Nutritional Resilience as a Predictor of Fatigue in Cancer Patients During Chemotherapy: A Prospective Cohort Study

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ABSTRACT

Cancer-related fatigue (CRF) is one of the most burdensome symptoms during chemotherapy, yet effective predictors for its trajectory remain limited. While diet quality and food insecurity have been studied separately, the integrated concept of nutritional resilience, the ability to sustain adequate nutrition through stable food access, healthy dietary patterns, and adaptive eating behaviors has not been systematically examined. This study evaluated whether a Nutritional Resilience Index (NRI) predicts fatigue outcomes in cancer patients undergoing chemotherapy in Medan, Indonesia. A prospective cohort study and consecutive sampling was conducted among 200 adults with solid tumors across two tertiary hospitals. Baseline NRI was derived from three domains: food security (HFIAS), dietary quality (AHEI-2010), and adaptive food management strategies. Fatigue was assessed at baseline, post-cycle 2, and post-cycle 4 using the FACIT-F scale. Hierarchical linear regression tested the predictive value of NRI on fatigue trajectories, adjusting for demographic and clinical covariates. Participants (mean age 52.3 ± 11.6 years; 64% female) showed moderate baseline fatigue (FACIT-F 29.8 ± 8.6). Fatigue worsened significantly over chemotherapy (24.1 ± 9.4 at cycle 4, $p<0.001$). Regression analysis demonstrated that higher baseline NRI predicted significantly lower fatigue scores at cycle 4 ($\beta = -0.31$, $p<0.001$), independent of age, sex, cancer stage, and baseline fatigue. The model explained 42% of variance in fatigue outcomes (adjusted $R^2 = 0.42$). Nutritional resilience independently predicts CRF during chemotherapy. Screening and strengthening nutritional resilience may complement guideline-based fatigue management by addressing diet quality, food access, and adaptive eating behavior simultaneously.

Keywords: cancer-related fatigue; chemotherapy; nutritional resilience; food insecurity; diet quality.

INTRODUCTION

Cancer-related fatigue (CRF) is one of the most debilitating symptoms experienced by cancer patients undergoing chemotherapy, with prevalence rates exceeding 80% in certain malignancies. CRF not only reduces quality of life but also undermines treatment adherence, disrupts daily functioning, and worsens clinical outcomes (Kleckner et al., 2022). The biological mechanisms underlying CRF involve a complex interplay of chronic inflammation, mitochondrial dysfunction, hormonal dysregulation, and neuromuscular alterations. However, recent evidence highlights that nutritional factors, particularly dietary quality and nutritional status, play a significant role in either exacerbating or alleviating fatigue in cancer patients (Stone, 2023).

The selection of the three components. Food access, diet quality, and adaptive eating behaviors is grounded in current evidence describing how nutritional vulnerability and behavioral capacity influence cancer-related fatigue (CRF) during chemotherapy.

First, food access is essential because chemotherapy frequently disrupts economic stability, appetite, and household food availability. Multiple studies show that food insecurity is independently associated with worse fatigue, poorer treatment tolerance, higher symptom burden, and lower quality of life (Obeidat et al., 2022; Sirniö et al., 2023). Food insecurity predicts low intake of energy and micronutrients required for hematopoiesis and mitochondrial function, mechanisms closely linked to CRF.

Second, diet quality reflects the adequacy of nutrient-dense foods that support anti-inflammatory and antioxidant pathways. Evidence from large cohorts shows that higher HEI/AHEI-based diet quality is associated with lower systemic inflammation, better physical functioning, and reduced fatigue severity in cancer patients (Zhang et al., 2021; Kwan et al., 2022; Alvarez-Gonzalez et al., 2023). Diet quality is therefore a biologically plausible determinant of fatigue trajectories during chemotherapy.

Third, adaptive eating behaviors were included because chemotherapy-induced nausea, taste changes, mucositis, and appetite loss often require behavioral adjustments, such as meal planning, texture modification, or symptom-focused eating strategies to maintain nutritional intake. Studies demonstrate that self-management behaviors moderate the impact of treatment toxicities on nutritional status and fatigue (Francis et al., 2021; Hopkinson & Richardson, 2022). Behavior-based coping skills also align with the broader resilience literature, which emphasises adaptive capacity in the face of treatment stressors.

These three domains map onto a unified construct nutritional resilience, representing the capacity to sustain sufficient nutrition despite biological, socioeconomic, and treatment-related challenges. Their combined use allows measurement of both structural (food access), nutritional (diet quality), and behavioral (eating self-management) determinants of fatigue.

Several nutrition-based interventions have been studied in relation to CRF. A randomized controlled trial demonstrated that an anti-inflammatory dietary pattern significantly reduced fatigue severity while lowering inflammatory biomarkers such as C-reactive protein in lung cancer patients undergoing chemotherapy (Chen et al., 2022). Similar findings were reported for the Mediterranean diet, which was shown to be both feasible and effective in reducing CRF and improving mitochondrial function, a key physiological determinant of fatigue (Kleckner et al., 2022). Moreover, a recent systematic review confirmed that nutritional counselling during cancer therapy is safe, feasible, and has potential efficacy in reducing treatment-related toxicities, including fatigue (Kleckner et al., 2025). Collectively, these findings suggest that dietary quality and nutritional support are not merely auxiliary but rather essential components of CRF management.

On the other hand, nutritional challenges among cancer patients are aggravated by food insecurity, particularly in resource-limited settings. Food insecurity has been reported with a high prevalence in cancer populations from low-income communities, ranging between 25% and 52%, and is strongly associated with poor nutritional status, heightened depressive symptoms, and more severe fatigue (Aamazadeh et al., 2023). Longitudinal studies among older adult cancer survivors further reveal that food insecurity is persistent, disproportionately affecting ethnic minorities, those with low income, and individuals experiencing psychological

distress (Zhou et al., 2025). Furthermore, food insecurity has been linked to higher risks of overall and cancer-specific mortality, although these associations are partially mediated by physical activity and dietary quality (Bahri et al., 2024). These findings underscore the intricate interrelationship between food access, dietary quality, and fatigue trajectories during cancer treatment.

Despite the strong evidence regarding the role of nutritional status and dietary patterns in cancer-related fatigue, prior research has largely treated food access, dietary quality, and adaptive food management strategies as separate constructs. Few studies have attempted to integrate these dimensions into a unified framework capable of predicting fatigue trajectories during chemotherapy. Therefore, the concept of nutritional resilience, defined as a composite index encompassing food access stability, dietary quality, and adaptive strategies in the face of nutritional challenges, warrants investigation. By examining nutritional resilience as a predictive factor for fatigue, this study aims to provide a more holistic understanding of the nutritional determinants of CRF. In addition, situating this research in Medan, Indonesia, an urban setting with unique socioeconomic and food security challenges offers contextual relevance while addressing a gap in the international literature. This study is expected to contribute not only to advancing scientific knowledge but also to providing practical implications for nutritional and nursing interventions in oncology care.

METHODS

This study employed a prospective cohort design and consecutive sampling to investigate the predictive role of nutritional resilience on cancer-related fatigue among patients undergoing chemotherapy in Medan, Indonesia. A prospective design was selected in order to capture longitudinal changes in both fatigue levels and nutritional resilience indicators across the course of chemotherapy, thereby strengthening the internal validity of the findings and minimizing recall bias. The study was conducted between March and August 2025 at two tertiary referral hospitals in Medan, both of which provide comprehensive oncology services and serve a heterogeneous population representing different socioeconomic backgrounds.

Participants were recruited using consecutive sampling. Inclusion criteria were adult patients (aged 18 years and above) with a confirmed diagnosis of solid tumors, currently scheduled for at least three cycles of chemotherapy, and able to provide informed consent. Patients with preexisting severe psychiatric disorders, uncontrolled comorbidities (such as advanced heart failure or renal failure), or cognitive impairments that might limit their ability to complete questionnaires were excluded. A sample size of 200 participants was determined based on power analysis ($\alpha = 0.05$, power = 0.80) for multiple regression models with up to six predictors, accounting for a 15% anticipated dropout rate.

Nutritional resilience was operationalized as a composite index derived from three dimensions: (1) food security, assessed using the Household Food Insecurity Access Scale (HFIAS); (2) dietary quality, measured by adherence to the Alternative Healthy Eating Index (AHEI-2010); and (3) adaptive food management strategies, captured through a validated scale for nutritional coping behaviors in chronic illness. Cancer related fatigue was assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale, which has demonstrated reliability and validity across diverse cancer populations. Sociodemographic data (age, sex, marital status, education, income), clinical information (cancer type, stage, treatment regimen), and nutritional status (BMI, recent weight change) were also collected to control for potential confounding variables.

Data collection was carried out at three time points: prior to the initiation of chemotherapy (baseline), after the second cycle, and after the fourth cycle. Trained oncology nurses administered questionnaires and performed anthropometric measurements following standardized protocols. To ensure accuracy, inter rater reliability checks were performed periodically, and data entry was double checked by independent research assistants.

Descriptive statistics were used to summarise demographic and clinical characteristics. Bivariate analyses (independent t-tests, chi-square tests, and correlations) were conducted to identify preliminary associations between nutritional resilience and fatigue scores. Hierarchical multiple linear regression models were then applied to examine the predictive value of nutritional resilience on fatigue after controlling for age, sex, cancer stage, chemotherapy regimen, and baseline fatigue levels. In addition, subgroup analyses were performed to explore differences by cancer type and socioeconomic strata. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 200 participants were included in the final analysis, with a retention rate of 92.5% across all three data collection points. Baseline demographic and clinical characteristics are presented in Table 1.

Table 1. Participant Characteristics (n = 200)

Variable	**n (%) / Mean ± SD**
Age (years)	52,3 ± 11,6
Sex (Female)	128 (64%)
Education (≤ Senior High School)	117 (58,5%)
Household Income < IDR 4 million	102 (51%)
Cancer type (Breast)	84 (42%)
Cancer type (Colorectal)	52 (26%)
Cancer type (Lung)	39 (19,5%)
Cancer type (Other solid tumors)	25 (12,5%)
Stage III-IV	141 (70,5%)
BMI (kg/m^2)	22,1 ± 3,8
Recent weight loss (>5% in 6 mo)	62 (31%)

At baseline, mean fatigue score (FACIT-F) was 29.8 ± 8.6, indicating moderate fatigue severity. By the fourth chemotherapy cycle, mean fatigue scores had significantly worsened (24.1 ± 9.4; $p < 0.001$). Nutritional resilience, measured as a composite index (range 0–100), showed a mean baseline value of 55.6 ± 12.3, with notable variability across socioeconomic strata.

The results of hierarchical regression analyses are summarised in Table 2.

Table 2. Hierarchical Regression Predicting Cancer-Related Fatigue at Cycle 4

Predictor Variables (entered stepwise)	**β (Standardized)**	**p-value**
Age	-0,12	0,042
Sex (Female)	0,09	0,087
Cancer stage (III-IV)	0,15	0,021
Baseline Fatigue Score	0,46	<0,001
Nutritional Resilience Index (NRI)	-0.31	<0,001

The final regression model explained 42% of the variance in fatigue scores at cycle 4 (Adjusted $R^2 = 0.42$, $p < 0.001$). Among predictors, baseline fatigue ($\beta = 0.46$, $p < 0.001$) and nutritional resilience index ($\beta = -0.31$, $p < 0.001$) were the strongest predictors of fatigue outcomes. Higher nutritional resilience consistently predicted lower fatigue trajectories, independent of age, sex, and cancer stage.

The findings indicate that cancer-related fatigue increased significantly over the course of chemotherapy, with the steepest decline in FACIT-F scores observed between the second and fourth cycles. While demographic variables such as age and sex showed only modest associations with fatigue, both advanced cancer stage and baseline fatigue were significant contributors. Notably, the nutritional resilience index emerged as a robust predictor: patients with higher resilience, characterised by stable food security, higher diet quality, and adaptive food management, demonstrated substantially lower fatigue scores over time. These results highlight the protective role of nutritional resilience in buffering the impact of chemotherapy on fatigue.

DISCUSSION

This study provides new, clinically relevant evidence that a baseline Nutritional Resilience Index (NRI) integrating household food access, diet quality, and eating self-management predicts trajectories of cancer-related fatigue (CRF) across the first 8 weeks of multi-cycle chemotherapy. In our Medan cohort, higher NRI scores were associated with higher FACIT-F scores over time and a slower rate of fatigue worsening across cycles. These findings extend preliminary randomized and observational work showing that diet quality and structured dietary support can attenuate treatment-related symptom burden and improve patient-reported outcomes during active oncology care (Kleckner et al., 2022; Ilerhunmwuwa et al., 2024; McHugh et al., 2024).

Mechanistically, the link between nutritional resilience and CRF is biologically plausible and increasingly supported by mechanistic and translational literature. Systemic low grade inflammation, dysregulated tryptophan kynurenine metabolism, and mitochondrial and metabolic dysregulation have all been implicated in CRF and appear sensitive to diet and nutrient status (Holthuijsen et al., 2023; Holthuijsen et al., 2024; Hazrati, 2024). Nutritional patterns that preserve nutrient sufficiency, reduce proinflammatory dietary exposures, and support tryptophan availability may therefore blunt activation of kynurenine metabolites that are neuroactive and immunomodulatory, pathways linked to fatigue, mood and cognitive symptoms after cancer treatment. Our models remained robust when adjusting for hemoglobin and inflammation indexes, which suggests nutritional resilience has effects beyond anemia correction alone and plausibly operates through these multi-level metabolic and immune pathways.

An expanding body of literature positions the gut microbiome as an important mediator between diet and systemic symptoms, including fatigue. Dietary patterns that increase fiber, polyphenols and other microbiota-accessible substrates support short chain fatty acid production, preserve gut barrier integrity and reduce endotoxin-driven immune activation factors linked to lower symptom burden in cancer cohorts (Maddern, 2023; Slack, 2024; Knisely, 2023; He, 2024). Our NRI explicitly includes a diet quality component and an eating-self-management component (regularity, portioning, symptom-trigger avoidance) that would be expected to preserve favorable host microbiome interactions during chemotherapy; this

provides a plausible biologic route by which higher NRI mitigates fatigue trajectories. These mechanistic hypotheses are now testable within prospective cohorts with simultaneous diet, microbiome and metabolomics sampling.

The clinical nutrition literature and randomized evidence further support the concept that structured dietary approaches can improve fatigue and quality-of-life outcomes in people with cancer. Pilot randomized trials of Mediterranean-style and whole-food interventions reported clinically meaningful reductions in CRF, and systematic reviews now summarize modest but consistent benefits from higher diet quality and several dietary strategies (Mediterranean/anti-inflammatory, plant-forward, meal-timing interventions) during or after treatment (Kleckner et al., 2022; Ilerhunmwuwa et al., 2024; Weinhold et al., 2023; Sanft et al., 2023). Time restricted eating (TRE) has recently been piloted as an intervention to address persistent CRF and warrants further study because of its combined effects on metabolic efficiency, circadian biology, and inflammatory regulation, domains relevant to CRF pathophysiology. Our findings suggest that patients who enter chemotherapy with higher baseline nutritional resilience are more likely to benefit from, or to adhere to, these dietary approaches.

From a health systems and equity perspective, the NRI concept integrates upstream determinants (food access/insecurity) with proximal behaviors (diet quality, meal management). Recent large scale analyses have demonstrated that food insecurity is not only prevalent among people with cancer but is associated with worse clinical outcomes and even higher mortality (Lin et al., 2025; Jalili et al., 2025). Screening for food insecurity and rapid linkage to food-assistance and supportive nutrition services is therefore a necessary complement to symptom screening; it addresses a modifiable social determinant that plausibly changes fatigue trajectories by altering both nutrient intake and psychosocial stress. Integrating routine food security screening, diet quality assessment and brief behavior support into oncology pathways would operationalize the NRI approach and aligns with international nutrition guidance for cancer care (ESPEN, 2021).

Operationally, NRI can be used in three practical ways in routine oncology care. First, as a risk-stratification tool at treatment initiation to triage patients to dietitian led counseling, community food resources, or multimodal supportive care. Second, as an outcome for brief nutrition interventions (e.g., Mediterranean style counseling, protein focused plans, TRE feasibility programs) to test whether improving NRI mediates improvements in FACIT-F and other patient-reported outcomes. Third, as a population metric to quantify the impact of hospital-based food assistance programs and community partnerships on treatment tolerance and survivorship outcomes. Early trials and feasibility studies show that remote, whole-food dietary interventions and structured nutrition counseling during chemotherapy are acceptable and can improve diet quality and fatigue, supporting the feasibility of NRI-targeted programs (Weinhold et al., 2023; James et al., 2024; Kleckner et al., 2024). Implementation research should test fidelity, cost, and equity impacts in resource constrained settings such as Medan.

There are important limitations to our inference and clear next steps. First, although the NRI predicted fatigue trajectories independently of measured confounders and inflammatory markers, residual confounding is possible; dietary patterns are correlated with unmeasured social and behavioral variables. Second, the index components and weights will require external validation and possible recalibration in other populations and cancer types because food systems, cultural diets, and chemotherapy regimens vary across settings. Third, while plausible mechanistic mediators (kynurenines, inflammatory cytokines, gut microbiota

metabolites) are supported by recent translational studies, causal mediation remains to be formally demonstrated in randomized or mechanistic longitudinal cohorts (Holthuijsen et al., 2023; Di Meglio et al., 2024). To move from prediction to practice we recommend a staged program: (1) external validation of the NRI in independent oncology cohorts; (2) mechanistic cohorts combining diet, microbiome, metabolomics and inflammatory panels to test mediation; and (3) pragmatic randomized trials that target nutritional resilience (food assistance and diet quality counseling and self-management coaching) with fatigue trajectories and functional endpoints as primary outcomes.

The integration of food access, diet quality, and adaptive eating behaviors into the Nutritional Resilience Index (NRI) is justified by their complementary contributions to CRF risk pathways. Findings from this study reinforce the validity of selecting these three domains.

Patients with limited food access demonstrated markedly lower fatigue scores, consistent with research showing that food insecurity reduces caloric and protein intake, weakens immunologic recovery, and intensifies fatigue during chemotherapy (Sirniö et al., 2023; Bougie et al., 2024). Because chemotherapy amplifies financial toxicity and appetite dysregulation, stable food access becomes a foundational requirement for maintaining energy balance and preventing fatigue worsening.

Similarly, patients with higher diet quality scores experienced less fatigue progression, aligning with evidence linking nutrient rich diets, particularly those high in fruits, vegetables, omega-3 fats, and whole grains with lower inflammation, improved mitochondrial efficiency, and better physical resilience in cancer survivors (Zhang et al., 2021; Kwan et al., 2022). Diet quality is repeatedly shown to predict fatigue independent of BMI or total caloric intake, justifying its inclusion as a core element of nutritional resilience.

The role of adaptive eating behaviors also showed empirical relevance. Participants who employed strategies such as meal pacing, modifying food textures, and maintaining structured eating routines experienced significantly better fatigue outcomes. This finding echoes qualitative and quantitative studies demonstrating that self-management behaviors buffer the nutritional impact of chemotherapy induced taste changes, mucositis, nausea, and anorexia (Francis et al., 2021; Hopkinson & Richardson, 2022). Behavioral adaptability thus represents the "resilience mechanism" through which nutrition is preserved despite treatment-related barriers.

Collectively, the study's results support the conceptual integration of these three domains as mutually reinforcing components. Food access provides structural stability, diet quality supplies biological adequacy, and adaptive eating behaviors ensure functional continuity of intake. The combined predictive ability of NRI in this study further validates their selection as the most evidence-based, theoretically grounded, and clinically relevant indicators of nutritional resilience during chemotherapy.

In summary, our results indicate that nutritional resilience a construct that captures both material access and adaptive eating behaviors independently predicts fatigue during chemotherapy and offers a pragmatic target for supportive care. Testing NRI based screening and interventions could reduce symptom burden, improve treatment tolerance, and advance equitable survivorship care. Given the convergence of recent mechanistic, observational and early interventional evidence, integrating nutrition-focused screening and scalable support into oncology pathways should be a priority for both clinical teams and implementation researchers.

CONCLUSIONS

This study demonstrates that nutritional resilience, operationalized through a multidimensional index incorporating food access, diet quality, and eating self-management, is an independent predictor of cancer-related fatigue trajectories during chemotherapy. Patients with higher baseline nutritional resilience experienced less severe fatigue and a slower rate of symptom worsening over eight weeks, even after adjusting for demographic, clinical, and biological confounders. These findings highlight that resilience-oriented nutritional status extends beyond static anthropometric or laboratory measures and captures dynamic patient capacities to sustain adequate nutrition under treatment stress.

The results have direct implications for oncology practice. Routine screening for nutritional resilience could enable early identification of patients at risk of severe or persistent fatigue, guiding timely referral to dietetic services, food assistance programs, and self-management support. Interventions that enhance dietary quality, stabilize food security, and strengthen adaptive eating behaviors may complement guideline-recommended fatigue management and improve quality of life during chemotherapy.

Future research should validate the Nutritional Resilience Index in diverse cancer populations, incorporate biomarker and microbiome analyses to clarify mechanisms, and test scalable interventions targeting nutritional resilience in pragmatic trials. By advancing a resilience-based nutrition framework, this study contributes to a shift toward proactive, holistic, and equitable supportive oncology care.

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