Improving self-management with eHealth in cirrhosis using a patient-centered approach

by

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ABSTRACT

Rapid adoption of internet-connected technology (ICT) by society has supported an unprecedented rate of change in hardware, software, and connectivity making the technology more accessible and user friendly. In turn, the application of this technology has reshaped how people communicate, acquire information, and integrate it into their daily lives. The ubiquitous nature of ICT has also impacted healthcare and self-care in a range of ways, from the presence of patient portals and access to healthcare professionals, to applications ("apps") and wearable devices that support healthy lifestyles. For those who are ill or have chronic diseases, ICT can provide disease-related information, medications, and apps to support self-management.

My dissertation explores the interface of ICT and individuals living with a chronic disease, cirrhosis and asks a series of contingent questions answered by four studies: (1) Are patients proficient with either computer and smart devices and, if so, why are they using it? A survey-based study (n=117) using validated tools (Computer and Mobile Device Proficiency Questionnaires) was conducted in cirrhosis. Patients were moderately proficient and high rates or internet usage and device ownership. (2) Next, I asked: is online cirrhosis information targeted to patients and care partners and, if so, how is it presented? A critical review of cirrhosis-specific webpages evaluated information accessibility, reliability, and transparency using validated tools (Web Resource Rating Tool and Quality Evaluation Scoring Tool). Low levels for these measures were found for all webpages and much could be done to improve online resources specifically targeted to patients and care partners. An in-depth look at hepatic encephalopathy webpages revealed complex medicalese language, inaccuracies, or negligible mention of non-pharmaceutical therapies. (3) For those living with cirrhosis, I asked what gaps, if any, were there about the self-management of hepatic encephalopathy? Following a systematic search and retrieval of the literature, the EPPI-Centre's mixed methods synthesis approach to analyse quantitative (n=16) and qualitative (n=7) articles from published research. Findings highlighted the need for repeated practitioner-initiated dialogue with consistent messaging about this common complication to prepare, learn, and share information and skills to improve health outcomes and quality of life. Online resources and tools could be valuable for non-pharmaceutical and pharmaceutical self-management. (4) What did individuals living with cirrhosis think of a web-based application for improving nutrition and exercise behaviours? The three domains of the capability, opportunities, motivation – behaviour change model (COM-B) were used to investigate the application. After interviewing 20 persons and exploratory descriptive analysis of the data, several opportunities were identified to improve the application in consideration of COM-B. An unexpected finding was the preference for more online classes and the universal curiosity to learn more about other patients and have online interactions. These two elements were helpful to retain users and support adherence in the first 4-6 weeks of app use; this correlates with the opportunity-social subdomain of the model. Inclusion of gamification elements, streamlining data entry and progress reporting, and more online classes were suggested by the users as other mechanisms to increase enjoyment, retention, and adherence.

While ICT has changed greatly in a short period of time, how we use it to support health needs is still evolving. App development and online content is driven by for-profit industries which are slowly evolving to meet user needs and user abilities. Research, like the series of findings presented here, is needed to describe the current landscape, gaps, and opportunities so that research can inform and benefit from advances in ICT.

Findings presented in this dissertation highlight the acceptability and potential utility of ICT to support self-management, which is greatly needed in complex, chronic diseases, such as cirrhosis. However, effective initiatives should be user-centered if they are to improve health outcomes and quality of life of patients and care partners. There is much opportunity for follow-on studies to continue the work presented here to advance the scope and accessibility of greatly needed eHealth self-management tools.

PREFACE

This dissertation is an original work by Kathleen Patricia Ismond. The research projects, of which this dissertation is a part, received research ethics approval from the University of Alberta Research Ethics Board:

- Computer and Internet Literacy Skills of Individuals Living with Chronic Diseases, **Chapter 2 "Assessing patient proficiency with Internet-connected technology and their preferences for e-health in cirrhosis"**, Pro00082756, 7/8/2019.
- Heal-Me Cirrhosis, **Chapter 5 "Initial patient perspectives about participating in an online, cirrhosis-specific nutrition and exercise intervention"**, Pro00087451, 3/19/2021.

Some of the research conducted for this dissertation forms part of a research collaboration, led by Tandon at the University of Alberta. Chapter 2 has been published as:

- **Ismond KP, Eslamparast T, Farhat K, Stickland M, Spence JC, Bailey RJ, Abraldes JG, Spiers JA, Tandon P. Assessing Patient Proficiency with Internet-Connected Technology and Their Preferences for E-Health in Cirrhosis. J Med Syst. 2021 Jun 5;45(7):72. Doi: 10.1007/s10916-021-01746-3.** I co-designed and conducted the study with Tandon. Eslamparast and Farhat collected the data with assistance of Stickland and Bailey. I completed the data analyses and interpretation with guidance from Spence, Abraldes, Spiers, and Tandon. I drafted the manuscript with critical edits provided by all. Tandon was the supervisory author.
- Chapter 3 was published as: **Ismond KP, Loch-Ismond E, Tandon P, Spiers J. An Evaluation of Online Cirrhosis-related Information Intended for Patients and Caregivers. Clin Gastroenterol Hepatol. 2022 Feb 16:S1542-3565(22)00180-X. doi: 10.1016/j.cgh.2022.02.024.** I conceptualized and planned the study along with Tandon and collected the data with Loch-Ismond. I completed the data analysis with assistance from Spiers and P Tandon and drafted the manuscript with input from all authors.
- Chapter 4 was published as: **Ismond KP, Spiers J, Tandon P. Identifying Opportunities for Hepatic Encephalopathy Self-Management: A mixed methods systematic review and synthesis. Can Liver Journal. 2022 October (accepted).** I conceptualized and planned the study along with Spiers and Tandon. I designed the

search strategy, completed data abstraction, and coding with their supervision. Data interpretation and synthesis was a joint effort involving all authors. I drafted the manuscript with edits provided by other authors.

DEDICATION

This dissertation is dedicated to those with cirrhosis and chronic disease who briefly shared their lives with me. I am grateful for their contributions upon which this dissertation has been built.

ACKNOWLEDGEMENT

Dr. Puneeta Tandon has been an inspiration throughout this dissertation as a mentor and my primary supervisor. Her dedication, knowledge, and commitment to research and medicine are unsurpassed. I am grateful to have benefited from her rays of fortitude, resilience, and truth-seeking. In the dual role of co-supervisor and teacher, Dr. Jude Spiers has provided unique experiences and learning with kindness and humour. From committee member, Dr. John Spence, I am grateful for his guidance navigating the complexities associated with behaviour change.

The research funding received from Mitacs and matching, unrestricted educational awards from Lupin Pharma Canada Ltd. and Astellas Pharma Canada, Inc. were greatly appreciated. I would also like to express gratitude for research funding for the four research projects from the Canadian Institutes of Health Research, Nutricia Foundation, and Alberta Innovates.

Thank you to the many experts and wonderful people who have been involved in one or the other with the research grant applications, collaborations, and knowledge sharing in the last several years in the development of Heal-Me, a web-based application (“app”) to support nutrition and exercise in chronic disease. Although the app is only mentioned in one thesis chapter, it has been a key focus of my research.

Thank you to my family (Leos, Ethan, Mum, Dad, Sylvia, Dan, Margaret, Judy, and Eva) and friends (Dave and Shelly) for overcoming not one but several of life’s challenges. This has been a remarkable journey for which we are stronger. My husband, my best friend, this is for you.

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CHAPTER 1.0 - Introduction

1.1 Orientation

Living with cirrhosis has been described by patients as isolating, vulnerable, filled with uncertainty, and coping with the social stigma of alcoholism[1]. A patient's self-management entails varying degrees of effort to be successful and can be influenced by factors, such as personal characteristics, resources, and health status[2, 3]. It is unclear what supports for self-management are needed in cirrhosis[4] and, if any, how these are delivered. With the availability of inexpensive mobile devices in 2007, health and lay communities have embraced digital technology as evidenced by over 350,000 health-related apps available in 2021[5]. Unlike other chronic diseases[6-10], there is limited research in cirrhosis on patient acceptability and digital technology platforms to improve or support self-management burdens despite the potential of this combination.

1.2 Background

1.2.1 Cirrhosis is a medically complex chronic condition

The World Health Organization defines chronic diseases or conditions as having a long duration and caused by either one or more genetic, physiological, environmental, or behavioural factors[11]. Globally, cirrhosis is the eleventh most common cause of death at 2 million per year[12]. Exact incidence and prevalence rates by a country's income level are unavailable or incomplete, especially in large areas where cirrhosis is prevalent, such as Africa[12]. Locally, 10% of Canadians have liver disease and are at risk for developing cirrhosis[13]. Compared to other causes of death in 2020, cirrhosis and liver disease were ranked tenth. Extrahepatic morbidities can develop which contribute to quality of life and mortality[12]. A Canadian consensus task force stated that cirrhosis is a "crisis in the making", bound to "overwhelm current facilities" if changes are not made[14]. To illustrate the increasing strain on the population and healthcare system, the cirrhosis prevalence rates increased almost 6-fold from 1992 to 2012 in Ontario, due in part to the obesity epidemic[15].

1.2.1.1 Definition and causes of cirrhosis

Cirrhosis is an advanced state of liver injury and scarring. The liver is responsible for a variety of essential physiological functions such as glucose and lipid metabolism, bile acid production, drug detoxification, and vitamin storage[16]. Several etiologies can result in chronic injury to the liver. The most common are viral infections (hepatitis viruses B and C), obesity, and alcohol-related liver disease, with a variety of additional causes including impaired bile flow, autoimmune, genetic, and vascular liver diseases. With chronic injury, the liver's healthy parenchymal cells are replaced with collagen fibres which creates scar tissue and causes the liver to stiffen (fibrosis). The accumulating fibrotic tissues interrupt the normal flow of blood through the liver resulting in complications related to portal hypertension and liver insufficiency. The transition from chronic injury to compensated cirrhosis can be asymptomatic and may require abnormal bloodwork, liver elastography (which measures liver stiffness), or liver imaging to detect[17]. This means that patients may not be aware of the onset of cirrhosis and a common explanation is, as this person reported, "It's hard to say when it [cirrhosis] started. Maybe a couple of years ago.[18, p. 220]"

1.2.1.2 Compensated liver

Once the diseased liver transitions to cirrhosis, it can compensate for its deteriorating function for some time. For individuals with a compensated liver function, their median survival time is 12 to 14 years[19]. Medical care focuses on managing the underlying causes of liver disease (e.g., alcohol abuse disorder, obesity, or viral infection), decreasing portal pressure via medications, and preventive screening for hepatocellular carcinoma and esophageal varices[17]. Common liver-related complications are usually not life-threatening (e.g., edema, varices) but require timely medical management and may involve hospital stays. In an American study of compensated patients, the most frequent complications reported were muscle cramps, poor sleep, pruritus, and falls. Each of these was independently associated with decreases in quality of life, which was measured with a visual analog scale[20]. Other conditions and events, such as comorbidities, hospital stays, and non-hepatic disabilities, affecting activities of daily living (e.g., bathing and dressing), can also contribute to the cirrhosis burdens and the complexities of medical management[20, 21].

1.2.1.3 Decompensated liver

Decompensation is defined as the development of ascites, esophageal variceal bleeding, or (overt) hepatic encephalopathy and is associated with a median survival of ~2 years[16, 22].

Bacterial infections are common in this stage and can hasten decompensation. Physical frailty, sarcopenia, and malnutrition can also exacerbate decompensation leading to death. Moreover, decompensation is associated with an increased symptom burden, high rates of health resource use, and unexpected health events. Without a transplant, patients have a high risk of mortality usually caused by either hepatic or extrahepatic organ failure[22]. Given the limited availability of donor organs, liver transplant candidates have varied and unpredictable waiting times. In 2020, 256 adult Canadian patients died or were removed from the transplant waitlist because of worsening health; 491 received transplants[23]. After a successful liver transplant, the five-year survival rates are as high as 84.1% in Canada[24].

1.2.1.4 Prognostic scores

To inform clinical management, the model for end-stage liver disease adjusted for sodium (MELD-Na) was developed to predict the risk for 90-day mortality. The MELD-Na score considers four blood measures (i.e., creatinine, bilirubin, INR, and sodium) and dialysis status[25]. Increasing scores indicate more advanced cirrhosis and higher mortality risk (e.g., scores of ≤ 17 and ≥ 32 have a <2% and 65-66% mortality risk, respectively). The Child-Pugh score predicts 1- and 2-year survival rates arranged into three alphabetical classes: A (100% and 85%, respectively), B (80%, 60%), and C (45%, 35%)[26]. The Child-Pugh score is based on three blood measures (total bilirubin, serum albumin, and INR) as well as the presence and severity of both ascites and hepatic encephalopathy. Most transplant centres list patients for transplant with a MELD of at least 15 and higher. Liver transplants are reserved for patients who have a risk of mortality from surgery that is less than not undergoing the transplantation[17].

The loss of muscle mass (sarcopenia) and muscle function (frailty) in cirrhosis can be improved with or prevented by nutrition and exercise[27, 28]. The Liver Frailty Index incorporates three measures: hand-grip strength, time to complete 5 sit-stands, and balance tests. Scores are associated with a risk of mortality[29]. Independent of the MELD-Na score, physical frailty in cirrhosis increases a patient's risk of mortality by 4-fold and hospitalization risk by 3-fold[30]. Thus, nutrition, regular exercise, and maintaining an active lifestyle are recommended to reverse sarcopenia and maintain or build muscle mass[31, 32].

1.2.1.5 Comorbidities

Apart from liver symptoms and complications, such as ascites, hepatocellular carcinoma, and acute kidney injury, patients living with cirrhosis have high rates of morbidities[17]. The Charlson comorbidity index is a standard tool used to assess the presence and severity of 17 common diseases in a range of health conditions (e.g., chronic obstructive pulmonary disease and congestive heart failure). This tool has been validated in cirrhosis[33]. In a Danish cirrhosis study of 14,976 patients, 62% had a Charlson index of 0 (no comorbidities), 21% had an index of 1, and 17% had an index of 2 or more[34]. In a United Kingdom study, the Charlson comorbidity index scores were reported for two age- and sex-matched groups: cirrhosis (n=4,537) and non-cirrhosis (n=44,403). Index scores of 1 or more were reported for 22.3% and 16.5% of the cirrhosis and non-cirrhosis groups, respectively[35]. The most common comorbidities in cirrhosis are chronic obstructive pulmonary disease, non-hepatocellular carcinoma cancers, and cardiovascular disease[34, 36]. Diabetes is a dominant morbidity with prevalence rates ranging from 27% to 56% depending upon the cirrhosis etiology as cited in a systematic review of 58 studies (n=9,705)[37]. The etiology of non-alcoholic fatty liver disease is associated with the highest rates of diabetes. Although not included in the Charlson comorbidity index, the comorbidities of obesity and mental health disorders have been reported in cirrhosis[34, 36]. This information underscores the collective high symptom burden and medical management (e.g., polypharmacy) experienced by those living with cirrhosis[38, 39].

1.2.1.6 Hepatic encephalopathy

Hepatic encephalopathy is a specific liver complication, in which elevated levels of ammonia in the brain are thought to be the primary causal mechanism[40]. Ammonia can cause inflammation, oxidative stress, and other pathophysiologic changes. Ammonia is mainly produced in the gut through digestive processes but is also generated and metabolized by other organs such as muscles, the brain, and kidneys. The healthy liver removes excess ammonia, but this becomes impaired in cirrhosis because of alterations in the inter-organ ammonia metabolism[40]. The incidence rate for hepatic encephalopathy in compensated patients is 10% to 14%; this rate increases to 40% after 5 years[40]. For those with decompensated livers, the incident rate is higher (16% to 21%). Prevalence estimates of the mildest form of hepatic encephalopathy range from 20% to 80%[40]. Medications resolve symptoms and decrease the risks of hospitalization and mortality[41]. Nevertheless, the occurrence of one overt episode is associated with a 42% risk of complication recurrence within 1 year[40]. This is a significant complication affecting many patients across the trajectory of cirrhosis.

The West Haven scale (grades 0 to IV) describes the severity of hepatic encephalopathy symptoms and guides medical management[42]. The term "covert" (grades 0 and I) refers to transient episodes of cognitive dysfunction, such as mild unawareness, apathy, or anxiety. These unspecific symptoms overlap with other common conditions, such as lack of sleep. Most often, these mild, episodic symptoms may be only obvious to the patient or people close to them [43]. Without obvious symptoms, specimen panels, or imaging, specialists use sophisticated cognitive tests and equipment to diagnose covert hepatic encephalopathy and initiate treatment. Examples of these are the Critical Flicker Frequency and the Stroop test. To help with diagnosis, specialists include the care partner's observations of the patient's behaviors[42]. Pharmaceutical treatment is not recommended at this covert stage unless requested by the patient.

"Overt" hepatic encephalopathy (grades II to IV) is associated with increasingly severe symptoms which range from disorientation, asterixis, and slurred speech through to coma[42]. While the unusual symptoms can be obvious, treatment involves the identification and treatment of possible precipitating factors (e.g., bleeding esophageal varices, constipation, infections, renal failure, or medications). After eliminating these causes, a diagnosis of overt hepatic encephalopathy is made[42, 44]. Treatment of precipitating factors coincides with the resolution of hepatic encephalopathy. The frontline therapy for overt cases is nonabsorbable disaccharides, such as lactulose dispensed as a liquid. The dose is self-titrated to achieve 2-3 bowel movements each day[42]. For recurrence (>1 overt episode), the antibiotic rifaximin (550 mg twice a day) can be added. Where the patient is intolerant to lactulose or has issues with titration, rifaximin alone is an alternative. Treatment is continued indefinitely to prevent recurrence and minimize severity; primary prophylaxis is not recommended.

Non-pharmaceutical therapies for cirrhosis, overall, and the prevention and management for hepatic encephalopathy involve nutrition and exercise. Nutrition guidelines specifically recommend that protein intake should be increased above the Canadian Food Guide levels for healthy adults (1.2 to 1.5 g/kg body weight per day instead of 0.8 g/kg body weight per day)[45]. As well, patients should eat frequently (approximately every 4 hours when awake) to reduce the duration and frequency of fasting wherein the liver switches to catabolic metabolism and loses muscle tissue[31, 46, 47]. However, increasing dietary protein seems counterintuitive since its digestion produces ammonia, a metabolite which has been associated with hepatic encephalopathy. Evidence supporting the safety of a diet high in protein comes from a randomized controlled trial in 20 patients with a history of hepatic encephalopathy. The intervention consisted of protein restriction for 14 days. While there were no differences in hepatic encephalopathy, there were significantly higher rates of protein breakdown in the restricted group (median (first quartile): 4.1 (3.6) g protein/kg/day) relative to the normal protein group (2.5 (2.4) g protein/kg/day p=.04)[48] measured using the glycine-N^{15} infusion method. Results from subsequent studies have provided additional support. First, high protein diets, meal size, and frequent snacking do not trigger hepatic encephalopathy nor increase plasma ammonia[49-51]. Second, the authors of a 6-study meta-analysis (n=1,795) concluded that sarcopenia and frailty were positively associated with hepatic encephalopathy (odds ratio (OR) 2.74, 95% confidence interval (CI): 1.87 - 4.01)[52]. Thus, protein restriction is not recommended in cirrhosis while maintaining a high protein diet is recommended to prevent and manage hepatic encephalopathy[28, 31]. Concerning fluid retention caused by increased portal vein pressure and complications of edema and ascites, patients are advised to restrict daily sodium intake to 5 g[53].

A second non-pharmaceutical approach to hepatic encephalopathy management is regular physical activity. Moderate exercise is indicated to prevent or reverse sarcopenia and frailty and is recommended for patients receiving treatment for hepatic encephalopathy[31, 54-58]. Although moderate-to-vigorous exercise increases ammonia levels, it has not been found to precipitate overt hepatic encephalopathy[59]. Muscles can both produce and metabolize ammonia.

Both covert and overt hepatic encephalopathy exert significant impacts on disease burden and health-related quality of life for patients[60, 61]. Even the mildest form of this complication (minimal HE) has been linked to a significant decrease in the quality of life of patients compared to age- and sex-matched healthy controls (9.8 ± 9.2 versus 4.3 ± 7.1, p <.0001) assessed by the Sickness Impact Profile survey[60].

1.2.1.7 Patient perspectives

As reported by those living with cirrhosis, the condition is stressful, debilitating, and a constant concern. In one study of 20 patients (Child-Pugh A:B/C, 13:7; M, 50%), most described their daily experiences as living on an “unpredictable roller coaster” because of their “fluctuating symptoms, worries, and disease progression”[62, p. 4532]. In a secondary analysis of transcripts from 15 patients (M, 47%) with advanced liver disease (but not on the transplant waitlist) and 6 family members, disease journeys typically involved a “shock of diagnosis, uncertainty concerning illness, lack of coordinated care, worrying symptoms, and the possibility of sudden death”[63, p. 284]. In turn, these events gave rise to emotional responses of “fear, anger, sadness, and guilt”[63, p. 284]. During decompensation and time spent on the transplant waitlist, the patients’ quality of life continues to decrease as symptom burdens increase. This requires more intensive self-management and exacerbates stress for patients[64] and care partners[65]. Looking at the human response to cirrhosis underscores the ongoing psychological toll and physical burdens that increase year after year against a background of aging, possible comorbidities, and strains on financial status.

1.2.2 Self-management

The term “self-management” describes the involvement of the patient in their medical care for asthma in the mid-1960s with publication in 1976[66]. Drawing on the theory of self-efficacy, self-management situates the individual (patient) as a change agent who has a significant influence on their health and health management[67, 68]. With a focus on outcomes, self-management includes three categories of activities: (1) medical management (learning about the diagnosis, following treatment regimens, and coping with symptoms); (2) social management (maintaining or adjusting life roles in response to their health); and (3) emotional management (managing depression, fear, anxiety, or other responses to the chronic health condition). Since then, the term “self-management” has expanded to include consideration of patient skills in problem-solving, decision-making, resource utilization, and forming partnerships with healthcare providers[69]. In 2019, van de Velde and colleagues published a review of 35 studies[70]. Following in-depth content analysis to the point of saturation, they presented 10 major and 4 minor attributes describing self-management in chronic diseases in a 14-part model. Their work emphasized two features: (a) the broad scope and evolving nature of a patient’s health-related activities in response to medical advancements, research, and societal changes (e.g., adoption of digital technology in health) and (b) the impact of the patient's readiness to engage in self-management.

To reflect on the consequential role of patients in their health management and outcomes, the Chronic Care Model presents a non-hierarchical, bidirectional relationship between patients and their healthcare teams unlike the traditional, paternal physician and patient relationship[71]. The original model was based on a review of interventions designed to improve care for those living with chronic diseases. Four factors influenced care and health outcomes: expertise and skill of the practitioner/medical team, patient education and support, team-based planning and delivery of care, and care integration with electronic medical records[71, 72]. A systematic review of 157 studies, conducted mainly in diabetes and hypertension, showed that interventions relating to the Chronic Care Model's self-management element (i.e., patient education and support) were often associated with improvements at the patient level[73]. A 2018 systematic review of 8 self-management frameworks supporting self-management in chronic illness from multiple countries showed the continued prioritization at program levels for patients and education for health professionals[74]. Notably, the frameworks only considered single chronic health diseases and did not have the flexibility to factor in multiple morbidities. This is an important consideration as symptoms can exacerbate, there may be treatment conflicts, and the time needed for self-management may increase[75]. In turn, these may cause patients to prioritize certain activities over others and impact their financial status.

In 2020, the Integrated Model for Patient-Centered Advanced Liver Disease Care was published specifically for cirrhosis that was partially based on the Chronic Care Model. Similar features concerning collaborative care were presented with the addition of the curative-to-palliative care progression and the acknowledgement of trade-offs to meet patient's goals[76]. Again, while this model has the advantage of specificity for advanced liver disease and could be applicable across the cirrhosis trajectory, it was designed for a single disease without consideration for the added complexities of patients with one or more comorbidities. This is especially important in cirrhosis where complications give rise to new morbidities such as hepatocellular carcinoma, portal hypertension, or hepatopulmonary syndrome.

While self-management requires patient involvement and consent, these activities also impact individuals within family and social networks to varying degrees.

1.2.2.1 Care partner

Integral to a patient's self-management, a care partner is a person who provides unpaid assistance in matters about the patient's health, well-being, functional independence, and quality of life[77]. In Canada, the term caregiver denotes informal carers in contrast to paid caregivers who have formal training[78]. However, "caregiver" implies a unidirectional relationship between the patient and carer. Since 2010, the term "care partner" has been increasingly used in North America and will be used hereon to better reflect the complex, bidirectional roles of each person in the dyad[79].

In chronic diseases, the roles of the care partner can be highly diverse and vary over time. As such, their contributions are referred to as "caregiving trajectories" in recognition of their dynamism[80]. Activities can range from assuming the role of a substitute decision maker to provide "physical, emotional, and financial support"[81, p. 42]. Importantly, the care partner is committed and supportive of the patient while acknowledging the patient's independence and self-care abilities[79].

Care partners in the context of serious chronic diseases and old age are viewed as essential contributors within the overall healthcare system[77, 82]. Although few published studies describe the roles and burdens of care partners in cirrhosis[83], it appears care partners have at least similar experiences as those in other chronic illnesses[84-88]. In a population-based study of older adults, those with cirrhosis received double the caregiving time as their age-matched comparators (p<.001)[89]. Continued alcohol use disorder, hospitalizations, and recurrent hepatic encephalopathy are elements that increase the burdens of care partners in cirrhosis requiring more attention and time[90]. Importantly, the Integrated Model for Patient-Centered Advanced Liver Disease Care depicts the patient alongside their care partner as a unit engaged in collaborative decision-making with healthcare practitioners[76]. Although the exact numbers of patients who have informal caregivers are unknown, proportions from two large North American studies (n=317 and n=129) indicate anywhere from 33.3% to 88.4%, respectively[91, 92]. From hereon, when referring to the patient and their self-management, the care partner is included in the dyad, even without explicit mention.

1.2.2.2 Hepatic encephalopathy self-management

Like other chronic diseases, healthcare expectations for the patient living with cirrhosis and hepatic encephalopathy involves attending clinic appointments and procedures, completing bloodwork, filling prescriptions, taking medications, and seeking the appropriate medical care for new, recurring, or worsening symptoms according to their severity. Patients continue managing other morbidities as well as psychosocial elements and alcohol use disorder or other addictions if present. Although lifestyle changes in nutrition and exercise are indicated for cirrhosis, they are highly relevant to hepatic encephalopathy management. Self-management activities are conducted against a background of varying severities of cognitive dysfunction. Recovery from overt episodes is variable but may be longer if the patient was initially hospitalized. Patients may also be advised to stop driving because of altered psychomotor skills attributed to this episodic complication leading to vehicle accidents [93].

Effective hepatic encephalopathy self-management is multifaceted involving medical and psychosocial management and an informed care partner[42]. This requires that the patient understands the complication well enough so they can communicate this information if the care partner is not present during the physician's visit. Medical management of hepatic encephalopathy with lactulose is not without its challenges. While the liquid is self-titrated in response to the bowel movements (aiming for 2-3 soft bowel movements per day), patients may experience unwanted side effects[42]. Since common medications (e.g., opiates, benzodiazepines, and sedatives) will not be prescribed or will be deprescribed while using lactulose, patients should be engaged to understand the rationale and cope with the ensuing effects of deprescribing[94]. In the ideal situation, patients will be able to titrate lactulose up and down, are aware of potential triggers, and can monitor their symptoms.

Other aspects of hepatic encephalopathy self-management overlap with cirrhosis non-pharmaceutical self-management practices, specifically nutrition and exercise. Nutrition self-management was challenging without patient-specific resources until the publication of "The

Nutrition in Cirrhosis Guide" in 2018, a resource co-designed with patients[95]. Exercise also plays a key role in the non-pharmaceutical management of cirrhosis and hepatic encephalopathy.

Patient perspectives are mixed regarding nutrition and exercise self-management recommendations for cirrhosis and specifically for hepatic encephalopathy. In this patient population, undernourishment is prevalent[27, 47]. Early satiety due to ascites can lead to undernutrition even in those with high body mass indexes, a condition referred to as "sarcopenic obesity"[96]. In general, those living with chronic diseases have sedentary lifestyles and this pattern persists in cirrhosis. In a study of 53 liver transplant candidates, they had similar activity levels as those with advanced chronic pulmonary disease or renal failure[97]. The candidates spent 75.9% of their waking hours in sedentary states and their average daily step count was 3,164[97]. A well-characterized and significant barrier to reducing sedentary time and exercise for patients with cirrhosis is fatigue[97-100].

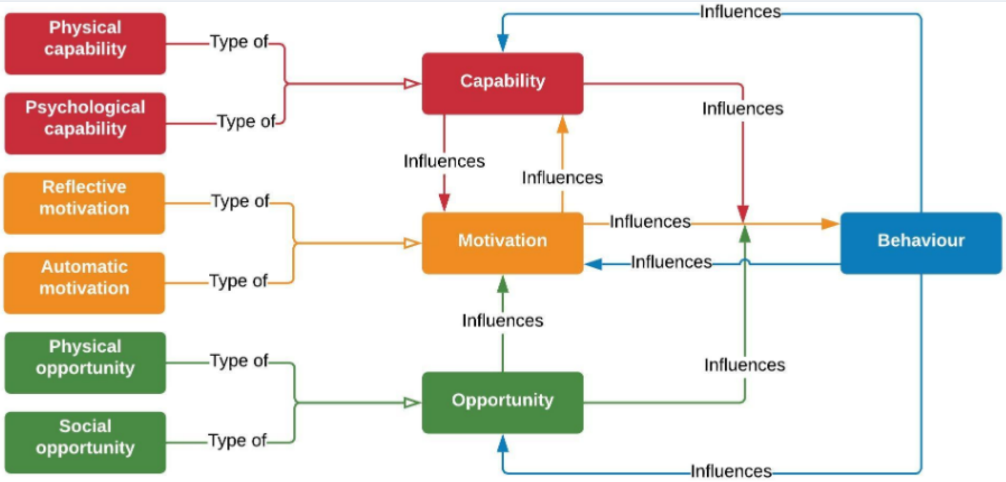
The goals of self-management in cirrhosis and hepatic encephalopathy entail a combination of pharmaceutical and non-pharmaceutical goals. For the latter goals, which include lifestyle changes, how do patients and their practitioners proceed with this information?

1.2.3 Behaviour change

Changing unhealthy to healthy behaviours can positively impact health outcomes as well as quality of life. In chronic disease, health behaviour change is an important element in self-management. The increasing prevalence of chronic diseases[101] and the relationship of many with lifestyle choices[102] indicate that the initial adoption and sustainment of healthy behaviours is not easy. Achieving and maintaining health-related behaviour change is complex and must be cognizant of the individual as well as their social, economic, and political environments[103].

To support this process, theory provides the description, logic, or explanation for certain behaviour and posits the influencing factors that can be manipulated for a behaviour to occur or not[104]. Theories are useful for proposing hypotheses about well-defined relationships between structural and psychological processes[105]. Process models are intentionally simpler, temporal representations of theories and describe behaviour but do not explain it, unlike theories[106]. Frameworks are systems or overviews, with multiple descriptive categories and relationships, that describe the behaviour of interest[106]. Behaviour change interventions benefit from using theory to understand if, how, and which mediator influenced the targeted behaviour; knowledge that can be used to efficiently refine an intervention or modify a theory[104]. The specific actions taken to change behaviour are referred to as behaviour change taxonomies and these can be linked to broader categories of mechanisms of action[107]. The linkages between a theory to a model, framework, mechanism, and taxonomy represent invaluable tools for theorists and interventionists through to policy makers[104, 106, 107].

Figure 1-1. The Capability, Opportunity, Motivation and Behaviour (COM-B) model.[108]



Capability is an attribute of a person that together with opportunity makes a behaviour possible or facilitates it.

Opportunity is an attribute of an environmental system that together with capability makes a behaviour possible or facilitates it.

Motivation is an aggregate of mental processes that energise and direct behaviour

Behaviour is individual human activity that involves co-ordinated contraction of striated muscles controlled by the brain.

Physical capability is capability that involves a person's physique, and musculoskeletal functioning (e.g. balance and dexterity).

Psychological capability is capability that involves a person's mental functioning (e.g. understanding and memory).

Reflective motivation is motivation that involves conscious thought processes (e.g. plans and evaluations).

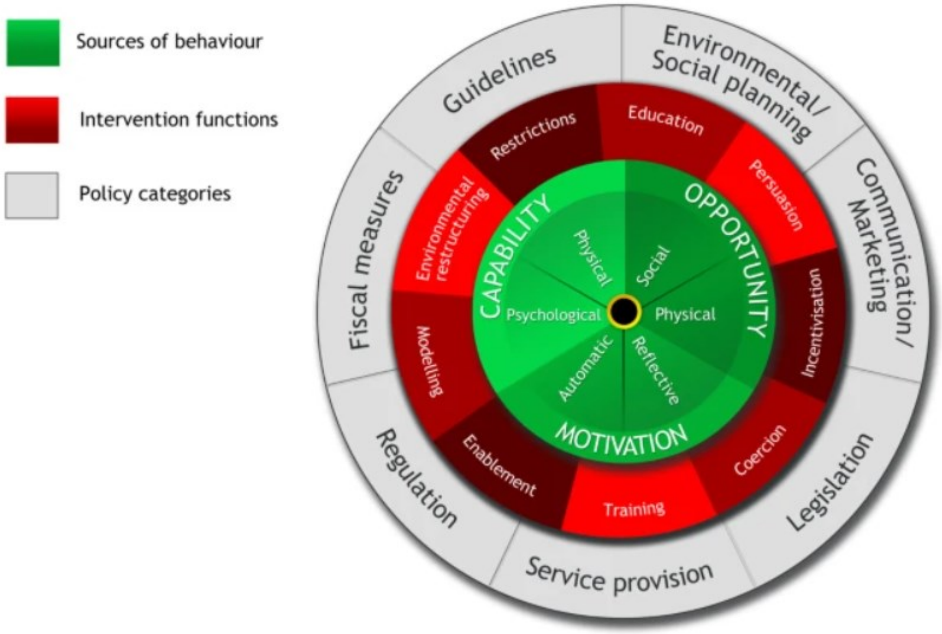
Automatic motivation is motivation that involves habitual, instinctive, drive-related, and affective processes (e.g. desires and habits).

Physical opportunity is opportunity that involves inanimate parts of the environmental system and time (e.g. financial and mterial resources).

Social opportunity is opportunity that involves other people and organisations (e.g. culture and social norms).

The "Capability, opportunity, motivation, and behaviour" (COM-B) model, by Michie and colleagues (Figure 1), was developed to "capture the range of mechanisms that may be involved in change, including those that are internal (psychological and physical) and those that involve changes to the external environment"[109, p 4]. By creating a model of behaviour, the authors sought to develop “a basis for designing interventions aimed at behaviour change”[109, p 5]. The model was an outcome of a three-part endeavour beginning with a systematic literature review identifying interventions that interventionists and policy makers could use and represented comprehensiveness, coherence, and linkage[109]. Subsequently, the 9 interventions and 7 policy categories meeting the usefulness criteria were used to construct a new framework (“Behaviour Change Wheel”, Figure 1-2) that linked behavior to interventions and policy categories. At the centre of the wheel is the behaviour change model – COM-B.

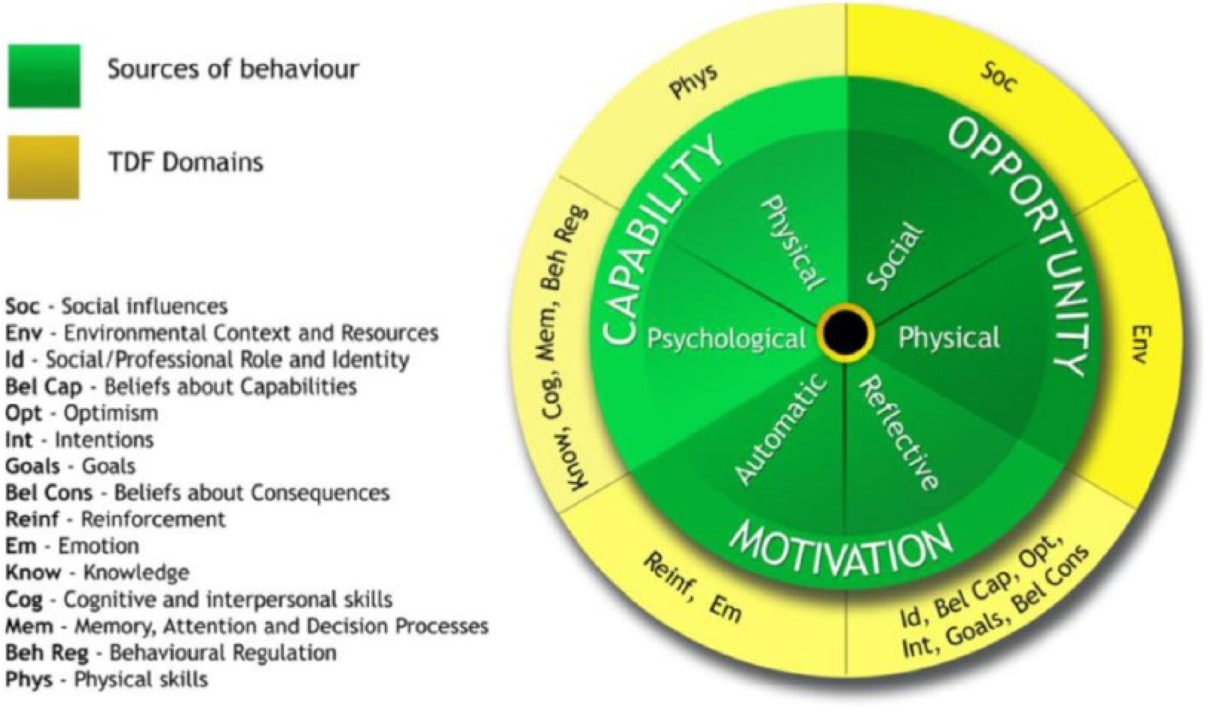
Figure 1-2. Behaviour Change Wheel.[109]



In the COM-B model, the capability domain describes person-oriented attributes needed to complete the behaviour. These can be physical (e.g., strength, chronic conditions) and psychological (e.g., knowledge, cognitive status) attributes. Opportunities are elements external to the person that influence behaviour. Such environmental elements can be physical (e.g., residential location) or social (e.g., family). Although complex, motivation is segregated here into either automatic (e.g., emotions) or reflective (e.g., planning). Together, Capabilities and Opportunities can influence each other and Motivation while Motivation influences Behaviour[110]. Highlighting the model’s cyclical nature and potential feedback mechanisms, the

Behaviour construct influences Capability, Opportunity, and Motivation. A systematic review of research literature using the framework and its related Theoretical Domains Framework (Figure 1-3) found it to be effective for identifying barriers and facilitators for interventions in 3,480 studies; only 28 actually incorporated it in intervention design and testing[111]. COM-B has been frequently used in multi-target interventions of variable durations and study sizes. It has quickly become a key framework in behaviour change studies (for example, 1,129 articles retrieved in PubMed on February 20, 2022) due to its effectiveness in intervention design and evaluation, including interventions using internet-connected digital technology, such as wearable activity trackers[112, 113].

Figure 1-3. Theoretical Domains Framework mapped to the COM-B model.[105]



Digital tools are rapidly changing and the capacity to obtain large amounts of passive data is increasing via wearable technologies, such as activity trackers[114]. This passive approach to data capture reduces the time for the user to enter their data into an application (“apps”) and reduces entry errors or biases. The passive data can be assessed repeatedly over time and the app can continually customize the programming at the level of an individual based on the person’s physiology, goals, and behaviours. The datasets can be analysed with sophisticated tools, such as artificial intelligence and complex adaptive systems design[115, 116], and this information can be used to create computerized simulations of complex behaviours to advance understanding[115]. Collection and use of passive data is an emerging research area that will benefit behaviour change and behaviour change theory. The COM-B model accommodates dynamic interactions between the domains and is well suited for use with large datasets[109].

1.2.4 eHealth

The ubiquity of internet-connected digital technology in contemporary society is useful to support health and healthcare in general, and healthy behaviour changes specifically[117]. "eHealth" is an umbrella term encompassing services, such as websites, telemonitoring, mobile apps, clinical information systems, and patient health portals. The term can be used as both a noun and verb, an unusual characteristic that reflects its importance in connecting the areas of health, information, communication, technology, and users[118]. Enabled by the availability of inexpensive smart devices for the public, beginning in late 2008 with the launch of the iPhone 7 and Google Android[119], eHealth was readily accepted and integrated into services offered by primary care in developed countries during the COVID-19 pandemic[120]. eHealth is a promising and scalable tool for supporting behaviour change for both self-management and preventive health as part of self-care[121].

In 2021, 97% of American adults used a cell phone and 85% of them had smart phones[122]. The wide range of ownership and use of smartphones speaks to the potential of eHealth interventions to narrow the geographic (urban versus rural) and socioeconomic divides to improve access, delivery, and utilization of healthcare[123]. Multiple studies have demonstrated improvements in clinical outcomes, quality of life, and reduced health care utilization with eHealth nutrition and physical activity programs for breast cancer survivors, rehabilitation, and multiple sclerosis[124-127]. eHealth has also been successful in supporting positive behavior change outcomes with programs for diabetes management and smoking cessation[128, 129]. Another feature of app-based programming is its flexibility to provide on-demand, pre-recorded programming or scheduled live sessions – options that accommodate patients' calendars and do not require transportation[100].

A drawback with eHealth is that all users, regardless of their state of health, decrease their app engagement over time thus reducing their potential to achieve healthy behavior changes and realize improvements in health-related outcomes[130]. The digital divide[131, 132] is a well-characterized barrier to eHealth while other aspects, such as app usability and user experiences, also impact eHealth usage. With time it has become apparent that designing digital solutions for the "average" person does not meet the unique needs of individuals and a tailored alternative is required, especially for populations with complex health issues, such as cirrhosis.

1.3 The rationale for research in cirrhosis self-management

At the time of designing this series of studies, there were several clinical and knowledge gaps concerning self-management in cirrhosis and hepatic encephalopathy. Many of these were prioritized by our patients or mentioned in the literature. First, non-pharmaceutical nutrition and exercise lifestyle programs (prehabilitation) are not integrated into routine cirrhosis and hepatic encephalopathy clinical care despite practice recommendations and trial evidence[28]. Second, although such programming had the potential to realize cost reductions of 2- to 6-fold[97, 133], the small cirrhosis population, dispersed across urban and rural areas, made it challenging to offer programs which were accessible to all. While online program delivery reaches anyone with an Internet connection, it was unclear if this approach was acceptable to patients or if they had the necessary technologies or proficiencies to derive benefit from it. Third, there was no scoping review or critical analysis describing the information available online to patients in cirrhosis and if there were online tools supporting self-management already available. Lastly, while internet-connected digital technology appeared promising for supporting self-management in chronic diseases, it was unclear what format, features, and program characteristics would be useful and relevant to patients with cirrhosis. Such elements impact program adherence which in turn directly influences clinical outcomes of nutrition and exercise behaviour change.

Evidence-informed health recommendations are successful if they consider the patient's perspectives as previously unidentified barriers may limit program uptake and adoption. During interview sessions, patients with cirrhosis expressed vulnerability as well as the need for self-control and togetherness[1, 134]. These and other studies highlighted a patient's need for support and engagement with others to strengthen their coping skills, minimize negativity, and provide self-control[135-137]. However, at the time, limited structured support was available to support cirrhosis-specific self-management education and supportive programming in clinics and hospitals[110, 138, 139]. As recently as 2019, cirrhosis quality measures were still being developed through Delphi consensus with healthcare practitioners[140]. While providing direction, these measures represent a first step to creating a framework to support and sustain meaningful self-management resources and tools that can be evaluated for their impact on clinical and patient prioritized outcomes.

Smart devices and online access have the potential to offer scalable support to many patients with chronic diseases by offering applications ("apps") to support their self-management activities. The authors' 2015 scoping review of 350 studies assessed this potential. Patient perceptions of the apps were moderate with 64.0% (224 of 269 studies) reporting positive experiences[141]. Outcomes related to self-management were minimal with a few of the 350 studies reporting improvements in patient self-empowerment, 15.4%; clinical outcomes, 14.0%; quality of life, 13.1%, and self-efficacy, 5.1%. However, this was just the beginning of healthcare app development, and barriers were anticipated. Many health apps experienced issues with usability, user experience, and accessibility from different devices while not considering patient contexts[142]. The potential of eHealth for self-management is promising but requires multidisciplinary teamwork to identify possible barriers along the development and implementation stages of a lifestyle change app relevant to cirrhosis and the complication of hepatic encephalopathy.

1.3.1 Addressing knowledge gap 1 – patient readiness for eHealth?

In cirrhosis, there is a research gap describing the prevalence of digital technology ownership, the proportion of people who have home access to the Internet, or the range of technology proficiencies of patients[143-145]. Such information is required to characterize and add context to the target user population for technology related to eHealth and self-management. In particular, the older age of patients and the urban and rural residential locations were known to have technology proficiency and accessibility[144, 145]. This is a concern as cirrhosis prevalence increases with older age and many patients are non-digital natives. Further, the high symptom burden in cirrhosis has an unknown influence on digital technology use. Thus, exploration and description of patient readiness for eHealth in the context of cirrhosis were warranted.

1.3.2 Addressing knowledge gap 2 – online cirrhosis content?

There are reviews of online content for patients with chronic illnesses, such as inflammatory bowel diseases[146] and chronic lung diseases[147]. This work identified the scope of available content as well its quality, accuracy, and accessibility (e.g., reading grade level). Findings could then inform interventions targeted at the gaps in the resources and enhance patient awareness and knowledge.

Before this thesis, it was not clear what online information existed specifically targeting patients living with cirrhosis nor how would this impact their self-management. An investigation of this nature should also explore the quality and reliability of the content using validated tools. Such an undertaking represented the second step in this dissertation which characterized online content that supported awareness and skills in self-management in cirrhosis and hepatic encephalopathy.

1.3.3 Addressing knowledge gap 3 – hepatic encephalopathy self-management?

Hepatic encephalopathy is a significant complication for many people living with cirrhosis, yet there is a paucity of research on self-managing it. Recognizing the substantial impact of this complication on both patients and care partners there was a need to assess the empirical literature describing patients' self-management capabilities and experiences. In this second study, an analysis of the quantitative literature provided insight into health-related outcomes associated with treatment adherence and patient education. The qualitative literature reflected the experiences of patients and care partners with hepatic encephalopathy self-management. A 2015 publication summarizing the unmet supportive needs of patients living with cirrhosis was a driving motivator in designing this mixed review study that focused on hepatic encephalopathy and gaps in self-management[4].

1.3.4 Addressing knowledge gap 4 – behaviour change app?

Cirrhosis and hepatic encephalopathy treatments entail pharmaceutical and non-pharmaceutical therapies. Continuing with a focus on non-pharmaceutical treatments, lifestyle intervention programs have shown promising health-related outcomes. The potential of eHealth to meet the needs of patients is high as the program content and delivery can support interactive engagements with an expert, offer customizable programming for each person, and provide flexible scheduling[100, 148]. In particular, this app intervention had the potential to improve adherence as previous interventions reported wide variations ranging from 14%[148] to 100%[149] and mixed health outcomes. A Cochrane systematic review of physical exercise in cirrhosis (6 randomized controlled trials, n=173) concluded that there was neither benefit nor harm and that further research was required[150]. However, the reviewed trials did not include an app-delivered nutrition and exercise intervention. In addition, it was not known what the patients' response would be to a virtual behaviour change program in this pre-COVID-19 period. If advances were to be made in the use of digital technology to support self-management, answers were needed regarding patient perceptions and experiences of app uptake and adherence. Thus, the exploratory descriptive study focused on patients' early experiences using an app to support healthy nutrition and exercise activities – self-management activities that need external expertise for guidance.

1.4 Thesis contents

1.4.1 Research questions and hypotheses

The overarching research question is: "What non-pharmaceutical opportunities are available to augment cirrhosis self-management skills?"

Thesis statement: eHealth can support lifestyle behaviour change in patients living with cirrhosis.

Hypothesis: A customizable, interactive nutrition and exercise online program will be accessible and relevant to patients.

A series of research questions were posed:

- Question 1: To what extent are patients with cirrhosis ready for internet-connected digital technology?
  - addresses Knowledge Gap 1

- Question 2: What is the scope and accessibility of online cirrhosis information that is specifically intended for patients?
  - addresses Knowledge Gap 2
- Question 3: What influences self-management capabilities and health outcomes in hepatic encephalopathy?
  - addresses Knowledge Gap 3
- Question 4: What are the early experiences of patients with an app-based program to support nutrition and exercise self-management in cirrhosis?
  - addresses Knowledge Gap 4

1.4.2 Structure

This is a paper-based thesis arranged so that one set of research questions and hypotheses is independently addressed in each chapter. The four original research chapters are intended for publication or have been published in peer-reviewed journals. To connect the research questions and results into a coherent story, the chapters are preceded by an overall introduction and end with a chapter providing general conclusions and future directions.

1.4.3 Limitations

I am a non-healthcare professional and, thus, the thesis does not approach the subject matter through the lens of an expert with knowledge or experience in medicine or healthcare. Through review and consultation with supervisors and colleagues who are experts in healthcare and those who live with cirrhosis, I have incorporated their feedback to ensure that each research phase, from question to data interpretation, was relevant, meaningful, and appropriate to the cirrhosis healthcare community. Limitations specific to each study are reported in each chapter.

As a phenomenon, self-management is complex and quickly becomes unwieldy to study if one considers all its nuances and perceptions. While appreciating these, I narrowed my thesis focus to prioritize patient activities that are directly involved in their medical self-management: nutrition and exercise therapy, medication adherence, and awareness and monitoring of cirrhosis-specific symptoms. Other elements essential for effective self-management and health outcomes are outside the scope and not discussed.

1.4.4 Methods

Chapter 2: *Are patients with cirrhosis ready for internet-connected digital technology?* This chapter reports a multicentre, cross-sectional study employing surveys to assess rates of internet-connected digital technology ownership in cirrhosis alongside frequency of Internet use and intention. Validated surveys (Computer and Mobile Device Proficiency Questionnaires[143, 151]) assessed participants' self-reported proficiencies using computers and mobile devices. The research objective was to learn if and how an urban, Canadian group of individuals living with cirrhosis perceived the virtual environment.

Chapter 3: *What is the scope and accessibility of online cirrhosis information that is specifically intended for patients?* This chapter is a systematic narrative review of online content specifically intended for an audience of people living with cirrhosis. Following a systematic search, the retrieved webpages were categorized and described. Validated surveys (Web Resource Rating Tool[152] and Quality Evaluation Scoring Tool[153]) were used to assess the reliability and accessibility of the content. Webpages specific to hepatic encephalopathy were reviewed in detail to assess the scope of information and its relevance to self-management.

Chapter 4: *What influences self-management capabilities and health outcomes in hepatic encephalopathy?* This paper is a synthesis of empirical evidence and patient perceptions of self-management behaviours and needs. The purpose of a mixed research synthesis is to "sum up" the knowledge about a phenomenon (i.e., hepatic encephalopathy self-management) by contrasting and comparing quantitative and qualitative data "to direct both practice and future research."[154, p. 1] This approach supported the identification of unique opportunities to improve both health-related outcomes and the quality of life for patients at-risk for or living with this cognitive dysfunction.

Chapter 5: *What are the early experiences of patients with an app-based program to support nutrition and exercise self-management in cirrhosis?* I used an exploratory descriptive approach to “understand the context or setting of issues”[155, p 48] regarding the patients’ early experiences in a lifestyle behaviour intervention. This study was embedded within a feasibility trial of the Heal-Me app[156], developed for patients living with chronic diseases, which had been tailored specifically to cirrhosis to meet the guideline recommendations for non-pharmacological therapy – nutrition and exercise. Interviews were the preferred approach for the collection of experiential data as it prioritized the emic perspective of the patient using the app. The study incorporated the COM-B model of behaviour change[109] and the Theoretical Domains Framework (TDF)[105] to identify facilitators and areas for improvement to support the early engagement of patients with the Heal-Me cirrhosis app.

1.4.5 Research contributions

Cirrhosis is a rare condition with an increasing prevalence and high symptom burden. The underlying assumption is that self-management activities improve clinical outcomes, quality of life, and reduce care partner burdens. However, there are few, high quality, evidence-informed resources specifically designed for patients. These are needed to improve their awareness of self-management activities and master skills. Mastery requires time and effort on the part of the patient. With infrequent access to cirrhosis specialists (clinic visits every ~6 months[157]), patients with compensated livers may find it challenging to learn, understand, and practice self-management skills informed by these visits alone without between visit support. Changing behaviour to adopt healthier lifestyles consistent with non-pharmaceutical management of cirrhosis and its complications also takes awareness, understanding, knowledge, and skills to be successful. In stark contrast, a systematic review of 4 randomized controlled trials about self-management interventions in cirrhosis concluded that the evidence was insufficient to suggest their benefit to patients[158]. The review highlighted the low quality of research and negligible overlap of the programs both of which makes conclusions challenging. Such a finding highlights the value of rigorous and well-implemented research designs.

This body of work is a stepwise suite of exploratory studies to improve our understanding of patients’ self-management needs in tandem with the potential of internet-connected digital technology as a supportive tool. In the era of patient-centered medicine, patient perceptions, education, knowledge, and beliefs are essential to maximizing their health-outcomes and health-related quality of life. Given the challenges imposed by cirrhosis regarding symptom burden and care regimens, patient engagement and skills in self-management are essential if they are to live well with their chronic disease(s). This series of studies progressed from assessing patient readiness for internet-connected digital technology and proficiency through to capturing patient experience using an eHealth app to support their self-management. In each of the four studies, new information is shared regarding the nature of self-management in cirrhosis. Against a background of medical care, it is realized the recommended but rarely acted upon are lifestyle behaviour changes in nutrition and exercise. As a non-pharmaceutical therapy, programming for frailty prevention impacts mortality risk as well as the risks of hepatic encephalopathy. In a stepwise manner, how externally supported nutrition and exercise programming is delivered has the potential to reshape healthcare delivery and patient engagement in lifestyle behaviours. I hope that this work will be useful and relevant to patients, providers, and researchers alike.

Separate to my thesis but produced concurrently are other knowledge translation activities to support self-management: "The Nutrition in Cirrhosis Guide"[159], cirrhosis websites (www.WellnessToolbox.ca, www.CirrhosisCare.ca), and the Heal-Me app (www.healmeapp.ca). These resources were developed with a focus on people living with chronic disease who have a wide range of health literacy and technology skills.

CHAPTER 2.0 - Assessing patient proficiency with Internet-connected technology and their preferences for e-health in cirrhosis

2.1 Introduction

All chronic liver diseases eventually progress to cirrhosis, a common endpoint where the accumulation of scar tissue causes portal hypertension-related complications and impedes normal liver function. Patients with compensated cirrhosis have a median survival time greater than 12 years[160]. Once the liver progresses to the decompensated state, indicated by complications such as ascites, hepatic encephalopathy (HE), or variceal bleeding, the median survival decreases to approximately two years[160]. Across the cirrhosis trajectory, patients receive complex medical care involving preventative screening (e.g., cancer, varices), treating complications, and managing their high symptom burden, including but not limited to pain, fatigue, and depression[161-163].

E-health solutions (e.g., websites, telemonitoring, mobile apps designed to perform specific functions) to support patient self-management and health services have been introduced in many chronic disease populations, such as cardiovascular diseases, fibromyalgia, Parkinson's disease, chronic kidney disease, HIV, cancer, and mental illness[164-168]. In cirrhosis, the "Patient Buddy" app has been created for individuals with a history of hepatic encephalopathy[169]. The term "e-health" is used as both a noun and verb indicating the intersection of health, information, communication technology, and various stakeholders[118]. E-health has been associated with improvements in general self-management skills, communications with healthcare professionals, quality of life, physical function, pain management, and health outcomes[164].

An underlying assumption of e-health is that users have ready access to Internet-connected digital technology and the skills to use it effectively. The reality is that the "digital divide" persists along lines of social inequalities (i.e., education, urban versus rural, income, age, and immigration status[170-172]) and influences the access and the ability to use e-health. Two barriers are common in cirrhosis, prevalence of low socioeconomic status[173-175] and that nearly one third of patients are 65 years or older[176]. From a patient's perspective, additional barriers may include cirrhosis severity, physical disabilities, or cognitive abilities[151, 177].

The purpose of this study was to characterize the readiness of patients with cirrhosis for e-health by: (1) assessing their Internet access frequency and digital technology ownership; (2) determining their digital literacy proficiency and identifying relevant predictors; and, (3) ascertaining their general attitudes and receptiveness to video conferencing and online health management programs by age group. Aims 1 and 2 considered the severity of cirrhosis as indicated by the Child-Pugh score[178, 179]. By understanding the skills and preferences of patients with cirrhosis, e-health solutions can be better designed to meet their unique needs and abilities. In turn, these e-health products may achieve a wider adoption and longer period of use leading to improved patient health outcomes[143].

2.2 Methods

A survey-based, cross-sectional study was used to capture self-reported information regarding computer and Internet proficiency and attitudes in patients living with cirrhosis. The study was approved by the Health Research Ethics Board at the University of Alberta (Pro00082756). A convenience sample of consecutively consenting patients was recruited from outpatient liver clinics at two tertiary care hospitals located in western Canada from July 2018 to February 2019.

Participants

Eligibility criteria required that participants be: 18 years of age or older; have a confirmed diagnosis of cirrhosis as determined by imaging, medical history, transient elastography, or liver biopsy; could provide informed written consent; and could read and write in English. Ineligible participants were transplant recipients or individuals who were unable to provide consent. There was no requirement for having previous digital technology or Internet access. This study had an intended enrollment target of 125 participants based upon previous studies of this kind[180-182].

Procedure

After written informed consent was obtained, patients were asked to complete a survey in a paper and pencil format to minimize bias regarding technology proficiency. Surveys were completed in a clinic exam room. The research assistant remained nearby to answer questions and review the responses for completeness. If a patient asked the research assistant for a digital version of the survey, a link to an the online version was provided via REDCap[183].

Participant Characteristics

To characterize the cohort, each participant's personal health number was used to access their electronic health records: age (years), biological sex, liver disease etiology, prognostic measures (model for end-stage liver disease-sodium [MELD-Na][25] and the Child-Pugh score, both determined with the patient's most recent blood tests), history of HE, cancer history, significant comorbidities, disabilities, and current medications. Patients completed a general survey about their level of education, household income, digital technology devices they owned, frequency of Internet use, and online communication preferences.

Outcome Measures

The Computer Proficiency Questionnaire (CPQ) captures information about the patient's computer and Internet skills[143]. The CPQ contains six domains assessing skills regarding computer basics, printing, communication, Internet, calendar, and entertainment. The Mobile Device Proficiency Questionnaire (MDPQ) characterizes the patient's skills with smart devices across eight domains: mobile device basics, communication, data and file storage, Internet, calendar, entertainment, privacy, and troubleshooting and software management[151]. The CPQ and MDPQ used a 5-point Likert scale (1=never tried; 2=not at all; 3=not very easily; 4=somewhat easily; and 5=very easily) and the questionnaires were scored as previously described[143, 151]. The total possible points for the CPQ and MDPQ were 30 and 40, respectively. These validated questionnaires have demonstrated significant relationships with the length and frequency of use of a specific technology[151]. Internal consistency for each scale is high with Cronbach's $\alpha \geq .98$[143, 151, 184].

A third questionnaire captured patient receptiveness about video calling with healthcare professionals **(see Supplemental-Figure 1)**. It was developed in-house for this study and was not validated before use. Patient responses to each of the seven statements were answered with a

Likert scale: 1=totally disagree, 2=somewhat disagree, 3=neutral, 4=somewhat agree, and 5=totally agree. Online delivery of healthcare programming was explored with the question "If our team provided you with the training to make you more comfortable with using the Internet, how interested would you be in participating in a personalized health management program delivered by an Internet-based app (e.g., receiving exercise information, dietary information, reminders, and motivational tips)?" Patient preferences regarding four discrete functional elements for the hypothetical personalized online program were captured with a 5-point Likert scale: 1=not helpful at all, 2=somewhat unhelpful, 3=neutral, 4=somewhat helpful, and 5=extremely helpful **(see Supplemental-Figure 2)**.

Data Analysis

Descriptive statistics (mean, standard deviation, median, frequency) were generated for participants organized by Child-Pugh (CP) classification (A *vs.* B/C). Between group comparisons were completed for categorical variables using the χ^2 test or Fisher exact test, for continuous variables using independent samples *t* test, and ordinal variables using the Mann Whitney U test. Correlation analyses between CPQ and MDPQ scores and the continuous variables of age, CP score, and MELD-Na score were completed. To construct the regression models, significant variables ($p<0.05$) from the correlational analysis were included with dichotomous (sex, HE, comorbidities, visual impairment) and categorical (cirrhosis etiology, household income, education) variables and then regressed against either CPQ or MDPQ. Non-significant predictors were eliminated manually one by one and the regression was rerun. Only variables that significantly contributed to the models were retained. When assessing attitudes and preferences regarding video calling and online programming, the Kruskal-Wallis H test was used to determine if age differences existed. Specifically, with alpha set at $p<.05$, pairwise comparisons between the age groups were performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons. Missing survey data were obtained from the study participant. All analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corporation, Armonk, NY).

2.3 <u>Results</u>

Description of Participants

One hundred seventeen patients were recruited (age range: 24 to 83 years; MELD-Na score range: 6 to 33; Table 1) of which 72 (61.5%) were men. Significant differences were found between the two study groups (Child-Pugh A versus B/C) for mean MELD-Na score, ascites, diuretics, and lactulose and/or rifaximin (*p* >.01 for each) which were consistent with cirrhosis severity. Many patients had significant comorbidities: diabetes (n=36; 30.8%); arthritis (n=33; 28.2%); any cancer (n=33; 28.2%); asthma, (n=14; 12.0%); or, myocardial infarction (n=10; 8.5%). A total of 14 (12.0%) participants reported a visual impairment. More than half of the respondents had attended post-secondary education (e.g., college, professional courses).

Digital Technology Ownership and Internet Behaviours

Participants' responses to questions regarding their digital technology ownership, Internet access, attitudes are presented in Table 2. Disease severity indicated by Child-Pugh scores (A vs B/C) was not associated with any of the relevant variables. From a list of 10 common digital technology devices, 90 (76.9%) patients owned a smartphone. This was followed by ownership of laptops (53.8%), desktop computers (48.7%), tablets (43.6%), and smart televisions (31.6%) which are Internet connected and function like a television and computer. Only one patient stated that they did not own any of the devices. Nine (7.7%) patients did not own a smart device nor a computing system while 71 (60.7%) owned both. Daily Internet use was reported by 72 (61.5%) patients. Only 14 (12.0%) patients had never accessed the Internet. The Internet was accessed either frequently or very frequently for communication purposes by 69 (59.0%) patients. One hundred (85.5%) patients reported that digital technology was most helpful for communicating with others. Though only 52 (44.0%) patients used the Internet frequently or very frequently to obtain information, 78.6% stated that digital technology helped them to make more informed decisions. In all, 82.9% stated that life was better because of digital technology use.

Digital Technology Proficiency

Since the CPQ and MDPQ assess technology proficiency in four of the same areas (communication, Internet, calendar, and entertainment), and a strong positive correlation (r=0.93) was observed between the two sets of scores.

Common markers for disease severity (e.g., the MELD-Na score, Child-Pugh score) were not related to either the CPQ or MDPQ. The only significant correlate was age which was included in the subsequent multiple regression analyses. The final CPQ model explained 40% of the variance (adjusted $R^2=0.403$), $F(6, 110)=14.071$, $p<0.001$ **(Table 3)**. Educational background impacted CPQ scores where graduates from grade 8 or high school had lower scores (26.4% and 23.3%, respectively) than their post-secondary peers. Age had a significant influence in the multiple regression model where each year of life changed the CPQ score by -0.8% (reducing proficiency). For the household income variable, only the sub-category of less than $25,000 significantly influenced the CPQ by -10.8% ($p=.02$). These variables were also significant correlates for the MDPQ model with no difference in direction of influence of the predictors and no additional predictors identified **(Table 3).** When examining the effect size of the predictors for the CPQ and MDPQ, the patient age variable (partial $\eta^2=.17$ and partial $\eta^2=.25$, respectively) outperformed education considering its cumulative yearly impact and the mean age of the study population of 58.2 years.

Video Calling Preferences

Figure 1 presents the responses to questions regarding patient opinions about this online form of communication. Most patients were receptive to using video calling with health care professionals and only 16 (13.7%) were totally against it. Seventy-nine (67.5%) patients expected that video calling with a healthcare professional would be confidential. Patients expected that video calling would be both quick to learn and easy to do thereafter. Seventy-seven (65.8%) patients agreed that video calls with healthcare professionals would be associated with a safe feeling. When asked if they could make video calls on their own, only 25 (29.1%) patients totally agreed. When asked if they were provided with training, 56 (47.9%) patients agreed that they could use video calling.

To determine the impact of patient age on their video calling preferences, a Kruskal-Wallis H test was run with patients categorized into three groups: Group A, 24-55 years (n=40); Group B, 56-63 years (n=39); and, Group C, 64-83 years (n=38). Patient age had a significant impact on responses for questions 1, 3, 4, and 6 (see **Figure 1** for survey results). Younger patients (Group A) were more receptive and positive about the use of video calling with healthcare professionals than older patients in Groups B or C (see **Supplemental-Table 1** for pairwise comparison details).

Online Personalized Exercise Program Preferences

Regarding interest in an online personalized health management program, 72 (61.5%) patients were somewhat or very interested, 12 (10.2%) were neutral, 21 (17.9%) were somewhat or very disinterested, and 12 (10.2%) did not know. Patient responses to the four elements of the online program (e.g., video content and motivational messaging) ranged across the entire Likert scale; a considerable proportion (range: 21.3% to 36.7%) of respondents did not consider these as helpful (see **Figure 2** for survey results**)**. A single element was neither favoured nor disliked by the entire study group. The Kruskal-Wallis H test identified that preferences about text messaging motivational tips were significantly impacted by patient age with younger patients preferring it more than older ones (Group A vs Group C; see **Supplemental-Table 2** for pairwise comparison details).

2.4 Discussion

To our knowledge, this is the first study evaluating digital literacy skills, Internet access, and digital technology preferences of patients with cirrhosis. Within our cohort, the main findings of this study were: (1) most patients owned or used technology in their homes with the majority accessing the Internet daily; (2) skills using either computers or mobile devices was moderate and significant predictors of proficiency were age, education, and household income less than $25,000 per year; and, (3) most were receptive to video calling with healthcare professionals and interested in online personalized health management programming.

Technology ownership in this cirrhosis study was similar to data presented in the Internet and digital technology component of the 2016 General Social Survey for Canada[185]: (smart device: 76% vs. 85%; computer: 71% vs. 68.4%, respectively). The 2-year difference between the studies likely increased technology ownership based on historical information. Our study participants reported that technology was even more useful for communication than the national average (86% vs. 77%, respectively), including its use to make informed decisions (79% vs.

52%, respectively) be more creative (64% vs. 36%, respectively). Overall, 83% of study patients believed that life was better because of technology versus 60% for Canadians of a similar age range. The median household income for the study group of $25,000 to $50,000 was below the average for the Edmonton region ($87,225) and province ($93,835)[186]. Despite limited finances, study patients had similar rates of technology ownership, Internet habits, and attitudes as other Canadians. This suggests that study participants value Internet and communications technology and financially prioritize these. Interestingly, when participants were grouped by their Child-Pugh score, no significant differences were found suggesting that these behaviours may be independent of cirrhosis severity.

The scores on the computer and mobile device proficiency questionnaires (CPQ and MDPQ, respectively) indicate that patients had moderate proficiency with these technologies. For comparison, one study reported a mean CPQ score of 33.3% (n=276) was attained by people with minimal computer experience while a mean score of 81.2% (n=76) was associated with several years of computer experience and computer ownership in older adults[143]. A second study reported a mean CPQ score of 78.2% for 116 adults from the general population[184]. MDPQ scores have been significantly correlated with both the length and frequency of use of mobile devices in adults (n=95)[151]. Specifically, MDPQ scores for the general population have ranged between 48% to 92% in the United States[151] and 33% to 90% in Spain[184]. Overall, our study patients had computer and mobile device proficiencies comparable to their healthy counterparts.

Measures of cirrhosis severity (MELD-Na, CP score), comorbidities, history of HE, and visual impairments were not significant predictors of either CPQ or MDPQ scores. However, the well-described barriers of age, education, and income impacted digital technology proficiency[180, 182, 187, 188], were significant predictors for our cirrhosis study group. Within the limits of our sample, this suggests that there are no unique digital divide barriers specific to cirrhosis.

Although descriptive studies have indicated that cognitive decline and episodic memory are barriers to both technology adoption and Internet use, two studies have found evidence suggesting other elements are involved[180, 182]. In addition to age and education, they found other predictors of technology proficiency: sense of control, inductive reasoning, perceptual speed, and psychomotor speed. They hypothesized that these additional predictors could compensate for cognitive and memory issues[180, 182]. Similarly, a history of HE was not a significant predictor of either CPQ or MDPQ scores. Notably, these patients were on lactulose or rifaximin as per practice guidelines[42]. Cognitive testing for covert HE was not conducted thereby making it unclear if this influenced digital technology proficiencies.

Patients with cirrhosis had positive perceptions and attitudes regarding video conferencing with healthcare professionals. For comparison, a 2016 study in England reported that only 50% of 270 adult patients attending one of three general practitioners' clinics were willing to use video consulting[189]. In this study, patients expected that videoconferencing should be confidential, it would be quick to learn, and easy to do once they received training. These same factors influenced the intention to use video calling for 256 adults (median age: 71 years) who were living independently at home[190]. In cirrhosis, e-health involving video calling must meet the design and usability needs across a broad age spectrum (20-80+ years).

Though patients were receptive to a virtual personalized health management program, there was variation in their preferences for program content and functional features such as motivational tips. This suggests that for any e-health tool to be successful, it needs to be customizable and offer flexible options for interaction with the user. In addition to adequate training, it was clear that patients also wanted to engage with the virtual program on terms that best suited their perceived needs and interests.

Strengths and Limitations

A study strength is that patients were recruited from three different clinic environments - a tertiary care outpatient liver clinic at an academic hospital, a liver transplant clinic and an outpatient clinic affiliated with an inner-city tertiary care hospital. This ensured that participants came from diverse socioeconomic backgrounds, residential locations, and health experiences thereby supporting the generalizability of the results, except to those at the extremes of homelessness and poverty. Though the CPQ and MDPQ have been validated, they rely on self-reported skills and may not be reflective of a person's true ability. Though we did not have the infrastructure and resources to do so, a more direct evaluation of digital literacy proficiencies would be to watch a patient perform tasks in real-time. Commercial online proficiency tests are available but extensive customization of the proprietary software is required for research making them impractical[191]. As inclusion criteria required English language proficiency, the results cannot be generalized to non-English speakers.

Though we were able to explore the influence of many cirrhosis-related and general health-related factors on computing and mobile device proficiencies, it was beyond the scope of the study to explore the predictive characteristics that correlated with CPQ scores, such as inductive reasoning, perceptual speed, and psychomotor speed[180, 182]. Our rationale for selecting the CPQ and MDPQ was their specificity for evaluating computing and mobile device skills, ease of assessment, and currency in consideration of the rapid changes in digital technology and Internet behaviours.

In conclusion, we found that patients living with cirrhosis are ready for e-health a long as it is provided alongside adequate training and support. The recent successes of e-health suggest that it will no doubt persist beyond the current pandemic[192, 193]. Only by building upon past work and integrating useful frameworks (i.e., Technology Evaluation and Assessment Criteria for Health apps[194]) will e-health solutions effectively improve patient care and health outcomes. It is becoming apparent that society is rapidly moving into an era where e-health access and possessing a minimum of technology skills are becoming basic necessities rather than a luxury or lifestyle choice. For the cirrhosis population, results of this study show that e-health strategies offer promising opportunities to support patient management and healthcare.

Table 2-1. Characteristics of participants by liver disease prognosis

Characteristic	Cohort	Child-Pugh A	Child-Pugh B or C	*p*-value
Participants (n)	117	60	57	
Men	72 (61.5%)	38 (63.3%)	34 (59.6%)	.68
Mean age in yrs (SD)	58 (11.2)	59 (9.3)	57.2 (13.0)	.37
Etiology of cirrhosis:				<.01
• Alcohol	39 (33.3%)	13 (21.7%)	26 (45.6%)	
• Hepatitis C	31 (26.5%	22 (36.7%)	9 (15.8%)	
• NAFLD†	25 (21.4%)	17 (28.3%)	8 (14.0%)	
• Other‡	22 (18.8%)	8 (13.4%)	14 (24.6%)	
MELD-Na mean (SD)	13 (11.0)	9 (2.2)	16.9 (6.3)	< .01
Listed for liver transplant	18 (15.4%)	6 (10.0%)	12 (8.8%)	.10
Dyslipidemia	32 (27.4%)	16 (26.7%)	16 (28.1%)	.87
Hypertension	48 (41.0%)	24 (40.0%)	24 (42.1%)	.82
Ascites	33 (28.2%)	3 (5.0%)	30 (52.6%)	< .01
History of variceal bleeding	21 (17.9%)	5 (8.3%)	16 (28.1%)	.01
Comorbidities§	77 (65.8%)	39 (65.0%)	38 (66.7%)	.85
On diuretics	61 (52.1%)	16 (26.7%)	45 (78.9%)	< .01
HE history (currently taking lactulose and/or rifaximin)	37 (31.6%)	0 (0%)	37 (31.6%)	< .01
Education:				.78
• Grade 8	12 (10.3%)	7 (11.7%)	5 (8.8%)	
• High school diploma	34 (29.1%)	16 (26.7%)	18 (31.6%)	

• Post-secondary school	71 (60.7%)	37 (61.7%)	34 (59.6%)	
Household income:				.59
• Participant chose not to report	10 (8.5%)	6 (10.0%)	4 (7.0%)	
• <$25,000	35 (29.9%)	15 (25.0%)	20 (35.1%)	
• $25,000 to $50,000	20 (17.1%)	12 (20.0%)	8 (14.0%)	
• >$50,000	33 (28.2%)	27 (45.0%)	25 (43.9%)	

† Includes non-alcoholic fatty liver disease (NAFLD) and cryptogenic cirrhosis.

‡ Includes hepatitis B, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and autoimmune hepatitis.

§ If the individual had one or more of the following: myocardial infarction, diabetes, asthma, arthritis, or any cancer.

Table 2-2. Characterizing patient technology ownership, Internet access, and perceptions by liver disease prognosis

Characteristic	All	Child-Pugh A	Child-Pugh B or C	*p*-value
Participants (n)	117	60	57	
Owns a smart device	99 (84.6%)	52 (86.7%)	47 (82.5%)	.53
Owns a computer/laptop	80 (68.4%)	40 (66.7%)	40 (70.2%)	.68
Does not own technology	1 (0.9%)	1 (1.7%)	0 (0%)	1.0
Frequency of Internet use:				.55
• Daily	72 (61.5%)	34 (56.7%)	38 (66.7%)	
• Weekly	15 (12.8%)	10 (16.7%)	5 (8.8%)	
• Monthly	16 (13.7%)	8 (13.3%)	8 (14.0%)	
• Not accessed	14 (12.0%)	8 (13.3%)	6 (10.5%)	
Patients frequently or very frequently used the Internet for†:				
• Communicating (e.g., email, Skype)	69 (59.0%)	33 (55.0%)	36 (63.2%)	.37
• Accessing information (e.g., news, health, government)	52 (44.0%)	25 (41.7%)	27 (47.4%)	.54
• Performing tasks (e.g., banking, online shopping)	49 (41.9%)	25 (41.7%)	24 (42.1%)	.96
• Leisure activities/entertainment (e.g., games, music, film, photos)	56 (47.9%)	26 (43.3%)	30 (52.6%)	.31
Digital technology helps with:				
• Communication (Y/N)	100 (85.5%)	53 (88.3%)	47 (82.5%)	.37
• Saving time (Y/N)	80 (68.4%)	43 (71.7%)	37 (64.9%)	.43

• Making more informed decisions (Y/N)	92 (78.6%)	48 (80.0%)	44 (77.2%)	.71
• Being more creativity (Y/N)	75 (64.1%)	39 (65.0%)	36 (63.2%)	.84
Life is better because of technology use (Y/N)	97 (82.9%)	50 (83.3%)	47 (82.5%)	.90
CPQ score, mean (SD)	72.8% (25.9%)	71.6% (26.2%)	74.1% (25.9%)	.61
MDPQ score, mean (SD)	69.3% (26.4%)	69.3% (26.2%)	69.3% (27.0%)	1.00

† Survey question used a 5-point Likert scale where 1=very rarely and 5=very frequently; data presented are the sums for responses "frequently" and "very frequently".

Abbreviations: CPQ, Computer Proficiency Questionnaire; MDPQ, Mobile Device Proficiency Questionnaire; N, no; SD, standard deviation; Y, yes.

Table 2-3. Standard multiple regression analyses against proficiency scores

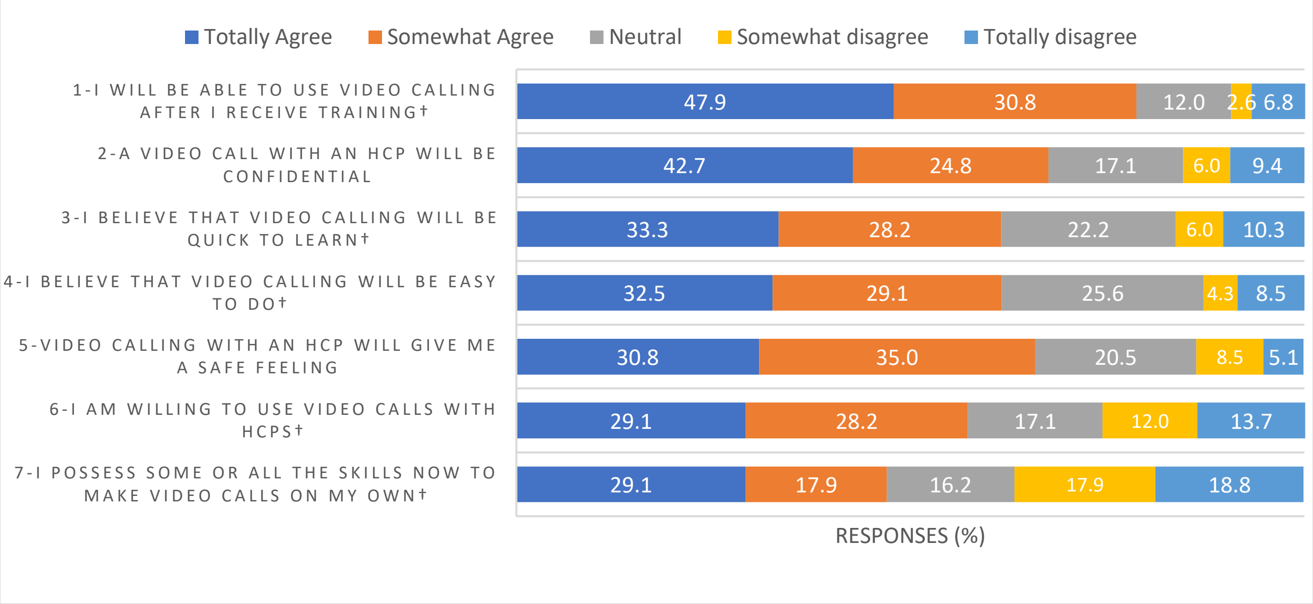
Variables		***B***	***SE_B***	**t**	**p-value**	**Partial Eta (η^2)**
(A) Computer Proficiency Questionnaire (CPQ)						
Constant		134.911	10.480	12.873	<.001	.60
Household Income	• Not reported	-3.915	7.046	-.556	.580	.00
	• <$25,000	-10.816	4.656	-2.323	.022	.05
	• $25,000 to $50,000	-4.434	5.446	-.814	.417	.01
	• >$50,000	0[a]				
Education	• Up to Grade 8	-26.386	6.630	-3.980	<.001	.13
	• Up to Highschool	-23.261	4.397	-5.290	<.001	.20
	• Up to Post-secondary	0[a]				
Age		-.830	.174	-4.770	<.001	.17
(B) Mobile Device Proficiency Questionnaire (MDPQ)						
Constant		143.287	10.290	13.925	<.001	.64
Household Income	• Not reported	-4.392	6.918	-.635	.527	.01
	• <$25,000	-13.375	4.572	-2.925	.004	.07
	• $25,000 to $50,000	-4.803	5.347	-.898	.371	.01
	• >$50,000	0[a]				
Education	• Up to Grade 8	-25.263	6.510	-3.881	<.001	.12
	• Up to Highschool	-21.322	4.317	-4.939	<.001	.18
	• Up to Post-secondary	0[a]				

Variables	***B***	***SE_B***	**t**	**p-value**	**Partial Eta (η^2)**
Age	-1.031	.171	-6.032	<.001	.25

Abbreviations: *B*, regression coefficient; SE_B, standard error.

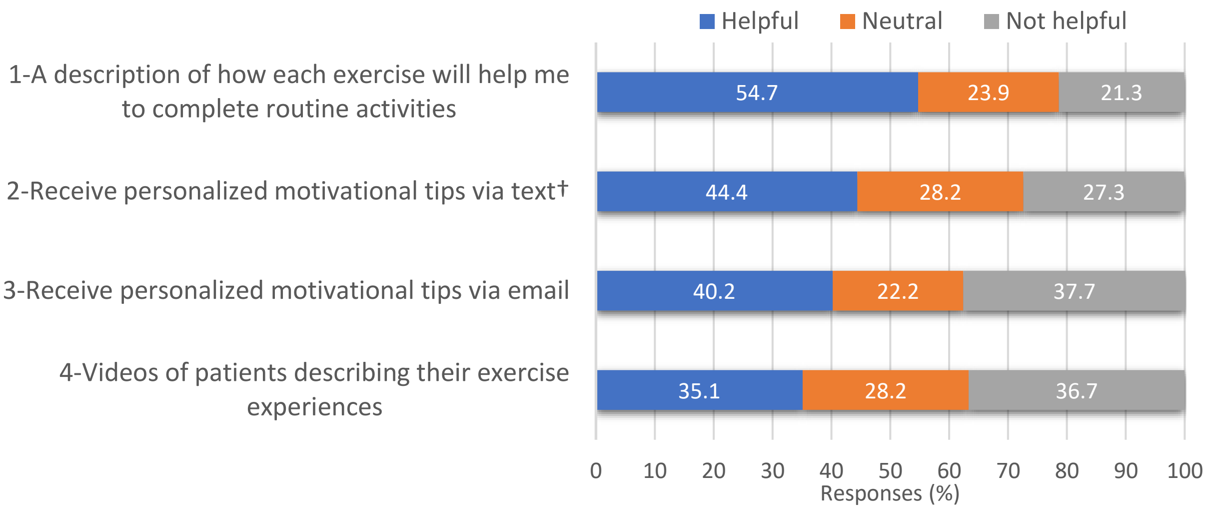
[a] Reference variable.

Figure 2-1. Opinions of study patients (n=117) regarding video calling.



† *p*<.05 for the Kruskal-Wallis H test indicating if there were differences by patient age group: 24-55 yrs (n=40), 56-63 yrs (n=39), and 64-83 yrs (n=38).

Figure 2-2. Preferences of study patients (n=117) regarding online delivery of personalized exercise programming



† *p*<.05 for the Kruskal-Wallis H test indicating if there were differences by patient age group: 24-55 yrs (n=40), 56-63 yrs (n=39), and 64-83 yrs (n=38).

CHAPTER 3.0 - An evaluation of online cirrhosis-related information intended for patients and caregivers

3.1 Introduction

Increasing Internet accessibility and changes in healthcare policy during the COVID-19 pandemic have hastened the era of e-health into reality. Some speculate that Internet access is no longer a privilege, but a basic need as online information and tools support many aspects of health, including prevention and self-management[195, 196]. Understanding and acting on health information from the Internet is not singly dependent on having Internet access[197]. Health literacy also depends on skills such as internet searching and navigation, critical thinking, and information synthesis[198-200].

Medical healthcare policy supports informed patients who can express their health preferences as part of a collaborative shared decision-making process with clinicians[201]. By conferring agency to patients, their deliberations need to be supported by quality information, such as patient decision aids, clinician communication, and e-health. When faced with a health-related matter, data from American adults (n=18,103) suggests that 69% seek information online as their first approach[202]. Individuals with chronic diseases use the Internet and eHealth more than healthy individuals[203]. Recognizing the importance of e-health, the US Department of Health and Human Services provided a range of initiatives and programming to facilitate ease of access to online health information. Unfortunately, at the 10-year program evaluation in 2020, the target of 45% was not met as only 37.4% (n=13,907) reported easy access experiences[202].

The stakeholders who create and deliver online health information have unique objectives ranging from supporting patient care through to consumerism. In chronic diseases, clinicians can direct their patients to reputable websites to obtain quality information to support their self-management and role in shared decision-making. Effective communication has been recognized as a priority to support patients, especially for conditions that are complex, such as cirrhosis.

Liver cirrhosis is a chronic, debilitating condition that requires extensive self-management skills. Both poly- and hyper pharmacy are prevalent in this patient population as they have many comorbidities. Medical care can involve specialists and allied health care practitioners in addition to the family physician.

The aim of this project was to evaluate cirrhosis information intended for patients and caregivers that was freely available online. Using validated tools, our objectives were to assess the information scope, accessibility, and reliability organized by the type of sponsoring organization. Information accuracy was assessed for a common complication of cirrhosis, hepatic encephalopathy, chosen because of its profound impact on patient health-related quality of life and care partner burden. Our hypothesis was that significant gaps would be discovered and that the study findings may be useful to inform how to improve online cirrhosis information to be congruent with practice guidelines and accessible to the information needs of those living with cirrhosis.

3.2 Methods

The Patient Advisory Committee of the Cirrhosis Care Alberta Trial created a list of cirrhosis-related topics they believed were relevant for patients and informal care partners[110]. Using this list, 19 search strings were generated: cirrhosis, hepatic encephalopathy, confusion cirrhosis, lactulose, infection cirrhosis, varices or banding cirrhosis, gastroscopy cirrhosis, bleeding cirrhosis, transjugular intrahepatic portosystemic shunt, TIPS cirrhosis, pruritus cirrhosis, itching cirrhosis, edema cirrhosis, ascites cirrhosis, paracentesis cirrhosis, hepatocellular carcinoma cirrhosis, cancer cirrhosis, self-management cirrhosis, and nutrition cirrhosis. Search strings were used without quotations, parentheses, or other modifiers. Search engines were selected based on usage rates, global region, and English language content: Google, Bing, Yahoo!, Ask.com, DuckDuckGo, Ecosia, Startpage.com, and Qwant[204]. Searches were performed without regional location limitations. The first three pages of search results for each search engine were retrieved (26-30 webpages) informed by previous work, in tens of millions of users, demonstrating that approximately 80%, 17%, and 3% viewed the first, second, and third pages of results[205]. Results marked as “ads”, “videos”, or “images” were not retrieved.

After removing duplicates, results were assessed against the inclusion criteria: freely accessible without registration or fees, and English text-based content with or without images, videos, or podcasts. To ensure the page was intended for patients, content was scanned to identify the target audience and often this was indicated in the headers and footers, such as “Patients & Caregivers” versus “Health Professionals & Researchers”. When the target audience was not explicitly indicated, the pronouns used on the webpage were scanned for “you” and “your”. As needed, the About page for the main website was reviewed to confirm or provide additional clarity regarding the intended audience. At this stage, exclusion criteria were webpages containing only videos or podcasts, pages that generated HTTP error codes (e.g., 404 Not Found, 400 Bad Request, etc.), and educational materials and publications for healthcare professionals.

The webpages were reviewed for parent website, copyright information, country of origin, and date of creation or revision. Webpages were categorized in two ways. First, by the type of sponsoring organization (i.e., business, not-for-profit, government, or healthcare system) identified by the parent or canonical website, and reinforced by the webpage’s Internet domain suffix, such as .com or .gov for business or government organizations, respectively. In the second approach, the number of webpages retrieved for an organization were considered resulting in two categories: specialized (2 or more webpages were retrieved from the same organization) or non-specialized (only 1 webpage was retrieved from an organization). The presence and frequency of multimedia per page was also recorded (i.e., videos, images, and podcasts) and advertisements. The main topic of a page, often indicated in the Uniform Resource Locator (URL) or page title, was noted.

Readability was assessed using four common methods (see Supplement-Table 1). The Flesch-Kincaid Grade Level (FKGL) analysis is based on sentence length and the number of syllables in a sentence with scores reported according to the equivalent American grade level[206]. Grade scores of 13 or more indicate post-secondary education. The Gunning Fog Index (FOG) is determined by the number of words per sentence, the number of words with 3 or more syllables, or complex words[207]. The Simple Measure of Gobbledygook (SMOG) Readability Formula is a common tool to measure health literacy levels[208]. SMOG measures the number of polysyllabic words in consecutive sentences. The Coleman-Liau Index (CLI) considers the average number of letters for 100 randomly selected words and the average number of words in sentences[209].

To evaluate the reliability of the webpages, two validated tools were used: the Web Resource Rating Tool (WRRT)[152] and the QUality Evaluation Scoring Tool (QUEST)[153]. The Health On the Net (HON) Foundation, established in 1996, offers a certification for websites complying with the 8 meta criteria of the HONcode (https://www.hon.ch/en/). The presence of the HONcode logo and date for each webpage was recorded. The web accessibility evaluation tool (www.wave.webiam.org), named WAVE by WebAIM, was used to check for errors on 268 webpages in March 2021 (only one (business) webpage was no longer functional). WAVE evaluates webpages against the success criteria of the Web Content Accessibility Guidelines (WCAG) 2.1 developed by the World Wide Web Consortium's Web Accessibility Initiative[210] and Section 508 of the Rehabilitation Act (29 U.S.C. § 794d)[211].

To assess content accuracy, webpages on hepatic encephalopathy were identified then evaluated two ways against authoritative clinical practice recommendations for hepatic encephalopathy published in 2013 and 2014[31, 42]. First, the number of information pieces provided were identified and then assessed against practice guidelines[31, 42]. Incongruencies with the guidelines were documented if present for each webpage. Second, a scoring tool was developed based on published guidelines and discussion with Hepatology specialists. It emphasized information useful for the patient and informal caregivers (see Supplement-Table 2). This approach was informed by the work of Schreuders and colleagues[212].

Statistical analysis. Data were descriptively analysed using frequencies, ranges, means, and standard deviations. Binomial webpage characteristics (e.g., presence of advertising, multimedia, HONcode) and type of organization sponsoring the webpage were assessed by the chi-square test for homogeneity with significant differences explored using a z-test of two proportions including a Bonferroni adjustment to correct for multiple comparisons. For measures with a continuous dependent variable (e.g., readability scores, reliability measures, and website errors), one-way analysis of variance (ANOVA) was used with the level of significance set to 0.5. In situations where homogeneity was violated, Welch's ANOVA was used instead. A Pearson correlation was used to assess the relationship between continuous measures. The independent samples t-test assessed differences between continuous measures of readability and reliability when webpages were dichotomously categorized as providing either specialized or non-specialized cirrhosis information.

3.3 Results

The search strategy retrieved a total of 4,351 webpages. After removing duplicate webpages and evaluation against the inclusion criteria, 212 webpages fulfilled eligibility criteria (Figure 1). The retained webpages were associated with 123 unique websites originating from 11 countries: United States 142 (67.0%), Canada 24 (11.3%), United Kingdom 21 (9.9%), New Zealand 12 (5.7%), Australia 5 (2.4%), and India 3 (1.4%). One webpage (0.5%) was retrieved for each of the following countries: Austria, Finland, Kuwait, Nigeria, and Slovenia.

History

Copyright dates were included in the footer of 166 (61.7%) webpages of which 139 (65.0%) were current in August 2020 and were accessible in August 2021. Only one government website included a copyright date (webpages 120-123 from www.myhealthalberta.ca). The mean copyright duration was 7.9 years (SD 8.9 years, range 1 to 23.5 years) with several webpages presenting content copyrighted since 1996 (webpages 13-20, 80, 81). A total of 157 (74.1%) webpages indicated the currency of the content and the mean time lapse of either creation or last review was 1.8 years (SD 2.1 years).

Characteristics when Webpages were Categorized by Organization Type

Webpages sponsored by businesses were the most common (94/212 or 44.3%) while not-for-profit organizations were the least common (41/212 or 19.3%) (Table 1). Webpages from the US dominated the business (78.1%) and health system (89.6%) categories.

For multimedia content, only 2 (0.01%) webpages contained podcasts, 22 (10.4%) included video content, and 104 (49.1%) presented images. There were 96 (45.1%) webpages that were text only. No significant differences were found by organization type (p=.220). Despite a broad range of search terms used, 71.2% of retrieved webpages covered 5 topics: esophageal varices, 39 (18.4%); hepatocellular carcinoma, 37 (17.4%); TIPS, 30 (14.2%); paracentesis, 25 (11.8%); and edema 20 (9.4%). Although hepatic encephalopathy is a common complication in cirrhosis, only 18 (8.5%) webpages were retrieved on this topic. A total of 12 (5.7%) webpages were retrieved that specifically presented complimentary and alternative medicines (CAM) for treating cirrhosis, liver cancer, edema, or other related symptoms.

Advertisements were found on 84.8% of business webpages (mean per page: 7.3), whereas government pages contained none. A statistically significant difference (p<.001) was found for the inclusion of advertisements by organization type. In the post hoc analysis, involving pairwise combinations using the z-test of two proportions with a Bonferroni correction, all comparisons were statistically significant (p<.05) except for between health systems and not-for-profits (p>.05).

Readability

These four standard measures, categorized by type of organization, ranged from grades 10 to 14 and showed minimal variation (Table 1). No significant differences were found for FKGL, FOG, or SMOG. A significant difference was found for CLI between organization categories (p=.046) with Welch's ANOVA. The Games-Howell post hoc analysis showed that the only significant difference occurred between government webpages (mean CLI=grade 10.5) versus business webpages (mean CLI=grade 11.7) (p=.031).

Reliability

The mean results for WRRT (18.4/100 SD 11.9) and QUEST (15.2/28 SD 5.6) indicated low rates of webpage content reliability. No significant differences were found when analysing the QUEST and WRRT results by organization type. When looking at the scoring allocation, a significant difference between organization type was identified for the WRRT section pertaining to "Transparency and Usability Criteria" (p=.003). A Tukey post hoc analysis showed a significant difference between the mean scores for governments (15.6) versus health systems (14.0) (p<.001). A strong positive correlation was found between the total scores for WRRT and QUEST, r=0.714 (p<.001).

Although only 61 (28.8%) of webpages had an HONcode logo, the difference between organization types was significant (p<.001). Post hoc analysis found significant differences (p<.05) between government (7.4%) and health system (12.2%) webpages versus businesses (43.8%) regarding this certification. Not-for-profits (27.5%) were not significantly different (p>.05) in any pairwise combination with other organization types.

Webpage errors, evaluated with the WAVE tool, were common with a mean of 9.7 errors per webpage (range: 0-96 errors). A significant difference was found for website errors categorized by organization type using Welch's ANOVA (*p*<.001). Games-Howell post hoc analyses showed significant differences for government webpages with 3.2 errors compared to not-for-profits (7.0 errors, *p*=.025), health systems (10.6 errors, *p*=.010), and businesses (12.1 errors, *p*<.001). In addition, a significant difference was found between not-for-profit and businesses (*p*=.004).

Characteristics when Webpages were Categorized as either Specialized or Non-specialized

When webpages were categorized into specialized versus non-specialized, based on the proportion of webpages retrieved per website, there were 144 webpages (numbered #1-144) from 55 parent websites and 68 webpages from 68 websites. No significant differences were found for any of the four readability measures using this categorization approach. However, significant differences were found for the WRRT and QUEST scores where specialized webpages had higher reliability scores. There was a statistically significant difference in WRRT scores between specialized (21.2) and non-specialized webpages (12.2) with a mean difference of 9.0 (95% CI, 5.8-12.3), *t*(202.7)=5.5 (*p*<.001). The mean QUEST scores of 17.1 and 11.2 for the specialized and non-specialized webpages, respectively, also showed a statistically significantly difference of 5.9 (95% CI, 4.5-7.3), *t(*210)=8.333 (*p*<.001).

Hepatic Encephalopathy Webpage Characteristics

There were 18 webpages that specifically addressed hepatic encephalopathy (business, 8; not-for-profit, 5; government, 4; and health systems, 1) from 5 countries. The mean number of patient-oriented topics on hepatic encephalopathy covered was 12.2/20 or 61.1%. Symptoms (100%) and diagnosis approaches (89%) were the most common topics while the least were medication effectiveness (17%) and guideline-based dietary recommendations (6%). Seventeen (94%) webpages described possible symptoms of HE with many emphasizing the variety. However, none of the pages differentiated between the types of physicians responsible for diagnosis (i.e., family physician versus specialist or hospitalist). The most comprehensive webpages addressed either 18 (#167) or 19 (#44) topics, some addressed less than 8 topics (#2 and #121). Few webpages described the roles of care partners in the early detection of HE symptoms, the benefits of liver-friendly nutrition in HE prevention and treatment, and post-transplant outcomes for HE. Despite the common side effects of lactulose, the frontline therapy for HE, this was infrequently mentioned (#44, 104, 121, 140, 167).

Information accuracy was low: 8 (44.4%) webpages recommended decreasing protein in contradiction to the 2013 dietary guidelines of hepatic encephalopathy in cirrhosis (#1, 19, 20, 31, 57, 104, 121, 171)[31]. In these webpages, protein consumption, especially red meat, was associated with the development of HE, while prevention recommendations centered on reducing dietary protein to lower the levels of ammonia. Exercise or physical activity to potentially treat this complication were mentioned in only 2 (11.1%) webpages (#44 and 158). Symptoms for the three types of hepatic encephalopathy (Types A, B, and C) were combined in 5 (27.8%) webpages without clarification, rendering the information misleading and confusing: "Hepatic (liver) encephalopathy (brain swelling with herniation, coma, death)…" (#19).

In spite of being patient-oriented, 9 (50%) webpages presented expert information, such as describing in detail the three types of hepatic encephalopathy and the West Haven Grading Criteria, mimicking the flow and content of the 2014 clinical practice guidelines[42]. Expert phrases and terms (e.g., "excessive nitrogen load", "pathogenesis", and physicians instead of doctors) were frequently encountered.

Five websites described that avoiding a liver disorder is the best approach to prevent hepatic encephalopathy, a suggestion that is not useful to those who already have the condition (#1, 20, 31, 37, 104). Although abstinence is recommended in cirrhosis, several webpages suggested moderate alcohol consumption (#20, 31, 37, 104). One website mentioned to avoid smoking since that is dangerous to everyone's health (#167). Though an objective statement, the rationale for inclusion on this webpage is unclear as there is no association between smoking and this cirrhosis complication.

Actionable patient-oriented information consisted of how to prepare for a clinic visit about hepatic encephalopathy symptoms and suggested questions to ask (#167), what to expect (#78), medications to avoid (#104), and the importance of making friends and family aware of changes in either personality or behaviours (#57). Readers were advised to seek medical attention if they experienced any of the listed symptoms. None of the webpages included tools (for print or download), examples, or "how to" suggestions for: tracking daily bowel movements when prescribed lactulose, ensuring adherence with other cirrhosis-related medications, list of medications with brand names to avoid, tracking sheet for daily protein intake and food frequency, or suggested conversations with family and friends to raise awareness of hepatic encephalopathy and their primary roles in facilitating timely diagnosis and treatment.

To translate expert medical information into lay English, webpage authors employed synonyms (e.g., poison in lieu of toxin) while others replaced hepatic encephalopathy with the abbreviation "HE" or shortened it to "encephalopathy". These well-intentioned edits to simplify the medical literature can become counterproductive (Table 2). For example, one website recommended "not being around toxins" (#37) was important to prevent hepatic encephalopathy.

3.4 Discussion

Patient-oriented, online cirrhosis information is readily accessible to those with Internet access. Following a systematic search and evaluation of cirrhosis webpages, 212 webpages, from 123 websites and 11 countries, were evaluated for readability and reliability. Overall accessibility of the content was low to moderate requiring a high school graduate level of education to digest the textual material with few multimedia elements. The majority of webpages were sponsored by business organizations most of which were located in the United States. For webpages with dated content, the information had been either generated or reviewed within the previous 2 years. Between August 2020 and June 1, 2021, only one of the 212 webpages was no longer accessible emphasizing the persistence of the perceived usefulness of cirrhosis information by the sponsoring organizations.

The Canadian Public Health Association recommends the use of plain language to present medical information in respect of national literacy rates. Text written at the level of grades 8 to 10 should be accompanied by visual aids (e.g. videos) to make the content accessible to everyone[213]. The American Medical Association (AMA) and National Institutes of Health (NIH) recommend that patient education materials should be written for grades 3 to 7[214, 215]. In this study, cirrhosis information expressly intended for patients was written for grades 10 to 13 (first year of post-secondary school). Readability scores were influenced by the names of medical procedures (e.g., transjugular intrahepatic portosystemic shunt, paracentesis) and cirrhosis complications (e.g., asterixis, esophageal varices). The readability of the cirrhosis content fell within the ranges reported in two studies. The first assessed 214 patient education articles developed by major gastroenterology societies and the NIH and had a grade level range of 8.0 to 16.0 (mean FKGL grade: 11.0 ± 1.9)[216]. The readability of online information about three endoscopy procedures from 10 professional organizations ranged from grade 3.7 to 20.0 with a mean readability of grade 10.3[217]. An assessment of a cirrhosis-specific leaflet revealed a SMOG grade level of 15.8[218]. Similar results have been presented for other chronic diseases, such as celiac disease[219], colorectal[212] cancer, and inflammatory bowel diseases[220]. After assessing the quality and readability of colorectal cancer screening patient materials, the authors concluded that the webpages were of only moderate perceived value to potential readers.

Reliability measures, QUEST[153] and WRRT[152], were congruent and highlighted the poor to moderate quality of the content. These tools were selected as they were specific for evaluating online material, were evidence-based, and had been validated. The voluntary HONcode certification is valued by the business community to promote the reliability and legitimacy of their online content to readers. Located typically in the footers of health webpages, the awareness and perceived value of HONcode by patients is unclear. Regardless of the readability and reliability of webpages, the prevalence of errors especially on business webpages, added an unnecessary layer of difficulty accessing the content.

This scoping analysis of the hepatic encephalopathy webpages showed much discrepancy in the interpretation and selection of information perceived to be useful to readers. The webpages often provided a laundry list of medical terms for symptoms, triggers, and treatments often combining the information for Types A, B, and C hepatic encephalopathy. For the experienced reader, this universal approach was confusing as Type A hepatic encephalopathy occurs in cases of acute liver failure which is medically unique and rare compared to either Type B (surgical trigger without a history of liver disease) and Type C (cirrhosis related) hepatic encephalopathy.This content and the persistent, erroneous content about a low protein diet emphasizes the importance of experts in the development and curation of patient health information to reflect current guidelines and best practices. Medical experts in turn ideally need to work in concert with patient advisors and content creators, who are skilled in effective strategies for patient education and knowledge translation, to develop plain language in concert with meaningful multimedia content.

With a focus on telling or describing the medical perspective of hepatic encephalopathy, most of the 18 webpages failed to provide actionable material or tools relevant to self-management against a medically complex background of cirrhosis. Overall, this is likely attributed to the need for a cohesive yet simple hepatic encephalopathy message that clearly defines the roles of patients and care partners and self-management activities to prevent or manage this common complication across the cirrhosis trajectory. In this light, the CirrhosisCareAlberta Consortium is researching its patient-oriented, cirrhosis-specific website developed collaboratively with researchers, cirrhosis specialists, and patients to provide accessible, evidence-based, multimedia content (www.cirrhosiscare.ca).

There were several study strengths, such as the use of two Boolean operators (i.e., and, or) in the search strategies while quotations, parentheses, or other modifiers specific to search engines were avoided. The goal was to mimic search behaviours of the public rather than information specialists or experts skilled in search engine optimizations. This approach increased the precision and decreased the accuracy of the webpage results. By way of example using the Google search engine, the search string – cirrhosis and hepatic encephalopathy – retrieved 1,490,000 results whereas the search string – cirrhosis and “hepatic encephalopathy” – retrieved 636,000 results. The former search string was used in this study. Another study strength was the use of the meta tools, QUEST, WRRT, and HONcode to assess the reliability of the webpages. Webpage error and accessibility evaluations are irregularly reported in studies assessing online health information due to the demise of the Lida Instrument by Minervation for validating health care websites due to the ongoing changes in website design and programming[221]. In its place, this study employed WAVE as an easy to use, comprehensive mechanism to evaluate webpages consistent with current guidelines and standards[210]. One study limitation was that content analysis was completed for a subset of webpages on hepatic encephalopathy. Ideally, all 212 webpages would be reviewed in detail for accuracy, relevance to self-management, and scope, however this represented a resource intensive activity and was external to the aims of the study.

In conclusion, this study highlights the wide range of information available for patients and caregivers for cirrhosis, an uncommon, medically complex, chronic condition. With content written for high school seniors and graduates in combination with low to moderate scores of information reliability, there is much opportunity for improvement in the delivery of online cirrhosis information. Instead of a focus on delivering descriptive medical information (e.g., pathophysiology, diagnostic procedures, and mechanisms of effect for medications), future work might consider a change in perspective to emphasize “how to…” information to improve their self-management skills. Such content would be in direct contrast to traditional clinical approaches but may be more relevant, actionable, and ultimately beneficial to those living with cirrhosis. With low rates of medication compliance, high medical needs, and frequent hospitalizations, a rethink of patient education strategies in cirrhosis is a timely enterprise that can be facilitated via the Internet.

Table 3-1. Webpage characteristics (means) for presented by type of sponsoring organization.

Characteristic	Total (n=212)	Business (n=96)	Government (n=27)	Health Systems (n=49)	Not for Profits (n=40)
General:					
Multimedia (Y, %)	54 (25.5%)	29 (30.2%)	5 (18.5%)	8 (16.3%)	12 (30.0%)
Advertisements (Y, %)	90 (42.5%)*	66 (68.8%)^{a}	0 (0%)^{b}	14 (28.6%)^{a,b}	10 (25.0%)^{a,b}
Readability: (grade levels)					
• FKGL	10.6 SD 2.6	10.8 SD 2.7	10.2 SD 3.1	10.2 SD 2.0	11.2 SD 2.8
• FOG	13.1 SD 2.7	13.1 SD 2.7	12.6 SD 3.3	12.6 SD 2.2	13.9 SD 2.7
• SMOG	9.8 SD 1.9	9.9 SD 1.9	9.3 SD 2.2	9.5 SD 1.5	10.2 SD 1.8
• CLI	11.4 SD 2.0*	11.7 SD 2.3^{a}	10.5 SD 1.9^{b}	11.3 SD 1.5^{a,b}	11.5 SD 1.7^{a,b}
Reliability:					
• WRRT	18.3 SD 11.9	17.8 SD 12.1	17.9 SD 8.6	17.4 SD 12.2	21.2 SD 13.0
• QUEST	15.2 SD 5.6	15.0 SD 5.8	16.6 SD 5.0	13.9 SD 5.7	16.5 SD 4.9
HONcode (Y, %)	61 (28.8%)*	42 (43.8%)^{a}	2 (7.4%)^{b}	6 (12.2%)^{b}	11 (27.5%)^{a,b}
WAVE Errors	9.7 SD 11.1*	12.1 SD 10.8^{a}	3.2 SD 4.0^{b}	10.6 SD 14.9^{a,c}	7.0 SD 6.52^{c}

* p<.05 between group differences

^{a,b,c} Different superscripted letters are used to indicate significant pairwise differences (p<.05)

Abbreviations: FKGL, Flesch-Kincaid Grade Level[206]; FOG, Gunning Fog Index[207]; SMOG, Simple Measure of Gobbledygook[208]; CLI, Coleman-Liau Index[209]; WRRT, Web Resource Rating Tool (WRRT)[152]; QUEST, QUality Evaluation Scoring Tool[153]; HONcode, certification from The Health On the Net Foundation; and WAVE, web accessibility evaluation tool.

Table 3-2. Examples of misleading or vague statements from webpages about hepatic encephalopathy.

Topic	**Content**
Description	*"When the liver has been damaged by cirrhosis, it may not be able to filter poisons from the bloodstream…" (#121)*
Causes	*"HE can be triggered by eating too much protein." (#1)* *"Eating too much red meat." (#19)* *"Eat low protein foods…" (#31)*
Treatment	*"These medications can draw ammonia, created by intestinal bacteria from your blood, into your colon. Your body will then remove the blood from your colon." (#2)* *"If you have a chronic liver problem, you'll likely have HE several times and need to treat it in the future." (# 19)*

Supplement-Table 1. Readability algorithms

Name of Measure **Year**	**Algorithm**
Flesch-Kincaid Grade Level (FKGL)[206] 1975	(0.39 x (total words/total sentences)) + (total syllables/total words) – 15.59 = FKGL
Gunning Fog Index (FOG)[207] 1952	(Average no. of words in sentences + Percentage of words with 3 or more syllables) x 0.4 = FOG
Simple Measure of Gobbledygook (SMOG)[208] 1969	• Identify 10 consecutive sentences at the beginning, middle and near the end of the text (30 sentences) • Count every word with 3 or more syllables • Take the square root of the nearest perfect square of the count total • Add 3 to get the SMOG Grade
Coleman-Liau Index (CLI)[209] 1975	(0.0588 x the average number of letters for 100 words) – (0.296 x the average number of sentences per 100 words) – 15.8 = CLI

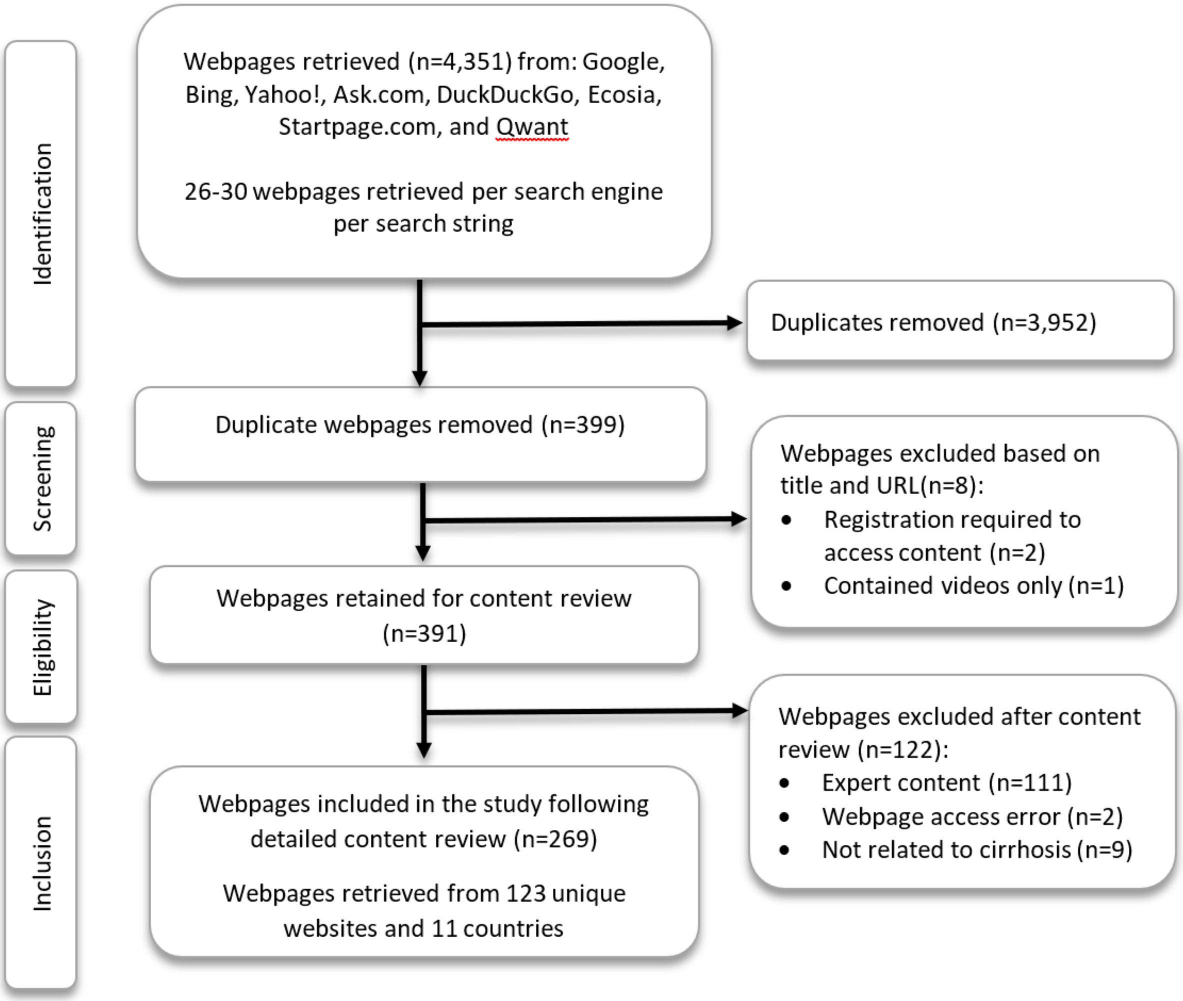
Supplement-Table .2. Scoring tool for assessing HE content scope. Each question had a value of 1 (no partial values used), with a possible total of 20 points.

1	HE descriptive definition mentioning those at-risk; may refer to ammonia, brain function, disrupted liver function, confusion
2	HE has a wide spectrum of symptom manifestations and severity ranging from subtle to coma (may refer to scoring systems or covert versus overt)
3	There are many possible precipitant(s) of HE in cirrhosis. Examples could include liver decompensation, dehydration, medical procedure (i.e., TIPS), bleeding, or medications. Should not include acute liver failure.
4	Symptoms of HE (e.g., fatigue, mood changes, irregular sleeping patterns, coma, asterixis, etc.)
5	Recommendation to contact a physician when HE symptoms are observed; may describe diagnostic role of the specialist relative to a family practitioner
6	Diagnosis – describes the importance of caregivers or family members for noticing HE symptoms before the patient or physician
7	Diagnosis of covert HE – use of cognitive tests such as the Stroop, animal naming test, Critical Flicker Frequency test, assessment may involve input from a caregiver regarding description of observed behaviour changes, frequency, and duration
8	Diagnosis of overt HE based on comprehensive clinical exam, assessment may involve input from a caregiver regarding description of observed behaviour changes, frequency, and duration
9	Diagnosis is not based on a single test or blood test for ammonia levels
10	Diagnosis of HE is made once *other causes* have been excluded
11	Treatment of HE – omit precipitating factors and monitor
12	Treatment of HE – effective pharmaceutical treatment is available, mainly reserved for overt HE
13	Treatment of HE – lactulose is the frontline pharmaceutical. May mention therapy side effects, mechanism of action, and treatment goal of 2-3 bm/d
14	Treatment of HE – rifaximin is also an effective pharmaceutical therapy. May include its use in combination with lactulose, side effects, or mechanism of action
15	Treatment of HE – mention of other pharmaceutical treatments (e.g., oral BCAAs, neomycin, metronidazole), possible side effects, and mechanisms of action
16	Prevention/Treatment of HE – protein amount (high protein 1.2-1.5 g/kg), may mention low sodium (2 g/d), may mention referral to a registered dietitian
17	Prevention/Treatment of HE – eat frequent meals and snacks throughout the date and have a late-night snack before bed, may mention referral to a registered dietitian

18	Recurrent HE – symptom monitoring, adherence to therapeutic regimens, when to seek additional assistance (e.g., psychological, homecare)
19	Value of prompt diagnosis leads to better health outcomes and quality of life
20	HE risk/prevalence/severity after liver transplantation

Figure 3-1. PRISMA flow diagram

Search strings (n=19): cirrhosis, hepatic encephalopathy, confusion cirrhosis, lactulose, infection cirrhosis, varices or banding cirrhosis, gastroscopy cirrhosis, bleeding cirrhosis, transjugular intrahepatic portosystemic shunt, TIPS cirrhosis, pruritus cirrhosis, itching cirrhosis, edema cirrhosis, ascites cirrhosis, paracentesis cirrhosis, hepatocellular carcinoma cirrhosis, cancer cirrhosis, self-management cirrhosis, and nutrition cirrhosis. Webpages were not retrieved if indicated as "ads", "videos", or "images".



CHAPTER 4.0 - Identifying Opportunities for Hepatic Encephalopathy Self-Management: A mixed methods systematic review and synthesis

4.1 Introduction

Cirrhosis is a medically complex, chronic disease representing the final common pathway for chronic liver disease etiologies. One of the cirrhosis-related complications that patients face is hepatic encephalopathy (HE), described as a wide spectrum of episodic, debilitating neuropsychiatric abnormalities with an incidence rate of 11.6 per 100 patient-years and a prevalence as high as 80% for all severities[42, 222]. Although HE manifests in different forms and severities, overt HE episodes can lead to long-term losses impacting self-identity, memory, and abilities[223, 224]. Notably, many of these HE experiences are similar to symptoms of post-traumatic stress disorder previously associated with critical or chronic illnesses[225], including cirrhosis[226].

The mainstay of current HE management includes minimizing precipitating factor(s) such as medications (e.g., benzodiazepines and opioids), alcohol use, or gastrointestinal bleeding[42, 44]. Lactulose is the front-line therapy followed by the addition of the non-absorbable antibiotic rifaximin if two or more episodes of overt HE occur[42]. Increasing evidence shows multi-way interactions between sarcopenia, frailty, and risk for HE[28, 227]. Research is continuing to determine if these factors as well as non-pharmaceutical therapies, such as nutrition and exercise, can improve clinical outcomes[228].

Conveniently, guidelines for nutrition and exercise in cirrhosis are the same before and after a diagnosis of HE. Briefly, key targets for nutrition include 1.2-1.5 g/kg of body weight per day of protein alongside an appropriate caloric intake and frequent meals and snacks (eating every 4 hours during waking periods, including a snack before bedtime)[31]. Similarly, although the details of the connection between exercise and HE requires further evaluation, regular physical activity can improve muscle mass and function[31, 54-58]. In turn, these may have the potential to reduce the risk for HE as muscle tissues are a secondary site for ammonia detoxification[57].

For patients, HE is the single largest decrement to their health-related quality of life with widespread ramifications ranging from employment and relationships to personal well-being[43, 229, 230]. Self-management includes activities related to medical management as well as emotional management and problem solving, decision-making, and interactions with the medical team[68, 76,

[231]. While care partners are of central importance in cirrhosis (the model for end-stage liver disease presents the patient and care partner as a team[76]), their care burdens can increase in response to the patient's HE symptoms and care pathway[61, 92].

Given the burden of HE, preventive management and rapid time to initial and recurrent diagnoses are paramount. An area of evaluation that has received nominal attention is the real-world effectiveness of HE self-management skills of patients and care partners. Given the abundance of HE literature, including both observational quantitative studies of HE-related self-management (i.e., medication management and knowledge) and qualitative studies of the self-described experiences of patients, care partners, or dyads, we chose to review the findings across both bodies of literature. The complexity of self-management against a background of HE merits a broader, integrative perspective through a mixed methods synthesis to build upon existing knowledge by finding new meaning and opportunities. Such an undertaking is needed to re-envision the HE care pathway so that it is practicable and relevant to all stakeholders (patient/care partner dyads and healthcare professionals). Using a mixed methods synthesis, we aimed to identify elements that impacted HE self-management in cirrhosis to improve HE-related health and burden of care for patients and care partners by identifying congruencies, incongruencies, and gaps in the findings.

4.2 Methods

A three-stage synthesis employing convergent configurative analysis (Prospero registration: CRD42022170017) followed the approach of the EPPI-Centre[232].

***Search strategy**:* A systematic literature search identified original research studies using keywords and Medical Subject Headings for "hepatic encephalopathy" in combination with either "liver cirrhosis" or "end-stage liver disease" (Supplementary-Figure 4-1). Information sources searched were PubMed, Medline, CINAHL, EMBASE, PsychINFO, and Web of Science. English-written studies that recruited adults with cirrhosis or their care partners (>18 years), were peer reviewed, and published (January 1, 2012 and September 20, 2021) were eligible (Table 4-1). The PRISMA flow tracked article selection processes[233]. KPI designed the search strategy and all authors consented on article selection.

Methodological quality assessment: Selected articles were assessed with the Critical Appraisal Skills Programme (CASP)[234]. No study was excluded based on quality alone.

Data abstraction: To guide this process, we used clinical practice guidelines, consensus statements, and recommendations regarding HE in cirrhosis by the International Society for HE and Nitrogen Metabolism (ISHEN)[31, 235-237], World Congress of Gastroenterology-1998[235], American Association for the Study of Liver Diseases, and European Association for the Study of the Liver[42]. Authors were sensitized to self-management concepts in chronic disease and were familiar with HE clinical management recommendations[70, 238, 239]. Data abstraction by KPI was reviewed by JAS and PT; disagreements were discussed until consensus was reached.

Data synthesis and configuration: In this theoretically exploratory study, a configuration approach for data syntheses was employed[240]. Synthesis 1 involved a narrative review of quantitative studies to answer: "How effective were the real-world HE self-management activities of dyads and influence of physicians in relation to the practice guidelines and recommendations?"[31, 241]. Findings were organized into categories. Synthesis 2 was a review of qualitative studies detailing the HE self-management experiences of dyads. Using inductive thematic analysis, data were assigned preliminary codes in a line-by-line manner followed by development of themes[232, 242]. Themes were supported with quotes from the literature; preference for Schutz's first-order construct data helped to minimize potential bias introduced by the secondary interpretations of other researchers[243]. Synthesis 3 compared the findings of Synthesis 1 and 2 using a standard methodological and conceptual matrix[240, 244]. This data integration, reporting matches, gaps, and mismatches between the datasets, was used to identify "real world" HE self-management opportunities (third-order interpretation); a second thematic analysis facilitated the generation of cross-cutting analytical themes[232, 240, 245]. All data analysis discussions ended in consensus; an expert external to the authors was available to achieve resolution but not used. Data management and analyses was supported with EndNote™20 (Clarivate, PA) and NVivo, v12 (QSR International Inc, MA).

4.3 Results

Studies included: Of 6,461 articles retrieved, 3,138 were unique and 25 fulfilled eligibility criteria (Supplementary-Figure 4-1). Six articles were included from readings: 16 quantitative and 7 qualitative studies. Most originated in high-income countries where participants were recruited primarily from clinics and hospitals associated with academic institutes.

Methodological quality: Overall, this study characteristic was generally good (Supplementary-Tables 4-1a, b, the methodological quality). This synthesis focused on data from either observational or baseline measures consistent with the real-world approach rendering interventional methodology questions non-applicable. Of note, the qualitative studies infrequently described the relationship between the Interviewer/Researcher and Participants or the presence of a care partner or patient. These pre-existing relationships could have influenced the interview outcomes.

Characteristics of studies: A total of 16 quantitative studies[246-261] were retrieved (cohort, n=12; case-control, n=3; randomized controlled trial, n=1) with the most common topic being knowledge assessment of patients[247-249, 254, 258, 261], care partners[254], or physicians[251, 255]. Several from North America and Europe evaluated HE medication adherence[246, 250, 253, 257, 260]. Four of the 7 retrieved qualitative studies[1, 61, 223, 224, 262-264] included care partners[61, 223, 224, 264] with 3 were authored by affiliates of nursing departments[1, 262, 263]. Unique to the qualitative studies, patient characteristics rarely mentioned disease severity (e.g., MELD or Child-Pugh), HE treatment, or HE severity. Several qualitative articles were excluded as patients' HE histories were not provided.

Findings from the Literature Reviews

Quantitative evidence-synthesis 1: A meta-analysis was not possible due to the heterogeneous topics and recruitment strategies. Instead, a narrative review was performed which produced 4 categories: (a) dyads had low levels of HE self-management awareness; (b) HE treatment adherence was variable; (c) non-pharmaceutical HE treatment was delivered heterogeneously;

(d) HE information sources were mainly specialists (i.e., hospitalists and gastroenterologists) (Table 4-2).

(a) Low levels of HE awareness

This was assessed as part of a survey study (n=3) or at baseline in interventional studies (n=4)[247-249, 252, 254, 258, 261]; 4 HE-oriented studies included some patients without a history of HE[247, 249, 258, 265]. In one study of 20 patients, only 35% adequately described cirrhosis in their own words[247]. Another reported that 24% of 551 patients said cirrhosis did not cause health problems even though each respondent had hepatic decompensation increasing their risk for HE[258]. In 52 patients without HE, only 17% were aware of the risk for HE and 8% “were aware that laxatives were prescribed to help remove such toxins through the bowel”[249, p. 216]. In two studies of patients with HE, 23% (9/39)[248] and 63% (22/35)[254] could not recall a diagnosis of HE. Care partner HE knowledge was also low; 48% of 31 individuals were aware the patient had HE diagnoses and only 6% were aware of HE treatments and effects[254]. While guidelines prioritize care partners to identify HE symptoms, 19% of 387 overt HE episodes “were identified solely based on care partner inputs”[252, p. 1731]. Results from self-reported survey studies of doctors, 70% of 201 Italian specialists “had not yet had an opportunity to read the EASL-AASLD joint guidelines on HE” by 2017[255, p. 828]. In 2020, 30% of German specialists “did not know the term CHE [covert HE], which was introduced by the EASL/AASLD guidelines in 2014”[251, p. 53].

(b) Low rates of HE treatment adherence

In a mixed HE cohort, only 54% of 28 patients (CP score 6-8) with 1 prior hospitalization were adherent to cirrhosis-related medications in the last 30 days due to forgetfulness (42%)[257]. A further “34% (n = 10) reported that they would adjust their medication if symptoms improved without consulting their doctor, 45% patients (n = 13) reported that ‘herbal medications’ [not specified] would help their liver and 76% (n = 22) reported that the liver cleansing diet would improve liver health."[257, p. 208] The reasons why patients were motivated to do these activities independently of their physician were not addressed in the study. In a second mixed HE cohort (n=100), 42% were fully adherent to their medications using the Morisky Medication Adherence Scale[266, 267]. In 1,708 patients who were on HE therapies when admitted to hospital, nearly one third were non-adherent (lactulose, 29%; lactulose + rifaximin, 21%; rifaximin, 18%)[246]. Again, the rationale for non-adherence was not explored. A retrospective review of HE-related hospital admissions estimated that 33% were due to medication non-adherence[253]. Using a minimum of 80% of proportion of days covered (PDC) in insurance claims as a measure of adherence to HE medications, the adherence rates at 3- and 6-months for 184 patients, with HE, were 16.4% and 10.1%, respectively[260].

Adherence to cirrhosis-specific nutrition guidelines was consistently low. In 78 patients (HE, 23%) where 80% were at risk of malnutrition, only 12% and 9% met their daily protein and calorie intakes, respectively[256]. In a study of 251 patients (mean MELD-Na: 17.2), 16% ate a late evening snack and 21% ate more than 3 meals or snacks per day[259]. Protein and calorie levels were 62-73% and 57-68% of the recommended levels, respectively. Furthermore, patients in this study reported food consumption issues pertaining to cirrhosis symptoms (e.g., early satiety (30%), poor appetite (27%), and recurrent vomiting (6%)), social myths (17%), and unpalatability of a low sodium diet (21%)[259].

(c) *Heterogeneous approach to non-pharmaceutical HE therapies by physicians*

Data from self-reported physician surveys regarding cirrhosis care was presented in 2 articles. In a 2020 German study of 54 general practitioners and 172 gastroenterologists, 28.3% and 63.7% circled correctly the recommended daily protein intake in cirrhosis and HE[251]. Conversely, no nutritional advice was given by 30.2% and 21.6%, respectively. In a 2017 Italian study, 44% of physician respondents believed there was solid literature to support the replacement of animal protein with vegetable and dairy proteins[255]. The authors wrote that inadequate dietary advice was prevalent in their experiences and drew attention to similarities initially seen in a 1999 UK survey[255]. In the single exercise study, 28% of 78 patients engaged in regular daily physical activity[256].

Qualitative evidence-synthesis 2: Interview-based studies exploring the HE self-management perspectives and experiences of patients and care partners were reviewed and resulted in 3 themes (Table 4-3).

(a) *Dyads were uninformed about HE*

Prior to a formal diagnosis of HE, most dyads were unaware of HE and its risks. “At first, it [the diagnosis] was a shock.”[224, p. 2564] When asked to describe how they felt after the first episode of overt HE, dyads used terms such as “surprise”, “lack of awareness”, “trauma”, and “fear”[61]. This unfamiliarity manifested in how the dyads referred to the complication as an object (i.e. “it” or “that”): “This (HE) has happened to me not 1, 2, or 5 times, …many times more.”[61, p. 4]

> “However, when she vomits, [. . .] we have the feeling, now it [OHE] is coming back. We actually wait for it to come. However, we are always with her, close to each other.”[224, p. 2564]
>
> “I do not go to parties anymore... So it (HE) leads to a kind of isolation.”[223, p. 473]

The corollary of being unaware of HE presumably lengthened the time to diagnosis and treatment:

> “I didn’t know it was possible that it affects the brain in that way, that his ability to think would be so limited [. . .] I thought he was lazy or drunk. If I had known, I would have pointed it out earlier.”[224, p. 2563]
>
> “I would have liked to have known more about the encephalopathy…had I known something like that could have been coming down the road, maybe I would’ve responded quicker.”[264, p. 4]

Even though care partners and family recognized unusual symptoms, getting a diagnosis from a general practitioner was often delayed; emergency services became involved when symptoms led to aggression, became severe, or overwhelmed the care partners[224].

(b) *How dyads learned about HE and self-management*

After recovering from overt HE, frequently patients and care partners needed more information about HE and how to manage the “it”[61, 224, 264]. Specialists were the primary source of information, but this often led to delays in mastering self-management skills:

> “And one of the medications that she’s on is the lactulose three times a day. It really wasn’t explained to us fully at first at that point in time like I feel it should have been…Our gastro doctor explained to us the functions and what it did, finally after a year and a half…”[264, p. 5]

While it is highly probable that the lactulose was fully explained to the dyad in the beginning, the information was not available when the dyad was ready to understand it. In other cases, care partners took the initiative to educate themselves about HE: "…I found the information online. Before I knew nothing, nobody explained it to me."[61, p. 3] Many had a "trial and error" or experiential approach to learning how best to manage HE on an individual basis: "I didn't know, so I just did."[224, p. 2564] Some developed creative solutions that were not part of the usual medical advice, such as how to track bowel movements across multiple washrooms, monitor symptoms using tests, or implement HE-related practices that were observed during hospital stays, such as adjusting diuretics[224].

(c) *HE treatment adherence and perspectives*

Treatment adherence was influenced by unwanted lactulose side effects[1, 61], while others titrated for 1 bowel movement per day[224]. Some struggled to understand their situation because of ongoing cognitive dysfunction: "And she wanted to get it, but she was unable to comprehend it because of the encephalopathy."[264, p. 5] Some dyads understood the therapeutic rationale for the laxatives: "I understand that being constipated is life-threatening to me."[1, p. 43] In turn, some care partners rationed protein in an errant effort to minimize ammonia production, while others found that a healthy diet and hydration was beneficial[224]. However, it was unclear if the dietary behaviors were based upon medical advice, poor recall, or independent thinking. "You control the protein… if I feel a little confused… I run to a colon cleanse/rectal laxative."[61, p 3] Observation, experience, and information improved HE self-management mastery: "…relatives indicated that having the knowledge and ability to detect HE resulted in less anxiety and greater control."[263, p. S28]

Quantitative and qualitative data synthesis-synthesis 3

In the third stage of the EPPI-Centre synthesis, the quantitative and qualitative themes were juxtaposed to identify congruencies, gaps, and incongruencies regarding HE self-management (Table 4-4). Briefly, there were 3 congruencies between the findings from the quantitative and qualitative studies. (1) There was consistent reporting about the low levels of HE awareness of patients and care partners before the first diagnosis. (2) Following a diagnosis of HE, the dyads had low levels of HE self-management and desired more information to support self-management. (3) Physician support of non-pharmaceutical care before and after a diagnosis of HE was inconsistent.

Next, there were 2 gaps in the findings where no information was available from either the quantitative or qualitative studies. One gap was the absence of observational or experiential data about nutrition or exercise as part of HE self-management. While exercise was mentioned, it was related to ascites rather than HE or general cirrhosis self-management[1]. These lifestyle changes appeared to be self-motivated rather than based on a clinician's recommendation:

> "… all the caregivers knew that laxatives and antibiotics are important treatments [for HE], but they also had their own interventions, such as diet and exercise."[224, p. 2566]

In one study, care partners rationalized the breakdown of dietary protein was a trigger for HE. Thus, they identified "certain foods as being high in ammonia. The care partners attempted to influence the course of OHE by avoiding these foods."[224, p. 2564] The second gap pertained to the absence of formal patient-oriented clinical guidance, like HE messaging and HE self-management goals, and resources, such as decision aids and worksheets, to educate and support HE self-management.

Across the studies, there was one incongruency in the findings regarding patient adherence to HE pharmaceutical treatments. While observational quantitative studies[246, 250, 253, 257, 260] indicated that treatment adherence was low and this deficiency contributed to re-admissions for HE, most qualitative studies presented quotes from patients and care partners where they believed they were doing the best they could under the circumstances[1, 223, 224, 264], with some engineering creative solutions for things such as HE symptom surveillance or how to record bowel movements across the day in different locations[1, 224].

Next, an analytic matrix was used to develop cross analytical themes, and this produced two recommendations: #1 *Engage the dyad early in the cirrhosis disease trajectory to incrementally enhance and reinforce (i) understanding and mastery of non-pharmaceutical preventive HE therapy (nutrition and exercise), (ii) recognition of HE symptoms, and (iii) knowing when to contact relevant medical support (e.g. general physician or cirrhosis specialist)*. Consistent messaging at each medical encounter will increase dyad awareness of HE, allowing them time to become familiar with the risk and preventive management activities before HE occurs, such as nutrition and exercise[28]. Early and frequent communication of this nature is a mainstay of care in other chronic diseases, such as diabetes[268, 269], thereby highlighting a gap in the patient-oriented approach of cirrhosis care. Communication consistency should persist following a diagnosis of HE to support ongoing surveillance and (non-)/ pharmaceutical prophylactic treatments. As patients have many touchpoints across the health system, such a distributive knowledge network can involve physicians, nursing, registered dietitians, and certified exercise specialists in any setting (e.g., inpatient, outpatient, emergency) to reinforce and collaboratively build upon the dyads' HE knowledge base to support self-management mastery. Conversations can be assisted by high quality, current, verified resources available online for both dyads and physicians (www.cirrhosiscare.ca, www.aasld.org) and EASL or AASLD annotated versions of the clinical practice recommendations or guidelines specific for dyads and non-specialist physicians. To make the conversations accessible and collaborative, consideration can be given to using descriptive terms such as "liver brain" or "brain fog" that may be easier to recall in stressful moments for the dyads. This empowerment promises to offer substantial benefits, including earlier time to treatment. A cirrhosis-specific diet and regular exercise has the potential to reduce the frequency or minimize the impact of covert HE so assistance of specialized health professionals to assist in lifestyle modification is important.

#2 In all healthcare visits, the patient-care partner dyads with a history of HE would benefit from sharing their accounts of HE symptoms, treatment adherence, and potential side effects with HCPs. This would reconfirm that the dyads were aware of their involvement in HE symptom surveillance, treatment adherence, and how their individual responses could be adjusted as needed. Physician-led frank conversations about the dyad's experiences can add important context to better understand unique HE self-management successes and barriers. Other times, prompting the dyad to describe their journey of suffering with a condition that impacts cognition can strengthen perceptions of trust and foster knowledge uptake and adoption. In turn, ongoing conversations can help the clinician continuously customize HE therapy to meet the dyad's changing needs and provide relevant solutions, such as managing lactulose side effects or reducing the risk of HE by prescribing rifaximin when indicated.

> "*… I think there should be other medications that could prevent these encephalopathies.*"[61, p. 3]
>
> *"I would have preferred ascites, since it can be punctured…. I know… other complications like varices can be treated. One banding and the problem is solved. But…, the encephalopathy is very difficult to handle."*[61, p. 3]

Regular HE conversations may highlight when the dyads should involve relevant community services, such as home care, housekeeping, meal delivery services, or respite care, to support self-management for the benefit of the patient and their care partner.

4.4 Discussion

Using the EPPI-Centre mixed methods synthesis we identified opportunities to enhance HE self-management based on real-world evidence. This multiphase study culminated in a conceptual and methodological matrix that compared quantitative findings with patient and care partner experiences with HE. The underlying theme was that patients, care partners, and physicians did not have the right information at the right time throughout the cirrhosis and HE continuum. This led to uncertainty and increased care partner burden, delays in obtaining a diagnosis, and suboptimal HE self-management.

While interventional studies have proposed specifics, here we suggest the adoption and implementation of a distributed knowledge network to disseminate basic HE information involving all practitioners associated with a cirrhosis dyad throughout the cirrhosis trajectory. This approach equips all network members (e.g., nurse practitioners, family medicine practitioners, dietitians, specialists) with patient-oriented information so they can deliver consistent messaging about both pharmacological and non-pharmacological (e.g. nutrition and exercise) self-management for HE in a format that is accessible to the dyads.

Critically, these practitioner-led conversations serve as a proverbial "gateway" for dyads to inform and discuss cirrhosis, the liver and its role in digestion, complications including HE, and outcomes. Learning new information is a lengthy process that occurs in discrete stages described by Bloom's taxonomy – remembering, understanding, application, analyzing, evaluating, then creating[270]. As cirrhosis care is extended over years, the frequency of physician interaction largely determines the speed of knowledge uptake, recall, and implementation. With many patients diagnosed with overt HE before their first clinic appointment with a gastroenterologist, other healthcare professionals are well-positioned to provide self-management support including general cirrhosis and HE information in a timely manner[271].

Knowledge takes on many forms and depends upon one's perspective and relationship with it[272]. Traditionally, patient education is treated as a one-time event with the assumption that the information provided is "explicit knowledge" – something that is readily understood by the patients and care partners. By replacing medical terms with lay English phrasing that evokes visual imagery (e.g., "brain fog" versus "hepatic encephalopathy" or HE), the burdens of memorization, understanding, and recall are minimized to increase accessibility. To support HE self-management, the practitioner's messaging should emphasize the imperative "how to" knowledge. While the content is similar between the descriptive and imperative knowledge types, the focus becomes more dyad-centered and procedural: "how to"… titrate lactulose or "when to"… call the specialist. Consistently providing accessible, general HE information is perceived as high value to the dyads because it increases the potential for recall when the information is needed while providing insight into the seriousness of the cirrhosis condition – something that can be underestimated. Repeated delivery and discussions at each physician encounter are needed against a background of fluctuating wellness, competing cognitive priorities such as appointment scheduling, reviewing bloodwork or imaging results, and new prescriptions or refills.

Repetitive HE messaging to patients, as part of a distributed knowledge network[273] in cirrhosis, holds promise to give the dyads opportunity to acquire tacit knowledge as they proactively increase their preventive HE self-management skills and awareness. This is in sharp contrast to the experiential HE learning approach that occurs in reaction to a diagnosis. Given the prevalence of HE and the negative impact on quality of life, educating and priming the dyads *a priori* across providers (e.g., across their distributed knowledge network) may broaden their autonomy, self-management skills, and reduce their care burdens.

Future researchers may look to the utility and usability of creating a repository of HE information intended for distribution by all practitioners. Such tools will need consensus from patients and care partners and employ accessible person-centered messaging for dyads. The dissemination mechanisms and the logistics will need to be assessed from both feasibility and implementation perspectives and assessed against the ideal of a distributed knowledge network. This work also supports future cirrhosis studies employing patient-centered self-management programs, such as the Chronic Disease Self-Management Program[274, 275].

Study limitations Outcomes from this synthesis were obtained with the assumption that "qualitative and quantitative research can address the same research questions and, thereby, yield findings about the same aspects of phenomena."[276]. More qualitative studies would have met inclusion criteria if data on HE histories or current medications were provided. In many excluded studies, HE-related symptoms were described by the interviewee or the authors' interpretations (e.g., falls, excessive sleepiness, confusion) but without diagnostic references. However, given the similarities between the qualitative and quantitative evidence, we believe the findings to be transferrable to the general cirrhosis patient population. The absence of qualitative articles from non-western countries or non-English language articles is acknowledged. There were few observational or interview-based studies regarding nutrition or exercise in those living with HE and cirrhosis and our findings may need updating as the evidence base grows. With 25 types of knowledge syntheses[277] available, the selected approach used has been well described facilitating its application to our study[232].

In conclusion, given the prevalence of HE and its negative impact on all domains of quality of life and health outcomes in cirrhosis, this is a priority research and clinical practice area. Cirrhosis and HE are at a watershed in dyadic-centered care combining learning theory with distributed knowledge networks to support improved self-management. Instead of a reactive approach to HE, by proactively teaching and installing surveillance practices for symptoms, cirrhosis is at a similar crossroads as was the practice of Alzheimer's medicine in 2011 which saw the prioritization of early detection and self-management mastery[278]. The culmination of this synthesis is to better align the practice of medical professionals with immediate and future dyadic self-management needs.

Table 4-1. Inclusion and exclusion criteria for retrieved articles

Quantitative Studies	Qualitative Studies
Inclusion Criteria • Clinical trials, observational cohort, case control, and randomized controlled trials that included baseline information prior to the intervention • Published in English • Observational studies pertaining to diagnosis and management of HE in patients with cirrhosis or their physicians • Patient or person self-management behaviors pertaining to HE in cirrhosis	Inclusion Criteria • In-depth perspectives and experiences of patients with cirrhosis and HE and their care partners pertaining to HE self-management, including diagnosis, treatments, perceived self-efficacy, communication, and HE symptom burden • Published in English • Any study employing interviews, focus groups, or journaling by study participants or observers that captured the experiences of patients with cirrhosis and HE as well as their care partners • Both stand-alone qualitative studies and qualitative evidence collected as part of a mixed methods study were eligible for inclusion
Exclusion Criteria • Pediatric-only studies • Outcomes that did not mention HE • Comments or editorial articles • Case reports, case series, systematic reviews, or conference abstracts	Exclusion Criteria • Studies where participants were not explicitly identified with a history of HE or experiences in either the Methods or Results sections • Studies where statements were not clearly linked with the patient's or care partner's HE experiences • Where the emic perspective of participants was not supported with exemplar quotations

Table 4-2. Details of the included quantitative studies

Author Year Country/Region Site(s)	Study Design	Participants Age (mean*) Male (%)	MELD (mean*) Child-Pugh (n)	Outcomes	Comments
Bajaj [246] 2019 North America 14 hospitals	Prospective cohort of patients hospitalized for non-elective reasons who were followed for 90 d post-discharge	Patients n=2810 57 yrs Male 61% HE Rx 60.8% at index hospitalization	MELD 20.3 CP score 10.0	- HE causes for admission or was diagnosed during hospitalization in 913 pts (32.5%), 272 pts were not on HE Rx - Main HE precipitant was any Rx (32%) - 487/1708 pts with HE hx were non-adherent to HE Rx at admission	99 pts (4.1%) on HE Rx at admission were discharged without HE Rx

Author Year Country/Region Site(s)	Study Design	Participants Age (mean*) Male (%)	MELD (mean*) Child-Pugh (n)	Outcomes	Comments
Beg [247] 2016 United Kingdom Tertiary hospital	Pre-/post - interventional study assessing effectiveness of a cirrhosis education module	Patients n=20 59 yrs Male 75.0%	CPA 10 CPB 6 CPC 4	At baseline: - 7/20 could write an adequate description of cirrhosis - 0/20 associated confusion/fatigue with cirrhosis - 3/20 knew to target 2-3 bowel movements per day - 5/20 identified medications to avoid	- Pts embarrassed to ask for clarification - Online cirrhosis information was confusing or conflicting - Educational intervention improved mean scores from 4 to 7.5 out of 10 (*p*<.001)
Garrido [248] 2017 Italy Academic hospital	Randomized controlled study assessing an HE education module on short-term knowledge and risk for HE-hospitalization rate over 1 yr	Patients n=39 61.8 yrs Male 79.5% HE hx 100% Control n=19	MELD 12.5 CP_{score} 7.1 CPA 14 CPB 23 CPC 2 6 pts ≥ WHC grade II	At baseline: - 30/39 recalled having an HE diagnosis - 5/39 could identify HE Rx - 3/39 effect of Hx Rx	Education intervention: HE pathophysiology indicated by arterial and venous blood flow to organs; limit meat, fish, egg intake; avoid hepatotoxic Rx

Author Year Country/Region Site(s)	Study Design	Participants Age (mean*) Male (%)	MELD (mean*) Child-Pugh (n)	Outcomes	Comments
Goldsworthy[249] 2017 United Kingdom Single hepatology outpatient clinic	Pre-/post-interventional study assessing an educational video about cirrhosis and self-management	Patients n=52 Median age 55.5 yrs Male 61.5%	n/a Attended clinic for median of 3 yrs	At baseline: - 9/52 knew about "HE risk and impaired toxin clearance" asked using a two-part question - 4/52 knew why laxatives were prescribed for HE (toxin removal)	Post-intervention, mean scores improved to 66.7% from 25.0% (IQR 16.7-41.7%) Excluded pts who did not know they had cirrhosis

Author **Year** **Country/Region** **Site(s)**	**Study Design**	**Participants** **Age (mean*)** **Male (%)**	**MELD (mean*)** **Child-Pugh (n)**	**Outcomes**	**Comments**
Hayward[266] 2017 Australia Single outpatient hepatology clinic	Cross-sectional survey-based study of self-reported adherence to medications	Patients n=100 58.4 yrs Male 65.0% HE hx 36%	Mean MELD 14.4 CPA 24 CPB 59 CPC 17	Medication adherence rates presented as MMAS score for cohort *vs* HE hx (n=36): - high (8): 42% *vs* 29% - medium (6 to <8): 6 37% *vs* 35% - low (<6): 21% *vs* 52% Odds ratio (OR) for low adherence predicted by: - BMQ necessity-concern domain ≤ 5 (OR 3.66, 95% CI: 1.18-11.4) - IPQ ≤8 (OR 8.2, 95% CI: 0.98-67.8)	Questionnaires: Morisky Medication Adherence Scale (MMAS)-8 questions, Illness Perceptions (IPQ), & Beliefs about Medications Questionnaires (BMQ) Excluded 5/120 (4.2%) because unaware they were taking medications for cirrhosis or had stopped taking them

Author Year Country/Region Site(s)	Study Design	Participants Age (mean*) Male (%)	MELD (mean*) Child-Pugh (n)	Outcomes	Comments
Labenz[251] 2020 Germany Members of professional gastroenterology societies	Cross-sectional survey-based study about HE management in their clinics	GIs n=172 GPs n=54 Age n/a Gender n/a	84.2% GIs provided care to ≥ 10 pts/yr 66.7% GPs provided care to <10 pts/yr	Nevers examines HE even if pt has obvious signs: - GIs 12.8% - GPs 29.6% Accurate explicit nutritional advice given: - GIs 63.7% - GPs 28.3%	CHE correctly defined: - GIs 39.0% - GPs 9.4% Potential triggers for HE events always explored: - GIs 69.0%
Landis[252] 2016 United States 30 clinic centres in US, Canada, UK, Taiwan	Prospective, observational cohort study of pts with OHE within 30 d of study enrollment, excluded liver transplant candidates, followed for a mean of 72 d	Patients n=265 59.9 yrs Male 61.0% OHE 100%	n/a	- 120 symptoms identified with OHE: confusion (78%), mental status change (57%), disorientation (48%), lethargy (46%), asterixis (45%) - OHE identified by patient's physician (34%), other physician (45%) or care partner (19%)	67% of OHE episodes occurred with patients on rifaximin - excluded pts taking long-acting benzodiazepines or barbituates - 28% HE dx had WH grade recorded

Author Year Country/Region Site(s)	Study Design	Participants Age (mean*) Male (%)	MELD (mean*) Child-Pugh (n)	Outcomes	Comments
Mandip[253] 2021 United States Tertiary care medical centre	Retrospective database review of HE admissions from Dec 2013-Dec 2017	Patients n=341 57.5 yrs Male 60.4% HE hx 100%	MELD-Na 20.5	HE precipitants: - Rx non-adherence 33.4% - Other 28.4% - Unknown 19.6% - UTI 9.1% - SBP 5.8% - GI bleed 4.7%	33.2% of admissions did not use HE order sets Adhered to 2014 AASLD HE guidelines
Montagnese[254] 2012 Italy Single centre	Cross-sectional survey-based study of HE	Patients n=35 Age 60 yrs HE hx 100% Male 34.3% Care partners, 31 Age n/a Male % n/a	CPA 9 CPB 18 CPC 8	Pts aware of: - HE hx 37% - HE Rx 6% - HE Rx effects 6% Pts aware of HE hx had higher SF-36 scores (49 vs 41, *p*=.04) Care partners aware of: - HE hx 48% - HE Rx 6% - HE Rx effects 6%	Caregiver Burden Index (CBI) tool used for care partners. Care partners aware of HE hx had higher CBI cores (29 vs 9, *p*=.008) With 100% of pts on HE Rx, 20 pts (57%) had WH gr I-2 OHE on study day
Montagnese[255] 2017 Italy 201 clinics	Cross-sectional 21-item survey of physicians about HE management	Specialists n=201 Age n/a Gender n/a	n/a	44% advised swapping out animal protein for vegetable and dairy protein	70% had not read EASL-AASLD guidelines published 2 years previously

Author Year Country/Region Site(s)	Study Design	Participants Age (mean*) Male (%)	MELD (mean*) Child-Pugh (n)	Outcomes	Comments
Palmese[256] 2019 Italy Academic outpatient clinic	3-d food diaries to assess dietary intake relative to cirrhosis nutrition guidelines	Patients n=78 Median age 61 yrs Male 67% 23% HE	MELD 12 CPA 28 CPB 37 CPC 8	Eating 4-6 meals & snacks per day: 53% Caloric intake was: - 12% adequate - 76% inadequate - 12% excessive Protein intake was: - 9% adequate - 83% inadequate - 8% excessive Daily physical activity reported by 28%	- 17% refused nutritional assessment

Author **Year** **Country/Region** **Site(s)**	**Study Design**	**Participants** **Age (mean*)** **Male (%)**	**MELD (mean*)** **Child-Pugh (n)**	**Outcomes**	**Comments**
Polis[257] 2015 Australia Tertiary hospital outpatient clinic	Cross-sectional 13-item survey of patients with CP 6-8 and 1 hospital admission	Patients n=28 Median age 57 yrs Male 83%	MELD 7.3 CP 11	- 34% would adjust or stop Rx on their own Improves liver health: - 45% herbal supplements - 76% liver cleansing diets Rx nonadherence in last 30 d was 54% Rx non-adherence due to: - 42% forget - 36% routine change - 32% sleeping - 25% ran out of Rx Self-motivation for Rx adherence in next 30 d: 2.58 out of 4.00 Belief in Rx effectiveness: 2.53 out of 4.00	Reported that patients were taking lactulose or rifaximin but did not indicate how many Had social support: 2.2 out of 3.0

Author Year Country/Region Site(s)	**Study Design**	**Participants Age (mean*) Male (%)**	**MELD (mean*) Child-Pugh (n)**	**Outcomes**	**Comments**
Rogal[258] 2020 United States Veteran Affairs claims database	Cross-sectional, survey-based study	Patients n=551 67 yrs Male 96%		My liver dx causes: - all health problems 8% - no health problems 24% 34% unsure of decompensation symptoms 14% unsure if had HE Decompensation uncertainty associated with lower HRQoL versus actual decompensation (*p*<.001) for both physical and mental summaries	Cirrhosis did not apply to them: 73/648 even though had ICD9/10 for cirrhosis codes and were screened by facility providers to ensure eligibility for study inclusion QoL measured using Veterans SF-36 giving summary scores for physical and mental components

Author Year Country/Region Site(s)	Study Design	Participants Age (mean*) Male (%)	MELD (mean*) Child-Pugh (n)	Outcomes	Comments
Sharma[259] 2021 India Single centre	Cross-sectional 21-item survey-based study	Patients n=251 51 yrs Male 79%	MELD-Na 17.2 CPA 83 CPB 116 CPC 52	No. of meals per d: - two: 13% - three: 67% - four: 19% - five: 2% - evening snack: 16% Diet influencing factors: - early satiety 30% - poor appetite 27% - abdominal fullness 25% - low sodium 21% - social diet myths 17% - vomiting 5% Percentage of guideline intakes for: - calories: 62-73% - protein: 57-68%	Excluded pts if had HE at nutrition assessment Strict vegetarians (no meat, egg, or any animal product except milk): 152 (61%)

Author Year Country/Region Site(s)	Study Design	Participants Age (mean*) Male (%)	MELD (mean*) Child-Pugh (n)	Outcomes	Comments
Vadhariya[260] 2020 United States State-wide administrative claims database	Retrospective cohort following pts for 1, 3 & 6 mos after ER visit or & hospitalization for HE from 2011 to 2018	Patients n=184 68.7 yrs Male 56.5% HE hx 100%	n/a	Within 30 d of discharge: - 36.4% did not refill HE Rx ≥80% adherence to Rx: - 16.4% at 3 mos f-up - 10.1% at 6 mos f-up	Rx adherence at 3 and 6 mos not associated with readmission during f-up
Volk[261] 2013 United States Hepatology outpatient clinic at a transplant referral centre	Pre-/post-interventional study using a 15-item survey assessing cirrhosis and HE knowledge	Patients n=150 Median age 57 yrs Male 59% HE 23%	Median MELD 8 (6-19) CPA 70% CPB 27% CPC 3%	At baseline: - 56% understood lactulose titration - 12% knew to eat a high protein diet - 44% avoided unsafe over-the counter pain medications	"Health maintenance" questions did not ask about awareness of HE symptoms Taking HE Rx did not improve scores for HE-related questions

* unless otherwise mentioned (e.g., median, range)

Abbreviations: CPA, Child-Pugh A; CPB, Child-Pugh B; CPC, Child-Pugh C; dx, diagnosis; f-up, follow-up; HE, hepatic encephalopathy; hx, history; MELD, model for end-stage liver disease; n/a, not applicable; PHES, psychometric hepatic encephalopathy score; Rx, prescription; SF26, Short Form Health Profile (SF36) questionnaire for quality of life; UTI, urinary tract infection; WH, West Haven

Table 4-3. Details of the included qualitative studies

Author **Year** **Country** **MMAT**	**Study Focus** **(Qualitative Approach)**	**Participants (n)** **Age (mean*)** **Health Status**	**Clinical Features Reported**	**Recruitment Site(s)**
Aghahosseini[262] 2017 Iran	Life experience while waiting for liver transplant (content analysis)	Patients n=10 - 41.4 yrs - Listed for LT	Etiology, gender, LT waitlist duration	Liver transplant clinic at academic hospital
Fabrellas [61] 2020 Spain	Assessing the psychological burden of HE on patients and care partners (hermeneutic phenomenology)	Patients n=15 - 61 yrs - 2 HE events requiring hospitalization or ED Care partners n=15 - 55 yrs	Etiology, gender, MELD, HE, PHES, medications, LT waitlist status	Liver unit in an academic hospital
Fagerstrom[1] 2017 Sweden	Life situation and self-care in patients with cirrhosis & its complications (content analysis)	Patients n=13 - Range 46-75 yrs - Decompensated	Etiology, gender	Gastroenterology clinic at an academic hospital
Gronkjaer[263] 2016 Denmark	Patient experience of OHE (systematic text condensation as per Malterud)	Patients n=8 - 61 yrs - History of ≥2 HE WHC grades II-IV; 4 taking lactulose of which 2 also took rifaximin	Etiology, gender, Child-Pugh score, MELD	Department of Hepatology and Gastroenterology at Aarhus University Hospital

Author Year Country MMAT	Study Focus (Qualitative Approach)	Participants (n) Age (mean*) Health Status	Clinical Features Reported	Recruitment Site(s)
Gronkjaer[223] 2018 Denmark	Patient experience with HE & the perceptions of their relatives (systematic text condensation)	Patients n=8 • 61 yrs • History of ≥2 HE WHC grades II-IV; 4 taking lactulose of which 2 also took rifaximin Care partners n=8 • 46 yrs	Etiology, gender, Child-Pugh score	Department of Hepatology and Gastroenterology at Aarhus University Hospital
Kunzler-Heule[224] 2016 Switzerland	Experiences of providing informal care to a relative with OHE as a complication of cirrhosis (interpretive phenomenology)	Care partners n=12 • 51.5 yrs • Cared for pts with ≥1 episodes of OHE (WHC grades II-IV)	n/a	Tertiary hospital outpatient clinic
Ufere[264] 2020 United States	Patients' and care partners' perceptions of transitional care burdens in end-stage liver disease (template analysis)	Patients n=15 • Decompensated livers receiving outpt care Care partners n=14 • 60.5 yrs (median)	Etiology, gender, MELD-Na, Ascites, HE, variceal bleed, listed for LT	Outpatient hepatology clinic at a tertiary care hospital

Ages are expressed as means unless indicated otherwise.

Abbreviations: ED, emergency department; HE, hepatic encephalopathy; LT, liver transplant; n/a, not available; PHES, Psychometric Hepatic Encephalopathy Score; OHE, overt hepatic encephalopathy; WHC, West Haven Criteria for HE

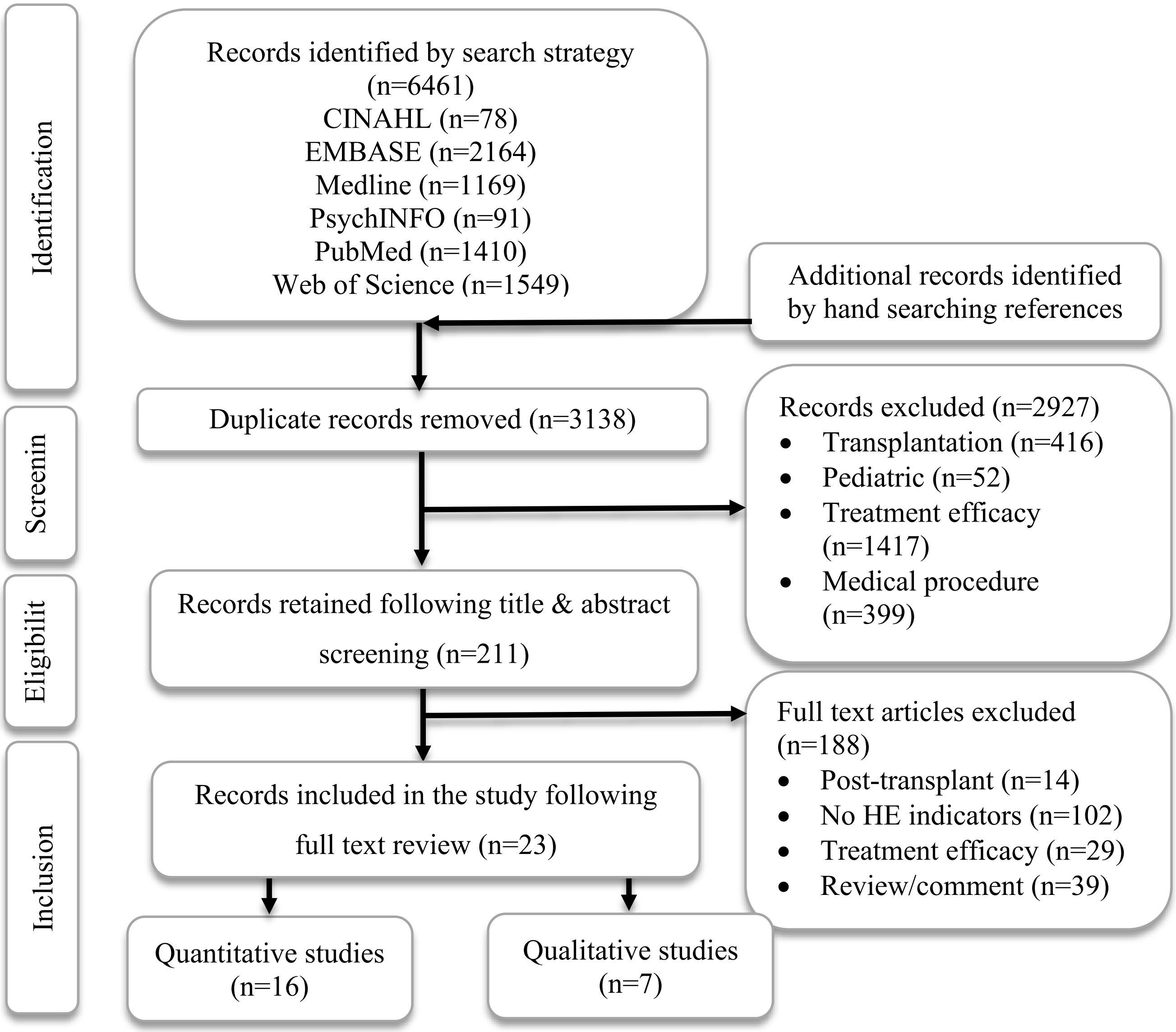
None = no MELD, Child-Pugh grade or score

Table 4-4. Methodological and synthesis matrix (congruency, black; incongruency, yellow; gap, red)

Quantitative Synthesis		Qualitative Synthesis	Cross Analytical Themes
Heterogeneous approach to non-pharmaceutical HE recommendations among physicians	↔	20 GAP	•Engage dyads early and regularly in lay English to implement non-pharmacologic preventive therapies for HE •Monitor HE symptoms and treatment burden to improve adherence
Dyads had low levels of HE knowledge about risk, diagnosis, and management	↔	Dyads were unaware about HE risk, prevention, diagnosis, or management	
GAP	↔	HE self-management skills took time to acquire and implement – “the unfamiliar”	
Low adherence to pharma and non-pharma treatments for HE	↔✗	High adherence to treatments due to fear of recurrence – “doing the best they can”	

Supplementary Figure 4-1. PRISMA flow diagram

("Hepatic Encephalopathy"[Mesh] OR "hepatic encephalopathy") AND ("Liver Cirrhosis"[Mesh] OR "End Stage Liver Disease"[Mesh] OR "end stage liver disease" OR (liver and cirrhosis)) limited to humans, English language, and published between January 1, 2012, through to September 20, 2021.



Supplementary Table 4-1a: Study evaluation using CASP tools for cohort, case control and randomized controlled studies (27)

Cohort studies	1. Did the study address a clearly focused issue?	2. Was the cohort recruited in an acceptable way?	3. Was the exposure accurately measured to minimise bias?	4. Was the outcome accurately measured to minimise bias?	5. (a) Have the authors identified all important confounding factors?	5. (b) Have they taken account of the confounding factors in the design and/or analysis?	6. (a) Was the follow up of subjects complete enough?	6. (b) Was the follow up of subjects long enough?	7. What are the results of this study?	8. How precise are the results?	9. Do you believe the results?	10. Can the results be applied to the local population?	11. Do the results of this study fit with other available evidence?	12. What are the implications of this study for practice?
Bajaj (74)	Y	Y	Y	Y	Y	Y	Y	N/A	Table 1	Y	Y	Y	Y	Patient education
Mandip (47)	Y	Y	Y	Y	Y	Y	Y	N/A	Table 1	Y	Y	Y	Y	Prescription education
Vadhariya (54)	Y	Y	Y	Y	Y	Y	Y	Y	Table 1	Y	Y	Y	Y	Long-term monitoring
Hayward (61)	Y	Y	Y	Y	Y	Y	Y	N/A	Table 1	Y	Y	Y	Y	Patient education
Landis (46)	Y	Y	Y	Y	Y	Y	Y	Y	Table 1	Y	Y	Y	Y	Patient education
Montagnese (48)	Y	Y	Y	Y	CT	CT	Y	N/A	Table 1	Y	Y	Y	Y	Patient education
Rogal (52)	Y	Y	Y	Y	Y	Y	Y	N/A	Table 1	Y	Y	Y	Y	Patient education
Labenz (45)	Y	Y	Y	Y	Y	Y	Y	N/A	Table 1	Y	Y	Y	Y	Physician education
Montagnese (49)	Y	Y	Y	Y	Y	Y	Y	N/A	Table 1	Y	Y	Y	Y	Physician education
Palmese (50)	Y	Y	Y	Y	Y	Y	Y	N/A	Table 1	Y	Y	Y	Y	Long-term monitoring
Polis (51)	Y	Y	Y	Y	CT	CT	Y	N/A	Table 1	Y	Y	Y	Y	Patient self-management
Sharma (75)	Y	Y	Y	Y	Y	Y	Y	N/A	Table 1	Y	Y	Y	Y	Patient self-management

Case control studies	1. Did the study address a clearly focused issue?	2. Did the authors use an appropriate method to answer their question?	3. Were the cases recruited in an acceptable way?	4. Were the controls selected in an acceptable way?	5. Was the exposure accurately measured to minimise bias?	6. (a) Aside from the experimental intervention, were the groups treated equally?	6. (b) Have the authors taken account of the potential confounding factors in the design and/ or in their analysis?	7. How large was the treatment effect?	8. How precise was the estimate of the treatment effect?	9. Do you believe the results?	10. Can the results be applied to the local population?	11. Do the results of this study fit with other available evidence?
Beg (41)	Y	Y	Y	Y	N/A	N/A	N/A	N/A	N/A	Y	Y	Y
Goldsworthy (43)	Y	Y	Y	Y	N/A	N/A	N/A	N/A	N/A	Y	Y	Y
Volk (55)	Y	Y	Y	Y	N/A	N/A	N/A	N/A	N/A	Y	Y	Y

Randomized controlled trial	1. Did the study address a clearly focused issue?	2. Was the assignment of participants to interventions randomised?	3. Were all participants who entered the study accounted for at its conclusion?	4. Blinding of: participants: investigators: assessors?	5. Were the study groups similar at the start of the randomised controlled trial?	6. Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?	7. Were the effects of intervention reported comprehensively?	8. Was the precision of the estimate of the intervention or treatment effect reported?	9. Do the benefits of the experimental intervention outweigh the harms and costs?	10. Can the results be applied to your local population/ in your context?	11. Would the experimental intervention provide greater value than any of the existing interventions?
Garrido (42)	Y	Y	Y	N/A	N/A	N/A	N/A	N/A	N/A	Y	N/A

CT = Cannot tell; Y = Yes

Supplementary Table 4-1b: Study evaluation using CASP tools for qualitative studies (27)

Studies listed by first author	1. Clear research aims?	2. Appropriate use of qualitative approach?	3. Research design appropriate?	4. Theoretical underpinnings present and coherent?	5. Relevant recruitment strategy?	6. Relevant data collection?	7. Researcher-participant relationship considered?	8. Ethical issues considered?	9. Data analysis was rigorous?	10. Clear statement of findings?
Aghahosseini (56)	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y
Fabrellas (24)	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y
Fagerstrom (57)	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y
Gronkjaer (58)	Y	Y	Y	Y	Y	Y	CT	Y	Y	Y
Gronkjaer (3)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Kunzler-Heule (4)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ufere (59)	Y	Y	Y	CT	Y	Y	Y	Y	Y	Y

CT = Cannot tell; Y = Yes

CHAPTER 5.0 - Initial patient perspectives about participating in an online, cirrhosis-specific nutrition and exercise intervention

5.1 Introduction

Sarcopenia and physical frailty are experienced frequently by people living with cirrhosis, occurring in 22% to 62%[27, 279] and 25%[29] to 38%[280] respectively. These conditions have been associated with worse clinical outcomes including longer hospital and intensive care unit stays, higher incidence of infection, reduced quality of life, and increased mortality[279, 280]. The causes of sarcopenia and frailty are multifactorial including factors such as inadequate nutrition, sedentary lifestyle, ageing[281, 282], and cirrhosis-related altered metabolic function and endocrine dysfunction[28]. Guidelines support the central role of nutrition and physical activity-based interventions as the main tenets of therapy for these conditions[28, 283, 284], with an online delivery modality as a potential strategy to promote participant convenience and broader dissemination. However, much still needs to be understood about patient perceptions and factors affecting adherence to virtually delivered nutrition and exercise programs in cirrhosis. This patient view is relevant to optimizing program delivery, adherence, and impact on clinical endpoints.

Adherence is a key factor associated with clinical benefit[148, 285, 286]. Although less is known about the adherence to nutrition interventions in cirrhosis, of the existing 11 exercise randomized controlled trials published to date[148, 286-295], 8 reported adherence rates[148, 286-288, 291-294]. Exercise interventions (controlled and uncontrolled designs) that were delivered in-person (supervised) have had consistently high rates of adherence (range: 82-97%[287, 291-293, 296]). The supervised aspect has also however been associated with the downside of reported barriers to study enrollment and adherence, such as transportation issues, scheduling conflicts, and willingness to take part[100]. In studies where patients exercised at home either all (unsupervised) or part of the time (semi-supervised) the adherence rates across studies have been variable ranging from 14%[148] to 100%[149].

Internet-connected digital platforms, such as smartphone applications ("apps"), represent an alternate delivery modality that address patient-specified barriers and offer new functionalities for customization. Apps have been used successfully in other chronic diseases like diabetes[297] and asthma[298] to support self-management activities such as medication adherence, tracking changes in biomarkers, and health behaviours. In the only un-supervised app-based cirrhosis study published to date, 20 of 26 (77%) participants watched at least one exercise video on their own during a 6-week exercise and nutrition intervention. The median number of repeated viewings was 9 with a wide range from 1 to 100 views, suggesting variable participant engagement[299].

Behaviour change theory can be used as a framework not only to inform the design of app-based lifestyle interventions to promote participant engagement[121], but also to understand why participants did or did not engage with these interventions[285]. The Capability Opportunity Motivation - Behaviour Change Model (COM-B) is one such framework. It has 3 major domains with 6 subdomains of capability (physical and psychological), opportunity (physical and social), and motivation (reflective and automatic). Actions influencing these domains can elicit the targeted behaviour. The domains in COM-B (capability, opportunity, and motivation) are subdivided into 14 smaller domains in its companion model – the Theoretical Domains Framework. The COM-B and TDF are designed to be used together in behaviour change research, implementation, and evaluation[300-303]. Theory-based interventions are an efficient approach to changing behaviours because the influence of discrete intervention elements can be assessed against the hypothesized mediator and its influence on the desired behaviour[104].

In advance of conducting a feasibility study of the intervention in cirrhosis, it was important to ask what were the early experiences of patients using an app-based program to support their nutrition and exercise self-management? The aim of the current study was to use a behavioural theory lens to explore the early experiences (4-6 wks) of patients enrolled in an 11-week study of the theoretically informed, web-based nutrition and exercise application Healthy Eating, Active Living, Mindful Energy (Heal-Me version 1). A 4-6 week time point was chosen to identify patient-perceived barriers and facilitators early on and to minimize the risk of losing the perspectives of patients who were unable to complete the full 11-week program.

5.2 <u>Methods</u>

This exploratory study employed a descriptive approach to capture the participants' emic experiences with, and perceptions of Heal-Me[304] to identify new viewpoints beyond those of the research team. The descriptive analysis approach allows researchers to stay close to the original data without the need to transform it or generate a theory. This analytical approach was congruent with the study goals of identifying facilitators and barriers to program uptake and usage[304] and facilitated the use of the COM-B and TDF to guide analysis.

Setting: Ethics approval (Pro00087451) was received from the Health Research Ethics Board, University of Alberta. This study was embedded within the Heal-Me Cirrhosis feasibility trial (ClinicalTrials.gov #NCT05033327). Patients were recruited (May-November 2021) from the parent trial providing a convenience sample of 23 patients from outpatient liver clinics and two tertiary care hospitals in western Canada.

Sample: Consecutive patients enrolled in the Heal-Me Cirrhosis feasibility trial as well as their care partners were invited to participate in order to obtain a maximum variation of experiences. Inclusion criteria for the parent trial included adults (≥18 years of age); cirrhosis (MELD-Na <26) diagnosed by imaging, medical history, transient elastography, or liver biopsy; fulfilled guideline-based prophylaxis for high-risk gastroesophageal varices; provided informed written consent; could read and write in English; and, had access to an internet-connected digital device in their home. Ineligibility criteria included hepatocellular carcinoma (HCC) outside of the Edmonton liver transplant criteria, non-HCC malignancy, end-stage renal disease on dialysis, post liver transplant status, deemed ineligible to participate in a virtual exercise program by their medical team, or listed for compassionate care.

Heal-Me Cirrhosis Intervention: The 15 behaviour change measures were [305] mapped to the domains in the COM-B [109] and TDF (version 2)[306] (Table 1). With nutrition and exercise interventions informed by cirrhosis practice guidelines[28, 283], the Heal-Me Cirrhosis intervention was delivered online over 11 weeks in a semi-supervised format. Accessed through the app, online videoconferences connected patients to 1-to-1 sessions with a trainer (registered dietitian, 3x; certified exercise specialist, 10x) and trainer-led group classes (nutrition, 5x; exercise, 10x). Independently, patients used the app to view their collaboratively-set weekly goals, enter protein intake, access follow-along exercise videos, check progress, and resources (Supplementary Figure 1-Heal-Me Cirrhosis logic model). Patients wore a step count tracker as an indicator of physical activity, although step goals were not assigned. Bimonthly draws for a coffee card were held (eligible patients answered program relevant questions) to share tips and tricks among the participants.

Data generation and analysis: Interviews were conducted after patients used the semi-supervised Heal-Me program for 4 to 6 weeks. During this timeframe, patients had met with their trainers, used the app to meet their goals, paired the activity tracker, and attended online group sessions. Participants could choose either an unrecorded private telephone call or recorded online videoconference for the 60-minute interview. Before asking questions, each interviewee gave verbal consent and protection of their confidentiality was discussed. The interview guide (informed by the COM-B model, TDF, and the Heal-Me Cirrhosis program) was semi-structured with open-ended questions; prompts were used to elicit extra or clarifying information (Supplementary Table 1-interview guide). Recordings were transcribed verbatim and reviewed for accuracy; notes were taken during the telephone interviews.

General health and cirrhosis-related data was abstracted from the patients' electronic medical records. Demographic and socioeconomic surveys were completed by participants as part of the parent trial. The EncephalApp Stroop test was administered at baseline, where >190 seconds identified covert hepatic encephalopathy[307]. The measures for the liver frailty index (LFI) were completed by one certified exercise specialist and interpreted using the online calculator at https://liverfrailtyindex.ucsf.edu/ (robust, LFI <3.2; pre-frail, LFI 3.2 to <4.5; frail, LFI ≥4.5)[308]. Quality of life was assessed using the EQ-5D-5L and EQ-VAS[309]. Digital technology proficiency was measured for the technology device the patient used most frequently: computer (CPQ) or smart device (MDPQ)[143, 151]. Adherence to the Heal-Me cirrhosis intervention was defined for each activity: attending ≥75% of nutrition and exercise group sessions, reaching ≥75% of assigned protein intake 3 days per week, or completing ≥75% of follow-along exercise videos.

Data analysis

For the interview data, a coding framework reflecting the COM-B model and Theoretical Domains Framework (TDF) components was created *a priori* in NVivo, version 12 (QSR International Inc, USA) to guide the content analysis. As needed, new codes were developed inductively to reflect the categories and subcategories. Interviewers maintained field notes across the study. Coding was reviewed amongst the team until agreement was reached and exemplar statements were selected.

Quantitative data from surveys, assessments, and medical records were collected using REDCap[310]. Descriptive statistical analyses were used to characterize the study participants (SPSS, v24 by IBM Corporation, US).

5.3 Results

Participant characteristics

Twenty patients and 3 care partners, all female spouses, were interviewed (Table 2). Three patients declined due to scheduling conflicts or health issues. Interviews were conducted when planned except for 3 delays where the patients had unrelated health complications. Three patients had histories of hepatic encephalopathy of which 2 were on lactulose or rifaximin during the study. The most common morbidities other than cirrhosis were arthritis (n=10), hypertension (n=10), and diabetes (n=9). The baseline LFI scores were robust=2, pre-frail=16, and frail=2; 5 patients fell at least once in the past year. Three patients were meeting their recommended daily protein intake according to three-day food records at baseline. No patients met the guideline-based exercise recommendations of 150 minutes of aerobic exercise and 2 days of resistance training per week[28].

The proportion of patients' EQ-5D-5L health-related quality of life measures ranging from "moderate" to "severe" for mobility, pain and discomfort, and anxiety or depression were 6 (30%), 10 (50%), and 5 (25%), respectively. Ten patients were employed of which 9 were full-time. Annual household incomes were above $70,000 for 14 patients. The 3 patients with low (<60%) digital proficiency scores successfully completed an online app training session and remarked it was easy to use. These three patients paired the activity trackers to their smartphones successfully while 2 others, who had higher technology proficiency scores, had challenges that were unresolved despite expert assistance from the trainers.

Participants' perspectives

Interview data were mapped to every domain in the COM-B model and TDF and there were no issues regarding data coding between authors. Following data interrogation, no patterns or trends were found between patient characteristics and experiences. All patients remarked they derived benefit from the program for their cirrhosis self-management (Table 3) even though not everyone was able to adhere to the program. By week 6, adherence rates for the 20 people were: group classes – nutrition 90% and exercise 75%; protein entry 55%; follow along exercise videos, 40%. All participants successfully used the app independently based upon the variety of activities they completed. Common reasons for non-adherence were work-related time pressures or unexpected health events. Participant #7 thought it was very positive they never "felt pressured" or "made to feel guilty" if they missed a group session. Everyone required varying degrees of modification to their programs.

COM-B and TDF outcomes

Capability – Physical

The nutrition and exercise components (i.e., diet, goals, exercise videos and 1-to-1 sessions with registered dietitians and certified exercise specialists) accommodated the broad range of dietary issues faced by patients with cirrhosis, such diabetes, nausea, and loss of appetite (*"I can eat… I just have no appetite." Participant #17)*, and physical needs, such as arthritis or mobility limitations (*"[The trainer] will change the exercises in place of the ones that I can't do, that do the same thing, but on a very light scale kind of thing." Participant #10*). Some patients saw their nutrition program as "impossible goals" that they could not reach for reasons such as symptoms (e.g., fatigue, nausea, and early satiety) or external demands on their personal schedules. In the first 6 weeks, unrelated health events required modifications to the exercise program for several patients *("When I had my back injury [study week 3], I went down to Level One exercises which were much easier." Participant #8*). Despite program adjustments, some patients desired even more tailoring: *"I don't like to push and ask for more modifications. It just seems like I'm asking for too much." Participant #17.*

Capability – Knowledge

Understanding the connections between nutrition, the liver's role in digestion, and the metabolic changes due to the cirrhotic liver was important and valued: *"Being aware of the amount of* *protein needed; I don't think I knew that before." Participant #8 and #8-B [nods head].* Preconceptions of already meeting healthy eating targets were notable barriers to wanting to gain new knowledge. *"I think our diet is fairly reasonable all considered." Participant #9.* Conversely, less feedback was provided about exercise or acquiring new skills even though the patients were informed to assess their perceived exertion and exercise frequency as part of their weekly goals. The comments regarding ease of use of the app and degree of engagement did not vary substantially between patients who tested positive for covert hepatic encephalopathy at baseline (n=9) and those who did not (n=11).

Capability – Behavioural regulation

Several participants experienced unwanted weight gain in the first weeks. *"I found that increasing the protein was leaving little room for fruits and vegetables, so I've been consuming more calories." Participant #8.* By increasing daily protein intake, most participants had to rebalance their calories. Several believed that this was a potentially avoidable consequence. Some expressed challenges with integrating the exercise videos into their schedules while others *"squeezed in"* the workouts. Overall, adherence to the Heal-Me cirrhosis program required that patients had to think ahead and plan their weekly activities (e.g., check ins, classes, individual activities): *"What I am getting out of it is back into a routine again." Participant #6.*

Capability – Memory, attention, and decision processes

According to the EncephalApp Stroop test, 9 patients had CHE at baseline. While some patients commented about their memory ("*I'll write it down somewhere. I have the perfect memory. It's right here [waves a sheet of paper]!" Participant #13)* or attention (*"I'm horrible at recording stuff." Participant #15)*, they were still able to use the Heal-Me app for nutrition and exercise according to app usage data and connect to group sessions. Tracking protein intake and eating frequency across the day helped patients realize where they could improve: *"I saw many dietitians and they all pushed the high protein, but it didn't really stick until I started really tracking it." Participant #4.* Protein tracking was a skill that could be acquired in a short time: *"When I first started, I needed the [protein] tracking to know. But I'm getting to the point now where I kind of know already before I track it." (Participant #8* after using the tracker for 6 weeks). During the first 6 weeks, several participants had life events occur including loss of a family member, starting a new employment position, visiting the ER, or being hospitalized. Patients temporarily halted the Heal-Me program (*"It is taking all my strength to focus on this* [new event] *right now." Participant #20*) and when they resumed (usually 2 weeks later), they needed the trainer's expertise to redesign or modify their exercise program.

Opportunity – Environment and resources

Over the 6 weeks, 95% (19) attended the live nutrition class and 75% (15) attended 3 or more of the 5 group exercise classes. The Trainer check-ins were unique compared to usual healthcare services and provided feedback within a reasonable timeframe: *"A Dietitian will just tell you, but there's no follow-up typically." Participant #4.* Others appreciated the relevance of the program customized to their situation: *"When I talk to the Trainer, it's about the program and how to make it work best for me." Participant #12.* Some indicated the weekly exercise check-ins were too frequent after the third week. All acknowledged that their time involved in Heal-Me was worthwhile (*"Oh yeah. I know it is!" Participant #15)* and estimated they spent 2 to 10 hours per week. This exceeded the intended 4 to 5 hours comments such as: *"It's fairly intense!" Participant #10*. Most participants commented that the protein entry could be improved: *"I have trouble with the app for entering the food… I have gotten a little confused with that." Participant #17.* Two patients at the lower end of the digital technology range had their spouses enter the protein into the app on their behalf. All liked the "at home" convenience of Heal-Me and appreciated that they did not have to be at the clinic or hospital (*"…that place that I hate.*" *Participant #13)*.

Opportunity – Social

Seeing other patients, hearing their questions, and the bimonthly draws fostered group wellbeing. *"The sense of community it brings, like we're all kind of battling this together." Participant #4.* The visual impact of other patients helped to normalize and focus their attention on their health and wellbeing. *"If I'm keeping up with some of the other patients and the Trainer, then I know that I'm doing them [the exercises] the right way. It's not my own interpretation." Participant #13.*

Motivation – Automatic

Satisfaction or a thrill, reflex reactions, were evoked upon receiving an achievement. *"Kind of like that little kid feeling when you get a gold star on the wall." Participant #4.* Trainer check ins and group classes created feelings of accountability and responsibility, automatic emotional reactions in response to trainer interactions.

Motivation – Reflective

Each of the five domains (i.e., intentions, beliefs about capabilities and consequences, reinforcement, and optimism) were coded. By the time of the study interviews, patients remained motivated with their programs, had good intentions to reach their well-defined goals, and were optimistic. Beliefs about their capabilities and consequences were informed by Heal-Me education and experiences. Reinforcement by protein tracking increased dietary awareness sensitizing them to their liver needs complimented with new knowledge from the nutrition classes. Some patients were motivated by the activity tracker (*"My friend!" Participant #2 or "It's a little bit more motivating when you can see yourself nearing your goal" Participant #17*). Most found the check ins and classes as positive reinforcements: *"Because it's an organized class, it gives me some accountability." Participant #3***.** Low adherence to the at-home follow along exercise videos was matched with negative comments: *"I don't like exercising" Participant #3;* or *"They are dull. Repetitive" Participant #14.* Conversely, other participants thought the scheduling flexibility of when and where they did their exercise videos helped their adherence.

Data that did not fit into the TDF domains were inductively coded: (1) "access to Heal-Me" with most commenting they would have liked this program within the first 6-12 months after being diagnosed with cirrhosis. *"When I first started going through where I see this specialist and everything because of the problems I have, I was more concerned in just not dying at the moment. So, I guess I wasn't looking at the big picture." Participant #1*; (2) "long-term access" – several requested access to Heal-Me recipes and follow along exercise videos after the study. *"I think the one thing that I'm a little disappointed with this is that we don't get access to the stuff after the study's over." Participant #8*); (3) In response to an interview question (if you had a magic wand how would you improve Heal-Me?) suggestions for future Heal-Me iterations ranged from proposing patient-initiated informal social interactions via an online forum or encouraging patient-to-patient conversations during online classes, offering more group exercise classes each week, enhancing the progress reporting (weekly, overall), and integrating more passive data collected from the activity tracker, such as sleep quality indicators.

5.4 Discussion

Feedback from 20 patients and 3 spouses about their early experiences using an online nutrition and exercise program (Heal-Me cirrhosis version 1) used a theoretically focused approach to identify facilitators and barriers to adherence. Several had covert HE while others were taking medications for past overt episodes. The prevalence of morbidities in addition to cirrhosis was consistent with other studies[311-313]. The patients had a low EQ-5D VAS score of 69 related to the population mean for Albertans of similar ages (45 to 65 years) is 83[314].

Overall, participants were positive about the Heal-Me cirrhosis program, and this was reflected in the adherence rates of ≥75% for the group classes. The daily protein entry was acceptable to patients, but technical issues led to a 55% adherence rate. In the absence of these issues, it is likely adherence would have been much closer to the predefined ≥75% level. Intentionally, the development of the Heal-Me cirrhosis app involved patients and experts from the initial conceptualization through to design and feasibility testing using a person-based approach[315] and interdisciplinary design team[316]. This approach helped to ensure that the app's goals and design were consistent with the patient user's health priorities and capabilities and considered their real-life contexts.

App user experience: Participants believed the app was easy to use after the initial training session commenting on ease of navigation and intuitive design. Both are key elements known to affect usability and acceptability of mobile apps in older people[317, 318]. That said, participants noted some areas that could be redesigned to improve the users' experience (e.g., protein entry screens).

Education: The nutrition classes had the highest adherence rates. Patients valued the "new" cirrhosis-specific nutrition information and the follow-up check ins with the dietitian. Interest was motivated by learning about the interactions between nutrition, the cirrhotic liver function, and overall health. In a cardiac rehabilitation study, patients expressed the need for relevant nutrition and health information (n=26)[319], showcasing how knowledge acquisition can motivate behaviour change. Fewer comments were received about a gain in exercise-related information. The exercise classes were focused on guiding patients through an exercise routine, and did not incorporate structured educational information about a deeper understanding of frailty, sedentary behaviour, and cirrhosis that may have helped motivate their exercising.

Healthcare provider engagement: The hybrid delivery of Heal-Me was used to customize the nutrition and exercise programs for each participant. Measures taken at baseline were useful to assign a general level, but subsequent modifications were needed for all patients to reflect preferences, health needs, context, and external pressures. Regular engagement with a healthcare practitioner has been more effective for changing behaviours than usual care[320]. This was also demonstrated in a cirrhosis app-based study (EL-FIT), where patients perceived enhanced care from healthcare practitioners as beneficial[299]. It should be noted that the trainers for Heal-Me Cirrhosis had to be familiar with cirrhosis as well as other health conditions (e.g., diabetes, shoulder injury) to make modifications to accommodate either pre-existing or new onset issues. Some participants, including 2 who later dropped out, perceived their programs were not tailored to their abilities however by their own choice, they had limited interactions with the trainers.

Activity trackers: The technology proficiency survey and app training session did not prevent issues with setting up the activity tracker. Others had difficulty reading the displays or noted that their steps counts were tracked incorrectly. Other researchers have mentioned similar usability issues with activity trackers[148, 299, 319]. While technical assistance was provided in this study, some participants still found the activity trackers challenging to use. Conversely, those who used the trackers found them to be motivational, liked the real-time feedback, and were unobtrusive; outcomes that were similar in other studies. In a pilot RCT[288], when patients living with cirrhosis received exercise counselling in addition to activity trackers, daily step counts increased (423±60 m versus 482±87 m, p=0.05). Although 21% of US adults regularly used an activity tracker in 2019[321], for studies in individuals with cirrhosis, it is likely that technical support may be required for trackers, and possible that the choice of different types of trackers (i.e. pedometers versus smart watches) may be beneficial.

Interactions: Modeling and social influence also affected motivation and acceptance of programming in our study. Here, the participants were committed to attending group classes and were motivated to engage in exercise by seeing patients, like themselves, and trainers during group classes. Most participants preferred group exercise classes over the follow-along exercise videos. The visual influence of patient-patient interaction, even in controlled, trainer-led encounters, cannot be underestimated. In previous trials, patients have requested the functionality to interact with other study members, such as social forums or direct messaging[299, 319]. The corollary of this is the potential importance of visual context on motivation. In a cirrhosis RCT (n=80), patients were to use the "Strong for Life" exercise videos in their homes as part of the intervention. This video series featured older adults (>60 years) in what looked to be a seniors' residence performing light exercises. The videos may not have resonated with the cirrhosis patients who were younger (median age, 62 years, IQR: 56, 66) and could have contributed to the low (14%) video adherence rates[148].

COM-B and TDF: Facilitators and barriers to early patient engagement with Heal-Me cirrhosis were identified using COM-B and TDF. While data were coded to each of the domains and recommendations, the three most valuable takeaways pertain to the domains of capability-physical, opportunity-social influence (modeling, interactions), and capability-knowledge. By designing a behaviour change intervention based on COM-B and BCTs, this facilitates its subsequent assessment at any time in the research trajectory. Further, assessment outcomes are readily associated with intervention components that merit further refinement or development in a transparent manner.

This study's outcomes were compared against the original list of BCTs (Table 1) upon which Heal-Me cirrhosis was designed. Next, additional BCTs were identified to further enhance patients' early program adherence and the targeted behaviour changes. In contrast to the health app industry, which has been focused on incorporating user feedback to promote app uptake and initial interest[322], healthcare needs interventions and research capable of addressing patient engagement with short-, medium-, and long-term app use, adherence, and changes in health outcomes. This requires theory-informed intervention design and iterative evaluation in a robust research framework for which the COM-B is well suited.

With a dearth of information about acceptability of self-management apps, especially for older adults, in general[319], this study shows promise of this type of healthcare delivery when the intervention is collaboratively designed in a patient centered manner.

Limitations: The overall sample size of the parent Heal Me cirrhosis feasibility study was small with only 20 patients and 3 care partners. Their characteristics however were consistent with cirrhosis with respect to morbidities, quality of life, physical performance, and technology proficiencies. The participants had a broad range with respect to living arrangements, employment, age, and household income, all factors that could have influenced their attitudes and adherence to Heal-Me cirrhosis. Limitations pertained to the need to schedule online group classes during business hours due to study team availability and wanting a critical mass for the sessions. This made it challenging to assess what adherence could have if more sessions were available. Recruitment of patients with high-speed internet prevented rural residents participating thereby limiting the generalizability of outcomes further. The set up of the activity trackers had mixed success and it could have been beneficial if more makes and models had been available to our patients. Issues pertaining to the usability of the Heal-Me program were documented, largely around the number of clicks required for protein tracking and will be addressed in its next version. The time commitment required for the study was intensive for some participants, and a more staged approach to intervention roll-out may be beneficial in future work.

In conclusion, this qualitative study provides a unique behaviorally focused lens on the early (within 4-6 weeks) views of patients participating in an online nutrition and exercise-based intervention. The three key items that influenced patient retention and adherence during the first 6 weeks of using Heal-Me cirrhosis were program customization and responsiveness (environmental context), awareness of nutrition in cirrhosis (knowledge-psychology), and interactions between patients and Trainers (social influence, behavioural regulation). Most participants in the trial required tailoring of their intervention to meet their individual needs. It is likely that this individualized approach may be required to optimize the impact of such interventions in patients with complex needs such as cirrhosis. The results of this descriptive work are not only relevant to other eHealth interventions as they inform health-related behaviour change elements, but will be used to refine the intervention for rollout in a larger RCT.

Table 5-1. Linkage of Behaviour Change Taxonomy v1 (93 BCTs) and mechanisms of action in the Heal-Me Cirrhosis program with the COM-B model and TDF v2. Note, the italicized, bolded text and gray cells are recommendations that reflect patient feedback.

Abbreviations: Mechanisms of Action: AB, Attitude to the Behaviour; BAC, Beliefs about Capabilities; BCC, Beliefs about Consequences; BR, Behavioural Regulation; E, Exercise Program; ECR, Environmental Context and Resources; Em, Emotion; FP, Feedback Processes; G, Goals; GAB, General Attitudes and Beliefs; I, Intentions; Id, Social/Professional Role and Identity; K, Knowledge; Me, Memory, Attention and Decision Processes; M, Motivations; MoA, Mechanism(s) of Action; N, Nutrition Program; R, Reinforcement; S, Skills; SI, Social Influences; Sim, Social Image; SL, Social Learning/Imitations; SN, Subjective Norms

Behaviour Change Taxonomy	**MoA**	**Description of Heal-Me Cirrhosis Program Elements**	**CAPABILITY**				**OPPORTUNITY**		**MOTIVATION**							
			Physical	Psychology			Social	Physical	Reflective						Auto	
			S	K	BR	Me	SI	ECR	BAC	BCC	I	Id	O	G	R	Em
8.1 Behavioural practice/rehearsal (modelling)	S, BAC	N: Online group nutrition classes show performance of the behaviour with Q&As E: Online group exercise classes show performance of the behaviour	🟨						🟨							
8.7 Graded tasks	S, BAC	N: Protein servings increased incrementally to reach behaviour outcome E: Exercise intensity and duration increase incrementally (but NOT the number of exercise sessions per week)	🟨						🟨							
4.1 Instruction on how to perform a behaviour	K, S, BAC	N: Recipes, online education classes, informational videos, and text documents E: Explanations in the extended follow-along exercise videos, Trainer instructions during online classes to correct or modify exercises ***-Online education classes about physical frailty, exercise, and cirrhosis***	🟨	🟨					🟨							

Behaviour Change Taxonomy	**MoA**	**Description of Heal-Me Cirrhosis Program Elements**	**CAPABILITY**				**OPPORTUNITY**		**MOTIVATION**							
			Physical	Psychology			Social	Physical	Reflective						Auto	
			S	K	BR	Me	SI	ECR	BAC	BCC	I	Id	O	G	R	Em
6.1 Demonstration of the behaviour	K, BAC, SL	N: Cookery videos and online nutrition demonstrations E: Demonstrate exercises or their modifications during online group sessions by lead instructor		🟨			🟨		🟨							
6.2 Social comparison	***SN, SI***	***For both N and E:*** ***Group classes: can draw attention to others' performance/progress for self-comparison*** ***Leaderboard: can see other's progress relatively to their own***					▨		▨			▨				
6.3 Information about others' approval	***SN, I***	***For both N and E:*** ***Leaderboard feedback from patients can promote, encourage, support, and connect with other patients using emojis or premade text***					▨		▨		▨	▨				▨
1.2 Problem solving (program adherence)	K, BAC, BR	N: Trainer collaboratively explores possible barriers to protein intake, makes relevant suggestions (e.g., other foods high protein milk, meal services, protein bars) – customization; ***After group classes, have a group discussion led by Trainer regarding issues and solutions to adherence*** E: Trainer collaboratively explores barriers, makes relevant suggestions to motivate patient to exercise (e.g., exercise with a buddy, find suitable time of day, different exercises) – customization ***After group classes, have a group discussion led by Trainer regarding issues and solutions to adherence***		🟨	🟨		▨		🟨							

Behaviour Change Taxonomy	MoA	Description of Heal-Me Cirrhosis Program Elements	CAPABILITY				OPPORTUNITY		MOTIVATION							
			Physical	Psychology			Social	Physical	Reflective						Auto	
			S	K	BR	Me	SI	ECR	BAC	BCC	I	Id	O	G	R	Em
11.3 Conserving mental resources	***BR, ECR, Me***	***E: Associate certain exercises with habitual activities. During commercials, could complete resistance exercises. While doing laundry, could do stretching or balance exercises. Parsing out exercises ensures they get done. Decreases the overall commitment time to exercising and may ease integration into existing schedules.***			▒	▒		▒								
2.3 Self-monitoring of behaviour	BR	N: Patients recorded their daily protein intake for each meal or snack with the app for a minimum of 3-4 days each week – ***Make reporting screens more detailed for day, week, and overall*** ***E: More data from the AT transmitted to the App and reported in detailed screens to support personal progress tracking***			🟨	▒			▒						▒	
2.6 Biofeedback	FB	***E: AT passively captures additional biometric data (sleep quality, heart rate) and will transmit data to the app for reporting***			▒	▒			▒	▒					▒	
3.2 Social support (practical)	ECR, SI	N: Trainer provides expert dietary and nutrition advice or suggestions; advised to engage in meal planning & preparations E: Exercising with the Trainers and other patients; advised to get an exercise buddy					🟨	🟨								
10.4 Social reward	R, SI	N: Trainer praises nutrition efforts as merited; bimonthly draws for responders; ***patients can praise one another on the progress board*** E: Trainer praises exercise efforts as merited; bimonthly draws for responders; ***patients can praise one another on the progress board***					🟨								🟨	🟨

Behaviour Change Taxonomy	MoA	Description of Heal-Me Cirrhosis Program Elements	CAPABILITY				OPPORTUNITY		MOTIVATION							
			Physical	Psychology			Social	Physical	Reflective						Auto	
			S	K	BR	Me	SI	ECR	BAC	BCC	I	Id	O	G	R	Em
12.1 Restructured the physical environment	ECR	N and E: Live classes via Zoom videoconference where patients interact with others and Trainers; provided resistance bands for exercise						■								
9.1 Credible sources	AB, GAB	N: Trainer is an RD (expert); program adheres to nutrition practice guidelines for patients with chronic diseases and age-related E: Trainer is an ES (expert); program adheres to recommendations for patients with chronic diseases							■							
15.3 Focus on past successes	BAC	N: Patient recalls when they were adherent or completed certain program elements (e.g., having a late-night snack) E: Patient recalls when they were physically active or when they were successfully adherent to the programming							■							
9.3 Comparative imagining of future outcomes	BACo	N: Trainer helps patient compare two futures with a high versus low protein diet E: Trainers help patient compare two futures with versus without exercising								■	■					
2.2 Feedback on behaviour	M, FP	N: Review recent protein intake; review progress relative to goal and protein tracking data; discusses patient perceptions E: Review recent physical health, motivation, exercise intensity; discusses patient's confidence and capability for future week									■					

Behaviour Change Taxonomy	**MoA**	**Description of Heal-Me Cirrhosis Program Elements**	**CAPABILITY**				**OPPORTUNITY**		**MOTIVATION**							
			Physical	Psychology			Social	Physical	Reflective						Auto	
			S	K	BR	Me	SI	ECR	BAC	BCC	I	Id	O	G	R	Em
2.7 Feedback on outcome(s) of behaviour	FP	N: Points and achievements earned for protein quantity and types tracked E: Points and achievements earned for completing the follow along exercise videos									🟨					
1.1 Goal setting (behaviour)	I, G, O	N: Agrees on number of protein servings per day informed by guidelines; rates confidence to achieve this E: Agrees on exercise intensity from level 1 to 4 and types of exercises for the following week; rates confidence to achieve this									🟨		🟨	🟨		
13.1 Identification of self as a role model	***SIm***	***N: Liver friendly diet is beneficial to rest of household and helping them improve their health. During online group sessions, can be a model for other patients.*** ***E: Exercise technique and progress can make a patient a good model for others during online exercise classes.***										▒	▒	▒		▒
1.6 Discrepancy between behaviour and the goal	G, FP	N: Every 3 weeks, review protein intake versus set goals E: Every week, review exercise sessions completed and perceived exertion intensity relative to set goals									🟨			🟨		

Behaviour Change Taxonomy	**MoA**	**Description of Heal-Me Cirrhosis Program Elements**	**CAPABILITY**				**OPPORTUNITY**		**MOTIVATION**							
			Physical	Psychology			Social	Physical	Reflective						Auto	
			S	K	BR	Me	SI	ECR	BAC	BCC	I	Id	O	G	R	Em
1.5 Review behaviour goal(s)	G	N: Review progress and confidence ***(as needed)*** with protein intake with positive outcomes leading to increased daily protein servings to reach target behaviour outcome of 1.2-1.5 mg/kg daily protein E: Review progress and confidence ***(as needed)*** of doing 3 exercise sessions each week, may adjust exercise intensity but never reduce or increase number of sessions per week												🟨		

Table 5-2. Patient characteristics (n=20) at baseline

Characteristics	Mean (SD)
Age (years)	60.4 (11.4), range: 30-79
Female sex (n)	8 (40%)
Cirrhosis etiology (n):	
- NAFLD	12 (60%)
- Alcohol related	5 (25%)
- Autoimmune hepatitis	1 (5%)
- Primary biliary cholangitis	1 (5%)
- Hepatitis C	1 (5%)
MELD-Na	9.0 (2.0)
Child-Pugh A : B (n)	13 (65%) : 7 (35%)
Listed for liver transplant, y (n)	2 (10%)
Ascites history, y (n)	6 (30%)
HCC, y (n)	2 (10%)
CHE, y (n)	9 (45%)
Liver Frailty Index	3.9 (0.5), range: 3.1-4.9
EQ-5D VAS	66.7% (18.9), range:
Device proficiency (CPQ or MDPQ)	85.7% (18.8), range: 45-100%
Post-secondary schooling, y (n)	12 (60%)
Employed, y (n)	10 (50%)
Living with another person, y (n)	16 (80%)

Abbreviations: CHE, covert hepatic encephalopathy measured with the EncephalApp Stroop test; CPQ, Computer Proficiency Questionnaire; HCC, hepatocellular carcinoma; MDPQ, Mobile Device Proficiency Questionnaire; MELD-Na, model for end-stage liver disease adjusted for sodium; VAS, visual analog scale.

Table 5-3. Patients' additional feedback to the app-based Heal-Me Cirrhosis nutrition and exercise program

"I think it's colorful and interactive. It definitely opens your eyes up to have someone weekly checking in with you to ask how are you doing and what can you do to increase it. So, it was really easy [to follow] once I got into a routine with it. I think it's really great to get people involved. I really like the biweekly draw." *Participant #4*
"It is an easy [to use] program." *Participant #10*
"Yes, I enjoy it. It builds me up, yes it does." *Participant #15*
"I think, overall, it's quite a good program. I find it quite beneficial. I learned a lot from it." *Participant #8*
"I definitely think I've been more immersed in the nutrition aspect of it. I think it has definitely been more beneficial for me. Especially now… understanding more about cirrhosis than I did before." *Participant #17*
"I really think it's very well done. All the other things just make it work… it's a bit of variety!" *Participant #12*
"Kind of an awareness, kind of knowing what's going on, where you need to go with it [cirrhosis self-management]". *Participant #9*
"I have all the support you know, and I talk with people, and I'm not alone." *Participant #13*
"This program is a 'good thing'." *Participant #16*
"I don't know exactly what I was expecting coming into it, but I'm not disappointed so that's a good thing. The app, it's very easy to use, so that's good." *Participant #1*
"I'm grateful for the fact that things [cirrhosis nutrition and exercise] are explained better than what I've gotten before." *Participant #3*

> “I think a group setting is helpful and when you're not face to face with people it's just that much easier. It’s not that I'm anti social or anti people. It's just more comfortable when you can do it in your own setting.” *Participant #17*

> “Because it's an organized class, it gives me some accountability.” *Participant 3*

Table 5-4. COM-B and TDF facilitators and barriers for Heal-Me Cirrhosis

COM-B	TDF	Learnings
Capability-Physical	Skills/Abilities	- Modify baseline data collection tools to improve initial customization of programming. - Offer 2 nutrition check-ins during the first 5 weeks to improve customization.
Capability-Psychology	Knowledge	- Include a group education class about the relationship between exercise, cirrhosis, frailty, aging, and health outcomes - Have trainer-led informal discussions to foster group cohesion and social interaction - Prevent unwanted outcomes by proactively addressing them as part of the program (e.g., unwanted weight gain)
	Behavioural Regulation	- Offer shorter but more frequent exercise sessions cued to daily activity (e.g., toothbrushing) to promote routine. - Send reminders via the app for time-sensitive activities - Increase the frequency of online group exercise classes recognizing the independent activity change is difficult
	Memory, attention & decision	- Exercise and nutrition online programming is accessible independent of hepatic encephalopathy - Make data entry simple to do in real-time to prevent errors or data loss
Opportunity-Physical	Environment, context & resources	- Simple to use data entry and navigation is critical to app use - Be aware that education specific to other morbidities and cirrhosis complications may be needed - Frontload trainer check-ins to customize programs - Offer program variety (e.g., exercise sessions of various durations and frequencies)
Opportunity-Social	Social Influence	- Provide regular, safe opportunities for patients to interact.

Motivation-Automatic	Emotion/ Reinforcement	- Include non-serious gamification elements to promote app use - Capture patient emotions or feelings in relation to an app activity to form positive emotions about a healthy behaviour - Share relative progress meters.
		- Include real-time progress indicators to help patients reach goals
Motivation-Reflective	Intentions, Optimism Beliefs about capabilities	- Tailor the program to address the motivations for participation (e.g., increased strength, fall prevention, weight loss)
		- Share program successes with new participants.
		- Regardless of etiology, find a common reference for all patients, such as aging and its relation to frailty

Figure 5-1. Logic model of

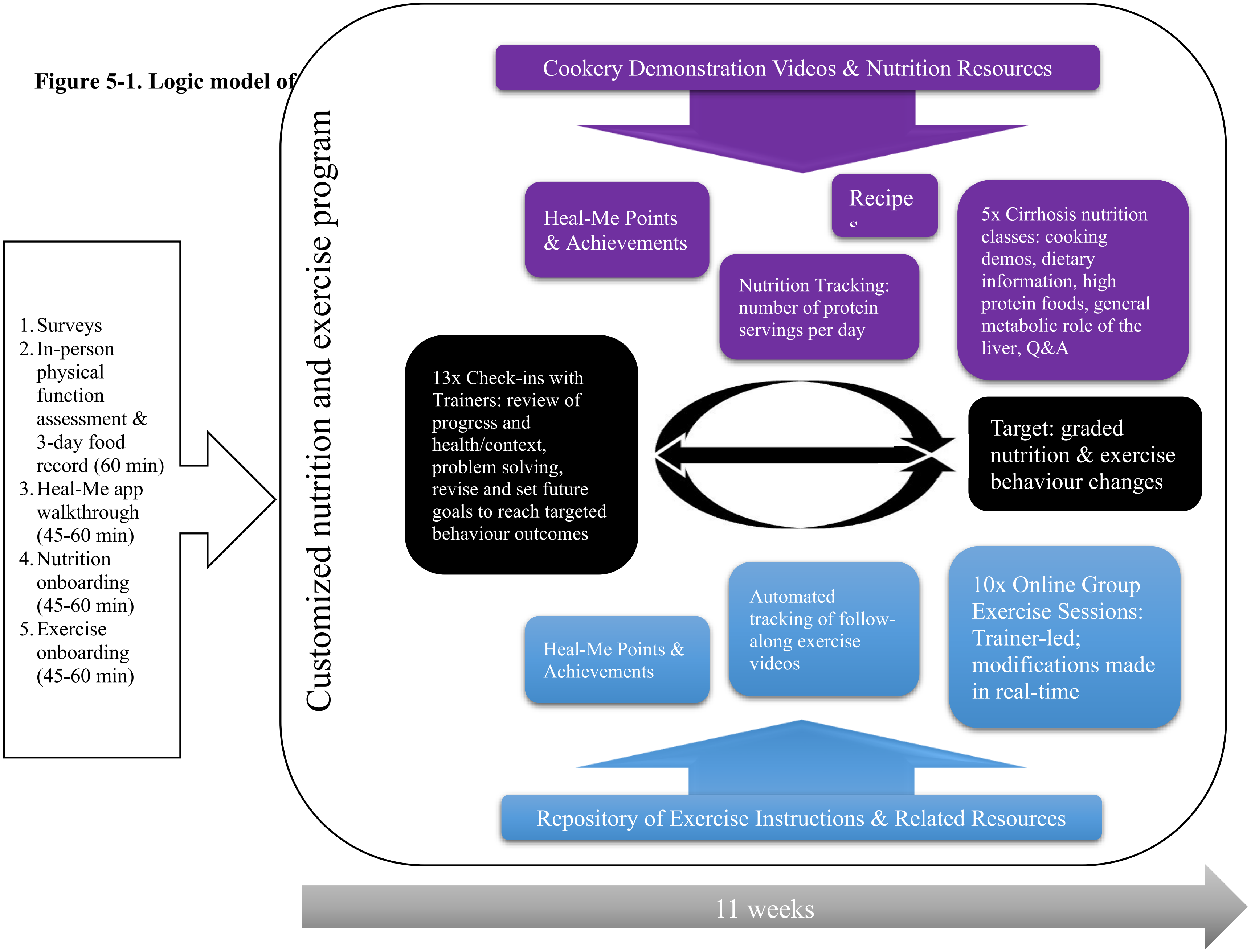


Table 5-Supplementary-1. Interview questions and COM-B domains

Questions	COM-B Model
Nutrition	
Before the study, how did you approach eating and your diet?	C-Psychology
Before the study, can you describe any interactions with registered dietitians?	C-Psychology O-Environmental
After using Heal-Me for 4-6 weeks, how has the program influenced your eating strategies?	C-Psychology O-Social O-Environment
How has tracking your protein altered your eating liver-friendly meals and snacks?	C-Psychology O-Environmental
How have the program features influenced your eating in the past month? Prompts: • Check ins with Trainer • Online group nutrition classes • Protein tracker • Recipes • Nutrition points • Achievements	C-Psychology O-Social, Environmental M-Reflective, Automatic
Exercise	
Before the Heal-Me study, please tell me about your physical activity?	C-Knowledge
What app features pertaining to exercise do you like and why?	M-Reflective
What app features do you not like and why?	M-Automatic, Reflective
Has the HEAL-Me app improved your level of activity in the past month? Please describe	M-Automatic, Reflective
How have the program features influenced your exercise and physical activity in the past month? Prompts: • Weekly check ins with the Trainer • Online group exercise classes	O-Social M-Automatic, Reflective

• Follow-along exercise videos • Instructions (video and text) Wearable activity tracker • Exercise points • Achievements	
General	
Have any of your family or friends been involved in any way with the Heal-Me program?	O-Social
Have you had any issues with using the app or following the programming thus far?	C-Physical
Do you feel the time invested with the Heal-Me app has been worthwhile?	M-Reflective
How long do you think you will use Heal-Me before feeling comfortable of taking charge without the support of the exercise specialist or dietitian?	M-Reflective
Have your attitudes about nutrition or exercise in cirrhosis changed in the past month?	C-Psychology O-Environment
Do you feel your technology skills have improved with using the app? Is this beneficial to you? Why or why not?	C-Psychology
Do you believe your knowledge of (nutrition/exercise) has improved because of Heal-Me program?	C-Psychology O-Environment
Reflecting on your experience, at what point do you feel that the program would be most suitable (e.g., diagnosis, listed for transplant)?	C-Psychology
Do you have anything you would like to share about your experiences with the HEAL-Me program or app?	O-Environment M-Reflective

CHAPTER 6.0 - Conclusion

"Let’s pony up here; let's start going! So, it was really easy once I got into a routine with it [Heal-Me cirrhosis]. It only took about a week and a half before it really started to make me think about things."

Participant #4

6.1 Summary

Across my dissertation, the human relationship with technology has been a common theme. Dating as far back as 3.3 million years ago, stone tools made by humans (the first form of technology) have been found by Kenya's Lake Turkana[323]. The lengthy history of hominin technology advancements has been ascribed by some to be a human "intrinsic motivation to manipulate objects"[324, p. 1]. This predisposition to modify the environment has led to the modern Internet of Things providing unprecedented access to information and communication platforms. The introduction of quantum computing and quantum internet, expected in the next several years[325], will once again change the nature of our interactions with information and each other. At the forefront of technological advancements predicted by 2030 will be the advanced application of digital technology for healthier living by offering self-management supports for physical and mental health[326].

While eHealth is prevalent in the endemic COVID-19 world, apps for healthy nutrition, improved physical activity, and enhanced self-management support infrequently help the user achieve the desired behaviour because of low retention rates (retention rates at 1 and 30 days are 20.1% and 3.8%, respectively[327]). Thus, there remains much opportunity to improve our understanding of human-technology interactions, especially in relation to the increasing burden of chronic diseases. With 44% of Canadians aged 20 years and older having at least 1 of 10 common chronic diseases[328], effective supports for self-management is a topic of interest to Canadians, healthcare systems, and policy-makers.

As an exemplar of chronic diseases, cirrhosis was the disease of focus in my doctoral research; a condition that is increasing in incidence nationwide[329, 330]. My overall goal was to assess non-pharmaceutical opportunities to enhance cirrhosis self-management skills. My dissertation consisted of a suite of studies examining how digital technology could support self-management in cirrhosis and its limitations. This research drew on knowledge from a broad range of areas, such as digital technology and accessibility, online patient communication, patient-centered care, and behaviour change. In each chapter, I reported on a specific study. Accumulatively, these study findings balance the unrealized potential of digital technology to support aspects of self-management, for example knowledge, awareness, and behaviour tracking, against limitations such as personalizing information to a person's particular context and interactions with healthcare practitioners and other patients. In the next sections, I will outline the main findings from each project.

Chapter 2: *Were patients proficient with internet-connected digital technology (ICT) and, if so, why were they using it?* In this cross-sectional, survey-based study, I reported high rates of digital device ownership by 117 number of Albertans living with cirrhosis. In the sample (age: 24-83 years; MELD-Na: 6-33), the participants owned smart devices (84.6%), computer systems (68.4%), or both (60.7%)[331]. Participants had moderate levels of technology proficiency for computers and smart devices (72.8% and 69.3%, respectively). Predictors of proficiency were household income <$25,000, education (primary or secondary school), and increasing age. Patients were using ICT primarily for communicating (59.0%), leisure (47.9%), and news (44.0%). A total of 61.5% participants were interested in online interactions with their healthcare practitioners. The outcomes indicated that individuals living with cirrhosis were moderately proficient with technology and had positive attitudes to online connections with their healthcare practitioners. These findings indicate that patient-oriented cirrhosis care could be expanded to include online communication platforms, resources, and apps to provide additional self-management support. At present, only two cirrhosis-specific apps have been described in the research literature (Patient Buddy app[169, 332] and EL-FIT[299]) indicating the ample opportunity for growth.

It should be noted that the research presented in Chapter 2 was designed and had completed data collection prior to the COVID-19 pandemic. This is pertinent as public heath restrictions, which began on March 15, 2020, in Alberta, led to rapid adoption of online health services. In the peri-COVID-19 era, Internet usage increased across Canada for all age groups, many who used online services for the first time[333]. This is likely similar for the cirrhosis population further supporting the adoption of apps to support self-management.

Chapter 3: *Is online cirrhosis information available specific to patients and their partners, and, if so, how is it presented?* Online information, specifically intended for individuals living with cirrhosis and their care partners, were evaluated using validated tools to characterize the freely available resources[334]. A systematic search using 8 search engines retrieved 212 unique webpages from 123 parent websites from 11 countries. The majority (71.2%) of the information was focused on five topics (esophageal varices, hepatocellular carcinoma, TIPS, paracentesis, and edema) and no "tools" were found that supported self-management, such as templates for a journal or record keeping, cues, or videos. After using a suite of common and validated assessments, including the Web Resource Rating Tool (WRRT)[152] and the Quality Evaluation Scoring Tool (QUEST)[153], I found that the webpages had low levels of accessibility, quality, and reliability. In-depth analysis of 18 webpages about hepatic encephalopathy showed limited scope of content and the inaccurate presentation of some information, specifically around non-pharmaceutical therapies, such as nutrition. This work highlighted the need for effective translation of well-curated knowledge in lay English considering the perspectives of those living with cirrhosis which contrasts to a point-form abridgement of clinical practice recommendations. Findings from this dissertation chapter have been incorporated into the development of the Cirrhosis Care of Alberta website (www.cirrhosiscare.ca).

Chapter 4: *What gaps, if any, were there that influenced self-management in hepatic encephalopathy?* When conducting the systematic literature review, I identified two sources of information regarding hepatic encephalopathy self-management: quantitative observational findings describing patient self-management behaviours and qualitative findings where patients and care partners described their personal experiences during interviews. To reflect the information from both source types, I conducted a mixed methods research synthesis using the EPPI Centre's approach[232]. After developing descriptive themes for each research approach (3 quantitative and 3 qualitative) pertaining to self-management, I then generated a cross-analytical theme that led to an action statement: the use of a distributed knowledge network of health practitioners to deliver accessible, consistent, lay information about hepatic encephalopathy at every healthcare encounter. Repetition of basic information and discussion improves awareness and knowledge about the complication and begins the process of long-term symptom monitoring. Proactively informing and supporting conversations about hepatic encephalopathy addresses a key knowledge gap identified in this synthesis: timely access to information to support self-management. By normalizing the risks, outcomes, and self-management responsibilities of this complication has the potential to reduce delays in diagnosis, improve pharmaceutical and non-pharmaceutical treatment adherence, and improve health outcomes for patients and care partners.

This chapter is a notable departure from the focus on internet-connected digital technology in cirrhosis care. Rather, this chapter is an acknowledgement of the potential for online technology to serve as an adjunct to practitioner-led conversations. As part of the distributed network was recommended in the synthesis, online, freely available, well curated resources are suited for providing information, tools, and reminders to support this dialogue and self-management. It is not intended for technology to replace practitioner-led conversations as these are dynamic, personal, non-linear, empathetic, and emotional[335-337], which is beyond the current and near future capability of artificial intelligence systems. As the practice of medicine evolves, AI is viewed as assistive tools that support clinicians rather than replace the "human" aspects of healthcare, including care coordination.

Chapter 5: *What were the early experiences of patients with an app-based program to support healthy nutrition and exercise behaviours?* Interventional studies in cirrhosis have shown a variable rate of adherence, especially if the intervention was delivered at home without supervision[27, 296]. However, individuals living with cirrhosis prefer home-based programming which creates tension between program adherence and improving health outcomes. Thus, we designed the Heal-Me app to provide a hybrid of supervised and unsupervised nutrition and exercise program tailored to the abilities of the patients. To understand early patient engagement with the app to identify facilitators and barriers for adherence, interviews were conducted in the first 4-6 weeks before participants dropped out or were lost to follow-up during the 11-week Heal-Me cirrhosis feasibility study. From this parent study (n=23), I interviewed 20 patients and 3 care partners. Interview transcripts were transcribed verbatim and analysed descriptively, guided by the COM-B model[109] and the TDF[306]. Analysis identified 22 learning outcomes from the patients and care partners which would improve the early experience with the program. Generally, Heal-Me cirrhosis was well received across a range of technology proficiency levels.

An unexpected finding was the patient prioritization of online patient-patient interactions as positive influences on motivation and adherence.

Though the Heal-Me app was designed and tested in concert with patients at all stages, these findings indicate the need to continuously engage active users to ensure that the app's design and functionalities match with expectations and needs. Rapid advances in the digital space are at odds with the conservative, develop, test, refine approach in healthcare research. Recognition is needed to increase the agile approach and maintain currency of the app to attract and engage users.

6.2 Limitations

Overall, this dissertation has several limitations that should be noted. Foremost, is the recognition that the digital divide is a current issue in Canada. In Chapter 2, the ability to take advantage of the Internet was assessed using a pen and paper survey. Nonetheless, the description of the study leading up to and during the study's consenting process may have negatively influenced recruitment of those without Internet or technology. Results from Chapter 2 indicated that only 14 (12.0%) participants had never accessed the Internet, although the reasons were not investigated, such as personal preference, locale, or device. In Chapter 5, there were 3 individuals who expressed interest in the Heal-Me study but were unable to do so because of Internet cost, absence of technology proficiency, or interest in improving their technology proficiency. Beyond this information, it was unclear how aspects of the digital divide influenced recruitment. The Government of Canada announced in April 2022 the "accessibility program for internet access"[338] in acknowledgement of the importance of Internet access of online healthcare services and resources during the COVID-19 pandemic.

Studies involving people living with cirrhosis (Chapters 2 and 5) were conducted in central Alberta with participants who were predominantly Caucasian, English speaking, non-immigrants with European descents. The majority were knowledgeable and proficient with internet-connected digital technology, had high rates of device ownership, and could readily access the Internet. Participants either owned or rented their homes indicating financial stability. Relative to other regions of North America, these individuals had a moderate quality of living. Thus, findings are likely not generalizable to other populations with different characteristics or regions elsewhere in the world.

The rapid rate of change in the digital technology and telecommunications space is driven by the commercial industry. In the space of time for researchers to conduct 3- to 5-year randomized controlled trials, the digital intervention or its functional components will likely become outdated or even obsolete[339, 340]. This highlights the value of agile, multidisciplinary research approaches to keep pace with and provide meaningful results to the app design and development economy[339]. Accordingly, this dissertation research spans a broad range of topics necessary to review, study, and critically assess the interface of online health tools and resources in relation to individuals living with cirrhosis. Many of the research findings presented may have limited value soon but they have contributed to understanding how to use and assess online digital products in healthcare to support those living with cirrhosis.

This suite of projects has allowed me to build a comprehensive picture of the potential of internet-connected digital technology in cirrhosis and self-management. This provides a context for considering implications for future research, education, and policy development.

6.3 Future research opportunities

6.3.1 Digital benchmarks in cirrhosis

Human-computer interactions have become routine in our environment. Findings presented in Chapters 2 and 3 can serve as a benchmark by which to measure progress of self-management support in cirrhosis. In this unregulated virtual environment, constant monitoring and assessment will be needed to ensure that individuals and their care partners are receiving accessible, relevant information reflecting the most recent clinical practice recommendations to prevent avoidable health outcomes, empower patients and their care partners, and offset resource costs on healthcare systems.

While there are over 50 different knowledge translation frameworks, the COM-B[109] and Theoretical Domains Framework[306] work as a cohesive unit and have been used effectively to inform the design or subsequent evaluation of behaviour change interventions. COM-B is sufficiently adaptable to accommodate other theories, such as Bloom's Taxonomy to assess patient, care partner, or practitioner knowledge. Follow-on studies will benefit from mixed research designs to understand how the interventions influence users' knowledge and behaviours. This is an emerging, multidisciplinary research area of importance to healthcare to ensure that the patient-dyad has support to participate in shared decision making. By understanding how to effectively communicate complex information that is relevant to self-management, ongoing evaluation is needed to keep abreast of both clinical practice recommendations and technology advancements. How information will be presented in a virtual reality environment will provide interesting and new challenges. Further, study outcomes will be helpful for shaping policy or care pathways to better reflect the knowledgeable and supported patient living with chronic disease.

While the benchmarking and monitoring are important activities to appreciate what patients and practitioners are accessing, there is opportunity to design and assess knowledge translation programs for targeted behaviours to achieve desirable health outcomes using theory-informed behaviour change and education models and taxonomies. Passive data capture, quantum computing, and artificial intelligence are unique advances in digital technology that can be used to new theories or refine existing ones.

6.3.2 Self-management of hepatic encephalopathy

Follow-on studies from Chapter 4 may involve the design, implementation, and evaluation of a distributed knowledge network for sharing basic information and initiating discussions about hepatic encephalopathy in a healthcare system. Study outcomes ideally would include acceptability and knowledge of all stakeholders and long-term sustainability. It will be insightful to understand possible barriers to implementation. In lieu of assessing common outcomes, such as knowledge recall, a study that captured longer term changes in patient and care partner attitudes to planning, goals, life decisions, and decision-makers would help to inform policy and practice.

It would be of interest to develop a patient decision aid, using the Ottawa Patient Decision Aid protocol[341], as an additional way to increase awareness of hepatic encephalopathy and community programs offering non-pharmacologic therapies in cirrhosis and hepatic encephalopathy. The decision aid could help the patient determine if or when they were ready to engage in healthy lifestyle changes that could facilitated or supported by their practitioners. This approach may empower patients by offering options they could choose from at that time or in the future. A patient decision aid involves systematic reviews, consensus, evaluation, and implementation by medical practitioners and patients. If favourable, the resulting tool could be important addition to the self-management toolbox for cirrhosis.

Future research to develop internet-connected digital self-management tools will be beneficial. Initial response to Heal-Me cirrhosis and attitudes to digital technology in healthcare support this. As with any app, context, usability, and relevance needs to be assessed and results incorporated into the product. That said, there are many possible options to pool together tools for medication tracking, how to vignettes, symptoms diary, and cues for discrete behaviours within the Heal-Me app to support cirrhosis as well as hepatic encephalopathy.

6.3.3 Heal-Me cirrhosis app

Already, version 2.0 of the Heal-Me app is being designed for use in an upcoming research study that was awarded funding in February 2022 from the Canadian Institutes of Health Research (App No. 474275 and App No. 469832). I am a co-applicant on the submission. Version 2.0 of the Heal-Me app will include many of the recommendations mentioned in Chapter 5. Following usability testing, features of version 2.0 will be assessed in two populations: liver transplant candidates and older adults. The core of the Heal-Me app (Tandon P, submitted) can be modified to deliver nutrition and exercise programming to any population opening the door to trials in other adult populations.

From the perspective of patients, it will be of more value to identify features that will increase patient program adherence over time and improve health related outcomes. In the Heal-Me cirrhosis study, participants were trained following a script that explained and demonstrated common app features over the course of 60 minutes. The training time was tailored to meet the technical proficiencies of the participants and any remaining time was spent discussing the overall Heal-Me cirrhosis program and answering questions. Although effective, this approach was resource-intensive for staff and participants. Remote learning and working have highlighted the barriers with online teaching. A large volume of resources is available online with different cost profiles and resource requirements. Elements which improve the effectiveness and acceptability of online device training that is supported by empirical research, are needed to support health-related apps and websites. The rationale for this is that the increasing complexity of the app requires longer learning curves and effort by the user. Thus, research into meaningful online education techniques will benefit participants and researchers alike.

6.3.4 Gamification

Gamification, the use of game elements in non-game contexts[342], has been used in many areas to increase a user's motivation to learn, change physical of psychological behaviour, or increase satisfaction[343, 344]. In the Heal-Me cirrhosis study, with data presented in Chapter 5, embedded gamification elements that were not discussed as part of the private Trainer encounters or group sessions. Although study participants could access the "Achievements" section in the app, there were no evaluations completed regarding the influence of the gamified elements on users. Recognizing this was a missed opportunity, further studies are in progress to assess the acceptability and influence of gamification elements on user engagement with the Heal-Me app.

6.4 Recommendations for Education and Policy

There is realistic hope that medical research advances will be able to cure early stages of cirrhosis or prevent it altogether. Already, research is available from the first xenotransplantation of a pig's heart into a human[345] as well as a 1,000-person trial assessing performance of a synthetic pancreas for type 1 diabetes[346-348]. However, this does not address immediate needs of the many who are living with chronic disease now. In 2019, it was estimated that 44% of Canadians aged 20 years and older had at least 1 of 10 common chronic diseases[349].

The outpacing of medical research in relation to medical care in chronic disease is demonstrated by the holdover of the structure and objectives of archaic healthcare systems that were originally designed for curative purposes[350]. Alongside this commitment to tradition is the slow reorientation of medical education regarding patient-centered care (PCC):

> **"**Few curriculum documents at 16 Canadian medical schools mentioned or described PCC concepts."[351, p. 1085]

Findings from this dissertation emphasize how healthcare delivery and expectations can change to better support those living with cirrhosis and other chronic diseases with a focus on self-management and appreciating the patients' and care partners' perspectives. "Telemedicine may prove to be the guiding force in the coordination of care between episodes for patients with cirrhosis."[352, p. 3854-3855] Both education and policy changes are required for healthcare to transition to meet the needs of contemporary patients. This is supported by the increasing number of apps and technology-centered interventions for individuals living with hepatitis C and cirrhosis or liver transplant recipients; in 2019, 12 studies technology-oriented studies had been published. If eHealth is to be fully taken advantage of in healthcare, its integration will require an overhaul of medical education and practice. In a survey-based study of 287 medical students in the United States, a key finding was that only 17.4% had "prior exposure to telemedicine"[353]. In another study conducted in the Netherlands, medical students were asked to respond to the aggregate statement, "I feel prepared to take advantage of the technological developments within the medical field."[354] Of the 303 medical students, the average score was only 4.8 out of 10. In a Canadian-led scoping review of 25 articles regarding medical education in eHealth, the authors concluded that change was needed in the curricula complemented with more learning opportunities[355].

6.5 Personal Learnings

Throughout the course of my graduate studies, I have learned much about cirrhosis, self-management, theory, and research processes among other things. An intimate part of this educational process has been to understand my niche and potential scope of research contributions.

Qualitative research My practical ambition to pursue a doctorate was to build my research capacity, especially in the areas of qualitative research and digital technology to support self-management. To pursue research in these areas, I needed the theoretical underpinnings by which to understand and interpret and report my findings. This was achieved through coursework, research experience, and interactions with my supervisors and team members.

Expectations Embarking on this study, I understood that those living with cirrhosis were characteristically sedentary, had a high symptom burden, and were frequently multimorbid. After completing the interviews, I have newfound appreciation for the effort participants put into the study. They wanted to do a "good job" and were sincerely interested in contributing to research and helping other people like themselves.

Digital technology in healthcare The era of virtual healthcare is just beginning as indicated by the acceptance of digital platforms as part of patient care, such as electronic patient portals. For healthcare apps, the ones pertaining to diabetes are the most advanced and sophisticated. The Libre lifestyle monitors blood sugar levels requiring minimal effort on the patient in comparison to the traditional finger pricking and blood measuring. Where there is a time savings, an improved process, or enjoyment relevant to the individual, a digital app will be successful. The challenge is to balance evidence-based medical guidelines for care with patient interests and what constitutes an acceptable level of perceived effort. I am hopeful that a combination of artificial intelligence and more extensive passive data capture than wearable activity trackers can represent a watershed for improving and sustaining healthy behaviour changes.

The mixed methods research synthesis was challenging Trying to tiptoe through the reality of clinicians and the burdens of patients was very interesting. It was easy to get wrapped up in the emotional stories presented in the qualitative studies and I had to reorient myself time and again to focus on the research objectives and salient information. Being aware of "emotional drift" and rationally counterbalancing it with was an essential learning experience.

In conclusion, I leave with a quote from one of the Heal-Me interview participants that captures the patient-perceived value of self-management support in cirrhosis:

> There's not a lot of people who will take the time and work with you and give you all that information. I mean, there's great resources online that you can find yourself… if you go digging and that's where I got a lot of my base information. "Okay, that's what's going on. This is what I've got to do to change it. Okay, let's go!" *Participant #4*

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APPENDIX 1

Chapter 3 was published as a research letter presented below:

Title: An evaluation of online cirrhosis-related information intended for patients and caregivers

Short Title: Online patient-oriented cirrhosis information

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Abbreviations: FKGL, Flesch-Kincaid Grade Level; FOG, Gunning Fog Index; SMOG, Simple Measure of Gobbledygook; CLI, Coleman-Liau Index; WRRT, Web Resource Rating Tool; QUEST, QUality Evaluation Scoring Tool; HONcode, certification from The Health On the Net Foundation; and WAVE, web accessibility evaluation tool.

With nearly 70% of American adults seeking online health information[202], the internet represents a powerful space to provide patients with evidence-based, usable education about their chronic conditions. While effective patient-oriented communication recommendations are available, the accessibility, reliability, and accuracy of online health content is largely unmonitored or evaluated. In a complex chronic disease, such as cirrhosis, understanding the online information landscape specific to patients can provide insight into resources that are available to support their self-management behaviours and to fill knowledge gaps.

The objectives of this study were to assess online cirrhosis information specifically intended for patients or informal caregivers regarding scope, accessibility, and reliability by different organization types. Detailed accuracy assessments were limited to hepatic encephalopathy, a common complication of cirrhosis selected because of its impact on patient health-related quality of life and caregiver burden.

Methods

To identify patient-specific online cirrhosis information that was freely available, 19 search strings were used with 8 search engines in August 2020 and reconfirmed in August 2021. The first three pages of results for each search were retrieved, screened for duplicates, then assessed against eligibility criteria (Supplementary Table-1). Webpage characteristics were recorded: parent website, copyright, country, creation or revision dates, media, advertisements, and topic. Readability was assessed using four common methods (Flesch-Kincaid Grade Level, Gunning Fog Index, Simple Measure of Gobbledygook, and Coleman-Liau Index) and reliability was evaluated with the Web Resource Rating Tool (WRRT)[152] and the QUality Evaluation Scoring Tool (QUEST)[153]. HONcode certification (https://www.hon.ch/en/) was also recorded. Accessibility was evaluated with WAVE by WebAIM (www.wave.webaim.org)[211]. Accuracy of hepatic encephalopathy content was informed by clinical practice recommendations[31, 42] and compared against topics relevant to patients suggested by hepatologists (Supplementary Figure-1A). Descriptive statistics were used to interpret the data using frequencies, ranges, means, and standard deviations. Chi-square, t-tests, and ANOVA were used with significance set to 0.5. Pearson correlations assessed the relationship between continuous measures.

Results

Of 4,351 webpages, 212 fulfilled eligibility criteria and were part of 123 websites from 11 countries: United States 142 (67.0%), Canada 24 (11.3%), United Kingdom 21 (9.9%), New Zealand 12 (5.7%), Australia 5 (2.4%), India 3 (1.4%), with one webpage (0.5%) retrieved for each of Austria, Finland, Kuwait, Nigeria, and Slovenia (Supplementary Figure-1B). Copyright dates were available for 166 (61.7%) webpages of which 139 (65.0%) were current in August 2021. The mean copyright duration was 7.9 years (SD 8.9, range: 1-23.5). Dates indicating content currency were available for 157 (74.1%) webpages and the time since last review was 1.8 years (SD 2.1).

Webpages sponsored by businesses were the most common (44.3%) while webpages from the United States dominated the business (78.1%) and health system (89.6%) categories. Only 2 (0.01%) webpages offered podcasts, 22 (10.4%) included videos, and 104 (49.1%) had images. The top five topics were covered by 71.2% of the webpages: esophageal varices (18.4%), hepatocellular carcinoma (17.4%), TIPS (14.2%), paracentesis (11.8%), and edema (9.4%). Twelve (5.7%) webpages presented complimentary and alternative medicines. Business webpages had a significantly higher number of advertisements than government pages (*p*<.001).

While readability was moderately high (range: grades 10-14), content reliability was low with minimal variation across the organization categories. Although only 61 (28.8%) of webpages had an HONcode logo, significant differences (*p*<.05) were found between government (7.4%) and health system (12.2%) webpages versus businesses (43.8%). WAVE analysis showed prevalent errors (mean: 9.7 per webpage, range: 0-96) and a significant difference was found between organization types (Welch's ANOVA, *p*<.001). When comparing 144 cirrhosis-specialized webpages to 68 non-specialized webpages specialized webpages had higher reliability scores. (WRRT: 21.2 vs 12.2, *p*<.001; QRRT: 17.1 vs 11.2, *p*<.001).

The 18 webpages on hepatic encephalopathy covered a mean of 12.2/20 (61.1%) patient-oriented topics. Symptoms (100%) and diagnoses (89%) were the most common while medication effectiveness (17%) and dietary recommendations (6%) were uncommon. Seventeen (94%) webpages described symptoms with an emphasis on variety. Two (11.1%) webpages described the roles of caregivers in the early detection of symptoms or nutrition in prevention and treatment. The symptoms for hepatic encephalopathy Types A, B, and C were merged in 5 (27.8%) webpages. Despite the common side effects of lactulose, patient self-titration, and known issues regarding medication adherence, these were only briefly mentioned in 5 webpages. Information accuracy was low – 8 (44.4%) webpages recommended decreasing protein intake or avoiding high protein foods. Physical activity was mentioned in only 2 (11.1%) webpages. Expert information and phrases were common (e.g., West Haven criteria and 'excessive nitrogen load'). Rather than supporting alcohol abstinence, 4 webpages suggested moderate alcohol consumption or consumption without reaching the point of intoxication.

Discussion

The aim of this critical review was to assess the scope, accessibility, and reliability of online cirrhosis information specific to patients and their informal caregivers. Of the 212 webpages included, the content scope was focused on cirrhosis complications and procedures. Accessibility of the information was limited due to limited use of visual aids[213] and high grade level of reading, well above the recommended grade 7 level[214, 215]. The prevalence of webpage errors, especially on business webpages, further limited content accessibility. The reliability measures, QUEST[153] and WRRT[152], were congruent and highlighted the poor to moderate quality of the content presented. These tools were selected as they were specific for evaluating online material, were evidence-based, and had been validated. The in-depth analysis of the 18 hepatic encephalopathy webpages highlighted the variation in information accuracy and consistency with guidelines.

Study limitations were the focus on English language and restriction of content analysis to hepatic encephalopathy. Ideally all retrieved webpages, in any language, would be critically reviewed for accuracy and patient-perceived relevance to self-management. However, these resource intensive activities were external to the study's primary objective.

Patient education is a necessary element to effective self-management. With low levels of knowledge retention following physician visits[356], online health information can be a resource of considerable value. The large number of educational webpages for cirrhosis (for-profit and not-for-profit) brings to light the motivations for development. It also raises the potential opportunity for a curated repository of relevant, high quality, actionable information that is accessible, freely available, and reliable that brings together medical experts, researchers, and patients. The multimedia website (www.cirrhosiscare.ca, in beta testing) is being evaluated as a potential approach to deliver information to support patient self-management.

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Table 1. Webpage characteristics (means) for presented by type of sponsoring organization.

Characteristic	Total (n=212)	Business (n=96)	Government (n=27)	Health Systems (n=49)	Not for Profits (n=40)
General:					
Multimedia (Y, %)	54 (25.5%)	29 (30.2%)	5 (18.5%)	8 (16.3%)	12 (30.0%)
Advertisements (Y, %)	90 (42.5%)*	66 (68.8%)^{a}	0 (0%)^{b}	14 (28.6%)^{a,b}	10 (25.0%)^{a,b}
Readability (grade levels)					
• FKGL	10.6 SD 2.6	10.8 SD 2.7	10.2 SD 3.1	10.2 SD 2.0	11.2 SD 2.8
• FOG	13.1 SD 2.7	13.1 SD 2.7	12.6 SD 3.3	12.6 SD 2.2	13.9 SD 2.7
• SMOG	9.8 SD 1.9	9.9 SD 1.9	9.3 SD 2.2	9.5 SD 1.5	10.2 SD 1.8
• CLI	11.4 SD 2.0*	11.7 SD 2.3^{a}	10.5 SD 1.9^{b}	11.3 SD 1.5^{a,b}	11.5 SD 1.7^{a,b}
Reliability:					
• WRRT	18.3 SD 11.9	17.8 SD 12.1	17.9 SD 8.6	17.4 SD 12.2	21.2 SD 13.0
• QUEST	15.2 SD 5.6	15.0 SD 5.8	16.6 SD 5.0	13.9 SD 5.7	16.5 SD 4.9
HONcode (Y, %)	61 (28.8%)*	42 (43.8%)^{a}	2 (7.4%)^{b}	6 (12.2%)^{b}	11 (27.5%)^{a,b}
WAVE Errors	9.7 SD 11.1*	12.1 SD 10.8^{a}	3.2 SD 4.0^{b}	10.6 SD 14.9^{a,c}	7.0 SD 6.52^{c}

* p<.05 between group differences

^{a,b,c} Different superscripted letters are used to indicate significant pairwise differences (*p*<.05)

Abbreviations: FKGL, Flesch-Kincaid Grade Level; FOG, Gunning Fog Index; SMOG, Simple Measure of Gobbledygook; CLI, Coleman-Liau Index; WRRT, Web Resource Rating Tool (WRRT)[152]; QUEST, QUality Evaluation Scoring Tool[153]; HONcode, certification from The Health On the Net Foundation; and WAVE, web accessibility evaluation tool.