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Review Article

Physical activity and exercise in liver cancer[☆]

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ABSTRACT

Sarcopenia and physical deconditioning are common complications in patients with liver cancer, which are frequently caused by insufficient physical activity and poor nutritional status, resulting in physical frailty and a significant impact on the patient's physical fitness. Notably, sarcopenia, frailty, and poor cardiopulmonary endurance have all been linked to higher mortality rates among patients with liver cancer. Exercise intervention significantly improves various health parameters in liver cancer patients, including metabolic syndrome, muscle wasting, cardiorespiratory endurance, health-related quality of life, and reduction in hepatic venous pressure gradient. However, the link between physical exercise and liver cancer is commonly overlooked. In this article, we will examine the impact of exercise on liver cancer and present the most recent evidence on the best types of exercise for various stages of liver cancer. This article also summarizes and discusses the molecular mechanisms that control metabolism and systemic immune function in tumors. In brief, physical exercise should be considered an important intervention in the prevention and treatment of liver cancer and its complications.

1. Introduction

Primary liver cancer is the sixth most common cancer and the third leading cause of cancer death globally.[1] Hepatocellular carcinoma (HCC) is the most common type. In 2020, China accounted for 45.3% of global HCC cases, resulting in an increased economic burden.[2,3] According to global statistics in 2020 approximately 56% of HCC is caused by the hepatitis B virus and 20% by the hepatitis C virus.[4,5] Non-alcoholic fatty liver disease is the most common emerging cause of HCC in developed countries.[6] Advances in the diagnosis and treatment of liver cancer have significantly improved the survival rates.[7–12] However, most patients are diagnosed in the middle to late stages, and even with curative treatment, the 5-year recurrence rate can reach 70%.[13] Cancer and its treatment can present significant physiological and psychological challenges, greatly affecting the patient's quality of life (QoL).

Currently, studies have demonstrated the safety and usefulness of incorporating physical activity (PA) into cancer treatments.[14–16] Since PA and exercise have been shown to have numerous health benefits. PA refers to all movements involving skeletal muscles that use energy, whereas exercise is a subset of PA that includes structured, planned, and repetitive activities.[17] For liver cancer patients, the goal of PA intervention is to increase muscle mass and functionality, prevent further skeletal muscle deterioration, improve cardiovascular fitness, and help patients maintain their independence in daily activities. Furthermore, exercise is linked to better clinical outcomes.[18–20]

Despite these benefits, patients with liver cancer have lower overall levels of PA than individuals with other chronic diseases or types of cancer. The reasons for this phenomenon are manifold and intricate. It primarily affects those in the decompensated stage, which is characterized by factors such as protein-energy malnutrition, resulting in associated sarcopenia (characterized by low muscle mass, strength, and functionality), physical limitations caused by ascites and lower limb edema, the need for recurrent hospitalizations due to decompensation events, hepatic

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encephalopathy (HE)), and depression, among others. Finally, these factors contribute to the development of frailty, a state characterized by a diminished physiological reserve that is associated with a lower QoL, poor clinical outcomes, increased mortality, and placement on the liver transplant (LT) waiting list, regardless of the model for end-stage liver disease (MELD) score.

In recent years, many studies have been conducted to investigate the feasibility and effectiveness of exercise interventions in the treatment of liver cancer, testing various types of exercise (resistance and/or aerobic), frequency, duration, intensity, and setting. Although exercise benefits patients with liver cancer, the optimal exercise intervention is still unknown, and maximizing adherence to such an intervention remains challenging. This article provides a comprehensive review of previous research on PA and exercise for individuals with liver cancer. It provides an insightful overview of the molecular impact of exercise throughout the cancer journey, including results from human interventions. Its goal is to provide valuable insights to both patients and healthcare providers while also shedding light on potential areas for future research in this field.

2. Safety of PA in liver cancer survivors

According to the guidelines and consensus recommended by the American College of Sports Medicine (ACSM) and the Chinese Anti-Cancer Association (CACA), cancer survivors can safely exercise moderately and avoid inactivity during and after treatment.[15,21] However, research into specific PAs for survivors with liver cancer is limited. Survivors of liver cancer are often diagnosed with cirrhosis, a condition that frequently causes a decline in liver function, as well as the development of varices, ascites, HE, and other complications. These factors restrict a patient's PA and promote sedentary behavior. The phenomenon of exercise-induced hepatic vein pressure gradient elevation has been a subject of particular interest among hepatologists.[22] Previous small-sample studies found that patients' portal pressure increased significantly when they exercised on a cycle ergometry.[23,24] In contrast, two hospital-based and three home-based exercise program studies, focused on patients with decompensated cirrhosis awaiting LT, and no adverse events of variceal bleeding during exercise were reported.[25–29] Furthermore, two studies conducted in South Korea combined mobile health (mHealth) and personalized exercise programs in 37 liver cancer survivors for 12 weeks, resulting in a significant increase in muscle mass with no complications or adverse reactions.[16,17] He *et al*.[30] conducted a 12-week aerobic exercise intervention for patients with HCC undergoing transarterial chemoembolization (TACE). The exercise group consisted of 82 patients who completed the study. The intervention significantly improved pain, fatigue, Pittsburgh Sleep Quality Index scores, and overall QoL compared to the control group ($P < 0.05$). Following further investigation,[31] it was discovered that aerobic exercise improved anxiety and depression symptoms in patients while also increasing serum levels of brain-derived neurotrophic factor, serotonin (5-hydroxytryptamine, 5-HT), and neurotrophin-3 (NT-3). Interestingly, no adverse events were reported during this study. This suggests that liver cancer survivors may safely participate in exercise rehabilitation programs. Patients at high risk can benefit from primary and secondary prevention before exercise, and PA interventions can be tailored accordingly.[22]

3. Benefits of PA in liver cancer survivors

Certainly, PA is linked to many health benefits, many of which are attainable by cancer patients. Exercise training can significantly improve muscle strength, cardiovascular function, physical fitness, and self-reported physical well-being. Furthermore, aside from the general health benefits, existing research suggests that exercise training has cancer-specific benefits. PA can influence tumor occurrence, progression, and metastasis via various mechanisms, while also increasing the efficacy of antitumor therapy.[15,32–37] While beneficial, antitumor treatments can cause fatigue, depression, anxiety, and lymphedema.[15] PA, as an adjuvant therapy, can supplement primary therapy while minimizing its side effects. Many studies have found that both pre- and post-diagnostic PAs can improve the survival rate of patients with tumors; however, the latter is more effective in improving patient outcomes.[38,39] Figure 1 depicts how PA affects patients with liver cancer.

3.1. PA reduces liver cancer risks

An increasing body of epidemiological research evidence suggests that PA may have a potentially positive effect on HCC. A 14-year pan-European prospective cohort study of 467,336 participants found that PA is significantly associated with a lower risk of HCC by comparing physically active and inactive people (hazard ratio (HR) = 0.55; 95% CI 0.38–0.80).[40] A Meta-analysis of data from 12 prospective cohorts in the United States and Europe, totaling 1.44 million participants, found that high *vs*. low levels of leisure-time PA were associated with lower risks of 13 different cancers, including liver cancer (HR = 0.73; 95% CI 0.55–0.98).[41] In a prospective cohort study involving 43,479 males, it was discovered that aerobic exercise had specific benefits in lowering the risk of digestive tract cancer.[42] The greatest benefit was observed at approximately 30 MET-hours per week (HR = 0.68; 95% CI, 0.56–0.83). In addition, a study found that preoperative exercise capacity is an independent predictor of event-free survival and liver function maintenance in patients with liver cancer and chronic liver injury after hepatectomy.[43] In conclusion, PA can lower the risk of developing liver cancer and improve its prognosis.

3.2. PA improves sarcopenia, cardiopulmonary endurance, and physical fitness

Sarcopenia and frailty are common complications of liver cancer and end-stage liver disease (ESLD).[44] Sarcopenia is characterized by a widespread loss of muscle mass, strength, and function, and it is directly linked to negative outcomes in patients with liver cancer.[45,46] Alterations in food intake, hypermetabolism, changes in amino acid profiles, endotoxemia, accelerated starvation, and reduced mobility may cause sarcopenia in cirrhosis.[47] Inflammatory cytokines released by tumor cells can reduce protein synthesis or cause protein denaturation, resulting in a reduction in skeletal muscle mass. To treat this condition, nutrient supplementation and PA are used.[48] Early interventions, such as nutritional support and exercise therapy, can help prevent muscle wasting while patients wait for or during treatment, improving their prognosis. Exercise rehabilitation can help to reduce inflammation, oxidative stress, and insulin resistance, thereby improving sarcopenia.[49] Furthermore, a Meta-analysis indicates that exercise therapy is a beneficial supplementary approach for enhancing VO_{2peak} in individuals with adult-onset cancer.[50] These findings hold significance in clinical practice as reduced VO_{2peak} is a common characteristic observed both during and after cancer treatment,[51] and is associated with increased symptom severity and unfavorable clinical results.[52] Similarly, a Meta-analysis of 65 studies on muscle strength and cardiopulmonary function in cancer patients discovered that exercise has a moderately positive effect on muscle strength and cardiovascular health.[53] Therefore, resistance exercise combined with aerobic exercise increases cardiopulmonary endurance,

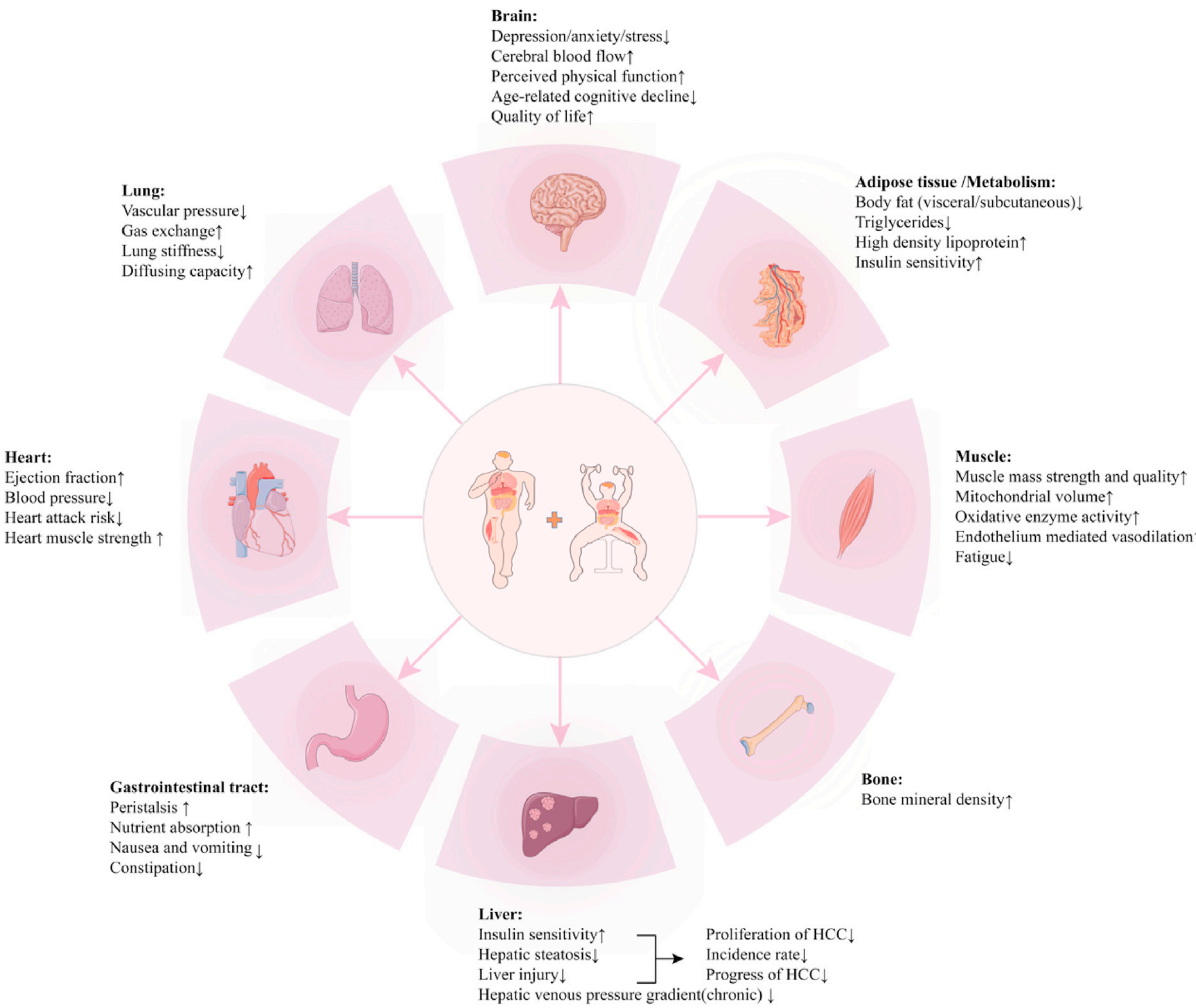

Fig. 1. Benefits of PA and exercise for patients with liver cancer. Exercise can improve cardiopulmonary function, reduce liver cell damage, increase bone density and muscle strength, regulate lipid metabolism, regulate portal vein pressure, improve negative emotions, and alleviate adverse reactions caused by cancer and anti-cancer treatments. Abbreviations: HCC, hepatocellular carcinoma; PA, physical activity.

muscle mass and function, which is one of the most significant benefits of PA for liver cancer survivors.

Liver cancer survivors typically have a history of cirrhosis before diagnosis, and as a result, their health deteriorates after cancer treatment, resulting in a steady decline in cardiovascular function, muscle strength, and endurance. A recent Meta-analysis of 9790 liver cancer survivors revealed that the combined prevalence of sarcopenia in HCC patients was 41.7%, and sarcopenia was associated with a decline in overall survival (HR = 1.93, 95% CI, 1.73–2.17) and a higher risk of tumor recurrence (HR = 1.75, 95% CI, 1.56–1.96).[54] Lee *et al.*[48] proposed that newly discovered sarcopenia after radiotherapy but before treatment is associated with a low survival rate among patients with liver cancer. However, two studies conducted in South Korea discovered that exercise can improve insulin resistance, physical fitness, and body composition in liver cancer survivors.[16,17] Another two studies conducted in Japan found that in-hospital exercise therapy can improve muscle mass and physical fitness in liver cancer survivors while preserving liver function.[55,56] Therefore, these studies suggest that despite facing health issues after treatment, liver cancer survivors can improve their physical condition and prognosis through PA.

3.3. PA improves symptoms, negative emotions, and health-related QoL

Liver cancer and its treatment can cause various symptoms, complications, negative emotions, and functional impairments, including pain, fever, fatigue, nausea, vomiting, loss of appetite, bloating, anxiety, depression, and sleep disorders, all of which negatively affect QoL.[57] Therefore, symptom management is not only necessary but also the primary goal of clinical care to maintain better QoL for liver cancer survivors. Studies have shown that PA significantly improves fatigue, sleep quality, depression, body and social function. Moderate-intensity aerobic exercise combined with resistance exercise can significantly reduce cancer-related fatigue (CRF).[58] Sun *et al.*[59] demonstrated that combining soothing music and walking exercise for 30–60 min/day can effectively alleviate fatigue, anxiety, and depression in elderly liver cancer survivors while also improving their sleep quality. Similarly, Jiang *et al.*[31] discovered that home-based aerobic exercises can reduce negative emotions like anxiety and depression in liver cancer survivors undergoing TACE therapy.

4. Molecular mechanisms of PA in the occurrence, development, and metastasis of liver cancer

Recent preclinical studies have revealed the impact of exercise on liver cancer, including the suppression of cancer cell proliferation, the promotion of apoptosis, the modulation of cancer metabolism, and the regulation of the immune microenvironment.[34,36,60,61] In mice models with cancer, voluntary wheel exercise reduced the occurrence and growth of cancer cells in mice models by 60%. Furthermore, the immune system of the mice became more responsive when the mice were pretrained for four weeks before being exposed to tumors. This suggests that a portion of the exercise's impact may include the destruction of cancer cells at the transplanted tumor site.[62] The relationship between exercise intensity and its effect on cancer cell proliferation has also been thoroughly studied. Moderate-intensity training has been shown to effectively inhibit cancer cell proliferation and induce apoptosis, whereas vigorous exercise can promote carcinogenesis. Conversely, low-intensity workouts may be less effective in inhibiting the proliferation of cancer cells.[63,64] The molecular mechanisms of PA in liver cancer are summarized below.

4.1. PA inhibits HCC cell proliferation and induces apoptosis

Several studies show that PA and exercise significantly reduce the proliferation and induce apoptosis of liver cancer cells.[36,59,60,62] Specifically, one study found that moderate swimming has a significant impact on inhibiting liver cancer growth and reducing lung metastasis, thereby increasing overall survival.[63] Further research found that moderate swimming altered dopamine (DA) levels in the brain and peripheral blood.[62] By activating the dopamine 2 receptor signaling pathway, DA plays a crucial role in inhibiting liver cancer growth and metastasis.[65] The dopamine 2 receptor pathway reduces cyclic adenosine monophosphate levels while inhibiting extracellular signal-regulated kinase 1/2 activation. The extracellular signal-regulated kinase signaling pathway increases the expression of transforming growth factor-beta 1 (TGF-β1),[66] a cell factor that can lead to invasive phenotype in tumor cells, particularly contributing to distant metastases like lung metastasis.[67] However, exercise has been shown to reduce the release of TGF-β1, thereby lowering the risk of HCC progression and metastasis, ultimately improving prognosis.[61]

Previous research in a mouse model has shown that changes in the expression of mitochondrial dynamics contribute to the division of mitochondria in samples from cancer patients, implying that mitochondrial division may play a role in tumorigenesis.[68] The protein dynamin-related protein 1 (DRP1) is essential for this process.[69] Furthermore, previous studies have shown that DRP1 can promote the proliferation and invasion of HCC.[70,71] Similar studies have found upregulation of DRP1 in various other cancer types including breast cancer,[69] lung cancer,[72] and colorectal cancer.[73] During exercise, the energy requirements of different tissues within the human body fluctuate, resulting in changes in mitochondrial metabolism.[74] Aerobic endurance training stimulates more mitochondrial activity than acute high-intensity training.[75] Zhao *et al*.[71] found that aerobic exercise reduces the expression of DRP1 while increasing the expressions of phosphorylated phosphatidylinositol 3 kinase (p-PI3K) and p-protein kinase B (PKB/AKT). The study suggests that DRP1 activates the PI3K/AKT signaling pathways. Phosphorylation events involving PI3K and AKT have been closely linked to tumor metastasis and proliferation.[76] Therefore, we conclude that exercise reduces mitochondrial division levels in mice with HCC, thereby slowing HCC progression. However, more research is needed to gain a better understanding of the precise mechanisms underlying the regulation of DRP1, so that future clinical applications can benefit from these findings.

Arfianti *et al*.[34] suggest that the inhibitory effect of exercise on liver cancer in obese mice appears to be a direct result rather than related to weight control. They discovered that exercise increased p53 Ser 15 phosphorylation in the liver. The impact of PA on p53 activation has been observed in various other tissues as well.[77,78] Furthermore, in addition to promoting DNA repair and inducing apoptosis, cellular responses to p53 activation such as cell cycle arrest. This arrest is facilitated by proteins such as p21 and p27, which inhibit cell cycle kinases.[77] It is plausible that the activation of p53 and subsequent expression of p27 may be one potential mechanism by which exercise reduces hepatocyte proliferation, thereby mitigating the promotion of hepatocarcinogenesis caused by obesity and insulin resistance.

In summary, exercise uses a multifaceted approach to slow liver cancer growth, including the inhibition of cell proliferation and the induction of apoptosis. Exercise achieves these effects by reducing cancer cell proliferation and increasing apoptosis (Fig. 2).

4.2. PA regulates metabolism

Adenosine monophosphate-activated protein kinase (AMPK) is an energy sensor in cells that links metabolism and cancer.[79] This critical homeostasis control hub can suppress cell proliferation when cellular capacity and biosynthesis are lacking.[80] Numerous physiological mechanisms, such as PA, activate AMPK. The liver is more responsive to metabolic demands during muscular exertion, and studies have shown an increase in AMPK activation following both short-term and prolonged exercise in rat livers.[81,82] AMPK phosphorylates the regulatory-associated protein of the mammalian target of rapamycin (Raptor), which inhibits the mammalian target of rapamycin (mTOR) complex 1 (mTORC1). The AMPK-mTORC1 signaling pathway contributes to growth suppression and hepatocarcinogenesis, with activation of this signaling pathway resulting in cell cycle arrest and apoptosis.[35,83] In hepatocyte-specific PTEN-deficient mice, the activation of AMPK was elevated immediately after acute exercise, which was accompanied by increased phosphorylation of Raptor at site Ser 792, AMPK's targeted site, resulting in decreased mTORC1 activity.[35]

In patients with liver cancer caused by non-alcoholic steatohepatitis (NASH), not only is there a disturbance in liver energy metabolism, but also impaired lipid metabolism. The accumulation of specific lipid species such as free fatty acids (FFAs) and free cholesterol damages liver cells via lipotoxicity.[84] This results in the production of reactive oxygen species (ROS), which causes cell death in hepatocytes. In response, HCC cells undergo compensatory proliferation, which contributes to the development of HCC.[85] Both ROS and toxic lipids activate a protein called c-Jun N-terminal kinase (JNK).[86] JNK activation causes the formation of phospho-c-Jun, which combines with c-Fos to create a transcription factor known as activator protein-1 (AP-1), which promotes cell proliferation. JNK activation has also been reported in cancer patients.[87] Notably, the absence of JNK1 in *foz/foz* mice provided complete protection from hepatic tumorigenesis.[34] Arfianti *et al*.[34] discovered that 8 weeks of exercise decreased JNK activation in *foz/foz* mice, possibly due to its ability to reduce exercise-induced hepatic lipid accumulation. Given that JNK1 suppression can regulate cell proliferation via c-Jun phosphorylation and AP-1 activity, reduced hepatocellular proliferation in exercising *foz/foz* mice may contribute to their resistance to HCC development.

In NASH, insulin resistance is a common feature. This causes an increase in insulin levels, which stimulates the liver to produce and release more insulin-like growth factor 1 (IGF-1).[88] The presence of IGF-1 increases the growth and survival of modified hepatocytes by

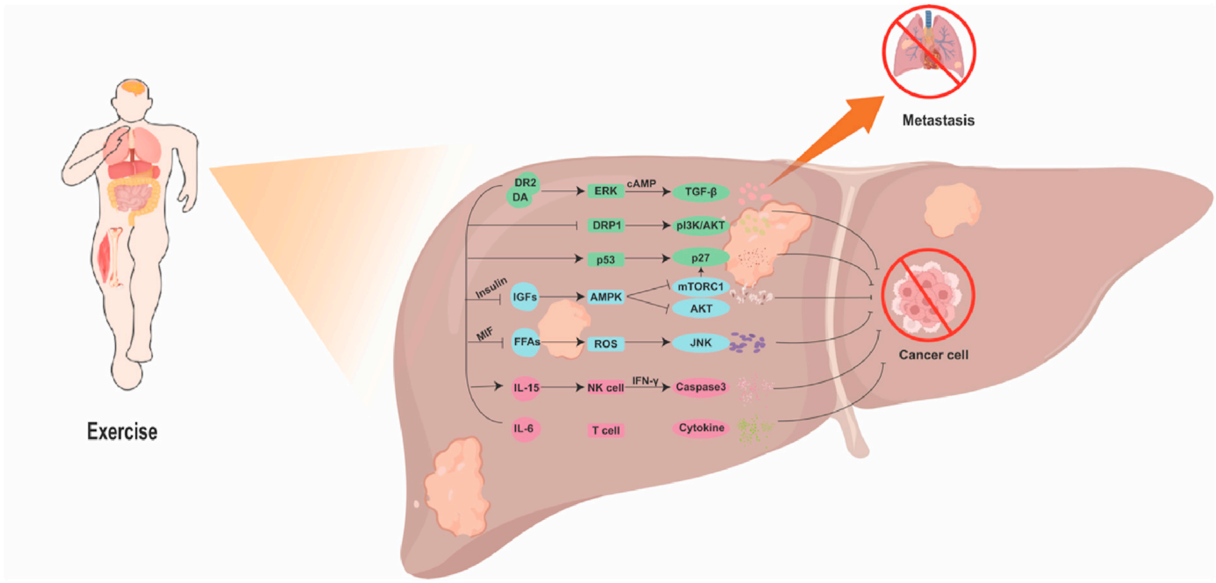

Fig. 2. Mechanisms of PA and exercise in the occurrence, development, and metastasis of liver cancer. Exercise inhibits the proliferation in cancer cells, induces apoptosis of cancer cells, regulates human energy metabolism, and regulates the immune environment to prevent the occurrence, development, and distant metastasis of HCC cells. Abbreviations: PA, physical activity; DA, dopamine; DR2, dopamine receptor 2; ERK, extracellular signal-regulated kinase; cAMP, cyclic adenosine monophosphate; TGF-β, transforming growth factor-β; DRP1, dynamin-related protein 1; AKT, protein kinase B; IGFs, insulin-like growth factors; AMPK, AMP-activated protein kinase; mTORC1, mammalian target of rapamycin complex 1; MIF, macrophage migration inhibitory factor; FFAs, free fatty acids; ROS, reactive oxygen species; JNK, c-Jun N-terminal kinase; IL-15, interleukin-15; NK cell, natural killer cell; IFN-γ, interferon-gamma.

activating the Akt/mTORC1 pathway.[34] Exercise regulates the secretion of IGFs and activates adenosine AMPK, especially in tumors with hyperactive Akt pathways.[33,36,89]

In summary, exercise can activate AMPK by improving mitochondrial function, which inhibits the mTOR pathway and reduces hepatic lipid accumulation. Furthermore, it regulates IGF-1 secretion, which effectively modulates the Akt and mTOR pathways. It also regulates interleukin-6 (IL-6) activity in skeletal muscles, all of which collectively contribute to the inhibition of cancer cell proliferation and induction of apoptosis (Fig. 2).

4.3. PA regulates the inflammation and immune environment

In terms of immune response activation via PA, natural killer (NK) cells are the most sensitive to exercise-induced mobilization, followed by T cells (including cluster of differentiation 4 (CD4)$^+$ and CD8$^+$), with B cells being the least sensitive.[90] NK cells, which are highly sensitive in mobilizing the immune system, play an essential role in innate immune defense. On the other hand, T cells act as cytotoxic agents and play an important role in adaptive immune responses. The rapid responsiveness of NK cells can be attributed not only to their strong reactivity to exercise but also to the activation of NK group 2 member D (NKG2D) and minor histocompatibility antigen 60 (H60a), as well as ligand C-type lectin-related protein b (Clr-b) from NK receptor proteins 1 ligand (NKR-P1B).[62,91] As pioneers in the innate lymphocyte family, NK cells have recently received recognition for their ability to manage both microbial infections and tumor progression.[92] In both clinical cases and animal studies, compromised or deficient NK cells have been linked to an increased susceptibility to various types of cancer.[93] Wang *et al.*[94] found that 12 weeks of endurance exercise can delay the invasion of tumor cells in Hepa1-6 cell-derived mice while increasing the expression of NK cells. The findings show that in the tumor model, pretrained mice had significantly higher IL-15 levels in their plasma. IL-15 in human skeletal muscle is the cytokine with the highest expression at the messenger ribonucleic acid (mRNA) level.[95] After exercise training, as a result of muscle contraction-induced secretion, the levels of IL-15 in the plasma rise.[96] Additionally, the expression of NK cell ligands Nkg2d and Rae-1 in liver tissue has increased. Furthermore, levels of interferon-gamma (IFN-γ) increased. Thus, exercise training can improve the recognition and cytotoxicity of NK cells. Furthermore, the caspase-3 apoptotic pathway in mouse liver tumor tissue was activated. Cell apoptosis is regarded as a typical antitumor process. Caspase-3 is an important mediator of mammalian cell apoptosis that can cleave many essential proteins.

IL-6 has both positive and negative effects on cancer, depending on the circumstances.[97,98] During exercise, skeletal muscles produce IL-6 to control immediate energy availability.[99] IL-6 produced during exercise can help prevent cancer by improving insulin sensitivity, promoting the production of anti-inflammatory cytokines, mobilizing immune cells, and reducing DNA damage in early malignant cells.[100–102] Conversely, chronic inflammation and the activation of tumor-promoting signaling pathways are facilitated by the continuous production of IL-6 by leukocytes at inflammatory sites, promoting tumorigenesis.[103,104] Several factors contribute to the contradictory effects of IL-6 in cancer, including the duration of exposure, mode of signaling, regulation from upstream sources, cell origin, and target cell specificity. Future research should concentrate on gaining a better understanding of the underlying mechanisms that drive these moderating factors. This knowledge will be crucial in understanding the precise role of IL-6 in cancer and guiding the development of more targeted therapeutic approaches including behavioral and pharmacological interventions tailored toward these moderators and their associated mechanistic pathways.

The secretion of various myokines by active muscles, which can have local or systemic effects on different organs, may contribute to the observed reduction in cell proliferation in both liver and tumor tissues. Indeed, certain myokines have been shown to inhibit the growth of tumor cells, implying that muscle-released factors may play a role in cancer prevention.[105] Furthermore, myokines released during exercise may directly reduce inflammation in the liver and protect against tumors.[106] More research is needed to confirm the role of myokines in preventing tumor development.

To summarize, PA can cause an immune cell mobilization reaction within the cancer microenvironment. This includes increasing the infiltration of NK cells, improving the immunomodulatory effects of cytokines, and facilitating T cell proliferation. Consequently, exercise can effectively slow cancer cell growth and prevent immune system deterioration (Fig. 2).

5. Implementation principles of exercise

Exercise is defined as a planned, organized, and repeatable PA intended to promote or maintain physical fitness. Generally, exercise programs designed to promote and maintain physical fitness and health include aerobic exercise, resistance exercise, flexibility exercise, and neuromuscular function training.[107] A comprehensive exercise prescription should adhere to the FITT-VP (frequency, intensity, type, time, volume, and progression) principles. Exercise programs for liver cancer survivors are designed to be individualized, gradual (step-by-step), and persistent.

5.1. Individualized

Exercise training for cancer patients may shift from a “one-size-fits-all” approach to more tailored strategies based on age, physical fitness, comorbidities, and complications. Furthermore, complex factors such as personal preferences and the external sports environment must be carefully considered.

5.2. Step-by-step

During exercise training, the intensity and duration of the exercise should be gradually increased in response to improvements in patient prognosis at various stages of the disease, physical fitness level, health status, and other factors. The patient’s physical fitness level should be regularly reassessed, and the exercise program adjusted as needed. Patients with liver cancer should always begin with low intensity, progress slowly, and be aware of liver disease symptoms.[108]

5.3. Persistence

Liver cancer survivors should follow exercise regimens as much as possible throughout the disease course, including before treatment, the perioperative period, the systemic treatment period, and intermission, as well as long-term survival. Although specific exercise regimens and goals may change over time, patients should always be encouraged to stick to and maintain good exercise habits.

6. Full-cycle management of PA

Exercise therapy for liver cancer survivors is a novel concept in the field of hepatology. Exercise rehabilitation should be managed across all disease, personnel, and regional cycles. The disease cycle begins on the day of diagnosis and ends with the patient’s death, and exercise adjustments should be made accordingly based on the disease’s stages and treatment methods. Simultaneously, health personnel must be well managed throughout the cycle, as this is a critical link between clinical rehabilitation and caring. Clinicians, rehabilitation therapists, and nurses should work together to create and integrate dual rehabilitation plans in and out of the hospital. Health professionals should incorporate PA programs into their patients’ daily lives and supervise them appropriately. The framework for PA programs for cancer survivors can be referred to the Exercise and Sports Science Australia's position statement on exercise guidelines.[109]

6.1. Assessment of PA readiness

In general, exercise risk assessments should be conducted before developing any specific PA program for patients with liver cancer to identify potential risk factors.[110] When designing a PA program for these patients, two critical aspects must be considered: (1) The presence of general complications, such as cardiovascular disease, skeletal and muscular disorders, metabolic disorders, and renal disease, which may preclude safe exercise. The World Health Organization guidelines for the general population should be followed in this regard.[107] (2) Liver cancer-specific complications, given that liver cancer patients frequently lack PA and may experience cardiovascular issues, metabolic disorders (such as diabetes and metabolic liver disease), and renal problems (such as hepatorenal syndrome). Therefore, a thorough medical evaluation is necessary before initiating any exercise regimen.[22] Specific assessment should include the following: (1) Evaluation of the patient’s medical history and current PA level, including age, disease history, family history, any impairments, and sports injuries before and after diagnosis; (2) Routine medical evaluations, including cardiopulmonary function, blood glucose, and lipid levels, evaluation of peripheral nerves and skeletal muscles for secondary lesions after treatment, and preexercise assessment of patients with known bone metastases to determine safe exercise modalities and volumes; and (3) Screening for liver cancer-related complications, including the model for MELD score, risk of variceal bleeding, presence of ascites, coagulation function, diuretic treatments, and assessment of HE (Table 1 for details).[21,102,108]

By integrating the evidence base on liver cancer staging, specific outcomes, and various exercise prescriptions, as well as general principles of exercise prescription, a solid foundation can be established to improve the QoL for patients with liver cancer. It is critical to incorporate cancer-specific considerations into all aspects of patient care, including assessment and initial exercise prescription, as well as exercise principles such as progressive overload, periodicity, and autoregulation. Furthermore, incorporating behavior change strategies, education, and monitoring is critical to ensuring patient-centered care that enables patients to develop the skills needed to reap long-term health benefits from exercise. The process is outlined below: (1) Assess patients, including their medical history, cancer diagnosis, treatment status, treatment-related side effects, and PA and exercise habits. (2) Prioritizing health issues based on risk and providing exercise recommendations to prevent or manage cancer- or treatment-related side effects. (3) Identify the patient’s capabilities for intervention, considering factors such as physiological limitations, economic status, psychosocial well-being, access to resources/support systems/preferences/self-confidence levels/barriers/facilitators to exercise participation. Also, consider the potential benefits of exercise. (4) Creating an exercise prescription based on the patient’s specific and regularly reassessing and modifying/updating the exercise prescription to reflect progress.[109]

6.2. PA prescription

The clinical spectrum of patients with liver cancer and those who have survived is extremely diverse. Therefore, exercise prescriptions for liver cancer survivors should be tailored to specific needs, such as their learning ability, type of work, living environment, and PA preferences. Currently, there is no specifically recommended PA prescription for liver cancer. Given the decline in body function and susceptibility to fatigue in liver cancer survivors,

Table 1
Screening results of patients with liver cancer and adjustments of exercise prescription.

Liver cancer-specific screening	Exercise prescription modification	References
MELD >20	• Case-by-case assessment to determine if a certified exercise professional referral is required for the patient to progress beyond the introductory exercise.	108
High-risk varices	• Ensure adequate primary or secondary variceal prophylaxis is in place before the program. • Avoid any exercise that increases intraabdominal pressure.	108
Ascites	• Low-to-moderate-intensity exercise can be performed when the accumulation of ascites is insignificant and/or does not affect balance. • Caregiver supervision is recommended.	108
HE	• Caregiver supervision throughout the entire process, including exercise physiologist supervision, if necessary.	108
Platelet<20×10^9/L, hemoglobin<80 g/L	• Initiate mild-intensity exercise under supervision while paying close attention to skin and mucosal bleeding before and after exercise. • Unless combined with unstable clinical status, severe thrombocytopenia is not a contraindication of PA. The patient can start with bed activities and ADL to avoid sedentary or bedridden status.	108
Diuretic treatment	• There is a risk of hypovolemia and hypotension during exercise.	108
Receiving immunotherapy or in an immunosuppressive state	• Encourage home exercise, use public fitness equipment with caution and prevent cross-infection. • Start with mild-intensity, high-frequency, and short-term exercise.	107
Accompanying osteoporosis, bone metastasis	• For patients with a high risk of fractures, a thorough clinical evaluation should be conducted before starting the exercise. • When performing resistance exercises, direct weight bearing on the lesion should be avoided. • High-impact load training and excessive flexion, extension, or twisting of the trunk should be avoided.	21,107

Abbreviations: MELD, the model for End-stage liver disease; HE, hepatic encephalopathy; PA, physical activity; ADL, activity of daily living.

most are unable to perform even moderate-intensity aerobic exercises as recommended by the American Cancer Society for at least 150 min/week.[111] The general exercise principles for liver cancer survivors are to begin slowly, progress slowly, and be aware of liver disease symptoms to reduce the risk of symptoms exacerbating.[108] The exercise prescription should be adjusted based on the patient's tolerance level. The variables that can be changed are as follows: exercise mode, intensity, duration, and frequency.[15] Adjustable variables in resistance exercises include reducing the number of training sets for each muscle group, lowering the resistance load, and increasing the rest time between sets.[112] In recent years, many studies have investigated various exercise strategies for liver cancer survivors. For example, O'Neill *et al.*[20] devised a 12-week multidisciplinary rehabilitation program following the surgery for esophagogastric and hepatopancreatic biliary cancer. The exercise component consisted of both on-site supervision and home-based intervention, which included aerobic and resistance exercises. The exercise intensity was adjusted based on the patient's physical fitness, which was measured with an accelerometer and a Borg perception scale. Resistance training (RT) was primarily aimed at exercising the major upper- and lower-body muscle groups while avoiding core muscle exercises that increase intraabdominal pressure. The center's initial research has shown that a 12-week supervised and family exercise program can lead to significant clinical improvements in cardiorespiratory function and overall well-being without compromising body composition. Tsuchihashi *et al.*[113] discovered that in-hospital exercise improved frailty in patients with HCC. In the exercise group, patients received individualized exercise therapy overseen by a certified physical therapist with expertise in cancer rehabilitation. Exercise sessions began on the day after TACE, except for patients with a temperature of 38.0 °C or higher or experiencing liver failure.

Exercise was performed five times per week, either in a dedicated rehabilitation room or on the hospital ward. The exercise program included the following four types of training: (1) stretching, including the quadriceps femoris muscles, hamstrings, hip adductors, gastrocnemius, back, and shoulder muscles. Each stretch was held for 10–20 s. Patients were encouraged to gradually increase the intensity until they experienced tightness and slight discomfort. The physical therapist demonstrated proper stretching technique and checked for signs of tightness or discomfort. The total time spent on stretching exercises ranged from 3 to 5 min. (2) The RT included four basic exercises: hip hinges, towel air pull-downs, squats, and calf raises. Each set had 10 repetitions, with a maximum of three sets per session. Physical therapists modified the exercise method and environment to ensure that patients could comfortably complete all 10 repetitions with their own body weight or manual resistance. The total time allocated allotted for RT was approximately 5 min. (3) Balance training: patients practiced one-leg or tandem stance exercises with parallel bars and handrails for support. The one-leg stance exercises required patients to maintain a horizontal posture while holding each leg up for up to 1 min. Tandem stance exercises required an upright posture with the feet aligned heel-to-toe in a straight line. These balance training exercises were done once on each side for about 5 min. (4) Aerobic training was done on a bicycle ergometer or while walking, with the exercise intensity adjusted to keep the perceived exertion rating between 11 and 13 on the Borg scale. The duration of exercise was gradually increased to 15 min, and individual intensity was adjusted during each session to meet exercise objectives.

Orange *et al.*[114] created a group-based virtual exercise intervention strategy for elderly liver cancer survivors that utilized teleconferencing to guide them through home-based exercise. The patients were invited to partake in virtual exercise sessions twice a week for 10 weeks, including a chair- or standing-based section. The method chosen was based on the patient's physical fitness, and each exercise lasted for 45 min, including a 10-min warm-up, 30-min aerobic and resistance exercises, and a 5-min static stretching and cool-down period. The exercises were performed at a moderate-intensity level on the 10-point Borg scale of perceived exercise (3–6). Unfortunately, the results of this strategy have yet to be validated. Table 2 shows the recommended FITT elements of exercise prescription for liver cancer survivors. The most recent relevant studies are listed in Table 3.

Currently, traditional RT is the most popular training method in exercise oncology. However, nontraditional RT methods such as eccentric training, cluster training, and blood flow restriction (BFR) training are gaining popularity. These training methods have been extensively investigated in exercise and clinical populations, including aging, cardiovascular disease, and type 2 diabetes. Nonetheless, these nontraditional RT methods have not been extensively investigated in patients with liver diseases. Nóbrega *et al.*[115] conducted the first trial of BFR-RT in patients with liver

Table 2
Recommended FITT for PA in liver cancer survivors.

Characteristic	Aerobic	Resistance	Flexibility and balance
Frequency	Starting from 4 days per week, target daily	2–3 days per week	2 or more days per week
Intensity	Moderate-intensity 40%–59% HRR, 64%–75% HR_{max}, RPE: 5–6 on a 10-point Borg scale. The exerciser should pass the talk test and be able to speak comfortably during exercise to ensure they are not overexerting themselves.	Starting from low intensity (such as 30% 1-RM), a small increase can easily complete 3 sets of 10–12 repetitive movements, which can increase resistance.	Stretch until there is a feeling of tightness or slight uncomfortable tolerable.
Types	Long-time rhythmic activities using large muscles (such as walking, cycling, shadowboxing, Baduanjin Qigong, jogging, swimming, etc.).	Free weight, resistance devices, or functional activities of one's own weight (such as sitting and standing transitions), targeting the upper and lower limb major muscle groups.	Stretches and balance exercises targeting the large muscles of the upper and lower body.
Time	Individuals who are "very reconditioned" may start with a 1min walk and 1 min rest, gradually increasing the walking time to shorten the rest time, with a goal of 40 min per activity.	3–4 sets each time, 8–12 repetitions per set, completing 3 sets.	1 set of 3 repetitions. Stretches can be held for 30–60 s for a total of 5–10 min.

Abbreviations: HRR, heart rate reserve; HRmax, maximum heart rate; RPE, rating of perceived exertion; 1-RM, 1-repetition maximum; FITT, frequency, intensity, type, time.

Table 3
Clinical trials of PA in liver cancer survivors.

Author, Year	Design	Population	Interventions	Key findings
Koya,[56] 2019	Case-control study	HCC patients who underwent TACE ($n = 209$)	Exercise group ($n = 102$): in-hospital exercise (2.5 METs, 20–40 min/day) involving stretching, strength, balance, and endurance training. Control group ($n = 107$): usual care.	ΔSMI ↑ Exercise was an independent factor for an increase in SMI (HR 2.13; 95% CI 1.215–3.846; $P = 0.0085$) in the logistic regression analysis.
Williams,[29] 2019	One arm	Adult patients on the waiting list for primary LT ($n = 20$); exclusion criteria: cardiovascular instability.	A 12-week HBEP, including ADS targets and twice-weekly resistance exercises.	No adverse events were reported, and there was a significant improvement in the ISWT at both 6 weeks (+50 m; $p = 0.008$) and 12 weeks (+210 m; $p = 0.008$), ADS score (+2700; $p = 0.008$), SPPBT score (+2.5; $p = 0.016$).
Wallen,[26] 2019	Pilot RCT	A potential candidate for liver transplantation ($n = 21$)	Exercise ($n = 21$): 2 supervised + 1 unsupervised sessions weekly, aerobic + circuit resistance exercises.	No adverse events occurred during the intervention period. Exercise training adherence was 95% (supervised) and 75% (unsupervised).
Kim,[15] 2020	One arm	HCC patients ($n = 37$)	Individually prescribed rehabilitation exercises: warm-up, stretching, aerobic, and upper/lower extremity muscle strengthening.	31 (84%) completed the 12-week intervention. Grip strength↑ 30s chair stand test ↑ The 6-MWT↑ Muscle mass ↑ The IPAQ-SF score↑ Without biochemical deterioration
Tsuchihashi,[113] 2021	Cohort study	HCC patients ($n = 181$)	Exercise ($n = 114$): 5 sessions/week, including stretching, strength, balance, and endurance training.	LFI↑ Exercise (OR: 2.38; 95%CI 1.240–4.570) and females (OR: 2.09; 95%CI 1.062–4.109) were identified as independent factors for the improvement of LFI.
He,[30] 2022	RCT	Hepatocarcinoma patients treated with TACE ($n = 183$)	3 months of home-based aerobic exercise	The scores of pain, fatigue, sleep quality, and QoL in the exercise group were statistically significantly better (all $P < 0.05$).

Abbreviations: HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; METs, metabolic equivalents; SMI, skeletal muscle index; HR, hazard ratios; HBEP, home-based exercise program; ADS, average daily step; SWT, incremental shuttle walk test; 6-MWT, 6-min walk test; IPAQ-SF, international physical activity questionnaire-short form; SPPBT, Shuttle-Plus Physical Performance Battery Test; LFI, liver frailty index; QoL, quality of life.

cirrhosis, evaluating its effects on neuromuscular parameters, functional performance, disease severity, and QoL outcomes. The study investigated the possibility of incorporating nontraditional RT protocols into exercise prescriptions for patients with liver diseases. Furthermore, traditional Chinese fitness exercises such as the Five Animal Frolics, Baduanjin, Qigong, and New Qigong have been studied on cancer patients.[116–119] According to research, except for high-intensity exercises like brisk walking in New Qigong, most forms of New Qigong involve very slow walking speeds, significantly slower than normal walking. Despite the slow walking pace, these exercises can produce moderate-intensity aerobic effects using a special breathing technique called "inhale-exhale". Qigong improved the overall QoL, CRF, and cognitive impairment.[120] This emphasizes the importance of "body adjustment", "breathing control", and "mind control" in traditional Chinese health practices related to fitness. These exercises are ideal for physically weak people, such as those who are currently undergoing or have recently completed cancer treatment, and they may also be used in liver cancer patients in the future.

6.3. Supervision of the PA process

Several studies have consistently demonstrated that supervised interventions are more effective than unsupervised ones. This can be attributed to increased guidance from exercise therapists, the use of specialized equipment, and strict adherence to protocol.[121,122] Despite its effectiveness, traditional exercise supervision, which typically involves in-person interactions at centralized locations, necessitates significant financial and human resources. Furthermore, it necessitates patients visiting hospitals or fitness centers, making it inconvenient, costly, and frequently impeding long-term adherence. A Meta-analysis investigating the PA preferences of cancer patients confirmed that most patients prefer unsupervised home-based activity programs.[123] To address this preference and improve adherence, telemedicine technology, intelligent assistive devices, and community resource collaboration networks can be used to develop hospital-based supervised exercise programs as well as home-based exercise training under intelligent supervision for liver cancer survivors.[55,56,113,114]

Incorporating these advancements not only improves the compliance of cancer survivors but also allows for cognitive changes in PA behavior. This approach promotes normalized exercise habits. Furthermore, careful monitoring of common complications and treatment-related side effects during exercise is essential.[16,17,30,31,114]

7. PA patterns in liver cancer survivors

7.1. Hospital-based PA

Patients with cirrhosis and liver cancer frequently develop various complications.[124] Specific exercises may increase portal venous pressure and reduce glomerular filtration rate, potentially exacerbating variceal bleeding and hepatorenal syndrome.[23,24] Considering safety concerns, most exercise rehabilitation programs for liver cancer survivors are held in hospitals or cancer rehabilitation facilities.[55,56,113] Previous research on hospital-based exercise rehabilitation has primarily focused on well-structured on-site training facilities, which frequently include gym equipment and direct supervision by exercise specialists. In China, because of a shortage of specialized exercise rehabilitation professionals, nurses guide most interventions for liver cancer patients.[30,49,125] Hospital-based exercise programs have the advantage of providing a certain level of supervision, allowing for increased training intensity and the use of specialized equipment. However, their impact on long-term exercise adherence is unknown. Furthermore, these programs require significant financial and human resources, necessitating patients' visits to hospitals or exercise facilities, making them impractical, costly, and detrimental to long-term adherence. Therefore, with the emergence of home-based self-management exercise programs that may address the aforementioned issues, healthcare providers should instruct patients on exercise and self-monitoring skills as patients transition from hospital-based to home-based self-management exercise programs.

7.2. Home-based PA

In recent years, several studies have been conducted to assess the benefits of home-based exercise programs in comparison to hospital-based exercise programs. In family-based programs, an exercise specialist typically performs an initial assessment, explains the program to the patients, and tailors it to their specific needs. The aerobic exercise component is typically performed using wearable activity trackers and daily target steps. With the widespread popularity of smartphones around the world, mHealth, a new technology that promotes exercise plans, has sparked interest not only among healthy people but also among patients suffering from diseases such as diabetes and heart disease.[126–128] mHealth encourages patients to exercise and provides real-time feedback, thereby increasing PA. Because of mHealth's ability to provide extensive information and reduce communication barriers with healthcare providers, it is an excellent tool for assisting liver cancer survivors in exercising safely outside of the hospital. mHealth combined with personalized exercise programs, can improve physical function in patients with HCC. Kim *et al.*[15] discovered that using the mHealth app and the internet of wearable devices to provide 12 weeks of personalized rehabilitation exercise for compensatory liver cancer survival during cancer treatment is both safe and efficient. The monitoring system consists of wearable devices and real-time communication chat services with healthcare professionals. No complications or biochemical deterioration were detected during the 12-week intervention period. Physical fitness improved statistically significantly when compared to the baseline level.

In home-based exercise rehabilitation, the most challenging aspect is patient compliance. Williams *et al.*[29] indicated that compliance among LT candidates decreased significantly after weekly phone calls were discontinued after the sixth week of rehabilitation. This lack of compliance may be caused by the complexity of the exercise programs. Ideally, as the patient's condition worsens, the intervention should be simpler. Although the use of wearable mobile trackers and other technologies is promising, some patients with HE or very serious liver diseases may struggle to use them, necessitating the assistance of a caregiver. Therefore, combining in-hospital caregiver supervision with home-based self-management rehabilitation and gradually transitioning from a hospital-based to a home-based rehabilitation program can maximize benefits. The characteristics of the two PA patterns are summarized in Table 4.

The 5G era will witness the development of mobile phone-based dynamic exercise intervention equipment, courses, and app applications, as well as exercise prescriptions. The new generation of sports equipment and courses with interactive functions tailored to the Internet of Things are gradually making their way into users' homes via live broadcasting, smart fitness equipment, and remote visual coaches.

8. Summary and outlook

Physical inactivity, sarcopenia, and frailty are extremely common and serve as independent predictors of morbidity and mortality in HCC patients. For various types of cancer, PA and exercise training are fundamental recommendations supported by guidelines. To safely increase the exercise levels of liver cancer survivors, implement a subtle support system that monitors their PA and alerts them before liver decompensation becomes critical. Wearable devices, such as smartwatches, fitness trackers, and heart rate monitors, can be used in conjunction with mobile exercise apps.

Table 4
Physical activity patterns in liver cancer survivors.

Aspect	Hospital-based physical activity	Home-based physical activity
Supervision	Professional direct supervision by healthcare providers	Lack of direct supervision, but convenience, flexibility, and cost-effective
Equipment and resources	Access to a wide range of equipment and resources	Limited equipment and resources available at home
Safety	With safety measures and emergency response systems in place, the possibility of reaching higher intensity	Safety measures may be limited at home: requires self-monitoring and safety awareness, risk of suboptimal intensity
Personalization	Tailored exercise programs based on individual needs	Personalization may be limited without a professional assessment
Social interaction	Opportunities for social interaction and support	Limited social interaction at home
Compliance	Higher compliance due to regular monitoring, but unclear adherence to the long-term	Requires self-motivation and discipline; Low adherence
Cost	Requires patients to travel, costs more	More "real-life", free

The real-time data on pulse, step count, and sleep provided by these wearables allows exercise professionals to customize programs for their clients. Exercise professionals can provide patients with more convenient PA support systems and set up appropriate alarm systems using smartphones and related Apps that help with exercise performance or programming. Nontraditional RT protocols, such as BFR training, are being investigated for inclusion in exercise prescriptions for liver cancer patients. Considering the exercise interventions supervised by healthcare professionals in the hospital, a gradual transition to a home-based self-management rehabilitation program can assist survivors in performing safe and effective PA. The integration of mHealth with personalized exercise programs allows survivors to safely exercise at home, which aligns with future development trends. In the future, more personalized, large-scale, and multicenter randomized controlled trials tailored for liver cancer patients will be required to provide robust clinical evidence support.

Authors' contributions

Haiyan Chen, Huimin Zhou, and Bo Wu contributed equally to this work and should be considered co-first authors. Haiyan Chen: Writing - original draft, Investigation. Huimin Zhou: Writing - original draft, Investigation. Bo Wu: Writing - original draft, Visualization, Software. Hanxiao Lu: Visualization, Software, Data curation. Jie Zhang: Validation, Investigation. Yan Zhang: Validation, Investigation. Yuanlong Gu: Validation, Funding acquisition. Guangwen Zhou: Validation, Supervision, Methodology. Jie Xiang: Writing - review & editing, Conceptualization. Jun Yang: Writing - review & editing, Visualization, Validation, Supervision, Project administration, Funding acquisition, Conceptualization. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that there is no conflicts of interest.

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