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REVIEW

The Role of Biomarkers in Acute Pain: A Narrative Review

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ABSTRACT

Acute pain, a critical aspect of patient care, presents a challenge due to its subjective nature and complex biological underpinnings. Biomarkers for acute pain promise a paradigm shift in how pain is perceived, diagnosed, and managed. The study of genetic, inflammatory, and neurotransmission markers associated with pain experience may hold the key for the development of personalized and effective pain management strategies. This narrative review explores the neurobiological pathways of acute pain, encompassing inflammatory responses and neurotransmission mechanisms. It synthesizes current research on the identification and clinical application of biomarkers, emphasizing their potential to enhance diagnostic precision, treatment effectiveness, and risk prediction. We underscore the promising role of acute pain biomarkers in identifying patients at risk for developing acute and potentially chronic pain, predicting patients' response to pharmacological interventions, and aiding in the development of novel therapeutic and pain preventive strategies. The evolving landscape of biomarker research not only deepens our understanding of pain mechanisms but also lays the foundation for more tailored and patient-specific healthcare interventions.

Keywords: Acute pain; Biomarkers; Inflammatory markers; Personalized pain management; Genetic; Pain

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Key Summary Points

Biomarkers offer a more objective pain assessment.

The understanding of neurobiological and inflammatory mechanisms of pain can aid in identifying pain biomarkers.

Acute pain biomarkers promise a paradigm shift in pain understanding, diagnosis, and management.

Acute pain biomarkers can be categorized as follows: genetic, inflammatory, neurotransmitter, opioid responsiveness, postoperative, and chronic pain predictor biomarkers.

Accurate pain assessment, personalized pain management, and early detection and prevention of chronic pain are the main goals of acute pain biomarkers in the clinical setting.

INTRODUCTION

Acute pain, a common and adaptive response to noxious stimuli, serves as a vital signal indicating potential harm to the body [1]. It is typically characterized by rapid onset and limited duration, and it is usually caused by trauma or tissue injury [2]. While acute pain is essential for survival, its complexity extends beyond the immediate nociceptive signals, encompassing intricate neurobiological processes [3].

The subjective nature and individual variations in pain perception pose challenges in accurate assessment, emphasizing the need for objective tools to understand and manage acute pain more effectively [4]. A biomarker is a measurable indicator of a biological state or condition, used to assess disease progression, response to treatment, or susceptibility. In the context of pain, biomarkers can help reveal underlying pain mechanisms, providing more accurate and individualized pain management strategies. Thus, the development of translational strategies such as well-validated biomarkers and precise clinical trial endpoints for pain is necessary to enhance pain management [5]. This review explores the emerging field of biomarkers, promising a deeper understanding of the genetic, inflammatory, and neurobiological patterns associated with pain experiences. Physicians would certainly benefit from this deeper understanding of underlying pain mechanisms, to provide optimal or at least better pain relief to each patient dealing with complex pain conditions [6]. The study of biomarkers presents an opportunity to unravel the intricacies of acute pain, paving the way for more personalized and effective pain management strategies. By examining the clinical implications and future directions, we seek to enhance our comprehension of acute pain and contribute to the ongoing discourse in pain research.

METHODS

According to SANRA criteria for the quality assessment of narrative reviews [7], we conducted a comprehensive literature review using PubMed and Google Scholar. The purpose of this study was to investigate the emerging field of biomarkers in acute pain, focusing on genetic, inflammatory, and neurobiological markers. An example of our search is as follows: (acute pain) AND ((biomarkers) OR (genetic markers) OR (inflammatory markers)). Other search keywords that we included to enhance our results included “neurotransmitters,” “opioid responsiveness,” and “chronic pain prediction.” Articles included in this review were selected based on their relevance to both clinical and basic medical research on acute pain biomarkers. Studies that were not published in English were excluded. This narrative review is based on previously conducted studies and does not include any new studies involving human participants or animals conducted by the authors. Hence, it does not require any approval by ethics committees.

THE NEED FOR BIOMARKERS IN ACUTE PAIN MANAGEMENT

The relationship between a patient’s self-report of pain and their concurrent regional brain activity is complex, as has been proved by several studies on acute pain. Many physiological and psychological (such as expectancy, anxiety, and mood) as well as environmental factors [8] profoundly alter the neural processing of nociceptive inputs, almost acting as central neural amplifiers or attenuators of the experience [9].

When assessing pain, the traditional "gold standard" of subjective assessment is the use of self-reported scales such as the numeric rating scale (NRS) and the visual analogue scale (VAS). However, the accuracy and utility of self-reporting can sometimes be limited or even not feasible [9]. Furthermore, assessors' predispositions can also have an impact on pain assessment [10], and the experience can be enhanced by positive expectancy or significantly reduced by negative expectation [11].

When communication between patient and assessor is limited or non-feasible (e.g., cognitive impairment, deep sedation, general anesthesia), physiological markers such as blood pressure, heart rate, and pupil diameter have also been used for the assessment of pain [8].

However, the use of specific biomarkers in clinical practice could lead to a more objective pain assessment and contribute to reduced fear and anxiety in patients experiencing pain [12].

Biomarkers are objective measures of biological or pathological processes or a pharmacological response to therapeutic intervention. A joint Food and Drug Administration (FDA) and National Institutes of Health (NIH) working group for developing biomarker endpoints and other tools identified seven distinct biomarker categories (namely, susceptibility/risk, diagnostic, monitoring, prognostic, predictive, safety biomarkers) that could be applied across all areas of biological research [13].

The pathophysiology of acute pain, involving neurobiological and inflammatory mechanisms, has laid a foundation for discovering possible diagnostic and therapeutic targets hidden in the acute pain pathway, as well as understanding and predicting the transition of acute pain into chronic pain, based on biological markers [14–16].

IDENTIFICATION OF ACUTE PAIN BIOMARKERS

In 1998, the National Institute of Health Biomarkers Definitions Working Group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [17]. The definition of biomarkers as objective and quantitative aspects of biological processes generates restrictions on their use, since the measurement of biological characteristics may not always reflect a patient's experience or sense of well-being [18], especially when it comes to such a multidimensional experience as pain.

On the other hand, pain is an invisible disability, and in order not to be missed or underestimated in clinical practice [19], the identification of biomarkers in the field of pain medicine is crucial. Biomarkers may also provide information about specific pathophysiological mechanisms that lead to pain, enabling specific decisions for each patient [19]. Additionally, these markers may provide new methods for detecting and quantifying pain, minimizing the need for self-reported pain scales, which can be impacted by psychological and cultural factors [19]. In this review, we discuss genetic, inflammatory, and neurotransmitter biomarkers, as well as biomarkers for opioid responsiveness and the prediction of postoperative and chronic pain (Fig. 1). Table 1 provides a detailed overview of these biomarker categories, their examples, and clinical relevance.

Genetic Biomarkers

While numerous gene mutations have been identified, there are few solid data on genetic biomarkers associated with the cause or inability to feel pain. For instance, mutations in the sodium channel Nav1.7 gene can cause loss or gain of its function, resulting in alterations in the sensitivity to pain such as loss of its perception [20], heightened pain sensitivity, and sudden burning pain [21]. The sodium voltage-gated channel alpha subunit 9 (SCN9A)

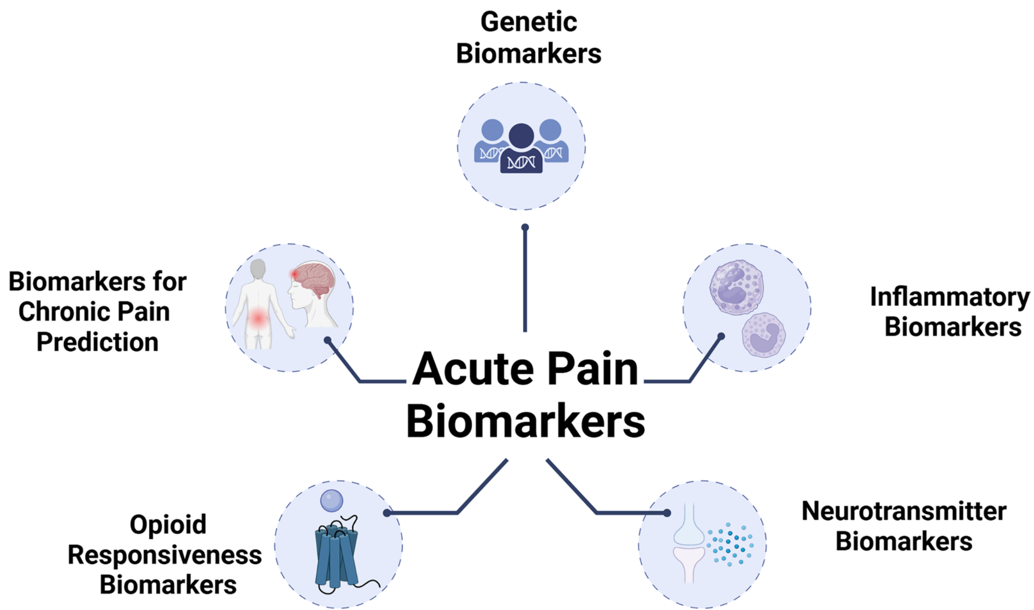

Fig. 1 An overview of acute pain biomarkers, highlighting five key domains: genetic, inflammatory, neurotransmitter, opioid responsiveness, and predictors of postoperative and chronic pain. (Created with BioRender.com)

gene, which also provides instructions for the making of Nav1.7 sodium channels, has been linked to acute postoperative pain, offering valuable insights for the use of SCN9A genotyping as a guide for postoperative pain control [22]. The discovery that familial pain conditions are caused by mutations in the sodium channel Nav1.7 led to advancements in the creation of sodium channel blockers that are specific for this receptor subtype [23].

Other channels' genes have also been studied as genetic markers for pain, with Piezo1/Piezo2 and transient receptor potential vanilloid 1 (TRPV1) being major examples [24]. TRPV1, also known as the molecular target of capsaicin [25], is a nonselective cation channel that detects noxious stimuli that induce pain, inflammation, hyperalgesia, and itch [26]. A gain-of-function mutation in the TRPV1 gene is associated with an impairment of pain and itch sensations in mice, providing a very promising genetic marker for targeting pain therapeutics. Adding to this, yet another human TRPV1 genetic variant (TRPV1^{K710N}) has recently been related to reduced susceptibility to painful chemical stimuli and nerve damage [27].

One mutation that can cause pain insensitivity involves the nerve growth factor beta (NGF) gene, which encodes nerve growth factor beta [28]. This gene mutation appears to differentiate the effects of NGF on the development of central nervous system (CNS) functions such as mental capacities, from those on peripheral pain pathways [28]. A more recently discovered mutation in the NGF sequence (NGF^{R100W}) reveals a dual role for NGF in peripheral nociception [29]. This mutation, while retaining trophic support, fails to engage pathways associated with nociception [29]. In experiments with rats, NGF^{R100W} induced chronic hyperalgesia but not acute hyperalgesia, highlighting the complex neuroplastic effects of NGF in peripheral nociception [29].

Genetic polymorphisms associated with acute pain have also been studied thoroughly in patients under radiotherapy (RT) for head and neck cancer [30]. This association encompasses variants in genes related to DNA damage/repair (e.g., XRCC1), variants in genes involved in inflammatory pathways and immune systems, including TNF-α and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ), and

Table 1 Overview of acute pain biomarkers: categories, examples, and clinical relevance

Biomarker type	Examples	Key features	Clinical relevance	References
Genetic biomarkers	SCN9A (Nav1.7), TRPV1, Piezo1/Piezo2, NGFR100W, XRCC1, TNF-α, NF-κβ	Genetic mutations and polymorphisms influence nociception (e.g., pain sensitivity, hyperalgesia, or analgesia)	Guide personalized interventions for postoperative pain (e.g., head and neck cancer) and novel therapeutic targets (e.g., sodium channel blockers)	[20–30]
Inflammatory biomarkers	TNF-α, IL-1β, IL-6, CRP, IL-2, IFNγ, IL-10, GM-CSF, G-CSF, M-CSF, NGF, BDNF	Cytokines, growth factors, and immune mediators regulate pain perception, resolution of inflammation, and nociceptor sensitization	Stratify acute pain prognosis (e.g., low back pain), identify subgroups for targeted therapy, and manage inflammatory pain mechanisms	[31–41]
Neurotransmitter biomarkers	Substance P, glutamate, GABA	Mediate nociceptive and sensory signaling; imbalance linked to heightened pain sensitivity or attenuation	Diagnostic markers for acute pain intensity; aid in targeting specific neurotransmitter pathways for intervention	[42–49]
Opioid responsiveness biomarkers	OPRM1 (A118G and rs67730 polymorphisms), endogenous opioids, endocannabinoids	Genetic polymorphisms and endogenous molecule levels affect opioid efficacy and individual responses to treatment	Predict patient responsiveness to opioids, minimizing adverse effects and guiding personalized prescriptions for acute and postoperative pain	[50–56]
Postoperative and chronic pain predictors	Omics-based biomarkers (proteomics, metabolomics), single-nucleotide polymorphisms (SNPs), functional MRI characteristics, A2CPS biosignatures, limbic brain functional and anatomical characteristics	Integrate biological and imaging markers to predict risk of chronic pain development from acute pain	Inform early intervention strategies, prevent pain chronification, and optimize multimodal postoperative care	[57–64]

A2CPS Acute to Chronic Pain Signatures, *BDNF* brain-derived neurotrophic factor, *CRP* C-reactive protein, *GABA* glutamate and gamma-aminobutyric acid, *G-CSF* granulocyte colony-stimulating factor, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *IFN-γ* interferon-gamma, *IL* interleukin, *M-CSF* macrophage colony-stimulating factor, *MRI* magnetic resonance imaging, *NF-κβ* nuclear factor kappa-light-chain-enhancer of activated B cells, *NGF* nerve growth factor, *OPRM1* opioid receptor μ 1, *SCN9A* sodium voltage-gated channel alpha subunit 9, *TNF-α* tumor necrosis factor, *TRPV1* transient receptor potential vanilloid 1 variants in genes regulating cellular processes that can influence pain sensitivity and response to treatment such as angiogenesis (e.g., EDN1), autophagy (e.g., ATG16L2, ATG10), and cell death (e.g., CCND1) [30].

The examination of genetic biomarkers can provide crucial insights into the multifaceted nature of pain perception. By analyzing and synthesizing this information, novel diagnostic and therapeutic targets can be unveiled.

Inflammatory Biomarkers

It is known that macrophages control the pathophysiology of pain by producing pro-inflammatory and pronociceptive mediators that induce pain via direct activation of nociceptors [31]. On the other hand, macrophages communicate bidirectionally with nociceptors that secrete neuropeptides that act on them [31]. The latest research indicates that macrophages also help to reduce inflammation and pain through phagocytic clearing of debris and generation of mediators that are pro-resolving and anti-inflammatory [32]. This interplay between macrophages and nociceptors may hide a new target for the control of inflammation and pain.

A wide variety of cytokines. including tumor necrosis factor (TNF), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interleukin-17A (IL-17A), interleukin-10 (IL-10), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), lipid mediators, and growth factors such as NGF or brain-derived neurotrophic factor (BDNF), have an influence on pain perception [33].

In the clinical realm, it has been demonstrated that individuals with acute, nonspecific low back pain (NSLBP) may have higher C-reactive protein (CRP) levels [34, 35]. This increase was linked to earlier recovery from back pain, offering a new potential prognostic marker for acute NSLBP [34]. Another study focusing on acute NSLBP also presented a marked increase in interleukin-2 (IL-2) levels and a significant reduction in interferon-gamma (IFNγ) levels compared to patients with chronic NSLBP, suggesting a distinct inflammatory profile [36]. In contrast, TNF-α production was higher in patients with chronic versus acute NSLBP [34, 36]. In a more recent systematic review that included both acute and chronic NSLBP studies, increased levels of proinflammatory biomarkers CRP, IL-6, and TNF-α, and decreased levels of the anti-inflammatory biomarker IL-10, were found to be indicative of an associated rise in systemic inflammation [37].

Also of interest is another study that compared serum inflammatory markers in patients with knee osteoarthritis and healthy pain-free control subjects using a clustering approach [38]. Differences were revealed on several markers, with caspase 8 (CASP-8), axin 1 (AXIN1), and IL-6 being the most significant ones. In addition, two distinct subgroups of patients with knee osteoarthritis were identified based on 23 protein biomarkers, displaying significant differences in pain scores and function. This suggested that deep phenotyping of inflammatory mediators may be associated with better treatment outcomes and lead to the development of stratified criteria for targeted therapy [38].

Various anti-inflammatory medicines are available in the market and can be incorporated into personalized therapy. These drugs include inhibitors of TNF-α (e.g., infliximab, adalimumab, and etanercept) or IL-6 (e.g., tocilizumab) [39]. Given the importance of several main cytokine candidates (such as TNF and GM-CSF) in defending immunological responses against infections, pain-targeting treatments must also take into account the negative effects of immunosuppression, particularly in chronic scenarios [33].

Adding to this, adaptation during the acute pain stage is conferred by active neutrophil-driven immune processes, and reduction of these inflammatory responses may facilitate the development of chronic pain in individuals with acute low back pain [40]. Consequently, despite the effectiveness of analgesia in the early stages of pain, managing acute inflammation may have adverse long-term results [40]. In mouse-based pain experiments, early steroid or nonsteroidal anti-inflammatory medication (NSAIDs) administration resulted in prolonged pain, even if it led to pain relief in the short term. Hence, early in the acute pain phase, NSAIDs and steroid therapies may warrant caution [40]. In our opinion, while these findings offer potential insights into inflammatory pain, it is essential to approach them with caution before translating them into clinical practice.

Further research on human biomarkers may help guide patient selection for anti-inflammatory treatments and improve long-term outcomes [49]. At present, the priority remains to treat acute pain as quickly and effectively as possible to reduce immediate suffering and prevent its escalation and chronification [41].

Neurotransmitter Biomarkers

Neurotransmitter biomarkers represent another interesting candidate for acute pain diagnostics and quantification. Substance P, found in both peripheral and central nerves, is released in response to noxious stimuli and has been studied as an acute pain plasma and salivary marker [12]. Animal studies have proposed that serum substance P might be a useful tool for pain assessment [42, 43]. Similarly in humans, significantly elevated substance P serum levels have been linked to acute postoperative pain [44], sickle cell disease pain [45], and dental pain conditions [46], underlining its role as a mediator of, or marker for, pain sensitization.

There is evidence suggesting that different pain conditions have distinct neurometabolic signatures [47]. Individuals suffering from migraine seem to have unique neurometabolic profiles, showing elevated glutamate and gamma-aminobutyric acid (GABA) levels in comparison to control subjects, which was not detected in individuals with other disorders [47].

It has been proven that an imbalance in excitatory and inhibitory neurotransmitters in some brain regions, such as the insula, leads to enhanced central pain processing and heightened pain sensitivity [48]. When comparing the posterior insula of patients with fibromyalgia to healthy controls, proton magnetic resonance spectroscopy indicates higher amounts of the excitatory neurotransmitter glutamate and lower quantities of the inhibitory neurotransmitter GABA [49]. On the contrary, in a rat-based neuropathic pain model, non-injured rats showed mechanical allodynia as a result of elevated intracellular glutamate and lowered GABA levels [48]. However, these promising neurochemical changes for the detection of pain have not been studied as thoroughly in acute pain as they have been in chronic or neuropathic pain models.

Biomarkers for Opioid Responsiveness

Previous research demonstrated that both genotype and phenotype status affect pain perception and opioid responsiveness [50–54]. One of the most widely studied genes in this sector is the opioid receptor µ 1 (OPRM1) gene. The OPRM1 A118G polymorphism reveals interindividual heterogeneity in postoperative opioid response, potentially suggesting the individual analgesic doses needed for pain control [50]. A meta-analysis found that A118G polymorphism carrier sensitivity to opioids was decreased, leading to increased opioid consumption and reduced nausea events, especially in acute postoperative pain management [51]. Another OPRM1 polymorphism (rs67730) has been linked to an increased likelihood of constipation in response to tramadol and a decrease in the risk of postoperative neuropathic pain development [53]. These results may lead physicians to the ultimate clinical objective of creating a precise prediction algorithm that can identify patients who will most likely benefit from opioids while also having minimal adverse effects and a low risk of drug abuse.

Opioid responsiveness also depends on the effect of endogenous molecules. A study examining the relationship between endogenous opioid function and morphine-induced analgesia found that circulating endocannabinoids may moderate this interplay [55]. In particular, endocannabinoids significantly mitigated the association between endogenous opioid function and morphine-induced pain relief. Lower endogenous opioid function predicted greater morphine analgesia only for those with lower endocannabinoids [55]. These findings may guide the development of mechanism-based predictors for personalized pain therapeutics depending on opioid responsiveness.

Early-life environmental factors also seem to play a role in the modification of nociception, inflammatory hypersensitivity, and morphine responses [54]. Fragmented maternal care leads to enhanced δ receptor expression which decreases acute nociception and precipitates morphine tolerance and vulnerability to persistent inflammatory hypersensitivity in mice [54]. Finally, epigenetic events, such as DNA methylation and non-coding RNA expression, play a crucial role in the persistence of pain after tissue injury; these mechanisms may also influence the expression of OPRM1, potentially affecting opioid responsiveness and pain sensitivity [56].

It is clear that opioid responsiveness is influenced by genetic, epigenetic, and environmental factors. Hence, a deeper study of these biomarkers could provide the potential for the development of a multifactorial targeting to optimize pain relief through opioids.

Biomarkers for Postoperative Pain and Chronic Pain Risk Prediction

Several kinds of signaling pathways are involved in distinct pathophysiological processes that lead from acute to chronic pain [57]. Both peripheral and central sensitization are caused by the duration and magnitude of the primary stimulus, which work together to intensify pain perception [57]. Thus, it is essential to reduce acute pain intensity and shorten its duration [58]. The diversity of biosignatures implicated in the transition of acute to chronic pain makes it easy to understand that the most effective way to address these intricate processes is through an early and multimodal treatment approach [59].

To better comprehend these passages, markers of pain need to be studied thoroughly and systematically. The Acute to Chronic Pain Signatures (A2CPS) program was started by the National Institutes of Health Common Fund for the purpose of producing a set of biomarkers, turning them into objective biosignatures, and finding new markers for the chronification of pain following acute injury, including surgery [60]. This study included markers on patient characteristics (e.g., gender, age), reported outcomes and behavior (e.g., pain intensity, psychological factors, disability), omics (e.g., proteomics, genomics, metabolomics, extracellular RNA), quantitative sensory testing, and brain imaging for the likelihood of developing chronic pain after surgery, or for resilience to it [60]. Thus, the prediction of acute to chronic pain transition cannot be based only on biological markers and metrics but needs a multidisciplinary approach to be as accurate as possible [61].

Brain imaging, especially functional magnetic resonance imaging (fMRI), has been used in the detection of acute pain but also in prognostics for the transition from acute to chronic pain [62, 63]. By combining limbic brain functional and anatomical characteristics with potential risk gene single-nucleotide polymorphisms (SNPs), it is possible to predict approximately 60% of the variance in the outcome following a subacute episode of low back pain [64].

CLINICAL APPLICATIONS

Pain Assessment

It is undebatable that pain diagnosis would benefit from the development of new objective markers. Five primary tactics have been the focus of current research on this topic, each with pros and cons [65]. These include autonomic nervous system monitoring, biopotentials, neuroimaging, composite algorithms, and biomarkers [65]. Despite increased efforts, there is currently insufficient evidence to support the widespread use of biological markers as objective measures of pain and nociception. However, biomarker research and composite algorithm development are promising avenues for future research.

The use of these markers would especially assist diagnostics in patient populations with limited ability to express pain, where facial expressions are often the only subjective indicators of pain (e.g., infants, children, people with disabilities). Recent research states that salivary hormones such as cortisol and alpha amylase, immunoglobins, and other biomarkers may be suitable for the diagnosis of acute pain in children [12].

Personalized Pain Management

Instead of focusing on finding biomarkers for estimating pain perception, a number of researchers are trying to develop biomarkers to enable mechanism-based pain condition categorization, forecast medication response, and provide individualized care [66].

Diagnostic and predictive biomarkers help in patient classification and redefine pain subtypes based on biological categories. Since there is no one-size-fits-all treatment for pain, the diagnosis determines the course of treatment. However, some types of pain may not serve as reliable diagnostic indicators, as they have specific underlying causes that require unique treatment strategies.

Over the drug discovery and development process, objective biomarkers and clinical trial endpoints are essential for defining pathophysiological subtypes of pain, assessing the effectiveness of novel drugs in targeting specific receptors, and forecasting their analgesic efficacy [5]. Pharmacogenetics may affect drug efficacy and individual responses to treatment [67]. For example, studies on commonly used analgesics like codeine have shown that its metabolism and bioactivation to morphine are mediated by the hepatic cytochrome P450 2D6 (CYP2D6) enzyme [68]. As a result, codeine's efficacy and safety are influenced by CYP2D6 activity, with its polymorphisms causing variability in therapeutic outcomes. Evidence supports this association and proposes analgesic strategies based on the CYP2D6 genotype [68].

Early Detection of Chronic Pain Risk and Preventive Strategies

Besides diagnostic and predictive biomarkers that have wide clinical use, prognostic markers also play a significant role in predicting the intensity of pain after trauma or surgery, in addition to their ability to forecast the transition from acute to chronic pain. These markers are not limited to identifying pain or disability in the present but also help us predict future chronic pain development and take necessary action. For example, they can be used to estimate the risk of persistent postoperative pain. Prognostic biomarkers monitor disease recurrence or progression, particularly in those already ill, and can identify individuals with a high probability of transition from acute to chronic pain [69].

Apart from patient characteristics such as female sex and young age that have been linked to higher intensity of pain, longer durations, and greater likelihood for chronic pain development [70], there are also some modifiable risk factors, such as high body mass index (≥ 25), severe preoperative pain, or psychological factors [71, 72]. Thus, identifying patients with modifiable risk factors for chronic pain as well as those with unsatisfactory treatment responses can guide physicians in providing comprehensive and interdisciplinary pain management and ensuring effective therapy for those at risk [71]. Given the complexity of the process, artificial intelligence (AI) would be helpful to personalize the approach to those patients [73].

To efficiently manage acute pain but also prevent the transition from acute to chronic pain, it is crucial to optimize analgesia in the acute pain and preoperative period, as well as during the postoperative and healing phases [71]. However, this optimization is not always easy to achieve, as the neurological processes underlying both nociceptive and acute inflammatory pain are essential for life. This means that medications that suppress inflammatory and nociceptive pain must be used carefully. In certain situations, such as during surgery or childbirth, the protective components of acute pain must be treated temporarily and under strict supervision [9]. In cases like postoperative pain or trauma, controlling inflammatory pain requires striking a careful balance between minimizing suffering and promoting recovery [9].

Although challenging, it is necessary to precociously treat acute pain episodes using multimodal analgesic approaches that target peripheral and central sensitization processes as well as any psychological risk factors in order to raise a barrier to the chronification of acute pain [72, 74]. For all the above, diagnostic acute pain markers and predictive chronic pain biomarkers could offer significant aid in clinical practice.

CHALLENGES, FUTURE DIRECTIONS, AND LIMITATIONS

Current Challenges

As pain is a subjective experience, influenced by physical and psychological components, both diagnosis and treatment are often expected to be challenging. Biomarkers hold the potential for unraveling this tangle; however, their discovery, validation, and use in pain therapeutics poses challenges as well [5]. Acute pain biomarkers can be categorized based on their role in pain perception and sensitivity—some reflect individual differences in pain susceptibility (a trait), such as genetic markers, while others, like inflammatory and neurotransmitter-related biomarkers, indicate real-time pain perception (a state) [63]. Recognizing these distinctions is essential for improving biomarker selection and interpretation in research and clinical settings.

Standardization and validation of biomarker assays requires thorough planning and consensus on the methodologies used for biomarker measurement, including sample collection and storage, and analysis of techniques to confirm their clinical utility and predictive value [75].

One of the goals of biomarker research in acute pain is the translation of findings into clinical practice. Efforts are needed to bridge the gap between research and clinical practice by developing user-friendly biomarker assays, establishing evidence-based guidelines for biomarker use, and providing training and education for healthcare providers.

Finally, the ethical and social implications of biomarker use in pain management must be carefully considered. Issues such as privacy, consent, and equity in access to biomarker testing require attention to ensure that biomarker-based approaches are implemented ethically and equitably [5].

Future Research Directions

In moving forward, directions in acute pain biomarker research should prioritize innovative and interdisciplinary approaches that foster collaboration among various fields, including basic science. There is an urgent need for research in this field, with clear opportunities to advance both precision and personalized medicine. Translational efforts are essential to bridge the gap between basic science discoveries and clinical applications, with a focus on precision and personalized medicine.

While we acknowledge that these aspects can create heterogeneity and variation in outcome measures, the synthesis of information remains important to help inform future directions in biomarker and pain research. Longitudinal studies integrating multiple layers of biological data can provide valuable insights into the trajectory of pain conditions and can guide therapeutic interventions. Validation and standardization of biomarkers are crucial steps for their clinical implementation, while advancements in machine learning and big data analytics offer opportunities for data-driven discoveries.

Patient-centered approaches should emphasize early detection and intervention, targeting specific biomarker panels for risk prediction and prevention of pain chronification. Future studies should also explore the cost-effectiveness and practical considerations of biomarker-based approaches, as these factors are crucial for their widespread adoption in clinical practice. Overall, future research endeavors should aim to optimize pain management strategies through a comprehensive understanding of acute pain biomarkers and their clinical implications.

Limitations

This narrative review provides a broad overview of acute pain biomarkers, but due to space constraints, not all biomarkers or recent studies could be covered in detail. While we focused on key biomarkers with clinical relevance, other promising markers were beyond the scope of this review. Additionally, the review primarily synthesizes available studies, which may vary in terms of methodology and patient populations. Some studies have limitations, such as small sample size and inconsistent biomarker measurement techniques, which may affect the reliability of the findings.

We have emphasized the most pertinent aspects of biomarker validation and their potential clinical applications. However, topics like the cost-effectiveness of these biomarkers and practical considerations for routine implementation were not deeply explored, as this was outside the scope of the current discussion.

By acknowledging these aspects, we aim to offer a clear and focused synthesis of the most important developments in the field, while encouraging further exploration of these evolving areas.

CONCLUSION

The exploration and validation of biomarkers for acute pain offer significant promise in transforming pain management practices and enhancing patient outcomes. Current research highlights the pivotal role biomarkers can play across various domains, including genetics, inflammation, neurotransmission, opioid responsiveness, and chronic pain risk prediction.

In clinical settings, biomarkers are beginning to bridge the gap between subjective pain assessments and objective biological data, assessing acute pain more accurately, monitoring its progression, and tailoring treatment strategies to individual patient needs. The use of biological markers could also aid physicians in identifying at-risk patients who may benefit from early intervention, as well as discovering and assessing new biological pathways and phenotypes related to pain and, as a result, novel biological therapeutic targets. Thus, the ongoing development of acute pain biomarkers not only holds the potential to revolutionize the approach to pain management but also underscores a shift towards more personalized and proactive healthcare solutions.

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Declarations

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REFERENCES

1. Carr DB, Goudas LC. Acute pain. Lancet. 1999;353:2051–8.
2. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain: United States, 2022. MMWR Recomm Rep. 2022;71:1–95.
3. Chou R, Hartung D, Turner J, Blazina I, Chan B, Levander X, et al. Evidence summary: opioid treatments for chronic pain. Agency for Healthcare Research and Quality (US); 2020 [cited 2024 Jan 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556247/.
4. Radnovich R, Chapman CR, Gudin JA, Panchal SJ, Webster LR, Pergolizzi JV. Acute pain: effective management requires comprehensive assessment. Postgrad Med. 2014;126:59–72.
5. Davis KD, Aghaeepour N, Ahn AH, Angst MS, Borsook D, Brenton A, et al. Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: challenges and opportunities. Nat Rev Neurol. 2020;16:381–400.
6. Rekatsina M, Paladini A, Piroli A, Zis P, Pergolizzi JV, Varrassi G. Pathophysiologic approach to pain therapy for complex pain entities: a narrative review. Pain Ther. 2020;9:7–21.
7. Baethge C, Goldbeck-Wood S, Mertens S. SANRA: a scale for the quality assessment of narrative review articles. Res Integr Peer Rev. 2019;4:5. https://doi.org/10.1186/s41073-019-0064-8.
8. Xu X, Huang Y. Objective pain assessment: a key for the management of chronic pain. F1000Res. 2020;9:F1000 Faculty Rev-35.
9. Tracey I, Woolf CJ, Andrews NA. Composite pain biomarker signatures for objective assessment and effective treatment. Neuron. 2019;101:783–800.
10. Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EKB, et al. Assessment of pain. Br J Anaesth. 2008;101:17–24.
11. Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med. 2011;3:70ra14.
12. Stendelyte L, Malinauskas M, Grinkeviciute DE, Jankauskaite L. Exploring non-invasive salivary biomarkers for acute pain diagnostics: a comprehensive review. Diagnostics. 2023;13:1929.
13. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016 [cited 2024 Nov 14]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK326791/
14. Besson JM. The neurobiology of pain. Lancet. 1999;353:1610–5.
15. Wang X-M, Hamza M, Wu T-X, Dionne RA. Upregulation of IL-6, IL-8 and CCL2 gene expression after acute inflammation: correlation to clinical pain. Pain. 2009;142:275–83.
16. Ji R-R, Chamessian A, Zhang Y-Q. Pain regulation by non-neuronal cells and inflammation. Science. 2016;354:572–7.
17. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69:89–95.
18. Strimbu K, Tavel JA. What are Biomarkers? Curr Opin HIV AIDS. 2010;5:463–6.
19. Larsson AO, Bäckryd E, Eriksson MB. Biomarkers in pain. Biomedicines. 2023;11:2554.
20. Yang Y, Mis MA, Estacion M, Dib-Hajj SD, Waxman SG. NaV1.7 as a pharmacogenomic target for pain: moving toward precision medicine. Trends Pharmacol Sci. 2018;39:258–75.
21. Dib-Hajj SD, Waxman SG. Sodium channels in human pain disorders: genetics and pharmacogenomics. Annu Rev Neurosci. 2019;42:87–106.
22. Zhang X. Genotypic analysis of SCN9A for prediction of postoperative pain in female patients undergoing gynecological laparoscopic surgery. Pain Phys. 2016;19:E151–62.
23. Alsaloum M, Higerd GP, Effraim PR, Waxman SG. Status of peripheral sodium channel blockers for

non-addictive pain treatment. Nat Rev Neurol. 2020;16:689–705.

24. Asimakopoulos T, Kourousi M, Varrassi G, Rekatsina M. Piezo channels in migraine and trigeminal pain syndromes: a systematic review of their role in pain pathways. Adv Health Res. 2024. https://doi.org/10.4081/ahr.2024.4.

25. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature. 1997;389:816–24.

26. Duo L, Hu L, Tian N, Cheng G, Wang H, Lin Z, et al. TRPV1 gain-of-function mutation impairs pain and itch sensations in mice. Mol Pain. 2018;14:1744806918762031.

27. He S, Zambelli VO, Sinharoy P, Brabenec L, Bian Y, Rwere F, et al. A human TRPV1 genetic variant within the channel gating domain regulates pain sensitivity in rodents. J Clin Invest. 2023. https://doi.org/10.1172/JCI163735.

28. Einarsdottir E, Carlsson A, Minde J, Toolanen G, Svensson O, Solders G, et al. A mutation in the nerve growth factor beta gene (NGFB) causes loss of pain perception. Hum Mol Genet. 2004;13:799–805.

29. Sung K, Ferrari LF, Yang W, Chung C, Zhao X, Gu Y, et al. Swedish nerve growth factor mutation (NGFR100W) defines a role for TrkA and p75NTR in nociception. J Neurosci. 2018;38:3394–413.

30. Salama V, Geng Y, Rigert J, Fuller CD, Shete S, Moreno AC. Systematic review of genetic polymorphisms associated with acute pain induced by radiotherapy for head and neck cancers. Clin Transl Radiat Oncol. 2023;43: 100669.

31. Chen O, Donnelly CR, Ji R-R. Regulation of pain by neuro-immune interactions between macrophages and nociceptor sensory neurons. Curr Opin Neurobiol. 2020;62:17–25.

32. Bang S, Xie Y-K, Zhang Z-J, Wang Z, Xu Z-Z, Ji R-R. GPR37 regulates macrophage phagocytosis and resolution of inflammatory pain. J Clin Invest. 2018;128:3568–82.

33. Baral P, Udit S, Chiu IM. Pain and immunity: implications for host defence. Nat Rev Immunol. 2019;19:433–47.

34. Morris P, Ali K, Merritt M, Pelletier J, Macedo LG. A systematic review of the role of inflammatory biomarkers in acute, subacute and chronic nonspecific low back pain. BMC Musculoskelet Disord. 2020;21:142.

35. Chen X, Wang W, Cui P, Li Y, Lu S. Evidence of MRI image features and inflammatory biomarkers association with low back pain in patients with lumbar disc herniation. The Spine Journal [Internet]. 2024 [cited 2024 Mar 19]; Available from: https://www.sciencedirect.com/science/article/pii/S1529943024000792

36. Teodorczyk-Injeyan JA, Triano JJ, Injeyan HS. Nonspecific low back pain: inflammatory profiles of patients with acute and chronic pain. Clin J Pain. 2019;35:818.

37. Pinto EM, Neves JR, Laranjeira M, Reis J. The importance of inflammatory biomarkers in nonspecific acute and chronic low back pain: a systematic review. Eur Spine J. 2023;32:3230–44. https://doi.org/10.1007/s00586-023-07717-1.

38. Giordano R, Ghafouri B, Arendt-Nielsen L, Petersen KK-S. Inflammatory biomarkers in patients with painful knee osteoarthritis: exploring the potential link to chronic postoperative pain after total knee arthroplasty-a secondary analysis. Pain. 2024;165:337–46.

39. Inflammatory biomarkers of low back pain and disc degeneration: a review—PMC [Internet]. [cited 2024 Feb 27]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5744892/.

40. Parisien M, Lima LV, Dagostino C, El-Hachem N, Drury GL, Grant AV, et al. Acute inflammatory response via neutrophil activation protects against the development of chronic pain. Sci Transl Med. 2022;14: eabj9954.

41. Pasqualucci A, de Angelis V, Contardo R, Colò F, Terrosu G, Donini A, et al. Preemptive analgesia: intraperitoneal local anesthetic in laparoscopic cholecystectomy: a randomized, double-blind, placebo-controlled study. Anesthesiology. 1996;85:11–20.

42. Yoon JS, Park J, Song R, Yu D. Substance P as a potential biomarker of pain assessment in dogs. Iran J Vet Res. 2019;20:289–92.

43. Tschoner T, Feist M. Substance P concentrations in the blood plasma and serum of adult cattle and calves during different painful procedures and conditions: a systematic review. BMC Vet Res. 2022. https://doi.org/10.1186/s12917-022-03304-6.

44. Lisowska B, Siewruk K, Lisowski A. Substance P and acute pain in patients undergoing orthopedic surgery. PLoS ONE. 2016;11: e0146400.

45. Brandow AM, Wandersee NJ, Dasgupta M, Hoffmann RG, Hillery CA, Stucky CL, et al. Substance P is increased in patients with sickle cell disease and associated with haemolysis and hydroxycarbamide

use. Br J Haematol. 2016;175:237–45. https://doi.org/10.1111/bjh.14300.

46. Ahmad M, Williams J, Al-Abbousi R, Wheater M. Substance P concentration in saliva of patients who report dental pain. J Adv Oral Res. 2014;5:1–5. https://doi.org/10.1177/2229411220140202.

47. Peek AL, Rebbeck T, Puts NAJ, Watson J, Aguila M-ER, Leaver AM. Brain GABA and glutamate levels across pain conditions: a systematic literature review and meta-analysis of 1H-MRS studies using the MRS-Q quality assessment tool. Neuroimage. 2020;210: 116532.

48. Watson CJ. Insular balance of glutamatergic and GABAergic signaling modulates pain processing. Pain. 2016;157:2194–207.

49. Foerster BR, Petrou M, Edden RAE, Sundgren PC, Schmidt-Wilcke T, Lowe SE, et al. Reduced insular γ-aminobutyric acid in fibromyalgia. Arthritis Rheum. 2012;64:579–83.

50. Hwang IC, Park J-Y, Myung S-K, Ahn HY, Fukuda K, Liao Q. OPRM1 A118G gene variant and postoperative opioid requirement: a systematic review and meta-analysis. Anesthesiology. 2014;121:825–34.

51. Zhang X, Liang Y, Zhang N, Yan Y, Liu S, Fengxi H, et al. The relevance of the OPRM1 118A>G genetic variant for opioid requirement in pain treatment: a meta-analysis. Pain Physician. 2019;22:331–40.

52. Turczynowicz A, Jakubów P, Niedźwiecka K, Kondracka J, Pużyńska W, Tałałaj M, et al. Mu-opioid receptor 1 and C-reactive protein single nucleotide polymorphisms as biomarkers of pain intensity and opioid consumption. Brain Sci. 2023;13:1629.

53. Vidic Z, Goricar K, Strazisar B, Besic N, Dolzan V. Association of OPRM1, MIR23B, and MIR107 genetic variability with acute pain, chronic pain and adverse effects after postoperative tramadol and paracetamol treatment in breast cancer. Radiol Oncol. 2023;57:111–20.

54. Singleton S, Sneddon C, Bakina A, Lambert JJ, Hales TG. Early-life adversity increases morphine tolerance and persistent inflammatory hypersensitivity through upregulation of δ opioid receptors in mice. Pain. 2023;164:2253.

55. Bruehl S, Burns JW, Morgan A, Koltyn K, Gupta R, Buvanendran A, et al. The association between endogenous opioid function and morphine responsiveness: a moderating role for endocannabinoids. Pain. 2019;160:676–87.

56. Mo K, Wu S, Gu X, Xiong M, Cai W, Atianjoh FE, et al. MBD1 contributes to the genesis of acute pain and neuropathic pain by epigenetic silencing of Oprm1 and Kcna2 genes in primary sensory neurons. J Neurosci. 2018;38:9883–99.

57. Voscopoulos C, Lema M. When does acute pain become chronic? Br J Anaesth. 2010;105(Suppl 1):i69-85.

58. Arendt-Nielsen L, Fernández-de-las-Peñas C, Graven-Nielsen T. Basic aspects of musculoskeletal pain: from acute to chronic pain. J Man Manip Ther. 2011;19:186–93. https://doi.org/10.1179/106698111X13129729551903.

59. Paladini A, Rawal N, Coca Martinez M, Trifa M, Montero A, Pergolizzi J, et al. Advances in the management of acute postsurgical pain: a review. Cureus. 2023;15: e42974.

60. Sluka KA, Wager TD, Sutherland SP, Labosky PA, Balach T, Bayman EO, et al. Predicting chronic postsurgical pain: current evidence and a novel program to develop predictive biomarker signatures. Pain. 2023;164:1912.

61. Paladini A, Vallejo R, Guerrero M, Pasqualucci A, Peppin JF, Pergolizzi J, et al. Answering big questions in pain medicine. Cureus. 2023;15: e43561.

62. Zhang Z, Gewandter JS, Geha P. Brain imaging biomarkers for chronic pain. Front Neurol. 2022. https://doi.org/10.3389/fneur.2021.734821.

63. Zhang L-B, Chen Y-X, Li Z-J, Geng X-Y, Zhao X-Y, Zhang F-R, et al. Advances and challenges in neuroimaging-based pain biomarkers. CR Med. 2024. https://doi.org/10.1016/j.xcrm.2024.101784.

64. Vachon-Presseau E, Tétreault P, Petre B, Huang L, Berger SE, Torbey S, et al. Corticolimbic anatomical characteristics predetermine risk for chronic pain. Brain. 2016;139:1958–70. https://doi.org/10.1093/brain/aww100.

65. Cowen R, Stasiowska MK, Laycock H, Bantel C. Assessing pain objectively: the use of physiological markers. Anaesthesia. 2015;70:828–47. https://doi.org/10.1111/anae.13018.

66. Mouraux A, Iannetti GD. The search for pain biomarkers in the human brain. Brain. 2018;141:3290–307.

67. Theodosopoulou P, Rekatsina M, Staikou C. The efficacy of 5HT3-receptor antagonists in postoperative nausea and vomiting: the role of pharmacogenetics. Minerva Anestesiol. 2023;89:565–76.

68. Crews KR, Gaedigk A, Dunnenberger HM, Leeder JS, Klein TE, Caudle KE, et al. Clinical pharmacogenetics implementation consortium guidelines for cytochrome P450 2D6 genotype and codeine

therapy: 2014 update. Clin Pharmacol Ther. 2014;95:376–82.

69. van der Miesen MM, Lindquist MA, Wager TD. Neuroimaging-based biomarkers for pain: state of the field and current directions. Pain Rep. 2019;4: e751.

70. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin: results from a general population Survey. J Pain. 2006;7:281–9.

71. McGreevy K, Bottros MM, Raja SN. Preventing chronic pain following acute pain: risk factors, preventive strategies, and their efficacy. Eur J Pain Suppl. 2011;5:365–72.

72. Matamala AM, Hanna M, Perrot S, Varrassi G. Avoid postoperative pain to prevent its chronification: a narrative review. Cureus. 2022;14: e22243.

73. Cascella M, Leoni MLG, Shariff MN, Varrassi G. Artificial intelligence-driven diagnostic processes and comprehensive multimodal models in pain medicine. J Pers Med. 2024;14:983.

74. Pak DJ, Yong RJ, Kaye AD, Urman RD. Chronification of pain: mechanisms, current understanding, and clinical implications. Curr Pain Headache Rep. 2018;22:9. https://doi.org/10.1007/s11916-018-0666-8.

75. Ou F-S, Michiels S, Shyr Y, Adjei AA, Oberg AL. Biomarker discovery and validation: statistical considerations. J Thorac Oncol. 2021;16:537–45.