

Review

Rehabilitation of Chronic Pain in Post-Critical Care Patients. A Narrative Review

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Abstract

Chronic pain in post-critical care patients is a multifaceted issue with profound implications for patient well-being and quality of life. This review aims to address the rehabilitation of patients who suffer from chronic pain following discharge from the intensive care unit (ICU). Despite growing awareness of the prevalence and impact of this condition, significant gaps in knowledge persist regarding the optimal rehabilitation strategies for these patients. To conduct this study, an extensive literature search was undertaken, encompassing peer-reviewed articles, clinical trials, and observational studies in Medline, Scopus, and Cinahl databases, using specific keywords. Studies were identified based on their titles, abstracts, and those that met the inclusion criteria. Sixteen studies were eligible for inclusion in this review, varying in methodology, assessment tool, assessment time, or follow-up. The findings of this review illuminate the existing gaps in knowledge by synthesizing evidence on the various rehabilitation approaches employed, their effectiveness, and the factors influencing patient outcomes. So far, healthcare professionals have targeted either pain treatment, finding an analgesic medication or the proper position/exercise, or pain management, helping the patient manage life despite the unrelieved pain. Conventional pain treatment or control has been replaced by pain rehabilitation, in which a biopsychosocial approach enables



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healthcare professionals to provide patients with the knowledge and skills to manage their pain and disability through personal multidimensional choices. Early rehabilitation programs, quick mobilization, and greater family participation should be encouraged. The strengths of this study lie in its thorough analysis of the available literature and the provision of valuable insights into the heterogeneous nature of chronic pain in post-critical care patients. However, limitations include the limited availability of high-quality randomized controlled trials in this domain. Overall, this review contributes to an improved understanding of rehabilitation strategies for chronic pain in post-critical care patients and underscores the need for further research to enhance patient care and outcomes.

Keywords

Chronic pain; interventions; management; post-critical care; rehabilitation

1. Introduction

In the last decades, as critical care and technology have advanced, the mortality in Intensive Care Units (ICU) has decreased. Hence, the challenge has been shifted to improve the long-term survival and quality of life of post-ICU patients across the lifespan. A large percentage of critically ill patients experience significant physical, cognitive, psychological, or social impairments several months or even years after discharge from ICU [1-3]. An essential clinical characteristic in critically ill patients during their stay in the ICU or after release, despite analgesia, is the pain they experience [4]. Chronic pain in survivors of ICU stays represents a critical issue that has not received the recognition it deserves within the healthcare community. While the primary focus in ICUs is often on immediate life-saving measures, the long-term consequences, such as chronic pain, are frequently overlooked [5]. However, increasing evidence demonstrates how pain is associated with the patient's long-term health outcomes and life quality. Peripheral and central sensitization are the keys to transitioning from acute to chronic pain. Studies emphasized pain intensity, location, duration, and the risk factors that affected it [6, 7]. An individual's well-being over time is related to an illness, disability, or disorder, usually described in healthcare by the term health-related quality of life (HRQOL). Differences in HRQOL have been extensively evaluated in the bibliography in critically illness survivors by general adult ICU populations compared to healthy control groups [8, 9].

Implementing systematic and integrated approaches to pain assessment seems to contribute significantly to documented clinical practices and efficient decisions for pain management. In particular, there was evidence of beneficial effects on pain intensity, length of stay in ICU, during mechanical ventilation, adverse events, complications, and mortality [10]. Some standard tools for pain assessment are (i) the Brief Pain Inventory (BPI) [11], the more often used; (ii) the Pain Self-Efficacy Questionnaire (PSEQ) [12]; and (iii) the Critical Care Pain Observation Tool (CPOT) [13], which finds implementation into ICU. As pain is among the basic modules in all (HRQOL) assessments, a well-established and validated questionnaire used to assess HRQOL in adults is the EQ-5D [14]. This tool provides a simple yet comprehensive way to measure a person's overall well-being by evaluating five dimensions of health: mobility, self-care, usual activities, pain/discomfort,

and anxiety/depression. Respondents rate their health status on each size, allowing for generating a single index score that quantifies HRQOL.

Rehabilitation for chronic pain following critical care encompasses a multifaceted approach aimed at improving the physical and psychological well-being of patients who have experienced prolonged stay in the ICU or undergone major surgeries [15]. This comprehensive rehabilitation process involves assessment and diagnosis, pain management strategies including pharmacological and non-pharmacological interventions, physical therapy [16], psychological support, patient education, lifestyle modifications, and long-term follow-up [17]. Research in this field continuously advances our understanding of effective pain management techniques and holistic care for these individuals, emphasizing the importance of a multidisciplinary team and individualized treatment plans to enhance their quality of life. Therefore, several clinical practice guidelines for pain management have recently been published [18-20]. The Society of Critical Care Medicine has developed (i) guidelines for pain, agitation, delirium, and mobility recommendations; (ii) tools to facilitate and implement the translation of guideline care recommendations into practice, and (iii) assessment of the long-term consequences of critical illness [21]. However, this review aims to shed light on the prevalence, the assessment tools, the risk factors, underlying mechanisms, and potential interventions related to chronic pain in ICU survivors, advocating for a more comprehensive approach to their care. Recognizing and addressing chronic pain in this context is not only crucial for improving patient outcomes but also for enhancing our understanding of the full spectrum of challenges faced by ICU survivors.

2. Materials and Methods

The method used for this review included a search in Medline/PubMed, Scopus, and Cinahl databases, using the keywords: “chronic pain”, “interventions”, “management”, “post-critical care” and “rehabilitation”. Two reviewers extracted data independently. Data was extracted by database querying, retrieving, or extracting specific information or data from databases. Studies were identified based on their titles’ and abstracts’ relevance, with those meeting the inclusion criteria to be retrieved (Table 1), with the latter to be examined for additional sources. The diagram of our search strategy is presented in Figure 1 [22]. Data was synthesized with narrative summaries presenting the review's findings. In the current study, a more interpretive approach was used to summarize results, such as "evidence statements".

Table 1 Review’s inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Time	Published between 01/01/2002 and 31/12/2022	Published before 01/01/2002 or after 31/12/2022
Language	English	No English
Sample	Related to chronic pain in adult patients after critical care	Related to paediatric populations, no - chronic pain or no - critical care/ICU
Measures	Pain assessment tool, incidence of chronic pain, risk factors/pain locations or nursing interventions were reported	Pain assessment tool, incidence of chronic pain, risk factors/pain locations or nursing interventions were not reported
Study	Primary research	Editorials, letters, reviews

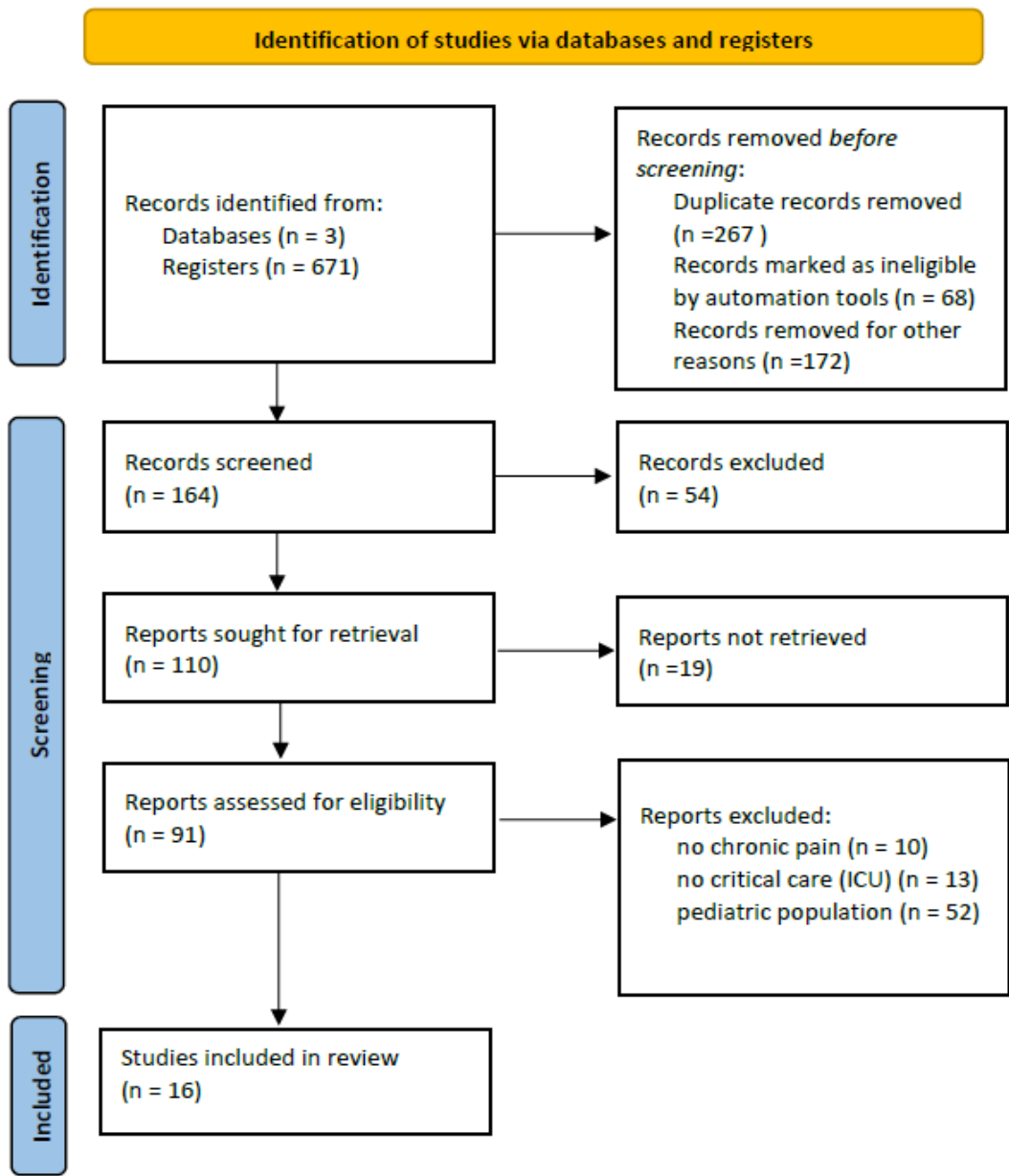


Figure 1 The diagram of the search strategy.

3. Results

Initially, 671 published articles were identified as relevant to the aim of the study. After applying the inclusion criteria, only sixteen research reports met the criteria for inclusion. Studies vary in the methodology, tool for pain assessment, the period when the pain was assessed or the follow-up, etc. Studies included in the current review have been summarized in Table 2.

Table 2 Studies included in the review.

Study - Country	Type of study	Pain assessment tool	Sample size (n)	Risk factors	Period of follow up (months)	Incidence of chronic pain	Pain location and intensity
Baumbach 2016 Germany [23]	Case-control study (observational study): septic/non-septic	German pain questionnaire	207 + healthy control, n = 46	No differences septic/non-septic	6	33.2%	moderate to severe (45% of those with chronic pain reported)
Battle 2013 Wales [24]	Retrospective study	BPI	196	increasing patient age and severe sepsis	6-12	44%	Shoulder (22%)
Boyle 2004 Wales [25]	Prospective repeated measures observational study	Pain Scale, Pain Self-Efficacy Questionnaire (PSEQ)	66 (1 month) 52 (6 months)	Ventilator hours 57.1 ± 93 and hospital LOS 26.4 ± 30.2	1 and 6 months	28% 47% 1 months 49% 6 months	Moderate to very severe pain (92% of those with chronic pain reported)
Choi 2014 Pennsylvania [26]	Prospective longitudinal descriptive study	Modified Given Symptom Assessment Scale	26	-	4	53.8%	
Devine 2019 UK [27]	Cross-sectional study Follow up	BPI and musculoskeletal assessment	47	None	12	66%	Lower limb (42%), the shoulder (39%), and the trunk/back (32%)
Garcia Lizana 2003 Belgium [28]	Prospective, observational study.	EuroQol 5D	96	Previous problems in the specific dimension, prolonged hospital	18	44%	-

				LOS and ICU readmission, high severity of illness on admission and degree of organ dysfunction during ICU stay			
Granja 2002 Portugal [29]	Prospective cohort study	EuroQol 5-D	275	the main diagnosis at ICU admission, especially multiple trauma and non-scheduled surgery, and variables related to patients' background such as age, and previous health status	6	45% (pain/discomfort)	-
Griffiths 2013 UK [30]	Prospective cohort study	EQ-5D	293	-	6 and 12	73% (6 m) 70% (12 m)	Moderate or severe pain
Hayhurst 2018 USA [31]	Multi-center Cohort study	BPI	295	No association with ICU opioid exposure	3 and 12	77% (3 m) 74% (12 m)	-
Korošec Jagodic 2006 Slovenia [32]	Prospective Observational study:	EuroQOL-5D	164 patients (98 trauma	Sepsis/trauma	24	56%	-

			and 66 sepsis patients)				
Langerud PAIN 2018 Norway [33]	Exploratory and longitudinal study	BPI	3 months (n = 118) and 12 months (n = 89)	The severity of illness, organ failure, ventilator time and ICU LOS	3 and 12	49.2% (3 m) 38.2% (12 m)	shoulder and abdomen (3 m), ankle/foot and shoulder (12 m)
Jenewein 2009 Switzerland [34]	Prospective with control group	Closed questions about pain related to the accident	90	Severe injury Psychological factors	36	44	-
Timmers 2011 Netherlands [35]	Prospective observation cohort study	EuroQol-6D	575	Independent Association of Sex, Age, and surgical classifications	3	57%	-
Valsø 2021 Norway [36]	Longitudinal descriptive secondary analysis of a randomized controlled trial	BPI	523	female sex, younger age, shorter ICU LOS, high level of PTS symptoms and ICU traumatic memories	3, 6, and 12	68%	Abdomen (43%), lower lumbar back (28%), and shoulder/forearm (22%)
Gélinas 2007 Canada [13]	Descriptive	Closed and open-ended questions based on Puntillo's study	93	Turning Breathing Chest tube removal	-	77.4	Thorax (sternal incision)

Choinière 2014 Multicentre Canada affiliated [37]	Observational prospective cohort study	Question of persistent nonanginal pain Pain Catastrophizing Scale	1247	Intense postoperative pain the first week Pre-existing persistent pain Preoperative anxiety Female sex, young age	3, 6, 12 and 24	40.1% at 3 m 22.1% at 6 m 16.5% at 12 m 9.5% at 24 m	Pain was rated as moderate to severe in 3.6% at 24 months
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3.1 Prevalence of Chronic Pain in Critical Care Survivors

Among the studies reviewed, most of them resulted in a prevalence rate of chronic pain of around 50% three months after critical care [24, 26, 28, 29, 32-35]. Boyle *et al.* reported that 28% of the patients experienced chronic pain after urgent care, with consequent significant reductions in physical function and general health [25]. Baumbach *et al.* [23] studied the prevalence, severity, and interference of chronic ICU-related pain (CIRP) and found that its prevalence was 33.2%. Griffiths *et al.* conducted a multicenter study of critically ill patients six and twelve months after discharge from the ICU [30]. Moderate or severe pain was reported from 73% and 70% of patients after six and twelve months, respectively, compared with 51% before admission. Mobility problems were reported by 58% and 54% at 6 and 12 months, respectively, compared with 32% before access. Hayhurst *et al.* [31] tried to assess pain intensity and interference in daily life three and twelve months after hospital discharge. A persistent pain symptom was reported from 77% three months after ICU discharge and 74% after twelve months. Moderate to severe pain was reported in 31% of patients three months after ICU discharge, which increased to 35% in twelve months. A recent study by Devine *et al.* concluded that there is a high risk of developing chronic pain for all ICU survivors [27]. Almost 66% of all respondents reported a "new" chronic pain no exist before ICU admission. A recent descriptive secondary analysis of a randomized controlled trial (RCT) studied the pain intensity, interference, and location at three, six, and twelve months after ICU discharge. Four days after ICU discharge, 68% of patients reported pain median, with 79% reporting moderate to severe pain [36].

Cardiac surgery patients are a frequent group of patients hospitalized in the ICU. Therefore, some studies have been conducted on this specific patient group. Gélinas [13] is based on a previous survey of Puntillo [38] that aimed to assess the pain of cardiac surgery ICU patients. In this study, 77.4% of the patients reported pain, while in Puntillo's study, 63% rated the intensity of the pain as moderate to severe [13]. A multicenter observational study of cardiac ICU patients showed an incidence of chronic pain of 40.1% at three months, which decreased to 9.5% after two years [37].

3.2 Location

The location of chronic pain in critical care survivors is presented also in Figure 2. The shoulder was constantly one of the main sites that were measured (22%) (at least six months after ICU discharge) [23, 36]. Devine *et al.* [27] reported the shoulder (39%) as the second site of pain at baseline assessment and Langerud *et al.* [39] as the first site after three months and second, after twelve months from ICU discharge. Other reported sites of pain included the lower lumbar back/trunk/lumbar spine (28% [36], 32% [27], and 9% [24]), abdomen (43% [36], 29% [39], and 4% [24]), and lower limbs (42% [27] and 9% [24]). Langerud *et al.*, also, found that ankle/foot pain occurred in 58.8% of cases as the first site of pain twelve months after discharge. [39]. Thorax was reported as the primary site of pain in cardiac surgery patients with a sternal incision [13, 37].

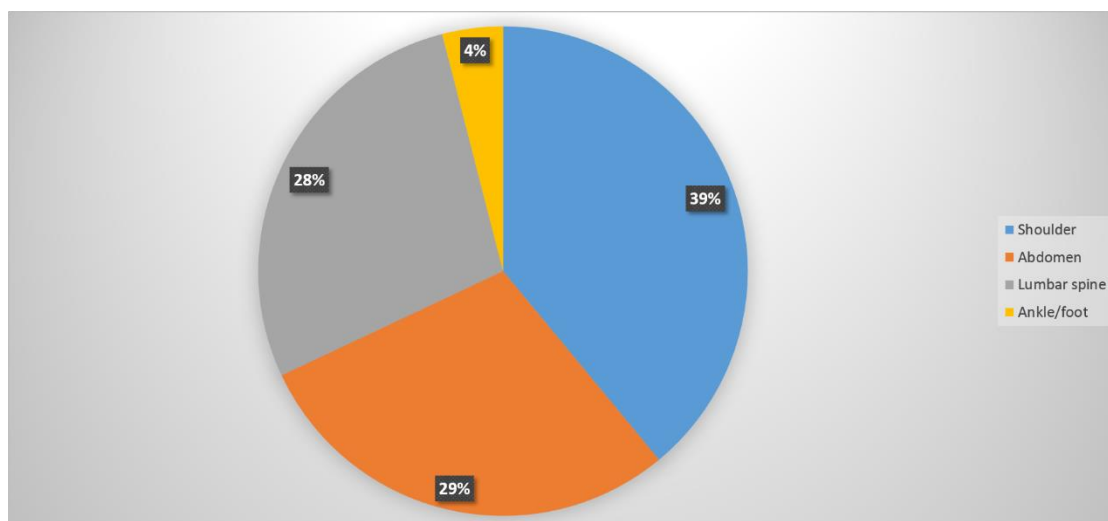


Figure 2 The location of chronic pain after 3-month discharge.

3.3 Assessment Tools

The main tools used in review studies to assess pain after ICU were EQ-5D [28-30, 32, 35] and BPI [24, 27, 31, 36, 39]. The EQ-5D is a validated questionnaire of HRQOL in adults developed by the EuroQol Group [40], widely used, and validated in a broad population [14, 41].

3.4 Potential Risk Factors Associated with Chronic Pain After Critical Care

Gélinas (2007) reported that 65.6% of ICU patients recalled being ventilated and described behaviors related to the presence of the tube and mechanical ventilation that should be considered for pain assessment [13]. Prolonged ventilator time was associated with pain after ICU discharge in two studies. Langerud *et al.* define ventilator days >75th percentile (twelve days) as a risk factor [39], while Boyle *et al.* showed a model that every additional ten hours on a ventilator can lead to an increased risk of chronic pain by 10% [25]. The same model showed that each other ten days in hospital LOS led to the same burden [25]. Langerud *et al.* reached the same finding and reported that ICU LOS of more than fifteen days is a potential risk factor, even one year after ICU discharge [33]. On the other hand, Valsø *et al.* came to a surprisingly different finding that shorter ICU LOS led to worse pain intensity [36]. A similar result was reported by Choinière *et al.* regarding longer post-ICU LOS reducing the odds of moderate to severe persistent pain [37]. Prolonged hospital LOS with possible ICU readmission has also been suggested as a risk factor by two other studies [25, 28]. Two other risk factors that have been reported were gender (mainly female) [30, 36, 38] and age (significantly younger) [29, 35-37]. In contrast, ICU opioid exposure showed no association with pain intensity at three or twelve months [31].

3.5 Rehabilitation Interventions for Chronic Pain After Critical Care

According to the bibliography, no original research was conducted to reduce chronic pain after discharge from the ICU. Ideally, chronic pain rehabilitation after ICU treatment begins with pain assessment and rehabilitation interventions within the ICU. Targeted nursing interventions during

acute admission could decrease potential risk factors, such as sharp pain, sepsis, length of stay, duration of mechanical ventilation, etc. [42].

4. Discussion

In the present review, the prevalence of chronic pain was 33-77%. Previous studies of chronic pain after ICU admission have estimated its majority in the year after discharge, with an extensive range from 14% to 77% [42] or 33% to 73% [43]. The significant deviation in the prevalence of chronic pain after ICU discharge is due to substantial differences in the study populations, the time of regular pain assessment, the tools used, and the participation rate.

Regarding the location of pain after critical care, patients report at least three different painful areas, mainly on the shoulder, the abdomen, the lower limb, the lumbar and cervical spine, the ankle joint, and the knee [33, 42]. There is a specific term for "Painful shoulder", as it is widespread due to central venous catheters in the area, prolonged bed rest, position changes and manipulations, and generalized muscle weakness. Also, the shoulder joint's stability and mobility are ensured mainly by the muscles and ligaments surrounding it and less by the bony solid structures [29].

Concerning the assessment tools, chronic pain after critical care has been associated with impaired HRQOL [44], constituting one of the five dimensions of the EQ-5D. The other four are mobility, self-care, ability to undertake usual activities, and anxiety/depression [41]. The Brief Pain Inventory (BPI) is a self-reported pain assessment tool widely used in research and clinical; consisting of twelve items and assessing two main factors: (i) the severity of pain and (ii) its impact on daily life. The first factor queries current symptoms, average symptoms, and pain intensity. In contrast, the second represents how pain relates to standard dimensions of feeling and function, such as general activity, mood, mobility, work, relationships, sleep, and enjoyment of life [45].

The severity of the illness seems to be the leading risk factor that may contribute to the development of chronic pain. This covers the first diagnosis on ICU admission, surgical classifications, APACHE II score, possible organ failure, severe sepsis, multiple trauma, etc. [24, 28, 29, 32, 34, 35, 39] From this perspective, there is a distinction between, for example, a scheduled surgery and an unscheduled surgery caused by a severe accidental injury. Even transition from the ICU to the surgical ward has been described as the most painful experience in 90% of patients (score ≥ 7 on a 0 to 10 scale) [46]. The prolonged use of endotracheal tubes and mechanical ventilation can lead to complications such as ventilator-associated pneumonia, tracheal stenosis, and ventilator-induced lung injury. These complications may necessitate further procedures, which can contribute to chronic pain in the long term [47]. Moreover, prolonged hospitalization exposes patients to a range of medical procedures and interventions, increasing the risk of complications and, subsequently, chronic pain. The psychological and emotional stress of extended ICU LOS can also contribute to the development of persistent pain [48]. In some cases, shorter ICU LOS could lead to worse pain intensity [36, 37], when the patients discharged from the ICU earlier may have received inadequate analgesia increasing the risk of experiencing more persistent postoperative pain at home [37]. Studies have shown that females may be more susceptible to chronic pain than males [49]. In critical care, female patients may experience pain differently or have distinct physiological responses to pain, which can influence their likelihood of developing chronic pain [44]. Age is another significant factor that plays a role in the development of chronic pain in critically ill patients. While older patients may have preexisting conditions that increase their vulnerability to chronic pain, younger

patients may be affected differently. Younger patients may have a longer life expectancy and, consequently, more years to manage pain if it becomes chronic [50].

Despite the lack of studies on pain rehabilitation interventions after critical care, there are opportunities to incorporate pain rehabilitation strategies in different environments, in the ICU, on the hospital ward, and at home, post-hospital discharge. According to “Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in ICU” (PAD guidelines), analgesics should be administered regularly in the presence of significant pain (i.e., BPS >5 or CPOT >3 [51]) and prior to painful interventional procedures. In addition to the administration of analgesics, which are the obvious choice for pain management, there is a list of rehabilitation interventions for chronic pain after critical care “at the bottom of the iceberg” (Figure 3).

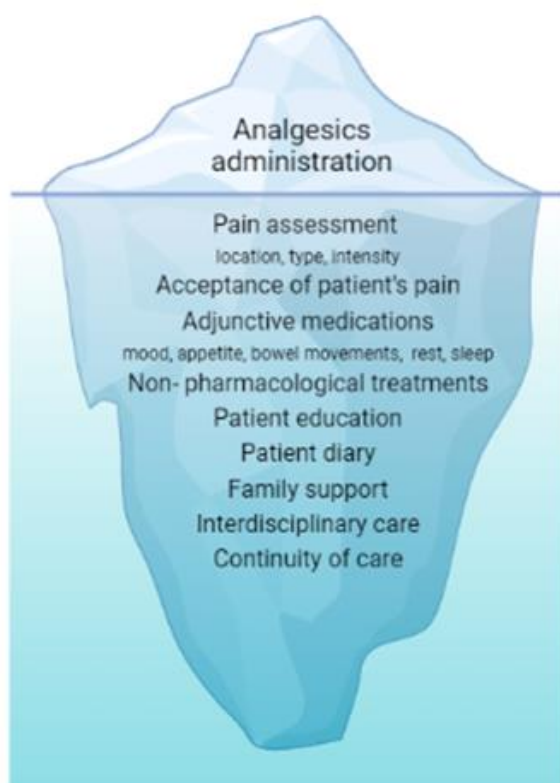


Figure 3 Rehabilitation interventions for chronic pain after critical care.

The effectiveness of chronic pain rehabilitation after critical care is determined by assessing pain and the personalized and flexible pain management plan from the acute stage of critical illness. In the acute phase of the disease, it is required multifactorial analgesia during and administration not only of analgesic drugs (Paracetamol, NSAIDs, opioids, and regional analgesia techniques) but also adjunctive drug administration, such as gabapentinoids, serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants [19, 52]. The most common intravenous analgesics in critically ill patients are opioids, e.g., morphine and fentanyl. To ensure optimal analgesia and reduce opioid use with its consequent side effects, it is useful to combine opioids with adjuvant medications. Alongside, non-pharmacological treatments like music therapy, psychological interventions, ensuring sleep, virtual reality techniques, acupuncture and TENS techniques are deemed necessary for optimal pain and cognitive and psychosocial rehabilitation [53]. Last but not

least, early mobilization and physical therapy have been associated with better survival and faster and better pain recovery [54, 55].

Utmost importance is also administering medications to improve mood, appetite, bowel movements, and the ability to rest, sleep, and titrate doses based on pain assessment, comfort/function goal, response to the current dose, and ability for daily activities. A holistic approach to chronic pain also includes patient education on pain management [56], including treatments, medication administration, side effects recognitions and discussions about the patient's concerns. Moreover, it is essential for healthcare providers to consider gender-specific factors when assessing and managing pain in the ICU. Finally, the interdisciplinary cooperation and communication among healthcare professionals will contribute to the continuity of care and the optimal rehabilitation of the patient at all levels [57].

The primary concern before any patient rehabilitation intervention is addressing pain. As outlined by the ABCDEF bundle (A: Assess, Prevent, and Manage Pain, B: Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT), C: Choice of analgesia and sedation, D: Delirium - Assess, Prevent, and Manage, E: Early mobility and Exercise, and F: Family engagement and empowerment [58-60], initial steps involve pain assessment using reliable behavioral pain scales like the BPS and CPOT [61, 62]. The bundle's remaining interventions are directly or indirectly linked to managing pain in critically ill patients. SAT and SBT have proven effective in reducing sedative use, delirium cases, mechanical ventilation duration, and ICU and hospital stays [54]. So far, early mobility is the only intervention to reduce delirium duration [55]. Regarding the last step of the bundle, physical therapy is safe, applicable, and effective for critically ill patients, even with mechanical respiratory support and renal replacement therapy [63]. A NICE guideline has recently been developed with recommendations for assessing and managing chronic pain (primary and secondary) in over 16s [41]. It includes, among others, patient-centered assessment, thinking about possible causes for the pain, social effects of chronic pain, and supporting and caring nursing plan. Moreover, chronic pain management, of NICE guidelines, consists of non-pharmacological interventions, such as physical activity, psychological therapy, acupuncture and electrotherapy, and pharmacological interventions.

A post-ICU rehabilitation service operates with a multidisciplinary team of healthcare professionals, including physicians, physical and occupational therapists, nurses, social workers, and psychologists. This team collaborates to assess and develop individualized rehabilitation plans for ICU survivors. The service requires dedicated facilities equipped with rehabilitation equipment and technology, ensuring patients receive comprehensive care. Staffing models prioritize patient-centered care, aiming to enhance functional independence, mental health, and overall quality of life. The primary outcomes include improved patient mobility and independence, reduced complications and readmissions, enhanced mental well-being, high patient satisfaction, and cost-effective care. Regular data analysis drives ongoing program improvement, making the post-ICU rehabilitation service an integral component in the continuum of critical care, aiding patients in their journey toward recovery and reintegration into the community.

5. Limitations of the Study

This study is not without limitations. The upper age limit was not included in the inclusion criteria and studies with patients over 65 years were included. It has been noticed that critically ill older

patients experienced no increased pain, anxiety or agitation twelve months after an ICU stay. In addition, HR-QOL in ICU survivors decreased, despite the improvement over one to six months. This decrease affected young people (<65) more than older people [25]. The difference in HR-QOL of older to young survivors resulted from the older people's different life expectations and perceptions which led to a more positive view of the situation [64]. This is a literature review and does not meet the criteria for a systematic review. Nevertheless, the current study confirms previous studies on chronic pain in critically ill patients after critical care. More systematic reviews with meta-analysis, randomized controlled trials and qualitative studies are needed on pain rehabilitation of patients after ICU discharge.

6. Conclusions

So far, healthcare professionals have targeted either pain treatment, finding an analgesic medication or the right position/exercise, or pain management, helping the patient manage life despite the unrelieved pain. The conventional pain treatment or management has been replaced by pain rehabilitation, in which a biopsychosocial approach enables healthcare professionals to provide patients with the knowledge and skills to manage their pain and disability through personal multidimensional choices. A complete understanding of the pathophysiological mechanisms of pain in the ICU and the improvement of risk factors could lead to interventions that can be absorbed and applied to rehabilitation programs. The key part of pain rehabilitation is the timely and accurate assessment of pain, especially in cases where communication with the patient is not possible. Early rehabilitation programmes, quick mobilization and greater family participation should be encouraged.

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Author Contributions

Authors' contribution in this work: Conceptualization, Evanthia Asimakopoulou; Funding acquisition, Evanthia Asimakopoulou; Methodology, Evanthia Asimakopoulou and Periklis Zavrdis; Data curation, Periklis Zavrdis; Data analysis, Evanthia Asimakopoulou and Periklis Zavrdis; Writing – original draft, Evanthia Asimakopoulou; Writing – review & editing, Evanthia Asimakopoulou and Periklis Zavrdis.

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Competing Interests

The authors have declared that no competing interests exist.

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