appropriate to the patient (Wu, Tan, Chen, Zhao, 2018a). Each patient has different signs, responds differently to drug effects, and has different body resistance. Adopting a treatment plan appropriate to individual patients can more effectively help patients to prolong their lives and reduce their financial burden. According to the data from the Adverse Drug Reaction Monitoring Center of the Chinese Ministry of Health, about 200,000 people die from adverse drug reactions every year in China. Up to 2.5 million patients require hospitalization due to adverse drug reactions at home. These figures show that under regular use and dosage, there will also be a large number of harmful reactions unrelated to the purpose of those drugs and show their different seriousness and harmfulness.

Tumors are usually a type of complex pathogenesis, with significant differences among individual patients, and drugs do not have characteristics of a sensitive population (Wu et al., 2019). In this way, the average utilization rate of those drugs will be low, and many people will not have any effect after taking the drug, and the disease will even worsen, which will affect treatment time. In targeted therapy, targeted drugs play an important role in improving the condition. The complexity of drugs and variability in the human body will make people too late to make a reasonable response. There are no established guidelines for using medicines, and most of them are based on the doctor's individual experience. Different doctors have different experiences and methods of medication. Such experience accumulation may be the result of long-term verification. The individual's experience has the doctor's judgment, and there is no more suitable medication scheme for individual patients. This empirical judgment is only a conventional medication mode suitable for most patients. Moreover, prediction models and tools based on modern machine learning technology have not been widely and reliably applied in clinical decision support systems.

The current situation in China is a common problem in many developing countries. There are problems such as a large population, few professional doctors, unevenly distributed medical resources, and underdeveloped medical technology. In order to improve the drug's effectiveness and solve the above problems, find a reliable medication method suitable for patients is necessary. We need to use technology to improve the utilization and supply of medical resources. For this reason, the accelerated development of intelligent auxiliary systems for artificial intelligence medical care is to meet the needs of countries and regions

facing these same problems (Chen, Ding, Zheng, Zhang, Yang, 2018; Davari et al., 2016; Kudo et al., 2020; Wu, Zhuang, & Tan, 2020). 1. Medical intelligent assistance system can use telemedicine through technical means and artificial intelligence to assist decision-making, and a doctor can face multiple patients and provide services to them at the same time. 2. An intelligent assisted diagnosis system can reduce the workload of doctors when facing a patient, improve the efficiency of diagnosis. 3. The system can select important information and provide auxiliary decision results and factors, assisting doctors to drill down to more hidden information, so that workload of doctors to a single patient can be reduced. Furthermore, the risk of inaccurate medication caused by expert's different personal experiences can also be avoided. On the other hand, more patients can benefit from accurate treatment methods, the waste of ineffective drugs can be reduced.

There are many uncertainties in the treatment process because the efficacy of targeted therapy is difficult to evaluate. A medication scheme is vital for patients in the process of cancer treatment. Assist doctors in providing personalized treatment for patients can reduce the blindness of medication. The method is based on efficient quantitative evaluation, extraction, and integration of patient and drug auxiliary information feature matrix. Through the relationship matrix decomposition and multi-source data feature matrix, a deep model is proposed to predicting and evaluating drug efficacy. It can help doctors comprehend and evaluate diseases and provide doctors with predictive drug efficacy evaluation results. On the one hand, the system extracts the individual similarity of patients and drugs, combined auxiliary information of patients and drugs, to mine the medication scheme suitable for individual patients. On the other hand, the system learns from the expert's experience, recommends a drug treatment plan suitable for the patient, provides supplementary treatment drug evaluation. For this reason, the auxiliary medical system provides relevant patients with analysis and evaluation of medication decisions, and then assists doctors in making secondary decisions. By considering experts' uncertainty in drug efficacy evaluation modeling, the proposed method demonstrates the potential hesitating choices in the face. This paper presents a suitable medication recommendation and prediction method based on patient and drug feature depth representation.

The contributions of this article are as follows:

1. A quantitative method for evaluating combined medications efficacy was proposed, and a sparse matrix for evaluating the efficacy of all medication schemes in different patients was established.
2. The drug analysis module uses the decomposition of the efficacy evaluation matrix combined with the encoder to extract deep relationship feature representation. By establishing the patient and drug auxiliary feature matrix, patient's therapeutic effect evaluation value for the drug can be jointly predicted.
3. Through evaluation results, it eliminates the interfering factors in the diagnosis process and assists the doctor in analyzing and evaluating the disease.
4. We collected data from three hospitals for experimental analysis. The analysis shows that our method performs well on the validation set. Tumor area and markers have a certain specificity. Combined with the proposed evaluation method, the efficacy of the disease state can be evaluated.

2. Related work

Machine learning is widely used to predict drug responses in disease treatment. (Yang et al., 2018) proposed a multi-task type algorithm. This method uses information obtained from one task to perform another task, predicts drug response by integrating the genomic characteristics of cell lines and drug targets and chemical information, and uses the ability of multi-task learning to provide a novel molecular basis for drug response opinion. Literature (He et al., 2018) proposed a machine learning method called Kernelized Rank learning, which uses drug

recommendation as a ranking problem to select the most effective drug. It sorts drugs according to each cell line's expected effect (patient), thereby avoiding the difficulty of accurately predicting the sensitivity of a given drug. Ding et al. (2017) used deep learning methods to identify information features from genomics data and trained classifiers to predict the effectiveness of drugs in cancer cell lines. The method can accurately predict the efficacy of the drug and also identify sensitive cancer cells.

Predicting the efficacy of drugs on cancer cells has been the focus of research, and kernel-based methods in machine learning (especially multi-kernel learning) can be used to solve such problems. It can integrate various types of complex biomedical information sources in the form of a kernel and understand its importance in prediction tasks. Cichonka et al. (2018) used time-and memory-efficient learning with multiple pairwise kernels method to predict the anti-cancer efficacy of drugs in a wide range of cancer cell lines. This method does not need to explicitly calculate a large number of paired matrices and is highly efficient, making it suitable for solving large, paired learning problems.

To better select drugs, some researchers have explored them. By identifying the interactions between known drugs and targets to analyze the characteristics of drugs, (Wen et al., 2017) developed a deep learning-based algorithm framework called DeepDTIs. The method first uses unsupervised pre-training to extract features from the original input and then applies interactive known label pairs to build a classification model. DeepDTIs can predict whether a new drug targets some existing targets or whether a new target interacts with some existing drugs. Aliper et al. (2016) proposed a deep neural network confusion matrix for drug relocation, and used the transcriptome data processed by the pathway activation scoring algorithm to train model. This allows deep learning neural networks based on transcriptome data to identify the pharmacological properties of multiple drugs under different biological systems and conditions. Ezzat et al. (2017) proposed a drug-target interaction prediction framework based on feature dimension reduction and ensemble learning to improve the prediction performance of drug-target interactions. Literature Turki et al. (2018) proposed a transfer learning algorithm to predict cancer drug sensitivity. This method achieves high prediction performance for the target task by transferring knowledge from the auxiliary data of related tasks.

Data integration can give us a deeper understanding of the mechanisms of cancer and drug synergy and help solve the problem of predicting drug combinations. Zitnik et al. (2018) proved that a comprehensive analysis of multiple types of omics data and pharmacological data could more effectively identify synergistic drug effects, thereby improving the accuracy of prediction. Chang et al. (2018) proposed a new type of deep learning model CDRscan, which is based on large-scale drug screening test data to predict the response of anticancer drugs, and tailors a cancer treatment method for each patient based on the genome of the tumor. He et al. (2020) proposed a new learning ranking method (pLETORG) to select the right medicine for patients. The pLETORG method uses drug potential carriers and cell line potential carriers to predict the drug sequencing structure of each cell line and uses the genome information of the cell line to understand the potential vectors. This method is effective in selecting new sensitive drugs.

Literature (Huang et al., 2017) developed a medical platform that can accurately predict the best drug therapy from the genomic profile of a single patient's tumor. The platform uses a highly versatile support vector machine (SVM) algorithm, combined with standard recursive feature elimination (RFE) methods, to predict personalized drug responses from gene expression profiles. The model has high accuracy in predicting drug response in various cancer cell lines. In modern medical research, intelligent diagnosis helps doctors analyze and judge the condition, which can effectively shorten the diagnosis time and reduce the rate of misdiagnosis. Wu et al. (2018a) designed a system model that can be used for non-small cell lung cancer drug treatment, related parameter analysis, and data decision-making. Through this model, an optimized treatment plan can be selected, thereby determining an

effective drug treatment method. Simultaneously, a system model based on probability analysis and decision-making was further established to calculate the probability of metastasis prediction in four different stages of non-small cell lung cancer, which plays a vital role in disease prediction (Wu et al., 2018b; Wu, Zhuang, & Tan, 2020). In addition, we have made some progress in the related work of the lesion extraction and recognition part of the pet image in our earlier work (Cui et al., 2020).

This study analyzes the framework of medical in-formation systems from three aspects: efficacy evaluation quantitative, extraction and integration of patient and drug auxiliary information feature matrix, and personalized medication decision-making models.

3. System design

An intelligent auxiliary treatment system assists doctors in analyzing and diagnose diseases. That helps to shorten the time and cycle of patient diagnosis and treatment, improves the medical efficiency of patients. When there are too many patients and insufficient medical resources, reduce the workload. This model proposes a drug efficacy evaluation and prediction scheme for assisting doctors with patient medication. At the same time, doctors can make secondary judgments based on predictive analysis of the model, provide patient's comprehensive analysis results as a reference, provide patients with more accurate and personalized medical services suitable for patients through secondary diagnosis.

3.1. Medication system structure

The medical drug evaluation system, it establishes two significant elements through patient relationship, targeted drug relationship, and target relationship: patient characteristics and targeted drug characteristics. The relationship between patients, patient's feedback on the use of targeted drugs, and the relationship between targeted drugs affect drug recommendation decision quality. To reduce the uncertainties in the treatment process, based on data and feature analysis, it builds a targeted drug evaluation system by collecting historical diagnosis, treatment records of patients, organizing drug use records of cancer patients in each period, and targeted drug characteristics.

Next, we give a brief introduction to that problem for drug decisions. When a patient is diagnosed with cancer, if the stage is not high, doctors will test a patient's cancer cells to determine pathological factors of cancer cells and their target. Drug targets are a more valuable research point in biology. Many people explore drug targets and targeted drugs to fight cancer (Zhang et al., 2016). Due to the variability of cancer drugs and resistance of cells, some drugs may fail in some cases and affect patient's treatment. Therefore, the diversity of drugs and targets makes it difficult for doctors to control methods and programs of use medication. The main reasons are as follows: ①. The cost of determining the target drug is unaffordable. ②. Unable to determine or judge the situation of patients after medication. ③. Changes in drug targets may lead to ineffective use of the drug. In order to reduce the uncertainties in the treatment process and better assist doctors in making more scientific and reasonable judgments on patients' medications, proposes model to predict medication schemes' impact on patients and recommend a feasibility scheme.

According to patient's historical medication feedback, they are combined with characteristics of tumor patients, such as tumor mutation genes, mutation site, family history, weight, age, gender, staging, tumor marker, PET index, CT index, SUV, symptoms, treatment measures, medication, therapeutic gene mutation site, and side effects, etc., to analyze similarities between cancer patients. Due to the heterogeneity of each person, it cannot intuitively determine whether a situation is the same among patients because tumor patients are not the same, only similar. Cancer patients are hardly the same because tumors are heterogeneous, and tumor genes are susceptible to mutation. For cancer patients, it cannot say that diseases of the same cancer patient are

precisely the same, and there is no comparability. What the system can do is to find the similarity of tumor patients as much as possible. The more similar patients, the more similar their treatment and rehabilitation are.

At present, the treatment of tumors is more inclined to identify a target for targeted therapy to reduce serious damage to people's bodies caused by radiotherapy and chemotherapy. Drug targets are binding sites of drugs and biological macromolecules. The drug treatment of tumors is continuously targeted as the targets change. Targeted drugs can block signal transmission of tumor cells and inhibit its growth of tumor cancer cells with less damage to people's bodies. Therefore, the study of drug targets is critical to suppress tumors. The similarity among drug targets directly points to the similarity among drugs. The identification of drug-target relationship pairs is significant to targeted drug development. It can evaluate the similarity among targeted drugs by their molecular structure, chemical structure, side effects, and the relationship between corresponding targets.

Based on the above analysis, the potential relationship information is first extracted between the patient and the targeted drug corresponding to the target. This information can explore potential relationships between patients and the targeted drug and then predict accurate drug treatment plans for the patient. It can reduce the number of drug tests in a cancer cell group and dig out more suitable treatment options to assist doctors in secondary diagnosis.

The evaluation process of the system is mainly composed of patients, doctors, decision-making modules, and treatment plans, as shown in Fig. 3. The diagnostic data generated by a patient is stored and analyzed by a cloud service center. The center's decision analysis module analyzes diagnostic and treatment data for patients. From the set of all possible treatment plans, a set of personalized medicines suitable for patients is screened. It provides doctors with a systematic evaluation plan and assists doctors in making a secondary diagnosis. The doctor gives the analysis results of secondary diagnosis and gives feedback on decision-making. Medical records are stored in the cloud service center, which provides new examples for the decision-making module. These new examples can complete the training model and gradually improve the accuracy of the prediction.

In the drug decision module, after extracting the patient and drug information and hidden feature representation of a patient's medication information, the extracted feature information is integrated through the neural network to train a prediction model. To facilitate the description of drug decision design ideas, we have defined the following:

It assumes that the collected patient set is Pat , medication scheme decision set Med , and feedback value e after drug used is obtained based on historical medication record feedback of these patients. We will use the simplified expression "medication" or "drug" for the "medication scheme" in the following paper. Based on the patient's medication record, it will get a sparse matrix E about patient and efficacy evaluation of the drug. Each e_{ij} in E represents the effect evaluation of patient Pat_i after selecting medication Med_j for treatment in this period. If patient Pat_i has used medication Med_j in historical records and has a record of its efficacy, it can evaluate its effectiveness and calculate an evaluation value. Therefore, $e_{ij} \neq 0$, which also means that the treatment of patient Pat_i after using medication Med_j has been observed. Assuming the treatment of patient Pat_i is not observed with or without medication Med_j , $e_{ij} = 0$. Besides, the method took the patient's and targeted drug's characteristics as auxiliary information to provide better drug recommendations. According to the characteristics of patients and drugs, similar information of patients and targeted drugs are extracted separately. By combining this similarity information, the relationship between patients and medications is analyzed. They use $Fp \in R^{|Pat| \times m}$ and $Fd \in R^{|Med| \times n}$ to represent a patient's characteristic information matrix and a targeted drug's characteristic information matrix separately, which are an auxiliary information matrix.

The extracted characteristic information of patients and drugs is

assumed to be the patient's potential factor vector and potential factor vector of the targeted medication scheme, which are represented by lp^{pat} and $ld^{med} \in \mathbb{R}^k$, respectively. Therefore, lp_i^{pat} and ld_j^{med} are potential factor vectors of patient pat_i and potential factor vectors of medication med_j , respectively, where k is the dimension of hidden space. Given a sparse scoring matrix E and auxiliary information matrices F_p and F_d , the goal is to learn the patient's potential factor lp^{pat} and potential factor ld^{med} of the targeted drug. The characteristics of the patient and medication are extracted from auxiliary information as feature vectors of a patient and medications.

In the process of collaborative filtering through neural networks, it integrated the potential patient characteristics and medication extracted from SDAEs and the potential representation of patient-drug relationships. Then, extracted features combination of patient and medication are connected with historical medication information of patient and drug to represent underlying vector to obtain corresponding patient and the drug potential vectors. In the collaborative filtering process, patient and drug potential vectors through matrix factorization are processes. In this way, the product of the elements corresponding to the patient's and the medication's potential vector is obtained. The output vector of calculation is input to a fully connected neural network layer.

In the model, the loss function consists of the reconstruction error of patient and drug feature extraction and prediction efficacy error of the medication scheme. The system defines a patient's evaluation of medication used in the range $(-1, 1)$ to specify the degree of patient recovery who has used targeted drug therapy. Among them, a negative value indicates deterioration condition, and a positive value indicates improvement condition. It is evaluated by e_{ij} , which represents efficacy evaluation of patient pat_i on medication med_j . Then, by inputting the noisy data in the SDAEs module, the patient potential factor lp^{pat} and the medication potential factor ld^{med} are embedded with historical medication information of patient and drug. At last, the input is connected to the neural network for training, thereby predicting the lack of patients evaluated E for targeted drug efficacy.

The proposed medication decision model is mainly divided into two steps, auxiliary information feature extraction stage of patient and targeted drug, and neural network training prediction stage of efficacy evaluation combined with patient's historical medication record feedback. In order to effectively predict the evaluation value of the unused drug of patients, it trains potential vectors of the patient and targeted drug through a neural network. It is possible to combine collaborative filtering to predict evaluation value e_{ij} of medication med_j by patient pat_i and find top-k medication schemes suitable for patient pat_i . The medication predicted can provide doctors with selectable and testable drug treatment options, while the system can recommend first k th medications with high evaluation value in patients' individual situations, allowing doctors to refer to these medication schemes during the second diagnosis choice and effect test before medication. In this way, patients can be provided with more alternative treatment methods, and a targeted drug treatment scheme more suitable for patients is found. Table 1 lists the common symbols used in our model.

3.2. Drug evaluation scheme design

For the drug evaluation method, first, an evaluation method of drug efficacy is introduced, then introduced the evaluation model for predicting drug evaluation efficacy based on the analysis of patient and drug data.

Fig. 2 shows a diagram of our drug auxiliary decision model. It divides the drug decision into three parts, and they are a feature extraction module for patients, targeted drugs, and a medication recommendation module, respectively. For feature extraction of the patient and medication, it integrates patient (medication) features into two aspects. On the one hand, it extracts patient-medication relationship characteristics from patient's medication relationships combined with the patient's

Table 1
Common symbols.

Symbol	Description
pat	patient set
med	medication scheme set
M	patient characteristic dimension
N	drug feature dimension
L	SDAE layers
$F_p \in \mathbb{R}^{ pat \times m}$	patient assistance information
$F_d \in \mathbb{R}^{ med \times n}$	targeted medication scheme support information
$E \in \mathbb{R}^{ pat \times med }$	medication evaluation matrix
lp^{pat}	patient latent vector
ld^{med}	medication potential vector
w_l	layer weight matrix
b_l	layer deviation vector

(medication) label. On the other hand, it extracts the feature vector of a patient (medication) from feature information (also called auxiliary information) of a patient (medication) itself. For the relational feature extraction, we establish a patient-medication relationship matrix and then initializes the patients' medication relationships and patient (medication) labels as codes to be embedded in the dense vector, obtaining a low-dimensional sparse vector, as described in Section 3.2.2. After that, by using two Stacked Denoising Auto Encoders (SDAEs) (Vincent et al., 2010), the auxiliary information of patients and drugs are used as the input of SDAE to obtain the patient (medication) potential factor matrix, as described in Section 3.2.3. Finally, the potential vector of the patient and medication is used as input of the neural network to learn the prediction model and finally generate a prediction score. Table 2 lists the common symbols used in our method.

3.2.1. Drug evaluation method

The role of molecularly targeted drugs is to "precisely attack" key targets during tumor growth so that normal cells will not or rarely be injured. The serum tumor markers in patients decreased compared with that before treatment, when surgery, chemotherapy, or radiotherapy was effective and increased significantly again in relapse. This situation indicated that the level of serum tumor markers was helpful to evaluate the therapeutic effect and predict tumor recurrence. Table 2 lists the common symbols used in our method.

The treatment of tumors can be judged by CT to determine tumor area and declining level of tumor markers to evaluate treatment effectiveness. It assumes that the tumor area before treatment, including spread area, is Tu_{area}^{bef} , and tumor marker mar_i level before treatment is $Tu_{mar_i}^{bef}$. The total area of the tumor after treatment is Tu_{area}^{lat} , and the tumor marker level is $Tu_{mar_i}^{lat}$. It defines the normal level of tumor markers as $[Tu_{mar_i}^{low}, Tu_{mar_i}^{high}]$, and $Tu_{mar_i}^{low}$ is generally 0.

It defines the extent of area reduction based on the change in the tumor area before and after treatment:

$$D_{area} = \frac{Tu_{area}^{bef} - Tu_{area}^{lat}}{\max\{Tu_{area}^{bef}, Tu_{area}^{lat}\}} \quad (1)$$

The change of tumor markers can also reflect diseases' treatment. The change of markers can reflect the effect of treatment to a certain extent. It defines the change of markers as:

$$D_{mar_i} = \frac{\left(Tu_{mar_i}^{bef} - Tu_{mar_i}^{high}\right) - \left(Tu_{mar_i}^{lat} - Tu_{mar_i}^{high}\right)}{\max\{|Tu_{mar_i}^{lat} - Tu_{mar_i}^{high}|, |Tu_{mar_i}^{bef} - Tu_{mar_i}^{high}|\}} \quad (2)$$

Therefore, it defines the efficacy evaluation method of drug combination therapy as:

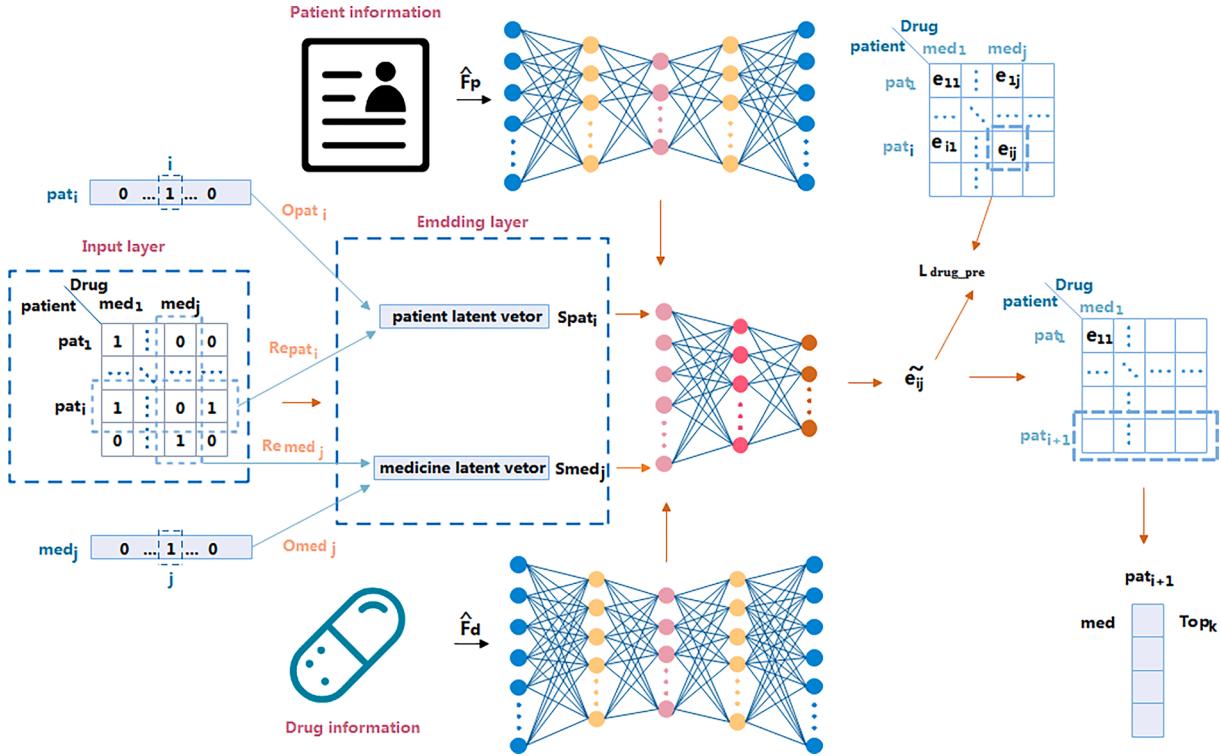


Fig. 2. Drug auxiliary decision model.

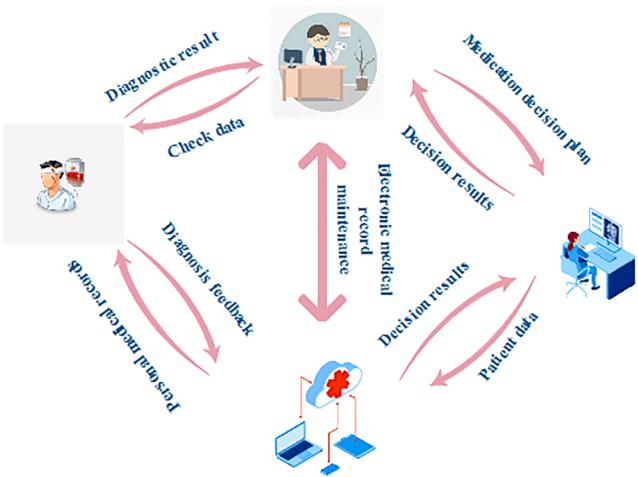


Fig. 3. System decision process.

$$e_{pat_i-med_j} = \zeta D_{area} \times (\varphi_{imp} \sum_{a \in imp} D_{mar_a} + \varphi_{low} \sum_{b \in low} D_{mar_b}) \quad (3)$$

where ζ , φ_{imp} and φ_{low} are the trade-off of area, non-small cell lung cancer tumor markers with high correlation, and tumor markers with low correlation, respectively. imp indicates a tumor marker set with high relevance to the evaluation of non-small cell lung cancer, and low indicates a tumor marker set with low relevance to non-small cell lung cancer. D_{mar_a} indicates the degree of change of a tumor marker that is highly correlated with the evaluation of non-small cell lung cancer, and D_{mar_b} indicates the degree of change of a tumor marker that is lowly correlated with the evaluation of non-small cell lung cancer.

3.2.2. Establishment of evaluation matrix

It will describe how to map medication records to embedding rep-

Table 2
Common symbols.

Symbol	Description
W_{pat}	weight matrix of encoder for extracting patient information
b_{pat}	deviation matrix of encoder for extracting patient information
W_{med}	weight matrix of encoder for extracting medication information
b_{med}	deviation matrix of encoder for extracting medication information
W_{pat}'	weight matrix of decoder to extract patient information
b_{pat}'	deviation matrix of decoder to extract patient information
$f\hat{p}$	corrupt patient assistance information
F_{pl}	output of patient assistance information l layer
e_{ij}	the effect evaluation of patient pat_i after using drug med_j
\tilde{e}_{ij}	the predicted effect evaluation value
re_{ij}	the using relationship of pat_i and med_j
o_{pat}	one-hot code represents patient's label
o_{med}	one-hot code represents drug's label

resentation for many patients and then to be able to extract similarities between patients. In the same way, the drug program does the same embedding expression. Then, the predictive model is trained in conjunction with auxiliary features, and adaptive evaluation of the targeted drug administration method is used to evaluate the patient's adaptability. According to the predicted evaluation value \tilde{e}_{ij} , a suitable targeted drug is selected.

It uses the method mentioned above to evaluate drug efficacy for the patient and record it in the patient-medication relationship matrix. The possible medication schemes of different targets in patients with intermediate and terminal stages, as examples, are shown in Fig. 4. Among them, a branch of the tree structure is a patient's possible medication scheme, which means that for patients in the intermediate and terminal stages, by determining the target, judging the type of disease (squamous cell carcinoma or non-squamous cell carcinoma), and then determining the corresponding medication scheme. The medication process of a patient with non-small cell lung cancer after a particular gene mutation

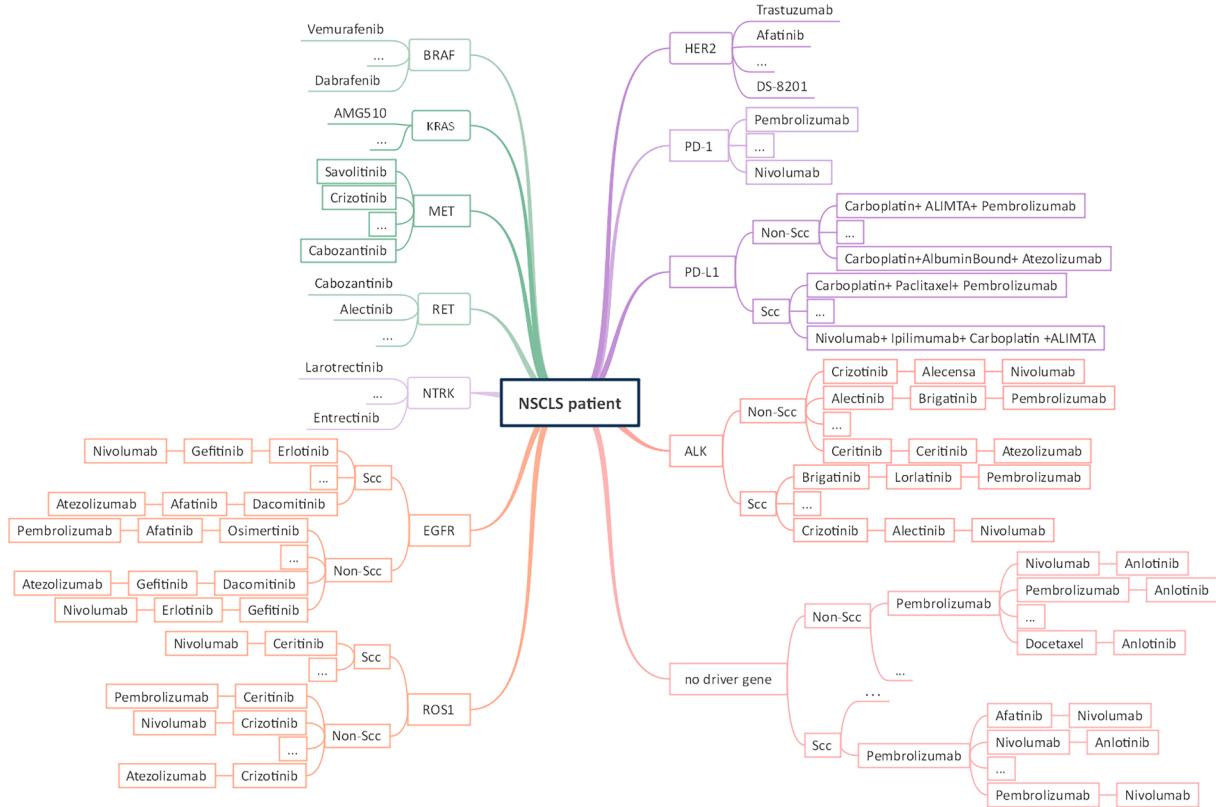


Fig. 4. Possible medication scheme options.

at a certain stage, such as EGFR, the medication scheme may include first-line therapy scheme, second-line therapy scheme, and back-line therapy scheme. In general, the drugs for the first-line treatment scheme are relatively mature and are the preferred option because of their good therapeutic effect and small side effects. These medication therapy schemes may be a single drug, but they may also be a combination of drugs (such as multiple targets). Obviously, drugs used by a patient are few compared to the drug decision set, and the relationship matrix formed between patient and medication must be sparse. Therefore, it builds a relationship matrix based on the patient's medication situation and combines patient and medication auxiliary information to train a model to predict the efficacy of patient and medication. Individualized medication scheme adapted to the patient are selected through the medication model, and the evaluation value of the relationship matrix is used as the selection index of medications. The relationship matrix between patients and medication and effect evaluation matrix is established as follows:

It knows that Pat and Med represent the set of the patient and the medication scheme, assuming that the efficacy evaluation matrix for patients and medications is $E = [e_{ij}]^{|\text{Pat}| \times |\text{Med}|}$, and its element e_{ij} indicates whether the patient pat_i has a medication record for the medication med_j . Moreover, if patient pat_i has a recorded efficacy evaluation value for item j medication med_j , then $e_{ij} = e_{\text{pat}_i-\text{med}_j}$, otherwise $e_{ij} = 0$. The goal of recommending medications by extracting hidden information is to generate a list of medications to reflect the more preferred medications for users.

$$e_{ij} = \begin{cases} e_{\text{pat}_i-\text{med}_j}, & \text{pat}_i \text{ use } \text{med}_j; \\ 0, & \text{otherwise} \end{cases} \quad (4)$$

In order to facilitate the extraction of similar characteristics between patient and medication, it set non-zero terms in the efficacy evaluation matrix to 1, forming the relationship matrix $Re = [re_{ij}]^{|\text{Pat}| \times |\text{Med}|}$ between patient and medication. Besides, it needs to give patient set and

medications set a representation representing themselves so that it can train hidden features of patients and medications according to the relationship matrix between patients and medications and labels themselves. A one-hot code represents the patient's (medication's) label. Assuming N elements, the most common discrete data representation is generally a vector of $N-1$ zeros and a single 1 to represent each element. In the model input layer, it uses relationship splicing between patient and medication and the patient's label as input. Specifically, the relationship feature vector between patient and medication is defined as:

$$Re_{\text{pat}_i} = [re_{i*}]^{1 \times |\text{Med}|} \quad (5)$$

The feature vector of the relationship between medication and patient is defined as:

$$Re_{\text{med}_j} = [re_{*j}]^{1 \times |\text{Pat}|} \quad (6)$$

In Fig. 3, the patient's feature information in the model input layer is represented as:

$$s_{\text{pat}} = [Re_{\text{pat}}, o_{\text{pat}}] \quad (7)$$

where $[]$ is a connector, similarly, the characteristic information of the medication is expressed as:

$$s_{\text{med}} = [Re_{\text{med}}, o_{\text{med}}] \quad (8)$$

However, when there is a large training set caused by the large number of patients and medications, the transformed vector dimension could be too high, and this discrete representation cannot reflect the relationship among elements of different categories. Therefore, it adds an embedding layer to the model to transform patient and drug representations from discrete data into continuous vector representations. In the input layer, it uses binary coding to input each element in the patient and medication set as a representation into the embedding layer. In the embedding layer, the sparse representation of patient and medication set in the input layer is mapped into a continuous vector representation

z_{pat}, z_{med} . The sparse vector of the input layer is made dense, and after reducing dimensionality, a low-dimensional non-sparse vector is obtained.

3.2.3. Patient and medication information feature extraction

Next, it adds additional information about patients and medications to assist in extracting more accurate similarity information, such as staging, medications, family history, SUV, weight, age, gender, tumor lesion density, targets, symptoms, tumor marker, lesion characteristics, pathological characteristics, immunohistochemical and category, therapeutic gene mutation site, side effects, mechanism, and therapeutic targets of a medication scheme, etc. As described in Section 3.1, the similarity information of patients and medications can help us predict unknown relationships. For the patient auxiliary information matrix F_p and medication auxiliary information matrix F_d , the module uses SDAEs to learn the underlying factors of patients and medications by minimizing the original input and reconstruction errors of a patient and medication auxiliary information features. The learned features are stored in an intermediate hidden layer vector. The specific details are described as follows:

It uses two SDAEs to complete the feature extraction of auxiliary information. The improved autoencoder is a neural network that learns specific features through input and output. By extracting features to generate an output close to input, it helps us to reflect original input content through the extracted features. SDAEs is a deep network model formed by stacking multiple DAEs. However, DAE is a variant of AE. It usually uses a corrupted version to reconstruct original input, which is more suitable for complex situations than original autoencoders. In the training process, noise is added so that the trained model can extract features and also have good results in noise pollution.

They are using patient auxiliary information as an example describes how to extract potential patient information. The SDAEs model is symmetrical in structure. For a five-layer SDAEs model, the training process from layer zero to layer two can be regarded as a coding process. This process abstracts noisy auxiliary information input F_{p0} into a more implicit expression F_{p2} . Similarly, the process from layer two to layer four can be regarded as a decoding process. This process reconstructs F_{p2} according to the original input. The value F_{p2} of middle-layer neuron trained from the encoder is an abstract representation extracted from original input data. Adding noise to the original input for training makes the trained model more robust and improves its generalization performance. Besides, the model can learn more stable feature representations and can also show good results in sparse data and pollution. After all, the feature information we collect is not complete and normalized. The module uses the SDAEs model to extract potential representations of auxiliary information for patients and medications, respectively, to improve the accuracy of patients' recommendations in case of sparse drug evaluation.

Specifically, it randomly set the elements in the original input patient information F_p to zero, construct F_p as noise-containing data \hat{F}_p , and input the noisy data \hat{F}_p into SDAEs. It assumes that SDAEs has a total of L layers, and F_{pl} represents the output of its l layer. In training, first, it initializes the weights, biases, and representation outputs of each layer by gaussian function:

- Weight parameter w_{pat}^l of the l layer is generated by $\mathcal{N}(0, \mu_{w_{pat}}^{-1} I)$;
- The deviation parameter b_{pat}^l of the l layer is generated by $\mathcal{N}(0, \mu_{b_{pat}}^{-1} I)$;
- The output F_{pl} is generated by $\mathcal{N}(\delta(F_{pl-1} w_{pat}^l + b_{pat}^l), \lambda^{-1} I)$

Among them, $\mu_{w_{pat}}$ and $\mu_{b_{pat}}$ are hyperparameters used for parameter initialization, w_{pat}^l and b_{pat}^l represent weights and deviations of the l -layer of the autoencoder for feature extraction of patient assistance information, $\delta(\cdot)$ represents a sigmoid function, and I is a unit vector.

It set the front $L/2$ layer as an encoder and the back $L/2$ layer as a

decoder. The patient's auxiliary information feature extraction is to learn two mapping functions, one encoding function and one decoding function $f_{pat}(W_{pat}, b_{pat})$ and $g_{pat}(W'_{pat}, b'_{pat})$. The coding function maps the patient's auxiliary information to the hidden layer, and the decoder reconstructs hidden representation into the patient's auxiliary information. W_{pat} and b_{pat} are the weight matrix and deviation matrix of the encoder, respectively, and W'_{pat} and b'_{pat} are the weight matrix and deviation matrix of the decoder, respectively. Two mapping functions are learned from the deviation of reconstructed information and original input information. Then use the trained encoder to complete feature extraction. For noisy source data \hat{F}_p , the hidden layer output of the encoder is $h_{L/2}^{pat}$:

$$H_{pat} = h_{L/2}^{pat} = f_{pat}(F\hat{p}) = \delta(W_{pat}F\hat{p} + b_{pat}) = \frac{1}{1 + e^{-(W_{pat}F\hat{p} + b_{pat})}} \quad (9)$$

The purpose of the decoder is to reconstruct original data F_p from noisy data $F\hat{p}$. The output of the decoder L layer is expressed as:

$$F_{pL} = g_{pat}(h_{L/2}^{pat}) = \delta(W'_{pat}h_{L/2}^{pat} + b'_{pat}) \quad (10)$$

It trains the model by minimizing reconstruction errors to learn potential representations of patient information and targeted medication information. That is, the output of the middle layer is a feature of the extracted patient and medication. The reconstruction error of patient auxiliary information is defined as follows:

$$L_{pat} = ||F_p - F_{pL_{out}}||_F^2 + \mu_{pat} ||\gamma_{pat}||_F^2 \quad (11)$$

where $\gamma_{pat} = W_{pat} + W'_{pat}$ is the parameter of the model, μ_{pat} is its regularization parameter, and $F_{pL_{out}}$ is the output of the L layer.

In the same way, it continues to use SDAEs to train feature extraction models on auxiliary drug information and learn potential representations of medication schemes from targeted medication auxiliary information. Then it represents extracted potential as a matrix of potential factors for patients and medications, H_{pat} and H_{med} . It enriches the relationship between patients and items by incorporating auxiliary information from the patient and targeted medications into a collaborative filtering process.

3.2.4. Medication evaluation process

In medication-assisted evaluation systems, the most important thing is to extract potential information through data representation and data analysis to help medication evaluation. In the process of medication evaluation, the potential representations of patients and medications are extracted respectively by auxiliary information of patients and medications and patient- medication relationship information. The underlying representation is used to obtain similarity information of patients and similarity information of medication treatment methods. The above process has described how to extract patient's and medication's embedded representation from patient and medication feature information. Next, the module combines the feature representations with a collaborative filtering process and then completes the training of the drug evaluation model through a neural network. Specifically, the latent vector representation of a patient and medication is connected, and the multilayer-neural network is used to learn the patient- medication adaptive relationship. Combining hidden links gives a predictive assessment of efficacy.

The previous section extracted potential representations of patients and medications from auxiliary information. Next, the module connects extracted potential representations of patients and medications with feature vectors of patient- medication relationships to obtain corresponding potential vectors. That is, $X_{pat} = H_{pat}^T z_{pat}$, $Y_{med} = H_{med}^T z_{med}$. In the collaborative recommendation process, it calculates the connection between the patient and elements of the medication potential vector and output calculated vector to a fully connected neural network. The

elemental connection of potential vector of the patient and medication can be defined as:

$$\sigma_{in}(X_{pat}, Y_{med}) = X_{pat} \odot Y_{med} \quad (12)$$

Among them, \odot , X_{pat} , and Y_{med} respectively represent the element-wise product of the vector, the potential patient vector, and the medication potential vector. The output of the model is:

$$\tilde{e}_{ij} = \sigma_{out}(w_{out}^T \sigma_{l-1}(\dots w_2^T \sigma_2(w_1^T \sigma_1(X_{pat_i}, Y_{med_j})) \dots)) \quad (13)$$

where w_{out}^T represents the transposition of the weight matrix of the output layer, and \tilde{e}_{ij} represents the evaluation value of the efficacy prediction of the treatment of patient pat_i using medication scheme med_j . $\sigma(\cdot)$ can be a non-linear activation function, and w can be learned from the training data. Therefore, it has a stronger learning ability than conventional matrix factorization (MF) (Koren et al., 2009). The original matrix factorization method relied on the bias of doctors' medications; that is, the analysis of historical medication records of patients relied on implicit feedback to provide patients with predictions. However, due to the sparseness of medication records, the implicit feedback method based solely on doctors' empirical preferences limits the performance of predictive models. Therefore, the auxiliary information is used to extract the potential factor representation, and the potential characteristics of the patient's medication relationship are used to extract the potential vector of the patient-medication to predict the efficacy of the drug. After that, the prediction model can achieve better performance.

3.2.5. Drug decision model

This section defines the loss function of the medication scheme decision method and explains how to optimize this function. In general, the loss function consists of reconstruction error of auxiliary information and prediction error of curative effect. The auxiliary information reconstruction error includes the loss of auxiliary information feature extraction for the patient and the medication. It can define loss function for patient feature extraction as follows formula (11). Similarly, loss function for feature extraction of medications can be defined as follows:

$$L_{med} = ||Fd - Fd_{L_{out}}||_F^2 + \mu_{med} ||W_{med} + W'_{med}||_F^2 \quad (14)$$

where μ_{med} is a model parameter and regularization parameter for extracting hidden features of the medication, and $Fd_{L_{out}}$ is the output of medication feature information after model reconstruction.

Algorithm 1: Learning algorithms for medication prediction

Input: patient Information Fp , Medication information Fd , patient-medication relationship matrix Re , patient label information o_{pat_i} , medication label information o_{med_j} , efficacy evaluation matrix E
Output: \tilde{e}_{ij} : predicted efficacy

- 1: $(\hat{Fp}, \hat{Fd}) \leftarrow getAddNoiseFeature(Fp, Fd)$ // Adding noise to the patient auxiliary information feature matrix Fp and the drug auxiliary information feature matrix Fd by randomly setting the elements in the matrix to 0
- 2: **For each layer** l in SDAEs for patients **do**
- 3: $w_{pat}^l \leftarrow \mathcal{N}(0, \mu_w^{-1} I)$ // Create weight matrix
- 4: $b_{pat}^l \leftarrow \mathcal{N}(0, \mu_b^{-1} I)$ // Constructing a deviation vector
- 5: $Fp_l \leftarrow \sigma(Fp_{l-1} w_{pat}^l + b_{pat}^l)$ // Corresponding patient information output layer vector
- 6: **End for**
- 7: **For each layer** l in SDAEs for medicine schemes **do**
- 8: $w_{med}^l \leftarrow \mathcal{N}(0, \mu_w^{-1} I)$ // Create weight matrix
- 9: $b_{med}^l \leftarrow \mathcal{N}(0, \mu_b^{-1} I)$ // Constructing a deviation vector
- 10: $Fd_l \leftarrow \sigma(Fd_{l-1} w_{med}^l + b_{med}^l)$ // Corresponding drug information output layer vector
- 11: **End for**
- 12: **For each patient** i **do**
- 13: $Re_{pat_i} \leftarrow getRelationfeature(re_{i*})$ // Get the patient's relationship feature vector
- 14: $Spat_i \leftarrow getEmbeddedfeature(Re_{pat_i}, o_{pat_i})$ // A patient's thermal code is o_{pat_i} , combined with the patient's relationship to the drug to get the user's label embedded representation
- 15: $H_{pat_i} \leftarrow getPatFeature(Fp, pat_i)$ // Extracting patient features

(continued on next column)

(continued)

Algorithm 1: Learning algorithms for medication prediction

- 16: $X_{pat_i} = \begin{pmatrix} H_{pat_i} \\ K^T Spat_i \end{pmatrix}$ // Extracting latent vectors for patients
- 17: **End for**
- 18: **For each medicine** j **do**
- 19: $Re_{med_j} \leftarrow getRelationfeature(re_{j*})$
- 20: $S_{med_j} \leftarrow getEmbeddedfeature(Re_{med_j}, o_{med_j})$ // A thermal code for the drug is o_{med_j} , and the label embedded representation of the drug is obtained by combining the relationship characteristics of the drug with the patient
- 21: $H_{med_j} \leftarrow getMedFeature(Fd, med_j)$ // Extracting drug characteristics
- 22: $Y_{med_j} = \begin{pmatrix} H_{med_j} \\ V^T S_{med_j} \end{pmatrix}$ // Extracting drug potential vectors
- 23: **End for**
- 24: **For each pair** (X_{pat_i}, Y_{med_j}) // Patient-and-drug pair (X_{pat_i}, Y_{med_j}) prediction scores
- 25: $\tilde{e}_{ij} = f(X_{pat_i}, Y_{med_j})$
- 26: $\tilde{e}_{ij} \leftarrow getEfficacyEva(X_{pat_i}, Y_{med_j}, w_{out}^T)$ // Predict score based on formula 13
- 27: **End for**

The prediction error of efficacy is represented by latent factors of patient and medication feature information extracted in Section 3.2.3 and patient and medication feature vector integration obtained in Section 3.2.2. The error of predicted effect evaluation value and actual calculated effect evaluation value is obtained through collaborative filtering by a neural network. Accurately, efficacy evaluation \tilde{e}_{ij} is predicted for the output of each (pat_i, med_j) pair. It takes into account the characteristics of implicit feedback, and the patient's efficacy evaluation can be regarded as a label for the efficacy of patients using medication s. If a patient has used a targeted drug regimen, the patient's condition after the medication is recorded. Based on records, it can obtain an assessment of improvement of the condition and obtain actually recorded effect evaluation value e_{ij} . Therefore, the model-based predicted efficacy evaluation value \tilde{e}_{ij} can be regarded as a prediction of improvement of the patient's treatment effect related to the medication regimen. It limits related effect assessment \tilde{e}_{ij} to $(-1, 1)$ so that it can distinguish the effect of effect, so it can be achieved using the tanh activation function. The loss function can be defined as follows:

$$L_{pre} = \sum_{(pat, med) \in E} (1 - e_{ij}) \log_2(1 - \tilde{e}_{ij}) + e_{ij} \log_2 \tilde{e}_{ij} + \mu_{pre} ||\lambda_{pre}||_F^2 \quad (15)$$

where λ_{pre} and μ_{pre} represent regularization terms and model parameters, respectively. E represents pair of instances where the treatment is effective and ineffective. They are a set of examples of patients who have not been tested and medication relationships or examples of patients who have not improved or worsened after treatment.

Therefore, the loss function of the medication decision model is expressed by the error of patient and medication feature information extraction and effect prediction error:

$$L_{drug-pre} = L_{pre} + \lambda_{pat} L_{pat} + \lambda_{med} L_{med} \quad (16)$$

where λ_{pat} and λ_{med} represent the hyperparameters of the loss function.

Algorithm 1 shows the algorithm used in the medication prediction model. K and V represent the weight matrix of patient and medication feature embeddings, respectively, and μ_w and μ_b are hyperparameters used for parameter initialization.

4. Experiments and discussion

4.1. Data sources

Data in this paper comes from the Ministry of Education Mobile Health Information-China Mobile Joint Laboratory and the PET-CT Center of the Second Xiangya Hospital of Central South University (Tan et al., 2018; Zeng et al., 2018). It collected, sorted, and analyzed

data of three affiliated hospitals in Xiangya. Tables 3 and Fig. 5 show the data collected by the medical system of three affiliated hospitals of Central South University. This data is stored and exchanged through medical data centers. It shows recorded data for all patients in three hospitals from 2004 to 2017 (Hu et al., 2017; Hu et al., 2016; Wu et al., 2018b). It collected most of the patient's data through the data center, including patient diagnosis, disease, surgery, care plan, drug selection, and other data, as well as patient image information, test information, diagnostic records, medication status, and other data collected from different departments. These data are sorted and classified to provide comprehensive information for doctors, nurses, and patients. Among them, HIS is a hospital information system; EMR is an electronic medical record; LIS is a laboratory information system; RIS is a radiology information system; PACS is an image archiving and communication system (Wu, Chang, & Yu, 2020; Wu et al., 2019).

Fig. 5 shows the data collection of three hospitals. These data records can help doctors analyze and study typical disease cases and find intelligent evaluation methods in data analysis. It screened out relevant information and drug information of patients with non-small cell lung cancer and selected patient information with relatively complete records as the basis for the study. Through the analysis of NSCLC's big data, data information is stored in the medical library of medicine, scientific research, and teaching. A total of 93,218 articles recorded different surgical methods in different departments and different types of surgery to improve surgery's success rate. A total of 40,631 articles recorded medical information and the nature of medicines selected by doctors, which ensured the convenient use of the hospital's medicine management data environment. It applies data stored in the hospital system to build an extensive data set, filter out relevant NSCLC patient data and organize it, and select data with more complete patient records. So that it can analyze the development of the patient's disease, data collection, and evaluation process, provide doctors with quick reference opinions, improve diagnosis' timeliness, and reduce the diagnostic error rate. All work is done under the verification of the doctor. The doctor provides part of the patient data. The whole research process uses desensitization data extracted from the database, and the analysis process is completed under the authorization of the hospital and the patient.

4.2. Evaluation

4.2.1. Model evaluation

To evaluate the prediction method's performance, it used an 8-fold cross-validation method because the method can provide a sufficiently accurate estimate of the actual error rate. It uses 80% of each hospital's data as the training set and 20% of data as a test set. Based on previous work experience (Vincent et al., 2010), we use 7-layer and 5-layer SDAE respectively. The size of each layer of the encoder for extracting patient information is 146, 80, 45, and 25, respectively, and the size of each layer of the encoder for extracting drug information is 47, 25, and 15 respectively. After that, tests are performed on different characteristic

Table 3

Three hospitals with different medical systems for data collection, including start time and end time.

Hospital name	System	Start time in collection	Finish time in collection
Xiang'ya hospital	HIS	01-01-2013	07-07-2017
	EMR	12-01-2010	11-01-2017
The 2nd Xiang'ya hospital	HIS	09-01-2011	11-05-2017
	EMR	09-25-2011	05-27-2017
	LIS	01-01-2004	05-31-2016
	RIS	02-01-2015	12-17-2017
The 3th Xiang'ya hospital	HIS	04-01-2004	12-05-2017
	EMR	04-01-2004	12-05-2017
	EMR document base	05-01-2016	12-09-2017

parameters and estimated efficacy parameters in the model, and the average error of the test experiment is calculated. In this way, testing and training will be repeated eight times to ensure the experiment's accuracy.

TP (true positive): The patient has used the drug regimen and produced better results consistent with predicted classification results.

FN (false negative): The patient has used the drug regimen and produced worse results consistent with predicted classification results.

FP (false positive): The patient has used the drug regimen and produced worse results than predicted classification results.

TN (true negative): The patient has used the drug regimen and produced better results than predicted classification results.

Top-k drug schemes that are predicted for patients include drugs that have been used by patients and have produced good results, which are examples of better classification results and are designated as PT. Similarly, top-k drug plans that are predicted for patients include drugs that have been used by patients and have produced a worse effect, which is a sample with a poor classification effect and is designated as PN.

It defines the following indicators as forecast results' evaluation as shown table 4.

The numbers of instances can be converted into a ratio between 0 and 1 through the above indicators' definition to facilitate standardized measurement.

It verifies the model's selected medication's prediction performance and analyzes the relationship between the selected K drug, and the actual effective drug is chosen precision $CPrec$, and the actual invalid drug is chosen error rate $CErr$. This indicator means the effect of method learning. As shown in Fig. 6, the number of predicted candidates plan increases as the selected number of drug treatment plan K changes, the prediction effect will become better and better, and the increase will be faster. It is indicating that the predicted medication is more inclined to clinically selected drugs. $CErr$ curves show that the proportion of wrongly predicted candidate treatments plan among invalid samples varies with K. Similarly, the number of wrong prediction samples will increase as the selected K increases, but growth will be slow. There are fewer wrong samples while the value of K is small. It indicates that the value of K affects medication treatment plan choose' accuracy. A certain degree of accuracy can be sacrificed by reducing the number of wrong prediction samples.

Fig. 7 shows the relationship between the trade-off of auxiliary information and curative effect evaluation with index Acc. It can be seen that as the proportion of area parameters in the calculation of effect evaluation becomes large, the accuracy will be relatively improved. The reason may be that unstable changes of tumor markers will lead to some errors in evaluating judgment effect. Moreover, the enlargement of the tumor area means that the condition of cancer is aggravated, and the area's decrease also symbolizes the disease's improvement. The other set of parameters is the weight of patient auxiliary information and medication auxiliary information. It can be seen that auxiliary information is important to improve the model performance. Medications Auxiliary information helps improve the accuracy of drug efficacy classification.

Fig. 8 shows the relationship between the trade-off of curative effect evaluation and auxiliary information with evaluation index Sen. It can be seen that the sensitivity parameter first increases and then decreases with the increase of marker weight, and the curve amplitude is large. The reason may be the area of cancer cells may not change much in some samples, and judging a case to be positive or negative merely based on the area may lead to a misdiagnosis. Similarly, the marker's sensitivity is relatively weak, and this situation will also occur when its trade-off is too large. The other set of parameters is the weight of patient auxiliary information and drug auxiliary information. It can be seen that the patient and drug auxiliary information have little difference in insensitivity.

Fig. 9 shows the relationship between the trade-off of auxiliary information and curative effect evaluation with index Spec. It can be seen

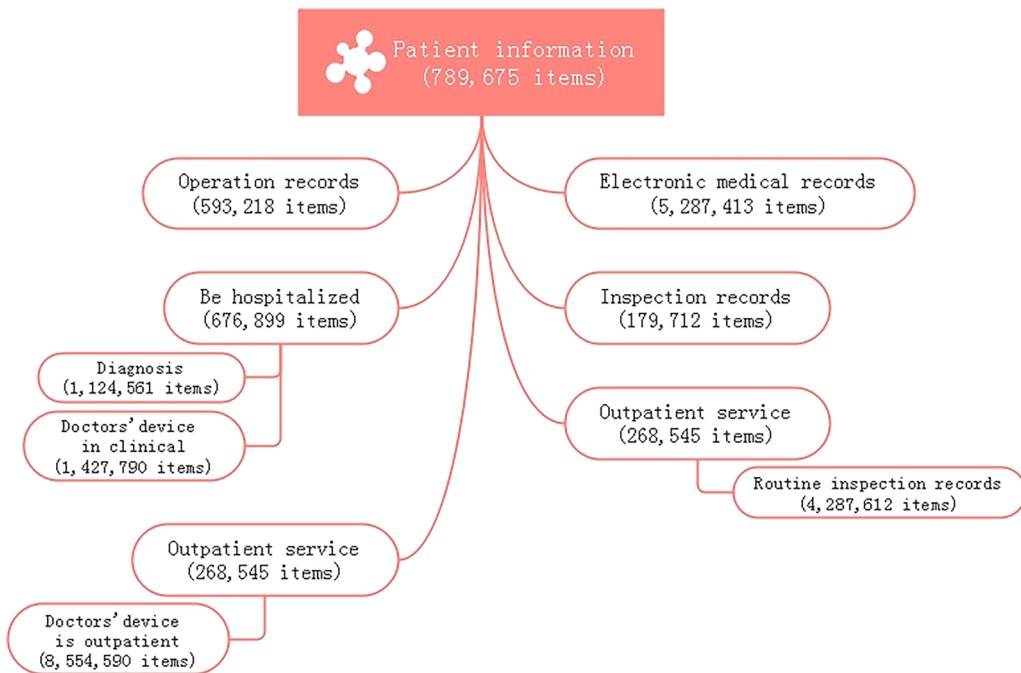


Fig. 5. Patient data collection.

Table 4
Evaluation indicators of forecast result.

Measures	Definitions	Formula
1.Accuracy	Predict the correct classification accuracy	$Acc = (TP + TN)/N$
2.Specificity	Predict classification specificity in negative samples	$Spec = TN/(TN + FP)$
3. Sensitivity	Measure the classification sensitivity of correct prediction	$Rec = Sen = TP/(TP + FN)$
4.Choose Precision	Actually effective precision in the selected drug	$CPrec = PT/TP$
5.Choose Err	The error rate of actual ineffectiveness in the selected drug	$CErr = PN/FP$
6.F1-score	Average weight of precision and recall	$F = 2 \cdot (Prec \cdot Rec)/(Prec + Rec)$
7. Kappa statistics	The degree of difference between the classifier and the random classification	$K = (p_o - p_r)/(1 - p_r)$
8. ROC area	Measure the effectiveness of the model (AUC)	

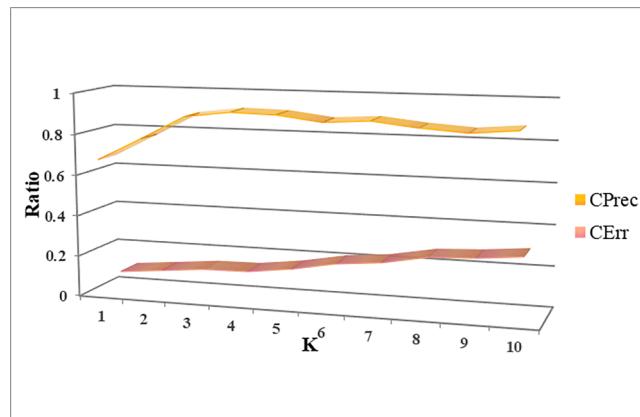
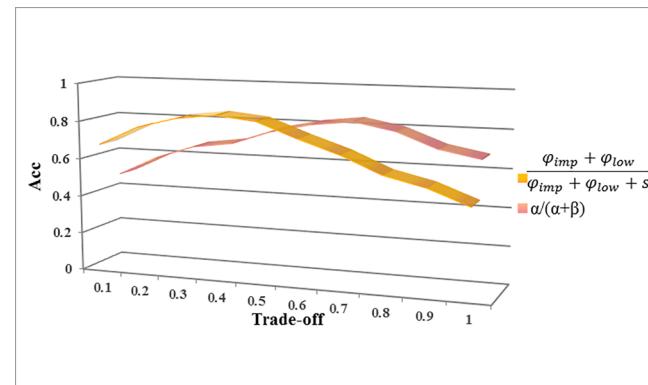
Fig. 6. The relationship between the selected K value and the prediction choose precision rate $CPrec$ and error rate $CErr$.

Fig. 7. The relationship between the trade-off of auxiliary information and the curative effect evaluation value with the evaluation index Acc

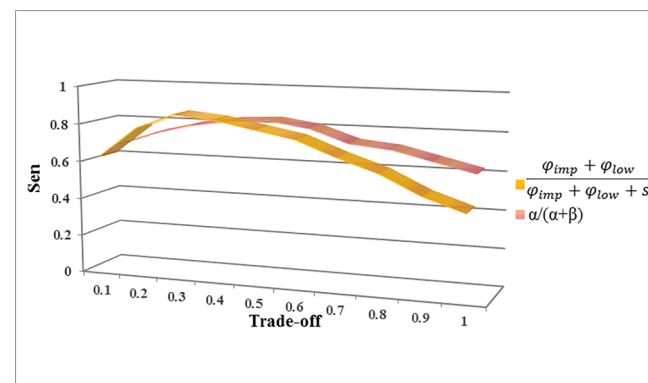


Fig. 8. The relationship between the trade-off of curative effect evaluation value and auxiliary information with the index Sen

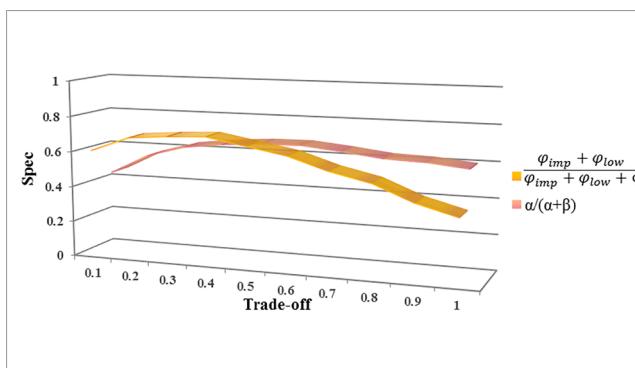


Fig. 9. The relationship between the trade-off of auxiliary information and the curative effect evaluation value with the index Spec

that as the trade-off of tumor marker increases, the Spec increases first and then decreases. The reason may be the area is specific for the evaluation method, and the specificity of tumor markers is limited. The other set of parameters is the effect of patient and drug auxiliary information on specificity. It can be seen that the patient's auxiliary information is more helpful to improve the specificity of efficacy prediction, and the larger the medication auxiliary information's trade-off, the greater influence on the prediction effect. The reason may be when the trade-off of the patient's auxiliary information is small, the patient's information cannot be considered better so that medication can not be targeted at the patient. Choosing the correct medicine for the patient helps improve model performance.

We use several deep learning models to replace the auxiliary feature extraction methods in the medication evaluation prediction framework MAPF, denoted as MAPF_DBN, MAPF_SAE, MAPF_AE, and the model MAPF_RemMat formed by removing the evaluation matrix part of the framework. Compared with these models and Huang et al. proposed method RFE + SVM used in our work, evaluation results of the performance of MAPF are shown in Table 5. As far as the data in the table is concerned, the performance of the proposed model shows better results than other methods. Besides, we have compared these methods' results with *t*-test. The results were found to be statistically significantly different from each other shown in Table 5. As far as the data in the table is concerned, the performance of the proposed model shows better results than other methods. Besides, we have compared these methods' results with *t*-test. The results were found to be statistically significantly different from each other ($P < 0.05$). The table shows that the effect of merely using AE for feature extraction is weak because it has only one layer, and the feature representation is not strong. Our proposed method is better than MAPF_DBN, especially in Spec, which improves 4%. It can be considered that because the data between the various indicators are independent of each other, the overall feature extraction training shows better performance than the layer-by-layer training and fine-tuning. Compared with MAPF_SAE, the proposed method has an average improvement of 6% in all indicators. It may be because many indicators in the information are incomplete and missing, so there will be a lot of interference and noise. The medication history data is also sparse, and data noise has a greater impact on the model's performance. MAPF can

effectively improve performance through noise reduction. By integrating the patient's related information and the medication's efficacy, it can learn the patient's test data to predict an effective treatment plan. By comparing RFE + SVM methods, our method has obvious advantages in specificity. It may be that some indicators of patients were not recorded, leading to the sparsity of features, so that RFE had insufficient reference in the process of feature selection, and the interference of missing data was not taken into account in the process of dimension reduction. Our method is significantly better than the model MAPF_RemMat with the relationship matrix removed, which shows that the relationship features of the patient medication evaluation feedback are embedded in the model, conducive to selecting medication schemes based on similar medical records and improving prediction performance.

Table 6 shows the using data sets from three hospitals to segment training and data sets testing. Each hospital used 20% of the total data as test sets and remain data as training sets, which were denoted as Xy_{12} , Xy_{13} , and Xy_{23} respectively. Then, the three hospitals select 20% of the total as the new test set by the ratio of each hospital data in the total, which is expressed as Xy_{123} . It can be seen that the model performs best on data set Xy_{123} , especially on the Recall indicator. This may be because experts in different hospitals have different medication experience and preferences, and the test sets selected in other hospitals have poor results, which reduces the robustness of the model. This means that the breadth of data affects the effect of learning, and learning more expert experience will help improve learning ability. In addition, the stability of MAPF is good, and the results tested under different conditions are not much different, only in the Kappa statistics. There are many reasons for this situation. It may be that there are fewer negative classes in the data, and the lack of some data makes the recognition ability weak.

4.2.2. Patient manifestation analysis

The section analyzed several significant tumor marker changes in patients and selected a set of markers with strong specificity in combination diagnosis as critical parameters to ensure such selected marker combination to be representative. Table 7 shows the general normal range of diagnostic parameters for tumor markers that are important for patients with non-small cell lung cancer. It analyzes each parameter's change through the statistical situation shown in Fig. 7. Our analysis results are as follows:

Fig. 10 shows the average results of several tumor markers CEA, CA125, SCC-Ag, and NSE from five sampling results of patient data in the past five years. From Table 4, it can be seen that the normal range values for the four tumor makers mentioned above are 0–5 ng/ml(CEA), 0–35U/ml(CA125), 0–1.2ug/l(SCC-Ag), and 0–16 ng/ml(NSE) respectively. The results of non-small cell lung cancer patients each year show that the average performance of tumor markers is more excellent than normal. From Fig. 10a, the average value of the CEA index of patients with non-small cell lung cancer is far beyond the normal range, and the average is five times more than that of normal people. From Fig. 10b, c, and d, the three tumor makers CA125, SCC-Ag and NSE index of patients with non-small cell lung cancer are three times higher than that of normal people on average. Data from the past five years show that patients are outliers on these several indicators. It can be seen that the combined detection of these several markers has certain specificity for patients with non-small cell lung cancer.

Table 5
Evaluation result for Different methods.

Method	Acc	Spec	Recall	F1-score	Roc area	Kappa statistics
MAPF_DBN	0.79	0.70	0.83	0.86	0.80	0.48
MAPF_SAE	0.76	0.68	0.79	0.83	0.77	0.42
MAPF_AE	0.71	0.66	0.73	0.79	0.70	0.33
MAPF_RemMat	0.75	0.67	0.77	0.82	0.75	0.40
RFE + SVM	0.79	0.62	0.83	0.87	0.76	0.40
ours	0.83	0.74	0.87	0.89	0.84	0.55

Table 6
Different data sets from different hospitals to segment the training and test sets.

Dataset	ACC	Recall	CPrec	CErr	F1-score	Kappa statistics
Xy_{12}	0.77	0.79	0.81	0.18	0.84	0.44
Xy_{13}	0.81	0.83	0.83	0.17	0.87	0.52
Xy_{23}	0.78	0.80	0.81	0.17	0.85	0.46
Xy_{123}	0.83	0.87	0.85	0.14	0.89	0.55

Table 7

Comparison of diagnostic parameters and decision data of non-small cell lung cancer with normal data.

CEA (ng/ml)	0–5
SCC-Ag (μg/L)	0–1.2
CA125 (U/ml)	0–35
NSE (ng/ml)	0–10.5

We randomly selected 1093 patients treatment history records with non-small cell lung cancer from three hospitals for statistical analysis, studying the relationship between four tumor markers and T, N, M, and TNM stages. Non-small cell lung cancer mainly includes two subtypes, adenocarcinoma and squamous cell carcinoma. The problem of whether tumor markers have a statistically significant effect on non-small cell lung cancer based on the clinical situation of patients would be analyzed. It analyzed two different types of non-small cell lung cancer patients. Fig. 11 shows the changes in tumor marker levels in cancer stages in patients with adenocarcinoma. It can be seen from the figure that CEA is related to the presence or absence of distant metastasis and metastasis site. Its expression is not significantly different in different T stages and N stages. Therefore, we can consider that the expression level of CEA in patients with adenocarcinoma with distant metastasis is significantly higher than that in patients without metastasis. The expression level in patients with stage IV b is significantly higher than that in patients with stage I + II + III and IVa. CA125 and NSE have some differences in the N stage, and there is no significant difference in the T stage. SCC-Ag has significant differences in TNM staging compared with CA125 and NSE. In conclusion, these several tumor markers are very sensitive to metastasis. The more metastatic sites, the higher its expression.

In squamous cell carcinoma patients, Fig. 12 shows the changes in tumor marker levels in squamous cell carcinoma patients' cancer stages. The expression level of SCC-Ag in patients with stage IV b was significantly higher than that in patients with stage I + II + III + IVa, but it was less related to T stage, N stage, and the presence or absence of distant metastasis. CEA and CA125 were not significantly different in each stage, with distant metastasis and IVb stage slightly higher than other cases. NSE has a certain difference in the N stage, and there is no apparent difference in the T stage. It can be seen that these several tumor markers are very sensitive to metastasis. The more metastatic sites, the higher its expression. The level of CEA in adenocarcinoma is significantly higher than that of other types of lung cancer. In comparison, the level of SCC-Ag in squamous cell carcinoma is significantly higher than that of other types of lung cancer. With continuous and dynamic observation, these four markers are highly clinical valuable for the evaluation of the lung cancer's condition, efficacy and prognosis.

Table 8 lists the sampling records of tumor markers of 20 NSCLC patients in the sample set after the system made the diagnosis and medication decision-making process for five cycles according to decision-making medication. It can be seen that the tumor markers have changed significantly before and after treatment, and a plenty of patients' sampling indicators have decreased significantly. Among them, the decrease in CA125 was more prominent, followed by CEA. In a few patients, the change in the sampling index is not apparent, which may be caused by systematic errors or detection errors. Overall, our system can effectively assist physicians in making better medication decisions for patients. It continuously gives of treatment results and conditions of new patients to system, so that the system can mutually provide feedback according to the patient's situation, completing the model training with newly added data examples through the online learning process. Eventually improve the accuracy of personalized medicine recommendations

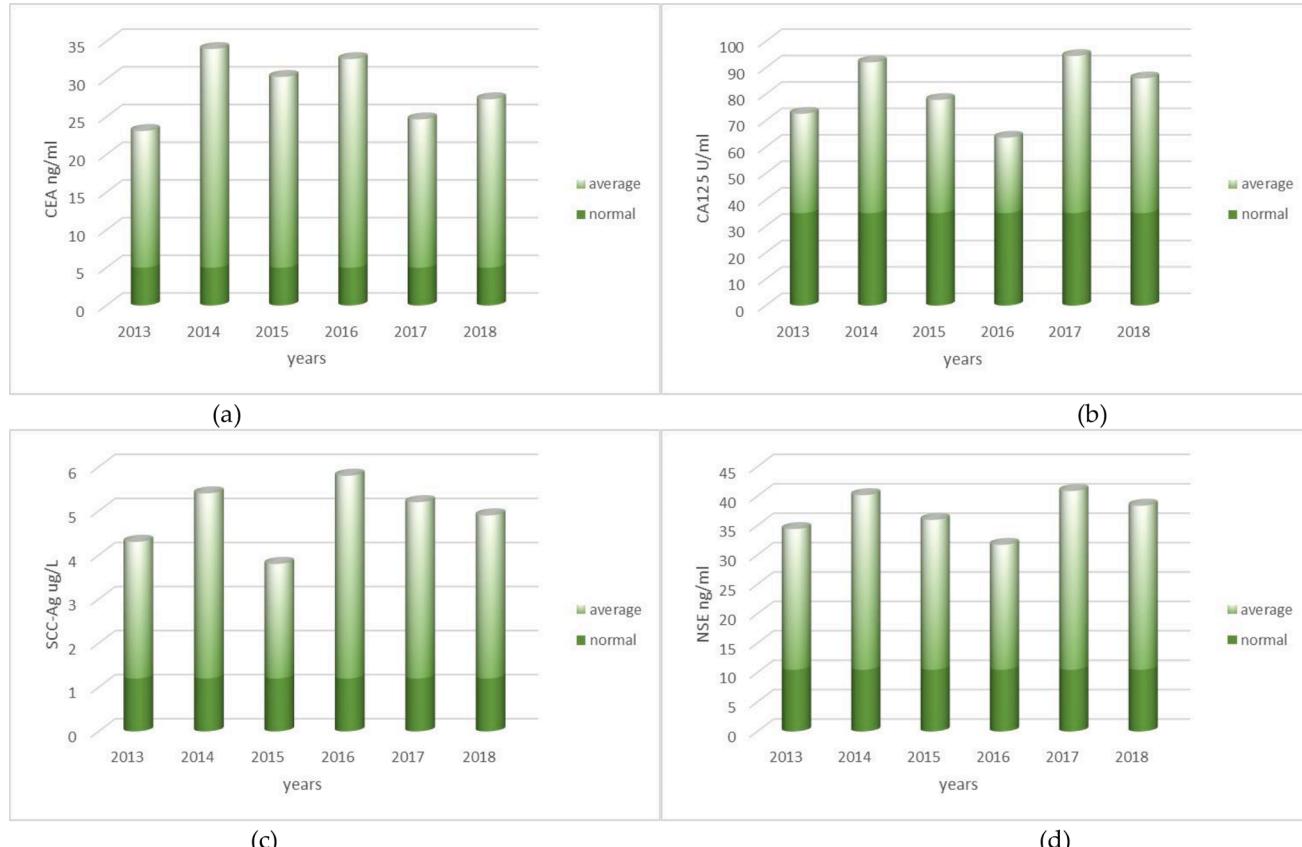


Fig. 10. (a) Patients CEA average performance in recent 5 years. (b) Patients CA125 average performance in recent 5 years. (c) Patients SCC-AG average performance in recent 5 years. (d) Patients NSE average performance in recent 5 years.

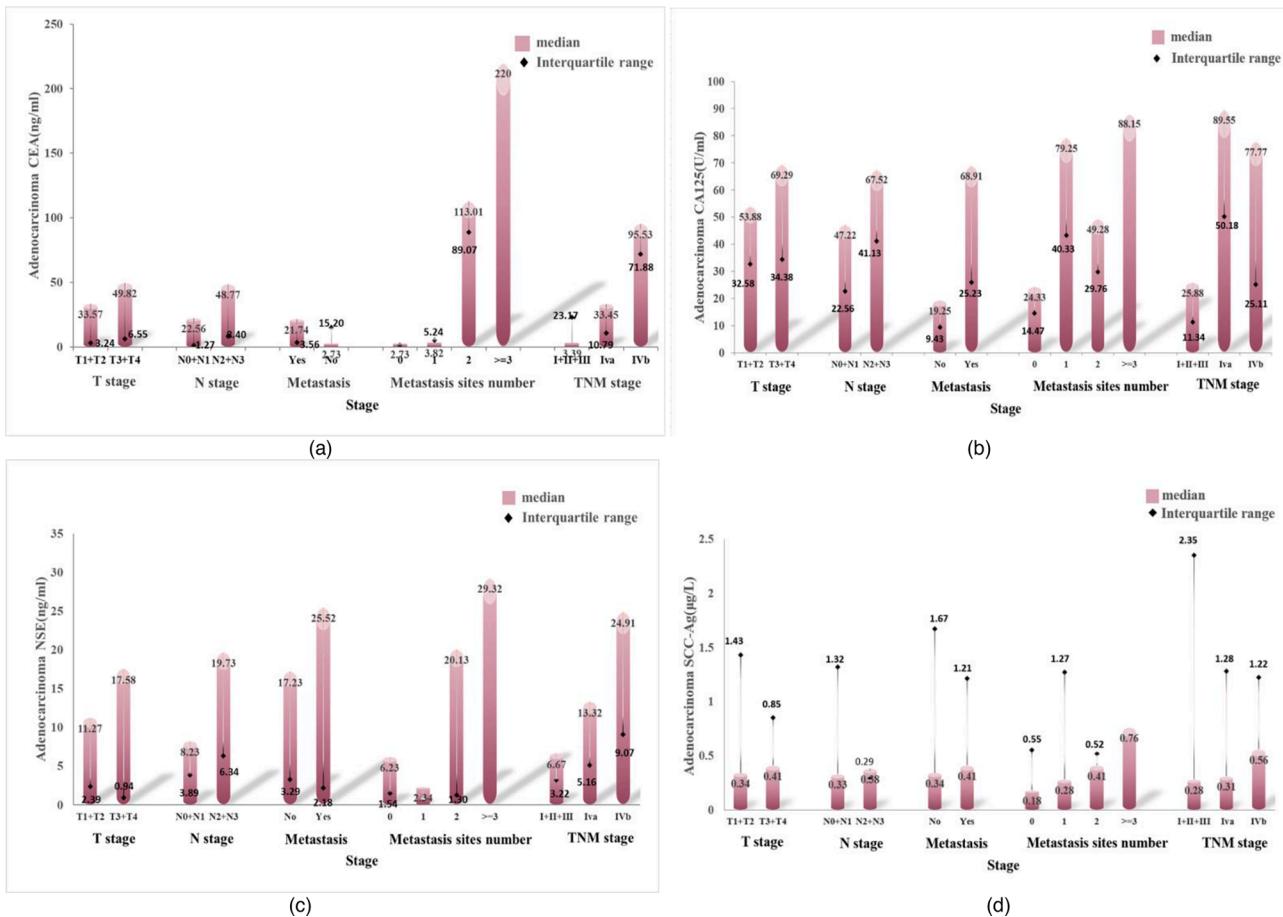


Fig. 11. The changes in tumor marker levels in cancer stages in patients with adenocarcinoma (a) The changes in tumor marker CEA levels in cancer stages. (b) The changes in tumor marker CA125 levels in cancer stages. (c) The changes in tumor marker NSE levels in cancer stages. (d) The changes in tumor marker SCC-AG levels in cancer stages.

for patients and provide doctors with more accurate services.

Fig. 13a-b illustrates the changes in sampling indicators for patients with adenocarcinoma and squamous cell carcinoma during third-line treatment. For patients with adenocarcinoma, through the above analysis process, patients with adenocarcinoma are more sensitive to CEA. Through the change of CEA and the efficacy evaluation value intuitively presented by the patient's treatment situation, the system assists the doctor's medication decision-making performance in selecting medication recommendations at different stages. In the figure, each node represents the response of the drug's efficacy during this medication cycle. It uses an evaluation value to reflect the medication's efficacy. When CEA rises, it can be considered that the condition is repetitive, and the drug may be resistant. Therefore, we reselected medications that were tailored to the patient's current condition. Similarly, for patients with squamous cell carcinoma, according to the above analysis, patients with squamous cell carcinoma have a higher sensitivity to SCC-Ag.

Similarly, the treatment of patients uses the changes in SCC-Ag and the evaluation of efficacy to reflect after medication. In the figure, it can be seen that at the beginning, the node fluctuates greatly, and the evaluation value is unstable and low. It can be considered that the patient has no apparent response to the medication at the beginning. After the system adjustment and reselection of the patient's adaptive medication, in the next medication cycle, the detection index of the market began to decline, and the evaluation value also increased. When the condition is repeated, it can be seen that second-line treatment and back-line treatment schemes have a more stable effect. A wide range of medications comes with a wide range of options. Choosing more suitable medications for patients can make each stage of the system recommended by the system

have a good improvement effect, helping doctors provide patients with a full range of life cycle treatment services. At the same time, it also helps patients understand their own situation in time, and promotes the early diagnosis of NSCLC.

Fig. 14 shows the accuracy of the auxiliary medication decision system. According to the medication records of patients with NSCLC, it can calculate the accuracy of doctors' decision-making and the accuracy of system prediction. It can be seen from the figure that the doctor's decision is accurate. In small sample data, the accuracy rate is as high as 99.6%. In the extensive sample data, the accuracy rate can reach 94.8%. Due to the small sample data, the accuracy can only reach between 0.4 and 0.6. This is because the sample size and training data are small, the training data is small, the generalization ability of the model is weak. In large sample data, as training data increases, the model generalization ability increases. The conclusion of the system model is enough to support the doctor's decision and can help the doctor to improve efficiency.

However, the medication diagnosis prediction expert system is only an auxiliary system, and it cannot replace doctors to make final decisions on the disease of NSCLC patients, even if a patient only wants to diagnose the disease through the system. Nevertheless, the doctor can use diagnostic opinions given by the system to assist them in choosing more suitable medications for patients' personalization, to conduct secondary diagnosis, improving work efficiency and reducing clinical training workload. As medical record data grows, prediction accuracy can be better improved.

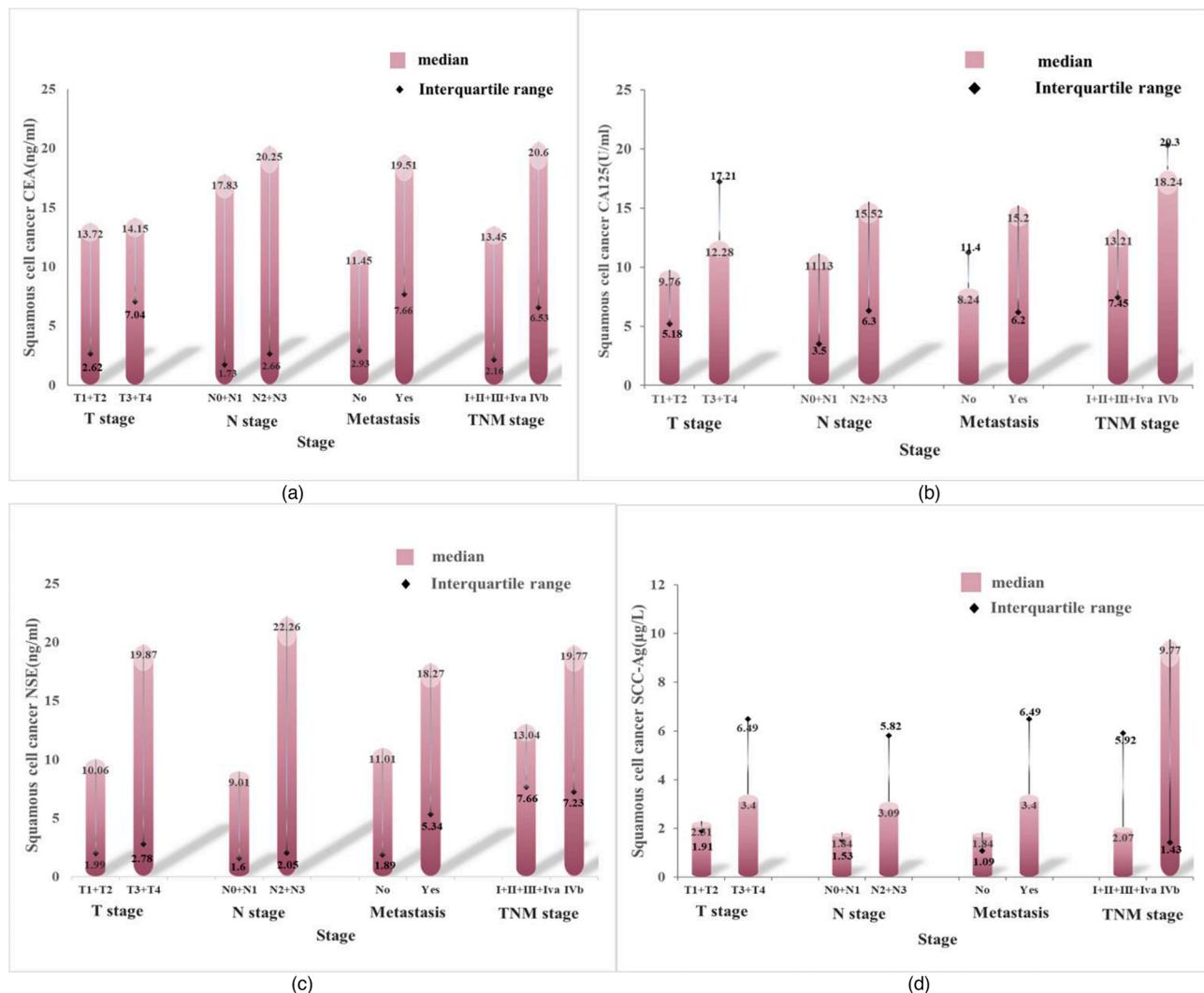


Fig. 12. The changes in tumor marker levels in cancer stages (a) The changes in tumor marker CEA levels in cancer stages. (b) The changes in tumor marker CA125 levels in cancer stages. (c) The changes in tumor marker NSE levels in cancer stages. (d) The changes in tumor marker SCC-AG levels in cancer stages.

Table 8

Data collection from the tumor marker record of the assist doctors analysis medication after five cycles.

Sample set	Before medication				After medication			
	CEA (ng/ml)	SCC-Ag (μg/L)	CA-125 (U/ml)	NSE (ng/ml)	CEA (ng/ml)	SCC-Ag (μg/L)	CA-125 (U/ml)	NSE (ng/ml)
1	36.71	2.74	45.33	13.41	5.13	1.66	16.51	13.23
2	39.51	3.36	38.41	15.68	13.42	1.12	33.22	14.70
3	43.13	2.58	29.57	24.32	17.33	0.65	31.14	18.55
4	53.64	2.65	47.32	21.63	23.3	1.93	41.87	14.36
5	37.33	1.41	49.22	19.57	31.72	0.98	32.48	21.68
6	69.93	3.52	49.36	22.38	29.17	0.17	26.27	16.26
7	63.74	2.61	78.35	25.22	18.32	2.90	43.52	18.33
8	35.92	3.34	49.57	21.31	24.86	0.65	35.85	20.19
9	78.39	4.79	72.11	28.56	29.78	1.34	47.68	18.56
10	46.34	2.47	37.55	17.11	16.36	1.37	34.52	14.78
11	50.72	1.45	61.49	21.36	41.54	1.65	62.15	19.59
12	40.63	3.57	39.52	16.58	12.32	0.92	20.79	9.77
13	62.19	5.24	70.33	29.74	36.23	2.14	42.50	21.68
14	54.50	3.52	78.58	32.44	42.37	1.82	36.92	28.36
15	45.62	3.92	54.38	15.93	21.14	1.37	35.80	14.53
16	63.20	2.34	58.22	17.33	9.12	0.75	29.87	12.91
17	15.14	0.45	17.59	9.57	11.53	0.30	23.15	7.62
18	61.35	2.42	67.42	14.33	13.92	1.26	32.48	15.30
19	50.75	3.30	69.38	15.38	16.15	0.91	28.97	11.58
20	48.36	1.77	49.68	15.54	10.48	1.52	35.51	8.15

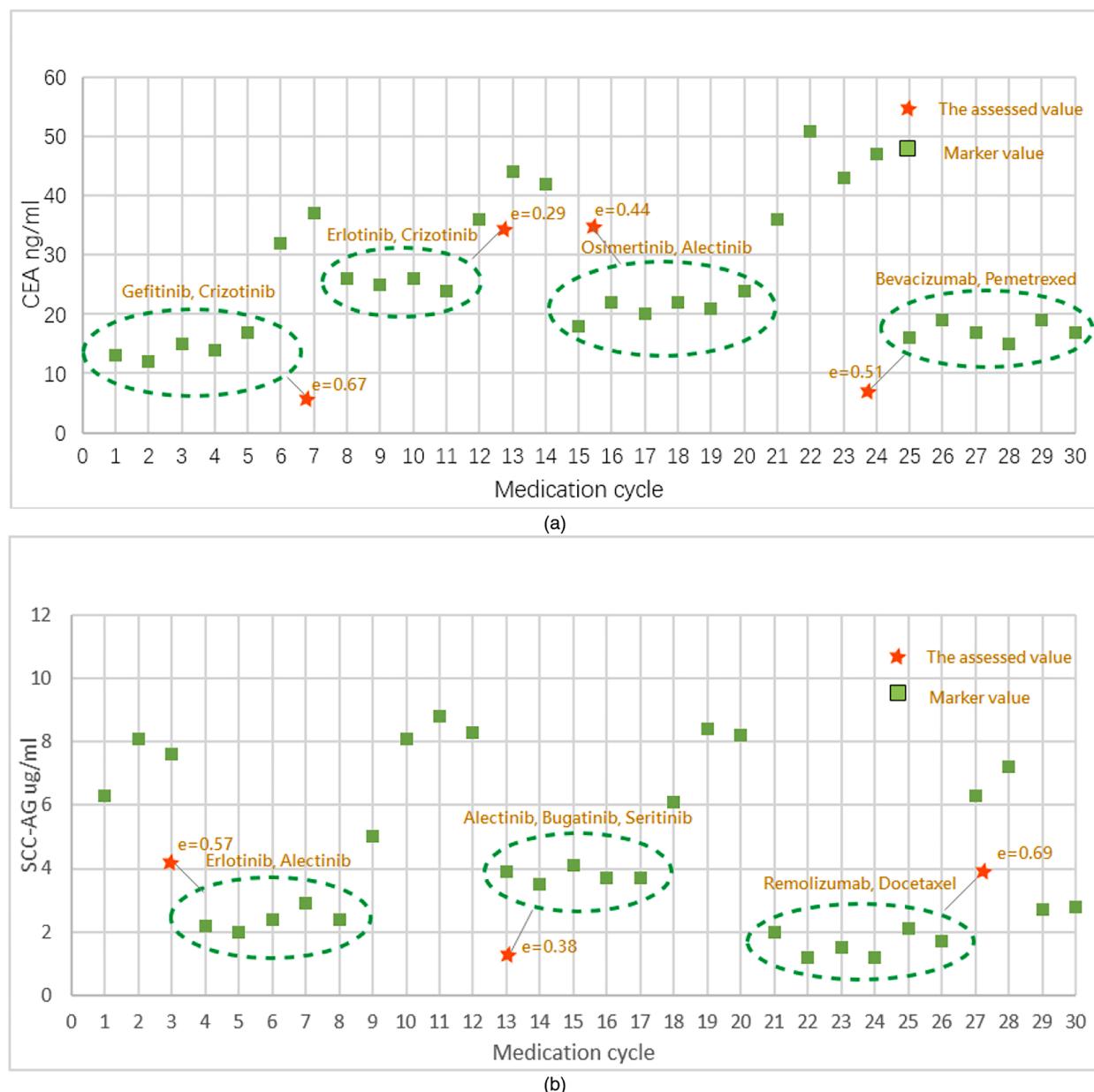


Fig. 13. (a) The changes in sampling indicators and therapeutic effect evaluation for patients with adenocarcinoma during drug treatment. (b) The changes in sampling indicators and therapeutic effect evaluation for patients with squamous cell carcinoma during drug treatment.

5. Conclusions and future work

This study established a method for evaluating and predicting the effects of curative effects based on data analysis and mining and laid the foundation for the establishment of a medical system for auxiliary treatment. Through the feature extraction of patient and medication auxiliary information, combined with the patient's historical medication relationship, the relationship matrix between patient and patient, drug and drug, and patient and drug can be established. Next, the potential vectors of the user and the way of medication are connected, and a multilayer network is used to learn the patient's efficacy evaluation prediction model after medication. Through the analysis of analysis parameters and clinical data, auxiliary information and assessment information can be used to promote the improvement of prediction accuracy. Therefore, the optimal decision-making model is selected so that it can provide fast and accurate analysis and evaluation of medication decisions suitable for patients and assist doctors in making secondary

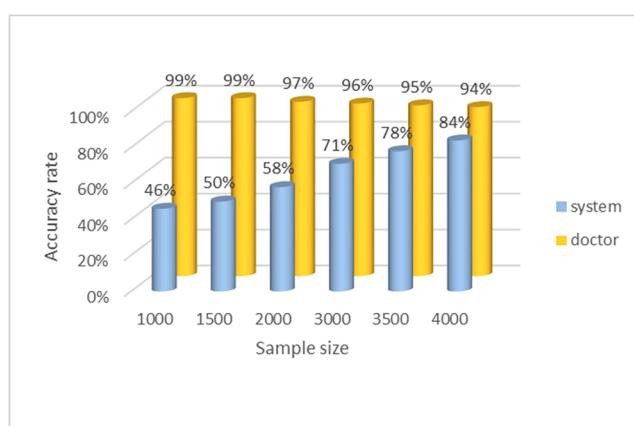


Fig. 14. Accuracy of diagnostic assistance treatment systems

decisions.

In the future, we will strengthen communication with doctors and explore more effective mathematical methods to integrate multi-source data. At the same time, organizing and improving the collected useful information, filtering out more representative information, and eliminating interference information. By introducing medical record information and adding semantic analysis and processing methods, be able to establish more accurate efficacy evaluation models and prediction models. It is also necessary to improve the performance of model online learning.

6. Statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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