ORIGINAL RESEARCH—CLINICAL

A Nonrandomized Pilot Study to Investigate the Acceptability and Feasibility of LivR Well: A Multifaceted 28-Day Home-Based Liver Optimization Program for Acute-on-Chronic Liver Failure

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BACKGROUND AND AIMS: Acute-on-chronic liver failure (ACLF) has a 22%–74% 28-day mortality rate and 30%–40% 30-day readmission rate. We investigated the acceptability and feasibility of a multimodal community intervention for ACLF. **METHODS:** A single-arm nonrandomized pilot study of consecutive participants with ACLF was conducted in a tertiary health service. Participants received weekly medical and nursing reviews, dietetics, physiotherapy, pharmacy, social work, addiction medicine, and neuropsychiatry, where indicated. A digital platform included remote weight monitoring and online surveys. The primary outcome was acceptability/feasibility. Secondary outcomes included safety, mortality, readmission, liver disease severity, and costs. **RESULTS:** Fifty-nine patients were enrolled with median age 51 years (interquartile range (IQR): 45–59); majority alcohol etiology (74%),and median Model for End-Stage Liver Disease Sodium score 16 (IQR: 12–21). LivR Well was acceptable with low attrition (8 of 59), adherence to the program including home visits (mean 8.4 ± 4.2) and consultations (mean 2.4 ± 1.5) per patient. This was supported by positive feedback and themes identified through a qualitative subanalysis. Feasibility was demonstrated by recruitment rate of 4.94 patients/month and 86% completion. Mortality was lower than expected at 3%, 30-day readmission rate was 15%, and median Model for End-Stage Liver Disease Sodium score reduced to 15 ($P = .01$). Median 6-month costs reduced from $30,454 (IQR: $21,953–$65,657) to $17,657 ($4249–$42,876) ($P = .009$). The total 6-month health-care cost was $1,868,859 (95% confidence interval 1,081,821–2,655,897) compared to $2,518,227 (95% confidence interval 1,959,610–3,076,844). **CONCLUSION:** LivR Well was acceptable, feasible, and safe with low short-term mortality and readmission rates. Health-care costs were reduced by 26% driven by a 40% reduction in 30-day readmission. Further evaluation includes a randomized controlled trial of LivR Well compared to standard care.

Keywords: Acute-on-Chronic Liver Failure; Cirrhosis; Interdisciplinary Health Team; Chronic Disease

Introduction

Acute on chronic liver failure (ACLF) is an increasing global health-care challenge, with high short-term mortality[1] and resource use. A large European study of over 1300 patients demonstrated that ACLF had a transplantation-free 28-day mortality of 33.9%, increasing to 78% when 3 or more organ failures were identified.[1] A large multicenter North American study calculated a 30-day mortality of 41% for patients hospitalized with ACLF.[2]

The absence of a universally accepted clinical definition for ACLF results in delayed diagnosis and variable guideline-based management.[3] Management is challenging due to the high frequency of multiorgan failure, high prevalence of underlying sarcopenia and frailty, and excessive resource use. Few patients fulfill eligibility criteria for liver transplantation and 3-month waitlist survival is close to 70%.[4]

Abbreviations used in this paper: **ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; CALD, culturally and linguistically diverse; CLDQ, Chronic Liver Disease Questionnaire; CLIF-C, chronic liver failure consortium; CTP, Child-Turcotte-Pugh; EASL, European Association for the Study of the Liver; ETG, ethyl glucuronide; HITH, hospital in the home; IQR, interquartile range; MELD, model for end-stage liver disease; RCT, Randomized controlled trial; SRS, supported residential service.**

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Integrated ambulatory health-care models have proven successful in conditions such as chronic heart failure, however ambulatory care for liver disease is often reactive, fragmented, and generally lacking a robust framework.[5] The burden of ACLF is rising worldwide with a 5-fold increase in annual costs of ACLF hospitalization from $320 million USD in $2001 to $1.7 billion USD in 2011 in one study.[6] A 30-day readmission rate of 34.4% and a 71% increase in total hospital costs between 2012 and 2018 was demonstrated at our tertiary health service,[7] and another Australian study of patients with cirrhosis found a 30-day readmission rate of up to 46% with annual readmission cost greater than $2.7 million AUD.[8] Globally, current literature estimates a 30-day readmission for those with hepatic decompensation at 23%–46%.[8–10]

There is a clear need for effective, accessible, and evidence-based treatment strategies to reduce the recurrence and high rates of rehospitalization and death. For new models of care to be adopted in complex health-care systems, upfront costs need to be justified with high-quality evidence,[11] which must address usability, feasibility, and acceptability to the patient, staff, and health-care system .[12] This pilot study was designed to 1) address uncertainties related to intervention implementation within a real-world tertiary health-care setting and 2) assess the potential clinical impact of LivR Well, which would inform the parameters of a larger randomized controlled pilot trial of this new model of community-based, technology-enabled ambulatory care for home-based care of ACLF patients.

Patients and Methods

Study Design, Setting, and Ethics

This is a single-arm nonrandomized pilot study. Adult patients with ACLF at a single tertiary network were serially enrolled between March 2021 and April 2022. ACLF was defined according to the Asian Pacific Association for the Study of the Liver (APASL) criteria due to our geographic location, as an acute hepatic insult manifesting as jaundice (serum bilirubin $\geq$85 mmol/L) and coagulopathy (International Normalized Ratio $\geq$1.5) complicated within 4 weeks by ascites and/or encephalopathy.[13]

We included patients who received a baseline assessment by a consultant gastroenterologist. Referral to allied health clinicians was defined as per Table 1 using primarily objective parameters (handgrip strength, diabetes, polypharmacy). Patients with greater than West Haven grade 2 hepatic encephalopathy at study screening, those receiving terminal care, those enrolled in an existing ambulatory care program eg for heart failure, inability to provide informed consent, residing outside the central 'Hospital in the Home' (HITH) catchment or residing in a residential aged care facility were excluded. Sex was identified as per hospital medical records.

The study context is Monash Health, a multicenter tertiary health-care network in Melbourne, Australia, servicing a population of approximately 1.2 million people.[17] The region has multiple large culturally and linguistically diverse (CALD) communities, a significant burden of socioeconomic disadvantage and the highest unemployment rates in the state of Victoria.[18] The intervention was delivered through the HITH program, an integrated ambulatory bed-substitution program providing 'hospital-level' care to patients in the community. The service was delivered via a combination of home visits, telehealth, and hospital-based ambulatory clinics. Patients who were otherwise ineligible for home-based HITH visits such as those with no fixed address or in whom their existing home situation did not meet the required occupational and safety standards for the HITH program, were temporarily accommodated at a supported residential service (SRS), funded by the hospital for the duration of the program.

All research was conducted in accordance with the Declarations of Helsinki and Istanbul. The study protocol was approved by the Monash Health Research Ethics Committee (QA/76264/MonH-2021-265,874(v1)). Informed consent was obtained in writing from all participants. All coauthors had

Table 1. Adjunct Referral Indications

Clinician	Indication for referral	Tasks
Physiotherapist	Sarcopenia[a], fall within last 6 mo, FRAT score >11	6-min walk test (baseline and at day 28) Low-intensity weight and resistance exercises
Dietitian	Sarcopenia, diabetes, alcohol dependence, MUST score $\geq$2	High-protein, high-energy, low-salt diet plan incorporating compact nutritional supplements including a late-night snack
Social work	Requiring long-term home support services, established disability, age >65 y	Referral for council services, aged care assessment, disability
Neuropsychiatry	Concern from medical team regarding cognition	Neuropsychiatric assessment
Pharmacist	Polypharmacy ($\geq$5 medications daily) and/or requiring titration of diuretic or lactulose doses	Patient and carer education, liaising with community pharmacy, organize blister pack
Addiction medicine	History of substance use disorder eg alcohol use disorder	Counseling, psychotherapy, and/or anti–craving medication prescription

FRAT, Falls Risk Assessment Tool[14]; MUST, Malnutrition Universal Screening Tool.[15]
[a]Sarcopenia is defined using the European Working Group on Sarcopenia in Older People hand grip strength cut off (<27 kg for males, <16 kg for females).[16]

access to the study data and have reviewed and approved the final manuscript.

Sampling and Recruitment

A sample size of N = 40 was determined in accordance with published guidelines for pilot studies and to allow for drop-outs.[19] Clinicians responsible for inpatient and outpatient care of ACLF patients were recruited to help identify, screen, enroll, and consent patients for the study. Eligible and consenting patients were recruited consecutively. The study ended after 13 months recruitment when the target sample size was met.

Processes, Interventions, and Comparisons

The LivR Well program included home-based nursing, weekly medical reviews, regular dietitian, and pharmacy consultations, and adjunct interventions including physiotherapy, social work, addiction medicine, and neuropsychiatry. Physiotherapy was contracted to an external organization; however, other allied health staff were employees from our health service. Patients were referred for screening and enrollment on discharge from an acute admission; from the emergency department; or outpatient clinics. Patients received nursing home visits 3 times per week for approximately 30-minute sessions (for assessment and observations alone) or up to 60 minutes when weekly blood tests were taken. A pool of nurses from the Hospital in the Home unit were provided with training for this protocol. The program was supported by a telehealth, Bluetooth scales for remote weight monitoring and a secure Azure cloud-based database for patient referral, screening, and electronic collection of study data.

Alcohol use was assessed through urine ethyl glucuronide (ETG), an ethanol metabolite and marker of alcohol use for up to 72 hours after ingestion[20] in patients with previous or suspected alcohol use disorder who denied active consumption. The urine sample was collected weekly at home by the HITH nurses or at clinic appointments if this was missed during the home nursing visit throughout the 28-day program, and again at week 12, and processed at an external laboratory associated with the state-wide liver transplant service. A qualitative "positive" or "negative" result was received within 1–2 weeks[21] with a detectable range 100–2000 ng/mL. Patients with a positive result were counseled and a referral to an addiction medicine specialist was offered.

Outcomes

The primary outcome was acceptability and feasibility. Quantitative acceptability data included i) overall attrition rates at 28 days, ii) the number of home visits conducted by HITH, and iii) the number of ambulatory clinics attended by the patient. Semistructured interviews were performed with patients, carers (with patient consent), and clinicians at the completion of the 28-day program. The interviews consisted of 19 questions (Appendix 1) and were conducted via telephone (in the context of COVID-19 pandemic policy) by 2 investigators (NN & ES) with consent for audio recording. Thematic analysis was applied to the interview transcripts using a 6-phase framework[22] with an inductive coding process to identify key themes. Feasibility was assessed using recruitment and retention rates, number of eligible participants required to recruit 40 patients, and rate of LivR Well completion. Both acceptability and feasibility were determined by recruitment rate, retention rate, and interview feedback. These criteria will primarily guide the feasibility of proceeding with a future definitive trial.

The secondary outcomes included change in liver disease severity using baseline and day 28 Model for End-Stage Liver Disease and Child-Turcotte-Pugh (CTP) scores, 30-day readmission, change in health-related quality of life, symptom burden and direct health-care costs. ACLF grading using the European Association for the Study of the Liver-Chronic Liver Failure (CLIF) Consortium (CLIF-C) was also applied due to the absence of a global consensus definition and grading system. Patient-reported outcomes were measured at baseline and longitudinally at weeks 6 and 12 from admission using the validated instruments (EuroQol 5 Dimensions English version for UK 2009[23] and Chronic Liver Disease Questionnaire [CLDQ][24]).

Descriptive cost estimates were derived from direct health-care costs, ie, health resource use involved with admission, consultations, pathology, radiology etc. In this single-arm feasibility study, there was no matched control group or estimation of external costs, ie, loss of productivity, or community health-care costs. Cost estimates were provided by the hospital finance department comprising medicines from the Australian Pharmaceutical Benefits Scheme, publicly available national health-care funding model data using the National Weighted Activity Unit for admissions, individual contractors for physiotherapy, and Medicare Benefits Scheme for outpatient clinic costs.

Statistical Methods

The mixed-methods study design included both quantitative analysis of clinical and costs data, as well as qualitative interviews. Statistical analysis was performed using Stata/IC 16.1 (StataCorp LLC, TX, USA) software. Patient characteristics were compared using Student's t test for normally distributed continuous variables or Wilcoxon rank-sum test for nonparametric continuous variables. Categorical variables were compared using Chi-squared test or Fisher's exact test for those with a frequency less than 20. A *P* value less than .05 was considered statistically significant. For the qualitative substudy, NVivo data management software (NVivo 20.3, QSR Int. USA) was used to identify and code themes. Two authors (NN and ES) validated the coding using verbatim transcripts. The study is presented following the Consolidated Criteria for Reporting Qualitative Research,[25] CONsolidated Standards Of Reporting Trials,[26] and STrengthening the Reporting of OBservational Studies in Epidemiology[27] reporting standards (included in the Appendix).

Results

Patient Characteristics

Sixty-six patients were serially assessed for eligibility between March 2021 and April 2022 (Figure 1) and those included were followed up for 12 weeks. Seven patients were excluded: 4 did not meet the ACLF criteria, 2 patients were declined, and 1 was already admitted to HITH for a concurrent issue. Of the 59 enrolled patients, 7 were recruited from the outpatient setting, and the remainder following an acute hospital admission. A total of 48 completed the program with 11 incomplete due to death

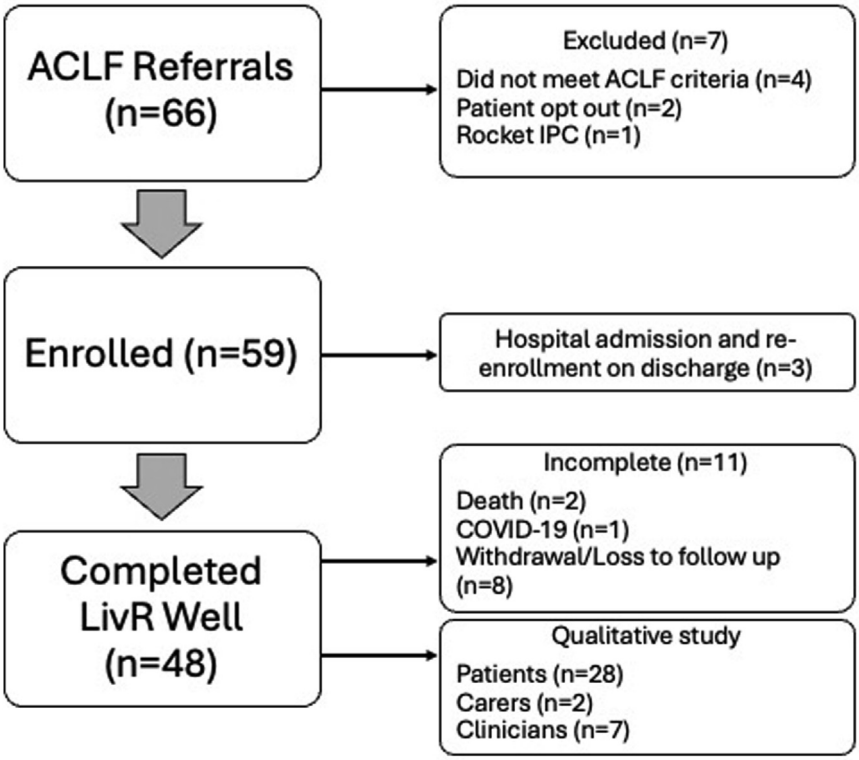

Figure 1. Patient flowchart.

(n = 2), COVID-19 requiring home isolation (n = 1) and patient request to discontinue the program (n = 8). Of these discontinued patients, 6 failed to attend any clinic appointments and 2 declined to continue after the first appointment. Multiple attempts to contact discontinued patients were made by the hepatology clinical nurse consultant by phone call and mobile text messaging. Three patients were admitted to hospital with liver-related complications and were re-enrolled upon discharge.

Baseline characteristics are shown in Table 2. The median age was 51 years (interquartile range [IQR] 37–59) and 66% were male. The median age-adjusted Charlson Comorbidity Index score was 4 (IQR: 3–5). An interpreter was used for 10 patients who spoke a language other than English, and 2 patients identified as Aboriginal or Torres Strait Islander. Nearly half the cohort (46%) had a CALD background. Three patients were provided temporary accommodation during the LivR Well program due to homelessness (n = 1) and living alone unsupported (n = 2). The median baseline Model for End-Stage Liver Disease Sodium (MELD-Na) score was 16 (IQR: 12–21) and 49% were Child-Pugh class B. The median CLIF-C ACLF score was 40 (IQR 33–46) for all comers and 46.5 (IQR: 41–49) for those with ACLF grade 1–3).

Acceptability

LivR Well was overall acceptable to patients who completed the program, carers, and clinicians, using both quantitative and qualitative measures. Up to 3 home visits per week were offered to patients with an mean 8.4 ± 4.2 visits conducted per patient. Patients attended a mean 2.4 ± 1.5 ambulatory clinics including 11conducted by telehealth due to COVID-19 isolation, transportation challenges, or missed face-to-face appointment. The attrition rate was 8 of 59 reflecting patients who dropped out before program completion. Examination of this subgroup demonstrates that all had alcohol use disorder, 3 were from a CALD background, and had readmission rates of n = 1 within 30 days and n = 2 within 90 days.

Feasibility was demonstrated by a recruitment rate of 4.94 patients per month and a retention rate of 81%. To recruit 40 patients, 44.75 eligible patients needed to be screened.

Twenty-eight patients, 2 carers, and clinicians including gastroenterologists (n = 2), hepatology clinical nurse consultant (n = 1), hospital medical officer (n = 1), pharmacist (n = 1) and HITH nurses (n = 2) participated in qualitative interviews. The remaining 20 patients declined to participate, or participation was not practical due to failure to answer phone calls, or absence of a language interpreter outside clinic appointments.

Main themes (acceptability, health literacy and insight, and autonomy) and subthemes (interactions with clinicians, nutrition, negatives, transport, medications, mental health, and alcohol use) were generated by an inductive approach to explore patterns and recurrent concepts. All participants described the program as a positive experience due to the quality of clinician interactions, “they were reassuring…good communicators”, education “made me a lot more aware of what I put into my body”, and a sense of improved wellbeing “I feel better, my liver count went down”. Patients

Table 2. Baseline Characteristics

Characteristic	Total (n = 59)
Age (y), median (IQR)	51 (37–59)
Sex, n(%)	
Female	20 (34)
Male	39 (66)
MELD, median (IQR)	16 (12–21)
CTP class, n(%)	
A	10 (22)
B	22 (49)
C	13 (29)
CLIF-C ACLF score, median (IQR)	40 (33–46)
CLIF-C ACLF grade, n(%)	
0	41 (69)
1	6 (10)
2	11 (19)
3	1 (2)
Etiology of liver disease	
Alcohol	43 (74)
MAFLD	3 (5)
Alcohol/HCV	5 (9)
Alcohol/MAFLD	1 (2)
Alcohol/HBV	6 (10)
ACCI, median (IQR)	4 (3–5)
Requires language interpreter, n(%)	10 (17)
Culturally and/or linguistically diverse background, n (%)	27 (46)
Employed, n (%)	3 (5)

ACCI, Age-adjusted Charlson Comorbidity Index; HBV, hepatitis B virus; HCV, hepatitis C virus; MAFLD, metabolic dysfunction-associated fatty liver disease; MELD, Model for End-Stage Liver Disease Score.

and carers reported improved access by provision of taxi vouchers, and clinical support, which reduced health-care system burden "you don't have to go to the emergency room". Benefits for clinicians included "building the trust of the patient" and "excellent collaboration between health-care providers and patients". Criticism of the program included home visits disrupting social events, and difficulty navigating the multicampus health service.

Improved health literacy and insight was frequently reported by participants who expressed progress in "management of health….more confident in seeking medical advice." This was attributed to patient education "he showed me a graph of my liver function…he could visually show me what my liver was doing" and self-reflection "I didn't realise how unhealthy I was." Only 5 patients mentioned alcohol intake reduction/cessation despite alcohol use disorder in all except 1 patient.

Patients highlighted increased autonomy "You feel like you've got more of an input into your own well-being." Many described a change from a passive to active self-management approach "I finally worked out that is what I need to do." Clinicians also observed patients having "greater ownership of their health."

Alcohol Use

Alcohol was the most frequent cause of liver disease as the sole etiology in 74% and a contributing factor in 21%. The median baseline MELD was 16 (IQR: 12–21) for those with alcohol as the sole etiology. Of those with primary or concurrent alcohol use disorder, 59% saw an addiction medicine specialist during the LivR Well program. The remainder either declined the referral or had been previously seen. Voluntary urinary ETG samples were collected in 38 patients with a history of or clinician suspicion for alcohol use disorder.Of these, n = 6 had an initial positive result with a detectable urinary ETG level of greater than 2000 ng/mL, of which 3 had another positive result at week 12 follow-up. A total of 8 patients had at least 1 positive urinary ETG sample during the program, including 1 patient previously diagnosed with nonalcoholic fatty liver disease.

Mortality and Readmission

The 28-day mortality rate was 3% with 1 death at day 16 and 1 at day 27 and no deaths at 30–90 days (Table 3). The death at day 16 occurred from progressive liver failure despite transfer to a liver transplantation service and the other at day 27 from sepsis and liver failure secondary to an ischial hematoma infection. The 30-day readmission rate was 15.3% and the 90-day readmission rate was 27.1% (Table 3, Figure 2).

Clinical Outcomes

There was a small but statistically significant improvement in MELD-Na score from 16 (IQR: 12–21) at baseline to 15 (IQR:11–18) at day 28, ($P = .01$). There was no change in CTP score (8 (IQR: 7–10) vs 7 (IQR: 6–9), $P = .11$) (Table 3).

Table 3. Clinical Parameter Changes and Readmission Rates

Variable, median (IQR)	Baseline (n = 59)	Day 28 (n = 48)	*P* Value
MELD-Na	16 (12–21)	15 (11–18)	.001
CTP score	8 (7–10)	7 (6–9)	.11
HGS female (kg)	17 (14–19)	18 (17–20)	.16
HGS male (kg)	31 (23–36)	32 (25–39)	.30
Sarcopenia, n (%)	16 (27)	11 (25)	.48
	Baseline	Week 6	*P* Value
CLDQ overall	4 (3–5)	5 (4–6)	.02
Self-reported health perception score	64% (42–77)	72% (50–80)	.05
		30-d	90-d
Mortality rates, n (%)		2 (3)	2 (3)
Readmission rates, n (%)		9 (15)	16 (27)

HGS, Hand grip strength; MELD-Na, Model for end-stage liver disease score with serum sodium.

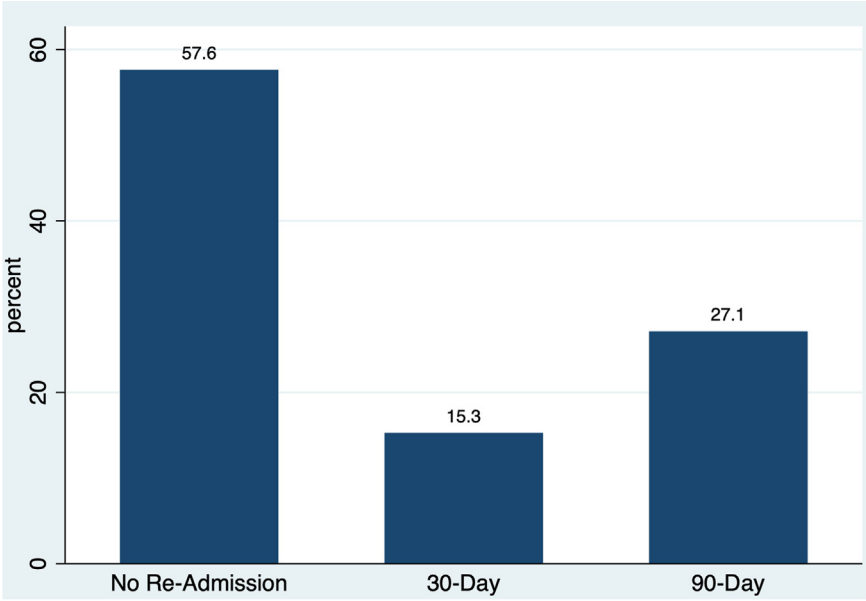

Figure 2. Hospital re-admission rates.

The incidence of sarcopenia defined by sex and hand grip strength using European Working Group on Sarcopenia in Older People criteria was 27% at baseline and 25% by day 28 ($P = .48$, Table 3).

All participants met the criteria for ACLF using APASL guidelines; however, only 18 participants had a CLIF-C ACLF grade greater than 0. The median CLIF-C ACLF score was 40 (IQR: 33–46) overall and 46.5 (IQR: 41–49) when excluding those with an ACLF grade 0. As seen in Table 4, an ACLF grade 1–3 was associated with both a higher median baseline MELD sodium (24 (IQR:20–29) vs 15 (IQR:11–17), $P < .001$) and CTP score (10 (IQR:8–11) vs 8 (IQR:7–9), $P = .01$) (Appendix 6). Additionally, ACLF grade 1–3 was associated with 30-day readmission ($P = .003$) but not 90-day readmission ($P = .50$). There was no significant association between ACLF grade and either attrition ($P = .69$) or mortality ($P = .13$).

Patient-Reported Outcome Measures

The median baseline CLDQ score was 4 (IQR: 3–5) and increased to 5 (IQR: 4–6, $P = .02$) by week 6 (Figure 3). There was a significant longitudinal increase in 'fatigue' (3.6 vs 4.6, $P = .02$) and 'worry' (3.8 vs 4.7, $P = .03$) (Appendix 2). Self-perception of health reported using the EuroQoL 5 dimensions visual analog scale improved but did not reach statistical significance (64% (IQR: 42–77) at baseline to 72% (IQR: 50–80), $P = .05$) (Appendix 3).

Descriptive Costs

The median total cost of the 28-day LivR Well program was $5757 AUD (IQR: 3544–7773) per patient, including direct health-care costs of HITH admission, a contracted physiotherapist at $182 AUD per home visit, temporary accommodation in an SRS for 6 patients; consultations from addiction medicine, dietetics, pharmacy, and social work, and nutritional supplements at $201.60 for 3 serves per day for 28 days, which is approximately half the recommended calorie intake per kilogram of body weight for patients with cirrhosis.[28] In the 12 months following admission to LivR Well, a total 40 patients were readmitted at least once, at a median cost of $7044 (IQR: $4340–$13,869) and median length of stay 3.2 days (IQR: 1–7). This compares favorably to a recent audit of our health service, which estimated a median cost of $16,197 AUD (IQR $7331–$39,868) for an admission with a cirrhosis-related complication.[7]

Table 4. Outcomes in Those With and Without ACLF Using EASL CLIF-C Grading

	ACLF grade 0	ACLF grades 1–3	*P* Value
Baseline MELD, median (IQR)	15 (11–17)	24 (20–29)	<.001
Baseline CPS, median (IQR)	8 (7–9)	10 (8–11)	.01
Attrition, n (%)	10 (17)	1 (2)	.69
30-d readmission, n (%)	2 (3)	6 (10)	.003
90-d readmission, n (%)	8 (14)	6 (10)	.50
Mortality, n (%)	2 (3)	3 (5)	.13

CPS, Child-Pugh score; EASL, European Association for the Study of the Liver.

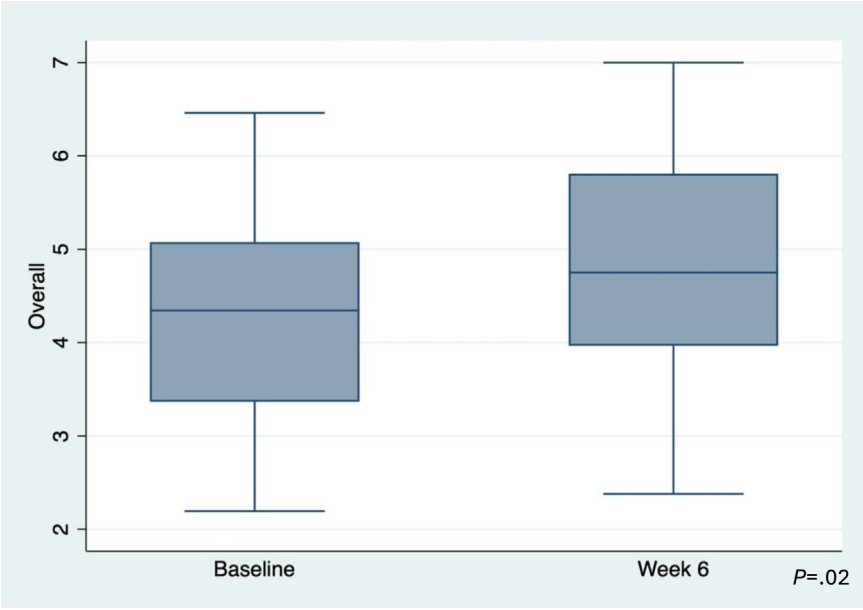

Figure 3. Chronic Liver Disease Questionnaire–overall score.

The median 6-month direct health-care cost reduced from $30,454 (IQR: $21,953–$65,657) before LivR Well to $17, 657 ($4249–42,876) ($P = .0085$) suggesting a sustained reduction in hospital resource use following completion of the 28-day program. This is also seen in a 26% reduction in total 6-month direct health-care costs from $2,518,227 (95% confidence interval 1,959,610–3,076,844) to $1,868,859 (95% confidence interval 1,081,821–2,655,897).

Discussion

LivR Well was found to be acceptable and feasible to patients with ACLF with high rates of engagement and positive qualitative feedback. Critical feedback focussed on the burden of health-care appointments and questionnaires generated by this intensive program, which may limit intervention fidelity and completion of study assessments in a larger study. In particular, improvement in health literacy can be attributed in part to our multidisciplinary education, with demonstrated benefits in self-care and the patient-provider relationship.[29]

This was a nonrandomized pilot study which was not intended to definitively assess the clinical efficacy nor cost effectiveness of LivR Well. Instead, this exploratory study was intended to address the logistics of integrating a coordinated multimodal program into routine clinical care and as part of a larger randomized controlled trial (RCT) in future. We anticipate that some components of LivR Well will have greater positive impact than others, but a key limitation of our study was the inability to delineate the individual impact of component. We hypothesize that the 2 highest impact components of LivR Well are the hepatology clinical nurse consultant for care coordination, and provision of nutritional supplements and home meal delivery due to the prevalence of both disease-related malnutrition and risk of food insecurity in this vulnerable cohort. We also acknowledge that LivR Well as a complex intervention may be difficult to replicate and scale across different health-care contexts and will address this as part of future studies.

We observed a lower 28-day mortality rate and 30-day readmission rate compared to published rates including mortality greater than 46%,[30] which will be investigated as part of a larger RCT. There were no serious adverse events. The median intervention cost of $5757 AUD per patient and median readmission cost of $7044 are lower than the admission cost for patients with cirrhosis at our health service, which is $9001 AUD-$20,162 AUD historically. Additionally,the low 6-month median direct health-care costs issimilar to that for ACLF alone and likely driven by a 40% reduction in 30-day readmission. There are multiple factors contributing to the low costs observed in our study including reduced hospital readmission,[7,31] length of stay,[6] and the bed-substitution model of HITH.[32] Despite lack of a control arm, these results collectively suggest that LivR Well has potential to be a cost-effective multimodal intervention for ACLF, but requires a larger scale RCT and cost-effectiveness analysis to delineate the true impact of LivR Well compared to current standard of nontransplant care.

The improved outcomes demonstrated are likely to be multifactorial, reflecting the impact of intensive support following discharge. Our readmission rate of 18% can be attributed to frequent interactions with clinicians, close monitoring of investigations, strategic approach to malnutrition, and proactively organizing preventative measures including variceal surveillance. Extrahepatic injuries were addressed using nutritional support targeting 35 kcal/kg daily,[28] physiotherapy, pharmacist support, alcohol rehabilitation, and specialist nursing coordination,[33] which have been shown to improve hospitalization rates and quality of

life in chronic liver disease, attributed to application of an integrated ambulatory program. Diagnosis of sarcopenia is crucial in patients with ACLF due to the associated morbidity, and the availability of effective interventions.[34]

In our Australian setting, alcohol use disorder comprises the largest contribution to chronic liver disease[35] and remains an important preventative and therapeutic target. Integrated care models have been used in populations such as our study cohort, where dual pathologies including cirrhosis coexist[36] but remain inaccessible in the standard ambulatory care setting. The approach provided in this intervention include screening, counseling, and prescription of anti–craving medication by the team of hepatologists, nurses, and addiction medicine specialists. In patients with established cirrhosis, ongoing alcohol use is associated with complications including variceal hemorrhage, ascites, and death[37] thus the reduction in confirmed alcohol use from 74% to 14% has the potential to impact key outcomes such as admission and mortality rates. We acknowledge the potential for urinary ETG testing to underestimate surreptitious alcohol intake due to the short time frame for a positive assay however it remains a practical and affordable tool in the clinic setting. The future RCT will provide greater insight into the impact of alcohol-related interventions by allowing comparison to the control arm, longer follow-up, and subanalyses of the impact of components such as addiction medicine specialists and biochemical monitoring on outcomes of interest.

There was a small but significant improvement in MELD-Na and in quality of life using the CLDQ. We will seek to verify these associations in the RCT with a larger sample size. Additionally, we hope to demonstrate faster time to hepatic recompensation through LivR Well compared to standard ambulatory care, as demonstrated through improvement in CTP class.

The digital platform aimed to improve efficiency and data security, with the potential to provide central infrastructure to a generalizable and mobile program. We found the digital interventions employed in this program enabled streamlined recruitment, remote monitoring, and enhanced patient education, all of which were crucial during the COVID-19 pandemic–related restrictions on face-to-face ambulatory health care. Future directions may include development of a simplified, generalizable, and technology-enabled protocol that can be implemented in any urban or regional health service with an existing hospital in the home program, in recognition of the widespread burden of ACLF[38] and benefits of accessible multidisciplinary care. "Telehepatology" employed during the COVID-19 pandemic has been found to be overall acceptable and feasible,[39] and could be used by select patients to improve both cost-efficiency and accessibility. However, we found that telemedicine using video calls was frequently unsuitable for this population who require medical examination for assessment of hepatic encephalopathy or ascites, have low digital and health literacy, and who frequently lack resources for reliable internet access. We have approached this issue by providing funded accommodation in the form of short term, SRS's for patients living out of the health service catchment or are ineligible for hospital in the home services, for the duration of the 28-day program.

Although no direct feedback was able to be obtained from the 8 patients who discontinued the program it is possible that the reasons for drop out were related to barriers to health-care engagement including alcohol use disorder and CALD background. The program itself attempts to address these challenges through referral to addiction medicine, social work, language interpreters, neuropsychiatry, and involvement of family/carers with patient consent. We plan to address this in the RCT through an intention to treat analysis, and accounting for a 20% drop-out in the sample size calculation.

This small single-arm study is limited by the lack of a control group but it provides support for proceeding with an RCT on a larger scale. We acknowledge the risk of selection bias toward a lower ACLF grade given that the most severe cases may have died during hospitalization before referral. This could be addressed in the future RCT by requesting referral on diagnosis of ACLF rather than immediately before discharge. While we are currently recruiting from a single site, simplification of the study protocol may allow generalizability to other health services. It is likely that the APASL criteria for ACLF underestimate mortality due to omission of organ failures in the diagnostic pathway.[40] The CLIF-C ACLF score incorporates the CLIF organ failure score, age, and white blood cell count, and has been demonstrated to be more accurate than both CTP score and MELD-Na scores in predicting 28-day mortality.[41] APASL diagnostic criteria were applied to this cohort due to clinician experience and Australian location however the predominance of alcohol excess in liver disease etiology in this cohort may carry greater similarity to that studied in CLIF-C validation.[42] Only 31% had an ACLF grade greater than 0 and 1 participant had an ACLF grade 3 thus this cohort may not reflect the severity and mortality attributable to those meeting CLIF-C ACLF criteria. Upscaling of resource-intensive programs is challenging and as such we limited follow-up to 12 weeks before discharge to regular care, which allows adequate follow-up for our short-term outcomes of 28-day mortality and 30-day readmission rates. The RCT will extend follow-up to evaluate the longer term impact.

Conclusion

LivR Well is a multidisciplinary and multimodal ambulatory care program for ACLF patients. Our feasibility study supported the acceptability, feasibility, potential efficacy, and cost effectiveness of such an intervention with lower than expected 30-day admission, 28-day mortality, and total health-care cost for this complex cohort. There was a small but significant longitudinal improvement in MELD-Na and in chronic liver disease–specific quality of life. We will further investigate the clinical and economic impact of LivR Well by undertaking a RCT comparing it to standard ambulatory care.

Supplementary Materials

Material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.gastha.2024.10.007.

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Ethical Statement:
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Data Transparency Statement:
Data, analytic methods, and study materials can be made available to other researchers on reasonable request. The preliminary data in this study were presented in poster format at International Liver Congress, London, UK, June 2022.

Reporting Guidelines:
Consolidated Criteria for Reporting Qualitative Research (Appendix 5), CONsolidated Standards Of Reporting Trials (Appendix 6), STrengthening the Reporting of OBservational Studies in Epidemiology (Appendix 7).