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RESEARCH ARTICLE

Navigating Hepatocellular Carcinoma Treatment in the Context of Frailty

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ABSTRACT:
The aim of this review is to explore the implications of frailty in the treatment of patients with hepatocellular carcinoma (HCC). Frailty, a multidimensional geriatric syndrome, has been increasingly recognized as an important predictor of adverse outcomes and mortality in various patient populations. This review specifically focuses on the prevalence of frailty in the cirrhotic population and its role as a prognostic tool for procedural and surgical outcomes of transplantation, hepatectomy and liver-directed therapies. Understanding the impact of frailty on HCC treatment can help guide clinicians in optimizing management strategies and improving patient outcomes.

Introduction:

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and represents a significant global health burden. It accounts for approximately 75-85% of all primary liver cancer cases and is responsible for a substantial number of cancer-related deaths worldwide.[1] The incidence of HCC has been steadily increasing over the past decades, primarily due to the rising prevalence of chronic liver diseases, including viral hepatitis, alcoholic liver disease, and non-alcoholic fatty liver disease.[2] Cirrhosis is present in 80-90% of patients with HCC, and regular surveillance for HCC is recommended for all cirrhotic patients to facilitate early detection and improve the chances of successful treatment.[3]

The management of HCC poses significant challenges due to its aggressive nature and the frequent presence of underlying liver dysfunction. Treatment options for HCC depend on various factors, including tumor stage, liver function, and patient comorbidities. Common therapeutic modalities include surgical resection, liver transplantation, locoregional therapies (including transarterial chemoembolization, ablation, and radioembolization), and systemic therapies (such as molecular targeted agents and immunotherapy).[3-4]

In recent years, the concept of frailty has emerged as a crucial consideration in the context of cancer treatment, including HCC. Frailty is a multidimensional geriatric syndrome characterized by decreased physiological reserve, diminished resilience, and increased vulnerability to stressors. It encompasses physical, psychological, and social aspects, and reflects an individual's overall health status and functional capacity. [5-6]

The significance of frailty in HCC treatment lies in its association with adverse outcomes, increased morbidity and mortality, and impaired treatment response. Frailty has been identified as a strong predictor of postoperative complications, prolonged hospital stays, reduced treatment tolerability, and decreased survival rates in various cancer populations.[6-7] Recognizing frailty in HCC patients is crucial for risk stratification, treatment decision-making, and optimizing patient outcomes.

Despite the growing recognition of frailty as an important factor in cancer care, its implications in the treatment of HCC remain understudied. Understanding the impact of frailty on HCC treatment outcomes including liver transplantation and surgical interventions such as hepatectomy and locoregional therapies, is crucial for developing personalized management strategies.

This review paper aims to explore the implications of frailty in the treatment of patients with HCC. Specifically, it will focus on prevalence of frailty among cirrhotic patients and the implications of frailty on perioperative morbidity and mortality for patients undergoing systemic, locoregional and surgical interventions for treatment of HCC. By synthesizing the existing literature on frailty and its impact on HCC treatment, this review aims to provide valuable insights for researchers and healthcare providers caring for this patient population. The knowledge gained from this analysis can guide the development of comprehensive and patient-centered strategies to optimize the care of frail individuals with HCC, ultimately improving treatment outcomes and enhancing the quality of life for these patients.

Definition, prevalence and pathophysiology of frailty in cirrhotic patients

Frailty is defined as a biological syndrome characterized by diminishing physiological reserve and heightened vulnerability to health stressors. Within the context of cirrhosis, the frail phenotype is primarily driven by hepatic-specific factors such as dysfunction of protein synthesis, muscle toxicity related to ammonia, and inactivity secondary to hepatic encephalopathy. These physiologic changes lead to a loss of muscle function known as physical frailty.[8]

There are multiple validated tools for assessing physical frailty. One of the most utilized assessment tools in surgical literature is the modified Frailty Index (mFI), which assigns frailty score for patients based on 5-11 patient specific factors/ comorbidities that can be found in the National Surgical Quality Improvement Program (NSQIP) database (Table 1). [9] Another validated tool for frailty assessment is the Fried Frailty Index (FFI) which assess 5 components of physical frailty: unintentional weight loss, weakness (grip strength), exhaustion, slow walking speed and low physical activity. The downside of this tool is that it relies on self-reported measures that can be difficult to ascertain from patients. [10] The Liver Frailty Index (LFI) is a tool has been specifically developed and validated in the cirrhotic population. It is comprised of three parameters: grip strength, chair stands, and balance testing. These assessments can be easily performed in the office setting and have demonstrated improved prognostic accuracy of predicting wait-list mortality for patients on transplant list. [11]

Table 1: Frailty Scoring Systems (NSQIP)

11 Factor Frailty Index	5 Factor Frailty Index
Functional dependent	Functional dependent
History of diabetes	History of diabetes
Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease
Congestive heart failure	Congestive heart failure
Hypertension	Hypertension
Cognitive impairment	
Delirium	
Stroke	
Cerebrovascular deficits	
Coronary artery disease	
Myocardial infarct	

In 2021, Tandon et al published a comprehensive review on the topic of frailty in the cirrhotic population in the Journal of Hepatology, which highlights the presence of common drivers of frailty in both aging and decompensated cirrhosis, including hepatic encephalopathy, sarcopenia, altered gut microbiota, bacterial translocation, endotoxemia, chronic inflammation, and toxic substances. Sarcopenia is defined as the progressive and generalized loss of muscle mass, which is a component of frailty and a common complication of cirrhosis. Sarcopenia and frailty are prevalent in a significant proportion of cirrhosis patients, ranging from 40% to 70% and 18% to 43% respectively. Both sarcopenia and frailty individually are associated with an increased risk of complications related to liver decompensation, such as ascites, hepatic encephalopathy, and infection. [12] The authors of this paper proposed a bidirectional relationship between progression of cirrhosis and frailty, as decompensation and acute-on-chronic liver failure (ACLF) can further exacerbate sarcopenia and frailty through factors like anorexia, ascites, hepatic encephalopathy, pro-inflammatory cytokines, reduced nutritional intake, and physical inactivity, which then in turns lead to further decompensation. Further research is needed to delve into the specific mechanisms and the impact of sarcopenia and frailty on the risk of decompensation in cirrhosis patients.

A recent prospective study published in 2022 by Wang et all in the Journal of Hepatology evaluated the effect of frailty on the risk of cirrhosis disease progression and death utilizing the LFI tool. They found that frailty was associated with a significantly increased risk of progression or death (HR, 2.45; 95% CI, 1.14-5.29) in patients with both compensated and decompensated cirrhosis. Additionally, frailty was associated with an increased risk of unplanned hospitalizations (2.32; 95% CI, 1.13-4.79), after adjusting for age, sex, and MELD score.[13] Therefore, frailty was identified as an independent predictor of adverse outcomes, even after accounting for other factors. These findings highlight the importance of considering frailty in the management and prognosis of cirrhosis patients, suggesting that early identification of frailty may enable interventions to improve outcomes and enhance patient care. [12-13]

Implication of frailty on surgical outcomes: waitlist transplant mortality

About one in ten individuals on the transplant waiting list are taken off because they have become "too sick for transplant." This decision reflects the clinician's assessment of the patient's global health status, that they are too frail or ill to survive or fully recover from the transplant surgery. Despite the consideration of frailty in making this decision, until recently there was no objective measure to guide crucial decision of determining who is considered "too frail" for transplant surgery. The Frailty Assessment in Liver Transplant Candidates Study (FrAI-LT Study) aimed to shed light on this topic by assessing the prevalence and degree of frailty in liver transplant candidates and evaluate the association between these frailty and waitlist mortality. This multicenter prospective study included data from 1,166 liver transplant recipients across eight medical centers in the United States from 2012 to 2019. The findings revealed that frail recipients of liver transplants had a higher risk of post-transplant mortality, with a cumulative incidence of death of 16% at 5 years among frail patients compared to 10% among non-frail patients. Furthermore, frail patients experienced significantly longer hospital stays after transplantation, increased intensive care unit utilization, and were more likely to be discharged to a rehabilitation facility.[13-14]

Frailty and the gender gap for waitlist mortality

There is a significant disparity between women and

men in receiving liver transplants in the United States, with women being 17% to 30% less likely to undergo this life-saving procedure. Consequently, women face a 30% higher risk of mortality while on the transplant waiting list compared to men.[15] The reasons behind this gender gap in wait list outcomes are not entirely understood, but some hypotheses suggest that it may be due to a lack of appropriately sized organs available for women, as well as potential underestimation of renal dysfunction in the MELD score, which is influenced by lower muscle mass and creatinine levels in women, however these factors alone do not explain the gender disparity. Given the reduced muscle mass, ammonia-related myotoxicity and impaired muscle function play a significant role in the frailty commonly observed in patients with cirrhosis.[16]

Lai et al sought to evaluate how frailty differs between men and women awaiting liver transplant and if it may contribute to the liver transplant gender gap.[15] This prospective cohort study involved 1,405 patients with cirrhosis awaiting liver transplant. The study found that women had higher frailty scores compared to men (mean [SD], 4.12 [0.85] vs 4.00 [0.82]; P = .003). Interestingly, this observation held true even when accounting for lower rates of medical comorbidities, similar disease severity scores, and comparable rates of complications associated with cirrhosis. After accounting for all these variables, the sex differences in liver frailty score (LFI) persisted at 0.16 (95% CI, 0.08-0.23) units higher in women than in men (P<0.001). The presence of frailty among women played a role in attenuating the association between female sex and mortality. The cumulative incidence of wait list mortality was 22.9% at 24 months compared to 14.8% at 24 months among men. Incorporating the sex difference in frailty improved model quality for estimation of wait list mortality and further statistical analysis demonstrated that frailty contributes to approximately 13% of the gender gap in wait list mortality.[16] These findings shed light on the role of frailty in explaining some of the disparities in liver transplant outcomes between men and women.

The effects of frailty on hepatectomy

Hepatectomy, when possible is a potentially curative treatment for hepatic malignancies. In an increasingly ageing global population, there is a growing number of frail and elderly patients who are being considered for hepatectomy. Data have shown that age should not be a limiting factor for liver resection, as it cannot accurately predict postoperative outcomes.[17] Instead, frailty can serve as a more reliable measure of the patient's overall health and functional reserves. Frailty is common in patients undergoing hepatectomy, with a reported incidence of 14–29% and some data suggesting an association with worse post-operative outcomes.[17-18] In a retrospective analysis of 152 patients who underwent hepatectomy, the relationship between age, frailty, and the primary outcomes of 90-day mortality, post-operative complications, and length of hospital stay were assessed. The study showed that frailty was an independent predictor of morbidity and mortality after hepatectomy. Despite acceptable short-term outcomes, frail patients were exposed to an increased risk of medical complications and prolonged recovery (36.3% vs. 26.1%, $p < 0.001$) as well as increased risk of post-operative mortality (6.6% vs. 2.9%, $p < 0.001$) compared to non-frail patients. Interestingly, comparison of outcomes between frail and robust patients within the elderly (>75) and younger patient subgroups demonstrated similar outcomes. Younger frail patient had a similar risk of 90-day mortality (OR 2.25, 95% CI 1.30–3.89) compared to robust elderly patients (OR 2.2, 95% CI 0.88–5.46). [18-19]

Frailty and locoregional therapy

While an interventional radiology procedure such as transarterial chemoembolization is seen as a minimally invasive, low-risk oncological therapy, it still poses many physiological challenges for patients. The procedure itself delivers chemotherapy agents to the liver, which carries a higher likelihood of toxicity in frail patients with altered metabolism. Patients undergo periprocedural fasting and receive opioid analgesics and anesthetic agents. They often experience postprocedural pain, nausea and vomiting, an unfamiliar hospital environment, and a period of immobility. Although these series of insults may be tolerable for a healthy patient with sufficient physiological reserve, they can result in higher risk of short-term complications and long-term mortality in frail patients, as we have observed from our own institutional analysis.

Based on our retrospective analysis of a cohort of 125 patients who underwent transarterial chemoembolization, frailty (as determined by mFI-5 scoring system) independently predicted higher risk of post-TACE complications and lower transplant-free-survival (median survival time 28.1 vs. 39.8 months, $p = 0.03$) after chemoembolization. Within the 30-day postprocedural period, frail patients were found to have a significantly higher likelihood of hepatic decompensation ($p = 0.01$) and greater risk of 30-day hospital re-admission

(p=0.03) for treatment of urinary retention as well as pulmonary and urinary tract infections.[20]

Frailty and systemic therapy

Systemic therapy is a very common treatment for many forms of cancer including unrespectable HCC. Cancer disproportionately affects older people, and with the aging global population, there will be more people with cancer diagnosis presenting for treatment including chemotherapy, targeted therapy, and immunotherapy. It is well known that chronological age alone is a poor predictor of treatment tolerance. In recent years, frailty assessment has emerged as a valuable predictive tool for chemotherapy intolerance, especially in older patients. While Eastern Cooperative Oncology Group performance status (ECOG-PS) is commonly used to assess a patient's ability to tolerate treatment, it fails to consider age, comorbidities, or other aspects of frailty. Several studies from different parts of the world have recognized the significance of frailty assessment in patient selection and risk stratification for systemic therapy, with some associating frailty with a higher risk of treatment-related toxicities and poor treatment tolerance.[21]

There have been 2 large scale prospective studies looking at a heterogenous sample of cancer patients that have demonstrated higher risk of chemotherapy related toxicity in frail patients. Hurria et al reported the results of a large prospective study from the Cancer and Aging Research Group, which included 500 patients across various institutions in the United States. The study showed significant associations between grade 3, 4, and 5 toxicities and geriatric assessment variables which included a performance-based measure of functional status, a memory concentration test, and self-reported measures of functional status, comorbidity, social support, psychological state and nutrition.[22]

The CRASH study was another prospective trial, which included 562 patients that showed geriatric instruments to have high predictive power for outcomes of chemotherapy.[23] There have not been any studies evaluating systemic therapy intolerance among frail patients with HCC. However, given that majority of patients with HCC have underlying liver dysfunction and associated sarcopenia and hepatic encephalopathy, these patients may be even more frail than patients with other malignancies, and therefore may experience a higher rate of systemic therapy-related side effects.

Given that frailty has demonstrated to be predictive of chemotherapy toxicity, presence of frailty may inform the dosage of systemic agents and frequency of follow-up, particularly among older patients. [22-23]

Frailty and radiotherapy

Currently, there is a lack of sufficient data regarding the impact of frailty on patient outcomes following radiotherapy. However, a recent observational study of 161 patients receiving radiation therapy showed that patients with higher frailty scores were 5.8 times more likely to receive a modified treatment regimen with a lower dose and shorter length of treatment. This study utilized the G8 test, which is a validated measure of frailty in the field of geriatric oncology that incorporates self-reported data of changes in food intake, weight loss, functional status, BMI, polypharmacy, and health status perception. The authors suggested that conducting an initial geriatric assessment could prove valuable in tailoring personalized therapeutic approaches for elderly patients.[24] Despite this, there have been no investigations thus far on how frailty influences outcomes in Yttrium-90 radioembolization treatment. Additionally, it remains unclear whether pre-treatment frailty can serve as a predictive factor for potential complications and whether it can be integrated into the treatment paradigm to determine appropriate dosages and treatment extent.

Is frailty reversible?

Emerging evidence from various studies suggests that frailty is indeed reversible to a certain degree through targeted interventions. Treatment modalities such as physical exercise, nutrition, and rehabilitation have been extensively studied, and their positive impact on frailty scores has been well-established. [25-28] Notably, a recent randomized-controlled trial focused on 60 patients with decompensated cirrhosis and mild hepatic encephalopathy (HE). The study found significant improvements in HE, muscle mass/strength, and overall quality of life following a 6-month dietary intervention.[25] The combination of exercise, nutrition, and cognitive strategies has shown even greater improvements in frailty scores among the general population, further reinforcing the potential for frailty reversal through multifaceted approaches.[29]

Moreover, studies focusing on patients with HCC also demonstrated the possibility of reversing frailty. In a multi-center observational study, patients with HCC who engaged in in-hospital exercise comprising a mixture of aerobic and resistance exercises experienced a significant improvement in the liver frailty index (LFI) compared to non-exercising patients. The positive

effects of exercise on frailty were identified as an independent factor for LFI improvement, emphasizing the potential benefits of physical activity in enhancing physical function among patients with HCC. [27-28]

Conclusion: Clinical implications and recommendations

Frailty, a multidimensional geriatric syndrome, has emerged as a significant predictor of adverse outcomes and mortality in the context of HCC. It has been explored in the cirrhotic population and shown to have profound implications for procedural and surgical outcomes, including liver transplantation, hepatectomy, and liver-directed therapies. Frailty's impact on these treatment modalities highlights its importance as a prognostic tool and a key consideration in clinical decision-making for HCC patients. Further research is needed to standardize its definition and understand its role in treatment decisions.

Continued efforts by hepatologists, medical and interventional oncologists, and surgeons to identify frailty and incorporate frailty concepts into treatment planning will be instrumental in developing more personalized management strategies and optimizing care for patients with cirrhosis and HCC. Moreover, utilizing this risk assessment, targeted programs involving exercise, nutrition, and neurocognitive strategies to improve functional capacity and frailty can be incorporated into routine clinical practice to optimize patients for procedures and medical therapy, thereby improving overall treatment outcomes.

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