Review

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Mechanisms and Clinical Assessment of Fear of Disease Progression in Amyotrophic Lateral Sclerosis

Ting Wang[1,*], Tao Jin[1,2], Zhuoyuan Cai[1,2], Zhen Yan[2]

[1]Department of Neurology, Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, 310006 Hangzhou, Zhejiang, China
[2]Motor Neuron Disease Diagnosis and Treatment Center, Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, 310022 Hangzhou, Zhejiang, China
*Correspondence: SCIyouxiang123@163.com (Ting Wang)
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Amyotrophic lateral sclerosis (ALS) is a progressive, life-limiting neurodegenerative disease characterized primarily by motor dysfunction, although cognitive and behavioral impairment occurs in a substantial subset of patients. Progressive functional decline and prognostic uncertainty may contribute to pronounced fear of disease progression (FoP). Increasing evidence suggests that FoP represents a distinct psychological response to the expected functional loss related to disease, rather than merely a secondary manifestation of ALS symptoms. To clarify the potential biological basis of ALS-related FoP, this review synthesizes current evidence regarding stress hormone pathways, autonomic nervous system (ANS) dysfunction, inflammation, and the gut-brain axis. Based on the available evidence, we propose that FoP may emerge from persistent mismatch between patients' perceived disease-related threats and their adaptive capacity to these challenges. Multiple interacting systems may contribute to this process, including dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, autonomic imbalance, sleep and circadian rhythm disruption, peripheral and central inflammatory responses, and changes in the gut microbiota that may influence emotional regulation and physical symptoms. These interacting processes may create a reinforcing cycle: ALS-specific pathological features may enhance FoP, while the neuroendocrine mechanisms associated with FoP may further aggravate the severity and burden of the disease, thereby increasing the complexity of disease management. Future studies should prioritize the development of molecular biomarkers, as these biomarkers may provide valuable guidance for establishing ALS-specific FoP assessment tools and developing novel therapeutic strategies.

Keywords: ALS; FoP; neuroinflammation; brain-gut-microbiota axis; clinical assessment

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal disorder that attacks both upper and lower motor neurons. Approximately 1.5 to 2.5 people per 100,000 are diagnosed with the disease each year worldwide, with a lifetime risk of about 1 in 400 [1,2]. The onset of ALS is often unpredictable, with most cases occurring without an apparent family history. The disease then progresses rapidly, with the transition from muscle weakness to dysphagia and eventually respiratory failure or death occurring within only 3–5 years [3,4]. The most distinctive feature of ALS is the preservation of consciousness despite the progressive deterioration of physical function, which may leave patients in a state sometimes described as a "locked-in" experience [5]. This condition can substantially amplify patients' fear of disease progression (FoP). Unlike general anxiety or depressive symptoms, FoP reflects specific concerns related to disease worsening, suffering, loss of independence, and becoming a burden on others [6]. Extensive research on FoP has been conducted in oncology, leading to the development and validation of various assessment scales and intervention strategies [7,8,9]. However, similar investigations remain limited in the field of ALS.

ALS-related FoP is not merely a passive reflection of physical decline, but may represent a predictable and modifiable clinical phenomenon. A deeper understanding of its underlying driving factors may facilitate the development of effective assessment and intervention strategies, ultimately improving psychological outcomes and disease management for patients. However, the biological basis and clinical management of ALS-related FoP remain insufficiently characterized. This review aims to summarize the existing evidence, explore the potential biological mechanisms underlying ALS-related FoP, and discuss available assessment approaches and potential intervention strategies.

ALS and FoP: A Disease-Specific Association

FoP represents a multidimensional syndrome involving psychological, physiological, and behavioral alterations. Patients may experience persistent concerns about future disease progression, functional decline, uncertainty,

and various losses that may occur during the disease course. These concerns are often accompanied by heightened physiological arousal, sleep disturbances, and fatigue. At the behavioral level, some patients may avoid disease-related information or future planning, whereas others may repeatedly monitor symptoms and seek reassurance [6].

ALS is especially likely to trigger FoP because the disease combines several highly threatening features: it is a progressive disease with no cure currently; the speed and pattern of its deterioration are highly unpredictable; motor, bulbar, respiratory, and communication functions are successively lost; and patients become increasingly dependent on caregivers and medical technology [3,4]. Unlike the insidious progression of many chronic diseases, ALS progression is usually visible and embodied. Every new fall, muscle twitch, choking episode, change in speech, or episode of breathing difficulty can create the perception that the disease has progressed to a more advanced stage.

What patients with ALS fear differs from generic death anxiety. Qualitative studies suggest that patients are often more afraid of the process of dying and of dependency than of death itself: choking, suffocation, being unable to communicate, becoming locked in a state of unconsciousness, burdening family members, losing their roles as a spouse or parent, and leaving children without support [10,11,12]. The period before diagnosis can intensify these fears. Vague symptoms, prolonged diagnostic delays, repeated doctor visits, and poor communication about the prognosis can all generate uncertainty in patients before a clear explanation of their condition is available [10,13,14,15].

The relationship between ALS and FoP is likely reciprocal, at least from a clinical perspective—although there is currently no evidence demonstrating a causally bidirectional relationship at the level of motor neuron degeneration. Clearly, ALS progression contributes to FoP by increasing the salience of disease-related threats, amplifying uncertainty regarding symptoms, and intensifying concern about anticipated dependency. Conversely, FoP may worsen the daily burden of the disease by disrupting sleep, ramping up autonomic arousal, increasing fatigue, making patients hypervigilant about symptoms, worsening depression, complicating family communication, and interfering with treatment decisions. It might also interact with stress and inflammatory systems that are relevant to ALS pathophysiology, but these links remain inferential. A cautious formulation is therefore that ALS progression intensifies FoP, and FoP may increase perceived disease burden and contribute to sleep disturbance, fatigue, symptom vigilance, and care complexity. The findings from studies of depression and anxiety in ALS provide indirect support for this hypothesis. For example, HPA axis dysregulation, characterized by a blunted cortisol awakening response, has been associated with depressive symptoms in patients with ALS [16]. Similarly, elevated peripheral inflammatory markers have been linked to accelerated functional decline and increased psychological distress [17,18]. Neuroimaging studies in ALS have identified structural and functional alterations in frontotemporal and limbic regions involved in emotional regulation, which may increase vulnerability to negative emotional stimuli [19]. Although these findings have not directly assessed FoP, they suggest a potential biological link between ALS progression and emotional distress, including fear related to disease progression.

Known Mechanisms of FoP

Neuroendocrine Stress Response and HPA-Axis Dysregulation

FoP can be understood as a state of persistent anticipation of disease-related threats, which may influence physiological adaptation through the neuroendocrine stress systems. The human stress response primarily involves coordinated activation of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS), including the release of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), cortisol, and the enhancement of sympathetic nervous activity [20]. Under acute stress conditions, this response serves a protective function. However, when threats persist and individuals have limited control over or predictability regarding future outcomes, repeated activation may increase allostatic load and contribute to dysregulated stress responses [21].

The cortisol awakening response (CAR) is a commonly used indicator for evaluating HPA axis reactivity, reflecting the rapid increase in cortisol levels after awakening and the adaptive response of the body to anticipated needs and chronic stress [22,23]. A study on patients with ALS revealed a blunted CAR, which was associated with clinical status and depressive symptoms [16], suggesting that alterations in stress regulation may affect patients' ability to adapt to persistent health-related threats. In other chronic diseases such as cancer and Parkinson's disease, higher levels of FoP are associated with changes in cortisol secretion patterns, such as a flattened diurnal cortisol slope and elevated nocturnal cortisol levels, suggesting that the HPA axis is in a state of sustained activation [24,25]. Dysregulation of the HPA axis may promote the formation and maintenance of FoP through multiple pathways. Continuous attention to danger signals brought by ALS symptoms can trigger a continuous anticipatory stress response, thereby interfering with the psychological adaptation process. Cortisol rhythm disorder may also interact with fatigue, cognitive function and sleep-wake regulation [26,27,28].

Autonomic Dysfunction, Sleep Abnormality, and Increased Stress Sensitivity

Autonomic dysfunction may be another important pathway mediating the development of FoP. Heart rate variability (HRV), as a non-invasive indicator reflecting the ca-

pacity for autonomic nervous regulation, has been used to evaluate the function of ANS in ALS patients, and has been reported to be related to the fear of disease progression and survival outcome [29,30]. These findings suggest that the pathological effects of ALS may not be limited to the motor nervous system but involve a wider range of neuroregulatory functions.

Sleep disorders, autonomic nervous dysfunction and HPA axis imbalance may interact with each other. In ALS patients, factors such as night hypoventilation, muscle spasms, pain, increased secretion, anxiety, limited activity and care needs may lead to decreased sleep quality. Polysomnography studies have also confirmed that sleep abnormalities are common in ALS patients [31]. On the other hand, chronic sleep deprivation can further enhance sympathetic nerve activity, affect cortisol circadian rhythm, and reduce the adaptability of patients to stress [26]. At the same time, FoP itself also makes patients continue to pay attention to disease changes and worry about future functional loss, which further aggravates anxiety and affects sleep.

Therefore, ALS, sleep disorders, autonomic abnormalities and FoP may form a mutually reinforcing vicious circle: ALS progression leads to physical symptoms, and symptom changes increase FoP in patients. Persistent fear and stress further disrupt sleep and autonomic stability, while decreased sleep quality and physical discomfort can heighten patients' attention to symptoms, thereby further aggravating FoP.

Coordination Between Emotional Processing and Neuroendocrine Stress Systems

FoP is not only affected by endocrine and autonomic dysregulation, but also closely related to emotion processing and disease threat assessment mechanisms. Emotional systems influence an individual's perception of disease progression by giving meaning to physical symptoms and assessing the severity and controllability of disease-related threats. When ALS patients interpret bodily signals as evidence of irreversible disease progression, these sensations may acquire a threatening meaning, thereby activating neural networks involved in fear learning, interoceptive processing, and prefrontal regulation. Studies have shown that some ALS patients have abnormalities in the frontotemporal and limbic systems, which are mainly involved in emotion regulation, threat processing and cognitive control; neurotransmitter changes such as glutamate excitatory toxicity, gabaergic dysfunction, and abnormal serotonergic and norepinephrine signaling may further affect threat assessment and stress reactivity [32,33]. Although these neurobiological changes have not been directly confirmed to be associated with FoP, they provide a potential mechanistic explanation for the susceptibility of ALS patients to persistent fear of disease progression.

Additionally, psychological and cognitive factors play important roles in the development and maintenance of FoP [6,34]. In ALS, the progressive and irreversible nature of the disease may predispose patients to repeatedly focus on physical changes and interpret minor symptoms as signals of functional decline. This continued expectation of disease progression, even when the objective functional status is relatively stable, may maintain FoP and further activate neuroendocrine and autonomic stress pathways, thereby forming a vicious cycle of "symptom perception-threat explanation-stress activation-fear reinforcement".

Common Mechanisms and Interactions Between ALS and FoP

Neuroinflammation and Peripheral Inflammation as a Shared Pathological Basis

It is increasingly recognized that ALS is not only a disease characterized by motor neuron degeneration, but rather a disorder featuring neuroinflammation and systemic immune dysregulation [35,36]. Growing evidence indicates that peripheral inflammatory biomarkers and alterations in immune-cell profiles are associated with disease progression and prognosis in ALS. These indicators include the neutrophil-to-lymphocyte ratio (NLR), the lymphocyte-to-monocyte ratio (LMR), and the Th17/Treg imbalance [37,38,39,40,41,42].

These inflammatory changes may contribute to FoP through two complementary mechanisms. First, enhanced inflammatory activity is often associated with accelerated or unpredictable disease progression, thereby intensifying patients' expectations and concerns about future functional decline. Second, peripheral inflammation may influence central nervous system function through cytokine signaling, vagal afferent pathways, and modulation of microglial and astrocytic activity, ultimately spreading to brain regions involved in threat processing and emotional regulation, including the amygdala and prefrontal cortex [43,44,45,46]. However, the relationship between inflammation and anxiety is complex and may vary according to the type, duration, and mediators of the inflammatory response. Moreover, peripheral inflammatory markers such as NLR and LMR do not directly reflect neuroinflammation within the central nervous system. Consequently, current evidence regarding the association between inflammation and ALS-related FoP is largely based on mechanistic inference and lacks direct clinical validation.

Overall, inflammation may represent not only the activity level of the disease but also a potential contributor to increased vulnerability to FoP through its effects on emotional regulation and threat processing. Nevertheless, this hypothesis still needs to be verified through longitudinal studies integrating inflammatory biomarkers, FoP assessments, and clinical disease progression data.

Brain-Gut-Microbiota Axis, Systemic Stress, and Emotional Vulnerability

The brain-gut-microbiota axis connects neural, endocrine, immune, metabolic, and gastrointestinal processes [47,48]. Studies have shown that chronic stress can alter intestinal motility and permeability, microbial community composition, immune signaling transduction, and neuroactive metabolite pathways. These changes at the intestinal level may subsequently communicate with the central nervous system through vagal, immune, endocrine, and metabolic pathways.

ALS has been linked to changes in the composition and diversity of the gut microbiota. Mechanistic reviews indicate that dysbiosis of the microbiota could influence neuroinflammation, immune modulation, blood-brain barrier integrity, microglial activation, and neuronal survival [49,50,51,52]. Microbial-derived metabolites, including short-chain fatty acids (SCFA) and tryptophan-related products, may affect both neuroimmune processes and emotional regulation. However, the current evidence for ALS is still preliminary, and no specific microbiome studies for FoP have been conducted.

For FoP, it is reasonable to hypothesize the gut-brain axis as a potential amplifier rather than a primary cause. Progression-related stress may disturb gut-brain signaling; dysbiosis and systemic inflammation may increase fatigue, gastrointestinal discomfort, sleep disturbance, and emotional vulnerability, which could conceivably be interpreted by patients as further signs of deterioration. This pathway is clinically plausible because patients with ALS commonly experience nutritional alteration, reduced mobility, medication effects, and gastrointestinal symptoms, all of which may interact with gut-brain regulation [53,54].

Autonomic Dysregulation and Progressive Functional Decline

Autonomic dysregulation lies at a plausible intersection of ALS pathology and FoP physiology. As ALS progresses, patients will repeatedly experience a series of inherently threatening physical symptoms, including muscle weakness, slurred speech, dysphagia, dyspnea, and loss of independence. These changes may promote sympathetic activation and enhance the perception of their bodily sensations. At the same time, the autonomic impairment related to ALS may reduce the flexibility of physiological regulation, thereby making patients more vulnerable to persistent stress [29,30].

Progressive functional decline may also lead to the impairment of social autonomy. The need for assistive devices, feeding support, noninvasive ventilation, home modifications, and caregiver assistance can intensify psychological feelings of being a burden on others and a loss of autonomy [55,56]. These stressors do not merely exist outside the disease mechanisms; they may also constitute part of the emotional and physiological processes encoded by the disease progression. For example, the fear of choking is not just a response to the bulbar dysfunction, but also involves interoceptive threat, family dependence, future planning, and the fear of losing control.

Taken together, these pathways may form a multilevel amplification cycle: ALS progression generates disease-specific threat signals; emotional appraisal converts these signals into FoP; activation of the HPA-axis and ANS sustains heightened alertness; sleep disturbance and inflammatory activity reduce stress tolerance; and increasing social dependence and caregiver burden reinforce fears of future functional loss.

These proposed biological pathways and their clinical consequences are summarized in Fig. 1.

Clinical Assessment of ALS-related FoP

ALS-related FoP has distinct disease-specific characteristics and is influenced by multiple interacting factors, including functional decline, respiratory and bulbar symptoms, stress responses, sleep disturbance, emotional processing, and caregiving-related factors. Therefore, relying solely on general FoP questionnaires is insufficient to comprehensively capture the unique features of FoP, nor can it identify the mechanisms underlying its persistence.

Existing Assessment Tools and Their Deficits

The Fear of Progression Questionnaire (FoP-Q) was originally developed for patients with chronic diseases to assess the fear related to disease progression across various dimensions, such as emotional responses, family and social relationships, occupational concerns, loss of autonomy, and coping strategies for anxiety [57]. However, this instrument was primarily developed based on the experiences of the general chronic disease populations and failed to fully consider the unique disease course and threat patterns of ALS. For ALS patients, their fears stem not only from the progression of the disease itself but are also closely related to the specific clinical events of the disease, including loss of respiratory function, dysphagia, impaired communication, reliance on respiratory support, and progressive loss of autonomy. Therefore, the universal FoP assessment tool may not fully cover the specific content and clinical implications of ALS-related FoP.

Current assessment approaches in ALS mainly focus on functional status and quality of life and generally do not directly assess ALS-related FoP. The revised ALS Functional Rating Scale (ALSFRS-R) provides a standardized assessment of bulbar, limb, and respiratory functions [58]. ALS-related quality-of-life assessment tools, including ALSSQOL, ALSSQOL-R, ALSSQOL-SF, and ALSAQ-40, further characterize the patients' experiences in terms of independence, communication, social relationships, and symptom burden [59,60,61,62]. However, although these tools provide important information about the

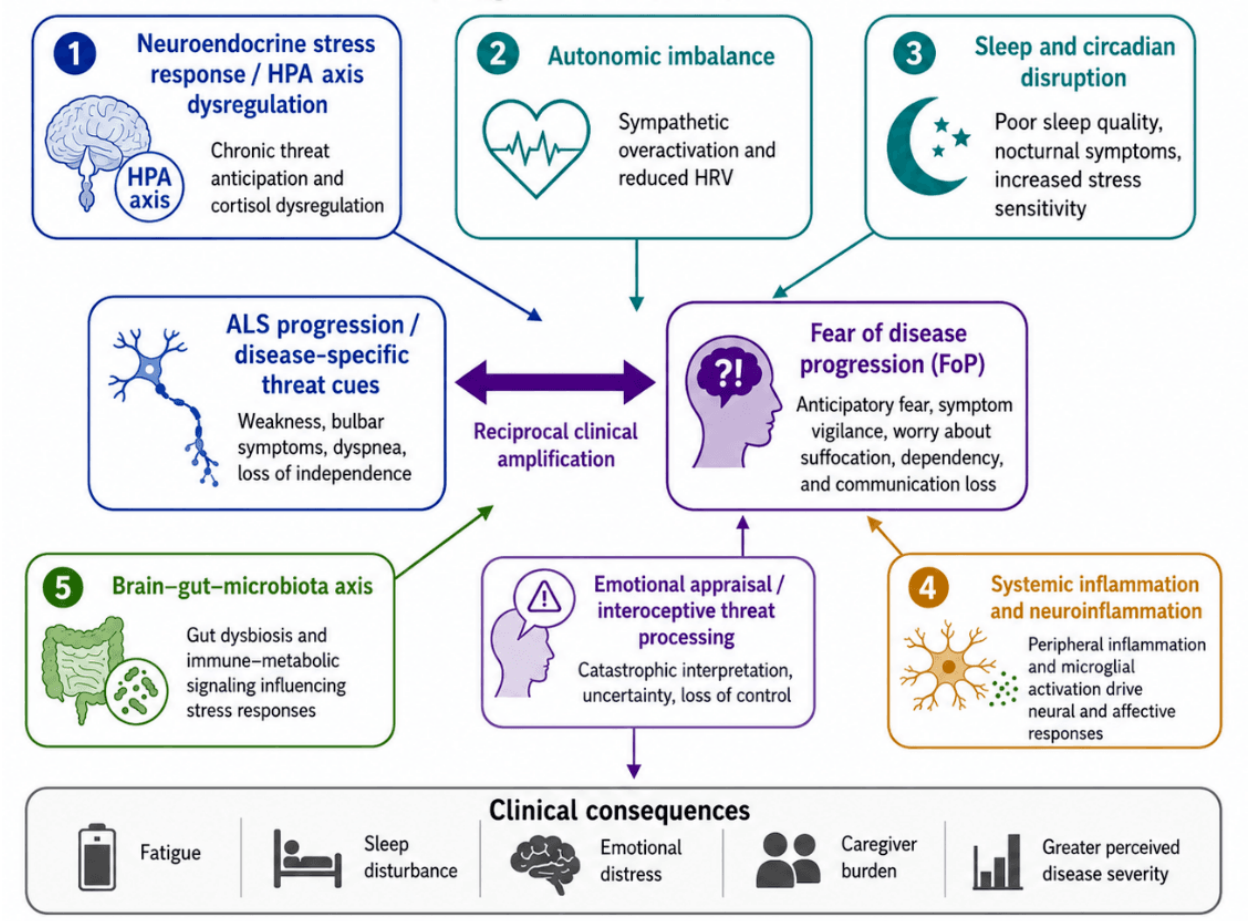

Fig. 1. Proposed integrative framework of biological, psychological, and clinical factors contributing to ALS-related FoP. Abbreviations: ALS, Amyotrophic lateral sclerosis; FoP, Fear of disease progression; HPA axis, Hypothalamic-Pituitary-Adrenal axis; HRV, Heart rate variability. The figure was generated using Microsoft PowerPoint version 16.0 (Microsoft Corporation, Redmond, WA, USA).

clinical factors associated with FoP, they do not directly assess fear of disease progression.

Among the existing approaches, FoP-Q-SF is the most commonly used screening instrument for FoP related to ALS in research. This 12-item short form reduces the assessment burden and has been widely applied in cancer and other chronic disease populations, with preliminary evidence supporting its feasibility and clinical relevance in ALS patients [9,63,64,65]. Nevertheless, FoP-Q-SF has several limitations. First, its items primarily reflect general concerns regarding disease progression and may not fully capture the unique fears experienced by patients with ALS. Second, it only provides an overall score of FoP severity, but cannot clearly determine the major factors contributing to FoP, such as functional decline, respiratory symptoms, sleep disturbance, psychological adaptation, or caregiving burden. Moreover, in advanced ALS, self-reported assessment may be affected by factors such as dysarthria, fatigue, limb impairment, and reliance on assistive communication devices.

Therefore, clinically validated tools specifically designed to assess ALS-related FoP remain scarce. Future research should develop ALS-specific FoP assessment methods that integrate functional status, biological markers, and psychosocial factors to enable more precise clinical evaluation.

Future Directions for an ALS-Specific FoP Assessment System

Assessment of ALS-related FoP should first consider what clinical questions need to be addressed. Unlike FoP in many other chronic diseases, the fear of ALS patients not only reflects the severity of fear itself, but also encompasses specific threats, disease experiences, and various factors that sustain this fear. Therefore, a single overall score may not fully capture the clinical characteristics of ALS-related FoP.

A more appropriate assessment strategy should address three key questions: How severe is the FoP of patients? What are patients most concerned about losing due to disease progression? Which functional, biological, and psychosocial factors contribute to the persistence or exacerbation of this fear?

A brief patient-reported measure remains necessary to assess overall severity of FoP while ensuring accessibility for patients with advanced ALS who may rely on augmentative communication devices. The assessment should also encompass ALS-specific sources of fear and the factors that may maintain or intensify FoP. In research settings, objective physiological measures may provide additional insight into the mechanisms underlying ALS-related FoP. HRV can reflect the status of autonomic nerve regulation, CAR can indicate the function of the HPA axis, and actigraphy can help characterize sleep-wake patterns. These measures are not intended to replace the patients' subjective experiences, but rather to explain why individuals with similar disease severity may experience different levels of FoP. Furthermore, ALS-related FoP is likely to change across disease stages, and the assessment tools should therefore be able to sensitively capture these transitions. In the early stage of ALS, concerns may focus on diagnostic uncertainty, future disease course, and prognostic communication. As the disease progresses, the focus of fear may shift toward declining mobility, speech and swallowing difficulties, and increasing care needs. In the advanced stage of ALS, respiratory-related fears, maintaining communication, dependence on others, end-of-life decisions, and dignity may become more prominent. Although proxy reports may sometimes be necessary, patients' own perspectives should be prioritized for as long as they retain the ability to communicate effectively.

Future research should establish the reliability, validity, and responsiveness of tools for assessing ALS-related FoP and determine whether FoP predicts clinically meaningful outcomes, including quality of life, sleep disturbance, caregiver burden, advance care planning, and healthcare utilization. Through longitudinal studies integrating the FoP assessments with ALSFRS-R trajectories, respiratory parameters, sleep indicators, HRV, inflammatory biomarkers, and potentially microbiome-related features, researchers may identify distinct biological and functional trajectories associated with different patterns of FoP.

Conclusion

FoP associated with ALS is not merely anxiety or fear of death, but a complex clinical distress that emerges as the disease progresses. It reflects patients' persistent concerns regarding the specific disease-related threats, which include loss of function, communication difficulties, respiratory decline, increased dependence, and caregiver burden. This review suggests that FoP related to ALS may be maintained through the interaction of biological, psychological, and social processes, including neuroendocrine stress responses, autonomic nerve dysfunction, sleep disturbance, inflammation, emotional processing, and caregiving-related factors.

The assessment and management of fear related to ALS remain at an early stage. Although general FoP assessment tools can be used for initial screening, they do not comprehensively capture the specific content of ALS-related fears or the clinical context in which they arise. Future research should develop ALS-specific FoP assessment tools and integrate psychological, functional, and biological indicators into longitudinal studies to clarify the potential mechanisms underlying FoP and its impact on patient prognosis.

Availability of Data and Materials

Not applicable.

Author Contributions

TW conceived the review, designed the search strategy, and drafted the manuscript. TJ, ZYC and ZY performed the literature search, collected and organized the relevant references. All authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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