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EDITORIAL

Beyond the score: Diet and exercise as modifiers of inflammation-based prognosis in lenvatinib-treated hepatocellular carcinoma

Héctor Vázquez-Lorente, Jorge Olivares-Arancibia, Julio Plaza-Diaz

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Héctor Vázquez-Lorente, Departament de Bioquímica i Biotecnologia, Universitat Rovira i Virgili, Reus 43201, Spain

Héctor Vázquez-Lorente, Julio Plaza-Diaz, Institut de Recerca Biomèdica Catalunya Sud, Hospital Universitari Sant Joan de Reus, Reus 43201, Spain

Héctor Vázquez-Lorente, Biomedical Research Networking Center for Physiopathology of Obesity and Nutrition (CIBERObn), Reus 43201, Spain

Héctor Vázquez-Lorente, Julio Plaza-Diaz, School of Health Sciences, Universidad Internacional de La Rioja, Logroño 26006, Spain

Jorge Olivares-Arancibia, AFySE Group, Research in Physical Activity and School Health, School of Physical Education, Faculty of Education, Universidad de Las Américas, Santiago 7500975, Región Metropolitana, Chile

Julio Plaza-Diaz, Biomedical Research Networking Center for Physiopathology of Obesity and Nutrition (CIBERObn), Alimentació, Nutrició Desenvolupament i Salut Mental, Departament de Bioquímica i Biotecnologia, Universitat Rovira i Virgili, Reus 43201, Spain

ORCID number: Héctor Vázquez-Lorente 0000-0003-0183-6902; Jorge Olivares-Arancibia 0000-0002-7186-3941; Julio Plaza-Diaz 0000-0002-5171-9408.

Corresponding author: Julio Plaza-Diaz, PhD, Senior Postdoctoral Fellow, Senior Researcher, Biomedical Research Networking Center for Physiopathology of Obesity and Nutrition (CIBERObn), Alimentació, Nutrició Desenvolupament i Salut Mental, Departament de Bioquímica i Biotecnologia, Universitat Rovira i Virgili, Carrer de Sant Llorenç 21, Reus 43201, Spain. julioramon.plaza@urv.cat

Abstract

Inflammation-based indices such as the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, and nutritional metrics like the prognostic nutritional index or controlling nutritional status, offer pragmatic risk stratification in hepatocellular carcinoma treated with lenvatinib, these scores being not immutable. Nutrition and physical activity can influence the pathways they capture: Systemic inflammation, immune competence, and skeletal-muscle status. Malnutrition, sarcopenia, and sarcopenic obesity are prevalent at baseline and often worsen on therapy, driving neutrophilia/lymphopenia and hypoalbuminemia that adversely shift scores and

health outcomes. Conversely, protein-adequate, anti-inflammatory dietary patterns, and structured physical activity may attenuate inflammatory signaling, preserve muscle mass, improve treatment tolerance, and ultimately reclassify risk. In this editorial, we comment on the article by Wu *et al* published in the recent issue of the *World Journal of Gastroenterology*. We advocate embedding standardized lifestyle assessments (dietary quality, prognostic nutritional index/controlling nutritional status, body-composition measures) and objective physical activity metrics (*e.g.*, accelerometry) alongside neutrophil-to-lymphocyte ratio/platelet-to-lymphocyte ratio/systemic immune-inflammation index at baseline and during treatment. Pragmatic clinical trials should test lifestyle interventions as adjuncts to lenvatinib using time-updated scores and hard endpoints. Framing these indices as dynamic and modifiable targets could strengthen the prognostic and guide supportive care in hepatocellular carcinoma.

Key Words: Hepatocellular carcinoma; Lenvatinib; Inflammation-based prognostic indices; Nutritional status; Sarcopenia; Anti-inflammatory diet; Exercise/physical activity

Core Tip: This article comments on Wu *et al*'s work, highlighting the prognostic nutritional index (PNI) as a powerful predictor of survival in patients with hepatocellular carcinoma treated with lenvatinib. Beyond its prognostic performance, the key message is that PNI reflects a dynamic and potentially modifiable state integrating nutrition, inflammation, and immune competence. Unlike static tumor characteristics, PNI may be improved through targeted lifestyle, nutritional, and supportive-care interventions. This perspective reframes inflammation-based scores from passive risk stratifiers to actionable clinical tools, supporting a more proactive and personalized approach to patient management, alongside systemic therapy.

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INTRODUCTION

Hepatocellular carcinoma (HCC) remains as a challenging malignancy because prognosis reflects not only tumor burden and biology, but also the functional reserve of a chronically diseased liver[1]. Over the last decade, the systemic-therapy landscape has expanded substantially, and contemporary practice guidelines position immune-based combinations as preferred first-line options for many patients with preserved liver function and performance status[2] Despite antiangiogenic multi-kinase inhibitors continue to play a central role in real-world care: Lenvatinib, supported by the phase 3 REFLECT trial[3], and demonstrated non-inferiority to sorafenib for overall survival (median 13.6 months *vs* 12.3 months) while offering clinically relevant gains in response and progression-related endpoints, it remains a key option when immunotherapy is unsuitable or as a subsequent systemic strategy[4].

Clinicians have increasingly relied on pragmatic, low-cost prognostic tools derived from routine blood tests against this evolving therapeutic backdrop[5]. Inflammation-based indices [*e.g.*, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII)], and immunonutritional scores [*e.g.*, prognostic nutritional index (PNI) and the controlling nutritional status (CONUT) score] are appealing precisely because they are simple, scalable, and broadly reproducible[6,7]. Importantly, in lenvatinib-treated HCC cohorts, baseline NLR and PLR have shown independent associations with survival and disease control, underscoring their bedside relevance [8]. However, these indices are still too often interpreted as static "baseline risk labels".

WHAT DO INFLAMMATION-BASED SCORES REALLY CAPTURE?

At face value, indices such as NLR, PLR, and SII appear to be simple arithmetic ratios. Biologically, they reflect the balance between pro-tumor inflammatory tone and anti-tumor immune competence within a disease that is itself inflammatory[9,10]. Neutrophilia can signal an activated myeloid compartment linked to cytokine-driven inflammation, angiogenesis, and tumor-promoting immune crosstalk, whereas lymphopenia is often interpreted as a marker of impaired adaptive immune surveillance and reduced cytotoxic capacity[11]. In HCC, where the tumor immune microenvironment is shaped by chronic liver inflammation and multiple immunosuppressive circuits, these shifts plausibly index host-tumor interactions rather than tumor aggressiveness alone[12,13].

Crucially, immunonutritional scores add information that purely hematologic ratios cannot. Hypoalbuminemia is not simply "malnutrition"[14]. Albumin is a negative acute-phase reactant that falls in systemic inflammation, and in HCC it also tracks hepatic synthetic dysfunction; two axes tightly coupled to treatment tolerance and outcomes[15]. When albumin is combined with lymphocyte count (as in PNI) or integrated alongside cholesterol and lymphocytes (as in CONUT), the resulting scores more explicitly capture a triad of physiologic reserve: Inflammatory load, immune capacity, and nutritional-metabolic status[16]. This helps explain why, in lenvatinib-treated cohorts, baseline nutritional status (by CONUT/PNI-class metrics) and maintenance or improvement of nutritional indices during therapy can relate to retention on treatment and discontinuation risk[17].

The clinical takeaway is that these indices function as integrative phenotypes, compressed readouts of host-tumor-treatment biology. Their prognostic value likely emerges because they summarize multiple interacting pathways that jointly determine whether a patient can sustain effective systemic therapy[12,18]. Interpreted this way, "risk scores" become early-warning signals for potentially addressable supportive-care needs, rather than fixed descriptors of fate[12,18].

MALNUTRITION, SARCOPENIA, AND SARCOPENIC OBESITY IN LENVATINIB-TREATED HCC

Malnutrition and skeletal-muscle abnormalities are not "side issues" in HCC. They are frequent co-travelers of cirrhosis and cancer that meaningfully shape prognosis and treatment tolerance[19]. Contemporary meta-analytic evidence suggests that sarcopenia is present in roughly approximately 40% of patients with HCC, and it is consistently associated with worse survival outcomes across disease stages and treatments[20-22]. Importantly, sarcopenic obesity adds an additional layer of clinical risk because adiposity can mask severe muscle mass depletion, complicating risk recognition when clinicians rely on weight or body mass index alone. Systematic reviews across populations with cancer support its adverse prognostic relevance[23,24].

Mechanistically, the pathophysiology of HCC creates a progressive muscle mass loss. In addition, chronic inflammation, reduced energy intake, impaired hepatic metabolism, and recurrent decompensation can drive negative protein balance and reduced functional capacity. In parallel, lenvatinib commonly produces appetite loss and weight loss in routine practice and in pivotal trial data, plausibly accelerating catabolism in already vulnerable patients[4,25]. Beyond symptoms, tyrosine kinase inhibitor therapy in advanced HCC has been linked to measurable skeletal-muscle decline over time. Even independent of radiographic disease progression, underscoring that muscle trajectories may reflect treatment-host interactions rather than "tumor burden alone"[26,27].

These clinical observations matter because baseline sarcopenia and early muscle mass loss have shown prognostic implications in lenvatinib-treated cohorts. Retrospective analyses indicate that pretreatment sarcopenia status can independently correlate with shorter overall survival under lenvatinib. Separate studies report that skeletal-muscle mass decreases during lenvatinib/sorafenib therapy and may relate to HCC prognosis[28,29]. More recent work also highlights the potential relevance of muscle quality (*e.g.*, myosteatosis) alongside low muscle mass in lenvatinib-treated HCC[29]. Multicenter data link higher CONUT to poorer survival under lenvatinib, and discontinuation due to severe adverse events has been associated with clinical profiles that include poorer nutritional status[30,31]. Collectively, these lines of evidence support the editorial premise. Deterioration in NLR/SII/PNI/CONUT during therapy is often a signal of unmet supportive-care needs, not an inevitability.

NUTRITION AND PHYSICAL ACTIVITY AS BIOLOGICAL MODIFIERS OF PROGNOSTIC SCORES

If inflammation-based and immunonutritional scores summarize host reserve, then nutrition and exercise may be considered potential upstream "biological levers". Major guidance documents emphasize systematic identification of malnutrition, frailty, and sarcopenia, and recommend pragmatic interventions, primarily derived from populations with chronic liver disease. Including adequate protein intake and structured physical activity, tailored to cirrhosis severity and functional status[32,33]. ESPEN guidance further notes that sarcopenic cirrhotic patients (including those with sarcopenic obesity) may require higher protein intake together with physical exercise to meaningfully rebuild muscle mass[33].

From the dietary side, two mechanistic targets may be potentially relevant to NLR/SII/PNI/CONUT. First, preservation of hepatic synthetic function and muscle mass (supporting albumin and physical resilience). Second, attenuation of systemic inflammation that can drive neutrophilia/Lymphopenia and hypoalbuminemia. While preliminary interventional evidence specifically in lenvatinib-treated HCC remains limited, broader preliminary randomized evidence indicates that Mediterranean-style dietary patterns may reduce selected inflammatory biomarkers (notably high-sensitivity C-reactive protein and interleukin-6), supporting biological plausibility with the potential modulate inflammation-linked risk phenotypes[34,35].

Nutrient-adjunct strategies that target muscle metabolism are also being explored in HCC patients on lenvatinib. For example, levocarnitine supplementation has been studied as a potential approach that may attenuate lenvatinib-related sarcopenia progression, illustrating that supportive interventions may, at least in principle, modify muscle mass trajectories during systemic therapy. However, these findings warrant further validation[36].

Exercise provides also a complementary pathway. In cirrhosis, randomized evidence shows that supervised progressive resistance training may improve muscle strength and mass and improve performance measures, while its efficacy in lenvatinib-treated HCC requires further validation[37]. Systematic reviews similarly suggest that exercise interventions can improve physical function and muscle-related endpoints in cirrhosis, albeit with heterogeneity in

protocols and outcomes[38,39]. In oncology more broadly, ASCO guidance highlights that exercise during cancer treatment improves fitness, strength, fatigue, and other patient-centered outcomes, especially the domains that shape dose intensity and treatment persistence[40]. Nutrition and exercise may act on the same biological axes captured by inflammatory and immunonutritional indices and could contribute to stabilizing risk profiles during therapy. Yet definitive, lenvatinib-specific interventional trials warrant further investigation before making strong causal claims.

From an implementation standpoint, existing liver-disease guidance already provides pragmatic targets. AASLD and ESPEN guidelines[33] recommend daily protein intake to be of approximately 1.2-1.5 g/kg/day in patients with cirrhosis, including those with sarcopenia, distributed across meals and including a late-evening snack to limit fasting-related catabolism. Importantly, protein restriction is discouraged even in patients with prior hepatic encephalopathy[32]. Regarding physical activity, both societies support regular low-to-moderate-intensity resistance exercise (2-3 sessions/week) in clinically stable patients, with adjustment according to Child-Pugh class and portal hypertension risk, favoring supervised or functional low-load exercise in decompensated disease and avoidance of excessive intra-abdominal pressure. Collectively, these recommendations underscore that nutrition and physical exercise interventions are feasible, safe, and adaptable in routine HCC care. In practice, this implies translating inflammation-based and immunonutritional scores into actionable supportive-care pathways aligned with AASLD and ESPEN guidance, rather than treating NLR, PNI, or CONUT as immutable baseline descriptors.

FROM BASELINE SCORES TO DYNAMIC MONITORING: A PARADIGM SHIFT

A single baseline NLR or CONUT score is clinically convenient, but biologically incomplete. Emerging evidence in lenvatinib-treated HCC supports the concept that on-treatment dynamics carry meaningful information[41,42]. Studies have evaluated NLR trajectories during lenvatinib as a window into the tumor immune microenvironment and prognosis, and independent analyses suggest that changes in NLR relate to treatment response or outcomes[41,42].

The same logic applies to nutritional indices and body composition. Multicenter cohorts have linked baseline CONUT to survival under lenvatinib. Additional work suggests that maintaining or improving nutritional indices during treatment associates with greater treatment retention and fewer discontinuations due to adverse events[30]. Meanwhile, multiple studies have documented measurable declines in muscle mass during lenvatinib therapy, and such trajectories can carry prognostic relevance. Making the case for serial body-composition assessment rather than "one CT at baseline" [27,29]. Operationally, dynamic monitoring is already aligned with liver-disease care principles. AASLD practice guidance on malnutrition/frailty/sarcopenia in cirrhosis emphasizes structured assessment and follow-up, reinforcing that repeated measurement is both feasible and clinically meaningful[32].

From an implementation standpoint, dynamic monitoring can be pragmatically aligned with routine oncology follow-up schedules. In clinical practice, inflammatory and immunonutritional indices (*e.g.*, NLR, PLR, SII, PNI, CONUT) could be reassessed at baseline and at regular intervals coinciding with imaging or treatment review (*e.g.*, every 4-8 weeks during the early treatment phase, then at longer intervals in stable patients)[43]. Muscle mass assessment may leverage routinely acquired cross-sectional imaging complemented, where imaging is unavailable, by bedside or outpatient tools such as bioelectrical impedance analysis, handgrip strength, or gait speed. Coordination across disciplines is essential: Oncologists and hepatologists define monitoring time points, dietitians interpret nutritional trajectories and initiate escalation strategies, and physical exercise professionals tailor and adapt physical exercise prescriptions in response to functional decline[44]. Such structured yet flexible pathways enable dynamic scores to inform timely supportive-care intensification rather than serving solely as retrospective prognostic markers.

The practical proposal, then, is a time-updated dashboard in which repeat NLR/PLR/SII and PNI/CONUT at predefined intervals. Pair them with muscle mass and functional measures trajectories and treat adverse "score trajectories" as triggers for intensified nutritional support and supervised exercise. Analogous to how dynamic biomarkers are increasingly used to guide adaptation of systemic therapy in other oncology settings[45,46].

IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE TRIALS

For clinical practice, the most pragmatic step is embedding standardized lifestyle and body-composition assessment into routine HCC pathways. Cirrhosis-focused guidance already provides an implementation blueprint that screen for malnutrition/frailty/sarcopenia and reassess longitudinally. Moreover, deploy a multidisciplinary approach that integrates hepatology/oncology with dietetics and exercise expertise[32,33]. ESPEN recommendations similarly support structured nutrition care in liver disease, including attention to sarcopenia and the role of combined nutrition plus exercise strategies[33,47].

However, implementation in advanced HCC requires careful risk stratification, as patients frequently present cirrhosis-related complications such as portal hypertension, ascites, sarcopenia, renal dysfunction, or hepatic encephalopathy. Lifestyle interventions should therefore be individualized following a structured assessment of liver function, recent decompensation events, bleeding risk, frailty, and functional capacity[48]. Exercise prescriptions should prioritize low-to-moderate intensity, progressive and resistance-focused modalities, favoring supervised or hybrid/home-based programs when appropriate, while avoiding high-intra-abdominal-pressure maneuvers in patients at high risk of variceal bleeding. Nutritional strategies should be symptom-adapted and feasibility-driven, emphasizing adequate protein and energy intake, small frequent meals, late-evening snacks, and escalation to oral supplementation when intake is insufficient,

under specialist supervision[49]. Continuous monitoring and multidisciplinary coordination are essential, as clinical status may change rapidly during systemic therapy.

For future trials, the key design evolution is to treat supportive care as a mechanistically grounded co-intervention rather than an optional add-on. Candidate trial frameworks include: (1) Protein-adequate, symptom-adapted dietary counseling (with escalation to oral supplements when daily dietary intake is compromised); (2) Supervised or hybrid/home-based resistance-focused exercise adapted for portal hypertension risk and performance status; and (3) Targeted metabolic adjuncts when justified (*e.g.*, interventions studied for lenvatinib-related sarcopenia)[36,37].

Inflammation-based and immunonutritional indices (NLR/SII/PNI/CONUT) can be positioned as intermediate endpoints alongside serial muscle measures. While hard outcomes should include treatment discontinuation, dose intensity, grade ≥ 3 toxicities, hospitalization, and survival. Evidence that nutritional indices relate to treatment retention and adverse-event discontinuation under lenvatinib supports the feasibility and clinical relevance of these endpoints[31].

CONCLUSION

Wu *et al*[10] recently published a study in *World Journal of Gastroenterology* compared different inflammation scores' prognostic values. Inflammation-based indices (NLR, PLR, SII) and immunonutritional scores (PNI, CONUT) have earned their place in HCC care because they are simple, inexpensive, and prognostically informative[30,41], despite their greatest clinical value may be missed when they are treated as fixed baseline labels. In lenvatinib-treated HCC, appetite loss, weight loss, and treatment-associated muscle decline are common. Clinically consequential, together with both nutritional status and muscle trajectories have been linked to retention on therapy and outcomes[4,27]. It is therefore necessary to interpret these indices as dynamic readouts of host biology as signals that can trigger timely nutrition and exercise interventions aligned with liver-disease guidance, rather than as immutable predictors[32,33]. Testing this paradigm in well-designed clinical trials could convert "prognostic description" into actionable supportive care, with the potential to improve tolerability, sustain effective dosing, and ultimately enhance outcomes in HCC patients receiving systemic therapy.

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