

Standardizing Individualized Efficacy Evaluation to Optimize Evidence-Using Pattern in Traditional Chinese Medicine—Preliminarily Establishing Traditional Chinese Medicine Evidence-based Case Reporting System

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ABSTRACT

Individualized treatment is a basic feature of Traditional Chinese Medicine (TCM), and individualized efficacy evaluation is also emphasized in TCM clinical practice. Individualized evaluation is in favor of improving intervention continuously, and optimizing the TCM evidence-using pattern gradually. Traditional case reports can better demonstrate the efficacy of individual, but lack of standardized design, making such evidence show a lower quality. Meanings, objectives and design elements of TCM individualized evaluation were discussed in this paper. Then based on the original work, design ideas and framework of TCM evidence-based case reporting system were established preliminarily. This work will improve the methodology of TCM individualized evaluation to realize the goal of optimizing TCM clinical evidence-using pattern.

Key words: Individualized evaluation, Transformation and using of evidence, TCM evidence-based case report system, Standardization

Abbreviations: CECS: TCM evidence-based case reporting system; EBM: Evidence-based medicine; EBP: Evidence-based practice; TCM: Traditional Chinese medicine; WM: Western medicine

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INTRODUCTION

Individualization runs through patients' most medical processes such as diagnosis, treatment, nursing, recovery and prognosis, and individualized evaluation reflects the clinical efficacy of individualized treatment. Because of individual differences, nonstandard individualized research and reporting methods, it is difficult to treat the result of individualized evaluation as a high-quality evidence as the group clinical trials. Differential treatment based on symptom is not only the basic principle of individualized treatment of traditional Chinese medicine (TCM)^[1], but it also makes the individualized efficacy evaluation of TCM become a common concern of both doctors and patients. How to locate the objective of individualized evaluation of TCM, play its positive role and regulate its methodology on the basis of the existing design has become an urgent issue to be solved.

CLINICAL NEEDS FOR INDIVIDUALIZED EVALUATION

Individualized treatment is the main activity of clinical practice of both TCM and Western medicine (WM)^[2].

Because of individual differences, general experience or evidence should be inspected through patients' multi-dimensional characteristics like age, gender, medical history, condition or previous efficacy and make some adaptive changes while using in clinic. Thus, under the guidance of evidence-based medicine (EBM), it is an important part of clinical practice to make individualized evidence-using project adapting to each patient on the basis of getting the best group evidence.

So far, the result of randomized controlled trials still remains the "Gold Standard" to determine whether the intervention is valid, but some invalid patients might be ignored while reporting the valid data of study group^[3], which indicates that real clinical patients within the scope of sample range might be invalid after treatment. Although it is difficult for invalid patients to avoid receiving the misuse of group evidence in clinical decision, the ongoing clinical intervention should be adjusted, gained or suspended through individualized efficacy evaluation. Evidence-based clinical practice (EBP) includes five steps which are, in order, raising questions, retrieving evidence, evaluating evidence, making clinical decision and reevaluation^[4]. The last step reevaluation, which is important for EBP

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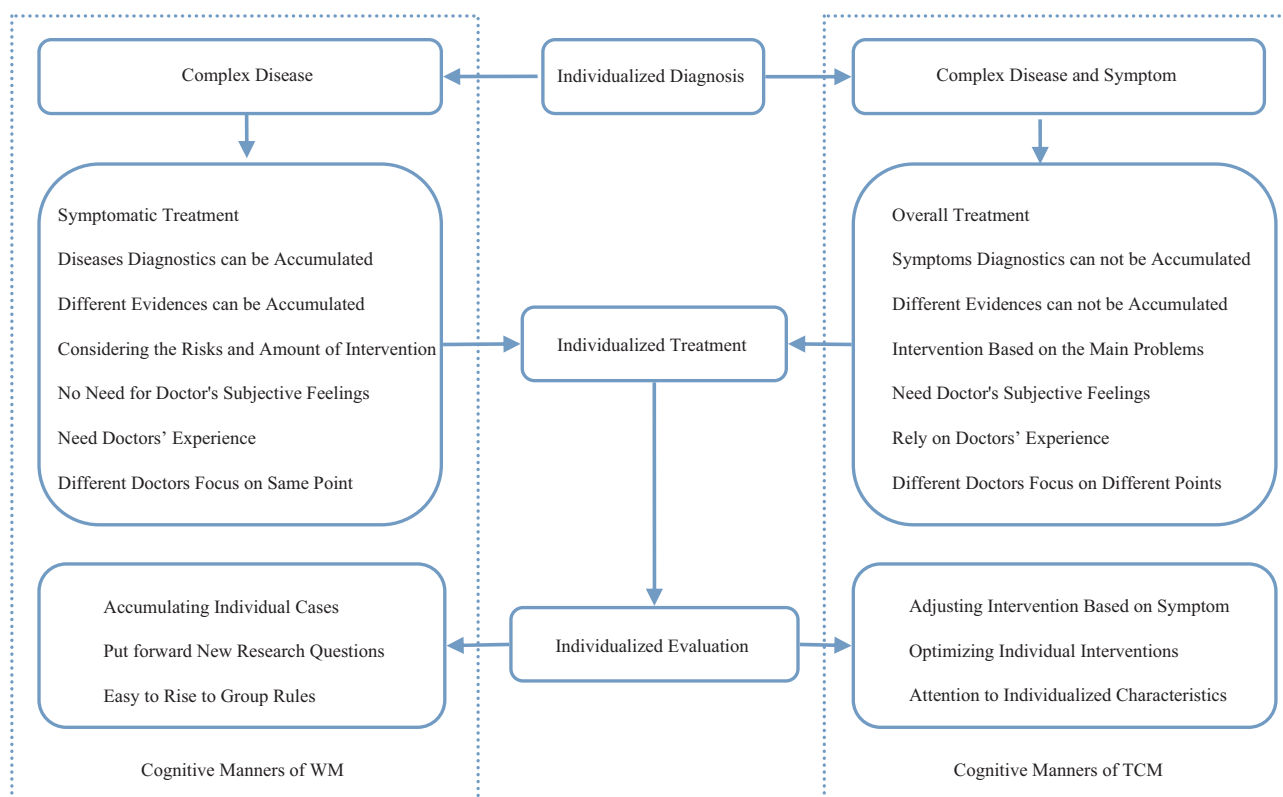


Figure 1. Differences of individualized medicine between TCM and WM

of both TCM and WM, should summarize the effectiveness and efficiency of using evidence to accumulate experience, raise consciousness and provide clues or ideas for the next clinical research. However, individualized reevaluation objectives have different emphases according to the different characteristics of TCM and WM.

OBJECTIVE LOCATION OF TCM INDIVIDUALIZED EVALUATION

1. Different Targets in Different Cognitions

Overall cognition is the main principle of TCM, seeking the correlations between intervention and overall feature in different disease stages. The overall feature is determined by many complicated factors such as disease causes, physical, pathogenesis, course, history, the primary and secondary syndromes, and could be generalized as a complex syndrome. Different patients or disease stages have different complex syndromes, and one complex syndrome cannot be simply accumulated by some single syndrome. Therefore, TCM constructs a kind of disease cognitive manners with obvious individualized characteristic.

In recent years, with the development of genes, proteins and other micro-level medical technology, WM had found that same tumor might has different genetic characteristics which should receive different treatments^[5], and different tumors can use the same kind of targeted drug therapy if they have similar genes or protein characteristics^[6]. This view is similar to a TCM theory which says “different treatments for the same disease and the same treatment for different diseases”.

The individualized characteristics of WM have created some new concepts with individualized characteristics just like individualized medicine or precision medicine^[7], refining the guidance for clinical decisions.

However, these individualized characteristics which are based on strict substantial corresponding relation are not similar to TCM syndrome differentiation with a subjective speculation process. The thinking manners of TCM, which aims to find out the relationship of complex “disease + syndrome” and interventions, is not as steady as the one of WM that is just the relationship of disease and interventions. On these grounds, WM could accumulate results of individual evaluation and re-analysis unknown common features based on its clear thinking manners then puts forward new scientific questions and solves them with clinical research methods. On the contrary, the accumulated individualized evaluation information of TCM might be influenced by unclear complex factors and subjective perception so that common rules of disease group are difficult to be extracted, but it exists some help for raising the experience and speculative forces level of physicians. Differences of individualized treatment between TCM and WM are shown in Figure 1.

2. Individualized Evaluation Target of TCM—to Optimize Evidence-Using Pattern

EBM advocates that clinical decision should be grounded on the current available best evidence. It divides clinical activities into two parts which are production and using of evidence, defining the clinical value of any kinds of intervention

according to the quality of its evidence and actual clinical efficacy. David Sackett, one of main founders of EBM, completed the concept of EBM in 1996 which included 3 elements: current available best evidence, doctor's experience and willingness of patients^[8], providing guidance for clinical evidence-using. But for a long time, the producers of evidence, including the investigator of original and secondary research, have generally considered that clinical decision is uncertain because of a immeasurable combination of experience and wishes of patients and doctors, so they prefer to put more focus on promoting the accuracy and quality of evidence rather than get involved in evidence-using specific details. Under the surrounding of positive evidence-producing methodology progress, there is still no effective research method to standardize the form of individualized evidence-using.

Treatment of TCM is a complex process with attempts and adjustment based on syndrome, and the group evidence used in the individual should be adjusted according to the actual situation of the individual. Influenced by the differences of experience, academic sects, drug-using habits and different information concerns, a strong subjectivity is shown at efficacy evaluation and evidence-using adjustments^[9].

On the one hand, diagnosis and evaluation of TCM do not depend on an objective examination with machine, but mainly rely on doctor's subjective perception. On the other hand, patients' acceptance of TCM intervention depends not only on price, but also influenced by culture and habits. Therefore, the traditional evidence-using pattern of TCM may make adjustments of intervention be influenced by subjective awareness of both patients and doctors rather than based on objective efficacy. Overall, this pattern requires a standardized research form to be corrected. Under the circumstances of booming development of evidence based TCM^[10-11], individualized treatment of TCM may have a different definition from WM which aims to find out microcosmic mechanism. It means to use the group evidences which are produced by clinical trials or systematic reviews on individual and adjust evidence-using based on the results of individualized evaluation. The dose and varieties of medicine, acupoints, intensity or time of moxibustion and even treatment ideas can be adjusted for TCM. The results of individualized evaluation should be reflected through recognized measurable indexes such as scale, imageological, physical and chemical examination rather than mere subjective perception. This is a better pattern for TCM individualized evidence-using rather than the classic definition of individualized medicine or precision medicine.

Although individualized evaluation results of TCM include so much personalized information that the extrapolation is limited, they are the patient's own personal attempt experience^[12] and the best evidences fitting to themselves. Therefore, individualized evaluation objective of TCM should be located to optimize the patient's own evidence-using pattern which means analyzing individualized efficacy information then adjusting intervention details dynamically. This will hopefully lead to a switch of EBP of TCM from "using best evidence" to "adjusting best practice pattern of evidence".

RESEARCH METHODOLOGY OF TCM INDIVIDUALIZED EVALUATION

1. Current Situation of TCM Individualized Evaluation

Currently, two methods are mainly used in TCM individualized evaluation. One is to collect the routine treatment information of different patients based on the real world data source while weaken the conformance requirements of classic randomized controlled trials (RCT) to the interventions and patients. Information could be converged to the database and cross-disciplinary data mining method finally contribute to conclude the efficacy of general or subgroups in diverse dimensions^[13]. Another is to collect individual data at different time and analyze the dynamic and time-order data of different intervention or exposure factors with longitudinal data analysis methods, leading to discover variables' characteristics in different disease periods^[14].

The methods above are not real individualized evaluation but an evidence-producing pattern indicates individualized data collection and group rules analysis. They focus on refining common rules and still remain group analyze characteristics^[15], leaving out some patients from common rules. It is difficult to avoid the problems caused by missing data because the information was mostly derived from real clinical condition^[16]. In addition, a larger sample size is needed to mine common rule because of big individual differences. There have been few success research examples to evaluate individualized efficacy.

2. The Advantages and Disadvantages of Case Report Study

Case report study, which focuses on single or several cases with common characteristics, can describe the disease information, condition, medication and outcomes of patients in detail and depict the efficacy by a dynamic way. However, it ranks a lower evidence level in the evaluation system of EBM since the contingency of individualized data, and the traditional TCM case report study still remains some following drawbacks.

2.1 Lack of Evidence in Intervention Decision-Making

The intervention reported in the case report always be determined just after analyzing syndrome, etiology and pathogenesis without recording source and evidence.

2.2 Missing and Inaccurate Data

The traditional case reports are often summarized after the whole therapy, and recall bias may lead to false information or missing data.

2.3 Outcomes are Mostly Feelings and Symptoms

The prescriptions evaluated in traditional case report are often from classic TCM books like "Treatise on Febrile Diseases (*Shang Han Lun*)", and reporters treat the unconvincing feelings and symptoms from classic rules as evaluation outcomes.

2.4 Lack of Quality Control

The traditional case report is usually finished by a single researcher, and it is difficult to supervise its quality or retrace to the data source

2.5 Obscure Diagnosis

Some diseases reported in case reports are determined by symptoms and diagnosis is indicated as TCM diseases names without rigorous WM check. Potential risks of the treatment might be left.

2.6 Reporting Standards Deficiency

Lack of a list of reporting standards will lead the author to report according to their own preferences, and some important information might be ignored.

2.7 Informed Consent

Patients usually do not know that their disease information will be reported to public.

2.8 No Project

Reminders of subsequent visit and follow-up for patients are often inexistence in traditional case report study and the visit way is onefold. Some patients might be loss to follow-up after transferring treatment.

Since the individualized efficacy evidence is not heterogeneous to patients themselves, case report study can be applied to evaluate individualized efficacy of TCM evidences and adjust the treatment project, optimizing the pattern of evidence-using. However, if we desire case report can effectively guide the treatment of individual and bring some inspirations for other physicians after its publication, some work need to be done to standardize the content of case report. The traditional form of case report also requires a combination with quality control methods and design elements of large-scale clinical trials to regulate its methodology.

3. The Standardized Essential of TCM Case Report Study

Standardization is a basic requirement of clinical research. On the one hand, reliable evidence, complete information, effective outcomes and objective analysis are guarantee of guiding adjustment of intervention for patients themselves; on the other hand, the structurized condition description is in favor of physicians to analyze reports' applicability, and detailed intervention instruction increased the repeatability of evidence. Based on the shortcomings of traditional TCM case report study and the general rules of clinical research, design features of TCM case report study are conceived as follows.

3.1 Diagnostic criteria

Strictly judging whether the patient meets the diagnostic criteria of both TCM and WM to ensure subjects compliance with the research purpose. Scanned copies of related laboratory and iconography examination report must be recorded to provide an objective clinical diagnosis. Diagnosis of traditional Chinese medicine, such as tongue and pulse,

should be recorded in detail. The pictures of tongue should be also gained if necessary.

3.2 Retrieving Evidence

Under the guidance of evidence-based medicine, retrieval is necessary before clinical decision to determine the best evidence. The retrieval scheme and results should be recorded to support the sources of interventions.

3.3 Digitization

Digital medical information and data can avoid text expression which is difficult to be analyzed, enhancing the persuasiveness and treatability of efficacy information.

3.4 TCM Characteristics

Syndrome, tongue and pulse should be involved in evidence retrieval, case diagnosis, intervention, outcomes and analysis of efficacy. The key intervention information of Chinese medicine, Chinese patent medicine, acupuncture, moxibustion and other therapies must be recorded in detail. Appropriate follow-up and subsequent visit time should be designed based on the characteristics of TCM intervention.

3.5 Real World Design

The intervention and its adjustment in each follow-up visit are recorded authentically based on the repeated measurement method. Multiple ways of visit were combined to be used in the real clinical situation.

3.6 Standardized Structure

A standardized and integrated case report is designed based on the list of Consensus-based recommendations for case report in Chinese medicine (CARC) formed in our original work by expert consensus method^[17].

3.7 Recognized Outcomes

Efficacy is evaluated by recognized outcomes which are retrieved from previous study and treatment protocol literature or gained from experts' proposal.

3.8 Controllable Quality

The data was guaranteed to be true, integrity, timeliness by way of control from a third party. The informed consent must be done for patients.

PRELIMINARILY ESTABLISHING TCM EVIDENCE-BASED CASE REPORTING SYSTEM

Based on the concepts and design elements above, the TCM evidence-based case report system (CECS) was established depending on the original work^[18], which aim to present an individualized evaluation of the group evidence and optimize the pattern of TCM evidence-using. CECS could collect and analyze patients' individualized data by central electronic data capture system (EDC) and evaluate their long-term individual curative effect then modify the following treatment

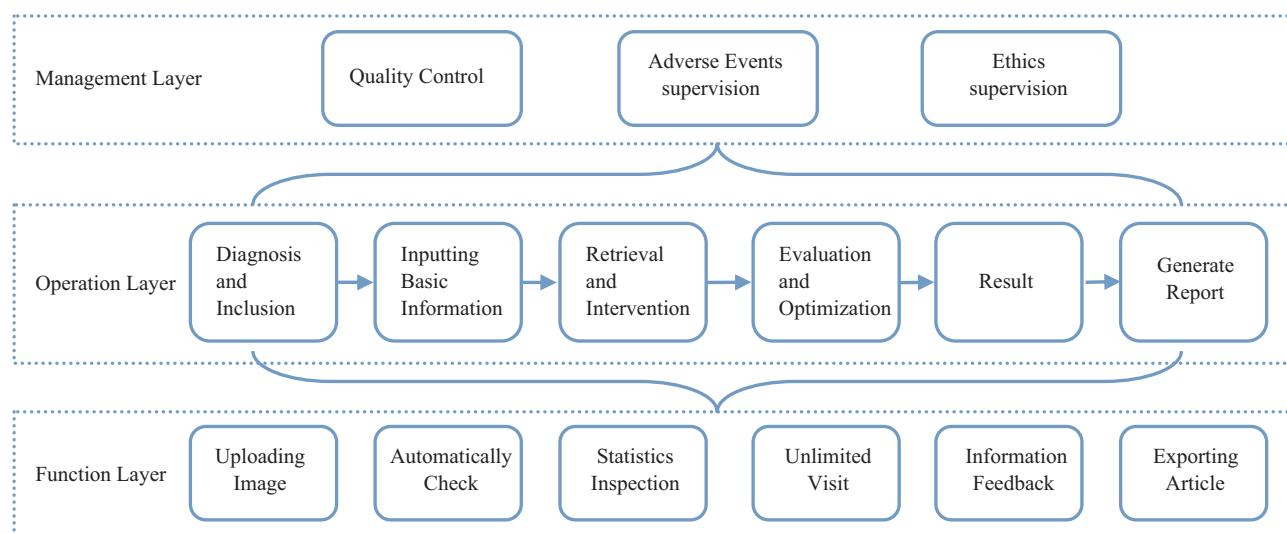


Figure 2. The structure of TCM evidence-based case report system

dynamically. Besides that, an article, TCM evidence-based case report, could be written under the help of CECS. CECS includes three work layers, and the structure of CECS is shown in Figure 2.

1. Management Layer

The management layer is composed of some administrative departments in the hospital and third parties. They are responsible for protecting the quality of the study and patients' rights. The researchers who review the ethical will supervise the patients recruitment and whether the treatment meet the ethical requirements. Inspector can remotely check the case report data and remind the researchers to modify errors in time. If an adverse event happens, researcher can also report it to the adverse events committee and ethics committee through CECS.

Unlike some software or data management systems which focus on dealing with the retrospective information, CECS can collect the prospective data instantly. We had to consider the ethics, security and integrity in the individual study. Before a series of case studies, researchers need to submit the study protocol, informed consent and case report form to research organization for ethical review. Managers in research organization will also be allocated to some accounts to regularly check whether researchers' behavior compliance with the study protocol in the ongoing study.

2. Operation Layer

This layer is the main part of CECS and the key way for researcher to record efficacy, which presents in structured database depending on EDC.

Firstly, researchers must make correct TCM and WM diagnosis before recruiting patients through inclusion and exclusion process, and input cases basic information, disease status of TCM and WM, comorbidities, concomitant medications and other information. Secondly, retrieving evidence and inputting the retrieval words, type, scheme and results, then determine the best evidence depending on the patient

characteristics. The quality of retrieved evidence should be evaluated by corresponding criterion and the operating points of the treatment should be inputting into CECS based on the list of CARC. Thirdly, a detailed record of the patient's disease information will be typed in CECS and the outcome should be measured to cognize efficacy of the evidence and modify the intervention based on the efficacy, physicians' experience and patients' will in each follow-up (no using evidence) or subsequent (after using evidence) visit. Telephone follow-up could be applied to touch the patients who has transferred to another hospital. Lastly, the end of case report study will declared if an endpoint happens such as cure, death, quit or any others, then an article can be exported for publishing after some text polishing.

Recording the prescription, adjustment and efficacy change in detail is the main task of the operation layer. In the system, the record form is set according to the items of CARC which divided TCM intervention into traditional Chinese medicine, Chinese patent medicine, acupuncture, moxibustion and the other TCM interventions. Different TCM intervention has different forms to fill to record the prescription, acupoints, dose and their adjustment. Some spaces were left to record other drug outside TCM treatment. In each visit, the individualized efficacy, including all indicators designed in clinical trial protocol, will be recorded.

3. Function Layer

In this layer, CECS provides functions of uploading relevant information (diagnostic imaging, physical and chemical inspection report, et al.), correcting wrong electronic data automatically, inspecting the behavior of researcher, analyzing statistical data, unlimited long-follow-up, connection among each role of researcher and exporting article TCM Evidence-based case report. Functions of this layer are provided by EDC, data management and statistical analysis staff together. With the functions above, CECS can dynamically evaluate individual curative effect in every point or stage; observe the intervention changes and occurring of

endpoint events through a long-term follow-up. The efficacy of evidence could be spread to other doctors by the exported article.

Efficacy evaluation is the main task of this layer. After the end of the study, dynamic efficacy and intervention data will be gained. The correlation between efficacy and intervention can be intuitively described. The efficacy can also be analyzed and compared among different periods or different adjustments of evidence. It depends on the research purpose.

CONCLUSION

TCM individualized evaluation should combine the complexity of TCM diagnosis-treatment and the superiority of elaborate dynamic case report, make rigorous clinical decisions rely on the evidence-based methods and group evidence, standardize data collection and improve the quality of case study. CECS establishes a new pattern to use evidence that doctor can perfect the intervention based on individualized efficacy and real change of patients in unlimited visit. Thereby, researchers can summarize the specific treatment discipline applying to the individuals, eliminate the unrepresentativeness and occasionality of individual data and develop a new way for TCM efficacy evaluation beyond the common rules of group study to promote the group evidence to be efficiently applied on individuals in EBP.

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