Nutritional Status as an Emerging Prognostic Determinant in Multiple Myeloma: From Biological Rationale to Clinical Risk Stratification

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Abstract

Background: Multiple myeloma is a biologically heterogeneous plasma-cell malignancy in which survival is determined not only by tumor burden, cytogenetic abnormalities, and response to therapy but also by host-related factors that influence physiological reserve and treatment tolerance. Nutritional impairment is increasingly recognized as one of these determinants. Patients with multiple myeloma are particularly vulnerable to malnutrition because of advanced age, chronic systemic inflammation, renal dysfunction, anemia, skeletal disease, reduced mobility, recurrent infections, and prolonged exposure to intensive antimyeloma therapies. These factors interact with cancer-associated catabolism to promote weight loss, hypoalbuminemia, sarcopenia, frailty, and progressive functional deterioration. Conventional prognostic systems, including the International Staging System, Revised International Staging System, and second revision of the International Staging System, provide robust assessment of disease-related risk but incompletely characterize host nutritional and functional reserve. Accordingly, nutritional indices such as the Nutritional Risk Index, Prognostic Nutritional Index, Geriatric Nutritional Risk Index, and Controlling Nutritional Status score have gained interest as inexpensive prognostic biomarkers. Emerging evidence indicates that adverse nutritional profiles are associated with inferior treatment response, increased toxicity, shorter progression-free survival, and reduced overall survival in multiple myeloma. Among these approaches, the Nutritional Risk Index is particularly attractive because it combines serum albumin with body-weight change using routinely available clinical information. This review examines the biological relationship between myeloma, inflammation, and nutritional deterioration; summarizes evidence supporting nutritional indices as prognostic tools; discusses their relationship with established staging, frailty, sarcopenia, and treatment outcomes; and proposes a clinically integrated approach in which nutritional assessment complements rather than replaces tumor-based risk stratification. **Keywords:** Hepatocellular carcinoma; Liver resection; Recurrence; Prognostic factors.

Keywords: multiple myeloma, nutritional risk index, malnutrition, prognosis

Introduction

Multiple myeloma (MM) is a clonal plasma-cell malignancy characterized by accumulation of malignant plasma cells in the bone marrow, monoclonal immunoglobulin production, and organ dysfunction that may include anemia, renal impairment, hypercalcemia, and osteolytic bone disease. Although major advances in proteasome inhibitors, immunomodulatory drugs, anti-CD38 monoclonal antibodies, autologous stem-cell transplantation, and cellular therapies have substantially improved survival, outcomes remain remarkably heterogeneous. Some patients achieve disease control lasting many years, whereas others experience early progression, treatment intolerance, or premature death despite apparently comparable antimyeloma therapy. This heterogeneity reflects the interaction between tumor biology, disease burden, treatment sensitivity, comorbidity, age, functional status, and physiological reserve. [1]

Modern prognostic evaluation has therefore evolved from clinical assessment to increasingly sophisticated models incorporating biochemical and cytogenetic characteristics. The International Staging System (ISS), Revised International Staging System (R-ISS), and second revision of the ISS (R2-ISS) have progressively refined disease-related risk stratification. Nevertheless, these systems remain predominantly centered on tumor burden and biological aggressiveness. They do not directly quantify the patient's capacity to withstand prolonged therapy, recover from complications, maintain functional independence, or preserve lean body mass during treatment. These host-related dimensions are especially relevant because MM predominantly affects older adults, in whom comorbidity, frailty, sarcopenia, and nutritional vulnerability frequently coexist. [2]

Malnutrition has traditionally been viewed as a consequence of advanced malignancy. Contemporary evidence suggests a more complex relationship in which nutritional deterioration may both reflect aggressive disease and contribute independently to unfavorable outcomes. In MM, chronic inflammation, marrow infiltration, renal dysfunction, skeletal morbidity, reduced mobility, infections, gastrointestinal adverse effects, corticosteroid exposure, and treatment-associated catabolism can collectively compromise nutritional reserve. Nutritional biomarkers may therefore capture a clinically relevant dimension that is only partially represented by conventional staging. The principal aim of this review is to examine the biological and clinical evidence supporting nutritional status as an emerging prognostic determinant in MM, with particular emphasis on the Nutritional Risk Index (NRI), while defining the research gap regarding its integration with established staging, frailty assessment, and contemporary treatment strategies. [3]

The Contemporary Prognostic Landscape of Multiple Myeloma

Accurate prognostication in MM has long been challenging because the disease encompasses a broad spectrum of molecular abnormalities and clinical phenotypes. Diagnostic criteria have evolved to include not only symptomatic end-organ damage but also validated biomarkers of imminent progression. At the biological level, primary immunoglobulin heavy-chain translocations, hyperdiploidy, secondary chromosomal abnormalities, alterations involving chromosome 1, deletion 17p, and mutations affecting oncogenic signaling pathways contribute to variability in disease behavior. These tumor-related factors are important determinants of treatment resistance and survival but do not fully explain why clinically similar patients experience different treatment toxicity and mortality. [4]

The ISS represented a major advance by demonstrating that two readily available laboratory variables—serum β2-microglobulin and serum albumin—could classify newly diagnosed patients into three prognostically distinct groups. β2-Microglobulin reflects both tumor burden and renal function, whereas albumin is influenced by systemic inflammation, hepatic protein synthesis, disease severity, and nutritional state. The inclusion of albumin within the original ISS is particularly important from a nutritional perspective because it indirectly introduced a host-related and inflammatory component into standard myeloma prognostication, even though the ISS was not designed as a nutritional model. [5]

The R-ISS subsequently incorporated high-risk cytogenetic abnormalities and serum lactate dehydrogenase (LDH) into the ISS framework, markedly strengthening biological risk assessment. More recently, R2-ISS incorporated additional weighting of individual risk factors, including chromosome 1q abnormalities, and improved discrimination among patients previously concentrated within intermediate-risk categories. These developments demonstrate how progressively detailed tumor biology improves prognostic accuracy. However, neither R-ISS nor R2-ISS directly measures weight loss, muscle depletion, dietary intake, nutritional reserve, frailty, or physical function, leaving an important host-related component of outcome insufficiently characterized. [6]

This gap is clinically meaningful. Two patients with identical R2-ISS categories may have dramatically different physiological states: one may be physically active with preserved muscle mass and normal nutritional intake, whereas another may have involuntary weight loss, sarcopenia, hypoalbuminemia, impaired mobility, recurrent infection, and reduced tolerance of combination therapy. A tumor-focused staging system may assign both patients a similar biological prognosis while failing to identify their substantially different probability of completing treatment safely. Nutritional assessment therefore should not be conceptualized as a competitor to molecular staging but as a potentially complementary dimension of risk evaluation. [7]

Biological Rationale Linking Multiple Myeloma to Nutritional Deterioration

The biological basis of nutritional deterioration in MM begins with the bone marrow microenvironment. Myeloma cells interact dynamically with stromal cells, osteoclasts, osteoblasts, immune cells, endothelial cells, and extracellular matrix components. These interactions generate a cytokine-rich environment that promotes malignant cell survival, angiogenesis, immune escape, osteolysis, and drug resistance. Interleukin-6 (IL-6) is particularly important because it functions as a major growth and survival signal for myeloma cells while simultaneously contributing to systemic inflammatory responses and altered protein metabolism. [8]

Persistent inflammatory signaling affects nutritional status through several pathways. Cytokines including IL-6 and tumor necrosis factor-α can stimulate hepatic acute-phase protein production while reducing synthesis of negative acute-phase proteins such as albumin. They also contribute to anorexia, lipolysis, proteolysis, insulin resistance, and increased resting energy expenditure. Consequently, hypoalbuminemia in MM should not be interpreted simply as inadequate dietary protein intake. It may represent an integrated marker of inflammation, disease burden, altered hepatic synthesis, catabolism, and nutritional compromise. This dual biological meaning partly explains why albumin is prognostically powerful but also why it is an imperfect standalone marker of nutritional status. [8]

Myeloma-related organ damage further accelerates nutritional decline. Renal impairment can produce metabolic disturbances, anorexia, dietary restriction, and altered protein balance. Anemia contributes to fatigue and reduced physical activity, promoting muscle loss. Osteolytic lesions, fractures, vertebral collapse, and chronic bone pain limit mobility and can produce a cycle of inactivity, deconditioning, and sarcopenia. Hypercalcemia may cause nausea, constipation, weakness, and reduced intake. Recurrent infections increase metabolic demands while temporarily suppressing appetite. These disease manifestations therefore create overlapping pathways through which higher tumor burden can translate into lower physiological and nutritional reserve. [1]

Treatment itself may compound these effects. Corticosteroids can alter glucose metabolism and body composition; proteasome inhibitors may cause gastrointestinal toxicity and neuropathy; immunomodulatory agents can contribute to fatigue and other adverse events; transplantation exposes patients to mucositis, infections, gastrointestinal symptoms, and prolonged catabolic stress. Modern continuous therapy means that nutritional challenges may persist over years rather than being restricted to a short chemotherapy period. Thus, baseline nutritional impairment can worsen during therapy, while treatment-associated deterioration may reduce dose intensity, delay recovery, and compromise subsequent treatment options. [2]

Malnutrition, Cachexia, and Sarcopenia: Related but Distinct Concepts

Malnutrition in cancer is multifactorial and should not be equated solely with low body mass index (BMI). A patient may have normal or elevated BMI while losing substantial skeletal muscle mass, and an obese patient may simultaneously be sarcopenic and nutritionally compromised. This distinction is particularly relevant in MM, where older patients may begin therapy with excess adiposity but relatively limited muscle reserve. Consequently, conventional anthropometry can underestimate clinically important deterioration when muscle loss is masked by stable body weight, fluid retention, or increased fat mass. [9]

Cancer cachexia represents a metabolically driven syndrome characterized by involuntary weight and muscle loss associated with systemic inflammation and abnormal metabolism. Nutritional supplementation alone may not fully reverse established cachexia because the underlying inflammatory and catabolic signals remain active. In MM, cachexia may be less visually obvious than in some advanced solid tumors, yet the combination of inflammation, age-related muscle loss, physical inactivity, renal dysfunction, and repeated treatment can result in substantial depletion of lean tissue. Recognition of this continuum is important because nutritional intervention is most likely to be effective when risk is detected before severe functional deterioration becomes established. [9]

Serum albumin remains one of the most frequently used biochemical markers in nutritional-prognostic models. Across cancer populations, low pretreatment albumin consistently correlates with inferior survival. Its prognostic strength probably reflects several biological domains simultaneously: systemic inflammation, disease burden, reduced hepatic synthesis, increased vascular permeability, protein loss, and nutritional depletion. Therefore, albumin is valuable precisely because it summarizes several unfavorable processes, but it cannot by itself distinguish potentially reversible undernutrition from inflammatory hypoalbuminemia. [10]

The practical implication is that nutritional assessment in MM should be multidimensional whenever possible. Weight trajectory, dietary intake, BMI, serum albumin, inflammatory markers, muscle mass, physical function, and frailty provide related but nonidentical information. Composite indices attempt to simplify this complexity into clinically usable scores. Among the most studied are the NRI, Prognostic Nutritional Index (PNI), Geriatric Nutritional Risk Index (GNRI), and Controlling Nutritional Status (CONUT) score. Each emphasizes different components of the nutrition–inflammation–immune axis and therefore may perform differently across patient populations. [9]

Nutritional Risk Index

The NRI is calculated from serum albumin and the relationship between current and usual body weight: **NRI = 1.489 × serum albumin (g/L) + 41.7 × current body weight/usual body weight**. The score combines a biochemical marker with a measure of weight change and can be calculated without specialized equipment. Its simplicity makes it attractive in MM clinics where routine laboratory data are already collected and where access to formal nutritional assessment, body-composition imaging, or dietetic services may be limited. [11]

A major strength of the NRI is that it captures two complementary signals. Declining body weight reflects loss of nutritional reserve, whereas albumin reflects systemic disease, inflammation, and protein homeostasis. In MM, this combination is biologically plausible because advanced disease may simultaneously lower albumin and induce weight loss through increased catabolism, anorexia, organ dysfunction, and reduced mobility. However, the NRI is not a pure measure of nutrition. Because albumin is inflammation-sensitive and body weight may be distorted by fluid retention, renal disease, edema, or inaccuracies in recalling usual weight, interpretation must remain clinically contextual. [11]

The most directly relevant evidence comes from the study by Zhang and colleagues in 638 patients with newly diagnosed multiple myeloma. Patients were stratified using an NRI cutoff of 89. Median overall survival was significantly longer among patients with high NRI than among those with low NRI, at 64 versus 43 months. Importantly, high NRI remained independently associated with improved overall survival in multivariable analysis, with a hazard ratio of 0.758. Age, performance status, transplant status, and LDH were also independent determinants, indicating that NRI added information rather than simply replacing conventional clinical variables. [11]

The same study showed that lower NRI was associated with an overall less favorable clinical phenotype. This is conceptually important because it supports the idea that nutritional deterioration lies at the intersection of host vulnerability and disease severity. An unfavorable NRI can therefore be understood as a clinical signal that the patient has less metabolic reserve with which to tolerate disease and therapy. Nevertheless, the observational design prevents a conclusion that improving NRI itself will necessarily improve survival; NRI may partly function as a marker of biological severity rather than a directly modifiable causal pathway. [11]

Broader Inflammatory and Nutritional Scoring Approaches

The relationship between nutrition and prognosis appears to extend beyond the NRI. A subsequent inflammatory and nutritional scoring study in 442 patients with newly diagnosed MM evaluated several routinely measurable parameters and constructed an Inflammatory Nutritional Score incorporating NRI, BMI, neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and albumin-to-alkaline phosphatase ratio. When combined with performance status, LDH, age, and C-reactive protein, the resulting prognostic model achieved meaningful discrimination in both training and validation cohorts. [12]

This approach highlights an important principle: nutrition and inflammation are biologically intertwined rather than independent prognostic domains. A low albumin concentration may indicate inflammatory activation; lymphocyte counts may reflect immune competence as well as nutritional status; BMI may incompletely represent body composition; and CRP provides complementary evidence of systemic inflammation. Models combining these variables may therefore capture host response to malignancy more effectively than isolated nutritional measures. The trade-off is increasing complexity and the risk of statistical overfitting unless scores are externally validated. [12]

The CONUT score uses serum albumin, total lymphocyte count, and cholesterol concentration to assess nutritional and immunometabolic status. In a study of symptomatic MM, Okamoto and colleagues found that a high CONUT score was independently associated with inferior survival. The effect was particularly notable in transplant-eligible patients, suggesting that nutritional reserve may influence the ability to benefit from intensive treatment. These findings support the concept that nutritional biomarkers are not merely markers of terminal disease but can identify prognostic differences even among patients undergoing active, potentially intensive therapy. [13]

Independent evidence from another cohort of 178 newly diagnosed patients also demonstrated shorter survival among individuals with high CONUT scores. In that analysis, CONUT remained an independent prognostic factor in patients with ISS stage I or II, suggesting that nutritional assessment may be especially useful for identifying vulnerable individuals within conventional lower-risk disease categories. More recently, a meta-analysis of nine studies involving 1,176 patients with MM found that higher CONUT scores were associated with worse overall survival and with greater bone marrow plasma-cell infiltration, further strengthening the association between disease burden, nutritional impairment, and survival. [14]

Prognostic Nutritional Index and Geriatric Nutritional Risk Index

The PNI is generally derived from serum albumin and peripheral blood lymphocyte count, thereby combining protein status with an immunological component. Its conceptual advantage is that lymphopenia may reflect compromised immune competence, systemic stress, and disease-related immunosuppression. In newly diagnosed MM, recent evidence has shown significantly shorter overall survival among patients with low PNI, whereas neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios were not independently informative in the same cohort. This suggests that albumin-containing composite indices may provide stronger prognostic information than isolated inflammatory ratios in some populations. [15]

Nutritional assessment may also remain relevant in the transplantation setting. A 2026 analysis of patients with MM undergoing autologous hematopoietic stem-cell transplantation identified PNI as one of the factors associated with post-transplant prognosis, together with LDH, pretransplant disease status, bone marrow involvement, and diabetes mellitus. Although methodological limitations and unusual event distributions require cautious interpretation, the study reinforces the concept that host nutritional reserve should be considered alongside disease response when evaluating transplant risk. [16]

The GNRI was originally developed for older individuals and substitutes ideal body weight for usual body weight, reducing dependence on patient recall. Because MM predominantly affects an older population, GNRI is conceptually attractive. A systematic review and meta-analysis encompassing 14 studies and 3,524 patients with hematologic malignancies found that low GNRI was associated with significantly inferior overall survival and progression-free survival. Although the analysis included several hematologic cancers rather than MM alone, it provides broader evidence that nutrition-related host vulnerability has consistent prognostic relevance across hematologic malignancy populations. [17]

NRI, PNI, GNRI, and CONUT should therefore not be viewed as interchangeable. NRI emphasizes albumin and weight change; PNI incorporates albumin and lymphocytes; GNRI is particularly applicable when ideal rather than previous body weight is preferred; and CONUT incorporates albumin, lymphocytes, and cholesterol. Different scores may perform differently depending on age, inflammation, renal function, treatment setting, and population characteristics. The absence of direct prospective head-to-head comparisons in contemporary MM remains a major limitation and an important research priority. [17]

Relationship With ISS, R-ISS, and R2-ISS

Nutritional assessment has an intriguing relationship with established MM staging because albumin already constitutes one of the two original ISS variables. This creates partial overlap between nutritional and conventional prognostic systems. A low albumin concentration can simultaneously lower NRI or PNI while contributing to a higher ISS category. Consequently, part of the association between nutritional indices and survival may reflect disease burden already represented within established staging. This statistical and biological overlap must be considered whenever investigators claim that a nutrition-based score provides independent prognostic information. [5]

Nevertheless, nutritional indices incorporate features that ISS does not. Weight loss, lymphocyte count, cholesterol, body composition, and sarcopenia represent dimensions of host reserve distinct from β2-microglobulin or cytogenetic abnormalities. The observation that NRI retained independent prognostic significance after multivariable adjustment supports the hypothesis that nutritional status adds complementary information. Similarly, CONUT has demonstrated prognostic discrimination even within lower ISS categories, suggesting that tumor burden and host vulnerability are related but nonredundant concepts. [11]

The R-ISS and R2-ISS improve assessment of tumor aggressiveness through cytogenetics and LDH but remain largely insensitive to physiological resilience. Future risk models could therefore combine a disease-specific component such as R2-ISS with a host-specific component incorporating nutritional risk, frailty, and muscle mass. Such a framework would more closely reflect clinical decision-making, where physicians already consider both disease aggressiveness and patient fitness when choosing induction intensity, transplantation, dose modifications, and supportive measures. [7]

Nutritional Status and Treatment Response

One mechanism linking malnutrition with survival is impaired treatment tolerance. Adequate nutritional and functional reserve is necessary to withstand repeated cycles of combination therapy, infections, cytopenias, gastrointestinal toxicity, and hospitalization. Patients with nutritional impairment may require dose reductions, treatment delays, early discontinuation, or less intensive regimens. Conversely, patients with preserved nutritional reserve may be more likely to receive and complete optimal therapy. This creates a clinically important pathway through which baseline nutritional state may influence outcomes independently of the intrinsic sensitivity of the myeloma clone. [9]

Observational MM data are consistent with this concept. In the NRI study, transplant status and performance status remained independent predictors alongside nutritional risk. This relationship suggests that patients with low NRI often accumulate multiple disadvantages: poorer performance, reduced treatment intensity, and possibly less frequent access to transplantation. Nutritional status should therefore be interpreted within a broader vulnerability phenotype rather than as an isolated laboratory abnormality. [11]

The clinical direction of causality, however, is complex. Aggressive MM may produce greater inflammation, lower albumin, weight loss, poorer performance, and reduced treatment response simultaneously. In this scenario, low NRI is partly a downstream marker of aggressive disease. Alternatively, pre-existing malnutrition and sarcopenia may genuinely reduce chemotherapy tolerance and immune competence. Both mechanisms can coexist. This bidirectional relationship explains why prognostic association alone is insufficient to prove that nutritional intervention improves myeloma-specific survival. Prospective interventional studies are necessary to establish whether correcting nutritional deficits changes clinically important outcomes. [9]

In routine practice, the most defensible application of nutritional screening is therefore not to use a low NRI as justification for undertreatment. Rather, it should trigger closer assessment, early dietetic involvement, evaluation for reversible causes of weight loss, physical rehabilitation when appropriate, optimization of comorbidities, and enhanced toxicity surveillance. Nutritional vulnerability may identify a patient who needs more supportive care to receive effective myeloma treatment, not necessarily a patient who should automatically receive less effective therapy. [9]

Frailty, Sarcopenia, and Nutritional Risk

Frailty is highly relevant in MM because chronological age alone poorly reflects treatment tolerance. The International Myeloma Working Group frailty model demonstrated that age, comorbidity, and functional assessment could stratify older patients into fit, intermediate-fit, and frail categories with substantially different survival, toxicity, and treatment-discontinuation risks. This established host fitness as a formal prognostic domain in MM and provides a conceptual foundation for incorporating nutritional assessment into geriatric myeloma care. [18]

Malnutrition and frailty overlap but are not synonymous. A patient may be frail because of functional or cognitive impairment despite relatively preserved nutritional parameters, whereas another may have marked nutritional depletion while remaining independent in daily activities. Similarly, sarcopenia may

occur without major weight loss. Consequently, the most clinically informative strategy may involve combining complementary measures rather than selecting a single universal score. Nutritional risk identifies metabolic reserve, frailty assesses broader vulnerability, and sarcopenia provides a structural measure of muscle depletion. [18]

The prognostic importance of sarcopenia has been demonstrated directly in MM. In a cohort of 322 patients with newly diagnosed disease, CT-based deep-learning assessment identified sarcopenia in more than half of patients. Median overall survival was 44 months among sarcopenic patients compared with 90 months among those without sarcopenia, and the adverse prognostic effect remained significant after adjustment for ISS stage, age, and high-risk cytogenetics. These findings are particularly important because they show that body composition can carry prognostic information independently of major tumor-related variables. [19]

Sarcopenia may ultimately prove to be an important bridge between nutritional assessment and functional prognosis. Unlike serum biomarkers, CT-derived muscle measurements directly characterize body composition; unlike weight, they are less influenced by obesity. However, routine implementation requires standardized anatomical landmarks, software, thresholds, and validation across sex and ethnic groups. Opportunistic analysis of CT or PET/CT examinations already obtained for MM assessment could eventually allow body-composition information to be incorporated without additional imaging or radiation exposure. [19]

Clinical Integration of Nutritional Assessment

A pragmatic clinical approach would begin with baseline nutritional screening at the time of MM diagnosis. Weight history, recent involuntary weight loss, BMI, serum albumin, renal and hepatic function, CRP where available, dietary intake, performance status, and relevant gastrointestinal symptoms should be documented. Calculation of an NRI or another validated nutritional index can be performed simultaneously because the required data are inexpensive and routinely available. A low score should prompt formal nutritional assessment rather than being regarded merely as another prognostic laboratory abnormality. [9]

For older patients, nutritional screening should ideally be integrated with frailty assessment. Patients identified as nutritionally vulnerable should be evaluated for potentially reversible contributors including uncontrolled pain, nausea, constipation, depression, poor dentition, infection, renal dysfunction, hypercalcemia, inadequate socioeconomic support, and treatment toxicity. Assessment of muscle strength or sarcopenia may further refine risk. Such evaluation recognizes that poor nutritional status is often multifactorial and that improvement requires coordinated management rather than isolated caloric supplementation. [18]

Nutritional assessment may also be valuable longitudinally. A baseline score captures only one moment in a chronic disease characterized by repeated treatment and relapse. Dynamic changes in albumin, weight, muscle mass, inflammation, and functional status may provide additional prognostic information. A patient whose NRI deteriorates during induction may have a different risk trajectory from one whose low baseline score improves after disease control. Serial measurements could therefore distinguish reversible disease-associated nutritional impairment from persistent vulnerability, but this hypothesis requires prospective validation. [11]

The most promising future model is therefore not “NRI versus R2-ISS,” but rather **tumor biology plus host biology**. R2-ISS, cytogenetics, molecular markers, response depth, and minimal residual disease characterize the malignant clone; NRI, sarcopenia, frailty, comorbidity, and performance status characterize the patient carrying that clone. Integrating these domains may produce more individualized predictions of survival, toxicity, treatment completion, and transplant suitability than either domain alone. [7]

Limitations of Current Evidence and Research Gaps

The nutritional prognostic literature in MM remains dominated by retrospective, single-center studies. Cutoff values differ among populations, treatments are heterogeneous, and nutritional indices are often measured only once at diagnosis. Many studies were performed before widespread frontline anti-CD38 therapy and may not fully represent contemporary outcomes. Furthermore, statistical independence does not establish biological independence because nutritional indices share components with conventional prognostic variables, particularly serum albumin. [11]

An additional limitation is the absence of a universally accepted nutritional reference standard in MM. NRI, PNI, GNRI, CONUT, BMI, formal nutritional assessment, and CT-defined sarcopenia each measure different components of the host state. Studies comparing these approaches directly are needed to identify which variable or combination provides the best incremental prognostic value beyond R2-ISS, cytogenetics, frailty, and treatment response. Analyses should also account for renal disease, edema, corticosteroid-related metabolic effects, inflammation, sex, age, ethnicity, and differences in body composition. [17]

Most importantly, the prognostic association between nutritional status and survival should not be interpreted as proof that nutritional supplementation alone improves MM survival. Randomized or well-designed prospective intervention studies are needed to determine whether individualized dietetic care, resistance exercise, rehabilitation, symptom control, and multimodal anti-cachexia strategies improve treatment completion, infection rates, quality of life, hospitalization, transplantation outcomes, progression-free survival, or overall survival. The distinction between a prognostic biomarker and a modifiable therapeutic target is central to translating this field safely into clinical practice. [9]

Future investigations should also explore dynamic risk prediction. Machine-learning and multivariable survival approaches can integrate continuously measured albumin, weight trajectory, CRP, lymphocyte counts, CT-derived muscle mass, molecular risk, treatment exposure, response, and frailty. Such models could identify changes in risk over the disease course rather than relying exclusively on baseline classification. However, complex algorithms should be compared with simpler tools to ensure that incremental predictive gains justify additional cost and complexity and that resulting models remain interpretable and externally generalizable. [12]

Conclusion

Nutritional status represents an increasingly important component of prognosis in multiple myeloma because it reflects the interaction between systemic inflammation, tumor burden, metabolic reserve, muscle integrity, frailty, and treatment tolerance. Evidence supporting the NRI, PNI, GNRI, CONUT score, and sarcopenia demonstrates that host-related variables can provide prognostic information beyond conventional disease characteristics. Among these approaches, the NRI is particularly attractive because it is inexpensive, reproducible, and immediately available from routine clinical data. Nevertheless, nutritional indices should complement rather than replace established systems such as the R-ISS and R2-ISS. The future of individualized myeloma prognostication is likely to depend on integrated models that simultaneously characterize tumor aggressiveness and host vulnerability, accompanied by prospective studies determining whether early identification and correction of nutritional impairment can translate prognostic information into improved clinical outcomes.

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