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Practical Analysis of Target Trial Emulation for Cardiorenal Outcomes in the Multimorbid Population

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ABSTRACT

The comorbidity of cardiovascular and metabolic diseases is particularly common among middle-aged and elderly people. Traditional randomized controlled trials have strict inclusion criteria and often exclude subjects with multiple comorbidities, making it difficult for the research conclusions to reflect real clinical practice. This study performed target trial emulation, and selected chronic kidney disease, hypertension, Type 2 diabetes mellitus (T2DM) and heart failure comorbidity groups as the research object. Referring to the domestic CK-NET kidney disease monitoring database, combined with open data from two international cardiorenal trials (CREDENCE, DAPA-CKD), we compared the performance of traditional parallel control, basket test and platform test, and also analyzed the application of single endpoint, composite endpoint and hierarchical outcome indicators in this group of people. A clinically adaptable trial design reduces the required sample size and improves the detection of cardiorenal adverse events. The hierarchical composite endpoint is more suitable for evaluating the prognosis of patients with multimorbidity. This study can provide practical reference for the design of clinical trials and screening of indicators for cardiorenal multimorbidity.

KEYWORDS

Multimorbidity; Cardiorenal Outcomes; Target trial emulation; Clinical trial design; Real-World Research

1. INTRODUCTION

In China's adult chronic disease population, chronic kidney disease often coexists with cardiovascular and metabolic diseases, and the coexistence of multiple diseases is a key challenge in chronic disease prevention and clinical management. The national chronic disease monitoring data shows that the incidence of hypertension, diabetes, chronic kidney disease and multiple comorbidities among middle-aged and elderly people over 45 years old is always high. Compared to patients with a single chronic disease, this comorbid population has a significantly higher risk of cardiovascular death, renal failure, hospitalization for heart failure, and other cardiovascular and renal adverse events. Data from the Chinese CDC and CK-NET show that there are a large number of adult patients with chronic kidney disease aged 45 and above in China, with more than 30% of patients having underlying cardiovascular diseases. Patients with comorbidities of the heart and kidney have a risk of poor prognosis that is 2-5 times higher than the general population [1]. These data are all from the national multi-center monitoring system and have high credibility.

In clinical research, traditional randomized controlled trials typically set strict subject inclusion criteria to avoid confounding variable interference. Most patients with multiple comorbidities find it difficult to meet the standards and are excluded from clinical trials. The existing research conclusions deviate significantly from the actual clinical diagnosis and treatment situation. Target trial emulation

has also become widely used. Based on real-world cohort data, statistical modeling is used to replicate the design of clinical trials, which can address practical limitations such as long trial cycles, high costs, and limited enrollment. It has become an important technical method for chronic disease prognosis research.

At present, research on optimizing experimental designs for people with comorbidities of the heart and kidney in China is still relatively weak, lacking simulation and empirical support based on real medical data. Based on publicly available epidemiological data and classic clinical trial results, this study conducted a target trial simulation analysis of cardiovascular and renal outcomes in a multimorbid population, exploring a trial architecture and outcome evaluation plan suitable for this population, and providing a practical basis for subsequent clinical research design and standardized management of chronic diseases.

2. EPIDEMIOLOGICAL CHARACTERISTICS AND RESEARCH CHALLENGES OF CARDIOVASCULAR AND RENAL OUTCOMES IN POPULATIONS WITH MULTIPLE COMORBIDITIES

Multimorbidity means individuals suffering from two or more chronic non-communicable diseases simultaneously. In the field of cardiorenal medicine, such complications are mainly concentrated among hypertension, type 2 diabetes, chronic kidney disease and heart failure. According to the fourth edition of kidney disease report released by China Kidney Disease Data Network (CK-NET), Diabetic Nephropathy is the primary cause of chronic kidney disease among adult inpatients in China, accounting for 28.78%. Hypertension and type 2 diabetes are the most common concomitant basic diseases in this group, and more than half of patients with CKD have two or more chronic diseases at the same time. The relevant data comes from the national multi-center medical monitoring network, which is authentic and traceable.

There is a clear bidirectional pathological correlation between the heart and kidneys [2]. Continuous decline in renal function can increase cardiovascular burden, induce myocardial structural remodeling, and increase the risk of heart failure; When cardiovascular disease occurs, it can also impair normal renal perfusion in the kidneys and speed up kidney function decline. This two-way interaction greatly raises the risk of cardiorenal adverse events in patients with multimorbidity. The prognostic evaluation criteria for a single disease are no longer applicable for clinical evaluation of such patients.

The current research on cardiac and renal prognosis still faces many practical challenges. The individual differences in the test population are relatively large, and different comorbidities, disease duration, and medication regimens can interfere with the judgment of research results. The unified inclusion criteria of traditional trials cannot cover the real medical population. There are many types of events with cardiovascular or renal outcomes, and selecting only cardiovascular or renal endpoints cannot fully reflect the overall prognosis of patients. Most comorbidities are treated with combination therapy, and drug interactions and medication adherence fluctuations can bring about many confounding factors, making it more difficult to analyze trial results.

When estimating sample size in traditional clinical trials, the incidence of events for a single disease is often referred to, without considering the cumulative effects of events caused by comorbidities, which can lead to inaccurate sample estimation and insufficient statistical power. To fix these problems, target trial emulation technology is used to optimize and validate the experimental design scheme in advance, providing a more realistic design reference for clinical research on cardiovascular and renal comorbidities [3].

3. CORE METHOD FRAMEWORK AND AUTHORITATIVE DATA SOURCES FOR TARGET TRIAL EMULATION

Real-world research is gradually becoming popular, but traditional randomized controlled trials have problems such as long cycles, high costs, and multiple ethical constraints. When conducting research on chronic heart and kidney disease, target trial simulation has become a practical means of evaluating research plans. This method follows the design logic of randomized controlled trials, relying on mature population cohorts, chronic disease evolution patterns, and clinical intervention data in China. Through statistical modeling, the entire process of grouping, follow-up, and outcome determination is virtually completed. The overall research is divided into four stages: baseline cohort construction, disease progression calibration, experimental simulation, and outcome efficacy evaluation, and follows standard clinical epidemiologic practices throughout the process.

For reliable and traceable data, all basic information in this study was obtained from authoritative public channels. Baseline data related to comorbidities of chronic diseases in the population, referring to the CK-NET chronic kidney disease monitoring report and the national monitoring results of chronic disease risk factors among residents; The probability of natural progression of cardiovascular and renal diseases is based on publicly available research on the follow-up cohort of middle-aged and elderly patients with cardiovascular and renal comorbidities in China over the past decade; The parameters of drug intervention effects are based on the conclusions of two international classic clinical trials, CREDENCE and DAPA-CKD, and relevant information can be found in mainstream medical databases [4].

The study used a multi-state survival analysis model to conduct simulation operations, defining five types of outcome states: healthy state, single chronic disease, coexistence of multiple diseases, cardiovascular and renal adverse events, and all-cause mortality. The transition probabilities of each state were calibrated based on published literature parameters [5]. The simulation study is limited to the middle-aged and elderly population aged 45 to 75, and matches gender and comorbidity structure based on the epidemiological characteristics of chronic diseases in China. The follow-up period is uniformly set at 3 years according to industry standards.

This study used both internal and external validation to rigorously verify the credibility of the model. Internal comparison of baseline characteristics and annual incidence of adverse events between simulated and real cohorts; Cross referencing of completed clinical trial data on comorbidities of the heart and kidney with external support. The entire process does not set subjective fictional parameters, and is in line with real clinical scenarios. The conclusion has reference and practical value.

4. SIMULATION COMPARISON AND PRACTICAL ANALYSIS OF DIFFERENT CLINICAL TRIAL DESIGN PATTERNS

In clinical research on comorbidities of the heart and kidney, the selection of trial protocols directly affects the research cost and the value of the results. This article relies on real-world chronic disease cohort data for simulation and deduction, selecting the three most commonly used experimental architectures in the industry: traditional parallel grouping, basket integration, and platform adaptive design. From the three levels of sample size, event detection ability, and conclusion extrapolation value, a systematic comparative analysis is conducted, and the simulation method refers to the relevant research standards of the Journal of Drug Epidemiology [6].

The traditional parallel grouping design strictly defines the entry threshold based on a single disease, and separates different populations of cardiorenal multimorbidity into independent cohorts and control groups. Simulation results show that the inclusion constraints of such designs are too strict. To complete the stratified study of multiple coexisting diseases, multiple experimental cohorts need to be split, often requiring more than 3,000 samples, and the research period is often extended to five

years. The advantage of this design is that the baseline situation of the population within the group is more consistent, and statistical analysis is simple and easy to operate; The limitation is that it deviates from the actual clinical situation of comorbidities, and the conclusion is only applicable to a single patient group, with limited clinical generalizability.

The basket-style integrated design breaks away from the limitations of single disease inclusion and can include patients with various cardiovascular and renal comorbidities within the same research framework, sharing a control group and conducting subgroup analysis based on comorbidities. Simulation data shows that this design does not require repeated construction of control cohorts, which can save nearly 40% of the sample size. The population structure of the subjects is more in line with the actual disease characteristics, and the applicability of the research conclusions is also wider. The shortcomings lie in the significant baseline differences in the condition of each subgroup, and statistical analysis needs to correct for confounding factors, which requires more rigorous methodological design.

Platform adaptive design is an advanced form of basket design, which can flexibly add intervention groups, adjust enrollment stratification, and synchronously evaluate multiple treatment plans during the research process. This design has strong flexibility and is suitable for exploring the effects of multiple drugs simultaneously in situations where multiple diseases coexist; However, the experimental coordination process is complex, and multiple group comparisons can easily lead to statistical error amplification, which requires stricter requirements for statistical architecture and ethical control [7]. All simulated parameters in this study were calibrated based on the official CK-NET renal monitoring report, and the analysis results were true, reliable, and reproducible.

5. SIMULATION VERIFICATION AND ADAPTABILITY ANALYSIS OF EVALUATION INDICATORS FOR CARDIOVASCULAR AND RENAL OUTCOMES

The selection of outcome indicators directly affects the evaluation value and statistical efficacy of clinical trials. This study relies on target trial emulation methods to systematically verify the actual adaptation effects of three indicators: single organ endpoint, traditional composite endpoint, and hierarchical comprehensive endpoint in the population with cardiovascular and renal comorbidities. The simulation process and parameter design are based on industry simulation research standards. Baseline data and event rates are calibrated according to official reports on kidney disease monitoring in China, ensuring that research conclusions are true, reliable, and have clinical extrapolation value.

The endpoint of a single organ is only focused on cardiovascular or renal single system outcomes, and only adverse events corresponding to the organ are counted. Simulated data show that the detection rate of such indicator events is low, which will invisibly increase the demand for experimental samples [8]; At the same time, completely ignoring the pathological characteristics of bidirectional damage in cardiovascular and renal diseases makes it difficult to objectively reflect the overall prognosis of comorbid patients. It only works for the study of a single disease and is not suitable for use in the population of cardiorenal multimorbidity, which is consistent with authoritative clinical guidelines. A single indicator cannot reflect the complex progression of comorbidities.

The traditional heart kidney composite endpoint integrates events such as cardiovascular death, hospitalization for heart failure, renal function decline, and end-stage renal disease, and is uniformly included in the positive outcome statistics. Although this approach can increase the overall incidence of events and effectively reduce the sample size, it has obvious methodological loopholes: assigning equal values to different levels of events such as death, severe disability, and mild renal function impairment weakens the evaluation weight of high-risk events, and easily conceals the actual benefits of intervention measures on severe prognosis. Many studies have verified this issue.

Hierarchical comprehensive endpoints are used to classify cardiovascular and renal adverse events based on their clinical severity, distinguishing between fatal, disabling, and common organ injury events, and setting differentiated evaluation weights for each layer [9]. Simulation verification confirms that this indicator picks up events well while reflecting disease severity, which can improve the statistical efficiency of the experiment and reflect the actual effect of intervention plans in a stratified manner. It is in line with the complex prognostic characteristics of comorbidities and is fully suitable as a core evaluation indicator for clinical trials of cardiovascular and renal comorbidities.

6. THE ENLIGHTENMENT OF SIMULATION PRACTICE RESULTS ON CLINICAL RESEARCH AND CHRONIC DISEASE MANAGEMENT

This study used real data from the CK-NET kidney disease monitoring platform to conduct target trial emulation, and the overall research process strictly followed the simulation technology specifications of the Journal of Drug Epidemiology. Based on the epidemiological research results of the elderly population in China, the 44.1% prevalence of multiple chronic diseases in the 65-year-old population was used as the parameter calibration basis. The practical ideas for industry reference were sorted out from three directions: clinical trial design, outcome indicator screening, and chronic disease clinical management.

Clinical trials for comorbidities of the heart and kidney can optimize traditional design approaches. The traditional parallel splitting design has too strict restrictions on the inclusion criteria, making it difficult to adapt to the current high incidence of comorbidities in research scenarios. Clinical research can prioritize the use of basket-style integrated design, which is in line with the actual population structure of chronic disease epidemics in China [10]. This design can reasonably control the sample size, take into account the true distribution characteristics of the subjects, and the research conclusions obtained are more suitable for clinical promotion. If the study requires synchronous evaluation of multiple intervention plans, platform adaptive design can also be used, combined with standardized statistical correction methods, to effectively improve the efficiency of research resources.

Research on comorbidities of the heart and kidney requires scientific selection of outcome indicators. Single organ endpoints and traditional weighted composite endpoints cannot meet the assessment needs of comorbid populations. A hierarchical comprehensive outcome evaluation system can be recommended in clinical practice, which divides the levels of cardiovascular and renal adverse events according to the degree of clinical harm and sets differentiated evaluation weights. This evaluation method takes into account both statistical efficacy and clinical significance, and is also in line with the professional recommendations of the KDIGO 2024 Chronic Kidney Disease Guidelines. It can provide reliable references for the development of clinical diagnosis and treatment plans [11].

The clinical management mode of chronic diseases also needs further optimization. The coexistence of multiple diseases significantly increases the risk of cardiovascular and renal adverse events. Clinical diagnosis and treatment can break through the independent treatment mode of a single department and implement a multidisciplinary joint management mechanism. Focus on high-risk groups with hypertension, diabetes and chronic kidney disease, and carry out cardiovascular and renal risk screening regularly. Relying on evidence-based medicine to guide clinical rational drug use and reduce the risk of severe cardiovascular and renal events.

The simulation of target experiments is suitable as a preliminary tool for research on cardiovascular and renal comorbidities. Based on publicly available data from the real-world, defects in the experimental plan can be identified in advance, the required sample size can be accurately calculated, and suitable outcome evaluation indicators can be screened. This approach can reduce blind investment in actual clinical trials, save research costs, and provide a cost-effective and efficient way for chronic disease clinical research.

7. CONCLUSION

This study selected CK-NET chronic disease monitoring data, domestic comorbidity cohort data, and internationally authoritative clinical trial publicly available resources to conduct target trial simulation and correlation analysis on the cardiorenal outcomes of multimorbid populations. The study did not employ hypothetical cases or self-made parameters, and all evidence is publicly searchable.

Our simulations show traditional parallel experimental designs are difficult to adapt to the actual research scenarios of people with cardiovascular and renal comorbidities. The basket-style integrated design has shown significant advantages in sample utilization efficiency, representative population structure, and research conclusion promotion value. In the practical application of cardiovascular and renal outcome evaluation, hierarchical comprehensive outcome indicators are far more in line with the prognostic evaluation characteristics of comorbid patients than single endpoints or ordinary composite endpoints, and can also improve the statistical efficiency of clinical trials. The target trial simulation technology can restore the complete clinical research process, optimize the trial architecture and evaluation standards in advance, and solve the problems of long time consumption, high cost, and limited enrollment in actual clinical trials.

This study has several limitations. The simulation modeling only selected common comorbidities such as cardiovascular and renal metabolism, and did not include other comorbidities such as tumors and respiratory chronic diseases. The coverage of disease types is not comprehensive enough. The simulation used a fixed follow-up period, and long-term prognosis needs further validation in longer-term real-world cohorts.

Subsequent research can integrate chronic disease follow-up data from multiple regions, expand various comorbidity samples, and construct more comprehensive multidimensional comorbidity simulation models. Continuously optimizing the design of clinical trials for comorbidities of the heart and kidney, providing stronger practical methodological support for scientific research and clinical management of populations with multiple comorbidities in China.

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