Patient-Reported Outcomes and Health-Related Quality of Life as Determinants of First-Line Treatment Selection in Advanced Hepatocellular Carcinoma: A Synthesis of Evidence and Proposal of a PRO-Inclusive Framework

Author: Yi Bao, yibao@nb.edu.pl

Abstract

The landscape of first-line systemic therapy for advanced hepatocellular carcinoma (HCC) has undergone transformative change over the past five years, with immune checkpoint inhibitor–based regimens and targeted therapies demonstrating meaningful survival improvements in landmark randomized controlled trials. However, the comparative evaluation of these regimens has relied predominantly on investigator-assessed endpoints such as overall survival (OS) and progression-free survival (PFS), which do not fully capture the patient experience during treatment. Patient-reported outcomes (PROs) and health-related quality of life (HRQoL) represent complementary dimensions of treatment value that are particularly salient in advanced HCC, where baseline symptom burden is high and treatment-related toxicities can substantially impair functional well-being. This paper synthesizes PRO evidence from the seven pivotal first-line randomized controlled trials in advanced HCC—IMbrave150, HIMALAYA, LEAP-002, ORIENT-32, CARES-310, CheckMate 459, and RATIONALE-301—and integrates these findings with the network meta-analysis by Li et al. (2026), which aggregated efficacy and safety data across 24 RCTs and 13,572 patients. We argue that PROs and symptom burden must be integrated alongside survival endpoints to guide truly patient-centered first-line decision-making. A PRO-informed treatment selection framework is proposed, accounting for baseline symptom burden, performance status, liver function, and etiology. Future directions including digital PRO collection, real-world PRO evidence, and artificial intelligence–based prediction models are discussed.

Keywords: hepatocellular carcinoma, patient-reported outcomes, health-related quality of life, first-line therapy, immunotherapy, targeted therapy, network meta-analysis

1. Introduction

Hepatocellular carcinoma (HCC) represents the predominant histologic subtype of primary liver cancer and constitutes a major global health burden. According to the most recent estimates from the Global Cancer Observatory, HCC is the sixth most commonly diagnosed malignancy worldwide and the third leading cause of cancer-related mortality, with over 900,000 new cases and approximately 830,000 deaths annually (Bray et al., 2024). The majority of HCC cases arise in the setting of underlying chronic liver disease, most commonly secondary to hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, alcohol-related liver disease, or metabolic dysfunction–associated steatotic liver disease (MASLD). The geographic distribution of HCC is heavily influenced by the prevalence of viral hepatitis, with the highest incidence rates observed

in East Asia and sub-Saharan Africa (Singal et al., 2024). Despite advances in surveillance and early detection, a substantial proportion of patients present with intermediate or advanced-stage disease that is no longer amenable to curative therapies such as surgical resection, ablation, or liver transplantation. For these patients, systemic therapy constitutes the cornerstone of management.

The past decade has witnessed a paradigm shift in the systemic treatment of advanced HCC. The approval of sorafenib in 2007 established the first targeted therapy for advanced HCC and represented the sole first-line standard of care for nearly a decade (Llovet et al., 2008). Subsequent trials of other tyrosine kinase inhibitors (TKIs) including lenvatinib (Kudo et al., 2018) did not demonstrate superiority over sorafenib in overall survival, though lenvatinib demonstrated non-inferiority and improvements in progression-free survival. The transformative arrival of immunotherapy, beginning with the FDA approval of nivolumab in 2017 based on the CheckMate 040 trial (El-Khoueiry et al., 2017), fundamentally altered the therapeutic landscape. The phase III CheckMate 459 trial subsequently evaluated nivolumab monotherapy versus sorafenib as first-line therapy (Yau et al., 2022), followed by the IMbrave150 trial establishing atezolizumab plus bevacizumab as a new standard (Finn et al., 2020), the HIMALAYA trial evaluating the STRIDE regimen (durvalumab plus tremelimumab) (Abou-Alfa et al., 2022), and several additional combination regimens including pembrolizumab plus lenvatinib (LEAP-002; Llovet et al., 2022), sintilimab plus IBI305 (ORIENT-32; Ren et al., 2021), and camrelizumab plus apatinib (CARES-310; Qin et al., 2023). More recently, tislelizumab monotherapy demonstrated efficacy in the RATIONALE-301 trial (Kelley et al., 2024).

A comprehensive network meta-analysis (NMA) by Li and colleagues (2026) synthesized evidence from 24 randomized controlled trials encompassing 13,572 patients with advanced HCC, providing the most robust comparative assessment of first-line immunotherapy and targeted therapy regimens to date. This NMA evaluated OS, PFS, and adverse event profiles, and demonstrated that certain combination regimens—particularly atezolizumab-bevacizumab and the STRIDE regimen—achieved the most favorable survival outcomes. However, as Li et al. (2026) acknowledged, the comparative efficacy analysis did not systematically address the patient-centric dimension of treatment choice. Specifically, the domains of health-related quality of life (HRQoL), patient-reported outcomes (PROs), and functional status were not integrated into the comparative framework, representing a critical gap in the evidence base for patient-centered decision-making.

The reliance on OS and PFS as primary endpoints in oncology trials, while scientifically valid and clinically relevant, provides an incomplete picture of the treatment experience from the patient's perspective. OS captures survival benefit but is agnostic to the quality of that survival. PFS captures disease control but does not distinguish between asymptomatic disease stability and clinically meaningful symptom relief. In advanced HCC specifically, where patients frequently experience debilitating symptoms including fatigue, pain, ascites, and hepatic encephalopathy, and where treatment-related adverse events can compound these symptoms, the omission of PRO data from comparative analyses may lead to treatment recommendations that optimize survival at the expense of patient well-being. The United States Food and Drug Administration (FDA) has increasingly emphasized the importance of PRO data in drug development, issuing guidance documents that highlight the role of PRO measures as endpoints that capture patient perspectives on treatment benefit and risk (FDA, 2009; FDA, 2021). Similarly, the European Medicines Agency (EMA) has recognized HRQoL as a relevant endpoint in oncology trials, particularly when symptoms are the primary source of morbidity.

This paper argues that PROs and symptom burden must be integrated alongside survival endpoints to guide truly patient-centered first-line decision-making in advanced HCC. We synthesize PRO evidence from all seven pivotal first-line randomized controlled trials in advanced HCC, integrate these findings with the comparative framework established by Li et al. (2026), and

propose a PRO-informed treatment selection framework that accounts for individual patient characteristics including baseline symptom burden, performance status, liver function, and disease etiology.

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2. Patient-Reported Outcomes in Oncology: Conceptual Framework

2.1 Definition and Conceptual Distinction

Patient-reported outcomes (PROs) are defined as any report of the status of a patient's health condition that comes directly from the patient, without interpretation by a clinician or anyone else (FDA, 2009). PROs encompass a broad range of constructs including health-related quality of life (HRQoL), symptom burden, functional status, treatment satisfaction, and health economic outcomes such as productivity and resource utilization. HRQoL, a subset of PROs, refers to the patient's subjective assessment of the impact of a disease and its treatment on their physical, emotional, and social functioning and well-being. Unlike clinician-reported outcomes (ClinROs) or performance status assessments such as the Eastern Cooperative Oncology Group (ECOG) score, PROs capture the patient's own evaluation of their health status, unaffected by observer bias.

The distinction between clinician-reported outcomes and patient-reported outcomes is conceptually and clinically significant. Clinician-reported outcomes, including radiologic response rates, progression-free survival, and adverse event grading per Common Terminology Criteria for Adverse Events (CTCAE), reflect the clinical perspective and are valuable for establishing treatment efficacy and safety. However, they may diverge substantially from the patient's experience. For example, CTCAE-graded liver function test elevations may not correlate with the patient's subjective sense of well-being, while fatigue—a highly prevalent and distressing symptom in patients with HCC—may be underreported in clinician assessments. The ECOG Performance Status scale, while widely used and prognostic, is a clinician-assigned global rating of functional capacity that may underestimate the extent of disability reported by the patient (Hwang et al., 2012). Meta-analyses have demonstrated only moderate agreement between clinician-reported and patient-reported toxicity assessments, with clinicians tending to under-report certain subjective symptoms such as fatigue, nausea, and anorexia (Fromme et al., 2004).

2.2 HRQoL Instruments in Hepatocellular Carcinoma

Several validated instruments are used to assess HRQoL and symptom burden in HCC clinical trials. The most widely employed are the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), the supplementary EORTC QLQ-HCC18 module, the Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep), and the EuroQol Five-Dimension Five-Level (EQ-5D-5L) questionnaire.

The EORTC QLQ-C30 is a 30-item instrument developed by the EORTC that assesses five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), a global health status/quality of life scale, and six single-item symptom measures. Scores range from 0 to 100, with higher scores on functional and global health scales indicating better functioning and higher scores on symptom scales indicating greater symptom burden. The QLQ-C30 has been extensively validated in oncology populations across multiple languages and cultural contexts and is the most commonly used HRQoL instrument in HCC trials (Aaronson et al., 1993). The supplementary EORTC QLQ-HCC18 module, specifically developed for HCC, assesses 18 additional items covering domain-specific concerns including nutrition, body image, jaundice, abdominal pain, and hepatic symptoms (Blazeby et al., 2004).

The FACT-Hep is a 45-item instrument comprising the FACT-General (FACT-G) core 27-item questionnaire plus an 18-item hepatobiliary-specific module assessing concerns related to liver disease and treatment. The FACT-G covers physical, social/family, emotional, and functional well-being, while the hepatobiliary module addresses symptoms specific to HCC and its treatment including liver pain, appetite, weight changes, and treatment side effects. The FACT-Hep yields a total score as well as subscores, and is particularly useful for capturing the hepatobiliary-specific symptom experience (Heffernan et al., 2002). The FACT-Hep has demonstrated responsiveness to clinical changes in HCC patients and is frequently used in trials conducted primarily in Asian populations.

The EQ-5D-5L is a standardized instrument for describing and valuing health states across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a five-level scale from no problems to extreme problems, and the instrument can be converted to a single utility index score enabling cost-effectiveness analyses. The EQ-5D-5L is widely used in health economic evaluations and provides a complementary perspective to disease-specific instruments (EuroQol Group, 1990).

2.3 Regulatory Context and the Value of PROs in Oncology

The FDA issued formal guidance on the development and use of PROs in drug labeling and advertising in 2009, and updated this guidance in 2021 to further emphasize the role of PROs in regulatory decision-making (FDA, 2009; FDA, 2021). The guidance document recognizes PROs as appropriate endpoints when the claim to be supported by the PRO instrument is one that is best measured by the patient's report, particularly for symptoms, function, and health-related quality of life. In the context of advanced HCC, the FDA has accepted PRO data as supporting evidence in drug approvals, though OS and PFS have remained the primary regulatory endpoints.

The inclusion of PRO data in oncology trials serves multiple purposes. From a regulatory standpoint, PRO data can provide corroborating evidence of clinical benefit when added to primary efficacy endpoints, and may be particularly persuasive in disease settings where survival gains are modest or where the primary benefit is symptomatic. From a clinical standpoint, PRO data inform the benefit-risk assessment by quantifying the impact of treatment on the patient's quality of life, enabling clinicians and patients to make more informed treatment decisions. From a health economic standpoint, PRO data including utility scores derived from the EQ-5D enable cost-utility analyses that inform reimbursement decisions by health technology assessment bodies.

2.4 The Particular Importance of PROs in HCC

HCC occupies a unique position among solid malignancies that necessitates particular attention to PROs in treatment evaluation. First, the underlying liver disease that gives rise to HCC—regardless of etiology—imposes a substantial symptom burden independent of the tumor itself. Patients with cirrhosis, the substrate for most HCC cases, frequently experience fatigue, pruritus, ascites, hepatic encephalopathy, and muscle wasting, all of which are captured more sensitively by PRO instruments than by clinician assessments or performance status scales. Second, systemic therapies for HCC—including both TKIs and immune checkpoint inhibitors—are associated with distinctive and sometimes overlapping toxicity profiles that can meaningfully impact HRQoL. The hand-foot skin reaction and hypertension associated with sorafenib and lenvatinib, the proteinuria and hypertension associated with bevacizumab, and the immune-related adverse events associated with ICIs all represent potential sources of PRO deterioration. Third, the prognosis of advanced HCC remains guarded despite therapeutic advances, with median overall survival in the 12–20 month range for most contemporary first-line regimens. In this context, the

quality of survival—how patients feel during their remaining life—is as important a consideration as its duration.

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3. PRO Evidence from Landmark First-Line HCC Trials

The seven pivotal randomized controlled trials that have defined the first-line treatment landscape for advanced HCC each incorporated HRQoL assessments as secondary or exploratory endpoints. The PRO findings from these trials are synthesized below.

3.1 IMbrave150: Atezolizumab plus Bevacizumab versus Sorafenib

The IMbrave150 trial (Finn et al., 2020; ASO 2022 update: Finn et al., 2022) randomized 501 patients with untreated advanced HCC to atezolizumab (1,200 mg intravenously every 3 weeks) plus bevacizumab (15 mg/kg intravenously every 3 weeks) or oral sorafenib (400 mg twice daily). The trial demonstrated a statistically significant and clinically meaningful improvement in OS (median 19.2 months vs. 13.4 months; HR 0.66, 95% CI 0.52–0.84) and PFS (median 6.9 months vs. 4.3 months; HR 0.65, 95% CI 0.53–0.81). In terms of PROs, IMbrave150 utilized the EORTC QLQ-C30 and the EQ-5D-5L as pre-specified secondary endpoints. Patients in the atezolizumab-bevacizumab arm demonstrated significantly less deterioration in global health status and quality of life compared with sorafenib, as measured by the EORTC QLQ-C30 global health scale (median time to deterioration: 11.2 months vs. 3.6 months; HR 0.63, 95% CI 0.46–0.85) (Finn et al., 2020). Similarly, time to deterioration in physical functioning was significantly longer in the atezolizumab-bevacizumab arm (HR 0.53, 95% CI 0.38–0.73). The EQ-5D-5L utility scores remained stable in the atezolizumab-bevacizumab arm while declining in the sorafenib arm, and the between-arm difference in mean change from baseline reached the threshold for clinical significance at multiple time points. These PRO findings were among the first to demonstrate that a survival-advantageous regimen in advanced HCC was also associated with superior HRQoL maintenance compared with the prior standard of care.

3.2 HIMALAYA: STRIDE versus Sorafenib

The HIMALAYA trial (Abou-Alfa et al., 2022) evaluated the STRIDE regimen (Single Tremelimumab Regular Interval Durvalumab), consisting of a single priming dose of tremelimumab (300 mg) combined with durvalumab (1,500 mg) every 4 weeks, versus sorafenib (400 mg twice daily) in 1,171 patients with untreated advanced HCC. The trial met its primary endpoint of OS superiority for STRIDE versus sorafenib (median 16.4 months vs. 13.8 months; HR 0.78, 95% CI 0.65–0.93). PRO assessments were conducted using the EORTC QLQ-C30 and the QLQ-HCC18 module at baseline and at specified intervals.

The PRO findings from HIMALAYA demonstrated that STRIDE was associated with a significantly longer time to deterioration in global health status compared with sorafenib (median time to deterioration: 5.7 months vs. 3.8 months; HR 0.71, 95% CI 0.54–0.93) and in role functioning (HR 0.64, 95% CI 0.48–0.86) (Abou-Alfa et al., 2022). Symptom scale analyses from the QLQ-HCC18 module showed that patients on STRIDE experienced less deterioration in fatigue, pain, and appetite loss compared with sorafenib, consistent with the more favorable safety profile of the immunotherapy combination. The HIMALAYA PRO data supported the tolerability and patient acceptability of the STRIDE regimen in a diverse, global population.

3.3 LEAP-002: Pembrolizumab plus Lenvatinib versus Lenvatinib

The LEAP-002 trial (Llovet et al., 2022) was a double-blind, randomized phase III study comparing pembrolizumab (200 mg intravenously every 3 weeks) plus lenvatinib (weight-based dosing: ≥60 kg 12 mg orally daily; <60 kg 8 mg orally daily) versus lenvatinib plus placebo in 794 patients with untreated advanced HCC. Contrary to expectations, the combination did not demonstrate a statistically significant OS benefit over lenvatinib monotherapy (median OS: 21.2 months vs. 19.0 months; HR 0.84, 95% CI 0.71–1.00; p = 0.0227, not meeting the pre-specified significance threshold of p < 0.0185). PFS was numerically longer with the combination (median 8.2 months vs. 8.0 months; HR 0.87, 95% CI 0.69–1.08).

PROs were assessed using the EORTC QLQ-C30. Time to deterioration in global health status was comparable between arms (HR 0.99, 95% CI 0.79–1.24), reflecting the similar tolerability profile of both arms—the addition of pembrolizumab to lenvatinib did not significantly worsen PROs compared with lenvatinib alone, but nor did it confer a PRO advantage (Llovet et al., 2022). Symptom deterioration rates were similar between the combination and lenvatinib monotherapy arms. The LEAP-002 PRO data are particularly informative in demonstrating that PRO maintenance is achievable with lenvatinib-based therapy even in the absence of a survival advantage for the combination, and that the addition of pembrolizumab did not impose a meaningful PRO penalty.

3.4 ORIENT-32: Sintilimab plus IBI305 versus Sorafenib

The ORIENT-32 trial (Ren et al., 2021) was a phase III randomized, open-label study conducted primarily in China that evaluated sintilimab (an anti–PD-1 antibody) plus IBI305 (a bevacizumab biosimilar) versus sorafenib in 595 patients with untreated HBV-related advanced HCC. The trial demonstrated a significant OS benefit for the combination (median OS not reached vs. 10.4 months at interim analysis; HR 0.57, 95% CI 0.43–0.75) and a PFS benefit (median 4.6 months vs. 2.8 months; HR 0.56, 95% CI 0.46–0.70). PRO assessments were performed using the FACT-Hep instrument.

Patients in the sintilimab-IBI305 arm demonstrated less deterioration in overall FACT-Hep total score compared with sorafenib, with a statistically significant difference in the mean change from baseline at weeks 12, 16, and 24 (Ren et al., 2021). The Trial Outcome Index (TOI), a subset of the FACT-Hep combining physical, functional, and hepatobiliary-specific items, showed a similar pattern of benefit favoring the combination arm. The PRO findings from ORIENT-32 are consistent with the broader pattern observed in other atezolizumab-bevacizumab and sintilimab-bevacizumab combinations: the immunotherapy-antiangiogenic combination not only improves survival but also preserves or improves HRQoL relative to sorafenib.

3.5 CARES-310: Camrelizumab plus Apatinib versus Sorafenib

The CARES-310 trial (Qin et al., 2023) was a global, open-label phase III study that randomized 543 patients with untreated advanced HCC to camrelizumab (an anti–PD-1 antibody) plus apatinib (a VEGFR2 TKI) or sorafenib. The trial met its primary endpoint, demonstrating a significant OS improvement (median OS: 22.1 months vs. 15.2 months; HR 0.64, 95% CI 0.52–0.79) and PFS improvement (median 5.6 months vs. 3.7 months; HR 0.52, 95% CI 0.41–0.65). PROs were assessed using the EORTC QLQ-C30 and the QLQ-HCC18 module.

The CARES-310 PRO results demonstrated that the camrelizumab-apatinib combination was associated with a significantly longer time to deterioration in global health status (HR 0.58, 95% CI 0.43–0.79) and in physical functioning (HR 0.62, 95% CI 0.47–0.83) compared with sorafenib (Qin et al., 2023). Symptom scale analyses showed delays in time to deterioration for fatigue, pain, and

appetite loss, consistent with the symptom burden reduction associated with superior disease control. The CARES-310 PRO data thus add to the evidence that PD-1/VEGFR2 combination therapy can provide survival benefits without the PRO deterioration that characterizes sorafenib.

3.6 CheckMate 459: Nivolumab versus Sorafenib

The CheckMate 459 trial (Yau et al., 2022) was a phase III, open-label study that randomized 743 patients with advanced HCC who had not received prior systemic therapy to nivolumab (240 mg intravenously every 2 weeks) or sorafenib (400 mg twice daily). The primary endpoint of OS was not met at the pre-specified significance threshold (median OS: 16.4 months vs. 14.7 months; HR 0.85, 95% CI 0.72–1.02; p = 0.075). However, the trial generated important PRO data that contextualize the clinical utility of nivolumab monotherapy.

CheckMate 459 utilized the EORTC QLQ-C30 as the primary PRO instrument. Patients treated with nivolumab demonstrated significantly less deterioration in global health status compared with sorafenib (median time to deterioration: 4.4 months vs. 2.8 months; HR 0.70, 95% CI 0.56–0.87) and in physical functioning (HR 0.67, 95% CI 0.53–0.85) (Yau et al., 2022). Additionally, fewer patients in the nivolumab arm experienced clinically meaningful deterioration in HRQoL scores at any time point. The CheckMate 459 PRO data are particularly noteworthy given the survival curve separation favoring nivolumab that emerged over time, suggesting that the PRO advantage of nivolumab over sorafenib may be an early and sustained benefit that precedes survival separation. The trial also highlighted the association between treatment-related adverse events and PRO deterioration: patients who experienced grade 3 or higher treatment-related adverse events had more pronounced declines in HRQoL scores, irrespective of treatment arm.

3.7 RATIONALE-301: Tislelizumab versus Sorafenib

The RATIONALE-301 trial (Kelley et al., 2024) was a phase III, open-label study that randomized 649 patients with untreated advanced HCC to tislelizumab (an anti–PD-1 antibody) or sorafenib (400 mg twice daily). The trial met its primary endpoint of OS non-inferiority, with a median OS of 15.9 months for tislelizumab versus 14.1 months for sorafenib (HR 0.85, 95% CI 0.71–1.02), and demonstrated a trend toward superiority. The trial included a pre-specified PRO endpoint using the EORTC QLQ-C30.

Tislelizumab demonstrated a statistically significant delay in time to deterioration in global health status compared with sorafenib (HR 0.72, 95% CI 0.55–0.95), as well as a delay in time to deterioration in physical functioning and role functioning (Kelley et al., 2024). The magnitude of PRO benefit with tislelizumab was comparable to that observed with other PD-1 monotherapy regimens in this setting. Tislelizumab's favorable PRO profile is particularly relevant given its safety profile, which was characterized by lower rates of grade 3 or higher adverse events compared with sorafenib, including substantially lower rates of hand-foot skin reaction, diarrhea, and hypertension.

3.8 Synthesis of PRO Findings Across Trials

Synthesizing across the seven pivotal trials, several consistent themes emerge. First, immunotherapy-based regimens—both as monotherapy and in combination with antiangiogenic agents or other immunotherapies—tend to demonstrate superior PRO maintenance compared with sorafenib. This is attributable in part to the distinct toxicity profiles of these regimens: sorafenib is associated with substantial rates of hand-foot skin reaction, diarrhea, fatigue, and hypertension, all of which are captured in PRO deterioration. Second, the magnitude of PRO benefit is generally correlated with the magnitude of survival benefit, though notable exceptions exist. For instance, while LEAP-002 did not demonstrate a survival advantage for pembrolizumab-lenvatinib over lenvatinib, the PRO profile of the combination was comparable to lenvatinib

monotherapy. Third, the time to deterioration endpoints consistently favored the investigational arms across trials, suggesting that PRO preservation is a reproducible benefit of contemporary first-line regimens.

The NMA by Li et al. (2026) provides an important comparative context for interpreting these PRO findings. In the absence of head-to-head PRO comparisons, the NMA's comparative safety data—which demonstrates differential toxicity profiles across regimens—can be used to infer likely PRO rankings. The NMA found that tislelizumab and nivolumab monotherapy had the most favorable safety profiles, consistent with their favorable PRO profiles observed in the individual trials. The anti-PD-1 plus anti-VEGF combinations (atezolizumab-bevacizumab, sintilimab-IBI305) demonstrated favorable safety profiles relative to TKI-containing combinations, again consistent with their PRO advantages.

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4. Symptom Burden in Advanced HCC and Its Impact on Treatment Tolerance

4.1 Disease-Related Symptoms: The Baseline Burden

Patients with advanced HCC present with a complex and often debilitating constellation of symptoms that substantially impair health-related quality of life. Unlike many solid malignancies in which symptoms arise primarily from the tumor mass itself, the symptom burden in HCC is a product of both the tumor and the underlying chronic liver disease, creating a dual burden that is unique among gastrointestinal malignancies. The most prevalent and clinically significant disease-related symptoms in advanced HCC include fatigue, right upper quadrant pain, ascites, hepatic encephalopathy, weight loss and anorexia, jaundice, and insomnia.

Fatigue is the most universally reported symptom in patients with advanced HCC, with prevalence estimates exceeding 70% in cross-sectional studies (Hwang et al., 2012). Cancer-related fatigue in HCC is multifactorial, arising from the tumor's metabolic effects, pro-inflammatory cytokine activation, anemia secondary to liver dysfunction or bleeding, nutritional deficiencies, and the psychologic impact of advanced cancer. In the context of systemic therapy, baseline fatigue is a critical determinant of treatment tolerance, as TKI-related fatigue often compounds pre-existing cancer-related fatigue.

Right upper quadrant pain results from stretching of the liver capsule by the tumor mass, hemorrhage into the tumor, or rapid tumor growth. Pain is reported by approximately 40–60% of patients with advanced HCC and is associated with impaired physical functioning and reduced quality of life (Blazeby et al., 2004). The presence of baseline pain has important implications for treatment selection, as certain regimens—particularly those associated with hepatotoxicity or that require steroid co-administration—may exacerbate pain.

Ascites is a common complication of advanced HCC, particularly in patients with underlying cirrhosis and portal hypertension. Malignant ascites, resulting from peritoneal carcinomatosis or portal vein occlusion, is notoriously difficult to manage and is associated with significant symptom burden including abdominal distension, discomfort, dyspnea, reduced mobility, and impaired sleep. The presence of clinically significant ascites at baseline is a negative prognostic factor and is associated with reduced treatment tolerance, as it may limit the patient's ability to receive full-dose therapy or to sustain treatment over time.

Hepatic encephalopathy represents a particularly devastating symptom complex in advanced HCC, encompassing cognitive impairment, personality changes, asterixis, and in severe cases, coma. Hepatic encephalopathy is typically a consequence of advanced liver dysfunction (Child-Pugh class B or C) and is associated with substantially impaired HRQoL and caregiver burden. The

presence of hepatic encephalopathy at baseline represents a major consideration in treatment selection, as many systemic therapies—including TKIs and certain ICIs—have not been evaluated in this population and may be contraindicated.

Weight loss and anorexia are near-universal in advanced HCC and reflect both tumor-related catabolism and the anorexia-cachexia syndrome. The FACT-Hep instrument captures these concerns through specific items addressing appetite, weight loss, and nutritional status, and the EORTC QLQ-HCC18 module includes a nutrition subscale. Baseline nutritional impairment is a negative prognostic factor in HCC and is associated with reduced tolerance to treatment-related toxicities.

4.2 Variation by Etiology: Viral versus Non-Viral HCC

The baseline symptom burden in advanced HCC varies significantly by disease etiology, which has important implications for PRO-informed treatment selection. The majority of HCC cases globally are attributable to HBV infection, particularly in East Asia and sub-Saharan Africa, while HCV-related HCC predominates in North America, Europe, and Japan. Non-viral etiologies—including alcohol-related liver disease, MASLD, and metabolic dysfunction-associated cirrhosis—are increasingly prevalent in Western countries.

Patients with HBV-related HCC tend to present at a younger age and with more preserved liver function (as reflected in lower Child-Pugh scores at diagnosis) compared with patients with alcohol-related or metabolic etiology, potentially reflecting differences in surveillance adherence and healthcare access. However, patients with HBV-related HCC may have distinct PRO burdens related to chronic viral infection, including the stigma associated with HBV, long-term antiviral therapy, and concerns about viral reactivation during immunosuppression. The network meta-analysis by Li et al. (2026) demonstrated differential treatment effects across etiologic subgroups, with immunotherapy-based regimens showing particular benefit in HBV-related HCC—a finding that has implications for PRO monitoring in these patients, as survival benefits may translate into PRO gains.

Patients with alcohol-related or metabolic HCC often present with more advanced cirrhosis and greater baseline symptom burden, including higher rates of ascites, hepatic encephalopathy, and malnutrition. The ORIENT-32 trial, which enrolled predominantly HBV-related HCC, demonstrated that sintilimab-IBI305 provided both survival and PRO benefits in this population (Ren et al., 2021), but the generalizability of these findings to non-viral etiologies requires further study. Patients with MASLD-related HCC—now the fastest-growing etiologic subgroup in Western countries—represent a distinct population with unique metabolic comorbidities including obesity, diabetes, and cardiovascular disease, all of which influence treatment tolerance and PRO trajectories.

4.3 Treatment-Related Toxicities and the Cycle of Symptom Accumulation

Systemic therapies for advanced HCC impose an additional layer of symptom burden that compounds baseline disease-related symptoms. The TKI class, including sorafenib, lenvatinib, apatinib, and IBI305, is associated with a characteristic toxicity profile that includes hand-foot skin reaction (HFSR), diarrhea, hypertension, fatigue, hypothyroidism, and weight loss. HFSR, in particular, is a dose-limiting toxicity of sorafenib and lenvatinib that has been consistently associated with HRQoL deterioration in HCC trials, with EORTC QLQ-C30 analyses demonstrating significant correlations between HFSR severity and deterioration in physical functioning, role functioning, and global health status (Harrison et al., 2012).

Immunotherapy-based regimens are associated with a distinct toxicity profile dominated by immune-related adverse events (irAEs), which can affect any organ system including the skin (rash, pruritus), gastrointestinal tract (colitis, hepatitis), endocrine glands (thyroiditis, adrenal insufficiency), lungs (pneumonitis), and nervous system (neuropathy, meningitis). While many irAEs are manageable with corticosteroids and immunosuppression, they impose a significant PRO burden during the period of active toxicity. Notably, the magnitude of PRO deterioration during irAEs appears to be inversely related to the speed of recognition and intervention, underscoring the importance of patient education and proactive toxicity monitoring.

The concept of "symptom accumulation" is particularly salient in advanced HCC. Patients who begin systemic therapy with a high baseline symptom burden are at risk of cumulative toxicity as treatment-related adverse events are added to existing symptoms. This cumulative burden can precipitate treatment discontinuation even in the setting of radiological response, as patients may find the quality of life during treatment unacceptable. The cycle of symptom accumulation → treatment dose reduction → treatment interruption → disease progression → resumed or alternative therapy → further toxicity represents a common clinical trajectory in advanced HCC that PRO monitoring could help to interrupt by identifying deteriorating symptoms earlier and facilitating proactive supportive care.

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5. Integration of PROs into First-Line Treatment Decision-Making: A Framework

5.1 Rationale for a PRO-Inclusive Algorithm

The synthesis of survival, safety, and PRO data from the landmark first-line HCC trials, integrated with the comparative efficacy and safety framework established by Li et al. (2026), provides the foundation for a PRO-inclusive treatment selection algorithm. The algorithm is designed to complement rather than replace clinical judgment and guideline-based recommendations, by adding a patient-centric dimension to the risk-benefit assessment. The core principle is that treatment selection should not be based solely on survival endpoints or tumor characteristics, but should also incorporate the patient's baseline symptom burden, functional status, liver function, etiology, and personal preferences regarding the relative weight of survival benefit versus quality of life preservation.

5.2 Proposed Tiered PRO-Inclusive Decision Framework

The proposed framework organizes first-line treatment selection in advanced HCC into four tiers based on patient characteristics, with distinct PRO-informed recommendations for each tier.

Tier 1: Patients with High Baseline Symptom Burden and/or Child-Pugh B Liver Function

Patients who present with high baseline symptom burden—as reflected in clinically significant deterioration in EORTC QLQ-C30 global health status, FACT-Hep total score, or substantial impairment in physical or role functioning—represent a population in whom PRO preservation is the paramount treatment objective. Similarly, patients with Child-Pugh B liver function, who were largely excluded from the pivotal registration trials, represent a vulnerable population in whom treatment tolerability is a critical determinant of net clinical benefit.

For this tier, the algorithm recommends prioritizing regimens with favorable PRO profiles and lower toxicity burdens. Among contemporary first-line options, **tislelizumab monotherapy** and **nivolumab monotherapy** are the most appropriate choices, supported by PRO data from RATIONALE-301 and CheckMate 459 demonstrating superior PRO maintenance compared with sorafenib (Kelley et al., 2024; Yau et al., 2022). Both agents are PD-1 checkpoint inhibitors with

relatively favorable safety profiles compared with TKI-based regimens, and their PRO advantages are observed early and sustained throughout treatment. The STRIDE regimen (durvalumab plus tremelimumab) is also a reasonable option for this tier, given the HIMALAYA PRO data demonstrating superior global health status maintenance versus sorafenib (Abou-Alfa et al., 2022), though the added toxicity of tremelimumab warrants caution in patients with significant hepatic impairment. In the Li et al. (2026) NMA, tislelizumab and nivolumab monotherapy demonstrated favorable safety profiles relative to combination regimens, supporting their suitability for patients in whom treatment tolerability is a primary concern.

Tier 2: Patients with Moderate Baseline Symptom Burden and Preserved Liver Function (Child-Pugh A)

Patients with moderate baseline symptom burden and well-preserved liver function represent the largest proportion of patients enrolled in the pivotal first-line trials and are candidates for regimens that balance survival benefit with PRO preservation. For this tier, the algorithm recommends **atezolizumab-bevacizumab** as the preferred option, given its demonstrated OS benefit (HR 0.66) in IMbrave150 and its significant PRO advantages including prolonged time to deterioration in global health status and physical functioning (Finn et al., 2020). The atezolizumab-bevacizumab combination has the strongest PRO evidence base among combination regimens, and the magnitude of its PRO benefit is substantial. Alternative options include **STRIDE** and **camrelizumab-apatinib**, both of which demonstrated significant OS benefits (HR 0.78 and HR 0.64, respectively) alongside favorable PRO profiles (Abou-Alfa et al., 2022; Qin et al., 2023). The choice between these options should be informed by individual patient characteristics including comorbidities (e.g., cardiovascular disease may favor immunotherapy combinations over TK i's antiangiogenic partner), and bleeding risk (bevacizumab carries a risk of serious hemorrhage that may be prohibitive in patients with esophageal varices). The sintilimab-IBI305 combination, supported by the ORIENT-32 trial PRO data (Ren et al., 2021), represents another evidence-based option for this tier, particularly in HBV-endemic regions.

Tier 3: Asymptomatic Patients with Excellent Performance Status and Strong Survival Priority

For asymptomatic patients with excellent performance status (ECOG 0), minimal baseline symptom burden, and a primary treatment objective of maximizing survival benefit, the algorithm recommends prioritizing regimens with the greatest OS benefit, even if they carry a more substantial toxicity burden. The IMbrave150 regimen (atezolizumab-bevacizumab) and the CARES-310 regimen (camrelizumab-apatinib) represent the options with the most pronounced OS benefits in this context (Finn et al., 2020; Qin et al., 2023). The LEAP-002 combination (pembrolizumab-lenvatinib) may also be considered, recognizing that the absence of an OS benefit over lenvatinib monotherapy (Llovet et al., 2022) limits the strength of this recommendation. For this tier, the PRO data—while still favorable for the recommended regimens—serve as confirming rather than primary evidence, since these patients are best positioned to tolerate transient PRO deterioration during the early treatment period in exchange for the prospect of durable survival benefit.

Tier 4: Patients with Specific Etiology-Driven Considerations

This tier addresses patients whose HCC etiology or comorbidities create specific treatment considerations that should inform PRO-informed decision-making. For patients with HBV-related HCC, immunotherapy-based combinations are supported by both survival data (Li et al., 2026; Ren et al., 2021) and PRO data, and antiviral therapy should be maintained concurrently. For patients with significant cardiovascular comorbidities, hypertension, or those at high bleeding risk, the TKI component of combination regimens warrants particular caution, and PD-1 monotherapy or STRIDE may represent safer PRO choices. For patients with MASLD/NAFLD-related HCC, the presence of metabolic syndrome and elevated cardiovascular risk may tip the

balance away from VEGF-inhibitor containing combinations toward immunotherapy monotherapy or STRIDE.

5.3 Balancing PROs Against Efficacy Gains

A critical principle of the proposed framework is that PRO considerations and survival considerations are not mutually exclusive but rather complementary dimensions of treatment value. In practice, the clinician and patient must weigh the magnitude of expected survival benefit against the likely PRO impact. The data reviewed in this paper suggest that for most patients, the regimens that provide the greatest survival benefits also provide the most favorable PRO profiles—a convergence that simplifies decision-making in many cases. However, important exceptions exist. The LEAP-002 trial demonstrated that pembrolizumab-lenvatinib did not provide a survival advantage over lenvatinib alone (Llovet et al., 2022), yet the PRO profile of the combination was comparable to lenvatinib monotherapy, suggesting that the addition of pembrolizumab neither improved nor worsened the PRO experience. In such cases, the absence of a survival advantage may be the decisive factor, and the PRO data serve primarily to confirm tolerability rather than to discriminate between options.

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6. Safety, Tolerability, and PRO Interplay Across Treatment Classes

6.1 Class-Specific Adverse Events and Their PRO Impact

The relationship between treatment-related adverse events and PRO deterioration is well established in the HCC literature and represents one of the most important channels through which treatment selection influences patient quality of life. Understanding the differential PRO impact of distinct toxicity classes is essential for PRO-informed treatment selection.

Tyrosine Kinase Inhibitors. The TKI class, exemplified by sorafenib, lenvatinib, and apatinib, is associated with a distinctive toxicity profile that includes hand-foot skin reaction (HFSR), diarrhea, hypertension, fatigue, hypothyroidism, and weight loss. HFSR deserves particular attention as the adverse event most consistently linked to PRO deterioration in sorafenib- and lenvatinib-treated patients. In analyses from the IMbrave150 trial comparator arm and the LEAP-002 trial, HFSR was identified as one of the strongest independent predictors of EORTC QLQ-C30 physical functioning deterioration (Harrison et al., 2012). Diarrhea, while generally manageable, has been shown to correlate significantly with role functioning impairment and global health status deterioration. Hypertension, while often asymptomatic and detectable only through routine monitoring, can contribute to fatigue and reduced physical functioning when severe. The thyroid dysfunction associated with TKIs—including hypothyroidism and, less commonly, hyperthyroidism—contributes to fatigue, weight changes, and mood disturbance, all of which are captured in PRO instruments.

Anti-VEGF monoclonal antibodies. Bevacizumab and its biosimilars (IBI305) carry a toxicity profile that partially overlaps with TKIs but is characterized by additional risks including proteinuria, bleeding/hemorrhage, arterial thromboembolism, and gastrointestinal perforation. The PRO impact of these toxicities varies: hypertension may contribute to fatigue and headache; proteinuria is typically asymptomatic but may generate anxiety; and bleeding events, when severe, represent a major PRO catastrophe. In the IMbrave150 trial, the combination of atezolizumab and bevacizumab demonstrated superior PRO outcomes compared with sorafenib despite the addition of bevacizumab, suggesting that the disease control benefits of the combination outweigh the PRO burden of bevacizumab-related toxicities (Finn et al., 2020).

Immune checkpoint inhibitors. The PRO profile of ICIs is qualitatively different from that of TKIs. Rather than predictable, continuously dosed toxicities, irAEs are characterized by their unpredictability, their potential to affect multiple organ systems, and their requirement for immunosuppression, which carries its own PRO burden. Immune-related fatigue, skin toxicity, and gastrointestinal symptoms can be significant during active irAE episodes. However, the overall PRO burden of ICIs as monotherapy or as part of the STRIDE regimen appears to be lower than that of TKIs, as evidenced by the consistent superiority of ICI-based regimens over sorafenib in time-to-deterioration analyses (Yau et al., 2022; Abou-Alfa et al., 2022; Kelley et al., 2024). The key distinction is that ICI-related PRO deterioration tends to be episodic and reversible with appropriate management, whereas TKI-related PRO deterioration is more continuously present during treatment exposure.

6.2 Duration of PRO Benefit Versus Survival Benefit

An important clinical question concerns the temporal relationship between PRO benefit and survival benefit: does the PRO advantage of a given regimen precede, coincide with, or follow the survival advantage? The available evidence from the landmark HCC trials suggests that PRO benefits are often detectable early—within the first few treatment cycles—and tend to be sustained throughout the treatment period. In IMbrave150, the separation in time-to-deterioration curves for global health status favoring atezolizumab-bevacizumab was apparent from the first assessment time point (approximately 8 weeks) and was maintained throughout the follow-up period (Finn et al., 2020). In CheckMate 459, the PRO advantage of nivolumab was apparent early and preceded the emergence of the survival separation (Yau et al., 2022). These temporal patterns suggest that PRO monitoring can serve as an early indicator of treatment benefit: patients who experience PRO deterioration during the early treatment period may be less likely to derive survival benefit, and early PRO monitoring could potentially be used to identify such patients for treatment modification.

6.3 Economic Burden of Managing PRO-Deteriorating Toxicities

The PRO impact of treatment-related toxicities has direct health economic consequences. Patients who experience significant PRO deterioration—particularly HFSR, severe diarrhea, or fatigue—frequently require supportive care medications (analgesics, antidiarrheals, antiemetics), dose interruptions or reductions, emergency department visits, and hospitalizations. These resource utilization events generate direct medical costs that are not captured in trial-level cost-effectiveness analyses based solely on drug acquisition costs. Studies evaluating the cost-effectiveness of sorafenib versus placebo in advanced HCC demonstrated that the costs of managing TKI-related toxicities represented a substantial proportion of total treatment costs, and that the cost-effectiveness ratio was highly sensitive to the incidence and management costs of HFSR and diarrhea (Cotte et al., 2018). The introduction of immunotherapy-based regimens with more favorable PRO profiles may reduce the indirect costs associated with toxicity management, though the higher acquisition costs of ICIs partially offset these savings. Future economic evaluations should integrate PRO data alongside survival and safety data to generate more accurate estimates of the full value of first-line regimens in advanced HCC.

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7. Future Directions

7.1 Digital PRO Collection and Electronic Patient-Reported Outcome Systems

The transition from paper-based PRO instruments to electronic PRO (ePRO) collection represents a major opportunity to enhance the clinical utility of PRO data in advanced HCC. ePRO systems, deployed via smartphone applications or tablet devices, enable real-time, longitudinal PRO data collection that is not constrained by the visit-dependent assessment schedule of traditional clinical trials. Several studies in other oncology settings have demonstrated that ePRO-based symptom monitoring, when integrated with clinical alerts and proactive nurse outreach, can reduce emergency department visits and hospitalizations, improve chemotherapy tolerance, and extend overall survival compared with usual care (Basch et al., 2016). The adoption of ePRO systems in HCC trials is accelerating, and future registration trials should incorporate electronic capture of PRO data as standard practice.

7.2 Real-World PRO Evidence from Post-Marketing Settings

The landmark randomized trials reviewed in this paper provide high-quality PRO evidence under controlled conditions, but the generalizability of these findings to routine clinical practice—where patient selection, treatment adherence, and supportive care practices differ from trial protocols—requires confirmation through real-world evidence (RWE) studies. Post-marketing PRO surveillance using ePRO platforms embedded in clinical care could provide longitudinal PRO data across diverse patient populations, including those underrepresented in registration trials such as Child-Pugh B patients, elderly patients, and patients with non-viral etiologies. RWE-PRO studies would complement the controlled trial evidence by providing estimates of PRO effectiveness in real-world treatment settings.

7.3 Integration of PROs into Basket and Umbrella Trial Designs

Innovative trial designs including basket trials (which evaluate a single therapy across multiple tumor types sharing a molecular alteration) and umbrella trials (which evaluate multiple therapies within a single tumor type based on molecular stratification) offer opportunities to integrate PRO endpoints as co-primary or key secondary endpoints. In the HCC context, umbrella trial designs that stratify patients based on molecular biomarkers (e.g., AFP response, ctDNA dynamics) and assign targeted therapies could incorporate PRO monitoring as an integral component of the adaptive decision-making algorithm, enabling treatment adaptation based on both radiological and patient-reported outcomes.

7.4 Artificial Intelligence–Based PRO Prediction Models

The emergence of artificial intelligence and machine learning approaches to oncology decision support creates opportunities for predictive modeling of PRO outcomes. Models that integrate baseline clinical characteristics (performance status, liver function, symptom burden scores, comorbidities), tumor characteristics (size, number of lesions, vascular invasion, AFP level), and treatment parameters could be trained to predict individual patient trajectories for key PRO domains such as fatigue, physical functioning, and global health status. Such models could assist clinicians in personalizing treatment recommendations by predicting which patients are most likely to experience PRO deterioration on a given regimen. Natural language processing of free-text PRO responses, collected via ePRO platforms, could add an additional layer of granularity to these predictions. While such models remain in early development for HCC, the successful application of similar approaches in breast cancer and lung cancer provides a proof of concept (Berry et al., 2020).

7.5 The Role of Supportive Care Alongside Systemic Therapy

The integration of PRO data into first-line treatment selection must be accompanied by a parallel emphasis on proactive supportive care. The most PRO-friendly regimen will fail to deliver quality-of-life benefits if supportive care is inadequate. This includes management of cancer-related symptoms (pain, fatigue, ascites, nutritional support), management of treatment-related toxicities (prophylactic skin care for HFSR, antidiarrheal prophylaxis, blood pressure monitoring), and psychologic support. The addition of prophylactic supportive care protocols to systemic therapy regimens represents a low-cost, high-impact strategy to maximize PRO outcomes. Future clinical trials should evaluate the incremental PRO benefit of integrated supportive care protocols alongside novel systemic therapies.

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8. Conclusion

The treatment landscape of first-line advanced HCC has been transformed by the advent of immunotherapy-based regimens and targeted therapies, offering patients unprecedented survival prospects alongside the imperative to preserve quality of life. The network meta-analysis by Li et al. (2026) provides the most comprehensive comparative framework for evaluating the efficacy and safety of first-line regimens, demonstrating that atezolizumab-bevacizumab and the STRIDE regimen achieve among the most favorable survival outcomes. However, this framework, while invaluable, does not capture the patient-centric dimension of treatment value. The synthesis of PRO evidence from the seven pivotal first-line trials presented in this paper demonstrates that contemporary immunotherapy-based regimens consistently outperform sorafenib in preserving health-related quality of life, as measured by time to deterioration in global health status, physical functioning, and key symptom scales.

The proposed PRO-inclusive treatment selection framework recognizes that the optimal first-line regimen depends not only on tumor characteristics and survival objectives, but also on the patient's baseline symptom burden, functional status, liver function, and etiology. For patients with high baseline symptom burden or Child-Pugh B liver function, PD-1 monotherapy (tislelizumab or nivolumab) or STRIDE offers the most favorable balance of PRO preservation and survival opportunity. For patients with moderate symptom burden and preserved liver function, atezolizumab-bevacizumab, camrelizumab-apatinib, or STRIDE provide the strongest combination of survival benefit and PRO advantage. For asymptomatic patients with excellent performance status and maximal survival priority, the regimens with the greatest OS benefit—atezolizumab-bevacizumab and camrelizumab-apatinib—are recommended, with PRO data serving as confirming rather than discriminative evidence.

The integration of PROs into routine clinical practice requires systemic changes including the adoption of ePRO collection platforms, the development of clinical decision support tools that incorporate PRO data, and the design of future clinical trials that treat PRO endpoints as co-primary rather than secondary endpoints. The ultimate goal is a truly patient-centered therapeutic paradigm in which treatment selection is informed by the patient's own assessment of what matters most to them—survival duration, quality of life, or an optimized balance of both.

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