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REVIEW

Current Situation and Prospects of Digital Therapeutics in the Field of Liver Diseases in China

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ABSTRACT

Digital therapeutics have developed rapidly in recent years, providing a new method for disease management. The burden of liver diseases in China is heavy, and there are obvious problems in disease management. This paper expounds on the definition and classification of digital therapeutics, introduces their application in liver disease treatment and management in detail, and analyzes their development prospects in the field of liver diseases and future challenges. Graphical abstract available for this article.

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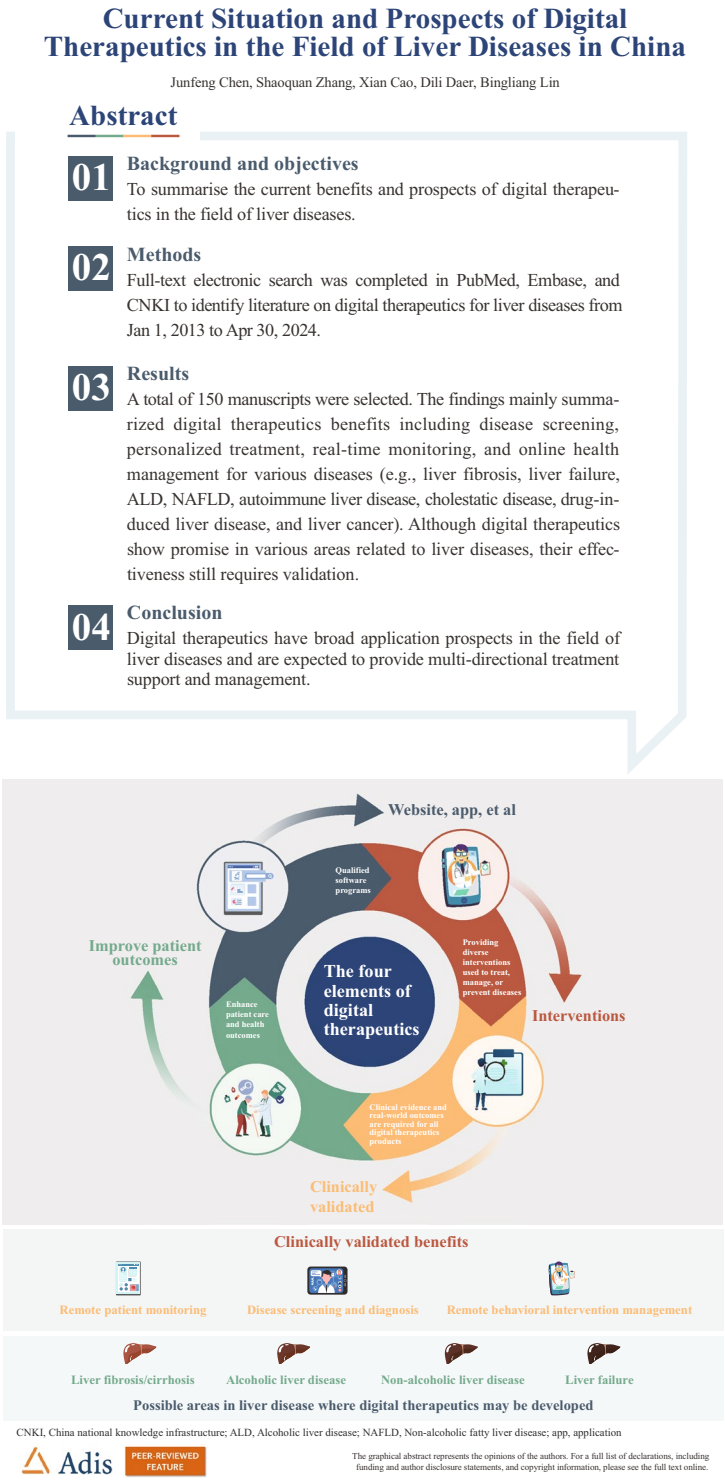
Graphical Abstract:



Keywords: Digital therapeutics; Liver diseases; Therapeutics; Disease management

Key Summary Points

Why carry out this study?

Patients experience a substantial burden from liver diseases, and it is clear that the conventional management of these health issues in China faces notable challenges. Digital therapeutics may be a novel approach to address these issues.

Digital therapeutics integrate disease data analysis, multi-omic data, and computational models to assist healthcare professionals in remotely tracking patients' health. They can also be paired with pharmaceuticals to enhance treatment outcomes, decrease medical expenses, and more effectively manage illnesses.

What was learned from the study?

Digital therapeutics mark a new era for individuals suffering from liver diseases. Their effectiveness has been confirmed across various stages, including liver disease detection, preliminary identification, ongoing care for chronic liver conditions, and post-transplant recovery. These therapies offer numerous benefits such as prompt and effective care, artificial intelligence (AI)-based forecasting, a variety of intervention strategies, easy access, and enhanced patient adherence.

Digital therapeutics are anticipated to enhance the processes of disease detection, tailored therapies, immediate health tracking, and virtual health management for a variety of liver conditions. Nevertheless, digital therapeutics encounter several obstacles, including concerns over data protection, adherence to technical specifications, validation of efficacy, distribution methods, regulatory backing, differences among various countries or regions around the globe, and acceptance by both medical professionals and patients.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.27969387.

INTRODUCTION

With the rapid advances in disease prevention, diagnosis, and treatment, the incidence of viral hepatitis is decreasing worldwide. However, the improvement in living standards has also led to a significant increase in the prevalence of various metabolic liver diseases. China has a higher prevalence and heavier burden of liver diseases worldwide, which leads to an enormous unmet clinical need for more effective methods for their prevention, treatment, and management [1]. In recent years, with the emergence of information technology, smartphones, and wearable devices, the development of digital health has made rapid progress, and given rise to a new field digital therapeutics, which has revolutionized medical models [2]. Digital therapeutics combine disease data and algorithms to help healthcare providers remotely monitor patients' conditions and can be combined with medications to improve treatment efficacy, reduce treatment costs, and better manage diseases [3].

At present, digital therapeutics have been tested and applied in many ways in the field of liver disease research, such as disease education [4], prevention [5], screening and diagnosis [6], intervention and management, and prognosis assessment [7, 8]. Several studies have shown that this approach can improve patients' disease [4], provide early warning of worsening patient conditions [7], and reduce the number of readmissions [5]. This review aims to describe the current burden of liver diseases in China, review the application of digital therapeutics in clinical practice for liver diseases, and explore the development prospects of digital therapeutics in the field of liver diseases.

METHODS

From January 1, 2013 to April 30, 2024, a comprehensive search was conducted in PubMed, Embase, and CNKI databases for controlled or observational studies in any language. The search keywords used Medical Subject Headings and related entry terms, including terms related to "digital therapy", "digital therapeutics", "mobile application", "app", "telehealth", "machine learning", and "liver", "cirrhosis", "liver failure", "NAFLD". A secondary search of the literature was conducted to include related literature cited in the manuscripts included in our primary search. A total of 150 manuscripts were selected.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CURRENT BURDEN OF LIVER DISEASE AND THE NEED FOR DISEASE MANAGEMENT IN CHINA

Liver diseases cause approximately two million deaths annually worldwide, accounting for 4% of all deaths [9]. Mortality in patients with liver diseases is mainly attributed to complications of cirrhosis and hepatocellular carcinoma. It is estimated that more than one-fifth of the Chinese population is affected by various types of liver diseases, mainly hepatitis B virus (HBV) and hepatitis C virus (HCV) infections; cirrhosis; liver cancer; non-alcoholic fatty liver disease (NAFLD); alcoholic liver disease (ALD); and drug-induced liver injury (DILI) [1].

Viral hepatitis, such as chronic hepatitis B (CHB) and chronic hepatitis C (CHC), has been a major health problem in China for many years. Owing to various efforts, the incidence of HBV-related diseases decreased by approximately 2.3% annually from 1990 to 2019, and the incidence of HCV-related diseases has decreased by about 1.8% annually [10]. However, the prevalence of hepatitis B surface antigen was still 6.1% in the general population in China in 2016 with 86 million cases of chronic HBV infection and approximately 10 million cases of chronic HCV infection [11]. If viral hepatitis is not treated in time or antiviral treatment is not appropriate, liver fibrosis, cirrhosis, and even liver cancer may develop, resulting in a very poor survival prognosis.

In addition, the burden of NAFLD in China has increased significantly with lifestyle changes. At the beginning of the twenty-first century, the prevalence of NAFLD in China was 23.8%; however, the prevalence reached 32.9% in 2018. By 2016, the number of patients with NAFLD requiring hospitalization exceeded that of patients with chronic viral hepatitis. In recent years, NAFLD has become one of the key topics of study for Chinese investigators. The burden of ALD is also alarming, with at least 62 million people currently affected [12].

There are seven million patients with liver cirrhosis in China, and the disease burden is high [1]. If the causes of chronic liver injury (such as hepatitis virus infection, fatty infiltration of the liver, and heavy alcohol consumption) are not relieved, repeated hepatocyte damage, repair, and fibrous scar tissue formation may lead to the gradual formation of liver fibrosis and cirrhosis [13]. If the disease develops further, cirrhosis may progress from a compensated stage to a decompensated stage (approximately 5–7% of patients in the compensated stage progress to the decompensated stage each year). The prognosis of patients with decompensated cirrhosis is poor, and the median overall survival decreases from > 12 years in compensated cirrhosis to 2 years in decompensated cirrhosis. Only a few patients with decompensated liver cirrhosis can be treated with drug therapy; liver transplantation should be considered for the remaining patients if related complications can be well controlled [13].

The management of liver diseases requires a balance of prevention, treatment, and self-management. Because most patients lack the necessary medical and health knowledge, they need to receive health guidance on disinfection and isolation methods, disease causes, drug effects and precautions, disease prognosis, and many other aspects [14]. Traditional intervention relies on hospital follow-up, but patient adherence and compliance are poor. With the support of internet

technology, digital therapeutics are expected to overcome these drawbacks.

APPLICATION OF DIGITAL THERAPEUTICS IN THE MANAGEMENT OF LIVER DISEASES

Definition and Main Categories of Digital Therapeutics

Digital therapeutics began to emerge nearly a decade ago. In 2017, the Digital Therapeutics Alliance (DTA) was founded, which clearly defined digital therapeutics as evidence-based, clinically validated software for the treatment, management, and prevention of diseases. Since then, relevant guidelines have been issued and green channels have been established nationally and internationally, accelerating the approval and marketing of digital therapeutic products.

Digital therapeutics can be used alone or in combination with medications, medical devices, or other therapies, providing comprehensive interventions through information (such as text, pictures, and videos on apps (applications)), physical factors (such as sound, light, electrical current, magnetic fields, and their combinations), and drugs to optimize patient care and health outcomes.

Digital therapeutic products can be divided into three categories according to their functions: prevention, treatment, and management. Preventive products, mainly aimed at people who do not develop diseases but belong to high-risk groups, can effectively prevent the occurrence of diseases by providing detection and preventive methods. Management and treatment products are mainly aimed at patients with confirmed disease, and management products can guide patients to achieve self-management to control their disease and reduce complications.

Application of Digital Therapeutics in the Treatment and Management of Liver Diseases

With the continuous progress of technology, digital therapeutics are being increasingly used in the field of liver diseases. The application of digital therapeutics in the field of liver diseases mainly includes screening, early diagnosis, management of chronic liver disease, and rehabilitation after liver transplantation. After completing the search, we manually reviewed all articles to identify studies that did not meet the inclusion criteria. The diseases covered with a higher proportion were hepatitis, cancer, cirrhosis, and NAFLD (Fig. 1).

Through online questionnaires, mobile apps, and the application of smart hardware, digital

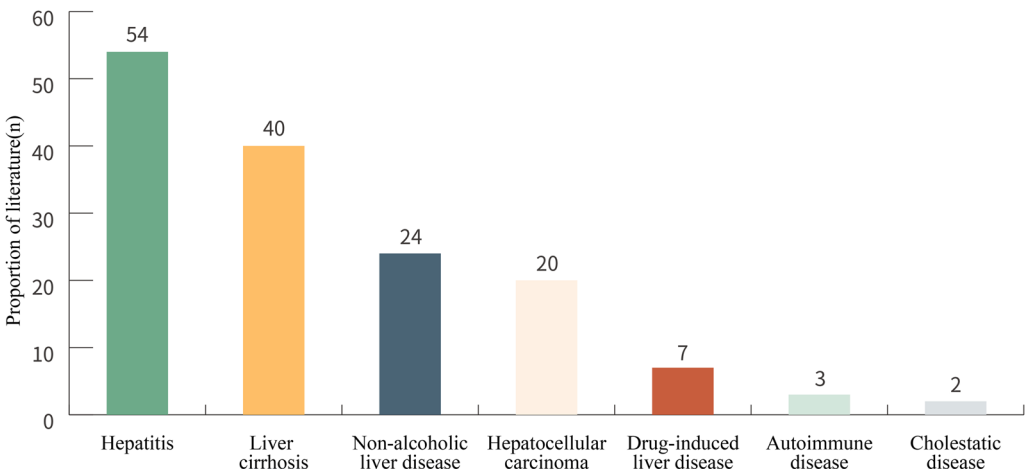


Fig. 1 Proportion of literature on the application of digital therapeutics in liver diseases

therapeutics can collect patient information and relevant data to help doctors understand patients' conditions and risk factors promptly, in time to detect liver diseases earlier and take corresponding intervention measures. Digital therapeutics have great potential in the early diagnosis of diseases such as hepatic encephalopathy and NAFLD and can assist doctors in quickly and accurately determining whether a patient has developed or is at high risk of disease through image recognition and deep learning technology. Digital therapeutics also play an important role in the management of chronic liver diseases; for patients with chronic liver diseases, long-term treatment and management are essential. Digital therapeutics, which allow easy access for patients, help doctors understand patients' conditions and treatment efficacy in real time by monitoring their lifestyles, physical signs, and drug usage data, and providing personalized rehabilitation advice and medication guidance to improve quality of life and efficacy. Digital therapeutics also play an active role in rehabilitation/disease monitoring after liver transplantation. Liver transplantation is an effective treatment for end-stage liver diseases such as liver failure and hepatocellular carcinoma, but the postoperative rehabilitation process is long and complex. With digital therapeutics, doctors can monitor patients' postoperative recovery at any time, including their liver function, immune status, and mental health, and adjust patients' rehabilitation plans as well as drug treatment regimens in time to promote rehabilitation.

Digital Therapeutics for Disease Screening and Diagnosis

Digital therapeutics play an important role in screening for NAFLD and the early diagnosis of hepatic encephalopathy.

Sorino et al. [15] utilized a web application powered by a neural network (NN) to assess the presence of 100 patients with NAFLD by analyzing height, weight, blood indicators, and other data, and found that its prediction results reached 77% accuracy compared with those of liver ultrasound. The NN-based web app is easy to apply, and the required parameters are easily found in healthcare databases.

Encephal, a smartphone app, has good reliability and sensitivity for the diagnosis of occult hepatic encephalopathy in patients with cirrhosis. The University of Virginia in the USA, Ningxia People's Hospital in China, and a private hospital in Curitiba in Brazil used the app for patients with cirrhosis (167, 58, and 99 patients with cirrhosis, respectively), and the test results were significantly consistent with the Psychometric Hepatic Encephalopathy Score (PHES, which is considered the gold standard for the diagnosis of hepatic encephalopathy). Furthermore, the app demonstrates exceptional accessibility, convenience, and user acceptability [6, 16, 17] (Table 1).

Digital Therapeutics for Remote Prevention Monitoring

Digital therapeutics can be used for remote home monitoring and education for patients with liver cirrhosis and liver transplantation to improve patient compliance and reduce readmission rates.

Ganapathy et al. [5] educated patients with cirrhosis and their caregivers on medication adherence, sodium intake, weight management, and disease symptoms through the smartphone Patient Buddy app. Patient data were monitored daily by the clinical team, and adherence and critical value alerts were automatically sent between patients/caregivers and the clinical teams through the app. According to the 30-day follow-up data after discharge, 17 of the 40 patients were readmitted, but none of them were hospitalized for non-hepatic encephalopathy. Most respondents rated the app favorably for its educational value.

In the UK, Kazankov et al. [18] used CirrhoCare® to follow up on 20 patients with cirrhosis, record data on vital signs, cognitive function, self-reported diet, and alcohol consumption, and provide two-way doctor–patient communication. The study revealed that the readmission and length of hospital stay were reduced in patients who received follow-up through CirrhoCare®. According to the free-text

Table 1 Studies on the treatment and management of liver diseases using digital therapeutics

	Name of app	Study design	Study population	Intervention or treatment	Control condition	Follow-up duration	Key conclusions
Digital therapeutics for disease screening and diagnosis							
Sorino et al. [15]	N/A	Randomized controlled trial	100 patients with NAFLD	NN-based app that could be used to predict NAFLD particularly its absence	Liver ultrasound	N/A	The NN-based app can be used to support NAFLD diagnosis, reducing healthcare costs and being easy to apply
Machado Júnior et al. [6]	Stroop EncephalApp	Cross-sectional study	99 patients with liver cirrhosis	Stroop EncephalApp test to detect CHE	PHES	N/A	Stroop App can be a useful tool with good sensitivity for screening CHE in the analyzed sample
Bajaj et al. [16]	EncephalApp (streamlined version of Stroop app)	Cross-sectional study	167 patients with cirrhosis and 114 controls	EncephalApp test to detect CHE	Paper and pencil cognitive battery	1–3 months	EncephalApp had good face validity, test–retest reliability, and external validity for the diagnosis of CHE
Zeng et al. [17]	EncephalApp	Multicenter, single-visit study	144 patients with cirrhosis	EncephalApp test to detect CHE	PHES	N/A	The EncephalApp Stroop Test can be an efficient screening tool for CHE in Chinese cirrhotic patients

Table 1 continued

	Name of app	Study design	Study population	Intervention or treatment	Control condition	Follow-up duration	Key conclusions
Digital therapeutics for remote prevention monitoring							
Ganapathy et al. [5]	Patient Buddy	Proof-of-concept study	40 patients with cirrhosis	Monitored patient data daily through a Patient Buddy loaded iPad, adherence and critical value alerts were automatically sent between patients/ caregivers and the clinical teams through the app	N/A	1 month	Patient Buddy was feasible in recently discharged patients with cirrhosis and their caregivers
Kazankov et al. [18]	CirrhoCare®	Randomized controlled trial	20 patients with cirrhosis	APP for daily patient data input and communication to hepatologist	Standard follow-up	A mean of 10 weeks	CirrhoCare® is feasible for community management of individuals with decompensated cirrhosis with good engagement and clinically relevant alerts to new decompensating events

Table 1 continued

	Name of app	Study design	Study population	Intervention or treatment	Control condition	Follow-up duration	Key conclusions
Ertel et al. [19]	N/A	Observational study	20 consecutive LT recipients	Telehealth home monitoring and an educational video program during the perioperative period	N/A	N/A	Telehealth home monitoring and video-based educational programs were feasible in LT recipients and seemed to be effective in enhancing the monitoring of vital statistics postoperatively
Lee et al. [20]	N/A	Randomized controlled trial	106 consecutive LT recipients	Telemedicine-based home management program included an electronic tablet and Bluetooth devices to support daily text messages, education videos, and video FaceTime capability	Standard care	90 days	The magnitude of effect on LT outcomes, hospital readmissions, and QOL suggested that the adoption of telemedicine has great potential for operations

Table 1 continued

	Name of app	Study design	Study population	Intervention or treatment	Control condition	Follow-up duration	Key conclusions
Rodrigues et al. [21]	N/A	Prospective cohort study	71 patients referred to a Victorian regional hospital's hepatitis C virus telehealth clinic	Clinical nurse consultant-led hepatitis C virus management via telehealth	N/A	N/A	Clinical nurse consultant-led hepatitis C virus management via telehealth allowed access to marginalized regional populations and achieved additional cost–benefit, efficiency gains and carbon footprint reduction
Digital therapeutics for remote behavioral intervention management							
Duarte-Rojo et al. [23]	Exercise and Liver FITness	Feasibility study	31 liver transplant candidates with cirrhosis	Exercise and Liver FITness app plus personal activity tracker and 15/30-min weekly calls with a physical activity coach	N/A	14 weeks	Exercise and Liver FITness app meaningfully improved physical fitness and met feasibility/adherence goals In-training daily step increase supported physical self-efficacy and intervention uptake

Table 1 continued

	Name of app	Study design	Study population	Intervention or treatment	Control condition	Follow-up duration	Key conclusions
Lim et al. [24]	Nutritionist Buddy (nBuddy)	Randomized controlled trial	108 patients with NAFLD	nBuddy mobile app for receiving dietary and lifestyle advice by a dietitian and measured body weight, ALT, AST, waist circumference, and blood pressure	Standard care	6 months	Lifestyle intervention enabled by a mobile app can be effective in improving anthropometric indices and liver enzymes in patients with NAFLD
Bloom et al. [25]	PGHD*Connect*	Feasibility study	25 patients with cirrhotic ascites	Bluetooth-connected scale, which transmitted weight data to PGHD*Connect* app and then via the internet to an electronic medical record and contact patients if the change was greater than 5 lb	N/A	4 weeks	The feasibility of a smartphone app to facilitate the management of ascites and reported excellent rates of patient and provider engagement

Table 1 continued

	Name of app	Study design	Study population	Intervention or treatment	Control condition	Follow-up duration	Key conclusions
Tincopa et al. [26]	FitBit	Feasibility study	40 patients with NAFLD	A Fitbit Zip to track step counts and provided personalized feedback on physical activity with tailored step count goals and motivational messages via email	N/A	6 months	A 6-month mobile-technology based pilot lifestyle intervention was feasible and acceptable to patients with NAFLD, promoting physical activity and clinical parameters in some patients
Zaharia et al. [29]	N/A	Feasibility study	24 patients with type 2 diabetes	A regular "whole food-based" low-calorie diet combined with app-based digital education and behavioral change program with weekly coaching calls	N/A	12 weeks	Novel approach combining digital education with a low-calorie diet resulted in effective improvements of NAFLD

Table 1 continued

	Name of app	Study design	Study population	Intervention or treatment	Control condition	Follow-up duration	Key conclusions
Mehta et al. [30]	AlcoChange	Feasibility study	65 patients with ARLD	AlcoChang associated breathalyzer provides a series of behavior change interventions to increase the likelihood of engaging in health-promoting and alcohol-reducing behaviors	N/A	12 months	Use of the novel digital therapeutic, AlcoChange, was associated with a significant reduction in alcohol use and an increase in the proportion of patients with ARLD attaining abstinence
Freer et al. [31]	Pro-Ex	Randomized controlled feasibility trial	28 patients with NAFLD	Home muscle strengthening program with increased protein intake from predominately plant-based sources and behavioral change support	Standard care	12 weeks	In patients with NAFLD a telehealth home exercise and dietary intervention was safe and improved habitual plant and animal protein intake

NN neural network, *NAFLD* non-alcoholic fatty liver disease, *CHE* covert hepatic encephalopathy, *PHES* psychometric hepatic encephalopathy score, *LT* liver transplantation, *QOL* quality of life, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ARLD* alcohol-related liver disease

feedback left by studied individuals, they found the equipment and the app easy to use.

In an observational study, Ertel et al. demonstrated that remote home monitoring and video education in the perioperative management of 20 liver transplant recipients can effectively improve their understanding of postoperative management and achieve the purpose of strengthening postoperative vital sign monitoring [19]. A randomized controlled trial was conducted to compare patient management with a remote intervention versus standard of care (no remote intervention) for liver transplant recipients. During the study, 106 patients were randomized (1:1) to one of two posttransplant care strategies: standard of care or telemedicine-based home management program. Patients in the remote intervention group received daily text messages and video education and had FaceTime sessions with the care team via tablets and Bluetooth devices easily. The study results showed that patients in the remote intervention group had a higher participation rate and greater adherence to vital sign monitoring (86%), a significantly lower 90-day readmission rate (28% vs. 58%, $P=0.004$), and improved quality of life [20].

Rodrigues et al. conducted a telehealth follow-up study involving 55 patients with hepatitis C in Australia, with 44 patients (80%) participating in at least one appointment. Out of 24 eligible patients, 21 (88%) received direct-acting antiviral therapy, and 14 out of 21 patients (67%) successfully completed treatment. Each patient saves an average of 46.5 km, 54.6 min, and 0.70 Australian dollars per visit. The study found that telehealth follow-up increased patients' medical participation, enabling them to complete HCV treatment and liver cirrhosis monitoring with additional cost–benefit and efficiency gains [21] (Table 1).

Digital Therapeutics for Remote Behavioral Intervention Management

Sending educational advice to patients with NAFLD and liver transplantation after cirrhosis through digital therapeutic programs or online platforms can improve the clinical performance and compliance of patients to some extent [22, 23].

After 14 weeks of an exercise intervention with the Exercise and Liver FITness (EL-FIT) app, Duarte-Rojo et al. ($N=31$) reported that patients' liver failure index improved from 3.84 ± 0.71 to 3.47 ± 0.90, 6-min walk test score increased from 318 ± 73 to 358 ± 64 m, and they achieved 57% adherence [23].

In the study by Lim et al., 108 patients with NAFLD who used the nBuddy app, which is available commercially in app stores with basic features accessible for free, to track their diet and physical activity and induce behavioral changes in addition to getting easy access to diet and lifestyle advice from a nutritionist were five times more likely to lose ≥ 5% of their body weight at 6 months than were patients who only received diet and lifestyle advice from a nutritionist [24]. In addition, the reductions in body weight, waist circumference, systolic blood pressure, diastolic blood pressure, and alanine transaminase (ALT) and aspartate transaminase (AST) levels at 6 months were greater in the nBuddy intervention group. Bloom et al. attempted to use the PGHD*Connect* program to record weight changes and contact patients if the change was greater than 5 lb ($N=25$). Bloom et al. found that only 24% of readmissions during the study were related to ascites, the participation rate was very good, and hepatology providers in the study generally found the program easy and helpful [25].

In the study by Tincopa et al. [26], investigators asked 40 patients with NAFLD to wear a Fitbit tracker to record their steps and upload data to an app, after which they received personalized guidance and motivational information online for 6 months; 59% of patients reported that Fitbit was easy to use and 66% felt step count feedback motivated them to increase their activity. Approximately 50% of the patients had a reduction in body weight, triglyceride levels, and other indicators, and 75% of patients experienced an improvement in motor function. Other studies have shown that digital interventions such as short online videos, WeChat programs, and apps can effectively improve the health of patients with type II diabetes easily [27–29]. Zaharia et al. reported that 30% of patients with NAFLD ($N=24$) had liver fat regression in a 12-week study, and these

digital therapeutic strategies can be used to treat patients with NAFLD and diabetes [29].

AlcoChange was applied to patients with alcohol-related liver disease at London Royal Free Hospital. Among the 65 recruited patients, 41 used AlcoChange as per the protocol requirements for 3 months (logging in more than 60 times within 3 months). The alcohol consumption of these patients significantly decreased, with the proportion of abstainers reaching 57.1% at the end of the third month of the study, much higher than the 22.2% in the other group. Meanwhile, the risk of readmission within 12 months in this group has significantly decreased [30].

Freer et al. randomly assigned 28 adults with NAFLD to either the Pro EX group (weekly 3–4 messages, and encourage plant-based protein intake) or the routine care group. After 12 weeks of follow-up, it was found that compared with the conventional care group, the Pro EX group had a 2.7 increase in 30-s sit-to-stand tests, a 46-min increase in moderate-to-vigorous physical activity, a weight loss of 1.7 kg, and an increase in protein intake of 35.2 g. Researchers believe that remote intervention in patients with NAFLD is safe and improves their exercise and dietary habits [31] (Table 1).

DEVELOPMENTS AND CHALLENGES IN THE APPLICATION OF DIGITAL THERAPEUTICS IN LIVER DISEASES

There have been some studies on the use of digital therapeutics in remote monitoring and disease screening for patients with liver cirrhosis and remote behavioral interventions for patients with NAFLD [5, 18, 24–29, 31]. It is also worth attempting to apply digital therapeutics in the analysis of risk behavior patterns of patients with liver diseases and patient self-management.

The Future of Digital Therapeutics in the Field of Liver Diseases

At present, digital therapeutics have already demonstrated unique advantages in disease education [4], prevention [5], screening and diagnosis [6], intervention and management [7], prognosis assessment [8], and many other aspects, such as timely and efficient treatment, artificial intelligence (AI) prediction, diversified intervention pathways and methods, easy access and high patient compliance. According to the above characteristics, with the progress of science and technology and the digital transformation of the medical industry, digital therapeutics have broad application prospects in the field of liver diseases and are expected to provide multidirectional treatment support and management.

Digital therapeutics have great potential for treating liver fibrosis and cirrhosis and can achieve accurate assessment and prediction of patient conditions by monitoring data from multiple dimensions, such as liver function indicators, histological examination data, and gene expression data. On the basis of these data, digital therapeutics can be used to develop personalized treatment regimens to improve the progression of liver fibrosis. Furthermore, bioinformatics studies have indicated that liver cirrhosis serves as a critical connection between autoimmune liver diseases and hepatocellular carcinoma, investigated fluctuations in transcription factor activities across the advancing phases of these conditions, and identified prognostic shared transcriptional patterns linked to these pathologies [32, 33].

Digital therapeutics also play an important role in the field of liver failure. By monitoring patients' physiological indicators, blood metabolites, and other data, digital therapeutics can predict or detect the risk of liver failure in a timely manner and provide management options. In addition, AI technology can also be applied to simulate and predict liver function to assist doctors in formulating more accurate treatment plans and improving the survival rate and quality of life of patients with liver failure. In terms of ALD, digital therapeutics can evaluate

the efficacy and relapse risk of patients in real time by remotely monitoring patients' alcohol intake, liver function indicators, psychological status, and other data. Niu et al. introduced a comparative liver–plasma proteomic study ($N = 596$) to examine alterations in the liver and plasma proteomes correlated with hepatic pathophysiology, and to detect circulating proteins that hold diagnostic potential for identifying liver fibrosis, inflammatory activity, and steatosis [34]. Moreover, digital therapeutics can also combine technologies such as virtual reality (VR) and cognitive behavioral therapy to reduce alcohol dependence and provide behavioral intervention and psychological support to promote recovery.

Digital therapeutics also offer new opportunities for NAFLD treatment. Digital therapeutics can predict the possibility of NAFLD development by monitoring patients' body weight, blood pressure, blood glucose, and other living habits and physiological indicators and developing personalized dietary intervention and exercise programs for high-risk patients or patients with existing diseases to promote weight loss and improve metabolic status, thereby reducing the risk of disease progression. In addition, digital therapeutics have potential effectiveness for other liver diseases, such as autoimmune liver disease, cholestatic disease, drug-induced liver disease, and liver cancer; furthermore, treatment plans can be adjusted in a timely manner to achieve individualized treatment by monitoring patients' immunological indicators, tumor biomarkers, and drug metabolism. Generating an in-depth proteo-transcriptomic profile of steatohepatitis and fibrosis throughout the progression of NAFLD may be a good way to explore the physiological mechanisms behind NAFLD in humans and determine the potential hepatic origin of prospective biomarkers found in the bloodstream [35, 36]. Moreover, digital therapeutics can also assist doctors in developing more accurate treatment plans through gene sequence analysis and tumor histological characteristics assessment.

Challenges of Digital Therapeutics

In addition to their development prospects, digital therapeutics still face some challenges in the field of liver disease, mainly in the following aspects:

1. Data security and privacy protection: digital therapeutics involve a large amount of sensitive information, including personal health information, activity trajectories, genetic data, etc. Therefore, data security and privacy protection should be secured when digital therapeutics are widely applied. It will be necessary to adopt effective data encryption and authority management mechanisms and perfect laws, regulations, and privacy policies to ensure patient data security.
2. Technical standards: digital therapeutics involve multiple technical fields, such as AI, big data analysis, and sensor technology. At present, however, there is no perfect technical standard for digital therapeutics, which makes it difficult to achieve interconnectivity between different digital therapeutic products.
3. Effectiveness verification: compared with the strict clinical trial standards for drugs and medical devices, there is still some room for improvement in the corresponding standards for digital therapeutics.
4. Channels of disbursement and policy support: at present, the coverage and payment standards of medical insurance payment for digital therapeutics are unclear. In addition, with the emergence of therapeutic methods, governments and insurance institutions need to formulate relevant policies to encourage and provide corresponding support for the development of digital therapeutics.
5. Doctor-patient acceptance and education and training: digital therapeutics are an emerging medical model, and there are differences in the understanding and acceptance of digital therapeutics between doctors and patients. On the one hand, doctors need to receive relevant training and education

to understand the principles, application scenarios, and operation methods of digital therapeutics. On the other hand, it is also necessary to enhance basic education, health education, and internet use education for patients to improve their understanding and awareness of digital therapeutics [37–39].

6. Differences among various countries or regions around the globe: considering the limitations of different cultures, healthcare systems, and technical support, the application of digital therapeutics in liver diseases requires a holistic and context-specific approach. As multiple digital platforms for record keeping are employed across the globe, there is potential for inconsistencies to gradually arise, which could be a significant limitation of digital therapeutics deserving of discussion.

Digital therapeutics have broad development prospects in the field of liver diseases. Disease screening, personalized treatment, real-time monitoring, and online health management for many diseases, including liver fibrosis, liver failure, ALD, NAFLD, autoimmune liver disease, cholestatic disease, drug-induced liver disease, and liver cancer, are expected to be achieved in many fields. However, digital therapeutics still face some challenges in terms of data security, technical standards, effectiveness verification, channels of disbursement, policy support, and doctor-patient acceptance. Only by overcoming these challenges and establishing a complete system around digital therapeutics can we better promote the application and development of digital therapeutics and provide better medical services to patients with liver diseases.

DISCUSSION AND CONCLUSIONS

Although viral hepatitis can be effectively prevented and treated, China is still experiencing large numbers of patients with liver diseases, and with changes in lifestyle and diet, the disease burden of metabolic liver disease is gradually increasing. Efficient treatment and management methods that can relieve pressure on the medical system and improve the participation and compliance of patients with liver diseases are urgently needed. Digital therapeutics represent a significant advancement for patients with liver diseases. The efficacy of these emerging therapies has been verified in liver disease screening, early diagnosis, chronic liver disease management, and rehabilitation after liver transplantation, and they have many advantages, such as timely and efficient treatment, AI prediction, intervention pathways and method diversification, and high patient compliance. On the basis of these advantages, digital therapeutics are expected to improve disease screening, personalized treatment, real-time monitoring, and online health management for many liver diseases, such as liver fibrosis, liver failure, ALD, NAFLD, autoimmune liver disease, cholestatic disease, drug-induced liver disease, and liver cancer.

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Declarations

Conflict of Interest. Bingliang Lin, Junfeng Chen, and Shaoquan Zhang have no conflict of interest to disclose. Xian Cao and Dili Daer are the employees of Takeda (China) Holdings Co., Ltd.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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