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Review Article

PAIN

Persistent pain in intensive care survivors: a systematic review

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Abstract

Background: According to earlier studies where the main aim has been quality of life, there is growing evidence of increased levels of persistent pain in survivors of critical illness. The cause of admission and several factors during intensive care may have associated risk factors for pain persistence. This systematic review aims to determine the incidence or prevalence of persistent pain after critical illness and to identify risk factors for it.
Methods: Six databases were searched, and eventually nine studies were included in the final systematic process. The validity of observational and cross-sectional studies was analysed using the National Institute of Health 'Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies'.
Results: The incidence of persistent pain after intensive care varied from 28% to 77%. Risk factors for persistent pain were acute pain at discharge from ICU, higher thoracic trauma score, surgery, pre-existing pain, organ failure, longer length of ventilator or hospital stay, and sepsis. No difference in incidence between medical and surgical patients was found.
Conclusions: New systematic, observational studies are warranted to identify persistent pain-related factors in intensive care to improve pain management protocols and thereby diminish the risk of persistent pain after ICU stay.

Keywords: chronic pain; critical care; incidence; intensive care; persistent pain; prevalence; risk factor

Editor's key points

- Six databases were searched, and nine studies were included in this systematic review of persistent pain after intensive care.
- The incidence of persistent pain after intensive care varied from 28% to 77%.
- There were multiple risk factors; further studies are warranted to identify the factors that may be modifiable in order to reduce the risk of persistent pain.

Persistent pain is a significant burden that affects approximately 20% of the adult population in Europe.[1] The definition of persistent pain varies, but pain can be considered persistent when it is prolonged for more than 3 months from onset, or if it continues for longer than the normal period of healing, and thus ceases to have a protective function.[2,3]

A recent review of health-related quality of life (HR-QoL) studies with longer follow-up time (>1 yr) after ICU discharge reported a varying prevalence of chronic pain in ICU survivors (14–77%).[4] The majority of the studies did not collect pain-specific outcome data, but pain was reported as a commonly problematic HR-QoL domain with tools, such as the EuroQoL-5D (EQ-5D) and the 36-Item Short Form Health Survey (SF-36). The greatest health improvements were found during the first

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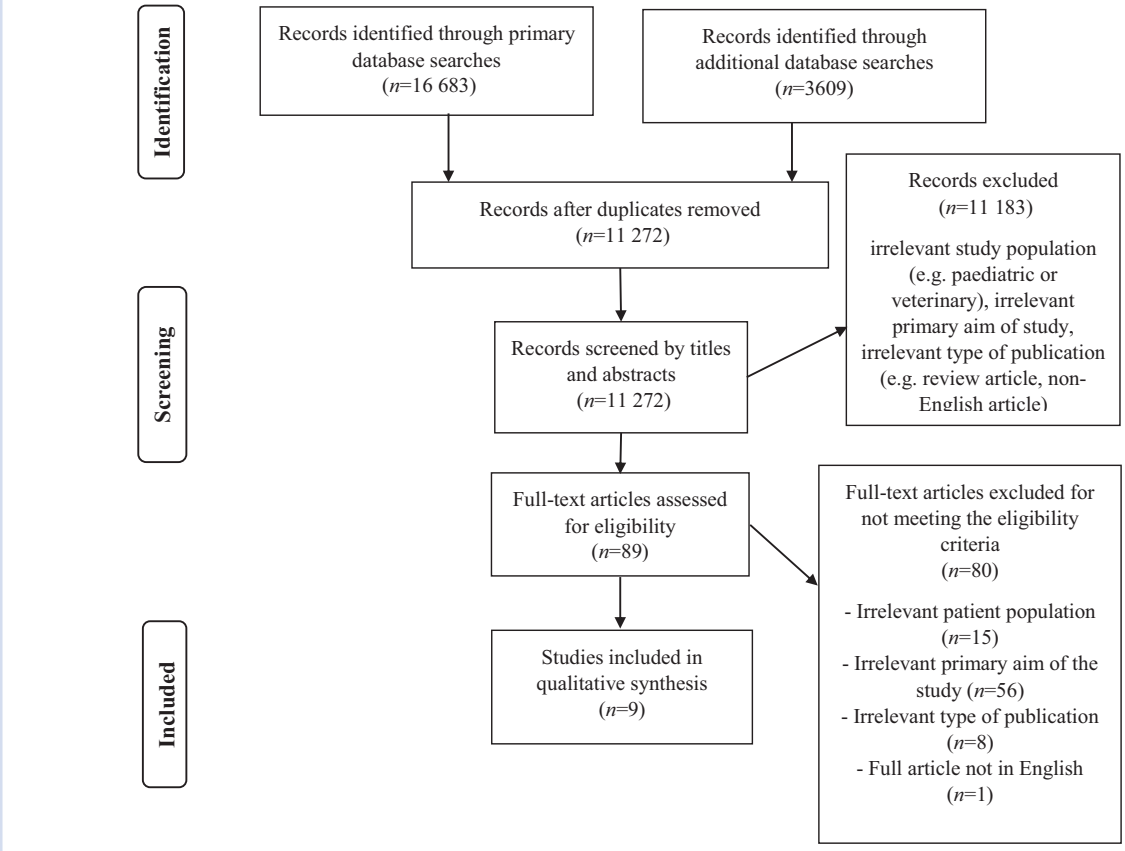

Fig 1. Flowchart of the article selection process.

year after discharge, with little further improvement in pain and all other health domains for all sub-groups.[5]

Critically ill patients might be particularly exposed to the long-term complications of acute pain because risk factors for pain chronification involve pre-existing persistent pain, the intensity of acute pain, and psychosocial vulnerability and factors related to the type of surgery or trauma.[6–8] Several factors might cause acute pain during intensive care, such as factors related to patient injury or illness, and therapeutic or diagnostic procedures.[9] Most studies of persistent pain focus on surgical patients, and its incidence after major surgery ranges from 20% to 50%.[7,10] However, there is some evidence that the incidence and intensity of acute[11] and persistent[12] pain is equal in both medical and surgical ICU patients. Underlying chronic illnesses and other medical conditions may also contribute to the pathogenesis of persistent pain. A limited number of studies have been conducted with persistent pain after critical illness and intensive care as the primary aim. However, only a few studies have used pain-specific tools in chronic pain research in ICU survivor populations. Because the management of critically ill patients and patient selection have improved, more patients survive intensive care, and thus the number of ICU survivors with persistent pain has increased along with the societal impact of ICU survivors.[1,13,14] According to a recent review by Kemp and colleagues,[4] persistent pain in ICU survivors may have an impact on the physical, mental, and cognitive impairments often seen after intensive care. As ICU survivors experience significantly persistent pain, the aim of this study was to systemically review the current knowledge on the incidence or prevalence of persistent pain after ICU discharge and to determine the underlying reasons for persistent pain and to summarise the methods used for pain evaluation.

Methods

The review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] The inclusion criteria were specified in advance, and the protocol for the study was published on June 17, 2016 in the International Prospective Register of Systematic Reviews (PROSPERO)[16] (registration no. CRD42016041489).

Search strategy and eligibility criteria

We searched the Medline (PubMed and Ovid), Cochrane, Cinahl, Scopus, Web of Science, and PsychINFO databases for eligible studies. The full search strategy is reported in Appendix 1. The database searches were performed on May 5, 2016, on March 10, 2018, and on July 30, 2019. The first search did not have a time limit, and the subsequent searches covered literature from the previous search date to the actual search date. All references retrieved from the databases were

Table 1 Summary of articles. †Quality of the studies was assessed with Quality Assessment Tool for Observational Cohort and Cross-Sectional studies.

Article	Year of publication	Study design	Study population (n)	Follow-up (months)	Pain questionnaire used	Response rate (%)	Quality of the study†
Archer and colleagues[18]	2012	Cross-sectional study	108	24	BPI	78	Fair
Battle and colleagues[19]	2013	Cross-sectional study	323	6	BPI	61	Fair
Baumbach and colleagues[20]	2017	Prospective observational study	84 patients, 44 controls	6	N/A	8	Fair
Baumbach and colleagues[21]	2016	Prospective observational study	207 patients, 46 controls	6	German pain questionnaire	20	Fair
Boyle and colleagues[22]	2004	Prospective observational study	99	6	PSEQ	53	Poor
Jeitziner and colleagues[23]	2015	Prospective longitudinal study	145 patients, 146 controls	12	NRS	89 at 6 months 85 at 12 months	Fair
Langerud and colleagues[12]	2017	Longitudinal explorative study	193	12	BPI	61 at 3 months 46 at 12 months	Fair
Hayhurst and colleagues[24]	2018	Prospective observational study	295	12	BPI	31 at 3 months 51 at 12 months	Fair
Carrie and colleagues[25]	2019	Prospective observational study	65	12	BPI	71 at 3 months 70 at 12 months	Good

exported to RefWorks® (ProQuest LLC.9, Ann Arbor, Michigan, United States).

RCTs and observational studies with the primary aim of determining the incidence or risk factors of persistent pain in intensive care survivors were considered eligible. Persistent pain was defined as pain lasting for at least 3 months after intensive care. We included only those studies consisting of patients older than 18 yr. Language was not a restriction in the database searches.

Study selection

At first, duplicate articles were identified using Refworks's automatic tools for duplicate location. Refworks has tools for both exact and close matches. The findings were further checked manually to ensure the findings were exact duplicates and then removed. Then, the eligibility of the articles was reviewed independently by four authors. Titles and abstracts were screened independently of each other by authors OM, MLK, MP, and JL. In addition, MB participated in screening the abstracts. Full-text articles were examined by OM, MLK, MP, and MB. Disagreements were resolved by consensus. SK was consulted as a final judge when disagreements remained unresolved.

Data extraction

Three authors (OM, MLK, MB) extracted data from the included studies. In addition, we identified the following characteristics in each of the selected studies: study design, response rate, number of individuals evaluated/interviewed, age group, persistent pain definition, incidence or prevalence of pain, methods used to identify the pain, and risk factors for it.

Quality of individual studies

Risk of bias within the studies was evaluated using the Cochrane risk of bias tool of RCTs. The validity of observational and cross-sectional studies was analysed using the National Institute of Health (NIH) 'Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies'.[17]

Outcome

The main outcome measures of this study were the incidence or prevalence of persistent pain at least 3 months after ICU discharge. The secondary outcomes included risk factors for persistent pain, and pain location and intensity.

Results

A total of 16 683 records were identified through the initial database search. A second database search yielded 1589 articles and a final search an additional 2020 articles. Five articles were discussed with SK and omitted. A total of nine studies were included in the systematic review. The details of the selection process are summarised in Fig. 1, and the description of the included studies presented in Table 1.

Table 2 Patient characteristics.

Study	Most common admission diagnosis	Mean or median* APACHE II	Mean or median* age	Mean or median* ICU LOS	Mean or median* ventilator days
Archer and colleagues[18]	Trauma	n/a	43.1	9.3	3.4
Battle and colleagues[19]	Surgical	15	61	6.2	2.1
Baumbach and colleagues[21]	Cardiovascular	16.92	63.93	8.68	2.9
Baumbach and colleagues[20]	Cardiovascular	16*	64.00*	4.83*	0.7*
Boyle and colleagues[22]	Medical	17*	62*	10.0*	3.9*
Jeitziner and colleagues[23]	Cardiovascular	20.5	68.72	4.57	n/a
Langerud and colleagues[12]	Surgical	n/a	55.1	9.0*	6.0*
Hayhurst and colleagues[24]	n/a	24*	59*	4.7*	1.91*
Carrie and colleagues[25]	Trauma	n/a	54*	9*	n/a

* = median value, no asterisk = mean value. ICU LOS, intensive care unit length of stay; APACHE II, Acute Physiology, Age, Chronic Health Evaluation II; n/a, not applicable.

Characteristics of the studies

Of the nine included studies, two were cross-sectional,[18,19] six were prospective,[20–25] and one was a longitudinal, explorative[12] study. All the included studies were single-centre studies, but three[12,20,24] reported results from two separate ICUs in the same university hospital. The evaluation of the quality of the studies was performed according to the quality assessment tool for observational cohort and cross-sectional studies[17] and is presented in Appendix 2. The quality of the studies was mainly fair,[12,18–21,23,24] but good in one[25] and poor in one[22] of the studies. The patient populations were heterogenous comprising trauma,[18,25] medical,[22] cardiovascular,[20,21,23] and surgical[12,19] ICU patients. The follow-up periods for patients varied from 6 months[19–22] to 2 yr.[18] Patient characteristics are presented in Table 2.

In most studies, the data were obtained prospectively from patients by questionnaires at different time points after ICU discharge. The response rate varied between 8% and 89%. If there was a control group, it was either a group of patients without pain[12,19] or without a specific disease,[21] a healthy control not treated in the ICU,[20,23] or a population norm.[22]

Definitions

The definition of persistent pain varied across studies. In a study by Boyle and colleagues,[22] chronic pain was defined as pain experienced every day for at least half of the days of the 6 month period since hospital discharge. One study[12] used the definition provided by Chanques and Jaber,[26] in which chronic pain is defined as pain exceeding an average healing period of 3–6 months. The definition by Kyranou and Puntillo[27] was applied by one study,[19] in which 'Pain exceeding the average period of healing of 2 to 3 months and ceasing to serve any apparent protective function is defined as chronic pain'. In one study, chronic ICU-related pain (CIRP) was defined as clinically relevant pain 6 months after ICU discharge lasting for at least 3–6 months and when patients attributed this pain to ICU stay.[21] Carrie and colleagues[25] defined chronic pain as a persistent chest pain requiring regular use of analgesics. One study[18] regarded a score of >4 as significant, whereas two studies[23,24] regarded a score of ≥1 in Brief Pain Inventory (BPI) as significant. Baumbach and colleagues[20] defined chronic pain as pain with an average intensity of ≥1 in BPI in the past 4 weeks.

Pain evaluation

In five studies, the Brief Pain Inventory-Short Form (BPI-SF)[28] was used to measure the outcomes of pain intensity and pain interference with daily activity.[12,18,19,24,25] Carrie and colleagues[25] also interviewed the patients during a follow-up visit. Other studies used the German pain questionnaire,[21] the numeral rating scale (NRS),[23] and the Pain Scale and Self-Efficacy Questionnaire (PSEQ)[22] to assess the frequency, intensity, and location of pain.

Incidence or prevalence of persistent pain after ICU stay

Three[19,22,25] studies reported the incidence and four[12,18,21,24] the prevalence of chronic pain. The incidence or prevalence of persistent post-ICU pain varied between 28%[22] and 77%[24] at least 3 months after ICU discharge (Table 3). The prevalence of pain at 3 months was slightly higher than that reported at 6 months and mostly higher than at 12 months. In the study with the highest incidence of pain at 3 months (77%), the incidence was still high (74%) at 12 months.[24] In the study with the longest follow-up period, up to 2 yr,[18] 36% of patients reported moderate to severe pain intensity and interference with daily activity.

Risk factors for persistent pain

Seven studies reported on the risk factors for chronic pain.[12,18–23] Hayhurst and colleagues[24] tested only opioid exposure as a predicting factor for persistent pain, and they

Table 3 Results of the studies. †Percentage of patients on pain medication. ICU LOS, intensive care unit length of stay.

Study	Incidence or prevalence of pain (%)				Possible risk factors for persistent pain
	At 3 months	At 6 months	At 12 months	At 24 months	
Archer and colleagues[18]				36	Fear of movement, pain catastrophising
Battle and colleagues[19]		44			Increasing age, severe sepsis
Baumbach and colleagues[21]		33.2			Pain during or before ICU stay
Baumbach and colleagues[20]		n/a			Small fibre deficits
Boyle and colleagues[22]		28			Longer hospital and ICU LOS, longer ventilator hours
Jeitziner and colleagues[23,†]		22	15		Pain during or before ICU stay, agitation after ICU stay
Langerud and colleagues[12]	49.2		38.2		Severity of illness, organ failure, ventilator time >12 days, ICU LOS >15 days
Hayhurst and colleagues[24]	77		74		n/a
Carrie and colleagues[25]	62		30		n/a

found no association between opioid consumption and pain intensity or interference.

In the study conducted by Battle and colleagues,[19] a primary admission diagnosis of surgery was found to be a risk factor in univariate but not in multivariate analysis. Similar results were reported in two other studies in which surgery during ICU stay was a significant risk factor for pain at 1 week[23] after ICU stay but not at the later time points.[12,23] Two studies reported that pain before or during ICU stay predicts persistent ICU-associated pain.[21,23] Jeitziner and colleagues[23] observed that presence of agitation after ICU stay predicted persistent pain 6 months after ICU discharge. In the study reported by Battle and colleagues,[19] severe sepsis and increasing patient age were associated with persistent pain after ICU discharge. Increased risk for persistent pain was observed in patients with increased severity of illness, organ failure, ventilator time of more than 12 days, or length of stay (LOS) in intensive care of more than 15 days.[12] Similar results were reported by Boyle and colleagues,[22] who noted that patients with persistent pain had longer hospital and ICU LOS and were ventilated longer than those without persistent pain.

Archer and colleagues[18] investigated the association between fear of movement and post-ICU pain 2 yr after high-energy trauma and found that those accounted for an additional 29% and 34% of the variance in pain intensity and interference. In another study, the somatosensory functions between the survivors of critical illness 6 months after ICU discharge and controls were compared. In *post-hoc* analyses, patients with small fibre deficit (SFD) reported significantly higher average pain intensity and pain-related disability scores compared with patients without SFD (2.5 *vs* 1.6).[22]

Location and intensity of pain

The most common sites of chronic pain were the shoulder,[12,19] abdomen,[12] and ankle/foot.[12] Shoulder pain was reported in 22% of patients at least 6 months after ICU discharge.[19] The number of patients reporting shoulder pain increased from 29% at 3 months to 56% at 1 yr and the use of analgesics also increased from 25% to 33%, respectively.[12] Interestingly, the most common sites of pain were not linked to the admission diagnosis.[12] In the blunt chest trauma population, most of the patients described their persistent pain as costal (37%), only 2% identified pleural pain, one out of 65 patients had both pleural and costal pain, and 22% had a neuropathic component in their pain.[25]

Most studies reported mainly mild to moderate levels of pain (NRS = 1.7–3.7).[12,18,20,21,23–25] However, in the study by Boyle and colleagues,[22] 92% of patients suffering from persistent pain reported pain that was moderate to very severe. Among blunt chest trauma patients, 23% had at least a moderate level of pain and 29% were still on strong opioids at 3 months follow-up. In the cohort of Hayhurst and colleagues,[24] moderate to severe pain was found in 31% and 35% of mixed intensive care patients at 3 and 12 months, respectively.[24] Two of nine studies found that pain intensity persists at 6 months and at 1 yr.[12,22] In older ICU survivors, bodily pain HR-QoL dimension scores 6 months after discharge were even better compared with the age-matched healthy control population.[23]

Discussion

To the best of our knowledge, this is the first systematic review to examine persistent pain after ICU discharge with a focus on the methods used for pain determination. A large-scale search of several databases revealed only nine eligible studies focusing on the incidence and risk factors associated with persistent pain after ICU stay. The highest incidence of persistent pain (77%) was observed at 3 months after intensive care, but even after 2 yr it was still 36%. This review revealed several patient, admission, or ICU-related risk factors for persistent pain, such as pre-existing pain, organ failure, longer length of mechanical ventilation or hospital stay, and sepsis. The study settings, patient populations, definitions of persistent pain, and response rates were very heterogeneous between the included studies. Only one study[24] addressed the

question of the relation between opioids used during ICU stay and the incidence or severity of persistent pain.

The incidence or prevalence of persistent pain after critical illness and intensive care was measured at different time points from 3 months to 2 yr, and a large variation, ranging from 28%[22] to 77%,[12] was found. Only two studies[12,24] included 12 month data to their analysis. At 12 months, incidence of pain ranged from 30%[25] to 74%,[24] although Hayhurst and colleagues[24] studied pain intensity and interference up to 2 yr after intensive care.

Our review with mixed intensive care survivors found the incidence of persistent pain in critically ill patients to be higher compared with the general population. The results are in agreement with the findings of an earlier study in a post-surgical population.[7] Population-based surveys in Europe[1,13,29] have estimated that 25–30% of adults experience persistent pain, and 19% of them reported moderate to severe intensity. In a recent systematic review, health before critical illness recalled by intensive care survivors was worse than population norms.[5] Thus, the patient population may have an impact on the results, but it is more likely that the definition of persistent pain and the methods used for data collection and pain evaluation lie at the root of the issue. In addition, most of the pain that people would consider persistent have pathology that rarely heals (e.g. rheumatoid arthritis) or it occurs in the absence of known pathology (e.g. fibromyalgia), and consequently normal healing time cannot be determined.[30]

Pain intensity is an important part of the clinical presentation of persistent pain.[31] The sensory intensity of pain is most commonly assessed with NRS because of ease of administration and scoring. The studies we reviewed, however, used BPI, and the average intensity of pain was mild to moderate[12,18,20–22] and tended to be the same at follow-up.[12,22] However, even mild albeit persistent pain may cause not only functional but probably also mental impairments[24] increasing the burden on society in terms of subsequent health care costs and pressure on social support systems.[4]

Patients with SFD had significantly higher average pain intensity, but none of the clinical parameters, such as sepsis or surgery, were associated with SFD.[20] Psychological factors, such as anxiety, and depression, may also play a significant role in both acute and chronic pain, and in the transition from acute to chronic pain as has been reported in more common chronic pain populations, such as lower back pain and post-surgical patients.[32,33] In these persistent pain populations, promising results have been achieved with cognitive behavioural training on pain perception and quality of life.[34] However, in the studies included in our review, no such finding was found except in one study,[23] where the presence of agitation after ICU stay was a risk factor for persistent pain. In trauma populations, the fear of movement and pain catastrophising accounted for more overall variance in pain intensity and interference than depressive symptoms.[18] Boyle and colleagues[22] reported a profound reduction in HR-QoL after ICU discharge, especially for the mental health domain.[22] According to Larsson and colleagues,[35] physical comorbidities, such as degenerative diseases, were more important than psychological comorbidities (e.g. depressive symptoms in predicting chronic pain). However, they also found that pain intensity, spread, and sensitivity were stronger predictors of the future pain situation, such as pain intensity, than socio-demographics and co-morbidities.[35]

In a large telephone survey of chronic pain in Europe and Israel,[1] close to half of the patients had pain in the back and more than 40% had joint pain, most frequently knee pain. Langerud and colleagues[12] used body maps to recognise the sites of pain at 3 months and 1 yr after discharge from the ICU. In their study, the shoulder was one of the most common sites of pain identified, a finding also reported by Battle and colleagues.[19] Invasive equipment located in this area, mobilisation methods during intensive care and intensive care-acquired weakness might be associated with shoulder pain.[12,19,36] However, the shoulder is also a common (46%) location of persistent pain in the general population.[37]

According to earlier surveys of chronic pain, the most common causes of pain are degenerative diseases, and trauma or surgery.[1,14] In this review, results concerning surgery as a risk factor for persistent pain after ICU care were conflicting or no difference was found in the incidence of persistent pain between medical and surgical patients.[12,23] There is still increasing evidence that bacterial, fungal, and viral pathogens can also directly activate nociceptors and elicit pain[38] and that there may be a close link between inflammation and acute, but also persistent pain.[39] Contrary to the findings of Battle and colleagues,[19] Baumbach and colleagues[21] found that sepsis per se seems to play a marginal role in the development of persistent ICU-related pain. In their study, however, in secondary analysis, C-reactive protein concentration was predictive for average pain ratings and interference scores.[21] The results of Boyle and colleagues[22] and Langerud and colleagues[12] also support the view that the severity of the critical illness has an impact on the development of persistent pain. In each of these studies, longer ventilator time and length of ICU stay were associated with persistent pain after intensive care. Emerging evidence suggests that pre-existing persistent pain increases postoperative pain intensity regardless of the type and extent of tissue trauma.[40] Accordingly, in the studies by Jeitziner and colleagues[23] and Baumbach and colleagues,[21] pain before ICU admission was associated with persistent pain after ICU stay. Thus, not all pain after ICU stay is related to the cause of the ICU stay, management of the disease or procedures undergone during the stay. Battle and colleagues[19] demonstrated that increasing age is a risk factor for persistent pain. However, in a study reported by Jeitziner and colleagues,[23] in which patients were older (mean age, 68 yr) and with higher Acute Physiology, Age, Chronic Health Evaluation (APACHE) scores (mean score, 20) than in other studies, critically ill older patients did not experience increased pain at 1 yr after an ICU stay. This finding is in accordance with the findings of a large general population survey,[1] in which pain was not found to be more common in older respondents than in younger respondents. Indeed, the 41–60 year age group appeared to be more likely to suffer from chronic pain than other age groups.[1] A recent study reported by Baumbach and colleagues[41] with critically ill patients demonstrated that lower age, female sex, increased inflammation (i.e. maximum CRP during ICU stay), pre-existing pain conditions, and increased levels of anxiety before ICU admission were predictive for chronic intensive care-related pain. The inflammatory state of intensive care patients may mitigate the effect of opioids and thus drive healthcare professionals to augment the opioid doses. This, in turn, exposes patients to the opioid-induced hyperalgesia, further adding to the pain problem of this patient population.[42] However, Hayhurst and colleagues[24]

did not find an association between opioid exposure during ICU stay and persistent pain. It is possible that the opioid doses used were not large enough to cause clinically significant hyperalgesia as there are studies that indicate that relatively high intraoperative opioid doses aggravate postoperative hyperalgesia and increase opioid requirements.[43]

The International Association for the Study of Pain (IASP) has defined chronic pain as an unpleasant sensory and emotional experience that lasts beyond the normal healing time for the tissue, that is pain lasting for 3 months or more 'in the absence of other criteria' (IASP 1986, updated 1994).[44] This definition leaves much to be desired in terms of clarity, and therefore after a peer review process, a group of pain experts defined chronic pain as 'persistent or recurrent pain lasting longer than 3 months'.[2] This definition also serves as the basis for the development of the ICD-11, in which chronic pain will be classified into seven clinically relevant groups.[45] In that categorisation, persistent post-ICU pain most closely falls into the group of chronic postsurgical or posttraumatic pain. Similar to our study, recent reviews[30,46,47] have found substantial heterogeneity in the characterisation of chronic pain, making comparison of prevalence estimates across existing studies of questionable value. The prevalence estimates may vary widely even in studies of the same population. They also found significantly lower persistent pain prevalence among interview studies compared with questionnaire studies and the effect seems to be larger for men than for women.[30] To evaluate the multiple dimensions of acute and persistent pain, several valid and reliable questionnaires are available. Each measure has its own strengths and weaknesses, and thus no one pain measure can be recommended for use in all situations. Because current pain may not accurately reflect a patient's overall pain experience, instruments such as the BPI scale provide important information regarding the patient's overall pain burden for a given period.[48] The BPI-SF is designed for use in patients with chronic diseases and conditions and those with post-surgical pain. The BPI-SF has well-established validity and reliability in patients with cancer, in whom it has exhibited sensitivity to change in longitudinal studies,[49] but also in people with chronic non-cancer pain.[50] This inventory can be both self-administered and administered over the telephone. The German pain questionnaire[51] and the NRS are unidimensional single-item scales for the assessment of average pain and interference with pain on an 11-point numeric rating scale (NRS; 0 = no pain to 10 = worst imaginable pain). The PSEQ determines a patient's functional disability and ability to cope with pain when performing normal activities. The PSEQ is a 10-item multiple-choice self-report measure (score range 0–60) of beliefs pertaining to self-efficacy, physical activity, and social function in the presence of pain.[52] It has been shown to be a significant predictor of success after therapy in heterogeneous pain populations.[53]

Validity of the studies

The validity assessment of individual studies is based on a checklist approved by the NIH.[17] The overall quality of studies was fair on a scale of good, fair, and poor as recommended by the assessment of quality tools provided by the NIH. Our goal was to include randomised controlled trials and observational studies in our analysis. However, our search did not reveal any randomised trials on the ICU population that focused on the chronification of pain after ICU stay. Only a few of the included studies presented data on pain before entering the ICU, and only one addressed the question of pain during ICU stay. Moreover, none of the studies acknowledge the well-known underlying psychosocial or economic factors in the prevalence of persistent pain. Even though these factors were not included in the tool used, the lack of them compromises the meaning of the value of these results.

Weaknesses and strengths of our review

We believe that our search strategy identified all relevant studies. A drawback of this systematic review is the low number of studies of interest despite the large number of publications identified. However, we did not change the inclusion criteria despite the low number of adequate studies. By including case series or opinions and letters, we could have obtained a broader view of the research question, but we do not believe this would have added to the validity of results and as such would not have improved our review. Furthermore, we decided not to include studies in which the main focus was on HR-QoL after intensive care despite the fact that pain is one domain in those studies and that pain is one of the domains that decreases quality of life after intensive care. One major concern in the HR-QoL studies is the lack of deeper analysis of the risk factors aimed at the domain of pain. Another confounding factor is that the studies used different definitions for the definition of persistent pain after ICU and applied separate methods to investigate both the incidence of pain and the risk factors. To assess the quality of observational studies, we used the quality assessment tool for observational cohort and cross-sectional studies provided by the NIH.

According to Oxman,[54] the expertise in the field of review of the authors may narrow the scope of the review. The authors of the present review present a heterogenous group; a medical student highly skilled in informatics (OM); three intensivists (MB, SK, JL), one of which also has palliative and pain medicine expertise (JL); and one general anaesthesiologist with a subspeciality in pain medicine (MLK). The authors come from three different university hospitals and have thus far had no common research projects.

The main aim of this systematic review was to define the incidence or prevalence of persistent pain after ICU stay. A secondary aim was to be able to identify risk factors for such pain. These aims together are relevant for both patients and care givers. It is therefore important to be able to identify those factors affecting the risk of pain chronification in order to be able to avoid these factors during ICU stay. It is also important for the patient to be aware of the risk of persistent pain because it may help the patients to cope with it. The findings of this review are of essential importance to the research community – we now know that we need uniform quality studies that address the persistence of pain after ICU stay, and randomised controlled analgesic studies that extend for longer than the initial ICU stay.

Conclusions

The findings from this study support the view that only a few studies have focused on persistent pain in critically ill patients after intensive care. The studies reviewed are heterogeneous and inconsistent in the definition of chronic pain but demonstrated that the incidence or prevalence of persistent pain is high for up to 2 yr after intensive care. Despite the conflicting results, it is obvious that the severity of critical illness has an impact on the development of persistent pain.

This confirms the need for further research to improve the ICU care and rehabilitation of intensive care survivors with an appropriate standardised assessment and management plan for chronic pain.

Authors' contributions

Study conception: all authors
Design of the article: all authors
Drafting of the article: OM, MB, JL, MLK
Critical revision of the text for important intellectual content: MB, MP, SK
All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Declarations of interest

MLK is head of the Acute Pain section at the Finnish Society of Anaesthesiology and a former editor-in-chief of the publication of the Finnish Association for the Study of Pain (Kipuviesti). The other authors declare that they have no conflicts of interest.

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Appendix 1. Search strategy: MEDLINE (Ovid) from 1946 to July 30, 2019.

1. critical care/ or intensive care units/ or burn units/ or coronary care units/ or respiratory care units/
2. (critical care or intensive care or icu* or intensive care unit* or burn unit* or coronary care unit* or respiratory care unit*).ti,ab,kw
3. 1 or 2
4. chronic pain/ or somatosensory disorders/ or hyperalgesia/ or hyperesthesia/ or hypesthesia/ or paresthesia/
5. (somatosensory disorder* or hyperalgesia* or hyperesthesia* or hypesthesia* or paresthesia* or allodynia*).ti,ab,kw
6. pain management/ or analgesia/
7. (pain management* or pain evaluation* or analgesia*).ti,ab,kw
8. (chronic adj3 pain*).ti,ab,kw
9. (persistent adj3 pain*).ti,ab,kw
10. (prolonged adj3 pain*).ti,ab,kw
11. (long term adj3 pain*).ti,ab,kw
12. (longterm adj3 pain*).ti,ab,kw
13. pain perception/ or nociception/
14. (pain perception* or nociception* or nociperception*) ti,ab,kw
15. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 3 and 15

Appendix 2. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Overall rating
Archer and colleagues[18]	Yes	Yes	Yes	Yes	Na	Yes	Yes	Yes	Yes	NA	Yes	NA	No	Yes	Fair
Battle and colleagues[19]	Yes	Yes	Yes	Yes	Na	Yes	Yes	Yes	Yes	NA	No	NA	NA	Yes	Fair
Baumbach and colleagues[21]	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA	NA	Yes	Fair
Baumbach and colleagues[20]	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	NA	Yes	NA	NA	Yes	Fair
Boyle and colleagues[22]	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	NA	No	NA	No	Yes	Poor
Carrie and colleagues[25]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	No	Yes	No	Good
Hayhurst and colleagues[24]	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	NA	Yes	NA	No	Yes	Fair
Jeitziner and colleagues[23]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	NA	No	NA	Yes	Yes	Fair
Langerud and colleagues[12]	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	NA	Yes	NA	No	Yes	Fair

Yes, criteria fulfilled; No, criteria not fulfilled; NA, criteria not applicable.

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured before the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g. categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

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