

Indian Journal of Modern Research and Reviews

This Journal is a member of the 'Committee on Publication Ethics'

Online ISSN:2584-184X



Review Article

Transition of Acute Icu Pain to Chronic Post-Icu Pain: Risk Factors and Prevention

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DOI: <https://doi.org/10.5281/zenodo.18657633>

Abstract

Background: Post-intensive care syndrome (PICS) encompasses a constellation of physical, cognitive, and psychological impairments that persist following intensive care unit (ICU) discharge. Among these, chronic post-ICU pain represents a significant yet underrecognized component that profoundly impacts quality of life and functional recovery. Pain experienced during critical illness can transition from acute nociceptive pain to chronic pain states through complex neuroplastic mechanisms involving peripheral and central sensitisation.

Objective: This review examines the epidemiology, pathophysiological mechanisms, risk factors, and evidence-based prevention strategies for the transition from acute ICU pain to chronic post-ICU pain.

Methods: A comprehensive review of current literature was conducted, focusing on studies published between 2012 and 2025, examining the incidence, mechanisms, and prevention of chronic pain in ICU survivors.

Results: Chronic pain affects 17.7% to 44% of ICU survivors, with the shoulder being the most commonly affected site. Key risk factors include prolonged ICU length of stay, severe sepsis, female gender, hyperinflammation, and post-traumatic stress disorder. The transition involves peripheral sensitisation, central sensitisation, neuroinflammation, and maladaptive neuroplasticity—prevention strategies centre on the ABCDEF bundle, multimodal analgesia, early mobilisation, and psychological support.

Conclusion: Chronic post-ICU pain represents a preventable complication of critical illness. Systematic implementation of evidence-based protocols during ICU care can significantly reduce the incidence and impact of chronic pain in survivors.

Manuscript Information

- ISSN No: 2584-184X
- Received: 12-12-2025
- Accepted: 20-01-2026
- Published: 16-02-2026
- MRR:4(2); 2026: 195-200
- ©2026, All Rights Reserved
- Plagiarism Checked: Yes
- Peer Review Process: Yes

How to Cite this Article

Nautiyal A. Transition Of Acute ICU Pain to Chronic Post-Icu Pain: Risk Factors and Prevention. Indian J Mod Res Rev. 2026;4(2):195-200.

Access this Article Online



www.multiarticlesjournal.com

KEYWORDS: Post-intensive care syndrome, chronic pain, central sensitisation, ICU survivors, multimodal analgesia, early mobilisation, ABCDEF bundle.

INTRODUCTION

The landscape of critical care medicine has witnessed remarkable advances over the past two decades, with intensive care unit (ICU) mortality rates declining significantly across developed nations. Between 2013 and 2016, survival rates following ICU admission increased substantially, resulting in an estimated 216 to 2353 ICU admissions per 100,000 population in Europe and North America. In the United Kingdom alone, more than 270,000 patients were admitted to critical care units in 2015-2016. This improved survival, while celebrated, has unveiled a new clinical challenge: the long-term sequelae experienced by ICU survivors, collectively termed post-intensive care syndrome (PICS).

PICS encompasses a triad of impairments affecting physical, cognitive, and mental health domains. Within this framework, chronic pain emerges as a particularly debilitating complication that can persist for months to years after ICU discharge. Pain is frequently identified by patients as a leading cause of stress and sleep disruption during critical illness, with many reporting severe pain as the most traumatic memory of their ICU stay. Unlike acute pain, which serves a protective physiological function, chronic post-ICU pain represents a pathological state characterised by neuroplastic changes that persist beyond the predicted healing period.

The transition from acute to chronic pain in ICU survivors involves complex mechanisms, including peripheral nociceptor sensitisation, central nervous system plasticity, neuroinflammation, and psychosocial factors. Understanding these mechanisms is essential for developing targeted prevention strategies. This review synthesises current evidence on the epidemiology, pathophysiology, risk factors, and prevention of chronic post-ICU pain, to guide clinical practice toward improved long-term outcomes for ICU survivors.

EPIDEMIOLOGY AND INCIDENCE

The true prevalence of chronic post-ICU pain has been challenging to establish due to methodological variations across studies, inconsistent definitions of chronic pain, and variable follow-up periods. However, recent well-designed cohort studies have provided more precise estimates of this important clinical problem.

A landmark retrospective analysis of ICU survivors in South Wales revealed that 44% of respondents reported chronic pain between 6 months and 1 year after hospitalisation. The shoulder emerged as the most commonly affected anatomical site, with 22% of survivors experiencing shoulder pain, representing a nearly two-fold increase compared to the general UK population prevalence of 11.7%. Other commonly affected sites included the lower limbs (9%), lumbar spine (9%), cervical spine (6%), upper limbs (6%), abdomen (4%), and pelvis (3%). More recent prospective data from a Dutch tertiary ICU examined 1,842 patients discharged between 2013 and 2016. Among one-year survivors ($n=1,368$), the estimated occurrence of newly acquired chronic pain was 17.7% (95% CI: 15.8-19.8%). The median pain intensity on the numeric rating scale was 4 (interquartile range: 2-6), with the impact being most evident on activities of daily living, social activities, and

mobility. Notably, neuropathic pain features were present in 50% of affected subjects, highlighting the complex nature of post-ICU pain syndromes.

A Greek ICU study focusing on the relationship between chronic pain and post-traumatic stress disorder (PTSD) found that 62.7% of survivors reported pain intensity greater than 3 on the numeric rating scale at 3 months post-discharge. Furthermore, approximately 32% of ICU survivors sought additional healthcare professional input specifically for chronic pain management, underscoring the significant healthcare burden imposed by this condition.

The variation in reported prevalence rates (17.7% to 62.7%) likely reflects differences in study populations, pain assessment methods, timing of assessment, and definitions of clinically significant pain. Nevertheless, the consistent finding across multiple studies is clear: chronic pain represents a substantial and prevalent problem in ICU survivors that warrants systematic attention and preventive efforts.

PATHOPHYSIOLOGICAL MECHANISMS

The transition from acute ICU pain to chronic pain involves a cascade of neuroplastic changes affecting both the peripheral and central nervous systems. Understanding these mechanisms is crucial for developing targeted interventions to prevent pain chronification.

Peripheral Sensitization

Acute tissue injury and inflammation in ICU patients trigger the release of various inflammatory mediators, including adenosine triphosphate (ATP), bradykinins, histamine, prostaglandins, neurotrophic factors, and cytokines. These mediators activate nociceptors and initiate neurogenic inflammation characterised by upregulated production of neuropeptides such as neurokinin A, substance P, and calcitonin gene-related peptide (CGRP). This process leads to peripheral sensitisation, characterised by reduced activation threshold of nociceptors, increased stimulus-induced discharge, and spontaneous activity. While peripheral sensitisation is typically reversible and confined to sites of tissue injury, prolonged or severe inflammation can contribute to more persistent changes.

Central Sensitization

Central sensitisation represents a fundamental mechanism in the transition to chronic pain and is defined as increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold afferent input. This phenomenon involves multiple molecular and cellular mechanisms:

1. Synaptic Plasticity: Persistent nociceptive input triggers long-term potentiation (LTP)-like changes at synapses in the dorsal horn of the spinal cord. These changes involve activation of N-methyl-D-aspartate (NMDA) receptors, mobilisation of intracellular calcium, and phosphorylation of various kinases, including protein kinase C (PKC) and calcium/calmodulin-dependent protein kinase II (CaMKII).

2. Receptor Modulation: There is a shift from GluR2/3-containing to GluR1-containing AMPA receptors, which are calcium-permeable and contribute to enhanced excitatory neurotransmission. Voltage-gated calcium channel subunits, particularly $\alpha_2\delta-1$, become upregulated in the dorsal horn following nerve injury.

3. Expansion of Receptive Fields: Central sensitisation recruits previously subthreshold inputs, expanding the receptive fields of dorsal horn neurons. This results in phenomena such as secondary hyperalgesia (pain in tissue distant from the site of injury) and allodynia (pain evoked by normally innocuous stimuli).

4. Loss of Inhibitory Control: Dysfunction of descending inhibitory pathways from the rostral ventromedial medulla and periaqueductal grey matter contributes to maintained central sensitisation. GABAergic and glycinergic inhibitory interneurons in the dorsal horn may also show reduced function.

Neuroinflammation and Glial Activation

Emerging evidence highlights the crucial role of neuroinflammation in driving central sensitisation and chronic pain. Glial cells, particularly microglia and astrocytes in the spinal cord and brain, become activated following painful insults. Activated glia release pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) and chemokines (CCL2, CX3CL1, CXCL13) that act as powerful neuromodulators.

Microglial activation involves several pathways: ATP stimulation of P2X and P2Y receptors, chemokine signalling through CX3CL1-CX3CR1 and CXCL13-CXCR5 axes, and colony-stimulating factor 1 (CSF1) signalling. These activated glial cells amplify pain signals through cathepsin S-mediated mechanisms and brain-derived neurotrophic factor (BDNF) release, which enhances NMDA receptor function and promotes synaptic strengthening.

The hyperinflammatory state common in ICU patients, particularly those with sepsis or acute respiratory distress syndrome (ARDS), may prime the immune system and nervous system for prolonged neuroinflammation, creating a substrate for chronic pain development.

RISK FACTORS FOR CHRONIC POST-ICU PAIN

Identification of risk factors for chronic post-ICU pain enables targeted prevention strategies for high-risk populations. Evidence from multiple cohort studies has identified several consistent risk factors.

Patient-Related Factors

1. Female Gender: A large Dutch cohort study identified female gender as a significant independent predictor of newly acquired chronic pain at one-year post-ICU. This finding aligns with broader chronic pain epidemiology, showing higher prevalence in women.

2. Age: Increasing patient age emerged as a risk factor in the Welsh cohort analysis, though this finding appears complex. Age-dependent decline in peripheral nociceptive function may

be offset by factors such as reduced muscle mass and poorer nutritional status in older patients.

3. Pre-existing Chronic Pain: Patients with pre-existing chronic pain conditions are at higher risk for pain persistence and may have already established central sensitisation mechanisms that are reactivated or amplified by critical illness.

ICU-Related Factors

1. Length of ICU Stay: Prolonged ICU length of stay consistently emerges as a significant risk factor. The Greek study found that each additional day in the ICU was associated with increased odds of chronic pain (OR=1.42; 95% CI: 1.03-1.95; $p=0.030$). Longer ICU stays typically involve more procedures, greater cumulative pain exposure, and prolonged immobilisation.

2. Hyperinflammation: Days spent in ICU with hyperinflammation were specifically associated with chronic pain development in the Dutch cohort. The systemic inflammatory response may drive both peripheral and central sensitisation mechanisms.

3. Severe Sepsis: The Welsh retrospective analysis identified severe sepsis as a significant independent risk factor for chronic pain, likely reflecting the intense inflammatory state and multiple organ dysfunction that characterise severe sepsis.

4. Prolonged Mechanical Ventilation: Duration of mechanical ventilation greater than 7 days is associated with ICU-acquired weakness and has been linked to chronic pain.

Psychological Factors

1. Post-Traumatic Stress Disorder (PTSD): A strong bidirectional relationship exists between chronic pain and PTSD in ICU survivors. The Greek study found that chronic pain was significantly associated with clinically relevant PTSD symptoms at 3 months (OR=10.04; 95% CI: 2.44-41.24; $p=0.001$) and 6 months (OR=11.90; 95% CI: 1.28-110.49; $p=0.029$) post-discharge.

2. Depression and Anxiety: These common sequelae of critical illness are well-established risk factors for chronic pain in general populations and likely contribute to pain chronification in ICU survivors.

3. Delirium: ICU delirium is associated with long-term cognitive impairment and may influence pain processing and reporting.

PREVENTION STRATEGIES

Given the significant burden of chronic post-ICU pain, prevention strategies implemented during and after ICU care are paramount. Evidence supports a multimodal, interdisciplinary approach targeting multiple mechanisms and risk factors.

The ABCDEF Liberation Bundle

The Society of Critical Care Medicine's ABCDEF Liberation Bundle represents the most comprehensive evidence-based framework for preventing PICS, including chronic pain:

A - Assess, Prevent, and Manage Pain: Systematic pain assessment using validated tools (Critical-Care Pain Observation Tool, Behavioural Pain Scale) should occur at regular intervals. Pain should be treated as the 'fifth vital sign.'

B - Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT): Daily interruption of sedation reduces cumulative sedative exposure, facilitates pain assessment, and enables earlier mobility.

C - Choice of Analgesia and Sedation: Prefer non-benzodiazepine sedatives (propofol, dexmedetomidine) and implement multimodal analgesia to minimise opioid exposure while maintaining adequate pain control.

D - Delirium Assessment, Prevention, and Management: Use validated screening tools (CAM-ICU, ICDSC) to identify delirium early. Non-pharmacological interventions, including reorientation and early mobility, are preferred.

E - Early Mobility and Exercise: Mobilisation should commence within 24-72 hours of ICU admission when hemodynamically stable. Physical and occupational therapy protocols should progress from passive range of motion to active exercises and ambulation.

F - Family Engagement and Empowerment: Family presence, participation in care, communication with the healthcare team, and access to ICU diaries can reduce PTSD risk and support patient recovery.

Implementation of the complete ABCDEF bundle has been associated with reduced ICU length of stay, decreased mechanical ventilation duration, lower delirium rates, and improved long-term outcomes. A 2024 multicenter prospective cohort study demonstrated that bundle adherence led to reduced ICU length of stay and percentage of patients requiring more than 7 days in ICU.

Multimodal Analgesia

The 2018 PADIS (Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption) guidelines emphasise multimodal analgesia as the preferred approach to ICU pain management. This strategy combines medications with different mechanisms of action to optimise pain control while minimising individual drug side effects.

Opioid-Sparing Adjuncts:

1. Acetaminophen: First-line agent for mild-to-moderate pain. IV acetaminophen may be particularly useful in mechanically ventilated patients. Doses typically range from 650-1000 mg every 6 hours (maximum 4 grams daily).

2. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): When not contraindicated by renal dysfunction, coagulopathy, or gastrointestinal bleeding risk, NSAIDs provide effective analgesia and anti-inflammatory effects. Careful monitoring is essential.

3. Ketamine: Subanesthetic ketamine (typically 0.1-0.5 mg/kg/hour IV) provides analgesia through NMDA receptor antagonism, which may prevent central sensitisation and opioid-induced hyperalgesia. The PADIS guidelines and 2018 ASRA/AAPM/ASA consensus recommend ketamine as an adjunct to opioid therapy.

4. Gabapentinoids: Gabapentin and pregabalin inhibit voltage-gated calcium channels upregulated by tissue injury and neuropathy. These agents may be particularly useful for patients with neuropathic pain components. However, caution is warranted regarding respiratory depression risk, particularly when combined with opioids.

5. Alpha-2 Agonists: Dexmedetomidine and clonidine possess analgesic properties through α_2 -adrenoreceptor stimulation. Dexmedetomidine provides sedation without respiratory depression and reduces opioid consumption.

6. Regional Anaesthesia: For appropriate patients, regional anaesthetic techniques (epidural analgesia, peripheral nerve blocks) can provide superior analgesia with minimal systemic effects.

Early Mobilisation and Rehabilitation

Physical immobility represents both a consequence and a risk factor for chronic pain. ICU-acquired weakness (ICUAW) affects more than 25% of ICU survivors and independently predicts chronic pain development. Early mobilisation protocols aim to prevent muscle atrophy, maintain joint range of motion, and interrupt the cycle of immobility-related complications.

A landmark study by Schweickert demonstrated that patients randomised to physical and occupational therapy within 72 hours of ICU admission regained independence at ICU discharge sooner than controls. Early rehabilitation reduces the duration of delirium, improves functional outcomes, and may prevent the development of chronic pain through multiple mechanisms, including preservation of muscle mass, prevention of joint contractures, and modulation of inflammatory responses.

Psychological Support and PTSD Prevention

The strong association between PTSD and chronic pain in ICU survivors mandates attention to psychological health. Studies in trauma populations show that patients exposed to clinical psychologists during ICU admission have a halved risk of anxiety and depression and significantly reduced PTSD prevalence at 12 months. ICU diaries, written records maintained by family members and healthcare providers, help patients understand their ICU experience, reducing PTSD symptoms in both patients and families.

CONCLUSION

Chronic post-ICU pain represents a significant and preventable complication affecting 18-44% of ICU survivors. The transition from acute pain experienced during critical illness to chronic pain involves complex pathophysiological mechanisms,

including peripheral sensitisation, central sensitisation, neuroinflammation, and maladaptive neuroplasticity. These changes are amplified by risk factors such as prolonged ICU stay, severe sepsis, hyperinflammation, inadequate acute pain management, and psychological trauma.

The multifaceted nature of chronic post-ICU pain necessitates comprehensive prevention strategies implemented throughout the continuum of critical illness and recovery. The ABCDEF Liberation Bundle provides an evidence-based framework that addresses pain assessment and management, sedation optimisation, delirium prevention, early mobilisation, and family engagement. Multimodal analgesia employing opioid-sparing adjuncts (acetaminophen, NSAIDs, ketamine, gabapentinoids, alpha-2 agonists) and regional techniques reduces reliance on opioids while providing effective pain control that may prevent sensitisation.

Early mobilisation and rehabilitation prevent ICU-acquired weakness and preserve functional capacity. Psychological support, including ICU diaries and early intervention for PTSD, addresses the strong bidirectional relationship between chronic pain and post-traumatic stress. Implementation of these evidence-based strategies requires institutional commitment, interdisciplinary collaboration, adequate resources, and cultural transformation.

As ICU survival continues to improve, the focus of critical care must expand beyond preventing death to optimising the quality of survival. Recognising chronic pain as a central component of PICS and implementing systematic prevention strategies represents a crucial step toward this goal. By addressing pain not merely as a symptom to be managed but as a potential precursor to long-term disability, clinicians can fundamentally improve outcomes for the growing population of ICU survivors.

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