Hepatocellular carcinoma management in older adults and its relation with frailty

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Abstract

Frailty, defined as a condition of extreme clinical vulnerability, is a crucial predictor of survival in elderly cancer patients. Frailty is not a specific disease but rather a combination of physical, cognitive, and social factors that compromise the patient's ability to effectively respond to stressful situations. The majority of patients diagnosed with hepatocellular carcinoma (HCC) are over 65 years old, making it essential to also assess comorbidities and conditions that may predispose to frailty, as these can influence prognosis. Therefore, identifying a clinical tool to standardize the concept of the "frail elderly patient" is essential to ensure an appropriate medical approach for this population. In this review, we examine various frailty assessment tools and evaluate their application in different therapeutic and management settings for elderly patients with HCC. Understanding the impact of frailty in elderly patients with HCC can help optimize clinical management, thereby reducing resource waste for the healthcare system and minimizing stress factors for the patient.

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Key words: aging, frailty, hepatocellular carcinoma.

Contributions: GM, conceptualization, manuscript preparation; VOP, manuscript editing and review.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: not applicable.

Patient consent for publication: not applicable.

Availability of data and materials: not applicable.

Funding: none.

Received: 24 September 2024.
Accepted: 2 January 2025.

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Licensee PAGEPress, Italy
Geriatric Care 2025; 11:13157
doi:10.4081/gc.2025.13157

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related death.[1] It is commonly recognized that age is an important risk factor for the development of HCC, and numerous studies have demonstrated an age-related increase in the development of this neoplasm in individuals over 75 years of age.[2,3] Therefore, the management of elderly patients with HCC is becoming routine in clinical practice. Still, it is significantly more complicated than that of younger patients due to comorbidities, including cardiovascular diseases, respiratory diseases, diabetes mellitus, and renal dysfunction.

The management of the patient with HCC involves multiple specialist professional figures, such as the hepatologist, the internist, the radiologist, the pathologist, the surgeon, the transplant surgeon, the oncologist, the radiotherapist, as well as the psychologist, nurses, and palliative care experts. The hepatologist/internist represents the reference figure and link between them in all phases of the patient's clinical history,[4] while the other members of the management group take on, from time to time, fundamental operational roles, depending on the stage of the tumor and shared therapeutic choice. The management of this tumor is particularly challenging, both because HCC most often arises in livers with pre-existing impaired function (90% of cases occur in cirrhotic livers) and because the therapeutic options are diverse, including, unlike other tumors, the possibility of organ transplantation. The objective of a multidisciplinary approach in the context of multidisciplinary clinical pathways is, therefore, to improve clinical outcomes in the individual patient through an evaluation that takes into account the best therapeutic opportunities.[5] Although multidisciplinary groups are increasingly widespread, particularly in reference centers, the available evidence demonstrating that the multidisciplinary approach improves the prognosis of patients with HCC remains weak, deriving from retrospective studies and comparisons with historical control groups.[6]

When choosing the therapeutic strategy to use in elderly patients with HCC, it is essential to also assess comorbidities and conditions that may predispose them to frailty, as these can influence the prognosis.[7]

Currently, the most effective methodology for managing elderly patients with a cancer diagnosis is the Multidimensional Geriatric Assessment (MGA). This tool can be valuable in oncol-

ogy practice for detecting impairments not identified at the time of observation, for its ability to predict treatment-related toxicity and overall survival across a variety of cancers and therapeutic settings, and, lastly, for its capacity to influence both the choice and intensity of treatment.

Therefore, it is useful, in order to optimize resources, to identify a screening tool that can distinguish frail elderly patients who should undergo an MGA from those who do not require its application.

Hepatocellular carcinoma in the elderly

Epidemiology

In Western populations, HCC rarely manifests before the age of 60, and in at least 90% of cases, it develops in a cirrhotic liver.[8] Several researchers have highlighted that HCC in elderly patients is more commonly found in women, likely due to their longer life expectancy. Secondly, elderly patients with HCC are more likely to be affected by hepatitis C virus (HCV). This could be explained by the observation that HCV infection generally occurs later in adulthood, while hepatitis B virus (HBV) infection is mainly acquired through mother-to-child transmission during the perinatal period.[9] It has also been observed in elderly patients that the onset of HCC in non-cirrhotic livers is higher than in younger patients. This is likely related to the fact that aging itself is a predisposing risk factor for carcinogenesis. This finding suggests that elderly patients with HCC may have better-preserved liver function than their younger counterparts.[10]

Risk factors

The risk factors for the development of HCC can be classified into two categories: those related to liver cirrhosis and those not related to it. The first group includes: HBV and HCV infection, alcohol dependence, genetic causes (such as hereditary hemochromatosis, α1-antitrypsin deficiency, and storage diseases), metabolic dysfunction-associated steatotic liver disease (MASLD), primary biliary cholangitis and autoimmune hepatitis. The second group includes: Asian race and age, cigarette smoking, and exposure to substances with carcinogenic activity, such as nitrosamines, vinyl chloride, and mycotoxins (such as *Aspergillus flavus*).[11] HBV and HCV are the main risk factors and are responsible for about 85% of HCC cases worldwide. Several retrospective studies have also highlighted an increased incidence of HCC in elderly patients with MASLD, especially when it is associated with metabolic syndrome, diabetes, and obesity.[12-14]

Screening in at-risk patients

Advanced age (>70 years) alone is not sufficient to justify stopping surveillance, as it does not rule out potential curative therapeutic options.[5] Elderly patients at risk of developing HCC should be included in an oncological screening program aimed at the early diagnosis of the neoplasm, thereby providing the possibility for curative treatments (transplantation, ablation, resection). The recommended interval for at-risk patients to undergo screening ultrasound is 6 months, and there is no evidence that reducing the observation intervals provides any benefit in terms of overall mortality or better diagnostic capability.[15-17]

Diagnosis

The investigations used for the diagnosis and study of HCC include contrast-enhanced computed tomography (CT), contrast-enhanced magnetic resonance imaging (MRI), and contrast-enhanced ultrasound (CEUS). In general, in patients under medical surveillance or with a newly diagnosed chronic liver disease, nodules ≥10 mm detected by ultrasound examination should be considered highly suspicious for HCC, requiring further characterization with CEUS or CT/MRI.

According to the European Association for the Study of the Liver/American Association for the Study of Liver Diseases guidelines, a nodule with a typical contrast enhancement pattern (wash-in followed by wash-out) >10 mm appearing on a cirrhotic liver does not require a biopsy confirmation. In cases where the lesion presents an atypical contrast pattern, the guidelines recommend performing a second contrast-enhanced imaging modality. A biopsy is recommended only if there is persistent doubt after the second contrast-enhanced examination.[18,19]

Overview: liver function, performance status, and tumor extent

The prognosis of patients with HCC does not depend solely on the extent of the tumor, making the traditional TNM staging system inapplicable. It is also necessary to consider the residual liver function and performance status.

Liver Function

Child-Pugh classification

The most widely used assessment tool, which is included in the staging systems for liver disease and HCC, is the Child-Pugh classification.[20] It considers several parameters, including encephalopathy, ascites, bilirubin, albumin, and prothrombin time prolongation. Each parameter is assigned a score ranging from a minimum of 1 to a maximum of 3. The total score can range from 5 to 15 points. The classification is divided into three groups: i) score of 5-6 – class A: patients with residual liver function and good performance status; ii) score of 7-9 – class B: this may include patients with moderately preserved liver function and patients with symptoms of decompensation; iii) score above 10 – class C: patients with marked signs of liver failure and a life expectancy of less than 6 months. For these patients, liver transplantation should be immediately considered, as any other type of oncological treatment cannot be considered due to an unfavorable risk-benefit ratio.

Model for end-stage liver disease sodium

As an alternative to the Child-Pugh classification, the Model for End-Stage Liver Disease Sodium (MELD-Na) is used to assess residual liver function.[21] This scoring system, proposed by the Mayo Clinic, evaluates the estimated 90-day survival after liver transplantation in patients with cirrhosis or end-stage liver failure. The MELD-Na considers variables such as bilirubin, international normalized ratio, creatinine, and sodium levels.

Although these tools are very reliable in assessing liver disease patients, they are limited in geriatric patients, as they do not adequately capture the overall health status and all the variables that may impact their functional abilities.[22]

Performance status: Eastern Cooperative Oncology Group Performance Status and Liver Frailty Index

In addition to liver function, it is also essential to assess the performance status of the oncologic patient. A useful tool for evaluating a patient's ability to tolerate oncological treatment is the Eastern

Cooperative Oncology Group Performance Status (ECOG-PS). This index is based on the analysis of five grades of functional limitation and provides a standardized assessment in relation to the patient and their clinical condition.[23-25]

In this context, the Liver Frailty Index (LFI) is another assessment tool designed to identify "frail" individuals among patients with liver disease. This tool is based on the evaluation of three physical performance tests: the hand grip test, which measures muscle strength, the chair stand test, and the balance test. Each test is assigned a score that allows for grouping patients into three categories: i) "robust" patients with a score of <3.2; ii) "pre-frail" patients with a score between 3.2 and 4.5; iii) "frail" patients with a score of >4.5.[26]

Therapy

The most appropriate therapeutic choice for patients with HCC must consider several prognostic variables. The most commonly used classification system is the Barcelona Clinic Liver Cancer (BCLC), with the latest guidelines published in 2022.[27] This system considers multiple factors, some of which are directly related to the tumor: tumor size, vascular invasion, lymph node invasion, and distant metastasis. Other factors consider liver function status: bilirubin levels, portal hypertension, and overall liver function preservation. Finally, performance status is assessed using the ECOG-PS. Based on these variables, five stages are identified (0, A, B, C, D) as follows. i) BCLC-0 (very early stage): a single nodule <2 cm, no invasion or metastasis, preserved liver function, no tumor-related symptoms; ii) BCLC-A (early stage): a single nodule, regardless of size, or up to 3 nodules, none >3 cm, no macrovascular invasion or metastasis, ECOG-PS=0; iii) BCLC-B (intermediate stage): multifocal HCC beyond the limits of stage A, preserved liver function, ECOG-PS = 0, no macrovascular invasion or metastasis. Stratified into three groups: i) well-defined nodules; ii) not eligible for transplantation with preserved portal flow and well-defined nodules; iii) infiltrative HCC extending throughout the entire parenchyma; iv) BCLC-C (advanced stage): vascular invasion or metastasis, ECOG-PS≤2, preserved liver function; v) BCLC-D (terminal stage): tumor-related symptoms, PS>2, compromised liver function, liver transplantation not feasible.

Patients with HCC have several therapeutic strategies available, including those in the following sections.

Liver transplantation

Liver transplantation is the gold standard for patients with HCC at BCLC-0 or BCLC-A stages, as it offers the highest cure rate among all available treatments. However, the number of patients on the waiting list far exceeds the number of available organs. Therefore, it is necessary to select patients who will benefit from this procedure, excluding those with a low life expectancy, those with dependencies, and those with poor adherence to follow-up and chronic therapy.[28-34]

The Frailty Assessment in Liver Transplant Candidates (FrAI-LT Study) examined how common and severe frailty is among liver transplant candidates and evaluated how frailty (assessed through the LFI) is related to mortality while waiting for a transplant.[35] This multicenter prospective study collected data from 1166 liver transplant candidates in eight U.S. hospitals between 2012 and 2019. The results showed that frail candidates had a higher risk of post-transplant mortality, with a cumulative 5-year death rate of 16% for frail patients, compared to 10% for non-frail patients. Additionally, frail patients had longer hospital stays after transplantation, greater use of intensive care units, and a higher likelihood of being discharged to rehabilitation facilities.

Advanced age by itself is not a reason for exclusion from the transplant waiting list, and several authoritative studies have shown that cirrhotic patients who underwent liver transplantation had comparable benefits to younger patients, with no substantial differences between the two groups in terms of recurrence-free survival at 5 and 10 years.[36-38]

Surgery

Surgical resection is considered for patients with small solitary tumors and preserved liver function in the absence of clinically significant portal hypertension. However, retrospective studies have shown that in 70% of cases, surgical resection can lead to recurrence, which may be due to either intrahepatic metastases (early recurrence) or the development of de novo HCC nodules (late recurrence).[39,40] In elderly patients, it has been observed that with the application of advanced surgical techniques and improved perioperative management, the differences in mortality due to complications compared to younger patients have narrowed, thus not precluding this option by default.[41,42]

In a retrospective analysis of 152 patients who underwent hepatectomy, the relationship between age, frailty, and major clinical outcomes at 90 days (such as mortality, postoperative complications, and length of hospital stay) was examined. The study found that frailty, determined using the Modified Frailty Index (mFI), was an independent predictor of morbidity and mortality after surgery. Interestingly, the comparison between frail and robust patients, both among the elderly (>75 years) and the young, showed similar results. Frail young patients had a 90-day mortality risk comparable to that of robust elderly patients.[43]

Radiofrequency ablation

A therapeutic option for patients who are not candidates for transplantation or surgical resection is thermal ablation or radiofrequency ablation (RFA). This technique involves inserting a needle into the nodule, guided by ultrasound, to induce coagulative necrosis through heat (the tip of the needle reaches temperatures between 60 and 100°C). RFA is considered a curative local treatment for tumors, with a good response in terms of survival and a high safety profile.[44] In elderly patients, who often have conditions that contraindicate surgery, RFA appears to be a valid therapeutic choice.[45]

Transarterial chemoembolization

Another therapeutic option for BCLC-B patients, particularly those who are not candidates for transplantation and have preserved portal flow, is transarterial chemoembolization (T.A.C.E.). This procedure involves embolization of the vessels supplying the tumor with microspheres containing doxorubicin through catheterization.[46] Although this procedure was previously contraindicated in elderly patients, recent studies suggest that improved survival in patients treated with T.A.C.E. is not affected by age. The procedure has a low risk of serious complications, such as cholecystitis, cholangitis, or bleeding (approximately 5%), and a near-zero mortality rate (0-0.48%). Survival rates are comparable when elderly and younger patient groups are compared.[47,48]

Based on a retrospective analysis by Rabei *et al*. of a cohort of 125 patients who underwent T.A.C.E., frailty (evaluated using the mFI scoring system) independently predicted a higher risk of post-T.A.C.E. complications and lower transplant-free survival (median survival time of 28.1 months *vs*. 39.8 months, p=0.03). Within 30 days following the procedure, frail patients showed a significantly

higher likelihood of liver decompensation (p=0.01) and an increased risk of hospital readmission within 30 days (p=0.03) due to urinary retention, as well as pulmonary and urinary tract infections.[49]

Transarterial radioembolization

Transarterial radioembolization is a locoregional treatment indicated for primary liver tumors that are unresectable and complicated by portal vein thrombosis. This procedure involves the transcatheter infusion of radioactive microspheres labeled with the isotope Yttrium-90 into the hepatic artery, which can deliver radiation directly to the tumor while sparing areas of the liver parenchyma not affected by the tumor. Studies in the literature have demonstrated a potential advantage of this method when used as neoadjuvant therapy in patients who are potential candidates for transplantation.[50]

Radiotherapy

Initially, radiotherapy (RT) was considered a treatment option only for terminal-stage HCC not suitable for other therapeutic choices or as palliative care. Currently, the situation has changed, as RT can be indicated at all stages of HCC.[51,52] It can be applied as a single therapy or in combination with local therapies in the early and intermediate stages, as a bridging therapy while waiting for liver transplantation, and as palliative therapy in advanced and terminal stages.[53]

A recent observational study involving 161 cancer patients undergoing RT 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 duration. This study used the Geriatric-8 (G8) test, a validated measure of frailty in geriatric oncology, which incorporates self-reported data on changes in food intake, weight loss, functional status, body mass index, polypharmacy, and perceived health status. The authors suggested that performing an initial geriatric assessment could be useful in personalizing therapeutic approaches for elderly patients.[54]

Systemic treatment

In advanced stages (BCLC-C stage) where portal vein thrombosis and/or extrahepatic metastases are present, access to locoregional treatments is excluded. In such cases, the only feasible option is systemic treatment. The first-line drug for treatment is the combination of atezolizumab and bevacizumab.[55,56]

It is well known that chronological age alone is not a good indicator of treatment tolerance. In recent years, the assessment of frailty has become a valuable tool for predicting intolerance to chemotherapy, especially in elderly patients.

Although the ECOG-PS is commonly used to assess a patient's ability to tolerate treatment, it does not account for age, comorbidities, or other aspects of frailty. Numerous studies worldwide have recognized the importance of frailty assessment in patient selection and risk stratification for systemic therapy. Some of these studies have linked frailty to a higher risk of treatment-related toxicity and lower tolerance to the treatment itself.

A prospective multicenter study conducted by Hurria *et al.* reported the results of a Cancer and Aging Research Group study involving 500 patients from various institutions in the U.S., showing significant associations between chemotherapy-related toxicity and variables from an MGA, which included measures of functional status, memory and concentration tests, comorbidities, social support, psychological state, and nutrition.[49]

There are no clinical trials evaluating intolerance to systemic therapy in frail patients with HCC. However, since most patients with HCC have liver dysfunction, sarcopenia, and hepatic encephalopathy, these patients may be even more frail than those with other malignancies and may experience a higher incidence of side effects related to systemic therapy.

Frailty indexing tools in hepatocellular carcinoma elderly patients

Frailty describes a condition of extreme clinical vulnerability due to significant homeostatic instability of the body, resulting from the dysregulation of multiple physiological systems, which in turn is a sum of the effects of aging and damage to these systems caused by chronic diseases or conditions experienced throughout life.

It is widely recognized that decompensated cirrhosis has clinical characteristics that, along with aging, contribute to triggering processes that lead to frailty. Among these, hepatic encephalopathy, sarcopenia, alterations in the gut microbiota, bacterial translocation, endotoxemia, chronic inflammation, and toxic substances are the main triggers of frailty in cirrhosis. Sarcopenia and frailty are prevalent in a significant proportion of patients with cirrhosis, up to 70% and 43%, respectively.[49] Liver decompensation and acute-on-chronic liver failure can further exacerbate sarcopenia and frailty through factors such as anorexia, ascites, hepatic encephalopathy, pro-inflammatory cytokines, reduced nutritional intake, and physical inactivity, which in turn leads to further worsening of liver decompensation.

Over the years, efforts have been made to address the need to identify "frail" elderly patients by validating frailty indexing tools. Numerous studies, most of which are observational, have been conducted on cohorts of elderly patients with HCC. Table 1 shows some of the indices and areas of application where these have been evaluated.[22,43,49,57-64]

Prognosis in the elderly patient: Geriatric Multidimensional Assessment and hepatocellular carcinoma

Currently, there is no unanimous consensus on which index to use, as none is considered more valid than the others. The most comprehensive method for managing elderly patients with cancer is the MGA, recommended by the International Society of Geriatric Oncology.[65] The MGA is a complex multidisciplinary diagnostic process aimed at defining the medical, socioeconomic, and environmental conditions, as well as the functional, physical, and mental status of elderly individuals. The areas of assessment in the MGA include the physical, psychocognitive, socioeconomic domains, and environmental conditions.

The study of the physical domain represents the first step in the diagnostic and evaluative process for geriatric patients. It aims to identify existing diseases (multimorbidity), distinguishing them from changes associated with aging and from geriatric syndromes. Various tools for measuring multimorbidity have been proposed, with the aim of stratifying patients from a prognostic perspective. Some studies show that the overall burden of comorbidity is associated with poorer survival in cancer patients.[66,67] The study of the physical health domain also involves observing the possible presence of heterogeneous conditions affecting multiple organs, even if they do not fall into specific disease categories but have a significant impact on disability: geriatric syndromes. These conditions include postural instability, falls, syncope/vertigo, urinary incontinence, delirium, cognitive deterioration, immobilization/bedridden syndrome, and pressure ulcers.

It is also important to assess nutritional disorders, ranging from pathological obesity to nutritional deficits (undernutrition). The latter is the more common form during aging, a period when energy requirements decrease, leading to a significant reduction in food and calorie intake. This contributes, in addition to the effects of chronic diseases, to what is referred to as "anorexia of the elderly".[68] Anorexia and malnutrition are strongly linked to the risk of developing sarcopenia. Sarcopenia is a clinical condition characterized by the loss of muscle mass and strength that occurs with aging and is commonly accompanied by a relative or absolute gain in body fat due to a reduction of about 25% in basal metabolism.[69] This process promotes the potential development and onset of sarcopenic obesity, which is a strong and independent risk factor for frailty, comorbidities, and mortality.[70,71]

Within the physical domain, it is also important to assess the patient's functional status, defined as the level of residual functional abilities, which helps determine the degree of psycho-physical disability to implement interventions that can ensure the preservation of the highest level of autonomy. Studies on elderly cancer patients show that functional status predicts survival, chemotherapy toxicity, postoperative morbidity, and mortality.[72]

The psychocognitive domain considers cognitive functions, mood, and behavioral analysis, which have a significant impact on the overall health status of the elderly patient. Studies that included cognitive screening as part of the MGA for elderly cancer patients found that up to 50% had abnormalities requiring further evaluation. These findings have significant implications for cancer care in terms of understanding the etiology of cognitive dysfunction (whether related to cancer or a pre-existing condition) and the impact of dysfunction on the ability to assess the risks and benefits of cancer therapy, adhere to treatment plans, and recognize signs of toxicity needing medical attention.[66] It is known that aging can lead to changes in cognitive functions, such as a slowdown in learning processes or changes in the speed of performance tests, which do not necessarily impact functional abilities. Therefore, it is crucial to distinguish between normal aging-related changes and conditions that may progress to pathology. This can be achieved through simple cognitive screen-

Table 1. Key tools for assessing frailty in elderly patients with hepatocellular carcinoma.

Evaluation method	Application area	Description	Evaluation	Results
Physical Frailty Phenotype (Fried *et al.*)	Surgery	Defines frailty as a reduction in physiological reserve	Considers muscle strength, unintentional weight loss, feelings of exhaustion, walking speed, and reduced physical activity level	Correlates with an increased mortality rate in post-liver transplant patients.[22]
Deficit Accumulation Index (Rockwood *et al.*)	Surgery	Uses a deficit index to assess frailty	The ratio between the sum of all age-related deficits detected in the individual patient and the total number of deficits considered in the assessment	Correlates with postoperative complications and reduced overall survival in patients with HCC.[57]
Modified Frailty Index-11 items (Velanovich *et al.*)	Surgery and systemic treatment	Shorter version (11 items) of the Rockwood frailty index	- Functional dependence - Heart failure - COPD - Diabetes - Hypertension - Cognitive decline - Delirium - Stroke - Cerebrovascular disease - Coronary artery disease - Myocardial infarction	Correlates with: increased risk of complications after hepatectomy; and reduced survival and higher incidence of systemic treatment toxicity.[43]
Modified Frailty Index-5 items (Subramaniam *et al.*)	Chemoembolization and surgery	Shorter version (5 items) of the Rockwood frailty index	- Functional dependence - Diabetes - COPD - Heart failure - Hypertension	Predicts: 30-day hospital readmission and complications in patients undergoing T.A.C.E;[49] and postoperative complications.[58]
Clinical Frailty Scale (Rockwood *et al.*)	Surgery	Based on clinical judgment to assess frailty	Functional status, resilience to stress, autonomy, cognitive status	Predictive of severe postoperative complications after liver resection in frail patients.[59,60]
Vulnerable Elders Survey-13 (Saliba *et al.*)	Surgery	Screening to identify vulnerable elderly individuals in the community	Age, self-reported health, physical functionality	Predictive of postoperative complications.[61,62]
Geriatric Prognostic Score	Surgery	Prognostic Frailty Index	Age, sex, type of cancer, stage, functional status, body mass index, and an MGA	Predictive of survival after hepatectomy.[63]
Kihon checklist	Surgery	Self-assessment test on various domains of frailty	Functional, physical, psychological, social, nutritional, cognitive, comorbidities	Predictive index for complications and 90-day mortality after liver resection.[64]

HCC, hepatocellular carcinoma; COPD, chronic obstructive pulmonary disease; T.A.C.E., transarterial chemoembolization; MGA, Multidimensional Geriatric Assessment.

ing tests useful for initial assessment, guiding patients to more appropriate diagnostic follow-ups.

The evaluation of the affective state completes this chapter of the MGA. Indeed, depression in the elderly is a disabling condition associated with functional and cognitive decline, significantly impacting the individual's health and overall well-being and their social environment. It is often underappreciated and underdiagnosed due to the mistaken belief that its symptoms are a normal part of the aging process, its atypical presentation, or because it is masked by concurrent cognitive deterioration or other neurological disorders, such as Parkinson's disease.

Socioeconomic status is an important indicator of the elderly patient's well-being. A thorough analysis can identify severe socioeconomic difficulties caused by high medical expenses, caregiver costs, and residential facility costs, which have a direct impact on the functional status and prognosis of patients over 70-80 years old. For this purpose, it is important to standardize this parameter using tools that address patients' needs. One of the most considered tests is the Medical Outcomes Study Social Support Survey (mMOS-SS).[73] It is a self-administered social support survey consisting of 19 items. The goal is to explore four domains in individuals with chronic conditions: emotional/informational support, tangible support, and positive social support (defined as interaction and affection). The questions are brief and easy to understand, making the tool applicable to patients of all ages. More recently, a simplified version, the mMOS-SS, has been used, consisting of two subscales that study two domains: emotional support and tangible support.[74,75]

The domain of environmental conditions, although last, is no less important. It examines the relationship between the patient's functional status, the risk of falls, and the suitability of the environment in which they live. The goal is to consider any structural modifications to the environment, including the use of assistive technology and mobility aids, to prevent or compensate for disabilities, especially in elderly individuals with balance and movement disorders.

Geriatric-8 as a new screening tool for geriatric assessment in the management of hepatocellular carcinoma

Systematic application of MGA to geriatric cancer patients may not always be necessary, as many of these patients can be treated according to standard treatment protocols without substantial modifications.[76]

Therefore, to optimize the management of medical resources, it may be useful to consider applying a screening tool to identify all elderly HCC patients who require an MGA. This approach offers benefits for both the rationalization of medical resource use within the healthcare system and avoiding unnecessary clinical and laboratory tests for the patient.

The G8 is a screening tool designed for elderly cancer patients to identify those who need a more detailed geriatric assessment. The domains analyzed include age, nutrition, mobility, neuropsychological issues, medication, and self-reported health status. The screening test has a simple scoring system ranging from 0 to 17. In the literature, a score of ≤14 is commonly reported as indicative of a potentially frail patient in most studies and requires a more in-depth geriatric evaluation.[77,78]

The G8 shares common questions with the short form of the Mini Nutritional Assessment (MNA). The selected questions from the MNA questionnaire include those related to nutritional status [(food intake (item A of the MNA), weight loss (item B), body mass index (item F)], motor skills (item C), psychological status (item E), number of medications (item H), and self-perceived health (item P). Age is categorized into three groups (<80, 80-85, and >85) and a score ranging from 0 (>85) to 2 (<80) is used. Consequently, the G8 score ranges from 0 (severely compromised) to 17 (not compromised at all).[78]

Bellera *et al*., in an article published in the Annals of Oncology, emphasized the need for a screening test to evaluate elderly cancer patients. The study aimed to test the applicability of the G8 as a screening tool by comparing it with seven reference tests from the MGA. The analysis of tests conducted on 364 cancer patients over the age of 70 demonstrated strong associations with at least one of the reference tests, and a threshold value of 14 for the G8 tool provided a good estimate of sensitivity (85%) without excessively compromising specificity (65%). Thus, the G8 showed good screening properties for identifying elderly cancer patients who might benefit from an MGA.[78]

The use of the G8 as a screening test for frailty in patients with HCC presents several promising future prospects, especially considering the importance of a multidisciplinary and personalized approach to managing elderly oncology patients. The G8 could be integrated into standard care pathways for patients with HCC, facilitating a rapid and systematic geriatric assessment that allows for early identification of frailty in elderly patients with HCC. This could lead to a more streamlined collaboration between oncologists, geriatricians, and other specialists, improving treatment planning and the allocation of healthcare resources.

Frailty as a reversible condition

Frailty is a common syndrome in the elderly characterized by increased vulnerability to adverse health events. In patients with HCC and liver cirrhosis, frailty is an important prognostic factor, affecting not only survival but also treatment tolerance. The consideration of frailty as a potentially reversible condition in elderly patients is a topic of growing interest in the scientific literature. Although frailty is generally considered a progressive phenomenon, evidence suggests that, under certain circumstances, it can be partially reversible through specific interventions.

Studies have shown that nutritional interventions, combined with personalized physical exercises, can improve muscle strength, and physical function, and consequently reduce frailty. Examples include protein supplementation and resistance exercises, which can enhance muscle mass and physical functionality.[79,80] Prehabilitation, which includes physical exercises, nutritional interventions, and psychological support before surgical or radiological treatments, has been associated with improvements in frailty in patients with HCC and cirrhosis. For instance, a rehabilitation program before liver resection can enhance functional capacity and quality of life.[81] Optimal management of comorbidities, such as diabetes or hypertension, along with targeted therapy to improve liver function, can reduce frailty. A prospective observational study by Lai *et al*., published in 2022, demonstrated that nutritional and exercise interventions can improve frailty, as measured by the LFI, in patients with cirrhosis undergoing liver transplantation. Improvement in frailty was associated with better survival and reduced complications.[82]

Conclusions

Frailty in elderly patients with HCC and liver cirrhosis is not necessarily an irreversible condition. Multidisciplinary interventions, including nutrition, physical exercise, and optimal management of comorbidities, can improve frailty and lead to better clinical

outcomes. However, it is important to recognize that reversibility may vary depending on the stage of cirrhosis, the degree of frailty, and the presence of other health conditions.[83]

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