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Physiological responses to pain in cancer patients: A systematic review

Serena Moscato[a,*], Pietro Cortelli[b,c], Lorenzo Chiari[a,d]

[a] Department of Electrical, Electronic, and Information Engineering "Guglielmo Marconi" – DEI, University of Bologna, Bologna, Italy
[b] IRCCS Istituto Delle Scienze Neurologiche Di Bologna, UOC Clinica Neurologica NeuroMet, Ospedale Bellaria, Bologna, Italy
[c] Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, Bologna, Italy
[d] Health Sciences and Technologies, Interdepartmental Center for Industrial Research (CIRI-SDV), University of Bologna, Bologna, Italy

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ABSTRACT

Background and objective: Pain is one of the most debilitating symptoms in persons with cancer. Still, its assessment is often neglected both by patients and healthcare professionals. There is increasing interest in conducting pain assessment and monitoring via physiological signals that promise to overcome the limitations of state-of-the-art pain assessment tools. This systematic review aims to evaluate existing experimental studies to identify the most promising methods and results for objectively quantifying cancer patients' pain experience.
Methods: Four electronic databases (Pubmed, Compendex, Scopus, Web of Science) were systematically searched for articles published up to October 2020.
Results: Fourteen studies (528 participants) were included in the review. The selected studies analyzed seven physiological signals. Blood pressure and ECG were the most used signals. Sixteen physiological parameters showed significant changes in association with pain. The studies were fairly consistent in stating that heart rate, the low-frequency to high-frequency component ratio (LF/HF), and systolic blood pressure positively correlate with the pain.
Conclusions: Current evidence supports the hypothesis that physiological signals can help objectively quantify, at least in part, cancer patients' pain experience. While there is much more to be done to obtain a reliable pain assessment method, this review takes an essential first step by highlighting issues that should be taken into account in future research: use of a wearable device for pervasive recording in a real-world context, implementation of a big-data approach possibly supported by AI, including multiple stratification factors (e.g., cancer site and stage, source of pain, demographic and psychosocial data), and better-defined recording procedures. Improved methods and algorithms could then become valuable add-ons in taking charge of cancer patients.

1. Introduction

Cancer pain is an umbrella term that comprises many heterogeneous pain conditions with different physiological characteristics [1]. Pain can be due to the presence of the tumor itself, oncological treatments (e.g., chemotherapy, surgery, or immunotherapy) [2], or tissue damage [3].

The International Association for the Study of Pain (IASP) defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [4]. IASP also disclosed general guidelines for pain classification [5] that can be used for cancer pain evaluation. They are based on four significant features:

(i) *Pathophysiological mechanism*: cancer pain can arise both as
  a nociceptive pain that can be either
    i somatic, the most frequent type of pain in the cancer population [6], or
    ii visceral, usually manifested after abdominal or thoracic surgery [7];
  b neuropathic pain, with a prevalence of 20% in the cancer population [1];
  c mixed pain, a combination of the two;
(ii) *Duration*: cancer patients usually suffer from chronic pain, which persists or recurs for more than three months [8], or breakthrough pain [9];
(iii) *Etiology*;
(iv) *Anatomic location*.

Regardless of its cause, pain is one of the most debilitating symptoms experienced by persons with cancer. On average, one-half of all cancer patients suffer from pain [10], and this percent-

* Corresponding author.
E-mail address: serena.moscato3@unibo.it (S. Moscato).

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age tends to become higher with the progression of the disease [11]. Furthermore, pain is detrimental to the psychological well-being of the subject. The reduced quality of life, in turn, reduces the adherence to therapy, which inevitably leads to adverse outcomes [12]. In addition to the personal and social impact, cancer pain also represents an economic burden [9]: the healthcare costs for oncological pain relief are almost five times higher than in the healthy population [13]. It should be added that, in this estimation, indirect costs related to patients' and caregivers' lower productivity are not taken into account [9,14].

According to the American Pain Society and the European Task Force on Cancer Pain, an appropriate pain treatment starts with an appropriate pain assessment [15,16]. Nowadays, in routine clinical practice, pain is assessed using scales and questionnaires to overview the pain experience. Scales are unidimensional ratings of pain intensity, while questionnaires give a more comprehensive evaluation as they keep track of different aspects of the pain experience, like the anatomical location and the time the pain is experienced [17]; some questionnaires are developed specifically for a particular type of cancer pain, as for the cancer-related neuropathic pain [3].

Although scales and questionnaires are state-of-the-art pain assessment tools (PAT), they suffer from several limitations. Since pain sensation is inherently subjective [18], the patient must be cooperative and non-cognitively impaired to communicate it [19]. Moreover, the memory of pain tends to be inaccurate and is often influenced by several context factors [20]. Specifically for cancer pain, patients tend to underrate their pain because it is supposed to be directly related to the worsening of the pathology [2]. Paradoxically, this could deteriorate the subject's health since pain acts as an alarm bell that alerts the body to take action to protect itself [21]. It can also happen that healthcare professionals leave out the pain assessment from their routine because they are more concerned about cancer diagnosis and treatment [6], so the evaluation is only carried out occasionally, usually in clinical settings.

Pain is a phenomenon of the utmost complexity that involves different physiological mechanisms at both the central and peripheral levels [22]. The conscious perception of pain is a result of higher brain center processes, collectively called the "Pain Neuromatrix" [23], which modulate the pain sensation based on the subject's attention, affective dimension, and cognitive appraisal [24]. These processes, in turn, disrupt the ordinary functioning of some physiological mechanisms.

The physiological systems mainly affected by the pain experience are the Central Nervous System (CNS) and the Autonomic Nervous System (ANS). The CNS can be monitored using non-invasive electrophysiological or brain-imaging techniques to detect activated brain areas and the connection patterns established following the pain experience [25]. As a result, the brain's processes in response to a stimulus can be reconstructed [26]. On the other hand, the effects of ANS activation in response to pain can be monitored indirectly by measuring several physiological functions [27], collectively called autonomic signals. The ANS, composed of the sympathetic and parasympathetic systems, represents the bridge between the central nervous system and the internal organs. The ANS actions follow the "fight or flight" principle [28]: they occur involuntarily to preserve the integrity of the subject. Autonomic signals are often exploited in the research field of "Emotion recognition" [29], and objective pain assessment is one of its branches.

One of the main advantages of exploiting autonomic signals is collecting them through wearable devices. With their relatively low-cost technology and progressive miniaturization [30], wearable sensors have become a valuable source of information about the health status both for healthy and diseased subjects, allowing continuous and unobtrusive monitoring even in real-world conditions [31]. In the last few decades, several research groups have focused on the link between pain and measurable physiological signals reflecting the disrupted mechanisms. Monitoring these signals could indeed provide additional tools for cancer pain assessment. Unlike scales and questionnaires, they would not require the subject's cooperation. Because physiological mechanisms are not affected by the subject's psychology, they also represent the pain status more objectively. Moreover, by using wearable devices, pain assessment could be carried out also outside the clinical context, when and where the pain is actually experienced. As an added benefit, healthcare professionals could dedicate the time of the visit to diagnosing and treating cancer instead of assessing pain.

On the other hand, such an approach imposes several challenges from a technical point of view. Physiological signals, especially those recorded by wearable devices, can be subjected to external noise and motion artifacts [32]. Thus, to overcome this issue, they must be subjected to a proper preprocessing step, in which signals are cleaned, and the effects of possible artifacts are mitigated. Another critical step is represented by the feature extraction [33]: once the signals are ready to be processed, it is crucial to extract those features that can capture the phenomenon of interest (pain in this case). Added to this is the feature selection step, in which only the features that best describe the phenomenon are selected and then used [34]. Lastly, complex algorithms needed to understand the underlying relationship between features and pain since it is likely not to be simply linear [35]. In this case, it is possible to use either classical statistical methods or artificial intelligence (AI) algorithms. The former can be applied to appreciate differences in different painful conditions, and, consequently, they can be used to develop models that link a given painful condition to a precise physiological response. The latter use machine learning and deep learning algorithms [36] that automatically learn physiological responses patterns linked to a given painful condition.

Pain monitoring and assessment through physiological signals are still in an exploratory phase. To date, several studies have investigated aspects of the relationship between pain and physiological systems, nicely recapped by three recent reviews. The latest review by Chen et al. [37] summarizes the most common pain and stress assessment methods, followed by a synopsis of the main physiological signals that could be recorded through wearable devices. Next, the paper by Naranjo-Hernandez et al. [38] offers an overview of sensors that can potentially be used for chronic pain assessment, offering fascinating insights on the signals to be exploited and the relevant algorithms for their processing. Finally, the survey by Werner et al. [39] is more technical, including details about AI algorithms developed for automatic pain recognition through physiological signals. However, these reviews did not address the association between pain and changes in physiological signals specific to the cancer population and the feasibility of conducting these assessments in real-world settings.

For these reasons, we aim to conduct a systematic review of studies investigating the effect of pain on cancer patients' physiological signals. Our specific objectives are:

- To assess which physiological signals have been investigated in relation to cancer pain;
- To understand which statistical methods have been used to assess the association between cancer pain and physiological signals;
- To compare (whenever possible) the results of different studies;
- To evaluate the diffusion of instrumental pain assessment also in real-world settings

All the studies on this topic will be collected, and the link between physiological signals and cancer pain experience will be critically appraised.

2. Materials and methods

2.1. Search strategy

We adopted the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines for the review protocol. PRISMA is "an evidence-based minimum set of items for reporting in systematic reviews" [40,41].

The primary research question of the current review is: "What are the physiological responses to pain in cancer patients?".

The secondary questions are:

- Which physiological signals are currently monitored in this patient group?
- Which methods are used to investigate the association between subjective pain experience and physiological responses?
- Do different studies provide consistent evidence about the role of physiological signals in relation to pain?
- In real-world settings, what is the diffusion of studies investigating the physiological effect on cancer pain?

The following eligibility criteria have been defined using the SPIDER search tool [42]:

- Sample: Cancer patients
- Phenomenon of Interest: Pain experience
- Design: Pain assessment
- Evaluation: Recording of physiological signals
- Research type: Quantitative Research

A systematic literature search of PubMed, Compendex, Web Of Science, and Scopus databases was conducted to October 2020. We limited searches to 1990 onwards and included only studies published in English and Italian.

Based on the eligibility criteria, the search string was: ((Pain* OR Nocicept*) [Title] AND (Automat* OR Predict* OR Measur* OR Evaluat* OR Recognition OR Estimat* OR Classif* OR Assess* OR Examin* OR Detect* OR Effect) [Title + Abstract] AND ((Physiologic* OR Peripheral OR Autonom*) [Title + Abstract] AND (Signal OR Signals OR Parameter* OR Variable* OR Measure* OR Result OR Results OR Nervous System)) [Title + Abstract] AND (Cancer OR Oncolog*) [Title + Abstract].

2.2. Study selection

We used the following inclusion criteria:

- Cancer patients (including comparisons with a control group)
- Measure of physiological signals
- Pain assessment through scales/questionnaires, or information regarding the intensity of a nociceptive stimulus, or expected change due to an intervention (painful or therapeutic)

and the following exclusion criteria:

- Animal experiments
- Scales or questionnaires only
- Case reports
- Assessment using biomolecules.

Duplicate publications were removed using Mendeley software [43]. In the first phase, two review authors (SM and LC) independently screened retrieved titles and abstracts and excluded irrelevant studies using Rayyan [44]. Disagreements were resolved by consensus. In the second phase, a reviewer (SM) searched the reference lists of the selected studies and other systematic reviews on similar topics to find additional papers.

2.3. Data extraction and quality assessment

The following information was extracted from each study:

- Year of publication
- Study objective
- Settings (clinical or real-world)
- Number of subjects and demographic data (age, gender)
- Cancer diagnosis
- Pain information and type of external pain stimulus (if any)
- Study type
- Pain ratings through scales or questionnaires, or intensity of the nociceptive stimulus, or pre-post intervention assessment
- Recorded physiological signals
- Recording procedure (e.g., duration, sampling frequency)
- Statistical methods (e.g., correlation, intergroup differences, before-after intervention) used to study the association between pain and physiological response

Based on the study design, included studies were divided into two categories:

- Concurrent validity studies, comparing state-of-the-art PAT and physiological signals;
- Sensitivity to change studies, evaluating physiological signals before and after an intervention (painful or antalgic).

Articles using the same physiological measures were clustered to investigate consistency across studies within these two categories.

To assess the quality of the studies, we selected two different tools for the two categories:

- Concurrent validity studies: Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool [45]. The physiological outcome resulting from the pain sensation is the *new diagnostic tool to be assessed in terms of accuracy and reliability*. At the same time, state-of-the-art PAT (i.e., scales, questionnaires) or the intensity of the nociceptive stimuli represent *the ground truth*: the term of comparison of the instrumental measurements. QUADAS-2 consists of thirteen questions related to four key domains:
- *patient selection: describe methods of patient selection and the included patients;*
- *index test: describe the index test and how it was conducted and interpreted;*
- *reference standard: describe the reference standard and how it was conducted and interpreted;*
- *flow and timing: describe any patients who did not receive the index tests or reference standard; describe the interval and any interventions between index tests and the reference standard.*
- Sensitivity to change studies: NIH Quality Assessment Tool (NIH-QAT) for before-after (pre-post) studies with no control group [46] . This tool consists of twelve signaling questions. We removed the Q12 (related to group interventions) since it is out of this systematic review scope.

For both tools, the risk of bias is assessed based on the answer to each signaling question (yes/no/info not available). We assigned an overall dichotomous risk of bias indicator based on the majority of answers, yes (low risk of bias) or no/not available (high risk of bias).

3. Results

3.1. Study selection

Searching the databases produced 1181 records. Once duplicates were removed, 1155 records were screened based on title and abstract, and 1102 were excluded because they were not within the

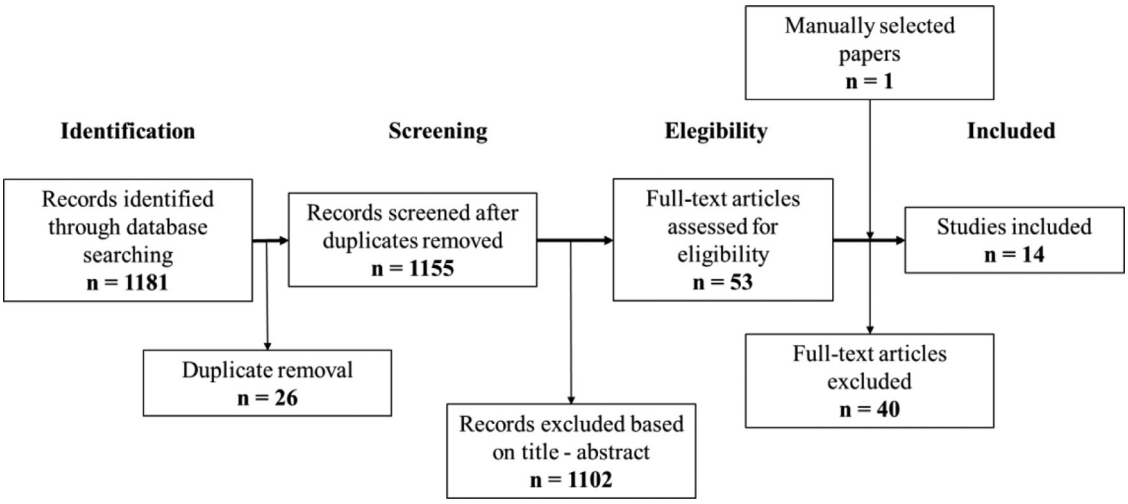

Fig. 1. PRISMA flow diagram.

scope of this review. We assessed the full text of 53 studies and retained 13 of them that met the inclusion criteria [47–60]. One additional article (Buvanendran et al. [60]) was identified during the final manual search among the references of [57]. In total, 14 journal articles were included (see Fig. 1).

3.2. Study characteristics

Descriptive characteristics of the fourteen studies are presented in Table 1. The included papers were published between 1993 and 2018. Three studies were based in the USA [49,52,60], two in Italy [50,58], and one each in France [47], Turkey [48], Japan [53], South Korea [54], Austria [55], Poland [56], UK [57], Israel [59], and Lebanon [51]. Five hundred twenty-eight subjects were enrolled in the selected studies (172 males and 356 females, 516 oncological patients and 12 healthy volunteers), with an average of 38 subjects per study (range: 9–100) and a mean age of 53 years (range: 4–75 years). Three studies are focused exclusively on breast cancer (hence the high number of women), while eleven include different cancer sites (Fig. 2).

With regard to the pain type, four studies enrolled patients suffering from neuropathic pain [47,48,57,59], mostly due to chemotherapy treatment (3/16); five studies involved patients subjected to a nociceptive stimulus (surgery [53,56], dental stimulation [50], and invasive procedures [51,54]). Two studies looked at cancer pain in general [52,58], and one each at breakthrough pain episodes [55], chronic pain [60], and metastatic bone pain [49].

Concerning the experimental settings, twelve studies were carried out in clinical settings and only two in real-world conditions. Furthermore, only five studies reported information about the duration of the recordings, while none of the studies included information about the sampling frequency of the physiological signals.

Physiological signals under investigation in the selected studies and the relative extracted physiological parameters are the following:

- blood pressure (BP) in seven studies [49–52,54,56,58]
  - systolic blood pressure (sysBP): maximum blood pressure during ventricles contraction
  - diastolic blood pressure (diaBP): minimum blood pressure before the next contraction
- electrocardiogram (ECG) in four studies [48,53,55,59]
  - parameters from Heart Rate Variability (HRV) analysis: they are related to the time variations between consecutive heartbeats
- photoplethysmography (PPG) in two studies [49,51]
  - parameters from HRV analysis
  - oxygen saturation (SpO2): the amount of oxygen carried by the hemoglobin in the blood
- respiration (Resp) in one study [52]
  - respiration rate: the pace at which breathing occurs
- electrochemical skin conductance (ESC) in one study [47]
- positron emission tomography (PET) imaging in one study [60]
- blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD-fMRI) in one study [57].

A brief description of the physiological parameters computed in the selected studies is presented in Appendix A.

Nine out of fourteen studies assessed the concurrent validity of physiological parameters against scales and/or questionnaires, while the remaining five evaluated the sensitivity-to-change of the physiological parameters to an intervention.

3.3. Concurrent validity studies

Only two [48,55] concurrent validity studies were carried out in a real-world context. In four studies [47,48,57,60], patients were divided into two or more groups based on their pain experience. The most-used tools (five studies [51,55,56,59,60]) were scales such as the Numerical Rating Scale (NRS) (3/9), Visual Analogue Scale (VAS) (1/9), and FACES scale (1/9). For neuropathic pain evaluation, ad-hoc questionnaires were used (3/9) [47,48,57], as the Leeds Assessment of Neuropathic Symptoms and Signs and the Neuropathic Pain Symptom Inventory. A graphical depiction about the main features of the concurrent validity studies is given in Supplementary Materials, Fig. S1.

In combination with scales and questionnaires, six physiological signals were exploited, four of which are autonomic signals: ECG (3/9), BP (3/9), PPG (2/9), ESC (1/9), BOLD-fMRI (1/9), and PET (1/9).

In eight out of nine studies, the features extracted from physiological signals were compared to pain assessment tools through correlation analysis, using Pearson's correlation coefficient [51,55,56,59], Spearman's correlation coefficient [47,50], both based on the distribution of the parameter [48] or a linear regression analysis [57], while five studies assessed the differences between two or more groups, using Wilcoxon test [47,59], the Mann-Whitney U test [57,60], or *t*-test and chi-square test for numerical and categorical variables respectively [48]. Only in one article did researchers investigate whether it is possible to use the extrapo-

Table 1
Descriptive characteristics of the included studies.

Refs.	Study objective	Settings	No subjects	Age *mean (std)* Gender	Cancer diagnosis (no.)	Information on pain	Study type	Pain assessment	Physiological signals(s)	Recording duration	Statistical analyses
Delmotte et al. [47]	To investigate how Electrochemical Skin Conductance (ESC) could be helpful in Oxaliplatin-Induced Peripheral Neuropathy (OIPN) diagnosis	Clinical	36	64 (11) - 18 F	Colon (12), Stomach (6), Liver (1), Pancreas (9), Rectum (7), Peritoneum (1). All with Oxaliplatin-Induced Peripheral Neuropathy	Neuropathic pain	Concurrent validity	Neuropathic Pain Symptom Inventory (NPIS)	ESC	–	Correlation, Inter-group differences, Classification
Yesil et al. [48]	To investigate whether neuropathic pain is associated with changes in cardiac sympathovagal activity in patients with breast cancer (BC)	Real World	70	48.2 (7.04) - 70 F	Breast cancer with chemotherapy-induced neuropathy	Neuropathic pain	Concurrent validity	Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)	ECG	24 h	Correlation, Inter-group differences
Uchida et al. [53]	To examine the effects of low-dose remifentanil on post-operative pain relief and heart rate variability after surgery	Clinical	20	59 (7) exp. group, 60 (11) control group - 20 F	Patients undergoing breast cancer surgery with pain (13), and without pain (7 age-matched)	Nociceptive pain (breast cancer surgery)	Sensitivity to change	Before and after the surgery, group comparison	ECG	–	Pre-Post intervention, Inter-group differences
Yu and Seol [54]	To test the effect of inhalation of lavender oil or linalyl acetate on pain relief	Clinical	66	60.9 - 29 F	Colorectal cancer (66)	Nociceptive pain (colorectal cancer surgery)	Sensitivity to change	Before and after antalgic therapy	BP	1 min before and after therapy	Pre-Post intervention
Masel et al. [55]	To study the changes in the ANS by measuring HRV during opioid therapy for cancer breakthrough pain (CBTP) in palliative-care patients with cancer and compare these changes with patient-reported pain levels on a NRS	Real World	10	62 (5.2) - 4 F	Advanced cancer (10)	Breakthrough pain	Concurrent validity	NRS	ECG	6 variable-length time windows before and after therapy	Correlation

(*continued on next page*)

Table 1 (*continued*)

Refs.	Study objective	Settings	No subjects	Age *mean (std)* Gender	Cancer diagnosis (no.)	Information on pain	Study type	Pain assessment	Physiological signals(s)	Recording duration	Statistical analyses
Wegorowski et al. [56]	To assess the possibilities of modifying the intensity of post-operative pain evaluated with VAS after surgical treatment for breast neoplasm offered by pre-emptive analgesia	Clinical	100	58.58 (12.01) - 100 F	Breast cancer (100)	Nociceptive pain (breast cancer surgery)	Concurrent validity	VAS	BP	–	Correlation
Boland et al. [57]	To compare areas associated with central pain processing in patients with multiple myeloma who had chemotherapy-induced peripheral neuropathy with those from healthy volunteers	Clinical	24	58 (IQR:35–67) - 10 F	Cancer patients with Multiple myeloma chemotherapy-induced peripheral neuropathy (MM-CIPN) (12) –healthy controls (12)	Neuropathic pain + Nociceptive pain (heat pain stimulation)	Concurrent validity	Total Neuropathy Score reduced version (TNS-reduced) - MM-CIPN vs healthy volunteers	BOLD fMRI	–	Correlation, Inter-group differences
Burrai et al. [58]	To test the differences in physiological parameters, pain-level, and mood-level between an experimental group subjected to live sax music and a control group who experienced only standard care	Clinical	52	64.3 (12.9) exp. group - 25 F, 64.6 (12.8) control group - 18 F	Metastatic cancer (45), non-metastatic cancer (7)	Cancer pain	Sensitivity to change	Before and after antalgic therapy	BP	–	Pre-Post intervention, Inter-group differences
Nahman-Averbuch et al. [59]	To evaluate the relationships between autonomic parasympathetic function and the perception of (i) spontaneous pain, (ii) experimental non-painful sensations, (iii) painful experimental sensations in chemotherapy-induced neuropathy patients	Clinical	27	56.5 (7.9) - 20 F	Breast (11), Lungs (2), Breast and Lungs (1), Ovary (2), Myeloma (2), Stomach (1), Oesophagus (1), Colon (3), Leukaemia (2), Hodgkin's Lymphoma (1), Sarcoma (1). All with peripheral neuropathy	Neuropathic pain + Nociceptive pain (heat pain stimulation)	Concurrent validity	NRS	ECG	5 min at rest, 1 min for deep breathing test, 15 s for Valsalva maneuver	Correlation, Inter-group differences
Buvanendran et al. [60]	To determine the difference in brain activity in cancer patients with moderate to severe chronic pain versus no pain	Clinical	20	50.15 (19.79) - 17 F	Lymphoma (11), Breast (2), Lung (5), Pancreas (1), Esophageal (1)	Chronic pain	Concurrent validity	NRS	PET	17 min scan	Intergroup differences

(*continued on next page*)

Table 1 (*continued*)

Refs.	Study objective	Settings	No subjects	Age *mean (std)* Gender	Cancer diagnosis (no.)	Information on pain	Study type	Pain assessment	Physiological signals(s)	Recording duration	Statistical analyses
Jane et al. [49]	To examine the effects of massage therapy	Clinical	30	51.7 (11.6) - 19 F	Lung cancer (11), breast cancer (11), head and neck (2), gastrointestinal (4), genitourinary (2)	Metastatic bone pain	Sensitivity to change	Before and after antalgic therapy	PPG, BP	–	Pre-Post therapy
Guasti et al. [50]	To test the pain sensitivity in athyreotic patients followed for differentiated thyroid carcinomas during profound, short-term hypothyroidism induced for clinical reasons and during LT4-replacement treatment, focusing on the potential interferences of blood pressure-mediated changes in pain perception that may occur in the two clinical conditions.	Clinical	19	49 (15) - 14 F	Thyroid carcinoma (19)	Nociceptive pain (electrical stimulation)	Concurrent validity	Dental pain sensitivity	BP	–	Correlation
Badr et al. [51]	To study the relationship between different indicators of pain, including self-reports, behavioral observations, and physiological measures, in children with cancer undergoing invasive procedures	Clinical	45	4–10 (range) - 17 F	Leukemia (23), Solid Tumors (22)	Nociceptive pain (access of a subcutaneous central venous port)	Concurrent validity	FACES rating scale, DOLLS rating scale	PPG, BP	–	Correlation
Ferrell-Torry and Glick [52]	To assess the effect of massage therapy on anxiety, relaxation, and the perception of pain in hospitalized cancer patients	Clinical	9	56.6 (range:23–77) - 0 F	Esophageal (2), rectum (1), prostate (1), stomach (1), lung (1), lymphocytic leukemia (1), mixed nodular lymphoma (1), poorly differentiated cancer with an unknown primary site (1)	Cancer pain	Sensitivity to change	Before and after antalgic therapy	BP, Respiration	–	Pre-Post therapy

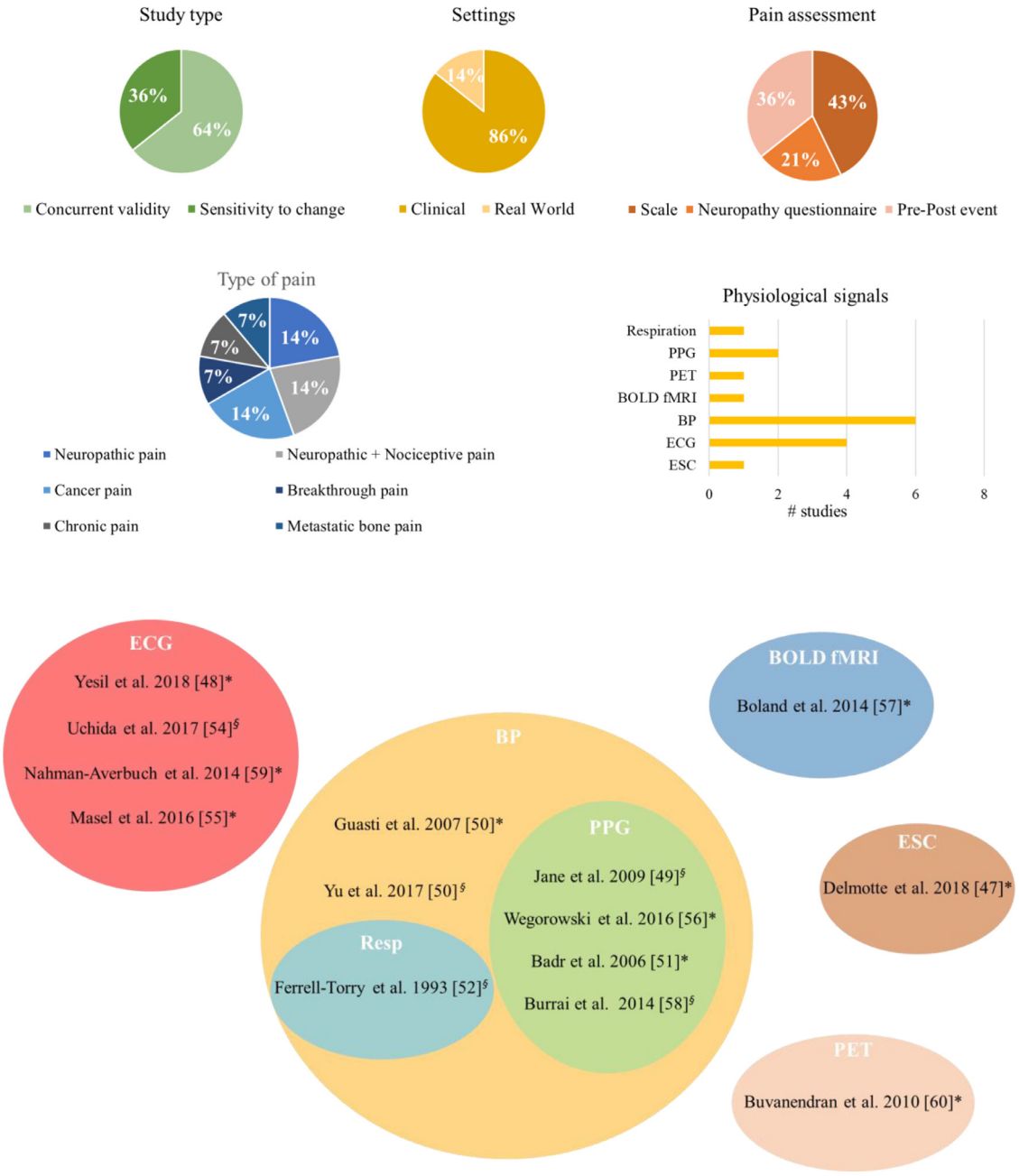

Fig. 2. Graphical representation of the salient features of selected studies: * concurrent validity studies; § sensitivity to change studies
ECG: Electrocardiogram, BP: Blood Pressure, BOLD fMRI: Blood-Oxygenated-Level-Dependent functional Magnetic Resonance Imaging, ESC: Electrochemical Skin Conductance, PET: Positron Emission Tomography.

lated physiological parameters to classify patients by whether they had pain or not by analyzing the Receiver Operating Characteristic (ROC) curve [47].

A total of 19 different physiological parameters were assessed in association with pain; 14 were significantly related to pain in at least one study. The most-used physiological parameters are those extrapolated by HRV analysis and BP.

We further divided the concurrent validity studies by physiological signal type: monodimensional signal (i.e., time-series) and neuroimaging techniques. The main findings of the selected studies about physiological parameters are presented in Table 2.

3.3.1. Monodimensional signal

Four monodimensional signals were used, from which 17 physiological parameters were derived. Twelve of the parameters were statistically significantly associated with state-of-the-art PAT, both in terms of correlation and intergroup differences.

Four of the physiological parameters were used in more than one study: heart rate, LF/HF ratio, total power, systolic blood pressure. Specifically, heart rate showed to be higher in patients with neuropathic pain [48] and correlated with a state-of-the-art PAT [51], but in the other two studies, it was not significantly associated with pain scales [55,56]. The LF/HF ratio, obtained as an output from HRV Analysis, was exploited in three different studies, resulting significantly higher in neuropathic patients and positively related to neuropathic scale only in one study [48]. In comparison, the results gathered by the other two studies were not statistically relevant [55,59]. Two studies assessed the behavior of total power, another parameter obtained by the HRV Analysis, which showed

Table 2
Main findings of the selected studies

Concurrent validity studies Monodimensional signals Ref.	Pain assessment	Physiological signal(s)	Physiological parameter(s)	Main results	Correlation with pain	Intergroup differences Pain	Significance level No pain	
Delmotte et al. 2018 [47]	Neuropathic Pain Symptom Inventory (NPIS)	ESC	Hands ESC	Significantly lower in the presence of painful neuropathy		55.4 (19.7) μS	77.6 (7.9) μS	p = 0.0003
				Significantly correlated with NPSI score	R = -0.69			p < 0.0001
			Feet ESC	Significantly lower in the presence of painful neuropathy		55 (15) μS	78.1 (6.6) μS	p < 0.0001
				Significantly correlated with NPSI score	R = -0.79			p < 0.0001
Yesil et al. 2018 [48]	Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)	ECG	SDNN	Significantly higher in NP patients		116.44 (26.44) ms	141.21 (26.02) ms	p = 0.001
				Negatively related to LANSS score	R = -0.391			p < 0.01
			SDAAN	Significantly lower in NP patients		109.78 (26.04) ms	132.12 (26.89) ms	p = 0.003
				Negatively related to LANSS score	R = -0.36			p < 0.01
			SDNNindex	Significantly lower in NP patients		41.5 (9.51)	49.33 (10.41)	p = 0.007
				Negatively related to LANSS score	R = -0.278			p < 0.05
			Total power	Significantly lower in NP patients		1764 (795.61) ms^2	2455.25 (991.02) ms^2	p = 0.009
				Not related to LANSS score	Data not shown			
			LF/HF	Significantly higher in NP patients		4.68 (1.82)	3.1 (1.34)	p < 0.001
				Positively related to LANSS score	0.256			p < 0.05
			HR	Significantly higher in NP patients		86.83 (9.28) bpm	80.63 (7.61) bpm	p < 0.05
Masel et al. 2016 [55]	NRS	ECG	Log LF/HF	Non-significant reduction after treatment	Data not shown			
				Decreased in all patients who had a reduction in pain of > 2 points, but remained unchanged in patients who had reductions of up to 2 points	Data not shown			

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Table 2 (*continued*)

Concurrent validity studies Monodimensional signals Ref.	Pain assessment	Physiological signal(s)	Physiological parameter(s)	Main results	Correlation with pain	Intergroup differences Pain	Significance level No pain	
			HF	Remained unchanged No significant correlation with NRS	Data not shown	Data not shown	Data not shown	
			LF/HF	Remained unchanged. No significant correlation with NRS	Data not shown	Data not shown	Data not shown	
			Total power	Remained unchanged. No significant correlation with NRS	Data not shown	Data not shown	Data not shown	
			pNN50	Remained unchanged. No significant correlation with NRS	Data not shown	Data not shown	Data not shown	
			HR	Remained unchanged. No significant correlation with NRS	Data not shown	Data not shown	Data not shown	
Wegorowski et al. 2016 [56]	VAS	PPG, BP	HR	No significant correlation with pain intensity	R = 0.143			p = 0.157
			SysBP	Positive correlation with pain intensity	R = 0.386			p < 0.001
			DiaBP	Positive correlation with pain intensity	R = 0.446			p < 0.001
Nahman-Averbuch et al. 2014 [59]	NRS	ECG	rMSSD	No difference between painful and non-painful-PNP groups		17.9 (range 3.3-24.8) ms	7.7 (range 4.5-26.6) ms	p = 0.237
				In non-painful-PNP group, lower rMSSD correlated with lower heat pain threshold. Not significant in painful-PNP group, significant correlation considering all the patients (with and without pain)	R = 0.433			p = 0.05
			LF/HF	No difference between painful and non-painful-PNP groups	3.2 (range 0.9-9.1)	4.4 (range 0.4-10.8)		p = 0.878
			Deep breathing ratio	No difference between painful and non-painful-PNP groups		1.12 (range 1.02-1.41)	1.14 (range 1.05-1.43)	p = 0.951
			Valsalva ratio	No difference between painful and non-painful-PNP groups		1.39 (range1.04-1.97)	1.42 (range 1.17-1.74)	p = 0.972
				Lower Valsalva ratio correlated with a lower level of pain change value	R = -0.495			p = 0.023
				Negative correlation with average pain ratings to the "test stand-alone" stimulus	R = -0.559			p = 0.008

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Table 2 (*continued*)

Concurrent validity studies Monodimensional signals Ref.	Pain assessment	Physiological signal(s)	Physiological parameter(s)	Main results	Correlation with pain	Intergroup differences Pain	Significance level No pain	
Guasti et al. 2007 [50]	Dental pain sensitivity	BP	SysBP	No association between blood pressure changes and pain sensitivity variations	Data not shown			
Badr et al. 2006 [51]	FACES rating scale, DOLLS rating scale	PPG, BP	HR	Significant correlations with 3 time points for FACES	R = 0.82, 0.71, 0.85			$p < 0.01$
				Significant correlations with 3 time points for DOLLS	R = 0.78, 0.97, 0.76			$p < 0.001$
			SysBP	Significant correlations with 3 time points for FACES	R = 0.59, 0.78, 0.91			$p < 0.001$
				Significant correlations with 3 time points for DOLLS	R = 0.75, 0.81, 0.79			$p < 0.001$
			SpO2	Not correlated to either the FACES or DOLLS scores	Data not shown			
Neuroimaging techniques Ref.	Pain assessment	Physiological signal(s)	Physiological parameter(s)	Main results	Correlation with pain	Intergroup differences Pain	Significance level No pain	
Boland et al. 2014 [57]	Total Neuropathy Score reduced version (TNS-reduced) - Patients vs healthy subjects	BOLD fMRI	BOLD response	Heat-pain stimulation evoked a BOLD response in healthy volunteers and patients		=	$p < 0.001$	
				Patients demonstrated significantly less activation in R superior frontal gyrus		-	+	$p = 0.03$
				Patients demonstrated significantly greater activation in L precuneus		+	-	$p = 0.01$
				Significant correlation of BOLD response with TNS-reduced version in the left operculo-insular cortex	+			$p = 0.03$
Buvanendran et al. 2010 [60]	NRS	PET	Brain activation	Patients with moderate-to-severe pain had increased regional glucose metabolism bilaterally in the prefrontal cortex		+	-	z-score > 3
				Unilateral activation was found in the right parietal precuneus cortex.		+	-	z-score > 3
				No areas of the brain showed decreased activity due to moderate-to-severe pain.	=			-

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Table 2 (*continued*)

Concurrent validity studies Monodimensional signals Ref.	Pain assessment	Physiological signal(s)	Physiological parameter(s)	Main results	Correlation with pain	Intergroup differences Pain	Significance level No pain		
Sensitivity to change studies Ref.	Intervention	Physiological signal(s)	Physiological parameter(s)	Main results	Longitudinal differences Before intervention	Intergroup differences After intervention	Experimental Group	Significance level Control Group	
Uchida et al. 2017 [53]	Antalgic therapy	ECG	HF	Significant increase before and after antalgic therapy for the experimental group	35.6 (14.3) ms^2	49.4 (3.0) ms^2			p = 0.01
				No statistical differences between groups			36.1 (9.0) ms^2	35.6 (14.3) ms^2	p = 0.933
			LF/HF	No statistical differences before and after antalgic therapy for the experimental group	2.3 (1.4)	1.6 (1.4)			p = 0.104
				No statistical differences between groups			1.9 (0.8)	2.3 (1.4)	p = 0.476
Yu et al. 2017 [54]	Antalgic therapy	BP	SysBP	Reduction after the antalgic therapy, not significant	Data not shown	Data not shown			
			DiaBP	Reduction after the antalgic therapy, not significant	Data not shown	Data not shown			
			HR	Reduction after the antalgic therapy, not significant	Data not shown	Data not shown			
Burrai et al. 2014 [58]	Relaxation therapy	BP, PPG	SysBP	No statistical differences before and after therapy for the experimental group	100 (80-160) mmHg	110 (80-130) mmHg			p = 0.644
				No statistical differences before and after therapy for the control group	100 (70-130) mmHg	100 (80-130) mmHg			p = 0.139
				No statistical differences between groups			110 (80-130) mmHg	100 (80-130) mmHg	p = 0.253
			DiaBP	No statistical differences before and after therapy for the experimental group	70 (50-110) mmHg	70 (60-90) mmHg			p = 0.868
				No statistical differences before and after therapy for the control group	70 (50-80) mmHg	70 (60-80) mmHg			p = 0.120
				No statistical differences between groups			70 (60-90) mmHg	70 (60-80) mmHg	p = 0.223
			HR	No statistical differences before and after therapy for the experimental group	74 (56-84) bpm	74.5 (50-104) bpm			p = 0.672
				Significant differences before and after therapy for the control group	74.5 (50-104) bpm	74 (55-98) bpm			p = 0.018
				No statistical differences between groups			74.5 (50-104) bpm	74 (55-98) bpm	p = 0.486
			SpO2	No statistical differences before and after therapy for the experimental group	98 (94-100) %	99 (94-100) %			p = 0.192
				Significant differences before and after therapy for the control group	97 (94-100) %	97 (91-100) %			p = 0.319
				Significant differences between groups			99 (94-100) %	97 (91-100) %	p = 0.003

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Table 2 (*continued*)

Concurrent validity studies Monodimensional signals Ref.	Pain assessment	Physiological signal(s)	Physiological parameter(s)	Main results	Correlation with pain	Intergroup differences Pain	Significance level No pain	
Jane et al. 2009 [49]	Relaxation therapy	PPG, BP	HR	No statistical differences before and after therapy	83.7 (17.2) bpm	82.9 (15.1) bpm		$p = 0.35$
			MAP	No statistical differences before and after therapy	88.8 (14.2) mmHg	90.1 (14.5) mmHg		$p = 0.26$
Ferrell-Torry et al. 1993 [52]	Relaxation therapy	BP, Respiration	HR	No significant differences before and after therapy	80.4 (16.5) bpm	77.2 (17.3) bpm		$p > 0.05$
				Significant decrease before and 10-minutes after therapy	80.4 (16.5) bpm	75.9 (16.3) bpm		$p < 0.05$
			RR	Significant decrease before and after therapy	22.6 (2.2) breaths/min	19.7 (2.5) breaths/min		$p < 0.05$
				Significant decrease before and 10-minutes after therapy	22.6 (2.2) breaths/min	19.8 (2.3) breaths/min		$p < 0.05$
			SysBP	Significant decrease before and after therapy	120.9 (14.7) mmHg	114.7 (16.8) mmHg		$p < 0.05$
				No significant decrease before and 10-minutes after therapy	120.9 (14.7) mmHg	115.1 (15.1) mmHg		$p > 0.05$
			DiaBP	Significant decrease before and after therapy	74.9 (8.6) mmHg	69.1 (7.0) mmHg		$p < 0.05$
				No significant decrease before and 10-minutes after therapy	74.9 (8.6) mmHg	73.1 (7.2) mmHg		$p > 0.05$
			MAP	Significant decrease before and after therapy	90.2 (7.0) mmHg	84.3 (6.7) mmHg		$p < 0.05$
				No significant decrease before and 10-minutes after therapy	90.2 (7.0) mmHg	87.1 (5.1) mmHg		$p > 0.05$

Means followed by similar superscript within a row did not differed significantly ($p<0.05$)

Table 3
Quality assessment for the two categories of studies.

	QUADAS-2 – Concurrent validity studies													
	Patients selection				Index test			Ref. Standard			Flow and Timing			
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Risk of bias
Delmotte et al. [47]	NA	N	NA	Y	N	NA	Y	Y	Y	Y	NA	Y	NA	High
Yesil et al. [48]	NA	N	Y	Y	N	NA	Y	Y	Y	Y	NA	Y	Y	Low
Masel et al. [55]	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	NA	Low
Wegorowski et al. [56]	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	NA	Low
Nahman-Averbuch et al. [59]	NA	N	Y	Y	Y	NA	Y	Y	Y	Y	NA	Y	NA	Low
Boland et al. [57]	N	N	Y	Y	N	NA	Y	Y	Y	Y	Y	Y	Y	Low
Buvanendran et al. [60]	Y	Y	Y	Y	N	NA	Y	Y	Y	Y	NA	Y	Y	Low
Guasti et al. [50]	Y	Y	Y	Y	N	NA	Y	Y	Y	Y	Y	Y	Y	Low
Badr et al. [51]	NA	N	NA	Y	Y	NA	Y	NA	NA	NA	NA	Y	N	High

	NIH QAT – Sensitivity to change studies											
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Risk of bias
Uchida et al. [53]	Y	N	Y	N	Y	Y	Y	NA	Y	Y	N	Low
Yu and Seol [54]	Y	N	Y	Y	Y	Y	Y	NA	Y	Y	N	Low
Burrai et al. [58]	Y	Y	Y	N	Y	Y	Y	NA	Y	Y	Y	Low
Jane et al. [49]	Y	Y	NA	N	NA	N	Y	NA	Y	Y	Y	High
Ferrell-Torry and Glick [52]	Y	N	N	Y	N	Y	Y	NA	Y	Y	Y	Low

NA = Not Available.

to be significantly lower in patients with neuropathic pain [48] and not significantly correlated with pain scale [55]. Finally, the systolic blood pressure was assessed in three studies, showing a significant positive correlation with two different pain scales [51,56].

3.3.2. Neuroimaging techniques

Two studies employed brain imaging techniques (BOLD fMRI and PET imaging) to assess pain. The information regarding the association between measured activity in specific brain areas and pain (i.e., positive correlation with pain, or higher in patients' group with pain) is presented in Table 2.

3.3.3. Study quality

The risk of bias is reported in Table 3. Seven out of nine studies in this category present an overall low risk of bias [48,50,55–57,59,60]. Both studies with an overall high risk of bias [47,51] lack information concerning the patients' selection procedures, the index test [47], and the reference standard [51]. Due to lack of information, the risk of bias about index test and flow and timing remains unclear for most studies.

3.4. Sensitivity to change studies

All five studies in the sensitivity-to-change group were carried out in a clinical setting. Four of them assessed the behavior of the physiological parameters before and after a therapy [49,52,54,58]. One of them evaluated differences before and after a painful intervention (i.e., surgery) [61]. BP was used in four out of five works, ranking first among physiological signals, followed by PPG (2/5), ECG (1/5), and Resp (1/5). In two studies, participants were divided into an experimental and a control group. Thus the intergroup differences could be assessed, besides the differences before and after the intervention. Pre-post differences were assessed by using *t*-test [49,53], analysis of variance (ANOVA) [52,54], or Wilcoxon test [58], while inter-group differences were assessed by using *t*-test [53] or Mann-Whitney U test [58]. The main findings of the selected sensitivity-to-change studies are reported in Table 2. A graphical depiction about the main features of the sensitivity to change studies is given in Supplementary Materials, Fig. SS.

All the sensitivity-to-change studies exploited monodimensional signals. A total of 8 different physiological parameters were assessed: six of them were found to differ significantly before and after the intervention in at least one study. The most used parameters were heart rate and blood pressure-related properties (systolic, diastolic, or mean arterial pressure), both exploited in four studies.

Four physiological parameters were used in more than one study: heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure. Specifically, heart rate was used in four studies, showing a common trend to decrease after an antalgic therapy in two of them [52,58] and no statistically significant change in the other two studies [49,54]. Parameters from blood pressure were extensively used in different studies. Results on systolic blood pressure show a reduction of different intensities after an antalgic therapy in two studies [52,58], and no significant results in another one [54]. Diastolic blood pressure was found to decrease after antalgic therapy in only one [52] out of three studies [54,58] significantly. Mean arterial pressure was used in two studies, decreasing significantly after an antalgic therapy in one study [52], while it did not significantly change in the other study [49].

3.4.1. Study quality

The risk of bias is reported in Table 3. Four out of five studies [52–54,58] present a low risk of bias. The overall high risk of bias for [49] is mainly due to patients' selection criteria (Q3, Q4, Q5). For all the studies, no information regarding the blindness of the examiner (Q8) was reported. All studies clearly defined the objective (Q1) and the outcome measures (Q7), had a loss of follow-up less than 20% (Q9), and the statistical methods were applied correctly to assess differences before and after the intervention, providing the related p-values (Q10).

4. Discussion

The primary purpose of this systematic review is to clarify the effects of pain on cancer patients' physiological signals. To do so, we investigated which signals are currently used, their concurrent validity with routine pain assessment tools, their sensitivity to change in pain levels, and the diffusion of instrumental pain assessment in real-world settings.

A majority of selected studies assessed the concurrent validity of physiological parameters against scales and/or question-

naires, while other studies evaluated the sensitivity-to-change of the physiological parameters to an intervention. The two categories of studies present consistent primary objectives: concurrent validity studies mainly aimed to assess the behavior of the physiological signals in relation to the patients' painful state, either via comparisons with state-of-the-art PAT or clustering subjects based on the different levels of pain. Sensitivity to change studies all focused on finding evidence through physiological signals of the efficacy of antalgic therapies.

4.1. Monodimensional signals

Most of the included studies use monodimensional signals to quantify some aspects of ANS activation. In concurrent validity studies, only four physiological parameters are present in more than one selected study. Despite the small sample size, both in terms of the number of studies and participants, and the lack of methodological information, it was still possible to find consistent results among these studies. When limiting to statistically significant results, heart rate, LF/HF ratio, and systolic blood pressure values consistently correlated with pain positively: the higher the self-reported pain, the higher the parameter's value. The same association was also found in sensitivity to change studies, which showed a decrease in heart rate and systolic and diastolic blood pressure after an antalgic therapy or an experimental relaxation procedure. Higher values of these parameters are attributable to a more active sympathetic than parasympathetic branch of the ANS [62], which is in line with what is expected during a pain experience. However, one should keep in mind that more complex interactions may play a role [35]: pain sensation triggers a complex net of neurological paths, which are not always activated linearly (if the relationship were linear, the higher the pain perception, the greater the activation of the monitored physiological function would be). It follows that a correlation analysis can only partially explain the relationship between pain and physiological signals. The assessment of non-linear relationships and more complex models involving different physiological signals might help address this problem. Indeed, an increasing number of studies in the emotion recognition field use artificial intelligence algorithms [63–65] because they are capable of extrapolating complex relationships between several inputs (physiological parameters) and a single output (pain perception).

Within the monodimensional signals set, a noticeable application is represented by the Electrochemical Skin Conductance, exploited only in one study [47], aiming to classify cancer patients with painful neuropathy. The Electrodermal Activity is a quantitative measure of the sympathetic nervous system [66], and it is widely used in the emotion recognition field, particularly in automatic pain recognition algorithms [67–69]. Future studies could involve using such signal, which proved to be well suited and can also be recorded by means of wearable devices.

4.2. Heart rate and heart rate variability

Heart rate is the most-used physiological parameter linked to pain assessment. The reference gold standard is the ECG signal, although recent research has focused more on heart rate estimated from the PPG signal. Its better convenience and pervasiveness justify this choice. Heart rate and the derived HRV parameters [62] extrapolated by the PPG are currently used in stress detection algorithms [70,71]. However, there are some concerns regarding the reliability of the PPG signals, which can be easily corrupted by external noise and motion artifacts leading to inaccurate HRV estimates [72].

HRV analysis is well-suited for real-world applications: Holter ECG is a long-established technique in routine clinical practice, while PPG can be easily embedded into a wearable device (e.g., a smartwatch or ring). Indeed, the only two studies run in a free-living context are based on HRV analysis using a 24 h Holter ECG device. Notably, the work of Masel et al. [55] showed the possibility of detecting pain episodes without active cooperation from patients. This result clearly highlights the possible disruptive role of automatic pain assessment in real-world settings: a tool to detect pain timely, even in unconscious patients, and, in turn, provide antalgic therapy at pain onset.

4.3. Neuroimaging techniques

Relevant information can also be deduced by neuroimaging techniques, giving the possibility to explore brain areas involved in pain perception. Such methods are valuable for research purposes since pain-activated CNS processes are still not fully understood. On the other hand, they cannot represent an alternative cancer pain assessment solution because of their bulky instrumentations and expensive procedures.

4.4. Study quality

The study quality assessment revealed a low risk of bias for eleven out of fourteen studies. We considered it appropriate to select two study quality tools, QADAS-2 and NIH-QAT, to assess the different sources of risk of bias for the two different study designs. QADAS-2 proved to be well suited for highlighting the primary sources of bias for the concurrent validity studies: it is worth noting the significant lack of information, especially for index test (i.e., physiological parameter) and flow and timing sections, for which the risk of bias remains unclear. For sensitivity to change studies, we chose NIH-QAT, conceived as a tool for before-after (pre-post) studies with no control group. Although some studies in this category were presented as randomized control trials, we were solely interested in physiological signals changes before and after an intervention. As a result, sensitivity to change studies proved to be less prone to bias than concurrent validity studies, except that there is no information available for any study on the blindness of the examiners (Q8).

4.5. Limitations

The studies included in this review displayed a marked heterogeneity in the type of cancer and pain source to be evaluated. Such heterogeneity is a direct consequence of the broad range of painful conditions grouped under the umbrella term "cancer pain" that includes all the painful conditions related to cancer, regardless of the primary cancer sites and the painful stimulus. More so, concurrent validity studies highlight the wide range of the currently available state-of-the-art PAT (e.g., NRS, VAS, neuropathy-specific questionnaires). Altogether, fragmentation and lack of accepted guidelines in pain assessment represent another hint that there is the need to promote and standardize this very delicate aspect of cancer patient management, as also highlighted in [73].

Available literature also shows a considerable lack of methodological information regarding the experimental procedures and measurement setups that partly prevent the replicability of studies. Even if physiological parameters are clearly time-dependent and often non-stationary, only five studies out of fourteen report the recording duration, and no one specifies the sampling frequency of the collected physiological signals. This underreporting represents a significant limitation and prevents accurate comparisons or meta-analyses for those studies based on time-dependent variables (e.g., parameters from HRV analysis) since the same parameter can assume a different meaning in different time frames [59].

A limitation in using physiological signals to assess pain is that physiological mechanisms can be further affected by personal factors, like gender [74], age [75], and health status (which is particularly true in cancer). In some cases, cancer pathology itself can lead to a change in physiological mechanisms, which can be misinterpreted and related to the pain experience [76]. This limitation should be overcome, in the future, by analyzing larger patient cohorts. .

4.6. Future directions

Cancer pain is a remarkably complex and multidimensional phenomenon that impacts the patients' psychological, social, and spiritual well-being [77]. As highlighted in the European Society for Medical Oncology position paper [78], a patient-centered approach is needed for cancer treatment, and this approach should also be translated to pain assessment. To reach this goal, implementing a biopsychosocial model [76] for pain assessment could overcome the limitations imposed by the current tools, providing a complete picture of the pain state that considers all the different aspects that converge in the pain experience.

The challenge of assessing cancer patients' pain in a free-living context is relevant but still largely unaddressed. Several smartphone apps have been developed to date that can provide pain management for cancer patients. Most are based on self-rated pain assessments [79,80], but a brand-new app— whose feasibility and acceptability are being assessed in a pilot study—exploits the smartphone hardware to record some physiological parameters like heart rate and activity level [81].

In this scenario, wearable and mobile technologies can represent a game-changer, offering a valuable source of novel information. Pervasive monitoring systems allow the collection of long-term multimodal physiological recordings in a real-world context, giving the possibility to extrapolate information that could not be otherwise obtained in clinical settings. Such an approach is perfectly suitable for those clinical trials that involve interventions in free-living scenarios, in which participants can freely conduct their daily activities while their physiological functions are being monitored. Moreover, such an approach allows recording the natural physiological response to pain, unlike those studies that analyze the acute reaction when an external nociceptive stimulus is applied.

In order to efficiently elaborate the information gathered by wearable sensors, a proper approach should be applied, and AI algorithms could offer a viable solution. AI algorithms can indeed help identify complex patterns in long-term multimodal physiological recordings [36]. These are the prominent aspects that should be considered before these methods can be translated into a tool to tailor and personalize the antalgic interventions:

- Big data approach: AI algorithms reach good performances if they are trained on large datasets. Thus, when setting a study protocol, it is necessary to collect a reasonable number of instances that will be used to train the algorithms to avoid the curse of dimensionality [82].
- The individual variability of the physiological response: we have a limited mechanistic understanding of interindividual differences in pain and analgesia response. This issue can be considered, for example, by conducting a leave one subject out cross-validation to train the AI algorithms in order to correctly manage the inter-subject variability [83].
- Confounding factors: physiological signals can be affected by several other factors in addition to pain. These factors can be accounted for by enriching the AI algorithms with information related, for example, to personal (i.e., age, gender, weight, height) or health data (i.e., pathology, depression, and anxiety levels). Based on the specific type of pain being investigated, researchers should then collect other information besides pain, including patient-reported outcomes, that can help in better understanding the physiological response linked to the experienced pain [84].

We are currently working on the design of innovative clinical trials, carried out in residential facilities by monitoring patients in their free-living, and thus collecting the pain response when and where it is experienced

5. Conclusions

This systematic review collected and pooled the knowledge regarding the behavior of physiological parameters in response to cancer patients' pain. Although the included studies were characterized by considerable heterogeneity, it was still possible to identify promising results relevant to develop new pain assessment tools for cancer patients based on physiological signals and, possibly, wearable sensors, paving the way to real-world scenarios.

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Availability of data and material

The data supporting this systematic review are from previously reported studies and datasets, which have been cited.

Code availability

Not applicable.

Declaration of Competing Interest

The authors declared that the research was conducted in absence of any commercial of financial relationships that could be configured as a potential conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cmpb.2022.106682.

Appendix A

Glossary of physiological signals and computed parameters

Physiological signal	Physiological parameter acronym	Explanation	Unit of measure
Electrocardiogram (ECG) / Photoplethysmography (PPG)	HR	Heart Rate	bpm
	SDNN	Standard deviation of NN intervals	ms
	SDAAN	Standard deviation of the mean of NN intervals	ms
	SDDNindex	Mean of the standard deviation of NN intervals	[]

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Physiological signal	Physiological parameter acronym	Explanation	Unit of measure
	rMSSD	Root mean square of successive differences	ms
	pNN50	Percentage of successive NN intervals that differ from one another by > 50 ms	%
	Total power	Total power	ms^2
	LF	Low Frequency	ms^2
	HF	High Frequency	ms^2
	LF/HF	Low frequency/High frequency ratio	[]
	Log LF/HF	Logarithm of Low Frequency/High Frequency ratio	[]
	Deep breathing ratio	Ratio of the longest RR interval over the shortest RR interval during deep breathing test	[]
	Valsalva ratio	Ratio of the longest RR interval after Valsalva maneuver over the shortest RR interval during the maneuver	[]
Photoplethysmography (PPG)	SpO2	Amount of oxygen-carrying hemoglobin in the blood relative to the amount of non-oxygen-carrying hemoglobin	%
Electrochemical Skin Conductance (ESC)	Hands ESC	Hands Electrochemical Skin Conductance	μS
	Feet ESC	Feet Electrochemical Skin Conductance	μS
Blood Pressure (BP)	SysBP	Systolic Blood Pressure	mmHg
	DiaBP	Diastolic Blood Pressure	mmHg
	MAP	Mean Arterial Pressure	mmHg
Respiration	RR	Respiration Rate	breaths/min

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