

Clinical Trial Protocol: National Taiwan University Hospital

IRB No. 202410060RINC

Study Title: Using telemedicine to assist in the clinical care of patients with decompensated cirrhosis.

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Study aim: A randomized clinical trial to compare the impact of telemedicine care and standard care models on medical care, satisfaction, and clinical outcomes in patients with decompensated cirrhosis.

I. Abstract

Chronic liver disease and cirrhosis are common diseases in Taiwan and were the 12th leading cause of death in 2023. If cirrhosis progresses to decompensated cirrhosis, the loss of liver function leads to various complications, such as hypoalbuminemia, ascites, jaundice, spontaneous bacterial peritonitis, esophagogastric variceal bleeding, hepatic coma, and hepatorenal syndrome. A study in Taiwan showed that among 476,158 patients with chronic hepatitis B, approximately 7.9% had decompensated cirrhosis. These patients face challenges such as multi-organ complications, complex monitoring, medication management, and frequent medical visits. The medical team needs to integrate various healthcare professionals to regularly monitor the condition and conduct liver transplant evaluations. Regarding medication management, patients must take multiple medications and adjust their dosages based on their condition. Frequent medical visits and hospitalizations impose economic and psychological burdens on patients and their families.

Since the COVID-19 pandemic, telemedicine and self-monitoring have become emerging care models. Telemedicine, which includes reviewing electronic medical records, remote monitoring, teleconsultation, medication management, and educational and psychological support, is particularly important for patients with decompensated cirrhosis. This research project utilizes a newly designed remote care model for cirrhosis patients to conduct a 12-month randomized clinical trial. The goal is to compare the clinical outcomes of patients with decompensated cirrhosis receiving "remote care" versus "standard care". The assessment includes changes in liver disease severity scores, unplanned hospitalization rates for cirrhosis-related complications, unplanned emergency room visit rates, days alive and out of the hospital, liver disease-related medical expenses (outpatient, emergency, and inpatient), as well as quality of life and patient satisfaction.

II. Study Objectives and Background Description:

Chronic liver disease and cirrhosis are common diseases in Taiwan, ranking as the 12th leading cause of death in 2023, with approximately 3,800 deaths annually. As cirrhosis progresses to decompensated cirrhosis, the liver becomes unable to effectively synthesize proteins, metabolize toxins, and maintain normal metabolic processes. This leads to complications such as hypoalbuminemia, ascites, jaundice, gastroesophageal varices, coagulation abnormalities, and hepatic encephalopathy. According to a recent study using Taiwan's National Health Insurance Research Database, among 476,158 patients with chronic hepatitis B, approximately 37,634 (7.9%) were diagnosed with decompensated cirrhosis. Because patients with cirrhosis often experience medical complications such as esophageal variceal bleeding, ascites with bacterial peritonitis, and hepatic encephalopathy, about five percent of these patients develop liver cancer each year. Clinical care for these patients faces the following challenges:

1. **Multi-organ Complications:** Cirrhosis patients often present with multiple complications, including ascites, hepatic encephalopathy, infection, and bleeding. This requires an integrated medical team for diagnosis and care, including specialists in hepatology, gastroenterology, and infectious diseases.
2. **Complexity of Monitoring:** Patients require regular monitoring of parameters such as body temperature, blood pressure, heart rate, respiration, blood oxygen, height, weight, abdominal circumference, urine output, and bowel movement frequency and color. Various tests, including liver and kidney function, electrolytes, blood counts, and coagulation function, are also necessary to ensure disease stability. Furthermore, patients may require evaluation and wait-listing for liver transplantation.
3. **Medication Management:** Patients with cirrhosis typically require multiple medications, such as liver-targeted therapies (e.g., antiviral drugs), diuretics (for ascites and lower limb edema), beta-blockers (to prevent esophageal variceal bleeding), and lactulose (for hepatic coma). Patients need reminders to take medications on time, and dosages often require frequent adjustments based on their clinical status.
4. **Frequent Medical Visits or Hospitalizations:** Due to the complexity of their condition, patients with decompensated cirrhosis often require frequent hospitalizations, which imposes significant economic, psychological, and caregiving burdens on patients and their families.

Since the COVID-19 pandemic, telemedicine and self-monitoring for chronic diseases have emerged as a novel medical model. Many individuals became accustomed to teleconsultations via phone or video during home isolation for COVID-19. Several telemedicine models have already been implemented for patients with decompensated cirrhosis:

1. **Reviewing Electronic Medical Records and Remote Monitoring:** Through electronic medical record systems, physicians can remotely view patient records and regularly monitor key physiological parameters, such as liver function, kidney function, and coagulation function.
2. **Teleconsultation:** Specialists can provide diagnostic and treatment recommendations via video conferencing without being physically present, which is particularly helpful for patients in remote

areas unable to travel to the hospital.

3. **Medication Management:** The management of certain chronic disease medications can be conducted via telemedicine, allowing doctors to adjust medication regimens remotely.
4. **Education and Psychological Support:** Through online education and counseling, patients and their families can better understand the disease and obtain necessary psychological support.

However, there is currently a lack of channels for home care interaction with healthcare providers. Providing remote care for cirrhosis that includes continuous monitoring of the disease course—such as vital signs, ascites or edema status, nutritional intake, medication adherence, and changes in consciousness—could enable early detection of patients progressing to critical illness. This would enable timely consultation and medical advice, potentially reducing unplanned emergency room visits, hospitalizations, and unscheduled outpatient visits.

This study intends to utilize a newly designed remote care model for patients with cirrhosis to conduct a randomized clinical trial. The study will compare the clinical outcomes of patients with decompensated cirrhosis receiving "remote care" versus "standard care". Outcomes measured will include changes in liver disease severity scores (MELD score), unplanned hospitalization rates for cirrhosis-related complications, unplanned emergency room visit rates, days alive and out of the hospital, liver disease-related medical expenses (outpatient, emergency, and inpatient), as well as quality of life and patient satisfaction.

III. Study Methods

(I) Research Method: Prospective randomized controlled study

(II) Patient Selection (Inclusion criteria):

1. Patients with decompensated cirrhosis with a Child-Pugh score of B or C
2. Age: 18 years or older
3. Regular follow-up at least once every 3 months

(III) Exclusion criteria:

1. Patients with concurrent active malignancy (if previously diagnosed, the patient must have been cured for at least 2 years)
2. Those with an expected survival of less than one year

(IV) Procedures:

Enrollment and Grouping: Participants will be assigned in a 1:1 ratio using block randomization based on their Child-Pugh score (B or C). Patients will be divided into:

1. **Standard Care Group** (Routine medical care, fixed follow-up schedule) - 60 participants
 - (1) Outpatient follow-up at least every 3 months (intervals may be shortened if the condition is unstable)
 - (2) Physical examination: Body temperature, blood pressure, heart rate, respiration, blood oxygen, height, weight, and abdominal circumference

- (3) Routine blood tests (CBC+DC, Albumin, total protein, T-Bil, D-Bil, AST, ALT, ALP, GGT, BUN, Cre, Na, K, PT, CRP, NH3)
- (4) Abdominal ultrasound at least every 6 months

2. Remote Care Group (Routine medical care, fixed follow-up schedule, and remote care) - 60 participants

- (1) Routine Care Portion: Same as the Standard Care Group above
- (2) Remote Care Portion: This employs a newly designed remote care model for cirrhosis patients. The "Chief i-Health" APP platform is for home use, requiring a username and password to log in; each participant will have a unique ID for data upload. The platform is developed by Chief Telecom Co., Ltd., and health data is stored in VM and Oracle database services within Chief Telecom's IaaS. Physical equipment is located in Chief Telecom's IDC (Neihu, Taipei). Data and images can only be viewed by the PI and research staff, and collected data is for this project only. Information security follows Chief i-Health security measures.
 - (a) Remote Physiological Monitoring: Smart bands will be provided for 24-hour use. Participants will daily measure and upload temperature, blood pressure, heart rate, respiration, blood oxygen, weight, steps, activity, calories, sleep, bowel habits, and frequency.
 - (b) Remote Continuous Care: Clinical trial staff monitor physiological data during working hours, providing consultations and arranging medical treatment if abnormalities or emergencies are detected.
 - (c) Active Outreach: Staff will call participants every 4 weeks to check health status (calls will be recorded).
 - (d) Image Uploads: Every two weeks, participants will use their phones to capture images (face, tongue, skin, urine, stool) and a 1-minute video (face and chest). Staff and doctors will evaluate these and provide feedback.

The clinical trial duration is 12 months, evaluating outcomes for both groups.

Primary Endpoint:

1. Change in Liver Disease Severity Scores (MELD score)

Secondary Endpoints:

1. Rate of All-Cause Unplanned Hospitalizations
2. Rate of All-Cause Unplanned Emergency Room Visits
3. Days alive and out of hospital
4. Quality of Life Score & Patient Satisfaction (CLDQ or EQ-5D-5L scores)
5. Feasibility and Adherence to telemedicine (percentage of days with successful uploads and response rate to calls)
6. Total medical expenses at NTUH related to liver disease (Outpatient + ER + Inpatient), excluding routine renal replacement therapy

IV. Statistical Considerations and Data Analysis

1. **Statistical Methods:** Continuous variables are described using the median and interquartile range, while categorical data are presented as numbers and proportions. Data are compared using the Mann-Whitney U test or the chi-square test between groups. A logistic regression analysis will be conducted for predictors of the study endpoints. All statistical analyses will be performed using Stata (version 18; StataCorp, College Station, TX, USA). All tests will be two-tailed, and $P < 0.05$ is considered statistically significant.
2. **Sample Size Calculation:** The number of participants for both groups was estimated based on previous relevant research results and reported hospitalization rates:
 - (1) Hospitalization rate for the Standard Care Group: 30%
 - (2) Hospitalization rate for the Remote Care Group: 10%With a two-sided 5% significance level and 75% power, the calculation results in 55 patients per group, totaling 110 patients.
Accounting for an approximate 10% dropout rate per group, 60 participants are required for each group (totaling 120 participants).
- (3) **Image Data Analysis:** Image data will be analyzed for physical signs using the model developed in the study "202002024RINB: Research on the Correlation Between Physical Sign Image Data and Health Status".
- (4) **Audio Data Analysis:** Audio recordings of phone calls with clinical trial personnel will be analyzed using artificial intelligence-based speech recognition.

V. References

1. Chien HT, Su TH, Huang H, et al. Real-world epidemiology, treatment patterns and disease burden of patients diagnosed with chronic hepatitis B in Taiwan. *Liver Int* 2023;43:2404-14.