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Review Article

Pathophysiological Insights into Post-Intensive Care Syndrome: Bridging Critical Illness and Long-Term Dysfunction

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ABSTRACT

Background: Post-intensive care syndrome (PICS) is a frequent complication of critical illness characterized by persistent physical, cognitive, psychological, and cardiopulmonary impairments. This narrative review summarizes the biological mechanisms underlying PICS and current approaches to its prevention and management.

Methods: A narrative review of contemporary experimental and clinical literature was performed to synthesize evidence on the pathophysiology, prevention, rehabilitation, and long-term management of PICS.

Results: PICS is driven by interconnected mechanisms and pathways. These pathways contribute to intensive care unit (ICU)-acquired weakness, cognitive impairment, psychological disorders, and chronic cardiopulmonary dysfunction. Emerging strategies, including biological phenotyping, multi-omics technologies, and precision rehabilitation, may facilitate individualized recovery. The review also highlights the impact of PICS on family members (PICS-F).

Conclusion: PICS is a heterogeneous multisystem condition requiring an integrated approach from ICU care through long-term rehabilitation. A better understanding of its biological mechanisms may support personalized interventions and improve long-term outcomes for ICU survivors and their families.

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Introduction

Advances in intensive care have led to a steady increase in survival among critically ill patients. Yet, survival alone does not equate to recovery. Many patients who survive a stay in the intensive care unit (ICU) continue to face lasting physical disability, cognitive impairment, and psychological distress that hinder their return to everyday activities and previous levels of functioning [1-3]. These persistent sequelae are collectively referred to as post-intensive care syndrome (PICS), a condition characterized by newly developed or aggravated impairments that can remain evident for months or even years after ICU discharge. Beyond reducing functional independence, PICS has a profound impact on patients' overall quality of life. Recent evidence indicates that approximately 50% to 70% of ICU survivors develop some form of PICS, underscoring its increasing importance as a major long-term consequence of critical illness [2-6].

Although considerable progress has been made in understanding the biological basis of PICS, current knowledge remains incomplete. Much of the existing literature has examined its physical, cognitive, and psychological manifestations as separate entities, with relatively limited attention to the complex interactions that connect these domains. Consequently, the biological processes responsible for the marked variability in long-term outcomes among patients with similar critical illnesses have not yet been fully clarified [4-5,7].

This narrative review brings together current evidence on the pathophysiological mechanisms underlying PICS, examines existing approaches to its prevention and management, and explores emerging opportunities for personalized rehabilitation and future research.

Factors Contributing to PICS

A wide range of risk factors for PICS have been identified, including factors related to both the patient and the ICU environment. These include advanced age, female sex, a history of mental health or cognitive disorders, greater severity of illness, prolonged immobility, bedridden status, the presence and duration of delirium during ICU stay, and negative experiences encountered in the ICU setting [8-10]. Additional risk factors include hypo- and hyperglycemia, hypoxemia, hypotension, and exposure to sedative medications. In addition, several ICU-related conditions and interventions have been linked to a higher risk of PICS, including acute respiratory distress syndrome (ARDS), sepsis, multiple organ failure, prolonged mechanical ventilation, and the use of systemic corticosteroids and sedatives [8].

Pathophysiology of PICS: A Multisystem Failure Model

Clinical studies have shown that PICS affects multiple organ systems, with manifestations involving the musculoskeletal, cardiovascular, and respiratory systems as well as cognitive and psychological function. Although the biological basis of these complications has not been fully elucidated and is likely driven by multiple interacting mechanisms, growing evidence has provided insight into several molecular and cellular pathways involved in their development. The following section summarizes current understanding of these mechanisms, highlighting the key biological processes thought to influence recovery after critical illness [4].

Muscular and Neuromuscular Dysfunction

Physical impairment is one of the most common long-term consequences among ICU survivors, with reports suggesting that as many as 80% of patients experience persistent functional deficits after hospital discharge [11].

Among these sequelae, ICU-acquired weakness (ICU-AW) and skeletal muscle atrophy are the most prevalent, primarily resulting from accelerated muscle protein breakdown during critical illness. Evidence indicates that patients may lose nearly 2% of their skeletal muscle mass each day while admitted to the ICU [12-13].

ICU-AW refers to clinically significant neuromuscular dysfunction that cannot be attributed to causes other than critical illness and its related treatments. It frequently occurs in association with critical illness polyneuropathy (CIP), critical illness myopathy (CIM), or the combined syndrome of critical illness neuromyopathy (CINM) [14].

The development of ICU-AW is influenced by numerous interacting risk factors. Sepsis, prolonged mechanical ventilation, multiple organ failure, hyperglycemia, extended immobilization, glucocorticoid exposure, and medications such as neuromuscular blocking agents have all been implicated in its pathogenesis through distinct but overlapping mechanisms [15-16].

Patients with ICU-AW exhibit profound structural and functional abnormalities within skeletal muscle. Prominent features include extensive muscle wasting and electrophysiological abnormalities, accompanied by selective loss of thick myosin filaments. This loss disrupts the normal actin-myosin balance, compromises sarcomere integrity, and ultimately reduces muscle contractile force. Alterations in muscle fiber composition have also been described, with type II fibers appearing more vulnerable to atrophy than type I fibers. Collectively, persistent negative protein balance resulting from prolonged immobilization, neuroendocrine dysregulation, systemic inflammation, metabolic disturbances, histopathological muscle changes,

degeneration of motor axons, and progressive muscle loss underlies the characteristic phenotype of ICU-AW [17-22].

Skeletal muscle dysfunction in critically ill patients is driven by several interconnected pathophysiological mechanisms. These include impaired microcirculation with reduced tissue oxygen delivery, mitochondrial dysfunction leading to diminished adenosine triphosphate (ATP) generation, and disturbances in cellular ion channel homeostasis, all of which contribute to impaired muscle performance and delayed functional recovery.

Although the pathogenesis of ICU-AW has not been completely clarified, accumulating evidence suggests that multiple biological mechanisms contribute to its development. Persistent negative protein balance, depletion of myosin and myoglobin-associated proteins, activation of major proteolytic pathways, including the ubiquitin-proteasome system, autophagy-lysosome pathway, calpains, and caspase-3, as well as mitochondrial dysfunction and abnormalities affecting motor neurons and neuromuscular junctions are all thought to play important roles [16,23].

The ubiquitin-proteasome system (UPS), the principal pathway responsible for regulated protein degradation in skeletal muscle, becomes markedly activated during critical illness. This response is driven by pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), together with oxidative stress, prolonged immobilization, and the physiological stress response. TNF-α and IL-1 enhance transcription of ubiquitin-related genes, thereby accelerating muscle protein breakdown. Increased ubiquitin expression facilitates the tagging of intracellular proteins for degradation and enhances the activity of both the 20S and 26S proteasome complexes, resulting in accelerated proteolysis of skeletal muscle proteins [16].

Prolonged immobilization also promotes activation of calpains and caspase-3 in both limb and diaphragmatic muscles. These proteases degrade cytoskeletal components and disrupt sarcomeric integrity by releasing actin and myosin filaments. The liberated proteins subsequently undergo ubiquitination through muscle-specific E3 ubiquitin ligases, particularly muscle RING-finger protein-1 (MuRF1) and Atrogin-1 (MAFbx), directing them toward degradation by the ubiquitin-proteasome pathway (UPP) [24].

The autophagy-lysosome pathway represents another major mechanism involved in muscle loss during critical illness. By mediating degradation of intracellular proteins, damaged organelles, and dysfunctional mitochondria, this system helps maintain cellular homeostasis but becomes excessively activated during immobilization, oxidative stress, and denervation [24]. Increased expression of the lysosomal protease cathepsin L has consistently been associated with muscle atrophy. Autophagic activity is regulated by several signaling molecules, including forkhead box O (FoxO) transcription factors, autophagy-related gene 7 (Atg7), mechanistic target of rapamycin (mTOR), and microtubule-associated protein 1 light chain 3 (LC3) [25]. Importantly, FoxO signaling functionally links the UPP and autophagy-lysosome pathway by coordinating both protein degradation and organelle turnover. Disruption of this regulatory network promotes excessive proteolysis and accelerates the progression of ICU-AW [16].

Mitochondrial dysfunction further contributes to muscle wasting by increasing the production of reactive oxygen species (ROS), particularly during prolonged inactivity. Elevated ROS levels amplify proteolytic signaling and exacerbate skeletal muscle degradation [20]. At the same time, systemic inflammation characteristic of critical illness induces endothelial activation and increased capillary permeability, leading to tissue injury, neural edema, cellular damage, and axonal degeneration [26]. Peripheral neuropathy further accelerates muscle loss through activation of the polyol pathway, depletion of nicotinamide adenine dinucleotide phosphate (NADPH), reduced availability of nitric oxide (NO) and glutathione (GSH), impaired microvascular perfusion, and heightened oxidative stress. Hyperglycemia compounds these effects by promoting the formation of advanced glycation end products (AGEs), which exert cytotoxic effects through oxidative pathways. Within peripheral nerves, protein glycosylation interferes with axonal transport and protein synthesis, ultimately contributing to axonal degeneration and secondary muscle atrophy [16].

Another important contributor to ICU-AW is dysfunction of the neuromuscular junction, where prolonged disuse disrupts communication between motor neurons and skeletal muscle fibers, leading to progressive weakness and muscle wasting [27]. In addition, critical illness and sepsis impair the insulin-like growth factor-1 (IGF-1)/Akt signaling pathway, an essential regulator of muscle protein synthesis and inhibitor of proteolysis. Reduced IGF-1 signaling suppresses anabolic activity while favoring catabolic pathways, thereby accelerating the loss of skeletal muscle mass during recovery from critical illness [22] (Figure 1).

Neurological and Psychological Dysfunction

Neurological complications, including cognitive impairment, are commonly observed in survivors of critical illness and represent major components of PICS. Evidence suggests that such impairments may affect more than three-quarters of ICU survivors [28-30].

The incidence of psychological disorders following ICU admission is reported to range widely between 1% and 62%, with specific estimates for depression, anxiety, sleep disturbances, and post-traumatic stress disorder (PTSD) reported as 62%, 57%, 36%, and 39%, respectively [29,31-35].

These neuropsychiatric sequelae appear to occur independently of patient age or prior neurological or cognitive history [29,36]. Multiple risk factors have been associated with their development, including acute respiratory distress syndrome (ARDS), severe sepsis, prolonged mechanical ventilation, delirium, glycemic disturbances (hypoglycemia and hyperglycemia), hypotension, trauma, stroke, hypoxemia, pre-existing comorbidities, baseline cognitive impairment, and exposure to sedative medications [1,31-32,36-38].

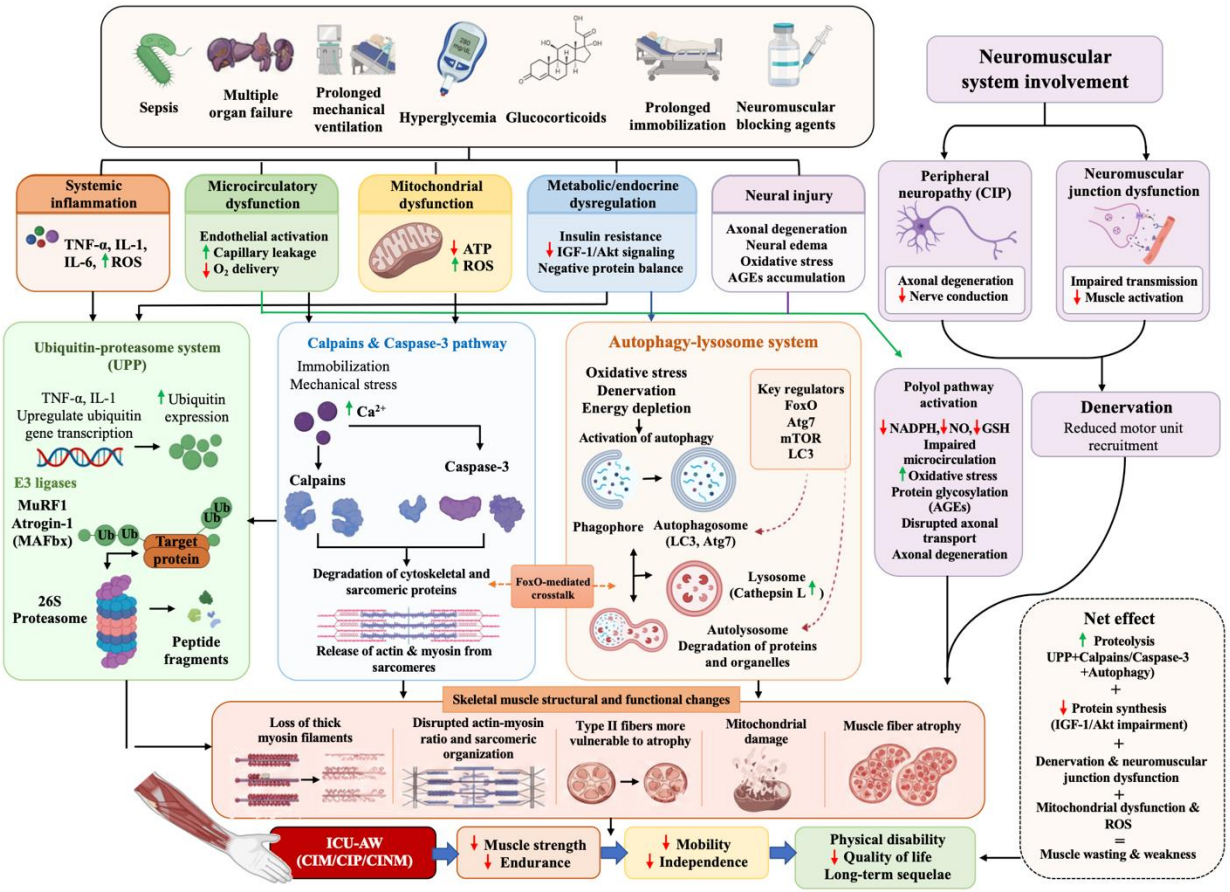

Figure 1- Molecular mechanism of muscular and neuromuscular dysfunction in PICS. (Note: CIP: critical illness polyneuropathy; CIM: critical illness myopathy; CINM: critical illness neuromyopathy; IGF-1: insulin-like growth factor-1; IL: interleukin; NMJ: neuromuscular junction; ROS: reactive oxygen species; TNF-α: tumor necrosis factor-α; UPP: ubiquitin-proteasome pathway.)

Cognitive deficits in ICU survivors may be persistent and involve multiple domains, including memory, attention, executive function, language processing, psychomotor speed, and concentration. Approximately one-third of patients continue to demonstrate measurable impairment up to one year after ICU discharge, with severity comparable to moderate traumatic brain injury (TBI) and Alzheimer's disease (AD) [1,38-39].

Multiple biological pathways have been proposed to explain the development of persistent cognitive impairment following critical illness. One potential mechanism involves neuronal apoptosis triggered by dopamine receptor activation in response to vagal nerve signaling. The vagus nerve can be stimulated by various factors, including mechanical ventilation-related lung stretch reflexes and inflammatory pathways mediated by interleukin-1 receptor (IL-1R), toll-like receptor 4 (TLR-4), and tumor necrosis factor-alpha (TNF-α). Interactions between vagal signaling and dopaminergic pathways may promote hippocampal neuronal apoptosis, thereby contributing to cognitive dysfunction after critical illness [40].

Systemic inflammation, particularly during sepsis, can also induce endothelial dysfunction, which represents

another important contributor to neurological injury. Inflammatory activation of the endothelium leads to increased expression of adhesion molecules and coagulation-related factors, resulting in disruption of blood-brain barrier (BBB) integrity. Loss of BBB function facilitates the migration of inflammatory mediators and circulating immune cells into the central nervous system, amplifying neuronal damage. Along with cerebral hypoperfusion and microvascular thrombosis, these changes increase vulnerability to ischemic injury and subsequent cognitive decline [41-42].

Other mechanisms involving impaired neurotrophic support have also been suggested. During sepsis, the release of heparan sulfate fragments may interfere with brain-derived neurotrophic factor (BDNF) signaling within the hippocampus, potentially contributing to deficits in learning and memory. Furthermore, elevated circulating interleukin-6 (IL-6) levels have been associated with neuronal injury, and experimental findings indicate that pharmacological inhibition of IL-6 signaling through monoclonal antibodies may attenuate brain injury related to mechanical ventilation [43].

Regarding psychological manifestations of PICS, several ICU-related factors have been identified as important contributors, including delirium, exposure to sedative medications, particularly benzodiazepines, and the use of vasopressors.

Patients who develop delirium during ICU admission are at significantly increased risk of subsequent psychiatric morbidity after discharge [1].

Underlying these clinical manifestations are multiple interacting pathophysiological processes, including central nervous system (CNS) inflammation, hypoxemia, hypoglycemia, impaired cerebral perfusion, electrolyte disturbances (hyponatremia and hypernatremia), reduced central cholinergic activity, increased dopaminergic tone, circadian rhythm disruption, and stress-induced elevations in glucocorticoids, all of which may contribute to delirium and longer-term neuropsychiatric sequelae in ICU survivors [44] (Figure 2).

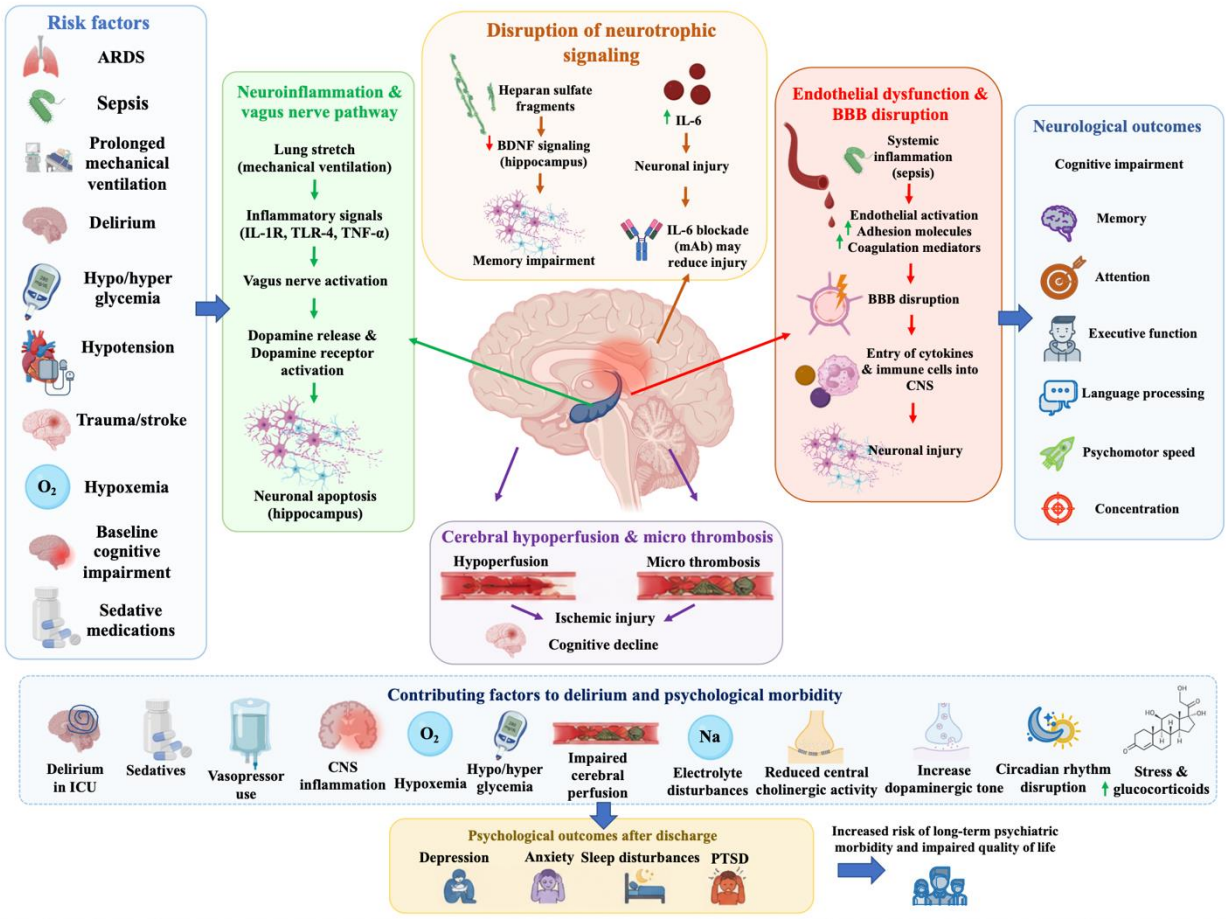

Figure 2- Molecular mechanism of neurological and psychological dysfunction in PICS. (Note: BBB: blood-brain barrier; BDNF: brain-derived neurotrophic factor; CNS: central nervous system; IL: interleukin; IL-1R: interleukin-1 receptor; TLR-4: toll-like receptor 4; TNF-α: tumor necrosis factor-α.)

Cardiopulmonary and Systemic Organ Dysfunction

The molecular mechanisms underlying the cardiovascular manifestations of PICS are complex and multifactorial. A hallmark of this process is persistent systemic inflammation, which may remain active even after the acute phase of critical illness has resolved and reflects a broader state of prolonged organ dysfunction following ICU admission [45]. Pro-inflammatory cytokines, particularly IL-1β, IL-6, and TNF-α, are key mediators involved in maintaining this chronic inflammatory response. Through their effects on endothelial function, vascular permeability, and coagulation pathways, these inflammatory signals create a pro-thrombotic state that may contribute to the onset or progression of cardiovascular complications, including heart failure (HF), myocardial infarction (MI), and atherosclerosis. Importantly, inflammatory signaling has been shown to independently contribute to cardiovascular disease progression; for example, inhibition of IL-1β has been associated with reduced cardiovascular events in patients with coronary artery disease (CAD), regardless of lipid levels [46].

Critical illness itself induces a marked hyperinflammatory response that may exacerbate pre-existing cardiovascular disease or trigger new-onset cardiovascular morbidity and mortality [45].

Interestingly, patients recovering from critical illness may exhibit a distinctive systemic state in which circulating pro-inflammatory markers are reduced, while normotension, hypocholesterolemia, and immunosuppression are present. However, this apparent state of systemic quiescence does not necessarily indicate complete resolution of inflammation or vascular injury, as persistent microvascular and endothelial abnormalities may continue after ICU discharge, largely as a consequence of oxidative stress. Enzymatic pathways involving myeloperoxidase and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase contribute to the generation of reactive isolevuglandins, which promote protein modification and further enhance inflammatory signaling, endothelial dysfunction, and atherogenic processes. These pathological changes may remain active beyond the acute phase of critical illness and contribute to the long-term cardiovascular burden observed in PICS survivors [46-50].

Long-term cardiovascular vulnerability after critical illness is also influenced by persistent disturbances in immune regulation and metabolic homeostasis. Acute critical illness induces profound immune activation and metabolic adaptation, including increased lactate and glucose concentrations, impaired high-density lipoprotein (HDL) function, and sustained insulin resistance. These alterations may contribute to ongoing vascular injury and accelerated atherosclerotic progression. Moreover, immune reprogramming involving trained innate immunity and immunosenescence can maintain a state of chronic low-grade inflammation, further promoting cardiovascular pathology [46]. Oxidative stress represents another important mechanism underlying cardiovascular complications in PICS. During critical illness and mechanical ventilation, excessive ROS generation results in oxidative modification of lipids, proteins, and nucleic acids, aggravating endothelial dysfunction and contributing to myocardial injury. Notably, disruption of the balance between oxidative stress and antioxidant capacity may persist even after recovery from the acute illness, increasing susceptibility to long-term cardiovascular complications among ICU survivors. Mitochondrial dysfunction, which often accompanies oxidative stress, further impairs myocardial energetics and increases susceptibility to chronic cardiac disease in PICS populations [46,51]. PICS is also frequently associated with chronic respiratory dysfunction, particularly in patients who have undergone prolonged mechanical ventilation. Mechanical ventilation, while life-saving in the setting of respiratory failure, may induce ventilator-induced lung injury (VILI) [52-53]. When combined with pre-existing organ injury, this process may lead to epithelial barrier disruption and extracellular matrix remodeling, ultimately resulting in pulmonary fibrosis and reduced lung compliance [43,52-55]. Another important contributor to respiratory morbidity is respiratory muscle weakness, which may arise both from critical illness itself and prolonged immobilization in the ICU. This weakness is commonly associated with CIM and CIP, resulting in reduced strength and endurance of the diaphragm and accessory respiratory muscles. Consequently, patients may experience prolonged difficulty in weaning from mechanical ventilation and an increased risk of respiratory infections and complications [55-58]. If unresolved, these pathophysiological changes may lead to long-term respiratory impairment even after recovery from the acute illness [52-53]. Clinically, this may manifest as persistent dyspnea, reduced exercise tolerance, and impaired quality of life among ICU survivors [55,58]. However, the precise mechanisms linking acute lung injury to chronic pulmonary dysfunction remain incompletely understood, and several interrelated pathways have been proposed [43,54].

A key pathway contributing to VILI involves the inflammatory response initiated by excessive alveolar distension during mechanical ventilation. This mechanical stress triggers the release of multiple pro-inflammatory cytokines, including IL-1β, IL-6, IL-8, TNF-α, CXC motif chemokine ligand-1 (CXCL-1), CXCL-10, and macrophage inflammatory protein-2 (MIP-2) [59-62]. These inflammatory mediators promote

vascular leakage, resulting in pulmonary edema and impaired oxygen exchange [59-61]. In addition, activation of nuclear factor kappa B (NF-κB) signaling by IL-1β and IL-6 further enhances downstream inflammatory responses. Ventilation with high tidal volumes has been associated with increased cytokine levels in bronchoalveolar lavage fluid (BALF), sustaining inflammatory injury within the lung. Persistent inflammation stimulates fibroblast activation and extracellular matrix accumulation, ultimately promoting fibrotic remodeling and loss of pulmonary compliance. Experimental data suggest that NF-κB-dependent induction of IL-6 may represent an important mediator in this process [59-63].

Experimental studies have further demonstrated that mechanical ventilation can aggravate pulmonary permeability and inflammatory cell recruitment, particularly when underlying inflammatory conditions are already present. During VILI, increased IL-33 expression has been detected in lung tissue, and translocation of its receptor has been proposed as a potential biomarker of injury. High-pressure ventilation increases IL-1β and MIP-2 concentrations in BALF and plasma, effects that may be reduced by IL-10 administration. IL-10 also decreases nitric oxide production in alveolar macrophages and downregulates the expression of heat shock protein-70 (HSP-70) and matrix metalloproteinase-9 (MMP-9). Although TNF-α contributes to inflammatory lung damage, TNF-α-derived TIP peptide may have a protective effect by maintaining alveolar-capillary barrier integrity. MMPs, particularly MMP-9, participate in extracellular tissue injury during VILI; however, their role may be context-dependent, with involvement in both tissue damage and repair processes [62-64].

Oxidative stress further intensifies VILI through excessive ROS generation, leading to disruption of alveolar epithelial integrity. Complement activation, including pathways involving C3 and C5b-9 complexes, also contributes to increased vascular permeability. Moreover, mechanosensitive ion channels such as transient receptor potential vanilloid 4 (TRPV4) participate in converting mechanical stress into intracellular injury signaling pathways [59-62]. Although inflammatory activation and extracellular matrix remodeling are necessary components of tissue repair following acute lung injury (ALI), uncontrolled activation of these pathways may contribute to chronic pulmonary disease and fibrosis after recovery [43].

Several pro-fibrotic cytokines, including IL-1β, IL-4, IL-5, IL-6, and IL-13, promote collagen accumulation through IL-17 signaling pathways and accelerate fibrotic remodeling [65]. During acute lung injury, activated alveolar macrophages, inflammatory cells, and fibroblasts release multiple pro-fibrotic mediators, including transforming growth factor-β (TGF-β), IGF-1, platelet-derived growth factor (PDGF), and connective tissue growth factor (CTGF). Signaling through transforming growth factor-β and SMAD-dependent pathways promotes extracellular matrix deposition and differentiation of fibroblasts into myofibroblasts, contributing to progressive and potentially irreversible fibrosis [66-69].

Coagulation-related pathways also participate in pulmonary fibrogenesis through activation of proteinase-activated receptors (PARs). These receptors can be stimulated by coagulation-associated enzymes, including thrombin, factor Xa, and other components of the coagulation cascade. Activation of PAR1 enhances the expression of pro-fibrotic mediators such as CTGF and PDGF and promotes local inflammatory cytokine production, further supporting fibrotic progression [70-71].

Epithelial-mesenchymal transition (EMT), a process in which epithelial cells acquire mesenchymal characteristics, represents another mechanism involved in chronic pulmonary remodeling and fibrosis. By promoting excessive extracellular matrix deposition and reducing lung compliance, EMT contributes to persistent structural changes within the lung and has been demonstrated in experimental models of mechanical ventilation-induced lung injury [72-76].

Oxidative stress is also a major contributor to chronic respiratory impairment, resulting from an imbalance between ROS generation and antioxidant defense mechanisms. Prolonged exposure to high oxygen concentrations and mechanical ventilation can intensify oxidative injury, causing DNA damage, lipid peroxidation, and disruption of protein function. These alterations activate cell death pathways in alveolar epithelial cells and further compromise alveolar-capillary barrier integrity. In addition, ROS-mediated upregulation of MMPs enhances extracellular matrix degradation and may interfere with effective tissue repair processes [77-78].

Mitochondrial dysfunction represents another important mechanism underlying chronic respiratory abnormalities in PICS. Mitochondria are essential regulators of cellular energy metabolism and apoptotic pathways, and their function may be impaired during critical illness due to the combined effects of hypoxia, inflammation, and oxidative stress. Reduced mitochondrial activity decreases ATP production while increasing ROS generation, thereby promoting cellular injury and apoptosis [78-79]. Within respiratory muscles, mitochondrial abnormalities impair contractile performance and contribute to muscle fatigue through disruption of calcium homeostasis. These changes further aggravate respiratory muscle weakness and reduce ventilatory efficiency. Moreover, mitochondrial

dysfunction can amplify inflammatory signaling, establishing a cycle of persistent inflammation and cellular damage that contributes to chronic respiratory impairment in PICS [79].

Taken together, disruption of the alveolar epithelial barrier, sustained inflammatory activation, and defective cellular repair mechanisms are major contributors to long-term pulmonary complications after critical illness. The alveolar epithelium is essential for maintaining pulmonary homeostasis, and its injury initiates signaling pathways that promote chronic lung damage and impaired regeneration [43,80-82]. Furthermore, persistent disease processes after critical illness may involve abnormal stem cell responses, resulting in DNA damage, cellular senescence, and prolonged pro-inflammatory states that collectively impair tissue regeneration and facilitate fibrosis [43] (Figure 3).

Post-Intensive Care Syndrome in Families (PICS-F)

The impact of PICS is not limited to ICU survivors themselves and may also affect their relatives and caregivers, a condition referred to as PICS-family (PICS-F). This syndrome reflects a broad range of emotional, psychological, and physical difficulties experienced by family members of critically ill patients. Studies have demonstrated that relatives may develop persistent psychological complications after critical illness, including anxiety, depression, PTSD, and complicated grief, which can continue from the acute hospitalization period into long-term recovery [83]. These psychological consequences may be accompanied by physical manifestations, such as impaired sleep, fatigue, and deterioration in general health status [83-84].

As many ICU survivors require ongoing assistance and support after discharge, family members frequently take on substantial caregiving roles. This increased responsibility may intensify caregiver stress and contribute to the development or worsening of PICS-F. Multiple factors related to the patient, caregiver, and healthcare system have been associated with PICS-F, including inadequate communication between healthcare professionals and families, limited opportunities for family participation in care, and restricted visitation practices, many of which may represent modifiable targets for intervention. Considering its effects on both caregiver health and patient recovery, early recognition and evaluation of PICS-F should be regarded as an integral part of comprehensive post-ICU care [2].

Prevention and Management Strategies

A number of preventive approaches have been proposed to minimize the risk and burden of PICS among ICU survivors. These approaches emphasize early identification of risk factors, optimization of ICU care processes, and implementation of structured evidence-based interventions aimed at improving long-term outcomes [1,8].

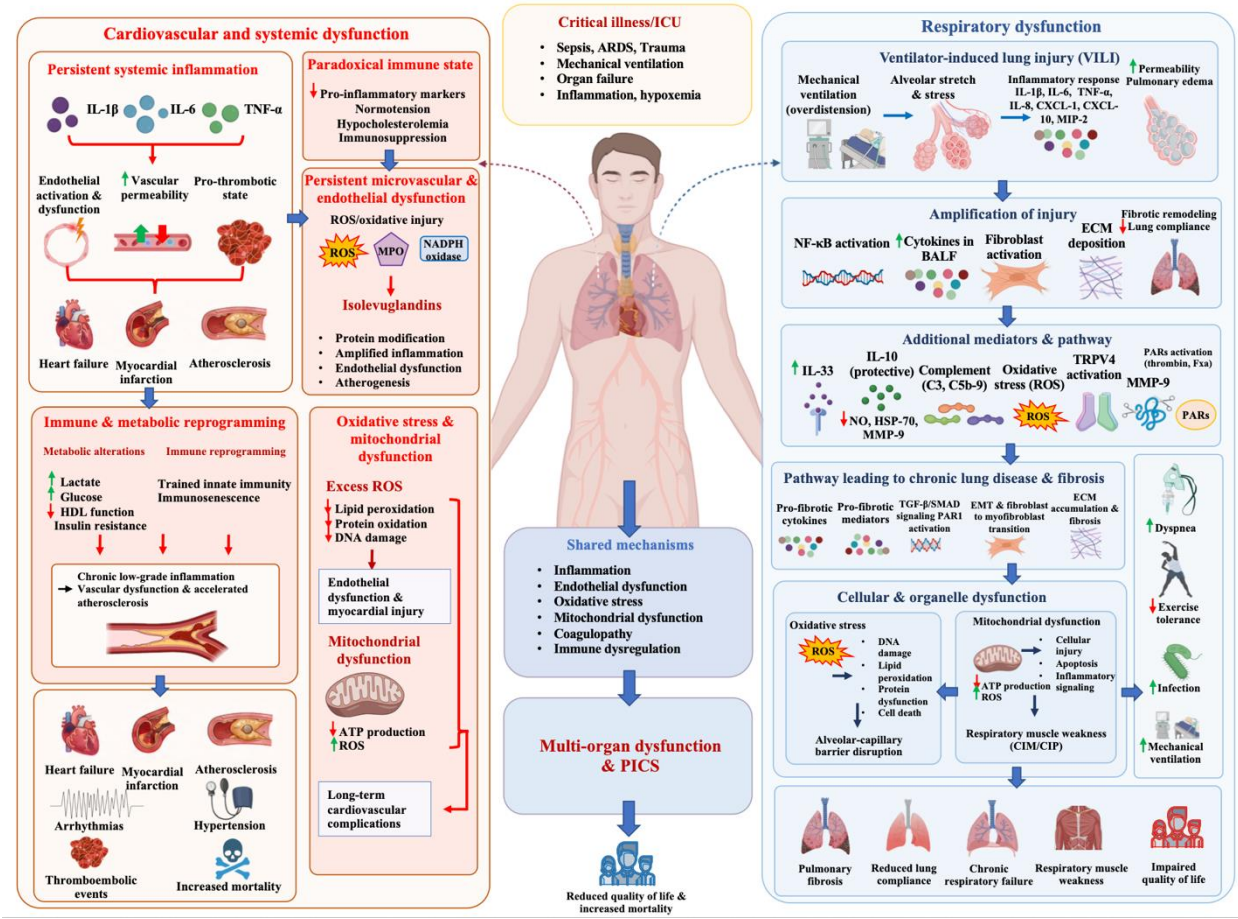

Figure 3- Molecular mechanism of cardiopulmonary and systemic organ dysfunction in PICS. (Note: ATP: adenosine triphosphate; CIP: critical illness polyneuropathy; CIM: critical illness myopathy; CTGF: connective tissue growth factor; EMT: epithelial-mesenchymal transition; HDL: high-density lipoprotein; IGF-1: insulin-like growth factor-1; IL: interleukin; MIP: macrophage inflammatory protein; MMP: matrix metalloproteinase; MPS: myeloperoxidase; PAR: protease-activated receptor; PDGF: platelet-derived growth factor; ROS: reactive oxygen species; TGF-β: transforming growth factor-β.)

The ICU Liberation "ABCDEF" bundle represents a cornerstone of current preventive strategies for PICS. It includes assessment and management of pain, breathing trials and spontaneous awakening, choice of sedatives, daily delirium monitoring, early mobilization, and family engagement. Delirium prevention represents a key element of this approach, given its strong relationship with increased mortality and persistent cognitive impairment after critical illness [5,8].

Overall, reducing the burden of PICS requires a comprehensive ICU-based strategy that extends beyond implementation of the ABCDEF bundle alone and addresses multiple modifiable contributors. Strategies such as minimizing exposure to sedatives, particularly through the use of non-benzodiazepine agents, regular assessment of sedation depth, and daily awakening trials have been associated with shorter durations of mechanical ventilation and reduced ICU length of stay. However, additional measures are necessary to achieve optimal outcomes. These include consistent implementation of bundle components, as inadequate adherence may limit its effectiveness, along with avoidance of excessive sedation and individualized approaches to analgesia and sedation management to reduce the risk of delirium and subsequent cognitive complications. Maintaining a supportive ICU environment that promotes sleep quality and normal circadian patterns, limiting medications associated with delirium, initiating early mobilization to prevent ICU-AW, and ensuring appropriate nutritional support are also important preventive measures. Collectively, these interventions highlight the value of a coordinated, multidisciplinary approach to reduce the long-term consequences of PICS [1,5,8].

Nutritional management also contributes to the prevention of PICS and ICU-AW by preserving skeletal

muscle mass through adequate energy and protein provision. Critical illness is frequently accompanied by accelerated muscle catabolism, loss of lean body mass, and adverse clinical outcomes; however, both insufficient and excessive nutritional delivery may be detrimental. Although achieving an appropriate balance between protein and energy intake may support recovery and potentially reduce PICS-related complications, the isolated use of protein supplementation has not demonstrated consistent benefits. Nutritional interventions should therefore be integrated with physical rehabilitation and exercise-based strategies to optimize muscle recovery. Despite investigations into anabolic approaches, including agents such as leucine, their clinical effectiveness remains uncertain [1].

In relation to PICS-F, promoting family involvement in ICU care, including structured and even brief visitation opportunities, may provide psychological benefits for both patients and relatives by reducing distress, improving communication, and enhancing emotional support during critical illness [1,5,8]. Furthermore, the development of dedicated post-ICU clinic models has been suggested as a potential strategy to address the complex and interconnected challenges associated with PICS and PICS-F. These multidisciplinary programs involve collaboration among healthcare professionals from different specialties to deliver comprehensive, patient- and family-centered care. Through structured follow-up, comprehensive clinical evaluation, individualized management plans, and psychosocial support, such models emphasize the close relationship between survivor recovery and family well-being [85].

Post-ICU Clinics as a Bridge to Long-Term Recovery

Post-ICU clinics provide a critical link between the acute phase of critical illness and the prolonged process of recovery after ICU discharge. Initially established in the United Kingdom in 1985, these clinics were designed to address the unmet needs of patients transitioning from intensive care to rehabilitation and long-term follow-up. By adopting a holistic perspective that considers survivors as individuals with interconnected biological, psychological, and social needs rather than as patients with separate isolated complications, these clinics facilitate comprehensive evaluation of multiple domains, including physical function, cognition, emotional health, and social well-being.

Early recognition of complications such as neuromuscular weakness, cognitive impairment, neuropsychiatric symptoms, and reduced functional capacity allows timely initiation of targeted rehabilitation and psychological interventions. Continued follow-up over time also enables clinicians to evaluate individual recovery patterns, an important consideration given the variable and often delayed course of recovery among patients with PICS. Furthermore, integrating ICU-specific information, including prior sedation exposure and episodes of delirium, into post-discharge assessments improves continuity of care and supports more individualized management strategies.

In addition, clinical pharmacists can play an important role by reviewing and optimizing complex medication regimens in these patients, identifying drug-related problems, minimizing polypharmacy risks, and ensuring safe, evidence-based pharmacotherapy throughout the recovery period. It is recommended that all high-risk patients who have stayed in the ICU for more than 48 hours be referred to post-ICU clinics after discharge to ensure structured follow-up and early intervention [1,8,86].

Precision Rehabilitation in PICS

Rehabilitation strategies for PICS are increasingly moving beyond uniform protocols toward more individualized and biologically oriented approaches that address underlying abnormalities in cellular metabolism, neuromuscular performance, and neuroplasticity. Conventional rehabilitation programs initiated during or after ICU admission, which commonly include physical and occupational therapy, home-based exercise programs, telehealth interventions, and, in some cases, cognitive training over a period of 6-12 weeks, have demonstrated benefits in functional recovery, activities of daily living, and selected psychological outcomes. However, their effects on improving muscle strength and cognitive function have remained variable.

Recent evidence indicates that rehabilitation may be more effective when integrated with complementary interventions, including nutritional optimization, metabolic support, sleep management, and early mobilization, rather than being implemented as a standalone strategy. Cognitive rehabilitation may also benefit from timing interventions during periods of increased neuroplastic potential. Structured programs such as goal management training are currently being evaluated, although supporting evidence remains limited. In contrast, psychological rehabilitation continues to lack clearly established standardized approaches, although follow-up interventions delivered by telephone may provide benefits in coping and emotional adjustment among patients and caregivers.

Importantly, rehabilitation should not be delayed until ICU discharge. Initiating preventive and restorative strategies during the ICU stay, including reducing unnecessary immobilization, avoiding excessive sedation, and preventing delirium, represents the foundation of a precision-based rehabilitation framework

designed to improve long-term outcomes in PICS survivors [52,87-89].

Future Directions: Biological and Systems-Based Research in PICS

Future research in PICS is increasingly moving toward a systems-oriented framework that incorporates biological stratification and individualized approaches. Conventional diagnostic classifications may not adequately reflect the considerable heterogeneity observed among PICS survivors, and upcoming clinical studies are likely to focus on biologically defined subgroups rather than relying solely on broad clinical categories. The application of multi-omics platforms, digital health technologies, and longitudinal recovery databases may provide deeper insight into the mechanisms driving PICS and facilitate the identification of more specific therapeutic targets. Progress in this field will depend on sustained multidisciplinary collaboration among ICUs, post-ICU clinics, and rehabilitation networks to promote continuity of care and effective integration of clinical data [85,90-91].

Conclusion

PICS represents a multifaceted consequence of critical illness, involving persistent impairments across physical, cognitive, psychological, and cardiopulmonary domains. Its pathogenesis is shaped by the interaction of several biological processes, including sustained inflammation, immune dysregulation, oxidative stress, mitochondrial impairment, and disrupted tissue repair mechanisms. Addressing the long-term impact of PICS requires an integrated continuum of care that combines preventive strategies, targeted rehabilitation, and structured follow-up after ICU discharge. Future research should focus on biological phenotyping and precision medicine approaches to better understand disease heterogeneity and develop personalized recovery strategies for ICU survivors and their families.

Authors' contributions

FA: formal analysis, investigation, methodology, visualization, writing original draft, review, and editing. KS: formal analysis, investigation, methodology, visualization, writing original draft, review, and editing. LSH, HJ, PD, ND, and ZA: writing the original draft. AM: review and editing. AN and MM: conceptualization, methodology, project administration, supervision, validation, review, and editing.

Data availability

Available from the corresponding author upon request.

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