A prospective cohort study on the epidemiological investigation, diagnosis, and treatment of hepatic encephalopathy

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1. Research Background

Hepatic encephalopathy (HE) is a common and serious complication in the course of chronic liver disease and acute liver failure. It presents with a wide range of neuropsychiatric abnormalities, from subclinical changes (mild cognitive impairment) to obvious disorientation, confusion, and even coma. This not only significantly affects patients' quality of life and survival prognosis but also imposes a heavy burden on healthcare systems.

The incidence of HE is approximately 11.6 cases per 100 person-years. Among patients with cirrhosis, the prevalence of overt HE is 10-14%, increasing to 16-21% in those with decompensated cirrhosis, and 10-50% in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS). The prevalence of minimal hepatic encephalopathy (mHE) ranges from 20% to 80%. China currently lacks national, multicenter epidemiological data on HE; in particular, the prevalence and disease outcomes of covert hepatic encephalopathy (CHE) need to be clarified.

Diagnosis of HE is also a major challenge. There remains a lack of definitive laboratory tests, and diagnosis mainly relies on exclusion. Although ammonia plays a key role in the pathophysiology of HE, studies have shown that blood ammonia cannot accurately identify HE, and there is no difference in lactulose treatment between patients with normal versus elevated ammonia levels. Currently, tools such as the Psychometric Hepatic Encephalopathy Score (PHES) are commonly used clinically, but their ability to predict overt HE (OHE) is limited by multiple factors. According to the West Haven criteria, HE is further classified into CHE and OHE. Research on CHE is relatively scarce, and many issues remain to be explored. First, diagnosing CHE is difficult. No laboratory method can diagnose or exclude it, and the diagnostic efficacy of existing tests for CHE requires further evaluation. Second, test performance is suboptimal; not all existing tests have undergone cross-sectional and longitudinal validation. Moreover, because cognitive ability is highly dependent on education and cultural environment, complex tests involving letter or math skills may show greater variability across different countries and cultures.

In the treatment field, although lactulose and rifaximin have been established as core drugs, many unmet clinical needs remain. Multiple mechanisms, including ammonia toxicity, inflammation, oxidative stress, and neurotransmitter abnormalities, participate in the pathogenesis of HE. A treatment strategy that merely reduces blood ammonia cannot fully control the disease. Patient tolerance to lactulose, optimization of primary and secondary prevention strategies in high-risk populations, and accumulation of clinical evidence for emerging therapies such as fecal microbiota transplantation and cell therapy all require further research.

In summary, given the increasing disease burden of HE, the inadequacy of early diagnostic tools, and the limitations of current treatment strategies, conducting epidemiological surveys of HE in the Chinese population, optimizing diagnostic processes, and exploring precision treatment strategies are of great clinical significance and social value.

2. Research Objectives

2.1 Primary Objective

To conduct an epidemiological survey of hepatic encephalopathy in the Chinese population and further explore its diagnosis and treatment.

2.2 Secondary Objectives

1. To investigate the diagnostic value of a newly developed mini-program for new-onset minimal hepatic encephalopathy and compare its efficacy with other tests; to explore whether long-term use of the new mini-program leads to differences in prognosis between patients who have experienced HE and those who have not; to evaluate patient and family compliance with and satisfaction towards the mini-program, as well as the feasibility of promoting this model in clinical practice; to assess the subsequent economic benefits of the mini-program...

2. To investigate the predictive value of the third lumbar skeletal muscle index (L3-SMI) for the prognosis of sarcopenia/frailty/malnutrition in the cirrhotic population...

3. To further evaluate the quality of life of patients with hepatic encephalopathy...

[etc...]

3. Study Design

This study is a prospective, multicenter cohort study. Cirrhotic patients and healthy individuals who meet the inclusion criteria will be recruited from outpatient clinics and inpatient wards. Baseline assessments will be completed, and relevant baseline data will be collected, including: demographic information, cirrhosis details (etiology, previous complications, prior hospitalizations or infections, medication use, TIPS), cirrhosis comorbidities, laboratory test results, imaging findings, results of various tests for hepatic encephalopathy, nutritional status, quality of life, physical measurements, etc. Grouping will be based on predefined endpoints. Different groups of participants will be followed up at month 1, 3, 6 after baseline, and then once every six months. At each follow-up, similar categories of data as baseline will be recorded. Finally, data will be integrated and analyzed, and validated in an external cohort.

4. Study Population

The study subjects are cirrhotic patients and healthy individuals. Recruitment will be conducted among patients attending hospital outpatient or inpatient departments who agree to follow-up. Enrolled individuals will be followed prospectively for 3 years. Patients are required to return for follow-up visits at 1, 3, and 6 months after their first outpatient visit or discharge, and then every six months thereafter. Follow-up will be conducted in person when patients return for visits.

4.1 Inclusion Criteria

(1) Cirrhotic patients and healthy individuals. Cirrhosis is diagnosed by physicians based on imaging, elastography, biopsy, or clinical symptoms.

(2) The patient and their accompanying family member own a smartphone, can

expertly use WeChat and mini-programs, and have a stable internet connection.

(3) Voluntarily sign informed consent, have good compliance, and fully understand this study.

4.2 Exclusion Criteria

(1) Age <18 years.

(2) Women planning to become pregnant, already pregnant, or breastfeeding.

(3) Incomplete required data.

(4) Unable to expertly use the WeChat mini-program or unstable internet environment.

(5) Presence of red-green color blindness or other uncorrectable visual impairment.

(6) Cardiac, pulmonary, or renal failure, or unstable vital signs.

(7) Unwilling to participate in the study or unable to sign informed consent.

(8) Any other condition that may interfere with study assessments, increase subject risk, or affect study completion, deemed unsuitable by the investigator.

(9) Participation in another clinical trial within the past 3 months or currently participating in another clinical trial.

5. Study Variables

·Exposure factors: Laboratory indicators, blood ammonia, data derived from the newly developed mini-program, MELD score, presence of other diseases (hypertension, diabetes, cardiovascular disease), variables for nutrition and sarcopenia assessment, medication regimens, etc.

·Outcome indicators: Death/discharge against medical advice, liver transplantation, TIPS, hepatic encephalopathy (OHE/CHE), frailty, sarcopenia, malnutrition, decreased quality of life, etc.

·Predictors:

(1).Demographic characteristics: age, sex, education level, anthropometric data (height, weight), etc.

(2).Past medical history and comorbidities: etiology of cirrhosis (viral hepatitis,

autoimmune, alcoholic, etc.), cirrhosis complications (gastrointestinal bleeding, ascites, splenomegaly, hepatic encephalopathy, etc.), comorbidities (hypertension, diabetes, cardiovascular disease, kidney disease, psychiatric disorders; infections, etc.), whether TIPS has been performed, etc.

(3).Laboratory indicators: complete blood count, liver and kidney function, coagulation, blood ammonia, electrolytes, C-reactive protein, procalcitonin; imaging indicators; frailty/sarcopenia-related indicators: handgrip strength (dominant hand), abdominal circumference, body mass index (BMI), etc.

(4).Scores and scales: Child-Pugh class, MELD score, MELD-Na score, PHES score, quality of life (scale), data from the mini-program, etc.

(5).Lifestyle habits (smoking, alcohol consumption, etc.), nutritional intake (protein, calories, etc.), etc.

(6).Medications at baseline (anti-HE drugs, dosage, frequency; psychiatric drugs; other drugs such as diuretics, etc.), medications used at outpatient visit/discharge and their frequency, etc.

(7).Record the number, reasons, and length of stay for unplanned rehospitalizations.

(8).Confounders: Severity of liver function, age, education level, etiology of cirrhosis, medication use, prior history of HE, etc.

·Effect modifiers: Child-Pugh class, age, etiology of cirrhosis, etc.

To control selection bias, clear and unified inclusion/exclusion criteria will be used, and participants will be enrolled through consecutive recruitment rather than convenience sampling. To control information bias, tests will be administered by different personnel at different time points to ensure information isolation; testers will be trained and standardized procedures established. Questionnaires will be administered in a quiet, private environment. For confounding bias, when comparing prognoses between groups with different test results, individual matching or frequency matching for important confounders (e.g., age, liver function) may be performed. Stratified analysis of confounders will be conducted during data analysis.

6. Sample Size Determination

$$n_{\text{患病组}} = \frac{Z_{\alpha/2}^2 \times \text{Sensitivity} \times (1 - \text{Sensitivity})}{W^2}$$

$$n_{\text{非患病组}} = \frac{Z_{\alpha/2}^2 \times \text{Specificity} \times (1 - \text{Specificity})}{W^2}$$

$$N_{\text{总}} = \frac{n_{\text{患病组}}}{\text{患病率}} + \frac{n_{\text{非患病组}}}{1 - \text{患病率}}$$

Referring to the reference "Detection of minimal hepatic encephalopathy in patients with cirrhosis based on the Stroop-CN model (NCRCID-CHESS 2106): a prospective multicenter study." The specificity was 0.595, sensitivity 0.667. The proportion of HE in the cirrhotic population is 50-80%, and W was set at 0.1. At a prevalence of 50%, the sample size was 358; at 80%, the sample size was 573. According to the formula, the sample size is calculated to be 358-573 cases. Assuming a dropout rate of 15%, approximately 421-674 cases are ultimately needed.

For the healthy population, using the formula $n = \left(\frac{Z \times \sigma}{W}\right)^2$, with Z=1.96, W=2, and standard deviation=10, approximately 98 individuals are needed. This is rounded to 120 for collection, which is a common sample size for establishing normal reference values in clinical diagnostic tests.

7. Statistical Analysis Plan

Data will be processed using SPSS, R, and GraphPad Prism 9. The K-S test will be used to analyze whether data follow a normal distribution. Normally distributed continuous data will be expressed as mean ± standard deviation (x±s); non-normally distributed continuous data will be expressed as median and interquartile range [M (P25, P75)]. Comparisons between two groups will be performed using independent samples t-test or Mann-Whitney U test. Categorical data will be expressed as frequency (percentage) and compared using chi-square test or Fisher's exact test. Further data analyses may include: Kaplan-Meier survival curves; Log-rank test for differences; multivariate logistic regression and Cox regression with competing risks to assess predictive ability; ROC analysis to compare the diagnostic efficacy of the

new test with existing tests; subgroup analysis to assess effect modifiers; sensitivity analysis; interaction testing.