TMR
DOI: 10.53388/ghr2020-06-014

REVIEW

Real world studies and their impact on the prevention and treatment of liver disease with traditional Chinese medicine

Jing-Hao Zhang, Chao Zheng, Xiao-Jun Zhu, Xin Zhang, Zhen-Hua Zhou, Man Li, Yue-Qiu Gao*, Xue-Hua Sun*

Abstract
With the development of clinical practice and transformation of the medical model, traditional Chinese medicine (TCM) research has attracted considerable attention. Randomized controlled trials of traditional Chinese medicine are unable to meet the need of clinical research, while the real-world studies are more in accordance with the characteristics of traditional Chinese medicine research. In this paper, the concept and characteristics of real-world studies, characteristics of traditional Chinese medicine research, and the advantages of and the application of real-world studies in the clinical research of traditional Chinese medicine, were reviewed to provide new ideas for TCM research.
Keyword: Real-world study, Traditional Chinese medicine, Clinical research

Background

Traditional Chinese medicine (TCM) is a valuable asset of the Chinese people and has received more and more recognition by the international community. This has provided a wide space for the development of traditional Chinese medicine. Evidence-based methods are used widely in clinical studies regarding traditional medicine. However, due to methodological limitations, the higher level of evidence from randomized controlled trials (RCTs) lack actual application value. Real-world studies (RWS) are comprehensive studies on the efficacy and safety of some intervention measures (such as diagnosis, treatment, prognosis) in a real-world population with little or no bias. Such studies can provide sufficient evidentiary support for traditional Chinese medicine clinical studies. Hence, RWS have broad clinical prospects in traditional Chinese medicine clinical studies.

1. Concept of real-world studies

RWS originate from efficacy clinical trials and refer to the non-randomized selection of intervention measures according to patients' conditions based on a larger sample (covering subjects with higher representativeness) and the implementation of long-term evaluation of significant outcome markers to further assess the external efficacy and safety of the intervention measure [1]. RWS cover a broad range of fields and can be used for studies regarding diagnosis, prognosis, etiology, etc., in addition to interventional studies.

2. Characteristics of real-world studies

RWS are patient-centric clinical studies that are conducted during real-world medical treatment to evaluate the efficacy and adverse reactions of intervention measures in broad real-world medical processes from the patient's perspective. The core concept of RWS is to maximally restore intervention measures to real clinical practice conditions [2]. Compared with other study methods, RWS have unique characteristics:

(i) Study objective: RWS are effectiveness trials that are more concerned with the actual medication statuses of patients. Interventions are carried out on patients in real-world environments to discover chronic and potential reactions and rare adverse events of the drug, discover new indications for the drug while validating general efficacy, evaluating the economics of the drug in routine clinical practice, and measuring the benefits of the drug or intervention measure among patients in a real-world environment [3].

(ii) Study population and sample size: RWS usually require a large sample size to comprehensively cover the population. The study environment should reflect basic medical measures performed in the broader

Department of Hepatopathy, Shuguang Hospital, Affiliated to Shanghai University of Traditional Chinese Medicine; Laboratory of Cellular Immunity, Shanghai Key Laboratory of Traditional Chinese Medicine, Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China.
***Corresponding to:** Yue-Qiu Gao. Department of Hepatopathy, Shuguang Hospital, Affiliated to Shanghai University of Traditional Chinese Medicine, NO.185 Puan Road, Huangpu District, Shanghai 200021, China. E-mail: gaoyueqiu@hotmail.com. Xue-Hua Sun. Department of Hepatopathy, Shuguang Hospital, Affiliated to Shanghai University of Traditional Chinese Medicine, NO.185 Puan Road, Huangpu District, Shanghai 200021, China. E-mail: susan_sxh@sina.com.

DOI: 10.53388/ghr2020-06-014

population [4]. However, there is no consistent consensus on the sample size required for RWS. In existing RWS, a large sample size (n > 500) was selected for the vast majority of studies, to ensure good representation [5].

(iii) Inclusion and exclusion criteria: RWS have broader inclusion criteria and fewer exclusion criteria. The enrollment criteria for subjects must ensure that there is consistency between the study population and the population from which experimental results are being generalized from [4] to reduce selection bias.

(iv) Randomization and control (intervention measure): In RWS, drugs or other intervention measures are selected according to the patient's actual condition and medication wishes, which is the biggest difference in experimental design between RWS and RCTs [6]. At the same time, in RWS, investigators do not restrict concomitant medications and medication conditions and treatment are carried out according to actual needs. Observation and recording are carried out to restore the most realistic clinical practice. Therefore, RWS can be considered as non-randomized, open-label, and non-placebo-controlled studies [7].

(v) Study duration and observation markers: Generally, RWS have a longer clinical observation and follow-up duration to observe for broad clinically significant markers, such as quality of life and mortality rate and not specific symptoms or characteristics [8]. This reflects the long-term effects and adverse reactions of new drugs and therapeutic measures to provide a comprehensive and better evaluation of health outcomes.

(vi) Data collection and analysis: RWS usually require the investigator to collect more comprehensive and more data. In addition to basic demographic characteristics, medical history, time of disease onset, clinical presentation, treatment, and hospital outcomes, some studies also require the use of case report forms to collect discharge follow-up data to obtain long-term outcome information [9]. With regard to statistical analysis, existing statistical methods should be flexibly used according to the type of data and actual trial requirements.

(vii) Quality control: The open-label characteristic of RWS will lead to significant observer bias. Hence, multivariate analysis, propensity score matching, and other statistical methods are usually used in RWS to control bias. However, the aforementioned methods can only adjust known confounding factors and it is difficult to control unknown or non-observed confounding factors [10]. Therefore, strict control measures should be used for data collection, management, and analysis, and a standard should be established to ensure study quality.

(viii) Ethical problems: RWS evaluate the final results of medical interventions and actual operations in a real-world medical environment. There are fewer restrictions on study duration, sample size, and other factors with regards to ethical principles. However, relevant regulations on medical ethics will still be complied with [1,6].

3. Characteristics of clinical studies in traditional Chinese medicine

Clinical efficacy is the basis for the survival and development of traditional Chinese medicine. In the past, traditional Chinese medicine only stopped at the conventional clinical study stage of diagnosis and treatment of individual patients and population clinical effects were mainly verified and transmitted through long-term clinical practice. Since the 1960s, traditional Chinese medicine and Western medicine both integrated the theories and methods of clinical epidemiology in population clinical studies [11]. However, the use of RWS in traditional Chinese medicine clinical studies is not as smooth as in western clinical studies. This is due to the characteristics of traditional Chinese medicine clinical studies: Firstly, complexity. Traditional Chinese medicine focuses on a holistic view, harmony between man and heaven, and disease differentiation and treatment. Traditional Chinese medicine treatment varies according to person, time, and place. Traditional Chinese medicine has characteristics such as complex intervention and personalized treatment, which manifest from the start to the end of traditional Chinese medicine clinical activities. The intervention is based on disease differentiation and treatment and includes acupuncture, massage, and music, psychological, and other auxiliary treatment. In addition, the treatment is adjusted according to dynamic evolution of the disease. The efficacy of traditional Chinese medicine is intimately associated with individual responses [12] and is affected by the place of production of medicinal materials, harvesting season, and preparation and storage methods [13]. Secondly, subjectivity. The entire disease differentiation and treatment process is mainly subjective. For example, the four diagnoses are affected by the physician's professionalism and patient perception and expression. Pharmacological treatment is affected by the medication habits and school of thought of the physician. Efficacy evaluation is affected by the patient's psychological factors and wishes. Most outcome markers for evaluating the clinical efficacy of traditional Chinese medicine are qualitative and lack objective evaluation criteria [13,14].

4. Strengths of using RWS in traditional Chinese medicine clinical studies

Due to the aforementioned characteristics of traditional Chinese medicine clinical studies, RCTs cannot fully demonstrate the efficacy advantages of traditional Chinese medicine. RWS provide a new direction in traditional Chinese medicine research, particularly efficacy evaluation for traditional Chinese medicine.

On the one hand, traditional Chinese medicine

emphasizes the "holistic viewpoint" and efficacy evaluation in traditional Chinese medicine focuses more on the overall condition of the patient, including the physical and mental aspects. RWS focus on markers with broad clinical significance, such as the degree of disability and quality of life, which fits perfectly with the "holistic viewpoint" in traditional Chinese medicine. Another characteristic of traditional Chinese medicine is disease differentiation and treatment, which does not advocate specific drugs/prescriptions for specific diseases. Prescriptions that are suitable for the patient are prescribed according to the patient's syndrome based on the clinical experience of the physician in combination with the environment and climate. In RWS, the inclusion and exclusion criteria are usually broad and patients can simultaneously suffer from other diseases, the patient's daily activities and diet may be irregular, and it is difficult to achieve inter-patient homogeneity; however, patients can be used as observation subjects [14]. In addition, blinding is not used in RWS and suitable intervention measures are administered according to the patient's wishes and in combination with the actual medical condition, which matches with disease differentiation and treatment in traditional Chinese medicine [15].

In addition, big data-based RWS are more favorable for the transmission and development of traditional Chinese medicine. For several thousand years, academic ideas and experiences in traditional Chinese medicine have been developed through teacher-student interaction and individual experience and practice. This often results in problems in scientific development and transmission and the subjectivity of the transmission method is often criticized. Big data technology based on data mining can extract previously unknown but potentially useful information and knowledge from a large volume of incomplete, noisy, blurry, and randomized databases. Techniques that are often used in big data can be employed on real-world data obtained in traditional Chinese medicine clinical practice to objectively present the unique ideas and practical experiences of thousands of years of traditional Chinese medicine (traditional Chinese medicine RWS) [16,17]. This will provide opportunities for discovering new patterns and characteristics in traditional Chinese medicine, through promoting innovation in the basic theory of traditional Chinese medicine, clinical diagnosis and treatment theory, and traditional Chinese medicine clinical evaluation methods, thereby promoting the transmission and development of traditional Chinese medicine [18].

5. Application of RWS in traditional Chinese medicine treatment of liver disease

RWS emphasize the use of epidemiological theory and methods to carry out observation studies, cross-sectional studies, or cohort studies, of which registry studies in observation studies are widely used in clinical practice [7]. In registry studies, observation study methods are employed for prospective or retrospective collection of clinical data from past projects or other relevant data for rational statistical analysis to achieve the expected aim of the study. In such studies, a specific characteristic disease, specific subject product, or specific effects/outcomes of specific medical services are evaluated. In registry studies, the investigator must collect data regarding demographic characteristics, patient history, time of onset, clinical presentation, treatment outcomes of registered patients according to the expected objectives, and even obtain specific long-term outcome data [19]. Some researchers pointed out that the real-world traditional Chinese medicine liver disease clinical study is based on a sharing system, with data usage as a core technology, and data collection is an important aspect. Effective organizational management measures are established for long-term health management follow-up work among liver disease patients, to provide condition monitoring and health education to patients, achieve dynamic monitoring, help patients to learn self-management, and improve self-efficacy and quality of life [20]. In recent years, attempts of RWS in traditional Chinese medicine treatment of liver disease were performed in the field of traditional Chinese medicine liver disease to implement real-world based studies on traditional Chinese medicine syndrome, medication patterns, and efficacy evaluation among hepatitis B patients [21-23]; studies on the clinical characteristics, traditional Chinese medicine data mining, and prospective studies among cirrhosis patients [24]; empirical studies on famed traditional Chinese medicine techniques [25], prophylactic regimens, treatment regimens, and efficacy evaluation of traditional Chinese medicine in the prevention and treatment of primary liver cancer [26-28]; real-world-based prospective cohort studies on fatty liver; real-world traditional Chinese medicine clinical studies based on biological sample databases; real-world-based case-control studies; and disease prediction model based on the sharing system [29]. At the same time, emphasis is placed on medical ethics problems in RWS [30]. These studies cover many areas of traditional Chinese medicine liver disease.

Summary

RWS is a research concept that has gradually obtained recognition since its proposal and is gradually used in clinical decision-making. Although confounding factors are present and require further confirmation of causal relationships, sample sizes are very large, costs are relatively high, and study results may not be significant, but RWS ensure the extrapolation of result and provide evidence of the efficacy and safety of routine clinical treatment measures. RWS will greatly promote the

DOI: 10.53388/ghr2020-06-014

development of traditional Chinese medicine. RWS can retain the features of traditional Chinese medicine without losing the scientific nature of traditional Chinese medicine studies at the same time. This will enable investigators to obtain scientific results that match real-world clinical conditions and provide innovative opportunities for the development of traditional Chinese medicine. However, drug-related RWS are still at the exploratory stage and require theoretical and practical attempts at exploration.

References

1. Li M, Shi JP, Yu HH. Relationship between the real world study, randomized controlled trial and single case randomized controlled trial in clinical therapeutic study. Chin J Epid 2012, 33: 342-345. (Chinese)
2. Li JY, Jiang ZH, Gao ZY. Practice of the Real-World Study on the Clinical Research of Traditional Chinese Medicine (TCM). World Sci Technol-Modernization Chin Med Mater Medica 2017, 19: 78-82. (Chinese)
3. Godwin M, Ruhland L,Casson I, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. BMC Med Res Methodol 2003, 3:28.
4. Gartlehner G, Hansen RA, Nissman D, et al. A simple and valid tool distinguished efficacy from effectiveness studies. J Clin Epidemiol 2006, 59: 1040-1048.
5. Gao YB, Wu Y, Zheng JW. Background, conceptions, methodology of the Real-World Study and its application in ophthalmology. Chin J Optometry Ophthalmology Visual Sci 2013, 15: 756-759.
6. Tian F, Xie YM. Real-world study: a potential new approach to effectiveness evaluation of traditional Chinese medicine interventions. J Chin Integr Med 2010, 8: 301-306. (Chinese)
7. Cao Y, Yi QF, Zeng XT. Overview of real world study. Med J The Chin People's Armed Police Forces 2017, 28: 400-403.
8. Kraemer HC. "Rules" of evidence in assessing the efficacy and effectiveness of treatments. Dev Neuropsychol 2003, 24: 705-718.
9. GRACE Investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: a multinational registry of patients hospitalized with acute coronary syndromes. Am Heart J 2001, 141: 190-199.
10. Huang ZS, Luo YT, Liu JL. Real world study methods and practice. J Evidence-based Med 2014, 14: 364-368. (Chinese)
11. Liu BY. Real world Traditional Chinese medicine clinical research. J Tradit Chin Med 2013, 54: 451-455. (Chinese)
12. Cui WF, Wang SH, Wang HL, et al. Method and Practice of Real world Clinical Research of Traditional Chinese Medicine. Methodological Research 2016,19:1586-1597.
13. Wang PY, Liu QX, Qiang HM. Overview of combining traditional Chinese medicine and evidence-based medicine. Henan Tradit Chin Med 2009, 29: 636-637. (Chinese)
14. Fu L, Zhou XP, Li GC. "Real-world Study"(RWS)-New Approach to Traditional Chinese Medicine Scientific Research. J Zhejiang Chin Med Univ 2013, 37: 1127-1129. (Chinese)
15. Xie Q, Jiang LJ, Liu BY, et al. Discussion on the Key Issues and Strategies about Carrying Out the Comparative Effectiveness Research of Chinese Medicine in Real-world. World Chin Med 2014, 9: 28-31. (Chinese)
16. Xu LY, Zhou Q, Yu HX, et al. The Knowledge Discovery of the Prescribing Regularity of Nonalcoholic Fatty Liver Disease Based on Zhang Yunpeng's Experience. World Sci Technol-Modernization Chin Med Mater Medica 2016, 18: 1046-1050. (Chinese)
17. Wu YG, Tan ZH. Research on Compatibility Law of Dementia Treatment Prescriptions and Modified Shuyu Pill based on Data Mining. World Sci Technol-Modernization Chin Med Mater Medica 2016, 18: 446-452. (Chinese)
18. Shao MY, Liu BY, Xie Q, et al. Exploration on Development Status and Trend of Clinical Research Data in Chinese Medicine. World Sci Technol-Modernization Chin Med Mater Medica 2015, 17: 1743-1747. (Chinese)
19. Cao FD. Real-world study and patient registration. Chinese Pharmaceutical Association, Jiangsu Provincial People's Government. 2012 Chinese Pharmaceutical Conference Proceedings of the 12th Chinese Pharmacist Week. Chinese Pharmaceutical Association, Jiangsu Provincial People's Government. (Chinese)
20. Tao JX, Guo MX, Li XD, et al. Exploration and practice of research outpatient on the health management model for chronic hepatitis B. Hebei J Tradit Chin Med 2017, 39: 844-847. (Chinese)
21. Li YR, Wang LX, Xie YM, et al. Study of clinical character and medicinal therapy of viral hepatitis in hospital based on real world. China J Chin Mater Medica 2014, 39: 3448-3453. (Chinese)
22. Wang HP. Study of the effects of Ruangan pills on hepatic function reserve and portal hypertension in hepatitis B cirrhosis patients based on real-world clinical data. Henan: Henan Univ Tradit Chin Med, 2017.
23. Lu YG. Examination of real-world medication patterns in 104 chronic hepatitis B patients treated with traditional Chinese medicine based on the clinical research integrated platform. Shandong:

Shandong Univ Tradit Chin Med, 2014.
24. Sha YH, Xie XM, Wang LX, et al. Study of the effects of Ruangan pills on hepatic function reserve and portal hypertension in hepatitis B cirrhosis patients based on real-world clinical data. China J Tradit Chi Pharmacy Med 2016, 31: 2087-2090. (Chinese)
25. Liu JH, Wei ZH, Lu DY, et al. Study on the medication rule of famous traditional Chinese physicians in the treatment of primary liver cancer based on data mining. China J Tradit Chi Pharmacy Med 2016, 31: 58-61. (Chinese)
26. Zhang Q, Shao MY, Liu YB, et al. Exploration of method construction of clinical efficacy evaluation of primary liver cancer based on real-world traditional Chinese medicine clinical data. J Tradit Chin Med 2019, 60: 1567-1571. (Chinese)
27. Nie Y. Real-world study based on the tertiary prophylaxis regimen of "tonifying the kidney to promote liver regeneration" in liver cancer. Hubei: Hubei Univ Chin Med, 2018.
28. He F. Real-world efficacy analysis of argon-helium cryoablation combined with traditional Chinese medicine in the treatment of malignant liver tumor. Guangzhou: Guangzhou Univ Chin Med, 2017.
29. Construction and application of a real-world traditional Chinese medicine liver disease clinical study system based on research outpatient. World Science and Technology-Modernization of Traditional Chinese Medicine 2017, 19: 1075-1077. (Chinese)
30. Li XD, Ba YM, Liu JZ, et al. Construction and application of clinical research on liver disease of the real-world TCM. World Sci Technol-Modernization Chin Med Mater Medica 2017, 19: 1161-1166. (Chinese)

Competing interests: The authors declare that they have no conflict of interest.

Acknowledgements: This project was supported by National Natural Science Foundation of China (81673935，81673938，81774256), project of three years' plan of Shanghai to further accelerate the development of traditional Chinese medicine [ZY(2018-2020) - cccx-2003-01, ZY(2018-2020) - cccx-2003-04].

Publisher's note: TMR Publishing Group Limited remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Citation: Zhang JH, Zheng C, Zhu XJ, et al. Real world studies and their impact on the prevention and treatment of liver disease with traditional Chinese medicine. Gastroenterology & Hepatology Research, 2020, 2 (2): 53–57.