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The Application of Real-world Study for Liver Diseases in China

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1. Abstract

Randomized controlled trials are the gold standard for eliminating bias in determining the efficacy and safety of medical products. However, the high costs, long duration, limited generalizability, and ethical or technical feasibility of RCTs have impelled investigators to look for real-world studies as alternatives. The use of data from the real world to address clinical and policy-making questions that cannot be answered using data from clinical trials is garnering increased interest in the liver disease research community. Data from patient registries, linked healthcare databases, and electronic health records can provide unique insights into patients, treatments, and outcomes in hepatology practice. In this review, we described the development of real-world studies in China. Then we discussed the key methodological considerations in real-world studies of liver diseases and illustrated how real-world data has been used to generate real-world evidence to support the decision for liver diseases. Real-world studies provide important information that can complement and even expand the information obtained in RCTs. The following key methodological challenges should be considered when conducting an RWS: a articulated research question; an appropriate study design; a fit-for-purpose data source; a critical applicability evaluation of RWD; and a state-of-the-art analysis method to minimize the bias.

2. Introduction

During the past several decades, liver diseases have been one of the leading causes of death and illness worldwide. According to the global burden of liver diseases, approximately 2 million deaths per year were due to liver diseases, which accounted for approximately 3.5% of all deaths worldwide [1]. In China, liver diseases affect approximately 300 million people, which has a major impact on the global burden of liver diseases [2]. It is estimated that over 20% of the population in China are affected by some kinds of liver diseases, including viral hepatitis, liver cirrhosis, Hepatocellular Carcinoma (HCC), Non-Alcoholic Fatty Liver Disease (NAFLD), Alcohol-related Liver Disease (ALD), and Drug-Induced Liver Injury (DILI), making liver diseases one of the major contributors of morbidity and mortality in China [3].

Viral hepatitis is the major cause of liver-related death worldwide. In 2016, World Health Organization (WHO) called for the global elimination of viral hepatitis by 2030, and set global targets of 65% reduction in deaths from hepatitis B and hepatitis C, and treatment of 80% of people living with these infections [4]. Countries in the Western Pacific have endorsed a regional action plan for these targets and identified several priority areas, notably evidence-informed policy guiding hepatitis action and data-supported hepatitis response [5]. Thus, the use of large-scale real-world data (RWD) to address clinical and policy-making questions is garnering increased significance in the liver disease research area. Data from Real-World Studies (RWS) can complement findings from traditional Randomized Controlled Trials (RCTs) and, if appropriately designed, can provide valuable information about practice patterns and patient characteristics in a real-world setting.

In this review, we described the development of RWS in China. Then we discussed the key methodological considerations in the RWS of liver diseases, and illustrated how RWD has been used to generate Real-World Evidence (RWE) to support the decision-making for liver diseases.

3. Real-World Study Development in China

It is well recognized that RCTs are still the gold standard for providing high-quality data that can evaluate the efficacy and safety of new treatments. However, the high costs, long duration, limited generalizability, and ethical or technical feasibility of RCTs have caused researchers to look for RWS as alternatives [6]. RWS can provide important information on the development of medical products, safety surveillance, outcome research, health care system evaluation, and medical quality improvement. Importantly, RWS has the potential to allow researchers to answer these questions efficiently while yielding answers relevant to a broader population of patients [7]. The value of RWS has been recognized by organizations such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These organizations acknowledge the importance of RWD in supporting marketed products and their potential role in supporting medical product development and decision-making for regulation and assessment.

The term "real-world study" was not explicitly used in China until 2010, when researchers from traditional Chinese medicine carried out RWS to evaluate traditional Chinese medicine interventions, mainly to accommodate the complexities of such intervention [8]. Since then, the Chinese research community began to accept the concept, and adopted the same definition as the international research community [9]. The systematic utility of RWE to support the decision-making for the assessment of medical products is still at the exploratory stage in China. In June 2019, China's National Medical Products Administration (NMPA) launched the Hainan Clinical Real-World Data Application Pilot Project [10]. This project planned to promote the application of RWE for clinical evaluation of medical products in China, which can shorten the time and cost of medical product registration in China and can be applied to support the clinical evaluation of medical devices throughout its life cycle. Then several guidelines for RWS have been issued by NMPA, including "Guidelines for Real-World Evidence to Support Drug Development and Review" [11], and "Technical Guidelines for Real-World Data Used in the Clinical Evaluation of Medical Devices" [12]. In March 2020, the NMPA approved the marketing application of the first medical device which used RWE collected in Hainan Medical Pilot Zone [13].

4. Methodological Considerations in Real-World Study

4.1 Study Design

Several classification schemes exist for epidemiology research designs [14, 15]. Under the FDA's RWE program, evidence from traditional clinical trials, which are often conducted with specific populations and in specialized environments, will not be considered RWE [16]. Real-world study designs are generally classified into two main categories: experimental (interventional) studies, including hybrid or Pragmatic Clinical Trials (PCTs), and observational (non-interventional) studies, including cross-sectional studies, case-control studies, and cohort studies [17].

4.1.1 Pragmatic Controlled Trials: In contrast to traditional RCTs, which are aimed to determine the efficacy and safety of an intervention under the ideal circumstance, pragmatic clinical trials aim to inform a clinical or policy decision by providing evidence for the adoption of the interventions into real-world clinical practice [18]. Pragmatic Clinical Trials (PCTs), which can be either randomized or non-randomized, are clinical trials that focus on the correlation between treatments and outcomes in a real-world practice rather than focusing on proving causative explanations [19]. To control for systematic biases, randomization and blinding are two essential design techniques commonly used in traditional RCTs. Randomization, which is often implemented in PCTs, results in pragmatic Randomized Controlled Trials (pRCTs). Pragmatic RCTs are also known as hybrid clinical trials, in which they combine the features of both RCTs and PCTs [20]. However, since pRCTs aim to provide information on the relative performance of real-world treatment regimes in routine care, blinding cannot be implemented.

Multiple direct-acting antivirals are available for the treatment of HCV, but comparative effectiveness of direct-acting antivirals using traditional RCTs is unavailable. Sulkowski and colleagues [21] conducted a pRCT to compare the effectiveness and safety of direct-acting antivirals for HCV genotype 1. A total of 3750 participants with HCV genotype 1 and compensated liver disease were recruited from 34 viral hepatitis clinics. Participants were randomized to three kinds of treatments, including Ledipasvir/Sofosbuvir (LDV/SOF), Elbasvir/Grazoprevir (EBR/GZR), and paritaprevir/ritonavir/ombitasvir + dasabuvir. This pRCT demonstrated that sustained viral response at 12 weeks for participants treated with LDV/SOF and EBR/GZR with few adverse effects. These two treatments were equivalent in effectiveness [21].

4.1.2. Observational Studies: Observational studies are essential tools for clinical epidemiology research, and they have the potential to advance the evidence for clinical practice and to complement the evidence collected from RCTs. Observational research can be conducted quickly and at a lower cost than RCTs and they often generate hypotheses that can form the basis of future confirmatory RCTs [22]. However, observational studies are at greater risk of bias, and attention needs to be given to the design and analysis of these studies to ensure that they are robust enough to guide clinical practice [23]. This limitation is particularly problematic when an observational study is used to evaluate the effectiveness of medical products and the expected or observed effect is relatively small. For instance, the effects identified in observational studies could not be reproduced in randomized trials or the effect sizes differed in direction or magnitude [24, 25]. Therefore, the findings of observational studies require

judicious evaluation when used to assess treatment effects [26].

4.2. Sources of Real-World Data

RWD, the basis of RWE, is the data relating to patient health status and/or the delivery of health care routinely collected from a broad range of sources [9]. (Table 1) describes several common RWD sources, including patient registries, health surveys, Electronic Medical Records (EMR), claims data, administrative databases, birth or death registries, and surveillance databases. Additionally, patient-generated data from smartphone applications and laboratory-generated multi-omics data are increasingly being considered for RWS.

Table 1: Data sources of real-world studies

Prospective data sources	• Pragmatic controlled trials (PCTs) • Prospective cohort studies • Patients registries • Health survey • Data collected from mobile devices • Multi-omics data
Retrospective data sources	• Electronic medical records (EMR) • Electronic health record (EHR) • Claims data • Administrative databases, • Birth or death registries • Surveillance database

4.2.1. Patient Registries: Patient registries are a key resource of RWD that can be used to generate RWE for liver diseases. There are two main types: disease registries, which are generally defined by diagnosis of a disease; or exposure registries, which are based on usage of a drug, device, or other treatment [27]. Patient registries are particularly useful for assessing 1) the natural history of diseases; 2) real-world safety and effectiveness; 3) prognosis and quality of life; 4) quality of care, and 5) cost-effectiveness of treatment strategies [28].

Advantages of patient registries over RCTs include the capacity to enroll a much larger and more diverse patient population with the potential for a longer follow-up period. This provides data that is more reflective of a real-world population and enables the study of longer-term outcomes, including the identification of more infrequent safety outcomes [29]. Registry studies also involve few or no required visits, evaluations, or procedures at specialist centers because the data are collected by the attending physician as part of daily practice [29].

To facilitate the real-world clinical study of the natural history, diagnosis, and management of chronic HBV infection, a nationwide, internet-based electronic platform, named the China Registry of Hepatitis B (CR-HepB) [30]. The aims of the patient registry are: 1) to demonstrate the clinical pattern and treatment profile of chronic HBV infection in China; 2) to evaluate the long-term efficacy and safety of antiviral therapy; and 3) to provide RWE for policy-making [30]. The demographic, medical history, virological, hematological, biochemistry, radiology reports, liver stiffness measurement, diagnosis, and treatment information of HBV patients has been recorded. Results from these registries have provided insights into the treatment patterns of the HBV patients in clinical practice, including switching from interferon to nucleos(t)ide analogues (NAs), and the steadily increasing usage of NAs in the past decade [31].

4.2.2. Administrative and Healthcare Claims Database: These studies involve retrospective analysis of data from administrative and healthcare claims databases containing treatment information and clinical information, such as diagnosis codes and hospital admissions/discharge dates [32]. These databases are particularly suited to longitudinal and cross-sectional analyses of healthcare utilization and costs at the patient, group, or population level [32].

The key advantages of administrative and healthcare claims database studies are that they can be performed relatively quickly and inexpensively compared with traditional RCTs, involve a very large established patient cohort, and can have a long follow-up period. This enables the identification of rare events, the determination of longer-term outcomes, and insight into the economic impact of interventions [33]. In some instances, database information can also be linked with clinical data, such as patient-reported outcomes, laboratory assessments, medical records, and physician surveys [34].

Antiviral therapy for CHB had been listed as a reimbursable expense in Mainland China since 2010. To assess the impact of this program on liver-related death for patients with Chronic Hepatitis B (CHB), data from the Hospital Discharge Database of Beijing and Death Certification Database was collected [35]. The findings proved that a reimbursement program for antiviral therapy is effective in reducing the risk of liver-related death for patients with CHB, especially for those without cirrhosis [35]. In a 2021 study, our group used the Basic Medical Care Insurance for Employees (BMCIE) database to investigate the dynamic changes of the clinical care cascade of CHB patients in Beijing, China [36]. The study demonstrated that the rate of CHB patients receiving HBV tests and antiviral treatment increased steadily from 2010 to 2018 in Beijing, China. To the end of 2018, entecavir and tenofovir had become the predominantly prescribed antiviral agents [36].

4.2.3. Electronic Health Record: EHR systems refer to electronic platforms that contain individual health records for patients [37]. Electronic health record studies are typically used to assess clinical treatments, procedures, and outcomes. Like claims database studies, EHR studies can be performed relatively quickly and inexpensively compared with RCTs, can involve a relatively large patient cohort, and can have a longer follow-up [38]. Databases enable longitudinal, patient-level data collection from multiple sources may contribute to more consistent recording and coding of information.

To determine whether diagnosis/procedure codes extracted from EHRs could be used to identify patients with decompensated cirrhosis, data from an observational study of patients from four large

healthcare systems was collected [39]. Evidence from this study demonstrated that an EHR-based automated algorithm may be used to successfully identify patients with decompensated cirrhosis. The algorithm could contribute to the timely identification and treatment of viral hepatitis patients who have progressed to decompensated cirrhosis [39].

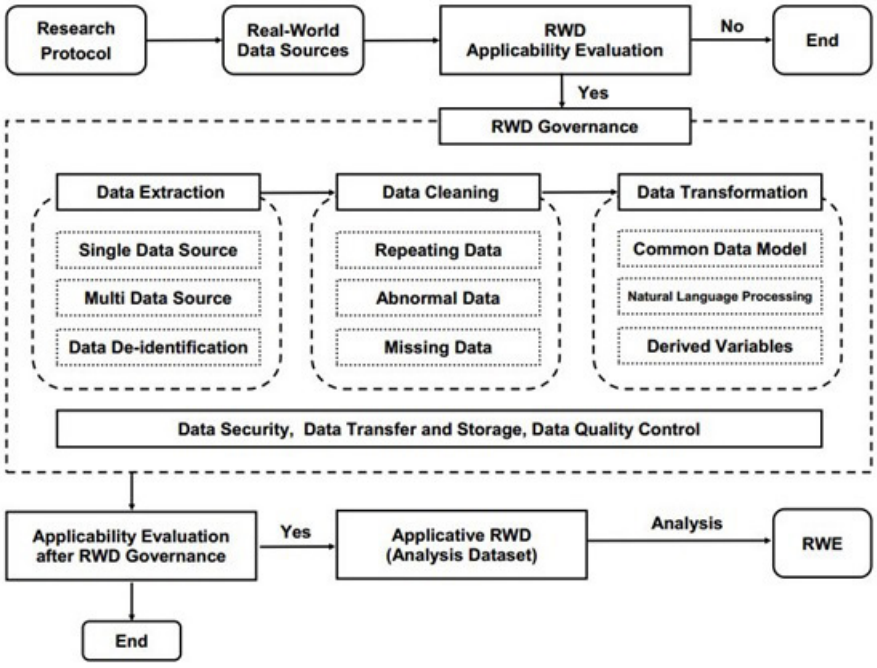
4.3. Applicability Evaluation and Governance of Real-World Data

The applicability evaluation of RWD is mainly used for retrospectively collected data. However, it also provides the guidance for prospectively collected data. As shown in (Figure 1), the applicability evaluation of RWD can be divided into two phases. The first phase is the preliminary applicability evaluation of RWD, and it includes the evaluation of the accessibility, ethics, compliance, representativeness, and completeness of RWD. This phase determines whether the RWD is able to meet the basic analysis requirements of the research protocol. The second phase evaluates the reliability and governance of RWD, and this phase determines whether the RWD can be used to generate RWE. For prospectively collected RWD, the first phase of the preliminary applicability evaluation is not required [40].

In studies using RWD, the quality of the primary data depends on its completeness and accuracy [41]. A critical consideration is the extent to which data are missing at random: random missing data decrease the precision of observations, whereas non-random missing data can lead to biased results. Thus, researchers working with RWD need to carefully consider the validity and reliability of RWD. Data quality can be checked using several methods, such as 1) validation studies compare electronic data from administrative sources against a random sample of patients; 2) electronic data sources can be analyzed to evaluate accuracy; 3) data cleaning involves checking for logical inconsistencies. The commonly used strategy of excluding records with missing data can severely bias results. Multiple imputation methods for mitigating the effect of missing data have been shown to decrease bias and improve precision.

Most studies of RWD include information from different data sets which need to be linked. Ideally, data linkage should be performed with a unique identifier, such as identity card numbers and government-issued health insurance numbers. This form of linkage is generally of higher quality than those of probabilistic linkage, in which each partial identifier (such as age, name, and address) is assigned a score based on how well it matches between data sets [42].

Another crucial step in working with RWD is deciding how to categorize patients, treatments, and outcomes. Study populations must be divided into clinically meaningful groups, which requires input from clinicians. These decisions must be made at the outset of the study, before conducting the main analysis. Otherwise, changing these critical cut-off values when the results emerge to obtain the expected or desired outcome would be tempting.



Figurer 1: Flowchart for applicability evaluation and governance of RWD [40]

4.4. Potential Biases

The biggest criticism of real-world studies is their potentially systematic error, which is also known as biases. These are broadly classified as confounding bias (due to lack of randomization), selection bias (due to procedures used to select study population), and information bias (measurement error) [43].

Confounding is the distortion of the treatment-outcome association when the groups being compared differ concerning variables that influence the outcome [44]. In real-world studies confounding by frailty is possible. As an example, older adults or close-to-death patients are less likely to be treated with preventive treatments. Thus, when comparing users with non-users of a particular drug to assess

outcomes, the non-user group is likely to have a higher mortality risk and make the drug look better than it really is [45]. As confounding obscures the "real" effect, it needs to be prevented or removed as much as possible. Confounding can be prevented by the use of randomization, matching, or stratification. The use of propensity scores is also a powerful tool for controlling measured confounding [46]. A propensity score is a summary score estimating the probability of treatment A v.s. treatment B based on patients' baseline characteristics. Once estimated, propensity scores can be implemented by matching, weighting, and stratification on the scores [47].

Selection bias occurs when the selected population is not representative of the target population. It includes bias resulting from inappropriate selection of controls in case-control studies, bias resulting from differential loss-to-follow up, incidence–prevalence bias, volunteer bias, healthy-worker bias, and nonresponse bias [48]. Selection bias can be reduced by the use of adjustment, stratification, sensitivity analysis, and propensity scores.

Information bias occurs during data collection and it can be caused due to inaccurate measurements or misclassifications of treatments, outcomes, or confounders [43]. The most important type of information bias is the misclassification bias which can be non-differential or differential. A misclassification bias is present when the detection of the exposure and/or the disease assessment is biased. Important examples of this bias are the studies about whether tenofovir is superior to entecavir in lowing the risk of HCC development in patients with CHB [49]. Studies demonstrated that tenofovir-treated CHB patients had lower cumulative incidence rate of HCC than those treated with entecavir. However, the follow-up time of tenofovir-treated CHB patients was usually shorter than entecavir-treated ones in these real-world studies. Disparity in follow-up time could be the most important confounding bias that influence the results [49]. Bias is an unavoidable problem in real-world studies. However, the correct selection of the study design, the careful choice of procedures of data collection and handling, and the correct definition of exposure and disease represent important prevention strategies for minimizing bias in real-world studies.

5. Conclusion

A well-designed RWS with critical methodological considerations can provide important information that can complement and even expand the information obtained in RCTs. The systematic utility of RWE to support the decision-making for the assessment of medical products is still at the exploratory stage in China. The widespread availability of large-scaled databases provides a great opportunity for the research community to gain important insights into the burden of liver disease, management of the liver diseases and patient outcomes in routine practice. Furthermore, the benefits, limitations and methodological challenges associated with the different forms of RWS must be carefully considered when interpreting the findings. The following key methodological points should be considered when conducting an RWS: a clearly articulated research question; an appropriate study design; a fit-for-purpose data source; a critical applicability evaluation of RWD; and a state-of-the-art analysis method to minimize the bias.

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