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STUDY PROTOCOL

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Quantitative evaluation of the impact of relaxing eligibility criteria on the risk–benefit profile of drugs for lung cancer based on real-world data

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Abstract

Introduction: Restrictive eligibility criteria in cancer drug trials result in low enrollment rates and limited population diversity. Relaxed eligibility criteria (REC) based on solid evidence is becoming necessary for stakeholders worldwide. However, the absence of high-quality, favorable evidence remains a major challenge. This study presents a protocol to quantitatively evaluate the impact of relaxing eligibility criteria in common non-small cell lung cancer (NSCLC) protocols in China, on the risk–benefit profile. This involves a detailed explanation of the rationale, framework, and design of REC.

Methods: To evaluate our REC in NSCLC drug trials, we will first construct a structured, cross-dimensional real-world NSCLC database using deep learning methods. We will then establish randomized virtual cohorts and perform benefit–risk assessment using Monte Carlo simulation and propensity matching. Shapley value will be utilized to quantitatively measure the effect of the change of each eligibility criterion on patient volume, clinical efficacy and safety.

Discussion: This study is one of the few that focuses on the problem of overly stringent eligibility criteria cancer drug clinical trials, providing quantitative evaluation of the effect of relaxing each NSCLC eligibility criterion. This study will not only provide scientific evidence for the rational design of population inclusion in lung cancer clinical trials, but also establish a data governance system, as well as a REC evaluation framework that can be generalized to other cancer studies.

KEYWORDS
cancer, clinical trials, electronic health record (EHR), real-world data (RWD), relaxed eligibility criteria (REC)

INTRODUCTION

Randomized controlled trials (RCTs) are the primary source of high-quality research evidence and recognized as the gold standard for evaluating cancer new drugs, techniques, and approaches. Eligibility criteria for clinical trials, which define the eligible and evaluable populations, are key factors in determining population representativeness and result generalizability.[1] Evidence has showed that eligibility criteria for cancer drug trials are becoming increasingly stringent, and the median number of enrollment conditions for lung cancer trials increased significantly from 21 in the 1990s to 46 in the 2010s.[2] Safety consideration and the need for improving homogeneity of study populations are believed to be part of the reasons for the prevalence of overly stringent eligible criteria in trials.[3] Meanwhile, the longstanding overly stringent eligibility criteria have caused critical problems, including low enrollment rates and lack of population diversity.[4,5]

It has been estimated that up to 20% of cancer trials fail to accrue sufficient participants,[6] with 86% of clinical trials

not meeting patient enrollment deadlines.[7] Growth in trial eligibility criteria has been identified as an independent risk factor associated with accrual failure. Lung cancer is the most common and lethal cancer worldwide, with non-small cell lung cancer (NSCLC) accounting for 85% of cases.[8] Substantial improvement in our understanding of NSCLC biology, acceleration in drug research and development (R&D), as well as significant survival improvement, have been achieved in the past decade.[9] However, it is suggested that less than 30% of advanced NSCLC patients are eligible for phase III drug trials, and the actual efficacy in 70% of ineligible patients is unknown.[10,11] More importantly, a generalizability issue has also been found to be widespread due to lack of population diversity, and that less than 30% of trials reported positive generalizability results in a real-world population.[12] Overly stringent eligibility criteria undeniably present a significant scientific and practical barrier, notably impeding the progress of drug R&D and inflating associated costs. Additionally, for patients with advanced tumors, participating in confirmatory trials could be regarded as an alternative of treatment regimen; therefore, irrational setting of eligibility criteria could also cause equity issue.[13]

Therefore, the US Food and Drug Administration (FDA) and the National Cancer Institute (NCI) have clearly pointed out that the current restrictions on eligibility criteria lack scientific basis and should be simplified and relaxed to ensure population diversity in clinical trials.[13] A series of guidelines and consensus have been issued to provide recommendations regarding appropriate eligibility criteria for clinical trials of cancer drugs or biological products since 2020.[14] Pharmaceutical enterprises are encouraged to be proactive in increasing the enrollment of underrepresented populations when evidence supports such inclusivity.[3] However, the advancement of REC is considerably impeded because the development of the above-mentioned guidelines and consensus relies primarily on expert opinions and lacks high-quality evidence due to the absence of superior and evaluable real-world data. Limited evidence is mainly based on data from a single-source electronic medical record system with limited sample size,[15,16] apart from one study published in 2021 which was conducted in a commercial database from the United States.[17]

China has the largest number of lung cancer patients, and the second largest number of related drug trials with the highest growth rate.[8,18] However, the setting of eligibility criteria in cancer drug trials in China has been found to be stricter than trials abroad in our study of age restriction.[19] Conducting sophisticated research and guiding the rational optimization of NSCLC drug trial eligibility criteria based on real-world patients in China is of considerable clinical significance and value. The remainder of the protocol details the primary aim, overall framework, and key design of the REC evaluation study concerning the risk–benefit profile of common regimens for NSCLC based on the integrated cross-dimensional RWD from China to be described in detail. Overall, the primary goals of the study include:

- Constructing the largest, integrated, cross-dimensional structured database for advanced NSCLC in China, thereby laying the foundation for the subsequent discovery of eligible patients and the conducting of real-world evaluations.
- Quantitatively assessing the impact of relaxing each eligibility criterion on the risk–benefit profile of treatment regimens for NSCLC in China, thus providing a scientific foundation for rational adjustments to population design in related trials.
- Establishing a comprehensive evaluation framework to adjust eligibility criteria in cancer drug trials and establish an all-in-one data governance system in China.

METHODS

Overall framework

This study is a quantitative evaluation of REC on the risk–benefit profile for drugs for NSCLC by combining artificial intelligence (AI) with RWD (Figure 1). An integrated cross-dimensional real-world dataset of NSCLC will first be extracted from the National Cancer Center (NCC) Tumor Information Database in China using deep learning methods. Thousands of randomized virtual cohorts for benefit–risk assessment will be created from the dataset by Monte Carlo simulations with combinations of eligibility criteria identified in NSCLC drug clinical trial protocols. Shapley values will be calculated to quantitatively assess the independent contribution by each eligibility criterion, for the purpose of succeeding evaluation over clinical efficacy, patient volume and safety, leading to REC recommendations. This study has been registered at ClinicalTrial.gov (ID:NCT06314542) and approved by the Ethics Committee of the Chinese Academy of Medical Sciences (ID: 23/483-4226).

Clinical trial protocols and eligibility criteria

Patients diagnosed with primary NSCLC in stage IIIb–IV will be the study population. A systematic selection of trials on NSCLC was carried out using the following filters: (1) randomized phase III trials, (2) treatments involving only drugs or biologicals, (3) the drugs selected in each arm were recommended for NSCLC in China, (4) at least 250 patients in each arm were found in an established dataset who match the description of the patients in the trials and (5) trial protocols were available. All the eligibility rules were directly extracted from the original trial protocols rather than from ClinicalTrials.gov, to ensure the completeness of the trial criteria. Then the programmatic coding of the rules was conducted by a group of experienced oncology data scientists and trial specialists.

In summary, involved criteria items mainly covers the following dimensions: vital signs, sociodemographic characteristics, disease history, disease diagnosis, biomarkers, laboratory tests and treatment course. In detail, the following items may be

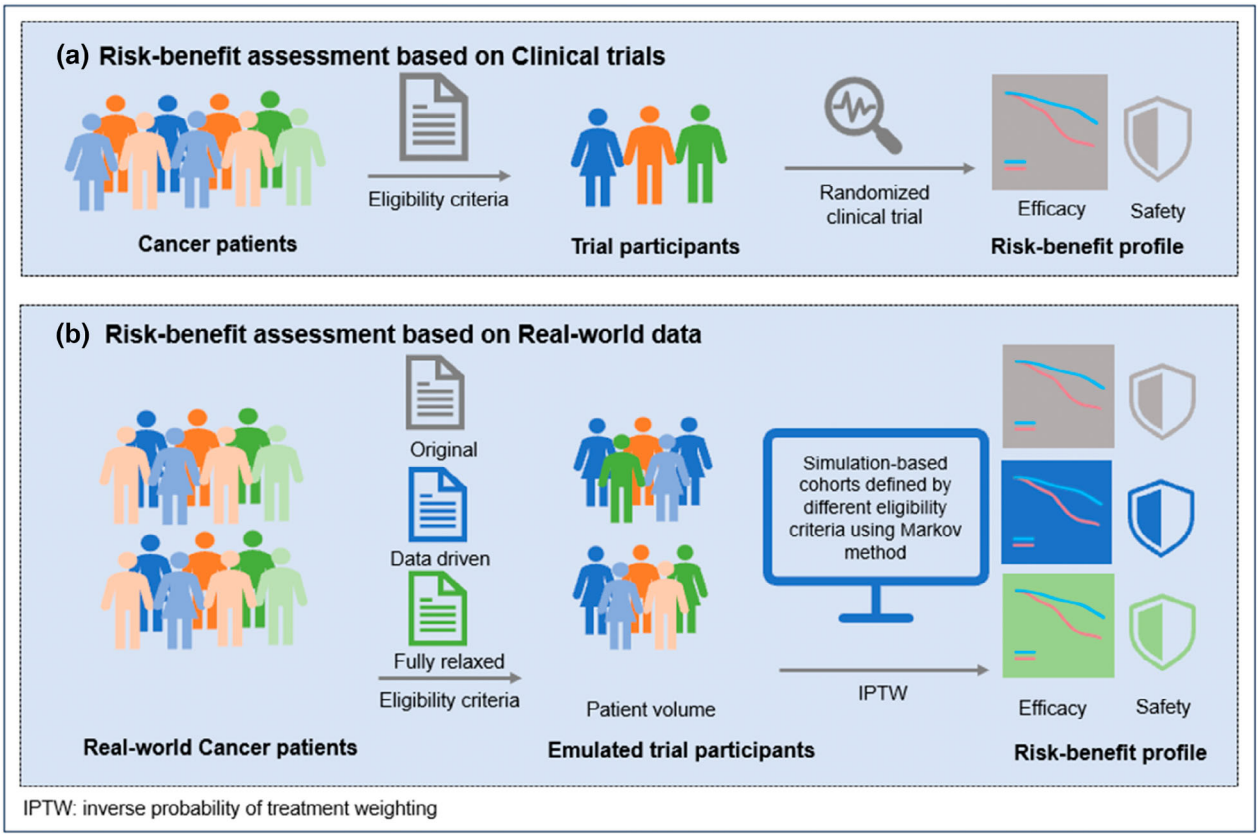

FIGURE 1 Framework for quantitative evaluation of the impact of relaxing eligibility criteria on the benefit–risk profile of trial protocols on drugs.

involved. (1) Vital signs: ECOG score, blood pressure, minimum expected survival, and so on. (2) Sociodemographic characteristics: sex, age, nationality, education and economics. (3) History of disease: history of allergies, mental disorders, substance abuse, alcohol abuse; have had or are currently suffering from a disease of concern, such as active pneumonia, hepatitis and so on. (4) Disease diagnosis: cancer type, clinical stage, pathological type tissue, metastasis of vital organs. (5) Biomarkers: ALK translocation, *EGFR* mutation, *KRAS* mutation, PD-1 expression and so on. (6) Laboratory tests: Liver function (ALT, AST, ALP, albumin, bilirubin, and so on), bone marrow function (hemoglobin, lymphocyte, neutrophil, platelet, white blood cell, and so on), kidney function (serum creatinine, urine protein, routine urine quantitation), coagulation function (PT, APTT, INR), virus test (HIV, HBV, HCV), QTC interval. (7) Treatment course: previous medication history, such as ALK inhibitors, CYP3A4 inhibitors, EGFR/ALK inhibitors, PD1/PD-L1, chemotherapy and corresponding outcome and so on.

Real-world dataset

Relevant RWD of study population was obtained from the National Cancer Center (NCC) Tumor Information Database in China, which integrates health data from nationwide hospitals under the guidance issued by the National Health Commission of the People's Republic of China in 2018.[20] As of the end of 2023, the platform has collected over 400 terabytes of data of more than 15 million cancer patients from over 1400 cancer hospitals and general hospitals in China.[21] We collected all the real-world data of patients with at least one medical visit to 54 hospitals (selected based on data integrity) within the study period, that is, January 1, 2013, to December 31, 2022 (Appendix 1).

Patients in the dataset are considered to be part of the real-world cohort if (1) diagnosed with NSCLC according to the tenth revision of the international classification of diseases (ICD-10) code; (2) diagnosed with stage IIIB, IIIC, IV NSCLC between January 1, 2013, and December 31, 2022 and (3) they had at least two documented clinical visits on or after January 1, 2013. A total of 230 881 patients diagnosed with advanced NSCLC were initially identified in the database. The median number of clinical visits and follow-up time was three and 288 days, respectively. The majority of patients in the database originate from tertiary hospitals, with 53 387 from general hospitals and 177 494 from oncology settings. Relative proportions may vary depending on the study cohort defined by protocol criteria. Data are deidentified and centrally managed to protect patient confidentiality. A unique web server access portal controlled by a firewall was specially developed to ensure data security.

Electronic health records (EHRs) of both inpatient and outpatient from hospitals involved are extracted from Electronic Medical Records (EMRs), Hospital Information System

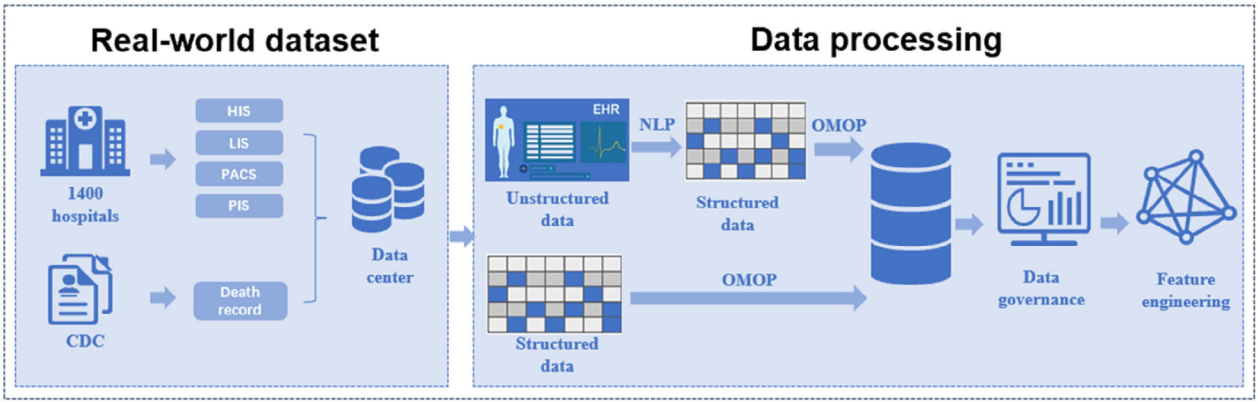

FIGURE 2 Real-world data processing flow.

(HIS), Laboratory Information Management System (LIS), Picture Archiving and Communication System (PACS) and Pathology Information System (PIS). The follow-up of each individual mainly relies on subsequent visit. To ensure the data completeness of patients' death outcomes, we retrieve the survival status and causes of death from the China Centers for Disease Control and Prevention (CDC), the official cause-of-death surveillance database, by matching patients' government IDs, or other identifiable information if government IDs are not available.[22] For lung cancer patients, the matching rate is expected to be as high as 50%[22] (Figure 2).

Data processing and quality assurance

All relevant medical information, both structured and unstructured data, are extracted and integrated for completeness. Structured data, such as laboratory test results, are harmonized across different EHRs and mapped to common terminologies, whereas unstructured data, such as EMR and biomarker reports, are processed and structured by natural language processing (such as named entity identification, relationship extraction, entity linking, information extraction, pattern mining). All structured data are then transformed and standardized by OMOP Common Data Model. International terminology standards, such as SNOMED, ICD, RxNorm and LOINC, will be applied to standardize medical information for further analysis.

Data quality control criteria are predefined for key variables for consistency and accuracy. Tools was developed and deployed for quality control of petabyte-level data, meetings the requirements of clinical data quality standard. Multi-source data validation, data quality model construction and implementation, as well as data quality control were conducted by ETL tools and qualities quality control tools. Data quality is mainly evaluated by data filling rate, recall rate and data accuracy.

Patient Finder and trial emulation

The first step will be developing Patient Finder, an automated workflow which identifies individuals in the real-world dataset who meet the eligibility criteria (encoded into rules) as originally published in the trial protocol. Patients are not filtered by the criteria of which their data are missing. Selected patients are then assigned to the treatment groups that are consistent with their treatment records in the database. To emulate the randomization and blind assignment in the trials, inverse probability of treatment weighting (IPTW) will be applied to adjust for potential confounding factors. A logistic regression model will be used to estimate the propensity score. In this study, the covariates include age, gender, composite race or ethnicity, histology, smoking status, staging, ECOG and biomarker status. Propensity score adjustment effectively balances covariates across the simulated treatment and control groups. The standardized mean difference (SMD) for every patient covariate between the treatment and control cohorts generated will be plotted to test if the cohorts are balanced.

The next step will be conducting survival analysis and safety comparison for all emulated trials, with hazard ratio of the overall survival, and odds ratio (OR) of serious adverse events (SAE) rate the as the outcome. Kaplan–Meier survival curves for each arm will be generated, and hazard ratios (HRs) will be estimated by Cox proportional hazard model. Odds ratios with 95% confidence intervals of SAE rate will be calculated. Patient volume and the number of eligible patients under each setting will also be calculated. Hypothesis testing with p-value less than 0.05 will be considered statistically significant.

Shapley value and REC recommendation

Due to the numerous and often correlated criteria, it is critical to quantitatively measure the contribution of each individual criterion. To this end, we will utilize the Shapley

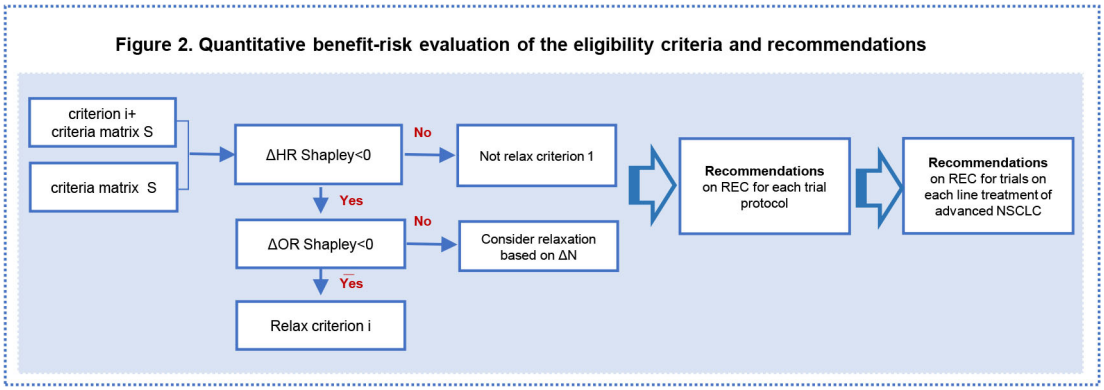

FIGURE 3 Quantitative benefit–risk evaluation of the eligibility criteria and recommendations.

value, a method originated from game theory, which measures the average marginal contribution of a feature value over all possible coalitions,[23] or specifically, the average of the marginal effect of each enrollment criterion on the treatment effect of the treatment regimen. The effect of relaxing eligibility criteria i on the clinical efficacy and on the safety of the trial regimen are denoted respectively by $\Delta HR_{Shapley,i}$ and $\Delta OR_{Shapley,i}$. For example, a positive $\Delta HR_{Shapley,i}$ indicates relaxing criterion i to increases the hazard ratio on average, and vice versa.

Our decision-making framework will recommend REC based on a comprehensive assessment of efficacy, safety, and patient volume on a per-trial basis (Figure 3). For each eligibility criterion i, the effect of relaxing the criterion on the clinical efficacy is first measured as $\Delta HR_{Shapley,i}$. Whenever $\Delta HR_{Shapley,i}$ becomes positive, indicating a decreased clinical efficacy after relaxing the criterion, the criterion will not be relaxed. In the cases where $\Delta HR_{Shapley,i}$ being negative, the effect on safety will be measured as $\Delta OR_{Shapley,i}$. If $\Delta OR_{Shapley,i}$ is positive, indicating an improvement in clinical efficacy, but a deterioration in safety, experts will be consulted for the overall risk–benefit profile jointly with the evidence of patient volume change. Otherwise, criterion will be relaxed, due to the benefit of better clinical efficacy as well as safety after the relaxation. The recommendation of NSCLC drug trials for each line of treatment will be made by averaging the recommendations on all trials in the same line.

As the median number of NSCLC eligibility criteria is estimated to be 46,[2] leading to as many as 2^{46} (over 70 trillion) combinations of possible combinations, it is computationally infeasible to exhaustively simulate and evaluate the results of virtual cohorts under all these conditions. Hence, Monte Carlo simulation, a computational method based on random sampling, will be conducted to evaluate changes in clinical efficacy, safety, and patient volume under relaxed, restricted, and data-driven scenarios for each criterion.[24] The simulation will be terminated when the Shapley estimate converges, with the standard error of the Monte Carlo mean below 0.001.

DISCUSSION

For confirmatory trials, the top priority is internal validity, which ensures the credibility of the conclusions of a causal relationship between treatment regimen and clinical outcome with moderate sample size. However, pursuing merely better internal validity can sacrifice external validity, which is the extent to which the findings apply.[25] This is exactly the dilemma we are attempting to break out of, that overly restrictive eligibility criteria for clinical trials harm the generalizability of the trial results to their target real-world patient populations. The results in the study we propose will not only provide scientific evidence for relaxing eligibility criteria of clinical trials on lung cancer, thus improving the generalizability of future trials and reducing treatment inequity, but also provide feasible framework of REC evaluation powered by artificial intelligence (AI) backed by great amounts of RWD.

This proposal has several limitations. First, relying on RWD from a regional database may limit the generalizability of our findings to other regions. Second, the inconsistency and incompleteness resides in our data sources could result in inaccuracy of our findings. While processing unstructured data is an additional important direction of our study, due to the challenges in natural language processing and the integrity of EHRs, the safety assessment in our study will be limited to the SAE rate, excluding PFS from the efficacy assessment. Nevertheless, our general framework holds the potential to derive insights from RWD which may shed new lights on clinical trial design and the development of scientific, efficient and unbiased enrollment strategies.

Strengths and limitations of study

This study will present the rationale, framework and design of REC evaluation on the risk–benefit profile of common regimens for NSCLC based on the integrated cross-dimensional database platform of the National Cancer Center (NCC) Tumor Information Database in China.

This study will establish a randomized virtual cohort using the propensity matching method to minimize population heterogeneity between trial and control arms, and quantitatively assess the independent contribution of each individual eligibility criterion using Monte Carlo simulation and Shapley values.

It will contribute to the REC evaluation framework, the data governance system of real-world data (RWD) from the NCC Tumor Information Database and provide scientific evidence for rational adjustments to lung cancer drug trial design.

The limitation of the study is that it only includes one tumor type of lung cancer.

AUTHOR CONTRIBUTIONS

Huiyao Huang and Ning Li contributed to framework planning and draft writing. Shuopeng Jia, Xin Wang, Huilei Miao, Hong Fang, Hanqing He, Dawei Wu and Yu Tang participated in the discussion of framework planning, data collection and quality control. All authors reviewed and revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors disclose no competing interests.

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APPENDIX 1: List of 54 hospitals covered by real-world data from January 1, 2013 to December 31, 2022

Name of hospital	Province	Region	Hospital type
Yunnan Provincial Tumor Hospital	Yunnan	Southwest	Oncology Specialist Hospital
Yinchuan First People's Hospital	Ningxia	Northwest	General Hospital
Chaoyang Sanhuan Tumor Hospital in Beijing	Beijing	North China	Oncology Specialist Hospital
Tianjin Tumor Hospital	Tianjin	North China	Oncology Specialist Hospital
Shanxi Tumor Hospital	Shanxi	North China	Oncology Specialist Hospital
Huaxing Tumor Hospital in Chaoyang District, Beijing	Beijing	North China	Oncology Specialist Hospital
Xiangyang Central Hospital	Hubei	South Central	General Hospital
The First Affiliated Hospital of Xinxiang Medical University	Henan	South Central	General Hospital
The Second People's Hospital of Foshan City	Guangdong	South Central	General Hospital
Hunan Tumor Hospital	Hunan	South Central	Oncology Specialist Hospital
Xinxiang Central Hospital	Henan	South Central	General Hospital
The Second People's Hospital of Yichang City	Hubei	South Central	General Hospital
Hubei Tumor Hospital	Hubei	South Central	Oncology Specialist Hospital
Huizhou First People's Hospital	Guangdong	South Central	General Hospital
Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	Hubei	South Central	General Hospital
Hainan Provincial People's Hospital	Hainan	South Central	General Hospital
The Second Affiliated Hospital of Guilin Medical College	Guangxi	South Central	General Hospital
Henan Tumor Hospital	Henan	South Central	Oncology Specialist Hospital
Hainan Tumor Hospital	Hainan	South Central	Oncology Specialist Hospital
Guangxi Medical University Affiliated Tumor Hospital	Guangxi	South Central	Oncology Specialist Hospital
The Second Affiliated Hospital of Dalian Medical University	Liaoning	Northeast	General Hospital
Liaoning Tumor Hospital	Liaoning	Northeast	Oncology Specialist Hospital
Southeast University Affiliated Zhongda Hospital	Jiangsu	East China	General Hospital
Anhui Medical University Affiliated Fuyang Hospital	Anhui	East China	General Hospital
Anhui Tumor Hospital	Anhui	East China	Oncology Specialist Hospital
Linyi People's Hospital	Shandong	East China	General Hospital
Fujian Tumor Hospital	Fujian	East China	Oncology Specialist Hospital
Xuzhou Tumor Hospital	Jiangsu	East China	Oncology Specialist Hospital
Jinan Central Hospital	Shandong	East China	General Hospital
Jiangxi Provincial People's Hospital	Jiangxi	East China	General Hospital
Anqing Municipal Hospital	Anhui	East China	General Hospital
The Fourth Affiliated Hospital of Zhejiang University School of Medicine	Zhejiang	East China	General Hospital
Jiangxi Tumor Hospital	Jiangxi	East China	Oncology Specialist Hospital
Zhejiang Provincial People's Hospital	Zhejiang	East China	General Hospital
Weifang Medical University Affiliated Hospital	Shandong	East China	General Hospital
Anhui Provincial Hospital	Anhui	East China	General Hospital
Zhejiang Hospital	Zhejiang	East China	General Hospital
Qilu Hospital of Shandong University (Qingdao)	Shandong	East China	General Hospital
The First Affiliated Hospital of Chongqing Medical University	Chongqing	Southwest	General Hospital

(Continues)

Name of hospital	Province	Region	Hospital type
Sichuan Tumor Hospital	Sichuan	Southwest	Oncology Specialist Hospital
Chongqing Tumor Hospital	Chongqing	Southwest	Oncology Specialist Hospital
Qijiang District People's Hospital of Chongqing City	Chongqing	Southwest	General Hospital
Qujing First People's Hospital	Yunnan	Southwest	General Hospital
Three Gorges Central Hospital of Chongqing City	Chongqing	Southwest	General Hospital
North Sichuan Medical College Affiliated Hospital	Sichuan	Southwest	General Hospital
Gansu Tumor Hospital	Gansu	Southwest	Oncology Specialist Hospital
Gansu Maternal and Child Health Care Hospital	Gansu	Southwest	General Hospital
Xinjiang Medical University Affiliated Tumor Hospital	Xinjiang	Southwest	Oncology Specialist Hospital
Shaanxi Tumor Hospital	Shaanxi	Southwest	Oncology Specialist Hospital
The First Affiliated Hospital of Xi'an Jiaotong University	Shaanxi	Southwest	General Hospital
Beijing Tumor Hospital	Beijing	North China	Oncology Specialist Hospital
Chinese Academy of Medical Sciences Tumor Hospital	Beijing	North China	Oncology Specialist Hospital
Inner Mongolia Autonomous Region Tumor Hospital	Inner Mongolia	North China	Oncology Specialist Hospital
Xingtai People's Hospital	Hebei	North China	General Hospital