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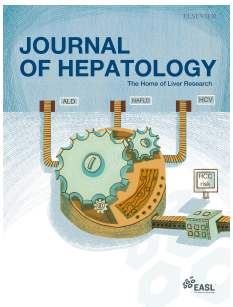

Evaluation of CirrhoCare® - A digital-health solution for home management of patients with cirrhosis

Konstantin Kazankov, Simone Novelli, Devnandan A. Chatterjee, Alexandra Phillips, Anu Balaji, Maruthi Raja, Graham Foster, Dhiraj Tripathi, Ravan Boddu, Ravi Kumar, Rajiv Jalan, Rajeshwar P. Mookerjee

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Novel digital-health system to diagnose and treat early new decompensation events in advanced cirrhosis

Daily patient data input and communication to hepatologist

- Measurements of hemodynamics, weight, water percentage, and cognitive testing
- Self-reported well-being and intake of food, fluid and alcohol
- Voice messages
- Text messages

Patient at home

Hepatologist

Direct two-way communication to patient

- Phone calls
- Text messages
- Community intervention, e.g. advice on fluid intake, adjustment of diuretic and laxative doses

A pilot study of CirrhoCare® - remote home management in patients with decompensated cirrhosis

- 20 patients with advanced cirrhosis

- Home management for a mean of 10 weeks

- 20 contemporaneous cirrhosis control patients receiving standard-of-care management

CirrhoCare® prompts early diagnosis of new decompensating events and their specialist intervention in the community

- High patient engagement

- Fewer and shorter readmissions than controls

- Markedly reduced unplanned paracentesis

- Improvement in disease severity scores

Title

Evaluation of CirrhoCare® - A digital-health solution for home management of patients with cirrhosis

Running title: Remote home management of decompensated cirrhosis

Authors

Konstantin Kazankov[1,2], Simone Novelli[1], Devnandan A Chatterjee[1], Alexandra Phillips[1], Anu Balaji[3], Maruthi Raja[3], Graham Foster[4], Dhiraj Tripathi[5], Ravan Boddu[3], Ravi Kumar[3], Rajiv Jalan[1,6], Rajeshwar P. Mookerjee[1,2]

Affiliations

[1]Liver Failure Group, Institute for Liver and Digestive Health, UCL Medical School, Royal Free Hospital, London, United Kingdom; [2]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; [3]CyberLiver Limited, Manchester, United Kingdom; [4]Barts Liver Centre, Queen Mary University of London, UK; [5]Gastrointestinal and Liver Services, University Hospitals Birmingham Foundation Trust, Birmingham, UK; [6]European Foundation for the Study of Chronic Liver Failure

Corresponding author:

Professor Rajeshwar P. Mookerjee

Institute for Liver and Digestive Health

University College London, Royal Free Campus; Rowland Hill Street; London NW3 2PF

United Kingdom

E-mail: r.mookerjee@ucl.ac.uk

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ABSTRACT

Background

Cirrhosis patients discharged from hospital following acute decompensation are at high-risk of new complications. This study aimed to assess the feasibility and potential clinical benefits of remote management of acutely decompensated cirrhosis patients using CirrhoCare®.

Methods

Cirrhosis patients with acute decompensation were followed with CirrhoCare® and compared with contemporaneous matched controls, managed with standard follow-up. Commercially available monitoring devices were linked to the smartphone CirrhoCare®-App, for daily recording of heart rate, blood pressure, weight, % body-water, cognitive function [CL-Animal Recognition Test (CL-ART) App], self-reported well-being and, intake of food, fluid and alcohol. The App had 2-way patient-physician communication. Independent external adjudicators assessed appropriateness of CirrhoCare-based decisions.

Results

Twenty-cirrhotic patients were recruited to CirrhoCare® (mean age 59±10 years, 14-male, alcoholic cirrhosis (80%), mean MELD-Na score 16.1±4.2) and were not statistically different to twenty contemporaneous controls. Follow up was 10.1±2.4 weeks. Fifteen-patients showed good engagement (≥4 readings/week), 2 moderate (2-3/week), and 3 poor (<2/week). In a usability questionnaire the median score was ≥9 for all questions. Five CirrhoCare®-managed patients had 8-readmissions over median of 5 (IQR 3.5–11) days, and none required hospitalization for >14 days. Sixteen other CirrhoCare-guided patient contacts were made, leading to clinical interventions that prevented further progression. Appropriateness was

confirmed by adjudicators. Controls had 13-readmissions in 8-patients, lasting median 7 (IQR 3–15) days with 4-admissions of >14 days. They had 6 unplanned paracenteses compared to 1 in the CirrhoCare® group.

Conclusions

This study demonstrates CirrhoCare® is feasible for community management of decompensated cirrhosis patients with good engagement and clinically-relevant alerts to new decompensating events. CirrhoCare® managed patients have fewer and shorter readmissions justifying confirmatory larger controlled clinical trials.

Lay summary

This first study of digital, real-time, home management for multiple complications of advanced cirrhosis, with CirrhoCare®, showed positive patient engagement and feedback in patients with mainly alcohol-related cirrhosis, following a recent hospital discharge. CirrhoCare® allowed early diagnosis of new complications for patients at home, prompting their hepatologists to intervene over >10 weeks follow-up. CirrhoCare® managed patients had fewer and shorter hospital readmissions, as well as less unplanned abdominal fluid drains than in a control group. CirrhoCare® is a promising tool for specialist, community management of cirrhosis patients, at-risk of new cirrhosis complications.

Highlights:

- CirrhoCare® has good patient engagement and user feedback in patients with decompensated cirrhosis for their remote home management
- The system detects early signs of new decompensation and allows timely intervention
- Remotely managed patients had fewer admissions than controls, and improved disease severity scores over 10 weeks
- CirrhoCare® may aid hepatologists with early diagnosis of new post hospital-discharge cirrhosis decompensation, facilitating prompt community intervention, thereby reducing hospitalizations

INTRODUCTION

Patients with decompensated cirrhosis, defined as the development of ascites, hepatic encephalopathy (HE), gastrointestinal bleeding or bacterial infection, are at a high risk of new acute decompensation (AD) events and re-hospitalization.[1, 2] The readmission rate for patients discharged after an admission for AD remains as high as 40 % [3], warranting early outpatient follow-up, ideally every 2 to 4 weeks, in order to detect possible new complications and guide appropriate management.[4] However, growing cirrhosis prevalence and over-burdened state healthcare systems cannot facilitate such intensity of follow-up, currently further challenged by the pressures exerted by the COVID-19 pandemic.[5] Furthermore, cirrhosis patients in rural or deprived areas may have limited access to specialist care, which negatively affects their outcomes.[6] Thus, there is an unmet need for tools to ensure timely, and equitable access to specialist liver care, to diagnose and manage new decompensation events, without the requirement for regular hospital reviews.

In this regard, digital therapeutic approaches show promise in remote patient management and have been successfully used in paediatric and adult liver transplant recipients in the post-transplant period.[7, 8] Digital monitoring has also been explored in cirrhosis[9]: Bloom et al. demonstrated good feasibility of a smartphone-based platform for weight monitoring of outpatients with cirrhosis and ascites, as well as the possible benefit of this approach for ascites control.[10] Similarly, smartphone-based assessment of cognitive function has been studied for detection of early signs of HE in cirrhosis patients [11], and a single study showed a potential for prevention of HE-related hospitalization within 30 days of monitoring, using a smartphone-based App in cirrhosis patients with the help of their caregivers.[12]

Thus, patients with decompensated cirrhosis may benefit from home monitoring, however, an integrated approach aiming to detect and manage the full spectrum of potential cirrhosis decompensating events, has not been evaluated. Furthermore, the duration of monitoring and engagement in cited studies has been largely limited to 30 days, whereas the risk of readmission for a new episode of AD and its impact on outcome, is highest over about 90 days.[3] Given this, and the pressures from the COVID-19 pandemic, we designed the present study of CirrhoCare® to assess multi-modal, digital home monitoring for 3 months, for patients with cirrhosis and recent hospital discharge with acute decompensation. Our primary aim was to assess feasibility and patient engagement over the duration of monitoring in patients with advanced cirrhosis. In addition, we hypothesized that CirrhoCare® would facilitate early detection of new deterioration and help to identify patients at risk of further decompensation triggering timely intervention.

PATIENTS AND METHODS

Study design and participants

Assessment in healthy volunteers

Seven healthy control subjects were assessed as part of an ethic for understanding biomarkers of cirrhosis evolution, under the Royal Free London Research Tissue Biobank, reference: NC.2017.16. These healthy individuals were studied to gauge functionality of the CirrhoCare® monitoring equipment as digital biomarkers, and to help assess synchronization of data through the CirrhoCare® App, that would allow oversight on the clinician dashboard. Any learning from healthy volunteer experience, including refinements to the system, optimization of data collection and presentation for ease of use on the patient-facing App, would then to be applied in the clinical pilot study of CirrhoCare®. Monitoring data from healthy individuals also helped establish a reference “normal” range for home monitoring, before application in cirrhosis patients.

Clinical pilot study of CirrhoCare®

We prospectively included and followed 20 consecutive patients with decompensated cirrhosis at the Royal Free Hospital in London, between 28.08.2020 and 16.12.2020 (Figure 1). All CirrhoCare® managed patients provided written informed consent and the study was approved by the London - Brighton & Sussex Research Ethics Committee (IRAS ID 285666; REC number 20/HRA/3843; NCT05045924) in accordance with the Declaration of Helsinki.

Inclusion criteria: age >18 years, cirrhosis diagnosed histologically, or based on clinical, radiological and biochemical characteristics, and a recent episode of hospitalization for AD.

Exclusion criteria: presence of acute-on-chronic liver failure (ACLF)[2]; untreated bacterial infection within 7 days, or gastrointestinal bleeding within 10 days before study inclusion; overt HE (grade II-IV[4]); active hepatocellular carcinoma or history of hepatocellular carcinoma that is in remission for <6 months; significant extrahepatic disease , e.g. congestive heart failure New York Heart Association Grade III/IV; chronic obstructive pulmonary disease with Global Initiative for Obstructive Lung Disease criteria>2; chronic kidney disease with serum creatinine >2 mg/dL or under renal replacement therapy; current extrahepatic malignancies; mental incapacity or language barrier precluding adequate understanding, cooperation or compliance in the study or with daily measurements; refusal or inability to give informed consent. After applying pre-screening for these criteria, 34-patients were approached for screening and given a patient information sheet; 20 of these patients passed the screening, gave consent for participation and were enrolled into the trial.

We screened 24 patients presenting with AD after the recruitment target of patients enrolled for monitoring was reached, as part of a continuously maintained database of acute cirrhosis decompensation used for audit purposes at the Royal Free London and identified 16 suitable patients based on fulfilling eligibility criteria for CirrhoCare® participation. Four other patients who were eligible for the CirrhoCare study and offered remote management but declined (felt unable to operate the CirrhoCare® App, n=3; did not have time for daily measurements, n=1), were also included as contemporaneous controls, completing the control cohort of 20 patients (Figure 1). Controls received standard-of-care clinical management including appropriate outpatient follow-up guided by their clinical requirements, as judged by their treating

hepatologist. The total observation time in this cohort was adjusted to match that of CirrhoCare® managed patients.

End points

Primary endpoint for CirrhoCare® was the feasibility of daily remote management, as determined by (i) patient CirrhoCare usage feedback-questionnaires and (ii) patient engagement activity logged on the CirrhoCare portal. Engagement was defined as good for an average of ≥4 measurements/week, moderate as 2–3 measurements/week, and poor as <2 measurements/week. The primary endpoint would be met by demonstration of at least 2 measurements/week (moderate or good engagement) in no less than 50% of patients. In addition, there was a qualitative assessment from the CirrhoCare® App feedback questionnaires.

Secondary endpoints for CirrhoCare® managed patients and controls included the following outcomes: (1) Liver related mortality, orthotopic liver transplantation (OLT), hospital readmissions and unplanned large volume paracentesis (LVP).

(2) Potential new cirrhosis-related complications (hepatic encephalopathy, ascites, dehydration with risk of acute kidney injury, infection or gastrointestinal bleeding) detected by the investigator team warranting patient contact/intervention.

(3), Changes in clinical disease severity scores (Model for End-Stage Liver Disease – sodium (MELD-Na) and CLIF-Consortium Acute Decompensation (CLIF-C AD) scores) during the monitoring period.

Independent adjudicator assessment of monitoring outcomes

Two independent, expert hepatologists from different institutions (GF and DT) were contacted, and once study results were available, given a detailed report of the clinical events that had occurred during monitoring, in conjunction with the monitoring measures that were available to the investigators at the actual time of the events (Table 4; Supplementary Section 2 and Supplementary Table 1). These adjudicators were asked to grade whether home monitoring and the resulting community interventions under CirrhoCare® management, were likely to have had a beneficial, neutral or negative impact on the patient's condition in each case. The adjudicators did not assess the disease course of decompensating events in the control group managed with standard follow-up.

CirrhoCare® Patient monitoring and management

All patients were issued and educated to the use of their monitoring equipment and the CirrhoCare® App, (CyberLiver Ltd, UK) on a supplied study-specific smartphone (including a SIM-card). The monitoring devices, commercially sourced from Withings, included: 1) a wristwatch (Withings Move), for determination of heart rate and movement 2) a blood pressure (BP) cuff (Withings BPM Connect; three automatic, consecutive measurements were taken and averaged) 3) A weighing scales (Withings Body+) with bioimpedance to record weight and body-water percentage (Figure 2A).

The patients also performed a daily, timed cognitive function test – Cyberliver animal recognition test (CL-ART) – on the CyberLiver ART App, integrated into the phone. The ability to pass the test, the number of attempts, and the time (in seconds) required to successfully

complete a test, were recorded and transferred to the Clinician dashboard for review. Furthermore, the patients entered their daily sense of well-being (in order from well to unwell: 'Fresh, Active, Well, Bit Tired, Dizzy, Weak'), and intake of fluid (amount and type of fluid, including a separate drop-down menu for alcohol beverages) and food (number of cooked and total meals), using drop-down menus on the CirrhoCare® App. The data (compliant with GDPR legislation) were then stored on a secure CyberLiver Cloud and ISO13485:2016 -certified, CE marked, platform, and presented real-time to the Investigator team on the CirrhoCare® Investigator dashboard (Figure 2B), which flagged alerts for daily review. The patients also had an opportunity for direct, 2-way communication with the Investigator team, by text and voice messages, in a closed-loop communication.

The patients received prompts to perform their measurements every morning at an agreed time convenient to the patients. If the participant failed to respond to the prompts, reminders were sent automatically with a 15-minute interval for a total of 3 prompts on a day. Furthermore, a reminder for a missing measurement could be sent by the Investigator team. A prompt for completion of the food and fluid chart appeared every evening at 8 pm. Moreover, a digital thermometer was provided to each patient. Whilst temperature was not a part of expected daily measurements, it could be measured if specifically requested by the CirrhoCare system based on monitored data.

Questionnaires

CirrhoCare® App usability questionnaires were done by the patients on their supplied smartphones at weeks 4 and 12, following a prompt on the App (Table 2). A free-text field was

made available for the patients to leave comments. Similarly, a Quality-of-life questionnaire was populated at the study start and 12 weeks, quantified as a self-reported percentage score of the patient's overall perception of their health and mood, whereby 0 was the worst possible and 100 the best.

Investigator assessment of monitoring alerts and triggers for change in management

The investigators (KK and RPM) were alerted to measurements deemed outside of pre-determined ranges on the clinician dashboard and could perform a phone call to clarify the patient's symptoms or prompt the patient for further information via the Investigator dashboard (Figure 2), such as a repeat measurement of a given parameter. The following deviations in the daily measurements were flagged as possible signs of deterioration: systolic BP <95 mm Hg or a decrease of >15 % from the patient's documented stable baseline; HR >90 bpm or an increase of >10 % from the patient's stable baseline; failed CL-ART App test, or >3 attempts required to pass the test, or CL-ART test time twice that of the patient's average for 2 days in a row; a report of well-being noted on the App when "Dizzy" or "Weak" are the responses for 2 days in a row; consistent increase/decrease of body water weight (>1.5 kgs) over 3 days; fluid intake <1000 ml/day; failure to perform measurements >2 days in a row in a previously compliant patient; concern expressed by the patient through text/voice messages on the Investigator dashboard. Notably, these thresholds were not absolute, and patient alerts were assessed individually by the investigating clinician with oversight of that patient's disease.

A change in community management as indicated by the alert threshold and individualized clinical need, could include advice on fluid intake; initiation, dose adjustment or withholding of diuretics, laxatives or Rifaximin; assistance to organize support for alcohol cessation; urgent

hospital review; hospital admission. All clinical interventions were in line with standard treatment guidelines, though facilitated through the CirrhoCare® system, under direct clinician oversight and based on the real-time patient data available.

Scheduled contacts

Telephone consults were performed 4 and 8 weeks after inclusion. A face-to-face consultation including clinical examination was done at the end of the study, at 12 weeks. Blood testing was done at inclusion and then at the 12-week visit, including full blood count, liver and kidney function tests, and prothrombin time/ international normalized ratio (INR). MELD-Na and CLIF-C AD scores were calculated for these time points.

Statistical analysis and reporting

For the primary outcome of feasibility, engagement with CirrhoCare was quantified by the number of patients performing measurements less that 2 times/week, 2 to 3 times/week and 4 or more times/week, and reported as poor, moderate or good engagement, respectively. Additionally, qualitative assessment of patient feedback through the in-App questionnaires on use of CirrhoCare monitoring and impact on their quality-of-life, was recorded.

A post-hoc statistical analysis was carried out, using Student's t-test and Mann-Whitney tests to compare normally and non-normally distributed variables, respectively, between CirrhoCare® managed patients and contemporaneous controls at study enrolment. For differences in proportions between these groups, we used the χ^2-test or Fisher's exact test. The paired t-test was used to assess changes in clinical disease scores from inclusion to the end of study.

The study was not powered to show differences in the incidence of clinical events such as death, orthotopic liver transplant (OLT), readmissions or large volume paracentesis (LVP) between CirrhoCare® managed patients and contemporaneous controls, for which reason no statistical testing was preformed regarding these variables.

All data are expressed as means ± standard deviations (SD), medians with interquartile range (IQR) or proportions, and P-values ≤0.05 were considered statistically significant. STATA version 14.0 ®StataCorp LP was used for data analysis. SQUIRE guidelines were used for reporting of this study.[13]

RESULTS

Home monitoring of healthy volunteers and system preparation for pilot study

Seven healthy volunteers (n=7, 5 male, mean age 37 years, with no known liver dysfunction) performed repeat measurements over a duration of 8 weeks. The initial testing facilitated trouble-shooting issues with Bluetooth connectivity between the hardware components and the CirrhoCare® system. Furthermore, data presentation was optimized (trends from previous days measurements) on the clinician dashboard, in addition to modification of drop-down menus such as fluid intake (amended to include nutritional supplements and alcohol-free beverages, and variation in glass-size measures), to improve fluid-balance accuracy, and use on the patient-facing App. (Figure 2). Some measurement methodological improvements also resulted from testing in healthy volunteers, such as positioning on the weighing scales for those with poor balance and triggering repeat blood pressure measurements. These system refinements and methodological knowledge were carried forward into the clinical study.

The descriptive statistics of monitoring measures in the healthy volunteers are shown in Supplementary Material, Supplementary Table 2, which was used to derive the respective “normal” reference standard values in healthy adult individuals, when monitored at home. The overall coefficient of variance for volunteer digital measurements was: heart rate 14 % (n=224 total measurements), systolic blood pressure 9 % (n=224), diastolic blood pressure 10 % (n=224), total weight 10 % (n=184), body water percentage 11 % (n=179).

Patient characteristics

The characteristics of CirrhoCare® managed patients and contemporaneous controls at inclusion and after follow-up are shown in Table 1. Control managed patients were older and

more often female, however, not statistically significantly different. The predominant cirrhosis etiology (>80%) was alcohol in both groups. Controls had slightly higher MELD-sodium scores, whereas the CLIF-C AD scores, and the number of admissions for disease decompensation within 1 year prior to study enrolment, were higher in the CirrhoCare® group; however, none of these differences were statistically significant.

Primary outcome: Feasibility and engagement

One patient (5%) withdrew consent within two weeks after study enrolment. Two other patients (10%) completed the study but performed measurements less than 2 times a week, deemed poor engagement. As such, the primary endpoint demonstrating feasibility through engagement with at least 2 monitoring measurements/week, was met by 85% (17/20) patients managed with CirrhoCare. Two patients performed their measurements 2 to 3 times/week (described as moderate engagement), whereas the remaining 15 patients (75%), performed measurements at least 4 times weekly (good engagement).

Patient reported usability data are shown in Table 2. The scores for the usability questionnaires performed at 4 and 12 weeks had a wide range, however the median scores were high (9 out of 10), and for all questions; at least two thirds of the patients scored 8 out of 10 or above. Furthermore, eight patients left feedback comments appreciative of the home measurement concept and the use of CirrhoCare® App (Supplementary Section 1).

Secondary Endpoints:

Patient outcomes during follow-up

CirrhoCare® managed patients and controls were followed for a mean 10.1 and 9.9 weeks, respectively (Table 1); in remotely managed patients this resulted in a total of 1397 patient-days of observation. One patient in the CirrhoCare® group and two in the control group died, whilst one patient in the remotely managed group received a liver transplant (Table 3).

Readmissions

Five of the CirrhoCare® managed patients had a total of 8 hospital readmissions (Table 3). Two of these readmissions (1 HE and 1 AKI with HE) were facilitated by the Investigators based on the signs of decompensation on the Investigator dashboard and resultant contact with the patients; both admissions lasted <4 days. The remaining readmissions included 3 GI bleeds in the same patient, and 3 further cases of HE. A specific description of the readmissions, including the monitored measures prior to deterioration, is provided in Supplementary Section 2 and Supplementary Table 1.

In standard care managed controls, 8 patients had a total of 13 readmissions (3 HE, 2 AKI, 4 infections -3 spontaneous bacterial peritonitis [SBP], 1 fluid overload, 2 hyponatremia, 1 fluid overload + AKI). The median length of hospitalization when readmitted was higher in this control cohort (Table 3), with some patients being admitted longer than 14 days, and importantly, controls required more days of intensive care support.

CirrhoCare® clinical alerts and resulting interventions

On 16 occasions in 12 different patients, Investigators contacted patients due to CirrhoCare® clinical alerts based on measurements and self-reported data, for changes they deemed not

severe enough to require hospitalization but felt might benefit from community-intervention, aiming to prevent re-admission (Table 4, Supplementary Section 2 and Supplementary Table 1). The following events were registered: 5 significant fluid accumulation, 2 early HE (triggers: 1 dehydration and 1 constipation), 6 dehydration (risk of AKI), 2 cases of alcohol relapse and 1 general malaise due to a probable viral infection (Table 4). The median time to first registered event was 18 (IQR 4–26) days. In these instances, after confirmation of clinical suspicion and repeat measurements, interventions such as advice on fluid intake, adjustment of diuretic dose or changing laxatives were implemented, guided by the CirrhoCare data, as relevant. Alerts were mainly based on individual deviations in cognitive testing, BP, HR and weight/hydration status (Table 4, Supplementary Section 2 and Supplementary Table 1).

Assessment of monitoring outcomes by independent clinical adjudicators

After reviewing the detailed description of events occurring during monitoring and the corresponding monitoring data, both independent expert adjudicators (GF and DT), agreed CirrhoCare® management was of beneficial impact in all cases when the Investigating team facilitated hospital readmission (Table 4). For instances of clinical alerts without readmission, GF noted interventions by CirrhoCare® helped avoid progression of cirrhosis complications in 12, and DT in 13, out of 16 cases, and thereby was beneficial; both noted neutral impact in the remaining cases (Table 4; Supplementary Table 1), and neither noted harmful impacts on any patient. This independent confirmation of absence of negative impact reassured that the safety endpoint of CirrhoCare® management was met.

Impact on disease severity

CirrhoCare® managed patients showed improvement in their biochemical parameters over the study with trends showing decreased MELD-Na (p=0.062) and CLIF-C AD scores (p=0.079), whereas controls did not (MELD-Na score: p=0.59, CLIF-C AD score: p=0.71) (Figure 3). Remotely managed patients had markedly less requirement for unplanned large volume paracentesis (LVP) than in controls (1 versus 6; Table 3)

Quality of life

In CirrhoCare® managed patients, quality of life quantified as a percentage score of the patient's overall perception of their health and mood, was a mean of 73 ± 19 at inclusion, and 72 ± 21 at the end of the study, p=0.92.

Investigator team interactions with the patients and CirrhoCare® System

The combined monitoring time for all patients was 1397 patient-days. During this time, the investigator team had contacts with patients based on technical issues and clinical alerts.

Technical challenges: The investigators contacted patients 66 times for guidance on performing the measurements correctly or related technical issues, including phone-network connectivity and/or failure of monitoring devices to blue-tooth connect to the CirrhoCare® phone-App. These were resolved by switching network SIM cards and/or re-installing the App. Moreover, 147 automatic reminders were sent out using the CirrhoCare® dashboard without need for direct patient contact, when measurements failed to appear on the clinician dashboard on a given morning.

Clinical alerts: Twenty additional repeat measurement requests were made via the clinician dashboard based on a physician-deemed abnormal initial value, with subsequent improved repeat measurement warranting no further action. The investigators also made 27 text or telephone contacts for intervention related to hospital readmissions or other events of deterioration, whilst 34 contacts occurred when early deterioration was suspected but discounted after a dialogue with the patient.

DISCUSSION

Cirrhosis patients have high readmission rates following an episode of acute decompensation[3] and prevention of recurrent new decompensation by conventional outpatient management, based on pre-determined scheduled visits, is challenging and not personalized to the needs and changing status of a given patient. More proactive strategies with early, specialist follow-up in day-hospital facilities, have shown promising results[14, 15] but are resource-intense and still require hospital attendance. In this regard, technological advances enable a new approach for specialist, remote management in the community, a necessity during a Pandemic when nosocomial infections are a concern. The opportunity created by COVID-19 to embrace technology when standard-care pathways were compromised, was the impetus for us to perform this first study of multi-modal, real-time, 12 week remote monitoring of patients recently discharged following acute cirrhosis decompensation.

Our key findings were high patient engagement and reported usability of the CirrhoCare® system and early detection of new signs of decompensation, allowing timely intervention by the Investigators preventing severe progression of complications. CirrhoCare® managed patients had fewer hospital readmissions and unplanned paracentesis compared with contemporaneous controls, whilst demonstrating improved disease severity scores over the monitored duration.

Eighty-five percent of the remotely managed patients met the primary endpoint of engagement with remote monitoring, which exceeded the reported compliance with medical therapy in

advanced cirrhosis patients [16, 17], especially those with largely alcohol-induced liver disease, and was comparable to a study of liver transplant recipients during their perioperative period, who are a more compliant group.[7] The high engagement we observed mirrors a recent study by Bloom *et al,* demonstrating that the majority of patients with decompensated cirrhosis have access to smartphones and are willing to use them in their disease management[18], highlighting the potential for scalability and uptake of smartphone-based management in these patients. According to the free-text feedback left by studied patients, they found the equipment and the App easy to use, whilst daily measurements gave them (and their caregivers) reassurance, purpose, and greater understanding of their disease, being made aware of signs of new complications developing, and empowering them to be more involved in self- care. In addition, some used interfacing with their CirrhoCare® App as a key replacement activity, promoting better patient engagement the longer they used CirrhoCare®. The daily measurement prompts ameliorated forgetfulness, a well-known reason for medication non-compliance in this population.[17] The few patients with low usability scores were largely those challenged by technical and phone network issues at the study outset, which were ultimately resolved during the study. No patient including the ones prone to HE withdrew due an inability to perform the measurements correctly. However, it is possible that this technology may not be suitable for all cirrhosis patients, particularly in the elderly and the frail.

Based on daily monitoring data, we arranged for 2 hospital readmissions (HE and dehydration/HE) and attempted contact on the day of hospitalization in another 2 (HE and rectal bleed). In one readmission, the patient failed to perform adequate measurements for 3 days prior to hospitalization. Of the remaining 3 readmissions not pre-empted by alerts from

CirrhoCare®, one was for a biochemically detected AKI with known concurrent cardiac failure as the likely complicating factor, while the two remaining admissions were acute rectal bleeds in a single patient, incurring no hemodynamic compromise, when the patient self-reported to the hospital.

Similar to alerts for hospital readmissions, clinical events not requiring hospitalization but identified by the Investigators, were generally dominated by episodes of HE, dehydration, or fluid accumulation, reflected by deviations in cognitive testing, hemodynamics and hydration status respectively, and consistent with previous reports focusing on either ascites or HE.[10, 12] Acute bleeding seems less easily identifiable; however, this potential limitation may not be of great impact for early diagnosis, since acute bleeding is immediately evident to the patient, usually triggering a call for help without delay. Notably, only one of our patients had potential infection as a likely precipitant of acute decompensation during monitoring, which contrasts with the literature[19-21] and may be attributed to the limited sample size in this pilot study, and possibly to improved overall management oversight of CirrhoCare® managed patients.

Previous studies of 30 day home monitoring in cirrhosis to manage ascites[10] and HE[12] reported some signal for reduced hospitalization.[12] Our patients had 38 % fewer readmissions compared with contemporaneous control patients observed in parallel; the length of hospital stay upon readmission were also shorter, including the length of stay in intensive care. Furthermore, they had markedly fewer unplanned paracentesis requirements and importantly, a greater improvement in MELD-Na and CLIF-C acute-decompensation scores, than the control cohort over follow-up. Although the cohorts were not randomized, they were well matched,

particularly with regards to severity of cirrhosis, degree of decompensation, number of decompensation-related hospitalizations in the last year, and prior healthcare engagement and social care support.

Besides hospital readmissions, the Investigators registered 16 episodes of deterioration and responded with community-interventions such as advice on fluid intake or adjustment of diuretics and laxatives. Clearly, not all these events would have progressed to acute decompensation, although we believe that we may have prevented progression to hospitalization in some cases, a notion shared by independent adjudicators, who critically reviewed the monitoring data and our actions. Thus, our data indicate a high sensitivity of CirrhoCare® to detect even more minor perturbations in monitored variables, likely to reflect early indications of decompensation. Inherently, this implies a risk for increased clinical contact time with resource implications in the absence of significant deterioration. However, in this regard, although in some instances contacts were made with patients not experiencing serious clinical changes to their condition, the actual number of telephone calls specifically to guide management was limited to 61, which is in fact lower than studies of 30-day cirrhosis home monitoring, when adjusted for the longer duration of monitoring.[10, 12] Moreover, from patient feedback, it is evident that patients deemed such contacts reassuring to their overall management. In this respect, it is important to acknowledge a potential ethical issue in terms of investigator response time to the measurements. In our proof-of-concept study, all measurements were assessed daily, including weekends, 1-3 hours after they appeared on the investigator portal and the patients were instructed to use conventional pathways to access care out-of-hours. Thus, meticulous patient education is crucial to align expectations between

the monitored patient and the clinical-care team, regarding monitoring data and reaction time, and from whom to seek help, particularly if CirrhoCare® were to be implemented on a larger scale in the future.

Considering provider effort, the 61 phone calls made should be interpreted in the context of daily remote management in 20 patients over a median of 10 weeks, for a total of 1397 patient-days. Thus, for the vast majority of monitored data, the assessment by the investigators was confined to confirming that the recorded measures were within the pre-defined range, individualized for each patient, which took a little less than 1 hour a day, and has clear potential for automatization for future scaling-up, with resolution of teething-troubles such as connectivity issues in our present study. Obviously, incorporating the CirrhoCare® system into routine hepatology care may face challenges in the acceptance of the approach by practicing hepatologists and their institutions but in our view, their workload should be reduced by allowing them to focus their attention on patients most at-risk of new decompensation events, whilst those that are stable could avoid unnecessary hospital visits. This in turn would lead to a more sustainable healthcare delivery for cirrhosis care and aligns with governmental policy in the UK with NHS-X, and DiGA in Germany, as examples of initiatives towards healthcare systems more suited to remote care delivery. However, the true impact of remote management of cirrhosis patients on healthcare utilization, provider-effort and delivery costs needs to be assessed in future studies.

A key strength of this study is the well-defined cohort of patients with decompensated cirrhosis, with few screen failures, ensuring a broad generalizability of our results to advanced cirrhosis patients. Moreover, this was a ‘real-world’ study, conducted during COVID, when ‘standard’

outpatient management was unfavorable emphasizing the potential for this novel approach. The most significant limitation of the study, however, was the lack of randomization, which could introduce selection bias, and the potential for extrinsic factors beyond CirrhoCare® intervention, contributing to improved clinical outcomes. This said, management of CirrhoCare® patients and controls were equally impacted by COVID challenges. Furthermore, the only scheduled appointments in the CirrhoCare® group were "routine" telephone consultations every 4 weeks, an established practice of the unit during COVID-19 for following-up discharged decompensated cirrhosis patients, and all patients (CirrhoCare® and Control groups) were managed in accordance with standard treatment guidelines for cirrhosis complications. Thus, our contention is that our data strongly supports a positive impact of CirrhoCare® home management on clinical outcomes, a notion shared by the independent expert adjudicators, albeit they assessed the CirrhoCare® group but not the Controls. However, the efficacy of such management was not a primary endpoint of this pilot study, and an adequately powered, randomized trial, is warranted.

A further limitation in the study is the potential to introduce bias when assessing feasibility in patients using new technology, recruited according to protocol screening criteria that excludes patients with historical poor compliance, disability and significant psychiatric history. As such, accounting for the patients screened and then excluded in this study (n=14), may be seen to impact the interpreted feasibility (17 out of 20 included subjects on CirrhoCare management). Clearly, some patients may be reluctant to use new technology or undergo monitoring, in the same way that some patients will be non-compliant with new medication and investigations. Importantly, we applied the same criteria to the prospectively screened controls and excluded 8 such patients in that group, and thereby have tried to limit the impact from such bias.

Notwithstanding the limitations of the study size, given the monitoring period of 12 weeks and limited dis-engagement once on-boarded into the study, we observed sufficient numbers of clinical events to test the potential utility of CirrhoCare® remote management, and to determine the feasibility of its use.

In conclusion, our results demonstrate that use of CirrhoCare®, a novel, multi-modal, real-time, digital home management system for cirrhosis is feasible, receives high patient engagement and allows early detection of new clinical events facilitating timely intervention to prevent progression of cirrhosis decompensation. This is likely to improve patient outcomes in advanced cirrhosis, and have positive health-economic impacts, though this clearly needs further evaluation in larger, controlled studies.

ABBREVIATIONS

ACLF, acute-on-chronic liver failure

AD, acute decompensation of cirrhosis

AIH, autoimmune hepatitis

AKI, acute kidney injury

BP, blood pressure

CLIF-C AD score, CLIF Consortium Acute Decompensation score

HBV, hepatitis B virus

HCV, hepatitis C virus

HE, hepatic encephalopathy

HR, heart rate

HRV, heart rate variability

INR, international normalized ratio

IQR, interquartile range

ITU, intensive therapy unit

LVP, large volume paracentesis

MELD-Na score, Model for End-Stage Liver Disease – sodium score

NASH, non-alcoholic steatohepatitis

OLT, orthotopic liver transplantation

SBP, spontaneous bacterial peritonitis

SD, standard deviation

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Table 1. **Patient characteristics at inclusion**.

	CirrhoCare® managed patients (n=20)	**Contemporaneous cirrhosis controls (n=20)**	**P**
Male : female	14 : 6	9 : 11	0.20
Age (years)	59±10	56±14	0.43
Aetiology (n, %)	Alcohol 16 (80 %) NASH 2 (10 %) HBV 1 (5 %) NASH/HCV 1 (5 %)	Alcohol 17 (85 %) NASH 2 (10 %) NASH/AIH 1 (5 %)	-
Previous admissions within 1 year	1.6±1.2	1.5±1.2	0.89
Sodium, mmol/L	136±4	135±4	0.59
White cell count, $x10^9$/L	6.5 (3.8–8.8)	5.5 (4.4–8.8)	0.92
Albumin, g/L	33.5 (31–36.5)	31 (28.5–33.5)	0.07
Bilirubin, µmol/L	35 (12–72)	40 (28–122)	0.17
INR	1.3 (1.2–1.4)	1.4 (1.25–1.55)	0.16

Creatinine, μmol/L	81 (61–105)	62 (53–78)	0.05
MELD-Na score	16.1±4.2	18±4.6	0.18
CLIF-C AD score	50±6.4	49.4±7.3	0.78
Follow-up time (weeks)	10.1±2.4	9.9±3	0.81

NASH, non-alcoholic steatohepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; AIH, autoimmune hepatitis; MELD-Na score, Model for End-Stage Liver Disease – sodium score; CLIF-C AD score, CLIF Consortium Acute Decompensation score

Table 2. Patient reported usability of CirrhoCare® App.

Medians (minimum – maximum) and number (percentage) of patients scoring 8 out of 10 or above.

	1st Response (after 4 weeks)	**2nd Response (at study conclusion)**
After set-up, I could use the App straight away	10 (4 – 10) 16 (89 %) >7	10 (4 – 10) 15 (88 %) >7
The App seems easy to use	9 (2 – 10) 15 (83 %) >7	10 (5 – 10) 14 (82 %) >7
Photographs and images used are self explanatory	10 (4 – 10) 16 (89 %) >7	10 (5 – 10) 15 (88 %) >7
The instructions on the App are clear and easy to understand	10 (2 – 10) 15 (83 %) >7	10 (2 – 10) 13 (76 %) >7
I feel comfortable using the app at home on my own	10 (1 – 10) 15 (83 %) >7	10 (2 – 10) 14 (82 %) >7
Navigation was easy to follow and consistent	10 (2 – 10) 15 (83 %) >7	10 (2 – 10) 13 (76 %) >7
I can enter comments and feedback easily	9 (1 – 10) 12 (67 %) >7	10 (2 – 10) 16 (89 %) >7

Table 3. **Disease outcomes in CirrhoCare® managed patients and controls.**

	CirrhoCare® managed patients (n=20)	**Contemporaneous cirrhosis controls (n=20)**
Death (n, %)	1 (5 %)	2 (10 %)
OLT (n, %)	1 (5 %)	0
Number of patients with readmissions (n, %)	5 (25 %)	8 (40 %)
Total number of readmissions (n)	8	13
Readmission length of stay (days)	5 (3,5–11)	7 (3–15)
Number of readmissions ≥ 14 days (n)	0	4
Time to 1st readmission (days)	24 (18–31)	29 (10,5–53)
ITU length of stay (days)	5	16
Number of unplanned LVP (n)	1	6

OLT, orthotopic liver transplantation; ITU, intensive therapy unit; LVP, large volume paracentesis

Table 4. Assessment of Investigator interventions based on monitoring outcomes, by independent physician-adjudication panel.

Event	**Independent physician assessment**					
	GF			**DT**		
	Beneficial	Neutral	Harmful	Beneficial	Neutral	Harmful
Readmissions						
HE, n=3	1	2	0	1	2	0
AKI, n=1	0	1	0	0	1	0
HE + AKI, n=1	1	0	0	1	0	0
Bleeding, n=3	0	3	0	0	3	0
Total readmissions, n=8	**2**	**6**	**0**	**2**	**6**	**0**
Clinical events not requiring hospitalization						
Fluid accumulation, n=5	4	1	0	4	1	0
Early HE, n=2	1	1	0	2	0	0
Dehydration, n=6	5	1	0	5	1	0
Alcohol relapse, n=2	2	0	0	1	1	0

General malaise, n=1	0	1	0	1	0	0
Total events, n=16	**12**	**4**	**0**	**13**	**3**	**0**

HE, hepatic encephalopathy; AKI, acute kidney injury

GT, Graham Foster; DT, Dhiraj Tripathi

Fig. 1. Recruitment of patients for remote management and contemporaneous cirrhosis controls.

A Consort diagram to reflect the recruitment of patients.

*Consensus decision by the study coordinators based on history of non-compliance, psychiatric or psychological issues and/or severe addiction.

**3 patients felt unable to operate the CirrhoCare® App; 1 patient did not have time for daily measurements.

***Found not suitable as cirrhosis contemporaneous control, as they would not have been eligible for remote management based on disability and history of non-compliance, psychiatric or psychological issues and/or severe addiction.

Fig. 2. CirrhoCare® concept of home monitoring and management.

(A) Using the supplied smartphone with CirrhoCare® App, wristwatch for heart rate and motion detection, blood pressure cuff and biompedance weighing scales, the patients performed daily home monitoring of pulse, blood pressure, weight and body fluid as well as a cognitive function assessment using the CyberLiver animal recognition test. Moreover, they provided their self-reported well-being and intake of food, fluid and alcohol, and had an option to leave a text or a voice message to the Investigator team.

(B) These data were Blue-toothed to the smartphone, stored on a secure cloud and presented on the Investigator Dashboard, as Clinical Alerts, for assessment by the Investigator. The Investigators used text messages or phone calls to communicate with the patients and change their management as dictated by the clinical situation.

Fig. 3. Scores of disease severity at enrolment and end of study in CirrhoCare® managed patients

and controls.

Paired T-test was used for comparison of the scores et enrolment and end of study, separately in CirrhoCare® managed patients and controls. (A) Model for End-Stage Liver Disease – sodium (MELD-Na) Score: CirrhoCare® managed patients, 16.5±4.3 vs. 15.2±3.2, p=0.062; controls, 17.7±4.7 vs. 17±6.3, p=0.59. (B) CLIF Consortium Acute Decompensation (CLIF-C AD) Score: CirrhoCare® managed patients, 50±6.7 vs. 46.7±7, p=0.079; controls, 48.6±4.5 vs. 47.8±7.9, p=0.71.

Fig. 1

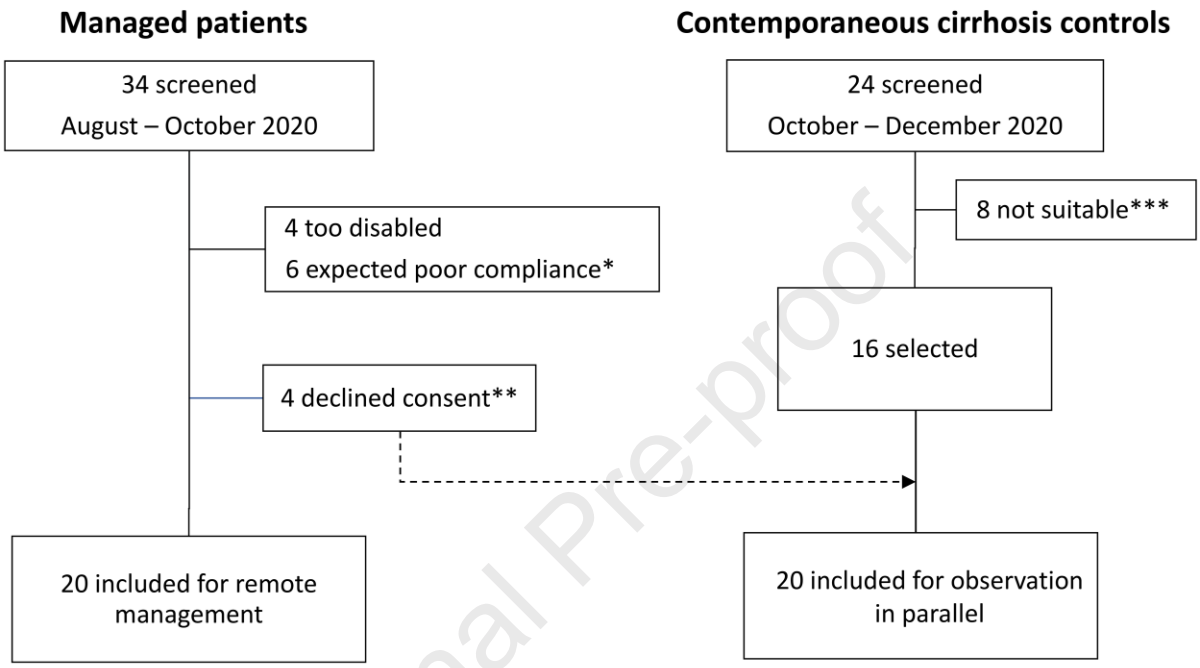
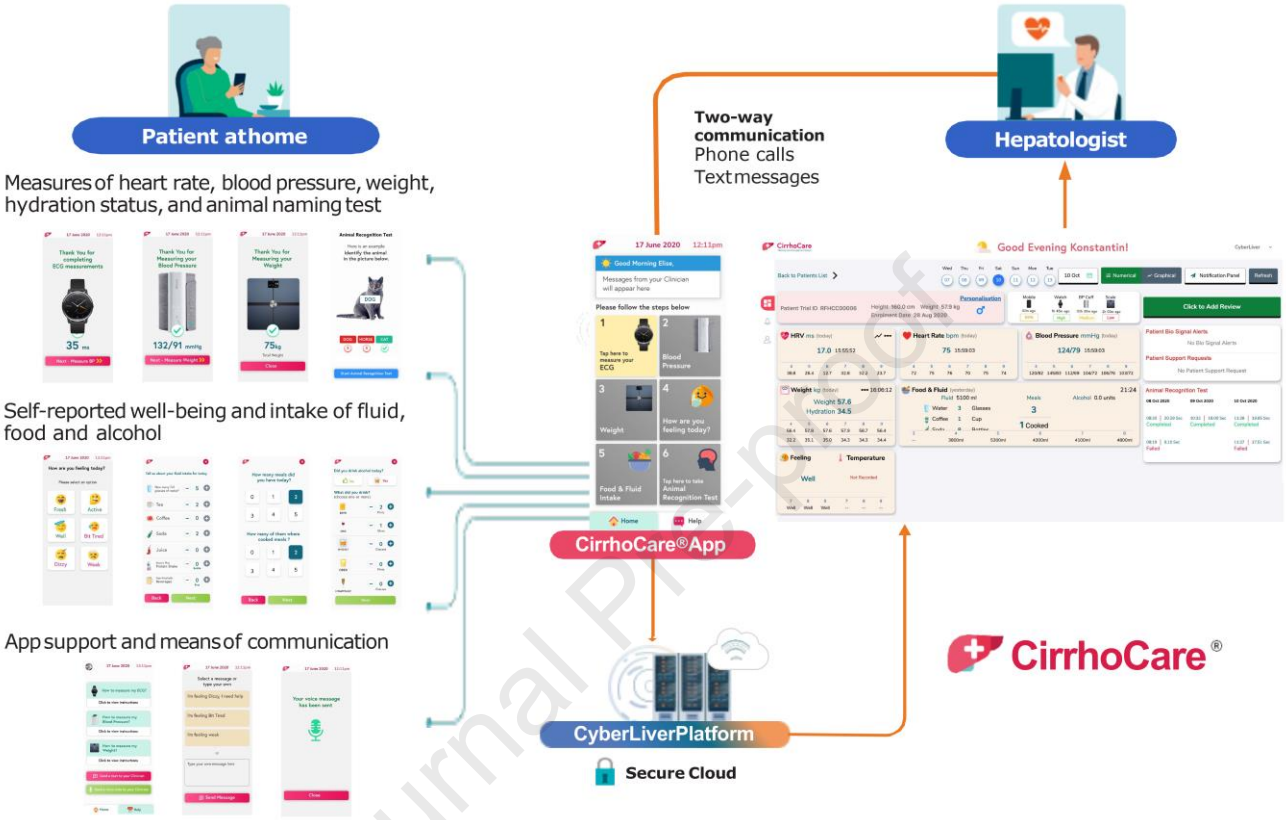


Fig. 2

(A)



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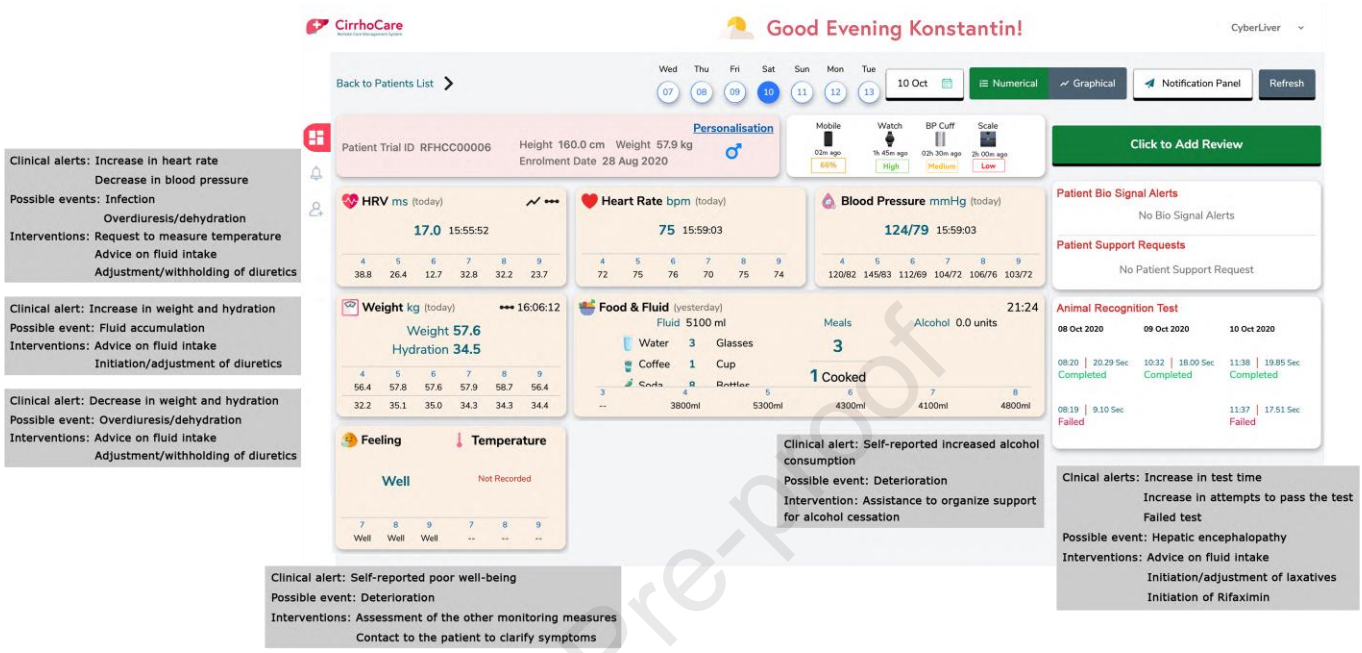
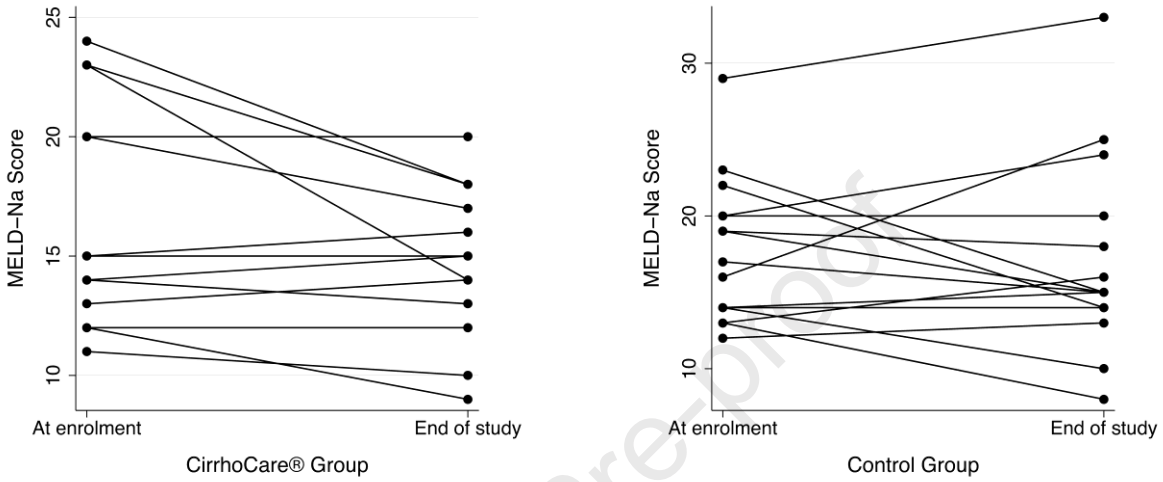


Fig. 3

(A)



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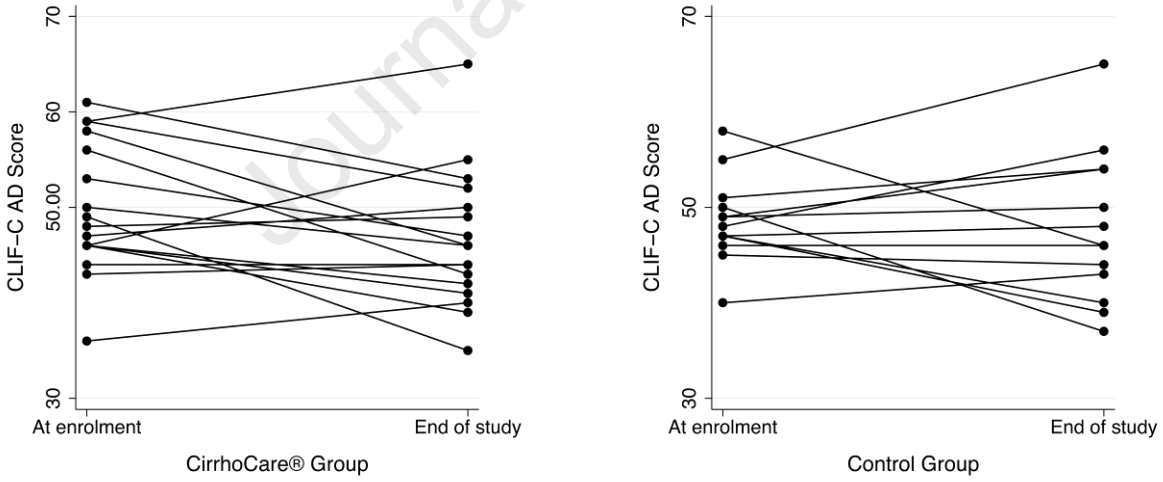

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Highlights:

- CirrhoCare® has good patient engagement and user feedback in patients with decompensated cirrhosis for their remote home management
- The system is able to detect early signs of new decompensation and allows timely intervention
- Remotely managed patients had fewer admissions than controls, and improved disease severity scores over 10 weeks
- CirrhoCare® may aid hepatologists with early diagnosis of new post hospital-discharge cirrhosis decompensation events, facilitating prompt community intervention, thereby reducing hospitalizations