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The invisible burden — The challenge of untreated hepatocellular carcinoma

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ABSTRACT

This editorial explores the situation of patients with hepatocellular carcinoma (HCC) who, due to advanced frailty, multiple health conditions, personal choice, or terminal disease stage, are not candidates for active cancer treatment. Despite progress in early diagnosis, a notable percentage of these individuals receive only comfort-oriented care. The article reviews how their prognosis is largely determined by the severity of liver failure and overall health status, while tumor features such as extent and vascular invasion, along with high tumor markers, further diminish survival prospects. It also discusses the influence of social context and patient decisions on outcomes. The editorial advocates for a care model focused on alleviating symptoms, respecting patient preferences, and improving quality of life through palliative interventions. It calls for more inclusive research and healthcare strategies that address the specific needs of these patients, emphasizing the importance of compassion, respect, and tailored support during the final stages of illness.

Keywords: Untreated hepatocellular carcinoma. Prognostic factors. Natural history.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a formidable global health challenge, ranking as the sixth most common cancer and the third leading cause of cancer-related death

worldwide (1). Advances in surveillance, diagnosis, and therapy have transformed the landscape for many patients (2). Yet, a substantial and often overlooked subset remains: those who, despite early detection or advances in care, receive no active oncologic treatment. This group—comprising patients with severe frailty, multiple comorbidities, treatment refusal, or terminal-stage disease (BCLC-D)—faces a markedly different clinical trajectory. Understanding the natural history and prognostic determinants in these patients is essential, not only for optimizing their care but also for informing ethical, social, and healthcare policy considerations.

THE SCOPE OF THE PROBLEM

While the implementation of surveillance programs has increased early detection rates, paradoxically, many patients diagnosed with HCC through screening ultimately receive only symptomatic or supportive care (3). The reasons are multifactorial and include advanced underlying liver disease, poor functional status, significant comorbidities, patient preference, or diagnosis at a terminal stage (2). These patients are frequently excluded from clinical trials, leading to a paucity of data to guide management and prognostication (4).

NATURAL HISTORY OF UNTREATED HEPATOCELLULAR CARCINOMA

The natural history of untreated HCC is shaped by the interplay between tumor biology, underlying liver function, and patient-related factors. In the absence of intervention, the disease course is typically aggressive, with median survival times varying dramatically by stage and patient characteristics (3,5,6).

- *Early-stage (BCLC-0/A):* median survival can exceed 2 years but untreated, these patients often experience tumor progression, liver decompensation, or both.
- *Intermediate-stage (BCLC-B):* median survival without treatment ranges from 10 to 17 months.
- *Advanced-stage (BCLC-C):* median survival drops to 3-7 months.
- *Terminal-stage (BCLC-D):* survival is often measured in weeks to a few months, with a median of 1-3 months.

Importantly, the cause of death in these patients is often multifactorial. While tumor progression is a major contributor, liver failure due to underlying cirrhosis or acute decompensation is a frequent and sometimes predominant cause. Infections, gastrointestinal bleeding, and metabolic complications also play significant roles.

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PROGNOSTIC DETERMINANTS IN UNTREATED HEPATOCELLULAR CARCINOMA

Liver function and reserve

The single most important determinant of survival in untreated HCC is the degree of underlying liver dysfunction. The Child-Pugh score and the Model for End-Stage Liver Disease (MELD) score are well-validated tools for assessing hepatic reserve (2) (4). In many cases, it is the progression of liver failure, rather than tumor burden per se, that dictates the timing and mode of death (3).

Performance status and frailty

Functional status, typically assessed by the Eastern Cooperative Oncology Group (ECOG) scale, is another critical prognostic factor. Patients with ECOG ≥ 3 have a dismal prognosis and are generally ineligible for active oncologic therapies (2). Frailty, increasingly recognized as distinct from chronological age, further compromises survival.

Tumor characteristics

While the impact of tumor burden diminishes in the setting of severe hepatic dysfunction or frailty, certain features remain prognostically relevant (1,3):

- *Tumor size and number:* multifocal disease (> 3 nodules) is associated with a 79 % increased risk of death.
- *Alpha-fetoprotein (AFP):* levels ≥ 1000 ng/mL predict rapid progression and poor survival.
- *Vascular invasion and extrahepatic spread:* both are associated with accelerated disease course and limited survival.

Comorbidities

Cardiovascular, renal, and pulmonary comorbidities are common in patients with HCC, particularly in older adults. These conditions not only preclude certain therapies (e.g., antiangiogenic agents, surgery) but also independently increase mortality risk. The presence of multiple comorbidities often tips the balance against any form of active intervention, relegating patients to supportive care.

Sociodemographic and psychosocial factors

Patient preference, social support, and health literacy play underappreciated roles in treatment decisions. Treatment refusal is more common among older adults, those living alone, or individuals with limited trust in the healthcare system. Women, interestingly, have been shown to have slightly better survival in some studies, possibly due to differences in tumor biology or healthcare engagement.

THE PARADOX OF SCREENING

The primary goal of HCC surveillance is to detect tumors at a stage amenable to curative therapy. However, the reality is more complex. A substantial proportion of patients identified through screening are ultimately deemed unsuitable for treatment due to advanced liver disease or frailty (3). This raises ethical questions about the utility and psychological impact of screening in populations with limited therapeutic options.

To address this, several strategies have been proposed (2,4):

- *Refining screening criteria:* limiting surveillance to patients with sufficient hepatic reserve and functional status to benefit from treatment.
- *Early geriatric assessment:* identifying reversible frailty and optimizing comorbidities before HCC develops.
- *Shared decision-making:* ensuring that patients understand the potential benefits and limitations of screening and treatment.

SUPPORTIVE AND PALLIATIVE CARE: THE MAINSTAY FOR UNTREATED HEPATOCELLULAR CARCINOMA

For patients ineligible for active treatment, the focus shifts to symptom management and quality of life. Common symptoms include pain, ascites, hepatic encephalopathy, pruritus, and fatigue (1). Early integration of palliative care has been shown to reduce hospitalizations, improve symptom control, and, in some cases, modestly prolong survival.

Key components of optimal supportive care include (1,2):

- *Management of ascites:* paracentesis, diuretics, and albumin supplementation.
- *Pain control:* opioids, adjuvant analgesics, and non-pharmacologic interventions.
- *Nutritional support:* addressing cachexia and malnutrition.

- *Psychosocial support:* counseling and support for patients and families.

Unfortunately, access to specialized palliative care remains inconsistent, and many patients die in hospital settings without adequate symptom control.

RESEARCH GAPS AND FUTURE DIRECTIONS

There is an urgent need for research focused on the unique needs of untreated HCC patients. Most clinical trials exclude those with poor performance status, advanced liver dysfunction, or significant comorbidities (4). As a result, evidence to guide prognostication and care in this population is limited.

Potential areas for future research include (1,2):

- *Development of frailty-specific prognostic models:* incorporating geriatric assessments, biomarkers, and patient-reported outcomes.
- *Inclusive clinical trials:* designing studies with broader eligibility criteria to reflect real-world populations.
- *Innovative care models:* integrating hepatology, oncology, geriatrics, and palliative care to provide holistic, patient-centered care.
- *Health policy initiatives:* ensuring equitable access to supportive and palliative services.

ETHICAL CONSIDERATIONS

The management of untreated HCC raises profound ethical questions. How should clinicians balance the imperative to do no harm with the desire to offer hope? What is the role of screening in populations with limited life expectancy? How can we ensure that patient autonomy is respected, particularly when cognitive impairment or social isolation is present?

Central to these questions is the need for honest, compassionate communication. Prognostic uncertainty should be acknowledged, and goals of care should be revisited regularly. Advance care planning, including discussions about end-of-life preferences, is essential.

CONCLUSION: DIGNITY AND INDIVIDUALIZED CARE AT THE FOREFRONT

Untreated HCC in frail, comorbid, or terminal patients represents a significant and growing challenge. The natural history is characterized by rapid progression, high

symptom burden, and limited survival. Prognosis is shaped by liver function, performance status, tumor characteristics, comorbidities, and social context.

To improve outcomes for this vulnerable population, we must move beyond a one-size-fits-all approach. This means:

- Prioritizing quality of life and symptom control over aggressive interventions.
- Incorporating geriatric and palliative assessments into routine care.
- Engaging in shared decision-making and advance care planning.
- Advocating for research and policy changes that address the unique needs of untreated HCC patients.

Ultimately, the goal is not merely to prolong life, but to ensure that every patient—regardless of treatment eligibility—receives compassionate, individualized, and dignified care. In doing so, we honor the fundamental principles of medicine and reaffirm our commitment to those most in need.

In this issue, González-Sánchez H et al. (7) investigate the demographic characteristics and survival outcomes of patients with untreated hepatocellular carcinoma, providing new insights into the natural history and prognostic determinants of the disease.

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