

Inflammatory Biomarkers and Cancer-Related Fatigue in Palliative Care: Clinical Interpretation and Nursing Assessment

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Abstract

Cancer-related fatigue is a multidimensional symptom that can remain severe despite rest and can substantially affect daily function in advanced cancer. This conceptual article examines how inflammatory and metabolic signals can be integrated with experienced fatigue in palliative and oncology care without treating biomarkers as direct measures of symptom severity. The synthesis supports a conditional interpretation: inflammatory biomarkers may strengthen or weaken particular clinical explanations when considered longitudinally and in context, but they do not establish the cause or intensity of an individual patient's fatigue. Nursing assessment therefore remains anchored in direct symptom evaluation, functional impact, temporal change, treatment context, and competing contributors. A proposed interpretation framework developed later in the article uses concordance and discordance between symptom and laboratory information to guide further assessment rather than to assign biomarker-based fatigue categories.

Keywords: Cancer-related fatigue, Inflammatory biomarkers, C-reactive protein, Cytokines, Palliative care, Nursing assessment

Introduction

Current clinical guidance therefore treats fatigue as an experience requiring systematic assessment and multimodal management rather than as a symptom that can be understood from a single laboratory or treatment variable [2] [1].

A large systematic review and meta-analysis found that fatigue affects a considerable proportion of patients, with prevalence varying by disease stage, population, measurement strategy, and study design [3]. These overlapping conditions make it difficult to attribute an individual patient's fatigue to any one biological pathway [4].

Inflammatory biomarkers are attractive in this setting because they provide measurable biological information and because systemic inflammation is biologically linked to cancer, treatment, host response, and sickness behavior. Clinical interpretation therefore requires a framework that preserves biological plausibility while distinguishing association from mechanism, mechanism from symptom experience, and symptom experience from functional consequence.

Conceptual scope

The analytical scope of this article separates four objects that are often compressed into one explanatory chain: the experienced symptom, the measured biological signal, the mechanism proposed to connect biology with experience, and the clinical interpretation made from their joint observation [5].

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Clinical guidance reinforces this distinction. Cytokines, C-reactive protein (CRP), blood-cell-derived inflammatory indices, metabolic intermediates, and related measures may indicate processes that are relevant to fatigue, but the symptom itself remains an experienced clinical phenomenon [6].

The framework developed in this article also distinguishes between between-person association and within-person interpretation. That result does not imply that a particular laboratory value can identify how fatigued one patient is at one clinical encounter.

Cancer-related fatigue as a clinical construct

CRF overlaps with a broader family of psychoneurological symptoms. Concept analysis of cancer symptom clusters demonstrates that fatigue may coexist with cognitive, affective, sleep-related, pain-related, and other somatic experiences [7]. This multidimensionality has two consequences for biomarker interpretation. First, biological pathways linked to fatigue may also influence neighboring symptoms. Second, a biomarker associated with a symptom cluster cannot automatically be interpreted as specific to fatigue.

Structured measurement is therefore fundamental. Clinical practice guidance identifies multiple instruments with evidence for CRF screening and assessment, reflecting the need to distinguish brief case identification from more detailed characterization [8].

Patients with CRF also do not form a single homogeneous clinical group. Longitudinal work has identified differing fatigue profiles associated with patient characteristics and co-occurring factors [9]. Such patterns are useful for recognizing heterogeneity but should not be mistaken for biologically fixed subtypes.

These distinctions are consolidated in **Table 1**.

Table 1. Differentiating the Clinical and Biological Domains Relevant to Cancer-Related Fatigue Interpretation

Analytical unit	What is directly observed	Primary clinical meaning	What it cannot establish by itself
Experienced fatigue	Patient-reported physical, cognitive, affective, or general fatigue	Presence, severity, pattern, interference, and change in the symptom	The biological cause of the symptom
Functional consequence	Reduced activity, participation, work, self-care, or role performance	Practical impact of fatigue and related illness burden	Whether reduced function is produced specifically by fatigue
Inflammatory signal	CRP, cytokine concentrations, leukocyte-related indices, or related inflammatory measures	Evidence that inflammatory activity may be present	Individual fatigue severity, symptom specificity, or causality
Neuroimmune process	Biological signaling capable of influencing central nervous system function	A plausible mechanism linking peripheral processes to symptom experience	That the mechanism is active in a particular patient
Metabolic/energetic process	Altered metabolic signaling, mitochondrial function, substrate use, or immunometabolism	A plausible parallel or interacting route to fatigue	A unique metabolic cause of the patient's fatigue
Host or disease modifier	Disease characteristics, treatment, genetic susceptibility, body composition, comorbidity, age, or related context	Conditions that may change the relationship between biology and fatigue	A deterministic prediction of fatigue
Competing/interacting pathway	Sleep disturbance, mood symptoms, pain, anemia, nutritional compromise, medication effects, or other contributors	Alternative or interacting explanations requiring clinical assessment	That inflammatory findings are irrelevant
Clinical interpretation	Joint appraisal of symptom, laboratory, temporal, treatment, and contextual information	Determines what additional assessment or explanation is most plausible	A validated biomarker-based diagnosis of CRF

Tumor and treatment-related inflammation

Cancer can generate systemic inflammatory activity through interactions among tumor cells, immune cells, stromal elements, tissue injury, infection, metabolic stress, and treatment-related processes. This heterogeneity argues against interpreting the presence of a biomarker association as evidence for a single biological route [10].

Inflammatory evidence is nevertheless meaningful at the population level. A recent systematic review and meta-analysis identified associations between CRF and inflammatory measures, including CRP and selected cytokines, while also documenting methodological heterogeneity and limitations in causal inference [11].

In a large breast-cancer cohort, greater pretreatment systemic inflammation was associated with clinically important fatigue at later follow-up, with interleukin-6 among the informative markers [12]. It cannot establish that inflammation has the same meaning in advanced palliative disease, where inflammatory signals may also reflect infection, rapidly progressive cancer, tissue injury, cachexia, or treatment toxicity.

Cytokine signaling

A systematic review examining IL-1 α , IL-1 β , IL-6, and tumor necrosis factor- α found mixed results across cancer populations and study designs; IL-6 showed comparatively recurrent associations, but findings were not sufficiently consistent to support a simple cytokine-to-fatigue rule [13].

Replication evidence reinforces this caution. In a large breast-cancer cohort examining inflammatory genetic variants previously associated with long-term CRF, most candidate associations were not consistently reproduced [14].

Experimental work provides another important counterexample. In a tumor model, fatigue-like behavior developed even when IL-1 signaling was not required for the phenotype [15]. Cytokine signaling should therefore be represented as one potentially contributory pathway embedded within a broader system rather than as an obligatory causal sequence.

CRP and acute-phase response

CRP is especially attractive clinically because it is widely available and reflects systemic acute-phase activity. This temporal variability is clinically important. A single CRP concentration cannot convey whether the inflammatory state preceded fatigue, followed treatment, accompanied infection, tracked disease progression, or changed independently of the symptom [16].

Associations have been reported between white-cell or platelet-derived inflammatory indices and different fatigue dimensions in patients receiving chemotherapy [17]. At present, they do not establish validated cutoffs for CRF identification or severity grading.

The same value becomes less informative when acute infection, tissue injury, medication effects, or progressive disease offer competing explanations. Conversely, severe fatigue with relatively modest CRP should not be treated as biologically unexplained; it may reflect neuroimmune processes not captured by CRP, metabolic dysregulation, anemia, sleep disruption, psychological distress, nutritional compromise, or other mechanisms.

Neuroimmune and neurotransmitter pathways

A clinically useful biomarker interpretation requires an intermediate account of how peripheral biological activity might become an experienced symptom. This creates biological plausibility for an inflammation-fatigue association without implying that peripheral inflammatory concentration and subjective fatigue should move in parallel at every time point [18].

Emerging molecular evidence is consistent with this more distributed model. These findings are valuable because they move beyond a single circulating marker, yet they remain observational molecular associations rather than validated bedside measures [19].

Tryptophan-kynurenine metabolism provides another bridge between immune activation, metabolism, and neurological function. Again, clinical meaning depends on context. A metabolic intermediate may participate in symptom biology without being specific to fatigue or sufficiently validated to direct individual management [20]. The resulting interpretation is therefore layered: peripheral inflammation may influence central function through neuroimmune and metabolic routes, but those routes are neither directly observable from fatigue scores nor inferable from a single peripheral biomarker.

Metabolic and energy dysregulation

Current synthesis describes energetic competition, mitochondrial dysfunction, altered substrate handling, treatment-induced metabolic change, and immunometabolic adaptation as plausible contributors to the reduction in available behavioral and physical energy associated with cancer and its treatment [21, 22].

In cancer and treatment models, reductions in physical activity can occur without a generalized motivational deficit [23]. It also reinforces the need to separate fatigue experience, activity behavior, and motivational state.

A second experimental line shows that fatigue-like and metabolic changes can persist through mechanisms that are not dependent on IL-6 signaling [24]. These findings do not demonstrate that IL-6 is unimportant in humans. They establish a more limited but conceptually important point: metabolic disruption can sustain a fatigue-like phenotype even when a commonly implicated inflammatory pathway is insufficient to explain it.

Other proposed mechanisms remain earlier in their evidentiary development. Their value for the present framework is to show that mechanistic uncertainty is structured rather than empty: several biologically plausible routes exist, and their relevance may differ between patients and over time [25].

Host and disease modifiers

Biological signals operate within patients whose disease states, treatments, physiology, and social contexts differ. These factors can alter both the probability of fatigue and the interpretation of laboratory abnormalities [26].

Host susceptibility may also modify the relationship between inflammation and symptoms. Such findings support interaction rather than determinism: a predisposition can change vulnerability without allowing a clinician to predict the severity of one patient's fatigue from genotype or inflammatory biology alone [27].

Evidence among working cancer survivors shows that CRF affects occupational functioning and is associated with a range of clinical and personal risk factors [28]. These findings should not be transferred directly to palliative populations, but they demonstrate why functional impact must be considered separately from fatigue severity.

Sleep, mood, nutrition, and anemia as competing/interacting pathways

The pathophysiology of CRF remains contested precisely because multiple routes can converge on a similar symptom experience. For clinical interpretation, this means that inflammation should be evaluated alongside other processes rather than positioned above them [29].

Sleep disturbance is particularly important because it can both worsen fatigue and share inflammatory correlates. Anemia can limit oxygen delivery and produce exertional exhaustion independently of CRP or cytokine concentration. Pain and medication effects add further pathways that may interact with sleep, mood, activity, and inflammation.

Evidence from advanced cancer makes this interaction clinically concrete. It demonstrates why a nurse or clinician encountering severe fatigue should avoid treating either the laboratory abnormality or the symptom cluster as self-explanatory [30].

These interacting relationships are summarized in **Table 2**.

Table 2. Mechanistic and Clinical Pathways That Can Converge on Experienced Cancer-Related Fatigue

Pathway or condition	Potential contribution to fatigue experience	Relationship to inflammatory interpretation	Key clinical distinction
Peripheral inflammatory activity	Sickness-behavior signaling; interaction with treatment and disease biology	May strengthen an inflammatory explanation when temporally concordant	Peripheral signal is not equivalent to symptom intensity
Neuroimmune signaling	Alters central processes related to arousal, motivation, cognition, sleep, and behavior	Provides a plausible bridge between inflammation and experience	Pathway activity is not directly established by CRP
Kynurenine/immunometabolic activity	Connects immune activation with metabolic and neuroactive pathways	May mediate or modify inflammatory associations	Metabolite relationships remain context-dependent
Mitochondrial/energetic dysregulation	Reduces capacity to sustain physical and cognitive activity	Can overlap with or operate partly independently of cytokine pathways	Metabolic dysfunction is not clinically identifiable from fatigue alone
Anemia	Produces exertional weakness and reduced physiological reserve	Can coexist with inflammatory disease but offers a separate explanation	Hemoglobin-related fatigue should not be attributed automatically to inflammatory signaling
Sleep disruption	Increases daytime exhaustion and cognitive difficulty	May interact bidirectionally with inflammatory activity	Sleep-related fatigue can persist without major inflammatory change
Mood/distress	Influences perceived effort, motivation, sleep, attention, and symptom burden	Can modify associations between biomarkers and reported fatigue	Depression/distress and CRF overlap but are not interchangeable
Nutritional compromise	Affects energy intake, muscle function, metabolism, and treatment tolerance	May coexist with cachectic/inflammatory processes	Nutritional mechanisms require direct assessment
Pain and symptom burden	Disrupt sleep, activity, cognition, and recovery	May share inflammatory pathways without being reducible to them	Symptom clustering does not demonstrate one causal mechanism
Treatment effects	Produce hematologic, inflammatory, neurological, endocrine, or metabolic changes	Can alter both biomarkers and fatigue simultaneously	Common exposure can create association without direct mediation

Progressive disease or infection	Increases systemic inflammatory signals and global illness burden	Can markedly elevate CRP independent of fatigue-specific biology	Acute clinical causes require priority assessment
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From biological signal to experienced fatigue

The central interpretive difficulty lies between biological observation and symptom experience. A person can experience substantial fatigue without a laboratory pattern that appears proportionate, and objective reduction in activity can reflect pain, weakness, environmental limitation, sedation, dyspnea, fear of falling, or caregiving circumstances rather than fatigue alone [31].

A biological signal therefore gains clinical meaning only after several questions are answered. Is it persistent or transient? Does the patient have infection, rapidly progressive disease, recent treatment, anemia, poor intake, uncontrolled pain, or severe sleep disturbance?

The relevant unit of interpretation is not the biomarker in isolation but the configuration of biomarker, symptom, time, competing pathways, and clinical context.

Functional consequences

Fatigue and function are related but nonidentical. CRF can interfere with self-care, mobility, treatment participation, social interaction, work, and meaningful activity, yet functional decline can also arise from pain, weakness, neurological impairment, cardiopulmonary limitation, sarcopenia, medications, environmental dependence, or progressive disease.

Functional impact helps determine urgency, care burden, safety risk, treatment tolerance, and the type of support required, but it cannot retrospectively identify the mechanism producing fatigue.

Limits of biomarker specificity

The strongest limitation of inflammatory biomarkers is not that they lack relevance; it is that their biological relevance exceeds their symptom specificity. Molecular signatures can reflect treatment exposure, host susceptibility, metabolic stress, and immune activation simultaneously.

Cytokine studies contain mixed findings; genetic associations may fail replication; experimental work demonstrates pathways that are not obligatorily dependent on particular cytokines; and metabolic mechanisms provide plausible parallel routes.

High inflammatory activity with relatively little fatigue may reflect individual resilience, timing, measurement mismatch, or inflammation arising from processes that do not substantially affect fatigue. Neither configuration should be treated as a failed version of an expected biomarker-fatigue correlation.

Figure 1 represents this mechanism-and-interpretation architecture.

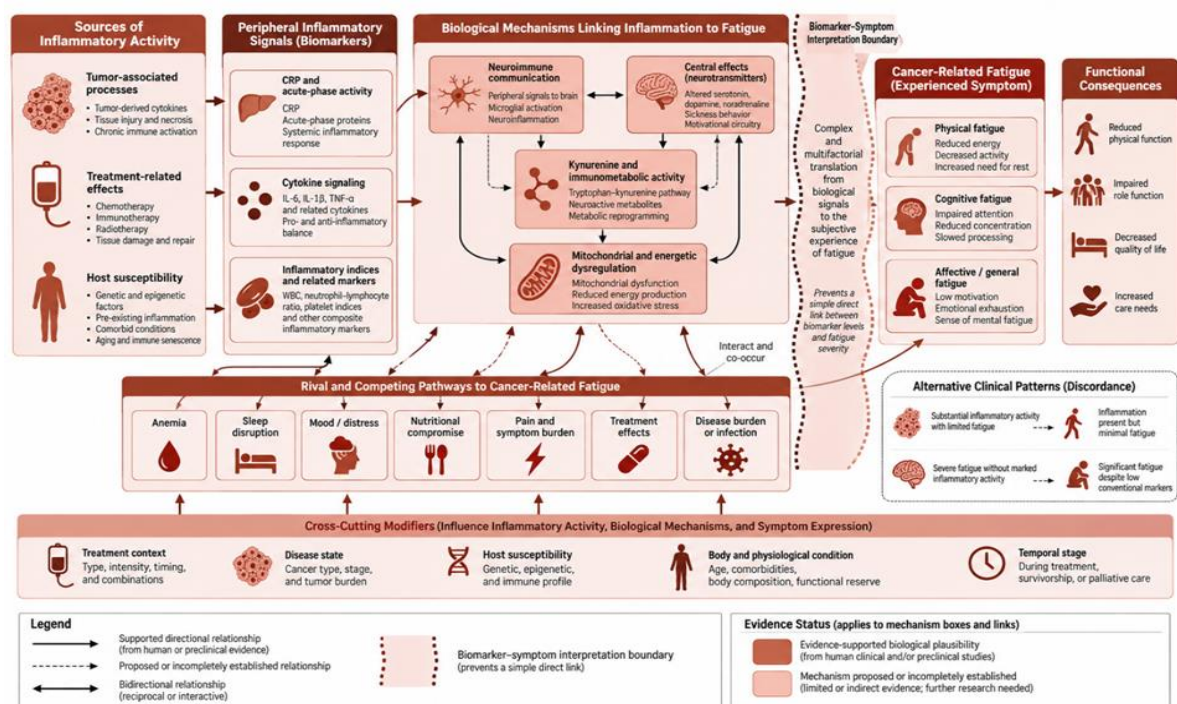


Figure 1. From Inflammatory Signal to Experienced Cancer-Related Fatigue: Mechanistic Routes, Competing Pathways, and the Biomarker-Specificity Boundary

Nursing fatigue assessment

Because fatigue is an experienced symptom, nursing assessment remains the principal clinical anchor even when laboratory data are available. Multidimensional fatigue instruments can be validated to distinguish physical, cognitive, and affective components of CRF [32], although instrument performance and practical suitability vary by language, population, treatment stage, and care setting.

The assessment should characterize onset, pattern, severity, temporal fluctuation, exertional relationship, cognitive or affective components, sleep quality, pain, mood, appetite and intake, medication changes, treatment exposure, infection symptoms, bleeding or anemia risk, mobility, and functional interference.

Service capacity also shapes what can be done with the information. The nursing contribution is especially important because nurses often observe longitudinal changes, connect symptom narratives with treatment and laboratory trends, and identify when a simple inflammatory explanation does not fit the patient's overall condition [33].

Integration of laboratory and symptom information

Integration begins by rejecting two opposing errors. The first is biomarker substitution, in which a laboratory value is treated as if it measures the patient's fatigue. The second is biological dismissal, in which laboratory information is ignored because no biomarker is sufficiently specific to diagnose CRF. A more useful approach treats laboratory data as contextual evidence whose meaning depends on symptom pattern, timing, disease state, treatment exposure, and competing explanations.

When fatigue and inflammatory activity increase together, the concordance can strengthen—but not prove—the plausibility of an inflammatory contribution. The next clinical task is to determine whether a common exposure explains both.

Discordance is equally informative. Severe fatigue with little change in conventional inflammatory measures should redirect attention toward anemia, sleep, mood, pain, nutrition, metabolic processes, neurological effects, medications, endocrine abnormalities, deconditioning, and other contributors.

In a multicenter randomized trial involving patients with advanced cancer, methylphenidate did not produce clinically meaningful superiority over placebo on the principal fatigue comparison [34]. It demonstrates that identifying clinically significant fatigue does not automatically identify a treatment-responsive mechanism, and it offers no basis for inferring pharmacological response from inflammatory biomarker status.

Laboratory and symptom information should consequently be interpreted as two partially overlapping evidence streams. Repeated measurements, when clinically appropriate, may therefore be more informative than isolated values because they allow clinicians to ask whether biological and symptom trajectories move together, separate, or change after treatment or another clinical event.

The proposed framework in the next section formalizes this joint interpretation without assigning diagnostic biomarker thresholds or treating inflammatory activity as a quantitative surrogate for experienced fatigue.

Proposed biomarker–fatigue interpretation framework

The proposed framework integrates five clinical elements: experienced fatigue, biological signal, temporal relationship, modifying context, and plausible competing pathways.

CRP, cytokines, blood-cell-derived indices, or other biological measures can increase the plausibility of an inflammatory contribution when their timing fits the clinical course, but their meaning changes when infection, disease progression, recent treatment, anemia, nutritional deterioration, sleep disturbance, pain, medication effects, or other conditions are present.

Discordance is not analytical failure; it can reveal that another pathway is more influential, that peripheral measurement incompletely represents the relevant biology, or that fatigue and inflammatory activity are changing on different timescales [35–38].

The relevant endpoint is not “inflammatory fatigue” as a categorical label but a reasoned decision about what should be assessed, monitored, investigated, or treated next. **Table 3** summarizes this application logic.

Table 3. Clinical Interpretation of Symptom–Biomarker Configurations in Cancer-Related Fatigue

Clinical configuration	Immediate interpretation	Priority questions	Appropriate nursing/clinical response	Interpretation that should be avoided
Fatigue worsens and inflammatory signal rises	Inflammatory contribution becomes more plausible	Infection? disease progression? recent treatment? tissue injury? cachectic change?	Reassess symptom dimensions, timing, vital signs, treatment exposure, concurrent symptoms, and relevant clinical investigations	Assuming the biomarker directly quantifies fatigue severity
Severe fatigue with little inflammatory change	Conventional inflammatory measures do not	Anemia? sleep disruption? pain? mood? nutrition? medications? endocrine or	Broaden differential assessment and review functional change	Concluding that the fatigue is nonbiological

	explain the symptom pattern	neurological contributors? metabolic mechanisms?		
Inflammatory signal rises while fatigue remains stable	Biological activity may be clinically important without substantial fatigue expression	What is the inflammatory source? Is the patient developing other symptoms?	Evaluate inflammatory causes on their own clinical merits and continue symptom surveillance	Predicting that severe fatigue must occur
Fatigue improves while inflammatory signal remains elevated	Symptom improvement and systemic inflammation may be partly independent	What changed clinically? intervention? sleep? pain? treatment? adaptation?	Preserve both trajectories in interpretation rather than forcing concordance	Treating persistent inflammation as evidence that reported improvement is invalid
Fatigue and biomarker both improve	Shared improvement is plausible but mechanism remains uncertain	Did treatment, disease control, infection resolution, nutrition, or another factor affect both?	Document temporal relationship and reassess function	Claiming that biomarker change proves mediation
Abrupt fatigue change after treatment with multiple laboratory abnormalities	Common treatment exposure may affect several systems simultaneously	Cytopenia? endocrine toxicity? inflammation? organ dysfunction? medication effect?	Escalate targeted assessment according to treatment and symptom context	Selecting one abnormal biomarker as the sole explanation
Persistent fatigue with multiple competing contributors	Multifactorial explanation is likely	Which contributors are reversible, burdensome, or clinically actionable?	Prioritize patient goals, reversible causes, symptom relief, and functional support	Requiring a single dominant mechanism before acting

Clinical interpretation zones

The framework uses qualitative interpretation zones rather than numerical biomarker thresholds. The first is symptom–signal concordance, in which fatigue and inflammatory activity move in the same direction within a clinically plausible time frame. This pattern increases confidence that inflammation may contribute, particularly when major alternative explanations are absent. It still does not identify the magnitude of that contribution.

A second zone is symptom-predominant discordance, characterized by substantial or worsening fatigue without a corresponding rise in routinely measured inflammatory signals. This configuration should prompt broader evaluation of hematologic, metabolic, neurological, sleep-related, nutritional, affective, treatment-related, and functional contributors. It may also reflect inflammatory mechanisms not captured adequately by the available peripheral marker.

A third zone is signal-predominant discordance, in which inflammatory measures rise while fatigue remains limited or stable. Here the laboratory change requires clinical interpretation, but it should not be converted into an expectation of symptom severity.

A fourth zone is multifactorial convergence, where inflammation, anemia, pain, sleep disturbance, poor intake, treatment toxicity, and progressive disease change together. In this situation, attempts to identify a single causal pathway may be less clinically useful than determining which contributors are reversible, dangerous, or most relevant to the patient's priorities.

These zones are deliberately qualitative. They organize clinical reasoning without creating unsupported CRP, cytokine, or composite-index cutoffs.

Boundary conditions and confounding

Several conditions can substantially alter the apparent relationship between inflammatory biomarkers and fatigue. Cytotoxic, targeted, endocrine, radiation, and immune-based therapies can affect fatigue through hematologic, inflammatory, neurological, endocrine, and metabolic routes at the same time.

Anemia can generate exertional exhaustion through reduced oxygen-carrying capacity while also occurring within an inflammatory disease state. Nutritional compromise and loss of muscle reserve can amplify physical fatigue, whereas analgesics, sedatives, and other medications may change arousal or activity.

A biomarker drawn shortly after treatment, during infection, or during rapid disease progression cannot be assumed to represent the same biological state as a value obtained during clinical stability.

Figure 2 depicts how these conditions alter the transition from laboratory observation to clinical interpretation.

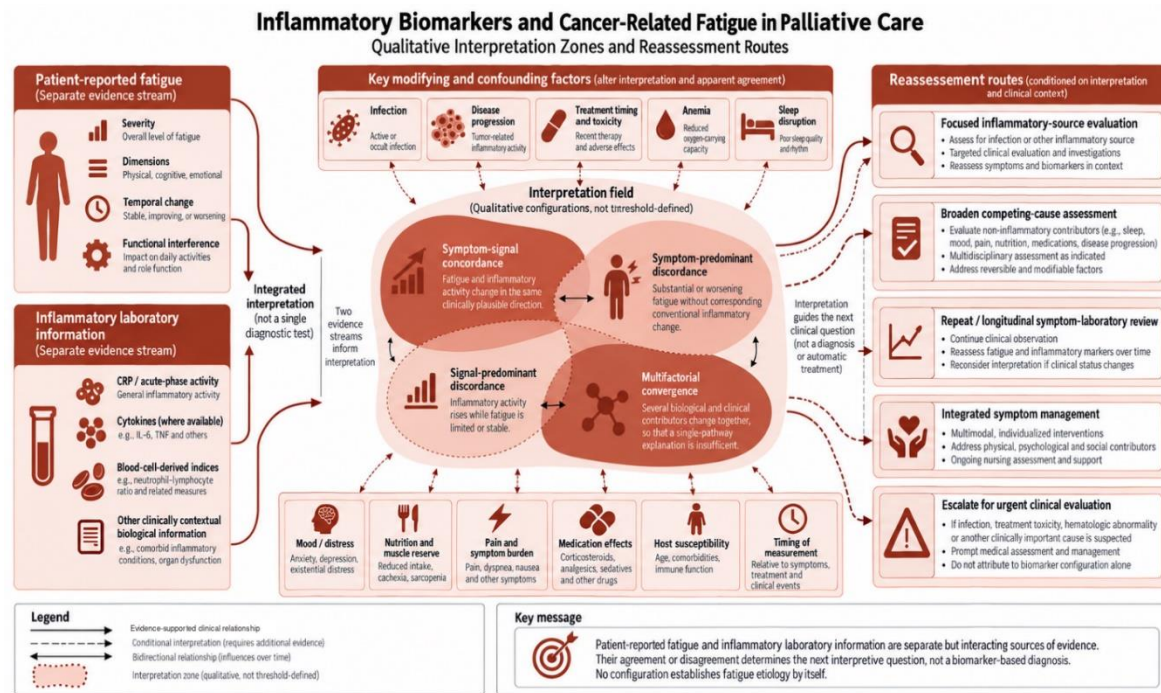


Figure 2. Qualitative Biomarker–Fatigue Interpretation Zones and Reassessment Routes

Implications for nursing assessment

The clinical value of this framework lies in preserving action even when causation remains uncertain. Interventions that improve fatigue through behavioral, educational, nutritional, activity-related, sleep-related, or other routes reinforce the importance of this symptom-centered approach [39, 40].

A randomized comprehensive program has demonstrated that CRF can improve through a multimodal intervention rather than a single biomarker-targeted strategy [41]. Broader evidence synthesis of nonpharmacological interventions likewise shows that multiple intervention classes can influence CRF, although effects and certainty vary across strategies and populations [42–44].

These findings should not be transferred indiscriminately to patients receiving palliative care. They instead demonstrate that fatigue can change through routes not captured by short-term inflammatory biomarker change [45–48].

The nurse's role is not to adjudicate molecular causality but to integrate trajectories and recognize when the pattern requires reassessment, escalation, or a different supportive strategy [49–51].

Research propositions

The framework yields several testable propositions. First, repeated measurements should explain clinically meaningful fatigue more effectively than isolated biomarker values when symptom and biological trajectories are analyzed on compatible timescales. Second, associations between inflammation and fatigue should vary by fatigue dimension because physical, cognitive, and affective experiences may have partly different determinants. Third, treatment exposure, infection, anemia, sleep, nutrition, and disease burden should modify apparent biomarker–fatigue relationships rather than merely contribute statistical noise.

Fourth, discordant cases are analytically important. Patients with high inflammation but limited fatigue and patients with severe fatigue but modest conventional inflammatory activity can help discriminate among competing mechanisms. Fifth, clinical prediction should improve when biomarker information is combined with patient-reported symptoms, timing, functional measures, and competing-cause assessment rather than interpreted alone.

Table 4 converts these propositions into research priorities.

Table 4. Research Priorities for Testing Biomarker–Fatigue Interpretation

Proposition	Preferred design feature	Key comparison	Discriminating observation	Clinical contribution
Temporal concordance is more informative than a single value	Repeated symptom and biomarker measurement	Within-person change across clinically defined periods	Whether biomarker and fatigue trajectories move together or separate	Clarifies temporal relevance

Fatigue dimensions differ biologically	Multidimensional symptom measurement	Physical, cognitive, affective, and general fatigue	Different strength or timing of biological associations across dimensions	Prevents overgeneralization from total scores
Clinical context modifies biomarker meaning	Prospective recording of treatment, infection, disease state, anemia, sleep, nutrition, and medications	Same biomarker pattern under different clinical conditions	Context-dependent alteration in symptom association	Improves bedside interpretability
Discordance distinguishes mechanisms	Enrichment or stratification by discordant symptom–signal patterns	High fatigue/limited inflammation versus high inflammation/limited fatigue	Different metabolic, hematologic, neuroimmune, or clinical profiles	Tests rival explanations
Multimodal models outperform biomarker-only models	Combined patient-reported, laboratory, functional, and clinical data	Biomarker-only versus integrated models	Added explanatory or predictive value from contextual variables	Supports clinically usable interpretation
Palliative-care populations require direct validation	Studies specifically enrolling advanced and palliative cancer populations	Palliative versus survivorship or curative-treatment cohorts	Differences in confounding, trajectories, and functional consequences	Limits inappropriate population transfer
Mechanistic evidence requires mediation testing	Designs with sufficiently timed intermediate measures	Association versus temporally ordered mechanistic model	Evidence that proposed intermediate pathways account for part of the relationship	Distinguishes correlation from mechanism

Results and Discussion

Inflammatory biology is relevant to CRF, but relevance and clinical specificity are different properties. Together, these findings support a contextual interpretation instead of a biomarker-defined fatigue phenotype [11, 13, 16]. The framework developed here places the patient's symptom experience at the center of assessment while retaining biological information as an important modifying evidence stream. Each contributes different information. This interpretation is especially important in palliative care, where multiple causal candidates frequently coexist. Under these conditions, a highly specific one-marker explanation is unlikely to reflect the full clinical state. The framework also gives discordance a productive role. If fatigue and inflammatory measures fail to move together, the result should not automatically be treated as measurement failure. For nursing practice, the most defensible use of biomarkers is therefore interpretive rather than substitutive. They cannot determine how fatigued the patient feels.

Limitations

This conceptual synthesis is constrained by heterogeneity in CRF definitions, measurement tools, cancer populations, disease stages, treatment exposures, biomarker assays, sampling schedules, and statistical approaches.

The literature also contains substantial survivorship and treatment-phase evidence, whereas advanced and palliative cancer populations have different burdens of inflammation, comorbidity, disease progression, symptom clustering, and functional decline.

They contain no numerical biomarker thresholds because the reviewed evidence does not justify such thresholds for individual CRF severity assessment.

Conclusion

Inflammatory biomarkers can contribute meaningful biological information to the assessment of cancer-related fatigue, but they cannot function as direct measures of an individual patient's fatigue severity. CRP, cytokines, and related inflammatory indices operate within a network that includes neuroimmune signaling, immunometabolism, energetic regulation, treatment effects, disease burden, anemia, sleep, mood, nutrition, pain, and host factors.

Clinical interpretation is therefore strongest when fatigue and laboratory information remain distinct but are evaluated together. Concordance can increase the plausibility of an inflammatory contribution; discordance can redirect assessment toward competing or incompletely measured pathways. Neither configuration provides a biomarker-based diagnosis.

For palliative and oncology nursing, patient-reported fatigue, its functional consequences, temporal pattern, and clinical context remain the foundation of assessment. Biomarkers add value when they refine the next clinical question, identify a competing condition, or clarify a changing biological context.

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