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EDITORIAL

- 2068** Combination treatment of inflammatory bowel disease: Present status and future perspectives
Triantafyllidis JK, Zografos CG, Konstadoulakis MM, Papalois AE
- 2081** Interplay between metabolic dysfunction-associated fatty liver disease and renal function: An intriguing pediatric perspective
Nardolillo M, Rescigno F, Bartiromo M, Piatto D, Guarino S, Marzuillo P, Miraglia del Giudice E, Di Sessa A
- 2087** Advancements in hemostatic strategies for managing upper gastrointestinal bleeding: A comprehensive review
Lee AY, Cho JY
- 2091** Understanding autoimmune pancreatitis: Clinical features, management challenges, and association with malignancies
Christodoulidis G, Kouliou MN, Koumarelas KE
- 2096** Probiotics: Shaping the gut immunological responses
Filidou E, Kandilogiannakis L, Shrewsbury A, Kolios G, Kotzampassi K

MINIREVIEWS

- 2109** Hepatocellular carcinoma and musculoskeletal system: A narrative literature review
Jadzic J, Djonic D

ORIGINAL ARTICLE

Case Control Study

- 2118** Urgent one-stage endoscopic treatment for choledocholithiasis related moderate to severe acute cholangitis: A propensity score-matched analysis
Zhou Y, Zhang YQ, Huang SJ, Liang Y, Liang X, Wali M, Feng YD

Retrospective Study

- 2128** Computed tomography-based radiomics to predict early recurrence of hepatocellular carcinoma post-hepatectomy in patients background on cirrhosis
Qian GX, Xu ZL, Li YH, Lu JL, Bu XY, Wei MT, Jia WD

Basic Study

- 2143** Taurine attenuates activation of hepatic stellate cells by inhibiting autophagy and inducing ferroptosis
Li S, Ren QJ, Xie CH, Cui Y, Xu LT, Wang YD, Li S, Liang XQ, Wen B, Liang MK, Zhao XF
- 2155** OSW-1 triggers necroptosis in colorectal cancer cells through the RIPK1/RIPK3/MLKL signaling pathway facilitated by the RIPK1-p62/SQSTM1 complex
Wang N, Li CY, Yao TF, Kang XD, Guo HS

LETTER TO THE EDITOR

- 2175** Circulating tumor DNA in liquid biopsy: Current diagnostic limitation

Liu SC

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Hepatocellular carcinoma and musculoskeletal system: A narrative literature review

Jelena Jadzic, Danijela Djonic

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Abstract

Musculoskeletal alterations in hepatocellular carcinoma (HCC) are less common than liver-related complications. However, they can significantly impact the quality of life and overall prognosis of patients with HCC. The main obstacle in the clinical assessment of HCC-induced musculoskeletal alterations is related to effective and timely diagnosis because these complications are often asymptomatic and unapparent during routine clinical evaluations. This narrative literature review aimed to provide a comprehensive overview of the contemporary literature related to the changes in the musculoskeletal system in patients with HCC, focusing on its clinical implications and underlying etiopathogenetic mechanisms. Osteolytic bone metastases are the most common skeletal alterations associated with HCC, which could be associated with an increased risk of low-trauma bone fracture. Moreover, previous studies reported that osteopenia, sarcopenia, and myosteatosis are associated with poor clinical outcomes in patients with HCC. Even though low bone mineral density and sarcopenia are consistently reported as reliable predictors of pretransplantation and post-transplantation mortality in HCC patients, these complications are frequently overlooked in the clinical management of patients with HCC. Taken together, contemporary literature suggests that a multidisciplinary approach is essential for early recognition and clinical management of HCC-associated musculoskeletal alterations to improve patient prognosis. Further research into the mechanisms and treatment options for musculoskeletal complications is warranted to enhance our understanding and clinical management of this aspect of HCC.

Key Words: Hepatocellular carcinoma; Osteopenia; Osteoporosis; Sarcopenia; Bone metastases; Bone fragility

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Core Tip: Musculoskeletal alterations have a powerful detrimental effect on the quality of life and prognosis of patients with hepatocellular carcinoma (HCC). The causes of HCC-induced musculoskeletal decline are complex and not yet fully understood. The biggest challenge in diagnosing HCC-related musculoskeletal changes is timely and effective diagnosis, as these alterations are often asymptomatic and may not be obvious during routine clinical evaluations. Therefore, a multidisciplinary approach to the clinical management of musculoskeletal alterations is essential in patients with HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, comprising 90% of patients with liver malignancy[1]. This type of malignancy typically develops due to end-stage chronic liver disease (around 80% of cases develop from cirrhosis)[2]. HCC rarely develops in the absence of liver cirrhosis or advanced liver fibrosis[3]. The highest incidence of HCC is found in Southeast Asia and North Africa where hepatitis B infection is endemic. In Western countries alcohol-associated and metabolic dysfunction-associated fatty liver disease and steatohepatitis are the predominant factors for HCC development[2,4-6].

Due to the aggressive nature of HCC, the prognosis of patients with HCC is poor (overall 5-year survival rate < 12%)[2], and HCC is the third leading cause of cancer-related deaths worldwide[1]. The estimated incidence of newly diagnosed patients with HCC is around 500000-1000000 per year, causing a global loss of 600000 lives each year[7]. Therefore, early identification of significant risk factors is essential to alter the disease course and improve patient survival and prognosis.

Screening programs for early detection of HCC improved survival in individuals with chronic liver disease who developed HCC[8]. Several prognostic systems have been developed over the years to identify the risk factors that could reveal poor prognosis in patients with HCC including[9]: The Barcelona Clinic Liver Cancer system[10]; the Cancer of the Liver Italian Program[11]; the Chinese University Prognostic Index score[12]; and the Child-Pugh score[10]. Still, all these scoring systems lack parameters considering the nutritional, functional, and performance status of patients with HCC[5]. Although long-term prognosis is dependent on the liver reserve and cancer staging[13], poor performance can significantly affect clinical outcomes in HCC patients. Therefore, the Eastern Cooperative Oncology Group scale was developed to provide an assessment of the performance and functional statuses in patients with HCC[14]. Recent advances in artificial intelligence-based risk calculations have enabled the integration of new risk factors that could significantly alter the clinical management of individuals with HCC[15].

The liver plays a central role in human metabolism, and patients with HCC are at a high risk of developing various complications. While the primary focus in the study of HCC traditionally revolves around liver-related complications (e.g., hepatic encephalopathy, portal vein thrombosis, ascites, variceal bleeding, and obstructive jaundice), recent investigations have shed light on HCC-induced complications in other organs and systems, including the musculoskeletal system. HCC is almost three times more likely to appear in males than in females, with an incidence of 5.5/100000 in males and 2.0/100000 in females[2]. Thus, it is reasonable to predict that sex-specific distribution of musculoskeletal alterations (which are more common in postmenopausal females) could be shifted toward males with HCC.

In addition, it is known that the age distribution of patients with HCC is related to dominant viral hepatitis in the underlying population and the age at which it was acquired. However, it is important to note that HCC reaches its highest prevalence among individuals older than 65 years[2,7,16]. Considering that older age is a major risk factor for developing major musculoskeletal alterations (osteopenia, sarcopenia, and/or osteosarcopenia) and based on the global rise of an aging population[17-19], musculoskeletal complications are steadily becoming a major health concern in individuals with HCC.

Recognizing the importance of musculoskeletal health within the global health agenda, the Global Alliance for Musculoskeletal Health recently made substantial attempts to create a global roadmap for improving musculoskeletal health[20]. The first step on this journey is understanding the complexity of determinants that can affect musculoskeletal health and evaluating the particular health-burden contribution of each of these determinants in individuals who are healthy, aging, or with chronic diseases (Figure 1). Given that musculoskeletal complications are preventable, it is essential to fully understand the interconnections between HCC and musculoskeletal health, which can be beneficial for developing more effective and cost-efficient management strategies and increasing the quality of life for individuals with HCC (Figure 1).

This article aimed to provide a comprehensive narrative overview of the contemporary literature related to the changes in the musculoskeletal system in patients with HCC by focusing on its clinical implications and underlying etiopathogenetic mechanisms. Also, this review aimed to identify potential gaps in the current literature and suggest directions for future studies in HCC-associated musculoskeletal alterations.

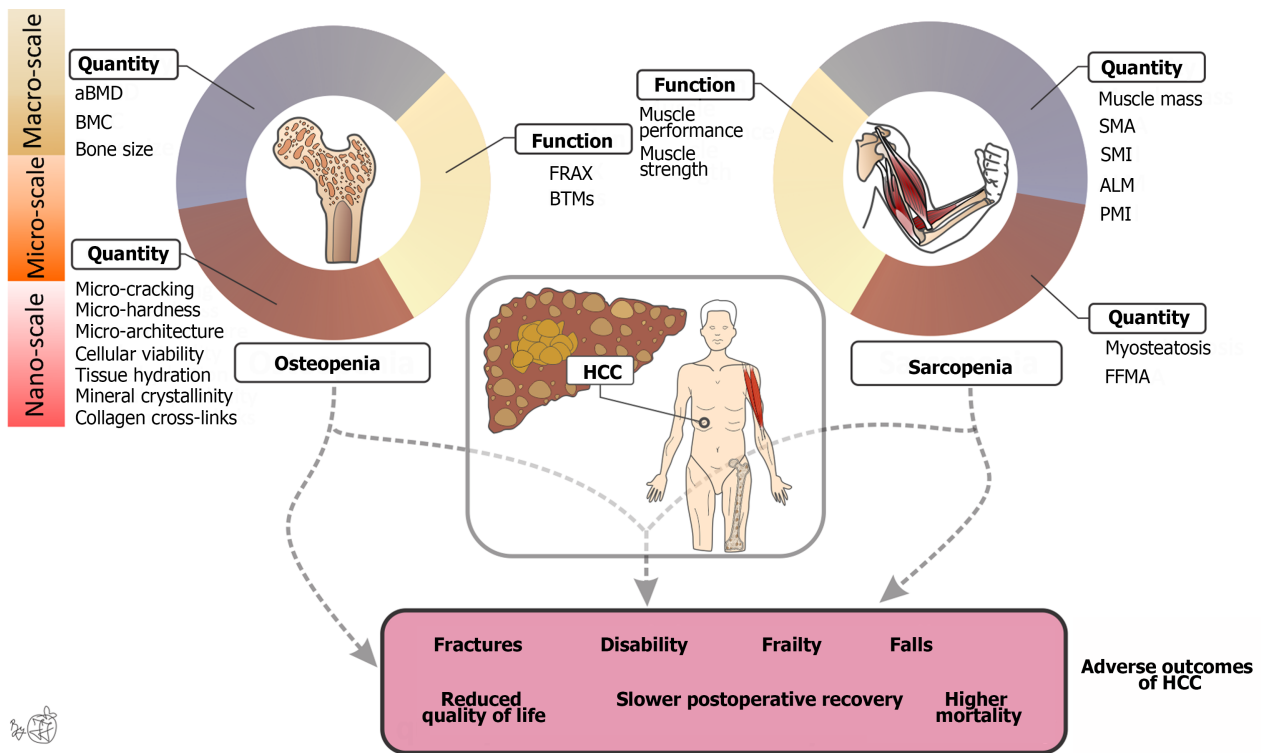


Figure 1 Role of musculoskeletal alterations in clinical management of patients with hepatocellular carcinoma. Various factors contribute to musculoskeletal decline in patients with hepatocellular carcinoma. A multiscale and multidisciplinary approach should be used to assess musculoskeletal health. aBMD: Areal bone mineral density; BMC: Bone mineral content; HCC: Hepatocellular carcinoma; FRAX: Fracture risk assessment tool; BTMs: Bone turnover markers; ALM: Appendicular lean mass; FFMA: Fat-free muscle area; PMI: Psoas muscle index; SMA: Skeletal muscle area; SMI: Skeletal muscle index.

LITERATURE SEARCH STRATEGY

An electronic search was performed using the PubMed/Medline, Embase, Cochrane, Web of Science, and CINAHL databases on November 25, 2023. To identify published articles on skeletal alterations in patients with HCC, we used the following search terms: “carcinoma, hepatocellular” OR “cancer, hepatocellular” AND “osteopenia” OR “osteoporosis” OR “bone mineral density” OR “bone metastases” OR “bone fracture”. To identify published articles on muscular alterations in patients with HCC, we used the following search terms: “carcinoma, hepatocellular” OR “cancer, hepatocellular” AND “sarcopenia” OR “myosteatosis”. Both authors independently reviewed the search results they obtained. Preclinical (basic science) and clinical studies written in English were included in this review. In cases of discrepancies, the dilemma was resolved through discussion, and both authors agreed with the final pool of studies included in the review.

SKELETAL-RELATED EVENTS IN PATIENTS WITH HCC

Bone metastases[21-24], pathological bone fractures[24,25], reduced bone mineral density (BMD)[26,27], hypercalcemia [28], and spinal cord compression[29] are among the most clinically relevant HCC-associated skeletal-related events.

The risk of bone metastasis in patients with HCC is not as prominent as in other common malignancies, such as gastric cancer, lung cancer, or breast cancer. There is a varying incidence of bone metastasis in patients with HCC of 3%-20% [30-32]. Substantial technological progress has been made in diagnosing and treating patients with HCC, which improved the overall survival rate, and bone metastases have become more commonly observed in recent years. Bone metastasis is reported in up to 38.5% of HCC patients at the initial diagnosis, while 11.7% of patients with HCC develop bone metastasis after surgical resection of the primary malignancy[4,33,34]. Moreover, the cumulative incidence of bone metastasis 1 year after diagnosis of extrahepatic disease in patients with HCC is 6.4%[35]. Bone metastasis in patients with HCC is most commonly diagnosed in the axial skeleton [vertebral column (up to 40%), pelvic bone, and ribs][31,34,36]. HCC-associated bone metastases are predominantly osteolytic (flake-like or erosion-like decline in bone density), but it could also be presented as osteoblastic metastasis and formation of expansive soft tissue mass[37,38].

Due to the aggressive disease course, studies investigating bone fractures in patients with HCC are very rare. Some data suggest that up to 13.2% of patients with HCC sustain bone fracture[25], but future well-designed large-scale prospective epidemiological studies are needed to analyze the fracture risk in patients with HCC. In cases when fracture risk analysis is not available, clinical surrogate markers of increased bone fragility are used to indirectly assess bone fracture risk. Reduced BMD (obtained by dual-energy X-ray absorptiometry) is widely accepted as a suitable surrogate marker in the clinical assessment of fracture risk[39,40]. According to recommendations by the World Health Organiz-

ation, individuals with a T score in the range between -1 to -2.5 are defined as those with osteopenia, while individuals with a T score lower than -2.5 are diagnosed with osteoporosis[41].

Although osteopenia and osteoporosis are commonly investigated in patients with various forms of chronic liver diseases[42], a recent shift has been directed at investigating HCC-associated BMD alterations (independent of bone metastasis)[26,27,43,44]. Sharma *et al*[43] demonstrated that vertebral BMD reduction, high tumor burden, and older age are important determinants of post-transplantation mortality in individuals with HCC. Miyachi *et al*[26] reported that preoperative low vertebral BMD was an independent risk factor for long-term outcomes after hepatectomy in male patients with HCC but not in female patients with HCC. Arguably, this sex specificity could be explained by the postmenopausal hormonal status of female subjects included in the study[26]. Most recently, Meister *et al*[44] and Müller *et al*[27] demonstrated that low BMD was associated with inferior survival in elderly patients with HCC undergoing partial hepatectomy or transarterial chemoembolization. These studies coherently implied that the integration of vertebral BMD measurement in a novel clinical algorithm could improve survival prediction and clinical management of patients with HCC and that using rehabilitation programs and specific antiresorptive therapy may further improve treatment outcomes among these individuals[26,27,43,44].

The current understanding of skeletal alterations in patients with HCC is limited by the small sample sizes in available retrospective studies as well as a modest number of these studies. Additionally, previous studies were conducted using vertebral BMD derived from multidetector computed tomography scans and not dual-energy X-ray absorptiometry, which is considered the “gold standard” in the clinical assessment of fracture risk. In addition, widely accepted up-to-date clinical methods used to assess skeletal status have certain limitations. For example, BMD is used as a two-dimensional surrogate marker of bone fragility even though it does not account for other intrinsic bone characteristics (bone quality; Figure 1). Moreover, BMD is in the physiological range in the majority of individuals with bone fractures, and anti-osteoporotic therapy has been reported to reduce fracture risk without affecting BMD[42]. Another important factor is the non-uniformity of the human skeleton, indicating that assessment of bone alterations in patients with HCC should be site specific.

Therefore, future studies should focus on resolving these limitations and on utilizing a hierarchical approach in analyzing the contribution of each bone fragility determinant in patients with HCC (Figure 1). The long-term benefit of multiscale and advanced assessment of bone fragility determinants could be creating a new patient-specific diagnostic algorithm that would provide a more accurate clinical assessment of the skeletal status in patients with HCC.

MUSCULAR ALTERATIONS IN PATIENTS WITH HCC

Recently, numerous research teams have begun studying age-related muscular alterations, which play a significant role in the deteriorating health and well-being of elderly individuals[45-47]. Muscular alterations are considered a natural course of aging[45-47], but these alterations could be exacerbated in various chronic comorbidities and malignancies. Among the most frequent muscular abnormalities that are prevalent in multiple tumors, including HCC, are sarcopenia[48-50] and myosteatorsis[51,52]. Sarcopenia is a condition characterized by a loss of skeletal muscle mass and deterioration in muscle strength and function, while myosteatorsis is characterized by intermuscular and intramuscular accumulation of adipose tissue[52].

A recent systematic review and meta-analysis revealed that the incidence rate of sarcopenia among patients with HCC was 42%[49]. However, there was substantial heterogeneity among the included studies (95% confidence interval: 0.36-0.48)[49]. The data suggested that 30%-40% of patients with HCC that developed from liver cirrhosis showed accelerated progression of sarcopenia at the time of diagnosis[51,53]. Also, the sex-specificity of HCC-associated sarcopenia was revealed in which the prevalence of sarcopenia was higher in studies that included predominantly male patients compared to studies conducted with fewer males (45% *vs* 37%, respectively)[49]. Lastly, the incidence rate of HCC-associated sarcopenia was reported to be higher in patients younger than 60 years when compared to older individuals [49,54]. Thus, previous studies suggest that sarcopenia could be a reliable predictor of inferior outcomes and lower survival rates in patients with HCC[55-59], possibly due to an increased risk of postoperative complications and reduced tolerance to chemotherapy.

Myosteatorsis has initially been neglected in previous studies, but research interest in myosteatorsis is currently increasing[52,59-62]. Previous data suggested a highly variable prevalence of myosteatorsis among individuals with HCC (15.2%-38.8%)[52,60-62]. Patients with HCC-associated myosteatorsis had a higher overall mortality rate compared to individuals with HCC who did not have myosteatorsis[60]. Moreover, the 5-year cancer-specific survival rate after hepatectomy was significantly worse in individuals with myosteatorsis in comparison to patients with HCC who did not have myosteatorsis[61]. These studies suggest that myosteatorsis could be associated with a reduced post-treatment survival rate in patients with HCC[52,60-62].

The current understanding of muscular alterations in patients with HCC is affected by the limited sample size in the available retrospective studies. These studies reported high variability and heterogeneity in the risk of developing muscular alterations in patients with HCC, suggesting that cautious interpretation of the pooled data is necessary. These studies used different diagnostic criteria when defining sarcopenia and myosteatorsis, which indicates that a uniform and standardized diagnostic approach should be applied in future studies. Further, multiple muscles or groups of muscles should be utilized to accurately assess sarcopenia and myosteatorsis. Muscle function, rather than muscle mass, could be an additional and powerful predictor that must be investigated in patients with HCC (Figure 1). Therefore, future well-designed clinical studies should focus on resolving these limitations to confirm the benefits of applying early screening and prevention measures (nutritional support and physical exercise). Since individuals with reduced muscle mass and/or

impaired muscle function have a greater risk of bone loss (osteosarcopenia), balance impairments, and fractures[46,63], clinical tools designed to simultaneously improve skeletal and muscle health are warranted in individuals with HCC.

ETIOPATHOGENETIC MECHANISMS LEADING TO MUSCULOSKELETAL ALTERATIONS IN HCC PATIENTS

Etiopathogenetic mechanisms leading to musculoskeletal alterations in patients with HCC are complex and not fully understood. Musculoskeletal alterations in patients with HCC are believed to result from the complex interplay between nutritional deficiencies, physical inactivity, hepatic dysfunction, hormonal/cytokine disruptions, and immunological imbalance (Figure 2), which could result in a loss of bone and muscle mass, impaired bone and muscular quality, bone and muscle tissue disorganization, and impaired musculoskeletal function[46,47,64].

The systemic proinflammatory milieu associated with HCC triggers the release of numerous cytokines, such as interleukin-6 (IL-6), tumor necrosis factor- α , cyclooxygenases, and prostaglandin E2[44,49,65]. Increased concentrations of cytokines play a pivotal role in HCC-induced cachexia, muscle wasting, and bone resorption, perpetuating the musculoskeletal alterations observed in these patients. It is unclear whether the systematic and local HCC-induced proinflammatory environment accelerates bone loss through stimulation of osteoclastogenesis and activation of the Wnt/ β -catenin pathway[51,66]. Liver dysfunction disrupts standard metabolic mechanisms and hormonal regulation, causing a decline in the serum concentrations of insulin-like growth factor-1 and sex hormones (especially unbound testosterone), thereby displaying a negative effect on the musculoskeletal system[49].

It has been commonly believed that the interaction between the skeletal and muscular systems is primarily mechanical. However, recent studies have demonstrated that bone and muscle tissues have additional endocrine and paracrine functions enabling complex bidirectional bone-muscle crosstalk[46,47]. Local and systematic effects of bone-muscle crosstalk are the foundation for understanding osteosarcopenia in individuals with various chronic liver diseases[46,47, 67,68], including HCC (Figure 2). Muscles release secretory factors known as myokines, that are implicated in positively or negatively affecting the bone independent of mechanical loading. Insulin-like growth factor-1, fibroblast-like growth factor 2, myostatin, irisin, brain-derived neurotrophic factor, osteoglycin, osteoactivin, IL-6, IL-7, and IL-15 are examples of bone-affecting myokines[46,51,69]. Myostatin, IL-6, and follistatin can facilitate the systemic hyperinflammatory state caused by HCC, especially in HCC that developed from advanced liver fibrosis and liver cirrhosis[51,70]. In addition, HCC can affect cellular processes, leading to cell autophagy, oxidative stress, and mitochondrial dysfunction, ultimately leading to musculoskeletal atrophy[49,71].

Currently, there are only a few known bone-derived factors that influence skeletal muscles. Osteokines secreted by osteoblast or osteoclasts and vascular endothelial growth factor derived by bone marrow mesenchymal cells are two examples. Further research into this field is needed[46]. Vascular endothelial growth factor is a crucial angiogenesis-driving factor in the primary HCC lesion as well as in osteolytic bone metastasis[4,24,34]. It has an activating effect on bone resorption through the OPG-RANKL pathway[44,72,73].

Some studies that suggest that the immunological nature of musculoskeletal alterations in HCC are based on poorly understood interactions between the skeletal, muscular, and immune systems and the HCC lesion[44,74]. It is hypothesized that certain anti-resorptive drugs may display significant anti-tumor effects *via* various immunological pathways [44]. It should be noted that changes in cellular metabolism and mitochondrial dysfunction are possible links in cancer-induced cachexia and musculoskeletal alterations[75,76]. These data indicate possible therapeutic value of various factors contributing to cellular oxidative metabolism in patients with HCC-associated musculoskeletal alterations, warranting further research[76,77].

Since understanding multifactorial etiopathogenetic mechanisms responsible for HCC-associated musculoskeletal alterations is still limited, future research should focus on resolving this complex interconnection. These new insights may lead to the development of new cutting-edge therapeutic modalities specifically designed to alleviate the musculoskeletal burden in patients with HCC.

CONCLUSION

Musculoskeletal alterations in HCC, though less common than liver-related complications, can significantly impact the quality of life of patients with HCC. Frequent musculoskeletal alterations associated with HCC are bone metastases, osteosarcopenia, and myosteatosis. However, these complications are frequently overlooked in the clinical management of patients with HCC. Due to the limited data regarding HCC-induced musculoskeletal alterations and its etiopathogenetic mechanisms, further multidisciplinary research on HCC-associated musculoskeletal alterations is needed to provide better clinical management and treatment options and to improve the quality of life in patients with HCC. Considering that individuals with lower bone mass are more likely to present with impaired muscle function and that individuals with impaired muscle function will develop skeletal impairment, clinical tools designed to simultaneously improve skeletal and muscle health are warranted in individuals with HCC.

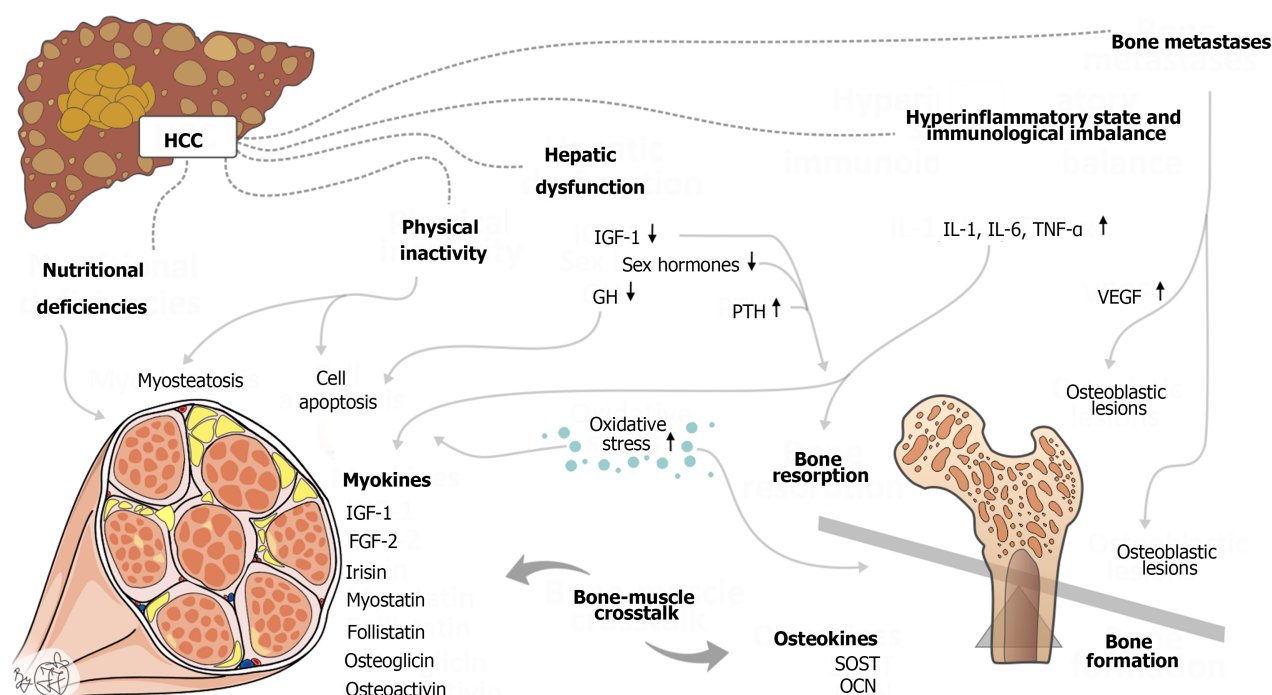


Figure 2 Schematic representation of possible etiopathogenetic mechanisms of musculoskeletal alterations in patients with hepatocellular carcinoma. The possible roles of multiple factors leading to musculoskeletal alterations in patients with hepatocellular carcinoma are shown. HCC: Hepatocellular carcinoma; IGF-1: Insulin-like growth factor 1; FGF-2: Fibroblast-like growth factor 2; GH: Growth hormone; IL: Interleukin; PTH: Parathyroid hormone; OCN: Osteocalcin; SOST: Sclerostin; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor.

FOOTNOTES

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REFERENCES

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
- Mittal S, El-Serag H. Epidemiology of hepatocellular carcinoma. *Pathol Epidemiol Cancer* 2016; **47**: 447-454
- Trevisani F, Frigerio M, Santi V, Grignaschi A, Bernardi M. Hepatocellular carcinoma in non-cirrhotic liver: a reappraisal. *Dig Liver Dis* 2010; **42**: 341-347 [PMID: 19828388 DOI: 10.1016/j.dld.2009.09.002]
- Yuan X, Zhuang M, Zhu X, Cheng D, Liu J, Sun D, Qiu X, Lu Y, Sartorius K. Emerging Perspectives of Bone Metastasis in Hepatocellular Carcinoma. *Front Oncol* 2022; **12**: 943866 [PMID: 35847843 DOI: 10.3389/fonc.2022.943866]
- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21492]

- 10.3322/caac.21660]
- 6 **Geh D**, Manas DM, Reeves HL. Hepatocellular carcinoma in non-alcoholic fatty liver disease-a review of an emerging challenge facing clinicians. *Hepatobiliary Surg Nutr* 2021; **10**: 59-75 [PMID: 33575290 DOI: 10.21037/hbsn.2019.08.08]
 - 7 **Gomaa AI**, Khan SA, Toledano MB, Waked I, Taylor-Robinson SD. Hepatocellular carcinoma: epidemiology, risk factors and pathogenesis. *World J Gastroenterol* 2008; **14**: 4300-4308 [PMID: 18666317 DOI: 10.3748/wjg.14.4300]
 - 8 **European Association For The Study Of The Liver**; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]
 - 9 **Cabibbo G**, Enea M, Attanasio M, Bruix J, Craxi A, Cammà C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. *Hepatology* 2010; **51**: 1274-1283 [PMID: 20112254 DOI: 10.1002/hep.23485]
 - 10 **Reig M**, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado A, Kelley RK, Galle PR, Mazzaferro V, Salem R, Sangro B, Singal AG, Vogel A, Fuster J, Ayuso C, Bruix J. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J Hepatol* 2022; **76**: 681-693 [PMID: 34801630 DOI: 10.1016/j.jhep.2021.11.018]
 - 11 **Daniele B**, Annunziata M, Barletta E, Tinessa V, Di Maio M. Cancer of the Liver Italian Program (CLIP) score for staging hepatocellular carcinoma. *Hepatol Res* 2007; **37** Suppl 2: S206-S209 [PMID: 17877484 DOI: 10.1111/j.1872-034X.2007.00186.x]
 - 12 **Leung TW**, Tang AM, Zee B, Lau WY, Lai PB, Leung KL, Lau JT, Yu SC, Johnson PJ. Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: a study based on 926 patients. *Cancer* 2002; **94**: 1760-1769 [PMID: 11920539 DOI: 10.1002/cncr.10384]
 - 13 **Subramaniam S**, Kelley RK, Venook AP. A review of hepatocellular carcinoma (HCC) staging systems. *Chin Clin Oncol* 2013; **2**: 33 [PMID: 25841912 DOI: 10.3978/j.issn.2304-3865.2013.07.05]
 - 14 **Wu H**, Xing H, Liang L, Huang B, Li C, Lau WY, Zhou YH, Gu WM, Wang H, Chen TH, Zhang YM, Zeng YY, Pawlik TM, Wang MD, Wu MC, Shen F, Yang T. Real-world role of performance status in surgical resection for hepatocellular carcinoma: A multicenter study. *Eur J Surg Oncol* 2019; **45**: 2360-2368 [PMID: 31543386 DOI: 10.1016/j.ejso.2019.09.009]
 - 15 **Mähringer-Kunz A**, Wagner F, Hahn F, Weinmann A, Brodehl S, Schotten S, Hinrichs JB, Düber C, Galle PR, Pinto Dos Santos D, Kloeckner R. Predicting survival after transarterial chemoembolization for hepatocellular carcinoma using a neural network: A Pilot Study. *Liver Int* 2020; **40**: 694-703 [PMID: 31943703 DOI: 10.1111/liv.14380]
 - 16 **El-Serag HB**. Epidemiology of hepatocellular carcinoma in USA. *Hepatol Res* 2007; **37** Suppl 2: S88-S94 [PMID: 17877502 DOI: 10.1111/j.1872-034X.2007.00168.x]
 - 17 **Greco EA**, Pietschmann P, Migliaccio S. Osteoporosis and Sarcopenia Increase Frailty Syndrome in the Elderly. *Front Endocrinol (Lausanne)* 2019; **10**: 255 [PMID: 31068903 DOI: 10.3389/fendo.2019.00255]
 - 18 **Leser JM**, Harriot A, Buck HV, Ward CW, Stains JP. Aging, Osteo-Sarcopenia, and Musculoskeletal Mechano-Transduction. *Front Rehabil Sci* 2021; **2** [PMID: 36004321 DOI: 10.3389/fresc.2021.782848]
 - 19 **Jadzic J**, Mijucic J, Nikolic S, Djuric M, Djonic D. The comparison of age- and sex-specific alteration in pubic bone microstructure: A cross-sectional cadaveric study. *Exp Gerontol* 2021; **150**: 111375 [PMID: 33940115 DOI: 10.1016/j.exger.2021.111375]
 - 20 **Briggs AM**, Chua J, Cross M, Ahmad NM, Finucane L, Haq SA, Joshipura M, Kalla AA, March L, Moscogiuri F, Reis FJJ, Sarfraz S, Sharma S, Soriano ER, Slater H. 'It's about time'. Dissemination and evaluation of a global health systems strengthening roadmap for musculoskeletal health - insights and future directions. *BMJ Glob Health* 2023; **8** [PMID: 37918875 DOI: 10.1136/bmjgh-2023-013786]
 - 21 **Bukhari S**, Ward K, Styler M. Hepatocellular Carcinoma: First Manifestation as Solitary Humeral Bone Metastasis. *Case Rep Oncol Med* 2020; **2020**: 8254236 [PMID: 33343953 DOI: 10.1155/2020/8254236]
 - 22 **Wang X**, Liu J. Hip joint and femur metastases as the first symptom of hepatocellular carcinoma detected by bone scintigraphy. *Radiol Infect Dis* 2015; **2**: 134-136 [DOI: 10.1016/j.jrid.2015.10.002]
 - 23 **Mantonakis EI**, Margariti TS, Petrou AS, Stofas AC, Lazaris AC, Papalampros AE, Moris DN, Michail PO. A pathological fracture and a solitary mass in the right clavicle: an unusual first presentation of HCC and the role of immunohistochemistry. *World J Surg Oncol* 2012; **10**: 50 [PMID: 22400493 DOI: 10.1186/1477-7819-10-50]
 - 24 **Huang Z**, Wen J, Wang Y, Han S, Li Z, Hu X, Zhu D, Wang Z, Liang J, Liang H, Chen XP, Zhang B. Bone metastasis of hepatocellular carcinoma: facts and hopes from clinical and translational perspectives. *Front Med* 2022; **16**: 551-573 [PMID: 35852753 DOI: 10.1007/s11684-022-0928-z]
 - 25 **Hirai T**, Shinoda Y, Tateishi R, Asaoka Y, Uchino K, Wake T, Kobayashi H, Ikegami M, Sawada R, Haga N, Koike K, Tanaka S. Early detection of bone metastases of hepatocellular carcinoma reduces bone fracture and paralysis. *Jpn J Clin Oncol* 2019; **49**: 529-536 [PMID: 30957835 DOI: 10.1093/jcco/hyz028]
 - 26 **Miyachi Y**, Kaido T, Yao S, Shirai H, Kobayashi A, Hamaguchi Y, Kamo N, Yagi S, Uemoto S. Bone Mineral Density as a Risk Factor for Patients Undergoing Surgery for Hepatocellular Carcinoma. *World J Surg* 2019; **43**: 920-928 [PMID: 30465085 DOI: 10.1007/s00268-018-4861-x]
 - 27 **Müller L**, Mähringer-Kunz A, Auer TA, Fehrenbach U, Gebauer B, Haubold J, Theysohn JM, Kim MS, Kleesiek J, Diallo TD, Eisenblätter M, Bettinger D, Steinle V, Mayer P, Zopfs D, Pinto Dos Santos D, Kloeckner R. Low bone mineral density is a prognostic factor for elderly patients with HCC undergoing TACE: results from a multicenter study. *Eur Radiol* 2023; **33**: 1031-1039 [PMID: 35986768 DOI: 10.1007/s00330-022-09069-8]
 - 28 **Bashir AM**, Mohamed AH, Mohamed HN, Ibrahim IG. Severe Hypercalcemia as an Initial Presentation of Advanced Hepatocellular Carcinoma: A Case Report. *Cancer Manag Res* 2022; **14**: 1577-1580 [PMID: 35509872 DOI: 10.2147/CMAR.S364996]
 - 29 **Liaukovich M**, Wu S, Yoon S, Schaffer J, Wang JC. Hepatocellular carcinoma presenting as spinal cord compression in Native Americans with controlled hepatitis C: two case reports. *J Med Case Rep* 2018; **12**: 282 [PMID: 30268151 DOI: 10.1186/s13256-018-1807-8]
 - 30 **Okazaki N**, Yoshino M, Yoshida T, Hirohashi S, Kishi K, Shimamoto Y. Bone metastasis in hepatocellular carcinoma. *Cancer* 1985; **55**: 1991-1994 [PMID: 2983871 DOI: 10.1002/1097-0142(19850501)55:9<1991::AID-CNCR2820550927>3.0.CO;2-F]
 - 31 **Kim S**, Chun M, Wang H, Cho S, Oh YT, Kang SH, Yang J. Bone metastasis from primary hepatocellular carcinoma: characteristics of soft tissue formation. *Cancer Res Treat* 2007; **39**: 104-108 [PMID: 19746218 DOI: 10.4143/crt.2007.39.3.104]
 - 32 **Lee YT**, Geer DA. Primary liver cancer: pattern of metastasis. *J Surg Oncol* 1987; **36**: 26-31 [PMID: 3041113 DOI: 10.1002/jso.2930360107]
 - 33 **Natsuizaka M**, Omura T, Akaike T, Kuwata Y, Yamazaki K, Sato T, Karino Y, Toyota J, Suga T, Asaka M. Clinical features of hepatocellular carcinoma with extrahepatic metastases. *J Gastroenterol Hepatol* 2005; **20**: 1781-1787 [PMID: 16246200 DOI: 10.1111/j.1440-1746.2005.03919.x]

- 34 **Ozer M**, Goksu SY, Lin RY, Ayasun R, Kahramangil D, Rogers SC, Fabregas JC, Ramnaraigh BH, George TJ, Feely M, Cabrera R, Duarte S, Zarrinpar A, Sahin I. Effects of Clinical and Tumor Characteristics on Survival in Patients with Hepatocellular Carcinoma with Bone Metastasis. *J Hepatocell Carcinoma* 2023; **10**: 1129-1141 [PMID: 37489126 DOI: 10.2147/JHC.S417273]
- 35 **Harding JJ**, Abu-Zeinah G, Chou JF, Owen DH, Ly M, Lowery MA, Capanu M, Do R, Kemeny NE, O'Reilly EM, Saltz LB, Abou-Alfa GK. Frequency, Morbidity, and Mortality of Bone Metastases in Advanced Hepatocellular Carcinoma. *J Natl Compr Canc Netw* 2018; **16**: 50-58 [PMID: 29295881 DOI: 10.6004/jnccn.2017.7024]
- 36 **Bhatia R**, Ravulapati S, Befeler A, Dombrowski J, Gadani S, Poddar N. Hepatocellular Carcinoma with Bone Metastases: Incidence, Prognostic Significance, and Management-Single-Center Experience. *J Gastrointest Cancer* 2017; **48**: 321-325 [PMID: 28891006 DOI: 10.1007/s12029-017-9998-6]
- 37 **He J**, Zeng ZC, Tang ZY, Fan J, Zhou J, Zeng MS, Wang JH, Sun J, Chen B, Yang P, Pan BS. Clinical features and prognostic factors in patients with bone metastases from hepatocellular carcinoma receiving external beam radiotherapy. *Cancer* 2009; **115**: 2710-2720 [PMID: 19382203 DOI: 10.1002/cncr.24300]
- 38 **Chen HY**, Ma XM, Bai YR. Radiographic characteristics of bone metastases from hepatocellular carcinoma. *Contemp Oncol (Pozn)* 2012; **16**: 424-431 [PMID: 23788922 DOI: 10.5114/wo.2012.31773]
- 39 **Cummings SR**, Karpf DB, Harris F, Genant HK, Ensrud K, LaCroix AZ, Black DM. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. *Am J Med* 2002; **112**: 281-289 [PMID: 11893367 DOI: 10.1016/S0002-9343(01)01124-X]
- 40 **Garnero P**, Delmas PD. Contribution of bone mineral density and bone turnover markers to the estimation of risk of osteoporotic fracture in postmenopausal women. *J Musculoskelet Neuronal Interact* 2004; **4**: 50-63 [PMID: 15615078]
- 41 **Lin YH**, Shih YT, Teng MMH. The Impact of the "Osteo" Component of Osteosarcopenia on Fragility Fractures in Post-Menopausal Women. *Int J Mol Sci* 2021; **22** [PMID: 34067582 DOI: 10.3390/ijms22105256]
- 42 **Jadzic J**, Djonic D. Bone loss in chronic liver diseases: Could healthy liver be a requirement for good bone health? *World J Gastroenterol* 2023; **29**: 825-833 [PMID: 36816627 DOI: 10.3748/wjg.v29.i5.825]
- 43 **Sharma P**, Parikh ND, Yu J, Barman P, Derstine BA, Sonnenday CJ, Wang SC, Su GL. Bone mineral density predicts posttransplant survival among hepatocellular carcinoma liver transplant recipients. *Liver Transpl* 2016; **22**: 1092-1098 [PMID: 27064263 DOI: 10.1002/lt.24458]
- 44 **Meister FA**, Verhoeven S, Mantas A, Liu WJ, Jiang D, Heij L, Heise D, Bruners P, Lang SA, Ulmer TF, Neumann UP, Bednarsch J, Czigany Z. Osteopenia is associated with inferior survival in patients undergoing partial hepatectomy for hepatocellular carcinoma. *Sci Rep* 2022; **12**: 18316 [PMID: 36316524 DOI: 10.1038/s41598-022-21652-z]
- 45 **Frontera WR**, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R. Aging of skeletal muscle: a 12-yr longitudinal study. *J Appl Physiol* (1985) 2000; **88**: 1321-1326 [PMID: 10749826 DOI: 10.1152/jappl.2000.88.4.1321]
- 46 **Smith C**, Sim M, Dalla Via J, Levinger I, Duque G. The Interconnection Between Muscle and Bone: A Common Clinical Management Pathway. *Calcif Tissue Int* 2024; **114**: 24-37 [PMID: 37922021 DOI: 10.1007/s00223-023-01146-4]
- 47 **El Miedany Y**, Mahran S, Elwakil W. One musculoskeletal health: towards optimizing musculoskeletal health in Egypt-how to be a bone and muscle builder by the Egyptian Academy of Bone Health and Metabolic Bone Diseases. *Egypt Rheumatol Rehabil* 2023; **50** [DOI: 10.1186/s43166-023-00199-5]
- 48 **Rier HN**, Jager A, Sleijfer S, Maier AB, Levin MD. The Prevalence and Prognostic Value of Low Muscle Mass in Cancer Patients: A Review of the Literature. *Oncologist* 2016; **21**: 1396-1409 [PMID: 27412391 DOI: 10.1634/theoncologist.2016-0066]
- 49 **Liu J**, Luo H, Huang L, Wang J. Prevalence of sarcopenia among patients with hepatocellular carcinoma: A systematic review and metaanalysis. *Oncol Lett* 2023; **26**: 283 [PMID: 37274463 DOI: 10.3892/ol.2023.13869]
- 50 **Ha Y**, Kim D, Han S, Chon YE, Lee YB, Kim MN, Lee JH, Park H, Rim KS, Hwang SG. Sarcopenia Predicts Prognosis in Patients with Newly Diagnosed Hepatocellular Carcinoma, Independent of Tumor Stage and Liver Function. *Cancer Res Treat* 2018; **50**: 843-851 [PMID: 28882021 DOI: 10.4143/crt.2017.232]
- 51 **Perisetti A**, Goyal H, Yendala R, Chandan S, Tharian B, Thandassery RB. Sarcopenia in hepatocellular carcinoma: Current knowledge and future directions. *World J Gastroenterol* 2022; **28**: 432-448 [PMID: 35125828 DOI: 10.3748/wjg.v28.i4.432]
- 52 **Chen BB**, Liang PC, Shih TT, Liu TH, Shen YC, Lu LC, Lin ZZ, Hsu C, Hsu CH, Cheng AL, Shao YY. Sarcopenia and myosteosis are associated with survival in patients receiving immunotherapy for advanced hepatocellular carcinoma. *Eur Radiol* 2023; **33**: 512-522 [PMID: 35864351 DOI: 10.1007/s00330-022-08980-4]
- 53 **Begini P**, Gigante E, Antonelli G, Carbonetti F, Iannicelli E, Anania G, Imperatrice B, Pellicelli AM, Fave GD, Marignani M. Sarcopenia predicts reduced survival in patients with hepatocellular carcinoma at first diagnosis. *Ann Hepatol* 2017; **16**: 107-114 [PMID: 28051799 DOI: 10.5604/16652681.1226821]
- 54 **Lim J**, Kim KW, Ko Y, Jang IY, Lee YS, Chung YH, Lee HC, Lim YS, Kim KM, Shim JH, Choi J, Lee D. The role of muscle depletion and visceral adiposity in HCC patients aged 65 and over undergoing TACE. *BMC Cancer* 2021; **21**: 1164 [PMID: 34715813 DOI: 10.1186/s12885-021-08905-2]
- 55 **Lanza E**, Masetti C, Messina G, Muglia R, Pugliese N, Ceriani R, Lleo de Nalda A, Rimassa L, Torzilli G, Poretti D, D'Antuono F, Politi LS, Pedicini V, Aghemo A; Humanitas HCC Multidisciplinary Group. Sarcopenia as a predictor of survival in patients undergoing bland transarterial embolization for unresectable hepatocellular carcinoma. *PLoS One* 2020; **15**: e0232371 [PMID: 32555707 DOI: 10.1371/journal.pone.0232371]
- 56 **Kobayashi A**, Kaido T, Hamaguchi Y, Okumura S, Shirai H, Yao S, Kamo N, Yagi S, Taura K, Okajima H, Uemoto S. Impact of Sarcopenic Obesity on Outcomes in Patients Undergoing Hepatectomy for Hepatocellular Carcinoma. *Ann Surg* 2019; **269**: 924-931 [PMID: 29064889 DOI: 10.1097/SLA.0000000000002555]
- 57 **Yang J**, Chen K, Zheng C, Lin J, Meng Q, Chen Z, Deng L, Yu H, Deng T, Bo Z, He Q, Wang Y, Chen G. Impact of sarcopenia on outcomes of patients undergoing liver resection for hepatocellular carcinoma. *J Cachexia Sarcopenia Muscle* 2022; **13**: 2383-2392 [PMID: 35854105 DOI: 10.1002/jcsm.13040]
- 58 **Guo Y**, Ren Y, Zhu L, Yang L, Zheng C. Association between sarcopenia and clinical outcomes in patients with hepatocellular carcinoma: an updated meta-analysis. *Sci Rep* 2023; **13**: 934 [PMID: 36650190 DOI: 10.1038/s41598-022-27238-z]
- 59 **Mardian Y**, Yano Y, Ratnasari N, Choridah L, Wasityastuti W, Setyawan NH, Hayashi Y. "Sarcopenia and intramuscular fat deposition are associated with poor survival in Indonesian patients with hepatocellular carcinoma: a retrospective study". *BMC Gastroenterol* 2019; **19**: 229 [PMID: 31888500 DOI: 10.1186/s12876-019-1152-4]
- 60 **Bannangkoon K**, Hongsakul K, Tubtawee T, Ina N, Chichareon P. Association of myosteosis with treatment response and survival in

- patients with hepatocellular carcinoma undergoing chemoembolization: a retrospective cohort study. *Sci Rep* 2023; **13**: 3978 [PMID: 36894658 DOI: 10.1038/s41598-023-31184-9]
- 61 **Yoshikawa K**, Shimada M, Morine Y, Ikemoto T, Saito Y, Yamada S, Teraoku H, Takao S. Clinical impact of myosteatoses measured by magnetic resonance imaging on long-term outcomes of hepatocellular carcinoma after radical hepatectomy. *BMC Surg* 2023; **23**: 281 [PMID: 37715229 DOI: 10.1186/s12893-023-02188-z]
 - 62 **Yi X**, Fu Y, Long Q, Zhao Y, Li S, Zhou C, Lin H, Liu X, Liu C, Chen C, Shi L. Myosteatoses can Predict Unfavorable Outcomes in Advanced Hepatocellular Carcinoma Patients Treated With Hepatic Artery Infusion Chemotherapy and Anti-PD-1 Immunotherapy. *Front Oncol* 2022; **12**: 892192 [PMID: 35651812 DOI: 10.3389/fonc.2022.892192]
 - 63 **Lee A**, McArthur C, Ioannidis G, Duque G, Adachi JD, Griffith LE, Thabane L, Papaioannou A. Associations between Osteosarcopenia and Falls, Fractures, and Frailty in Older Adults: Results From the Canadian Longitudinal Study on Aging (CLSA). *J Am Med Dir Assoc* 2024; **25**: 167-176.e6 [PMID: 37925161 DOI: 10.1016/j.jamda.2023.09.027]
 - 64 **Zebaze R**, Ebeling PR. Disorganization and Musculoskeletal Diseases: Novel Insights into the Enigma of Unexplained Bone Abnormalities and Fragility Fractures. *Curr Osteoporos Rep* 2023; **21**: 154-166 [PMID: 36494594 DOI: 10.1007/s11914-022-00759-2]
 - 65 **Yang YM**, Kim SY, Seki E. Inflammation and Liver Cancer: Molecular Mechanisms and Therapeutic Targets. *Semin Liver Dis* 2019; **39**: 26-42 [PMID: 30809789 DOI: 10.1055/s-0038-1676806]
 - 66 **Yang YJ**, Kim DJ. An Overview of the Molecular Mechanisms Contributing to Musculoskeletal Disorders in Chronic Liver Disease: Osteoporosis, Sarcopenia, and Osteoporotic Sarcopenia. *Int J Mol Sci* 2021; **22** [PMID: 33807573 DOI: 10.3390/ijms22052604]
 - 67 **Kang KY**, Kang Y, Kim M, Kim Y, Yi H, Kim J, Jung HR, Park SH, Kim HY, Ju JH, Hong YS. The effects of antihypertensive drugs on bone mineral density in ovariectomized mice. *J Korean Med Sci* 2013; **28**: 1139-1144 [PMID: 23960439 DOI: 10.3346/jkms.2013.28.8.1139]
 - 68 **Jadzic J**, Milovanovic PD, Cvetkovic D, Zivkovic V, Nikolic S, Tomanovic N, Djuric MP, Djonic D. The altered osteocytic expression of connexin 43 and sclerostin in human cadaveric donors with alcoholic liver cirrhosis: Potential treatment targets. *J Anat* 2022; **240**: 1162-1173 [PMID: 34978341 DOI: 10.1111/joa.13621]
 - 69 **Tagliaferri C**, Wittant Y, Davicco MJ, Walrand S, Coxam V. Muscle and bone, two interconnected tissues. *Ageing Res Rev* 2015; **21**: 55-70 [PMID: 25804855 DOI: 10.1016/j.arr.2015.03.002]
 - 70 **Choi K**, Jang HY, Ahn JM, Hwang SH, Chung JW, Choi YS, Kim JW, Jang ES, Choi GH, Jeong SH. The association of the serum levels of myostatin, follistatin, and interleukin-6 with sarcopenia, and their impacts on survival in patients with hepatocellular carcinoma. *Clin Mol Hepatol* 2020; **26**: 492-505 [PMID: 32646201 DOI: 10.3350/cmh.2020.0005]
 - 71 **Phillips T**, Leeuwenburgh C. Muscle fiber specific apoptosis and TNF-alpha signaling in sarcopenia are attenuated by life-long calorie restriction. *FASEB J* 2005; **19**: 668-670 [PMID: 15665035 DOI: 10.1096/fj.04-2870fje]
 - 72 **Jones DH**, Nakashima T, Sanchez OH, Kozieradzki I, Komarova SV, Sarosi I, Morony S, Rubin E, Sarao R, Hojilla CV, Komnenovic V, Kong YY, Schreiber M, Dixon SJ, Sims SM, Khokha R, Wada T, Penninger JM. Regulation of cancer cell migration and bone metastasis by RANKL. *Nature* 2006; **440**: 692-696 [PMID: 16572175 DOI: 10.1038/nature04524]
 - 73 **Takayanagi H**. Osteoclast differentiation and activation. *Clin Calcium* 2007; **17**: 484-492
 - 74 **Takayanagi H**. Osteoimmunology: shared mechanisms and crosstalk between the immune and bone systems. *Nat Rev Immunol* 2007; **7**: 292-304 [PMID: 17380158 DOI: 10.1038/nri2062]
 - 75 **Carson JA**, Hardee JP, VanderVeen BN. The emerging role of skeletal muscle oxidative metabolism as a biological target and cellular regulator of cancer-induced muscle wasting. *Semin Cell Dev Biol* 2016; **54**: 53-67 [PMID: 26593326 DOI: 10.1016/j.semedb.2015.11.005]
 - 76 **Penna F**, Ballarò R, Beltrà M, De Lucia S, García Castillo L, Costelli P. The Skeletal Muscle as an Active Player Against Cancer Cachexia. *Front Physiol* 2019; **10**: 41 [PMID: 30833900 DOI: 10.3389/fphys.2019.00041]
 - 77 **Sun X**, Sun G, Huang Y, Hao Y, Tang X, Zhang N, Zhao L, Zhong R, Peng Y. 3-Bromopyruvate regulates the status of glycolysis and BCNU sensitivity in human hepatocellular carcinoma cells. *Biochem Pharmacol* 2020; **177**: 113988 [PMID: 32330495 DOI: 10.1016/j.bcp.2020.113988]



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