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IN

INFORMATION AND COMMUNICATION TECHNOLOGY FOR HEALTH

IMPLEMENTING MULTIPLE AI-BASED STRATEGIES TOWARD AUTOMATIC PAIN ASSESSMENT IN CANCER PATIENTS. THE PASCALE INVESTIGATION

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Abstract

This document describes the preliminary results of the research activities carried out within the Ph.D. in Information and Communication Technology for Health (ICTH) on the topic of automatic pain assessment (APA) in cancer patients at the Department of Electrical Engineering and Information Technologies (DIETI) of the University of Naples "Federico II".
This research line is dedicated to advancing innovative strategies grounded in artificial intelligence (AI) methodologies with a central focus on objectively probing pain features within the context of oncological patients. The overarching goal is to collect and comprehensively analyze multimodal and multidimensional data. Clinical assessment and data collection is performed through conventional in-person evaluations as well as synchronous and asynchronous telemedicine modalities.
In pursuit of these objectives, the research endeavors to leverage several state-of-the-art AI approaches for developing methodologies that transcend traditional subjective pain assessment methods. Behavioral-based APA investigations, including facial expressions of pain and multiple speech analyses, and biosignal studies are performed. Multimodal parameters are integrated to study different cancer pain phenomena that are less understood and difficult to investigate.
The aspiration is to pave the way for more effective and personalized pain management strategies by unravelling the intricate layers of pain experiences in cancer patients.

Keywords
Cancer Pain; Automatic Pain Assessment; Artificial Intelligence; Machine Learning; Natural language processing; Biosignals; Electrodermal activity; Breakthrough Cancer Pain

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Abbreviations list

(Alphabetical order)

AI: artificial intelligence

ANS: autonomic nervous system

APA: automatic pain assessment

AU: action unit

BPI: brief pain inventory

BTcP: breakthrough cancer pain

CDA: continuous decomposition analysis

CNN: convolutional neuronal network

ECG: electrocardiography

ECOG: Eastern Cooperative Oncology Group Performance Status

EDA: electrodermal activity

EEG: electroencephalography

HRV: heart rate variability

MCA: multiple correspondence analysis

MED: morphine equivalent dose

ML: machine learning

NRS: numeric rating scale

PCA: principal component analysis

RNN: recurrent neural network

ROC: receiver operating characteristic

SVM: support vector machine

TDA: time domain analysis

TTP: trough-to-peak

VAD: valence-arousal-dominance

VAS: visual analog scale

1. Chapter:

Background. Automatic Pain Assessment

1.1. Challenges in Cancer Pain Assessment

Pain is one of the most common and debilitating symptoms in cancer patients. It is estimated that up to 55% of patients experience pain during anticancer treatment and this percentage rises to 66% for those with metastatic, advanced, or terminal disease [1]. While for effective pain management, an accurate assessment of the symptoms is mandatory [2], pain assessment according to unidimensional pain ratings such as the 0-10 numeric rating scale (NRS) and the Visual Analog Scale (VAS) have important limitations. They are susceptible to reporting bias influenced by psychosocial factors, including tendencies to catastrophize or underreport pain [3]. Multidimensional scales, on the other hand, are assessment tools used to evaluate and quantify various aspects of pain, considering that pain is a complex and subjective experience that encompasses more than just the intensity of physical discomfort. These scales such as the Brief Pain Inventory (BPI) which assesses both the intensity and interference of pain [4], and the McGill Pain Questionnaire [5], also available in a short-form instrument [6], for evaluating various aspects of pain, including sensory, affective, evaluative, and miscellaneous qualities, consider multiple dimensions of pain, including sensory, emotional, cognitive, and social aspects. Although these tools are particularly useful in clinical settings to provide a comprehensive understanding of a patient's pain experience, they do not provide an objective and exhaustive measurement of pain [7]. The key limitations of multidimensional pain scales include their inherent limited specificity. This gap arises because some of these scales are intentionally crafted to provide a comprehensive overview of various facets of the pain experience. However, this broad approach may lack the necessary granularity to effectively assess and differentiate between specific types of pain or cater to the unique characteristics of distinct medical

conditions. Additionally, response bias is another noteworthy limitation. This bias can manifest when patients, out of concern or apprehension, consciously or unconsciously alter their responses to pain assessments. For instance, individuals may fear that reporting higher levels of pain could lead to an increase in prescribed medication or more aggressive treatment measures, influencing their self-reported pain scores. Furthermore, pain is inherently subjective, and self-reported assessments rely on the individual's interpretation and communication of their pain experience. This subjectivity can introduce variability and potential bias in the results [8].

To gain a comprehensive understanding of the strengths and benefits of the pain assessment tools at our disposal and, more importantly, to proactively evaluate the feasibility of incorporating objective pain data into established standards of practice, it is crucial to emphasize the fundamental distinction between nociception and pain as separate processes. Nociception refers to the physiological mechanism by which our body detects and responds to potentially harmful stimuli or noxious input. It is essentially the body's sensory system that alerts us to potential tissue damage or injury. This process involves the transmission of signals from specialized nerve receptors (nociceptors) to the central nervous system, where the information is processed. On the other hand, pain is a subjective and multifaceted experience that goes beyond the mere detection of noxious stimuli. Pain involves the interpretation and perception of these signals by the brain, encompassing not only the sensory aspect but also the emotional and cognitive dimensions. In other words, while nociception is a biological process, pain is a complex psychophysical phenomenon that can vary greatly from person to person. Nociception, indeed, is just one of the components responsible for pain expression and a multitude of biopsychosocial elements concur to structure complex clinical scenarios [9].

In this intricate context, the realm of pain assessment can be explored through multifaceted evaluations, encompassing both behavioral and instrumental approaches, leveraging the capabilities of artificial intelligence (AI) methodologies for comprehensive pain analysis. Consequently, investigations are directed toward the advancement of automatic pain assessment (APA) systems. The aim is to isolate the nociceptive component of pain, by setting its weight within the perceived symptomatology. Many research groups are engaged in this field of study and the integration of objective strategies into multifaceted subjective pain pathways is ongoing [10]. For example, computer vision

and machine learning (ML) techniques have been successfully applied in assessing pain from facial expressions [11]. The results show that APA may be a feasible way for a comprehensive and holistic pain assessment.

1.2. Strategies for APA research and targeted brain regions

The term APA serves as an umbrella encompassing a broad range of research approaches and methods. A classification based on the neurological and neurophysiological targets of these diverse modalities can offer a robust and meaningful categorization. The exploration of pain and its mechanisms encompasses a diverse array of strategies, each tailored to target specific brain regions and their intricate processing mechanisms. Briefly, the neocortex unravels the cognitive intricacies, the limbic brain delves into the emotional nuances, and the reptilian brain – the oldest layer of the brain, formed by the brainstem including medulla, pons, cerebellum, midbrain, globus pallidus, and olfactory bulbs – unveils the instinctual responses. This holistic approach, utilizing various tools and methodologies, not only broadens our comprehension of pain but also paves the way for innovative therapeutic interventions targeting specific facets of the intricate pain experience. Consequently, contemporary methodologies tend to incorporate multimodal techniques that integrate different observable behaviors with neurophysiological elements [12]. (Figure 1).

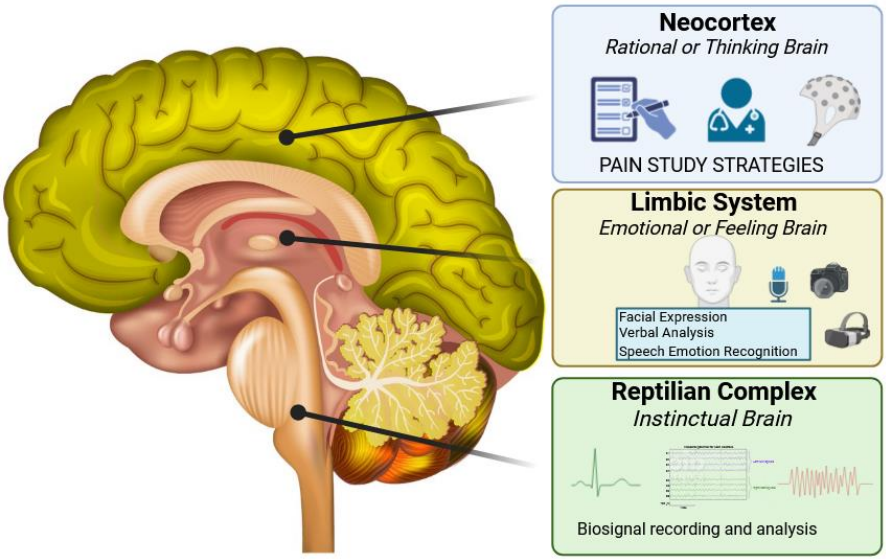

Figure 1. *Strategies for pain investigations. The potential strategies that can be employed for pain studying are broadly categorized based on the specific brain regions targeted and their respective processing mechanisms. The neocortex, particularly the somatosensory area, plays a pivotal role in elaborating pain-related information, including its location, intensity, and quality. It assists in discerning the source of pain in the body and assessing its severity. The investigation of these mechanisms relies on various techniques, including imaging, tools, clinical examinations, and instrumental methods such as EEG. The limbic brain is recognized as the seat of emotions, and the study of pain processes within this region is primarily conducted through behavioral approaches (e.g., facial expressions, and speech emotion recognition). Finally, the reptilian brain (i.e., brainstem), the most ancient part of the brain, governs instinctual responses. The study of pain in this context involves the recording and analysis of a range of biosignals.*

1.2.1. Neocortex APA investigations

A fundamental player in this intricate network is the neocortex, especially the somatosensory area. This cerebral domain assumes a critical role in unraveling the complexities of pain-related information, offering insights into its nuanced facets such as location, intensity, and quality of the sensorial input. It serves as the cognitive hub that aids in the identification of the pain's origin within the body and the evaluation

of its magnitude. The arsenal of techniques employed in investigating these neocortical mechanisms is vast and sophisticated. Imaging technologies, clinical examinations, questionnaires, and instrumental methods like electroencephalography (EEG) collectively contribute to dissecting the intricacies of pain perception. Through these tools, researchers can decipher the neural patterns associated with pain, providing a window into the brain's response to noxious stimuli. Accumulating evidence, for example, suggests that chronic pain is linked to structural and functional alterations in the brain [13]. Notably, EEG presents an avenue for monitoring these changes and serves as a tool for investigating “pain biomarkers” [14]. Distinctive neuronal activities in the sensorimotor cortex, such as an elevation in theta and gamma oscillations, may signify specific pain states [15]. Additionally, studies have revealed that the gamma band predominantly predicts acute thermal pain [16], and the peak alpha frequency recorded at the bilateral temporal scalp correlates with verbal pain reports during both stimulation and rest [17]. In a recent study, Chen et al. [18] introduced a multilayer convolutional neuronal network (CNN) model for objective EEG-based pain detection. Ten volunteers underwent a series of 15 movement tasks (M) (e.g., jogging on a running machine) and viewed 15 short videos (V) depicting pain scenes. Following data acquisition and preprocessing, the model's validation tested its ability to distinguish between "nonpain" and "pain" states. Concerning the model overall performance, the area under the receiver operating characteristic curve (AUC) was 0.83 and 0.81 for M and V, respectively. Several other attempts using EEG datasets were made. Misra et al. [15] employed a support vector machine (SVM) algorithm, a typical supervised ML algorithm, for binary classification (e.g., pain/no-pain). Levitt et al. [19] utilized SVM for obtaining pain phenotypes from EEG features in individuals with chronic lumbar radiculopathy and those scheduled for neuromodulation therapy. K-nearest neighbor (KNN), another ML classifier, requires no training phase and is highly sensitive to noisy samples. Nezam et al. [20] collected EEG and electromyogram (EMG) signals, employing SVM and KNN decision tree models to evaluate different pain levels, achieving classification accuracies exceeding 80%. In a different study, Elsayed et al. [21] combined signal processing techniques and ML strategies to analyze brain signals related to pain, categorizing them into four levels of pain intensity. The developed classifier demonstrated an accuracy of 94.83%. These findings, supported by other studies, suggest that normalized alpha power in the

central brain region may serve as a reliable marker for chronic pain, with potential clinical utility [22]. Addressing typical ML issues, such as overfitting and underfitting, is crucial. Random forest (RF), another ML approach, was employed by Vijayakumar et al. [23] to predict pain scores in healthy subjects, achieving high intrasubject and intersubject accuracies of 93% and 89.5%, respectively. Predictive modeling holds promise in pain medicine, particularly for complex conditions like chronic pain. Vuckovic et al. [24] used artificial neural networks (ANN), SVM, and linear discriminant analysis to identify spinal cord injured individuals at risk of developing central neuropathic pain, achieving accuracies surpassing 85% in all models. Moreover, recent evidence suggests that EEG features can predict the effects of pain treatments [25].

1.2.2. Behavioral-based APA research

The limbic system is a complex set of brain structures and pathways that play a crucial role in regulating emotions, memory, and certain aspects of behavior. It is often referred to as the "emotional brain" and is involved in the formation and processing of emotions and emotional responses. Therefore, it emerges as a pivotal arena for understanding the emotional dimensions of pain. Renowned as the epicenter of emotions, this region has become the focal point for behavioral approaches in pain studies.
In this context, research is highly complex. The limbic system, indeed, is not a distinct anatomical and functional structure but rather a network of interconnected regions within the brain. Key components of the limbic system include the hippocampus, located in the medial temporal lobe, and primarily associated with the formation of new memories and the conversion of short-term memories into long-term ones; the amygdala, situated near the hippocampus, and functionally essential for the processing of emotions, particularly fear and pleasure (emotional memories); the hypothalamus, responsible for regulating various physiological processes, including body temperature, hunger, thirst, and circadian rhythms and hormones release; thalamus, interconnected with limbic structures, and acts as a relay center for sensory information, directing signals to the appropriate areas of the cortex and limbic system; cingulate gyrus, a part of the cerebral cortex involved in various

functions, including emotion formation and processing, as well as the regulation of cognitive processes such as attention and decision-making. Behavioral pain assessment methods entail the observation and recording of an individual's behavioral responses to pain and the subsequent analysis of collected data to identify patterns and trends. For APA aims, different strategies are commonly employed. They mostly include facial expression analyses and speech analyses. Other less investigated behaviors address the connections between body posture and pain. In a captivating study, Walsh et al. [26] devised a stimulus set, and during the validation phase, they identified "head averted," "gaze downward," and "forward body lean" as prevalent body postures associated with pain, as portrayed by actors. Building on these observations, the study proposed that diminished head motion and modified postures could serve as indicative pain behaviors. For instance, Werner et al. [27] discovered that head movements and postures commonly exhibit a downward or pain-location-oriented orientation.

1.2.2.1. Facial expressions analyses

Observing facial expressions and employing speech emotion recognition techniques form the crux of investigations into how pain intertwines with our emotional landscape. By scrutinizing these behavioral cues, researchers can gain valuable insights into the subjective, affective components of pain experiences. Facial expressions play a pivotal role in non-verbal communication, particularly when conveying pain to others. Consequently, extensive research has been dedicated to studying facial expressions as an indicator of pain behavior, with the aim of enabling automatic and objective pain assessment [28,29]. Moreover, facial expressions of pain exhibit consistency across various factors, including age, gender, cognitive states (e.g., noncommunicative patients), and different types of pain, and may even correlate with self-reported pain levels [30].
Facial expressions indicative of pain can be categorized into two types: voluntary and involuntary physical manifestations. The former is consciously initiated by the cortex and can be controlled in real time but tends to be less fluid and displays more variability in movement. Involuntary facial expressions, on the other hand, are unconsciously triggered by subcortical processes and are characterized by symmetrical, synchronized, reflex-like movements of facial muscles, giving them a seamless appearance.

Action Units (AUs) are specific facial muscle movements or activations used to describe and analyze facial expressions. The concept of AUs was introduced in 1978 by psychologists Paul Ekman and Wallace V. Friesen as part of their Facial Action Coding System (FACS), which serves as a comprehensive tool for describing and analyzing human facial expressions [31]. FACS defines and categorizes 46 individual AUs, each representing a distinct movement or combination of movements of facial muscles, such as raising the eyebrows, wrinkling the nose, or pursing the lips. Manual analysis of this process can be highly intricate, but with the emergence of AI techniques, there has been a shift toward computer-mediated automatic detection of pain-related behaviors, employing various AI-based image processing strategies [32]. Consequently, the adoption of AI methodologies holds substantial promise and value within the realm of APA, especially in assessments based on facial behaviors.

1.2.2.2. Speech analysis and APA

Speech analysis is the process of studying and examining spoken language to extract meaningful information, identify patterns, and draw insights. This analysis can encompass various aspects of speech, including acoustic features, linguistic content, intonation, rhythm, and more. Speech analysis is often used in different fields for diverse purposes, such as speech recognition, emotion recognition, speaker identification, language identification, speech pathology, and other aims. In the case of speech or vocal emotion recognition, the analysis is centered around the acoustic features of the voice, including pitch, tone, rhythm, and intensity to recognize patterns associated with different emotional states. During the 1970s, Paul Ekman delineated the so-called discrete model of emotions encompassing six fundamental emotions including anger, disgust, fear, joy, sadness, and surprise [33]. An alternative viewpoint was introduced by Russell and Mehrabian [34] who, in their dimensional approach, showed that emotions can be situated along three primary dimensions namely valence (ranging from positive/pleasurable to negative/unpleasurable), arousal (spanning engaged to not engaged), and dominance (reflecting the level of control and individual has over their emotional states). According to this circumplex model, an affective state is viewed as a circle in the two-dimensional bipolar space.

Moreover, a three-dimensional model called the pleasure-arousal-dominance (PAD) model or Valence-Arousal-Dominance (VAD) was subsequently introduced by Mehrabian and Russell [35]. This model provides three independent dimensions including pleasure (valence), which ranges from unhappiness to happiness and expresses the pleasant or unpleasant feeling about something, arousal, the level of affective activation, ranging from sleep to excitement, and dominance, which reflects the level of control of the emotional state, from submissive to dominant [36].

AI has a flourishing application strategy in this realm of research. Sentiment analysis is a natural language processing (NLP) technique used to determine and extract subjective information from written or spoken language. The goal of sentiment analysis is to understand the sentiment, attitude, or opinion expressed in a piece of text, whether it is positive, negative, or neutral. Sentiment analysis often employs ML models to automatically classify the sentiment of a piece of text. These models are trained on labeled datasets, where human annotators have categorized the sentiment of each text sample. Common ML algorithms used for sentiment analysis include SVM, Naive Bayes, and deep learning models like Recurrent Neural Networks (RNNs) and CNNs. In addition to ML and deep learning models, sentiment analysis can also use lexicon-based approaches. Lexicons are dictionaries that associate words with sentiment scores. The sentiment of a piece of text is then determined by aggregating the sentiment scores of its individual words.

Language analysis in the context of pain assessment involves two key processes: language feature extraction and classification. A foundational element in this realm is the verbal taxonomy of pain, which serves as the cornerstone for research endeavors. The pain descriptor system (PDS), comprising 24 descriptors and 8 subcategories [37], provides a robust classification framework. Leveraging this classifier, diverse investigations, including survey analyses on pain-related issues, can be effectively conducted [38].

Taking the evolutionary leap in language analysis for assessing pain, the application of NLP represents a pivotal advancement. NLP, an AI field, aims to harness rich knowledge resources to understand, extract, and retrieve data from unstructured written and spoken texts [39]. It merges computer science, AI, and linguistics, focusing on tasks such as classification, annotation, and prediction. NLP finds applications in diverse areas, from language-enabled applications to virtual assistants and chatbots.

The various phases of NLP encompass tokenization, morphological and lexical analysis, syntactic analysis, generation of parse trees, named entity recognition, semantic analysis, and speech analysis. In the medical domain, NLP has proven instrumental in applications such as computerized clinical decision support systems, healthcare management improvement through feedback analysis, and the development of tele-triage services using chatbots [40,41].

However, the unique challenge faced by NLP in pain-related analysis lies in the subjective and often ambiguous nature of the concept of "pain." With its multifaceted nature encompassing physical discomfort, emotional suffering, and biopsychosocial elements, accurately analyzing and understanding pain through text-based data sources becomes inherently challenging [42]. To address this, various lexicons have been developed, such as the one validated by Chaturvedi et al. [43], comprising 382 terms useful for selecting pain-related elements from electronic health record databases.

In pain management, NLP can find application in summarizing clinical notes and developing dialogue systems, such as chatbots, for patient interaction and pain management support. Additionally, NLP can contribute to the development of question-answering systems, providing patients with accurate and up-to-date information about pain management. Furthermore, in the realm of pain research, NLP was used for extracting information (e.g., pain location, intensity, and duration) from text-based data sources like electronic medical records and patient-reported outcomes [42]. This enables a more comprehensive understanding of the patient's pain experience, facilitating the identification of patterns or trends in pain management. Notably, Naseri et al. [44] developed a method for automatically identifying and categorizing pain reported by physicians in clinical notes, even in cases where the pain is not recorded through structured data entry, using the MetaMap and NegEx algorithms for medical terms' extraction [45].

Continual improvements in algorithms for NLP applications in pain research, such as Word2Vec and GloVe, highlight the dynamic nature of this field. These algorithms, working on linguistic corpora datasets, contribute to the analysis of representative words, sentences, and phrases in a given language for a specific argument. Notably, a systematic review evaluating NLP applications in low back pain and spinal disease showcased a diverse range of rule-based and supervised or unsupervised ML approaches [46], underlining the versatility and ongoing advancements in leveraging NLP for pain-related studies [47,48].

1.2.3. Brainstem APA research

Delving even deeper into the neurological hierarchy, the reptilian brain, the most ancient part of the brain, governs instinctual responses. Studying pain in this primitive context necessitates the recording and meticulous analysis of a spectrum of biosignals. These signals, ranging from autonomic responses to subtle physiological changes, unveil the instinctual reactions that pain triggers at the most foundational level of the human brain.

Various biosignals, including the electrocardiogram (ECG), heart rate variability (HRV), electrodermal activity (EDA), and brain imaging techniques like functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), are commonly utilized to measure brain activity related to pain [15,49]. In a recent study, Cao et al. [50] identified potential respiratory features associated with pain from photoplethysmography (PPG) data in postoperative patients enrolled in the UCI iHurtDB pain protocol [51]. The researchers employed five ML algorithms, namely ADABoost, XGBoost, random forest, SVM, and KNN classifiers. All five classifiers demonstrated satisfactory accuracies. The authors conducted a comparative analysis with the findings of Thiam and Schwenker [52], who utilized 65 automatic respiratory features and an effective fusion architecture method.

Among biosignal strategies, EDA and ECG signals showed innovative and pivotal roles in pain assessment. Notably, preliminary findings have indicated rapid responses elicited by specific stimuli, whether sensory or emotional, in EDA signals [53]. Within the HRV analysis, RR intervals are based on ECG signals. Importantly, well-documented literature has established the correlation between these signals and pain or stress [54,55].

The ECG signal records the superficial electrical activity of the heart. Temporal variations in inter-beat intervals offer a measure of HRV, which is closely tied to the functioning of the autonomic nervous system (ANS) [56]. HRV is influenced by the dynamic interplay between the sympathetic and parasympathetic branches of the ANS, known as sympathovagal balance. These branches work antagonistically to regulate heart rate according to the body's changing requirements. Alterations in this equilibrium, reflected in HRV fluctuations, can result from physiological factors (e.g., circadian rhythm) and pathological conditions (such as diabetes and post-infarction situations) [57]. These

fluctuations can also indicate physiological responses to stress and pain scenarios [54]. The RR series, representing the intervals between successive R waves of the QRS complex on the ECG waveform, were computed to extract time-domain HRV parameters.
The EDA signal is an indicator of sympathetic nervous system activity and has been efficiently applied in tasks related to pain recognition [54,58]. This approach serves as a valuable marker for assessing pain-induced neurocognitive stress by detecting alterations in the electrical properties of the skin, stemming from sweat gland activation, and resulting in an elevation in skin conductance. The continuous variations in skin conductance are termed the skin conductance level (SCL), while the transient responses occurring within seconds are referred to as the galvanic skin response (GSR). Both SCL and GSR contribute to the tonic and phasic components, where the former represents a fundamental level of conductance (i.e., SCL) with gradual fluctuations. Conversely, the phasic component captures the brief changes in the EDA signal (i.e., skin conductance responses, SCRs) triggered by the presentation of a stimulus. Typically, the EDA signal is quantified in microsiemens (μS), and notably, this component can provide insights into the overall autonomic response to pain [58] (Figure 2).

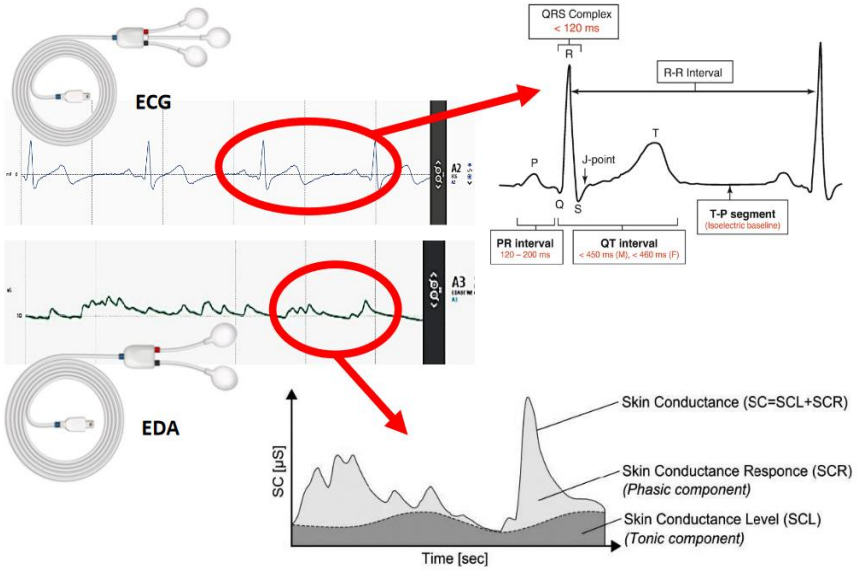

Figure 2. *Biosignals processing and analysis to extract pain-related features. Abbreviations: ECG, electrocardiogram; EDA, electrodermal activity.*

Accelerometer signals provide measurements of motor activity along the three principal axes of an orthogonal Cartesian plane. Chen et al. [59] demonstrated the correlation between accelerometer signals and stress-induced pain in patients. Within the proposed framework, they are utilized to quantitatively assess motion-associated pain (Figure 3).

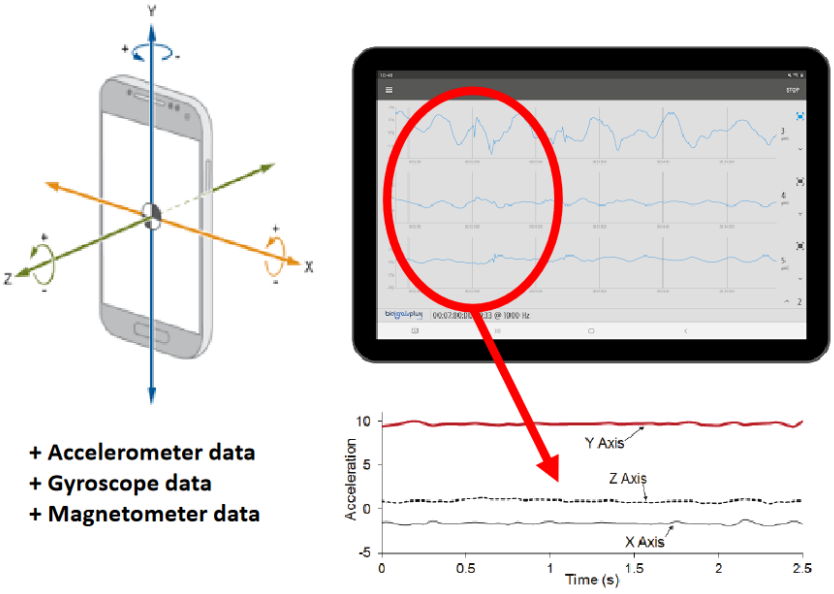

Figure 3. *Fusion of additional smartphone sensor data to extract motion features.*

Despite these premises, it is important to note that the use of these techniques is still in its infancy, and further developments are needed for their widespread implementation in clinical practice.

2. Chapter:

Study Design and Methods

2.1. Study Rationale

In recent years, substantial efforts have been dedicated to the advancement of APA methods. These endeavors have encompassed various aspects of research, including the establishment of comprehensive datasets and the refinement of sophisticated classification algorithms [54]. However, despite the considerable progress achieved in this field, a significant void persists within the literature pertaining to the automated evaluation of pain specifically in the context of cancer patients [60]. Obviously, the absence of comprehensive studies and automated tools tailored to the unique pain experiences of individuals grappling with cancer represents an important research gap. Cancer-related pain is a multifaceted phenomenon that demands specialized attention due to its distinct characteristics, which may differ from other forms of pain. Factors such as the underlying cancer type, stage, treatment modalities, and individual patient variability all contribute to the complex landscape of pain in this population [61].

To address this research deficit, there is an increasing need to develop and validate APA systems that are tailored to the nuances of cancer-related pain. These systems should not only consider the subjective clinical aspects (qualitative pain assessment) of pain perception but also adapt behavioral and physiological elements (quantitative pain assessment) to the dynamic nature of cancer treatment and symptom management. In other words, by acknowledging this research gap and striving to bridge it with innovative APA strategies the goal is to enhance our ability to provide more effective pain management strategies for this vulnerable population.

Given these premises, the study 'Pain Assessment in Cancer Patients by Machine Learning (PASCALE)' has been conceptualized and developed (ClinicalTrials.gov ID NCT04726228). This study entails a multi-professional collaboration between clinical and cancer research centers

from the Istituto Nazionale Tumori di Napoli, Fondazione Pascale, and research centers affiliated with the Dipartimento di Ingegneria Elettrica e delle Tecnologie dell'Informazione (DIETI) at the University of Naples Federico II including the Urban Eco Research Center (Proff. F. Cutugno, N.V. Vitale) and the Bioengineering (Proff. F. Amato, M. Romano, A.M. Ponsaiglione). Moreover, the pivotal contribution of the AGATA group (Artificial Intelligence in Anesthesia) led by Professor Elena Giovanna Bignami from SIAARTI (Società Italiana di Anestesia, Analgesia, Rianimazione e Terapia Intensiva) has been indispensable.

2.2. Study Aims

The study aimed at data collection, implementing APA techniques, and investigating phenomena related to oncological pain.
Data collection is the key step for the development of APA systems as it can act as ground truth for the training of automated systems. Although several generic datasets on pain are available [62], there is a need to develop specific datasets based on subjects suffering from oncological diseases. Multimodal and multidimensional datasets could be the key to effectively training automatic systems in this clinical setting. In this study, we implemented two datasets: multimodal for audiovisual material, and multidimensional for physiological data such as biosignals and clinical information.
The development and implementation of techniques for the study of the objective phenomenology of pain is another aim of the project. To achieve this goal, the study employs a dual-pronged approach. Firstly, it concentrates on the utilization of behavioral methodologies, which involve observing and analyzing observable pain-related behaviors and responses in patients. Secondly, it delves into the realm of biosignals, where advanced technologies are employed to analyze physiological data and patterns associated with pain.
About mechanisms of different cancer pain phenomena**,** cancer-related pain is an umbrella term. It encompasses a spectrum of pain experiences that can arise in individuals diagnosed with cancer. This type of pain is often multifaceted, and it can be categorized into two main phenomena: background pain and breakthrough cancer pain (BTcP). Background pain in oncology refers to a persistent, continuous pain that patients with cancer may experience throughout their disease course. This pain can vary in intensity from mild to severe and is typically present most of the time. Background pain is often associated with the underlying cancer

itself, which may be pressing on or invading nearby tissues, nerves, or organs. It can also result from cancer-related treatments, such as surgery, radiation therapy, or chemotherapy. The location, quality, and intensity of background pain can vary depending on the type and stage of cancer and its specific impact on the patient's body. The other cancer pain type, BTcP, is a distinct and intense flare of pain that occurs suddenly despite adequate control of background pain with opioid therapy. This type of pain is a frequent condition and can affect up to 70% of patients suffering from chronic pain of an oncological nature [63]. These episodes of pain "breakthrough" the baseline pain level and are characterized by their rapid onset and short duration. BTcP is often severe, causing a significant spike in pain intensity that can be emotionally distressing for patients. Common triggers for BTcP include movements, coughing, or specific activities (incident or predictable BTcP). It can also be caused by changes in tumor activity or the effects of cancer treatments. Most episodes of BTcP are not predictable and occur in the absence of any specific activity (idiopathic or spontaneous BTcP) [64].
Despite clinical evidence of various manifestations of oncological pain, the mechanisms underlying these clinical expressions, including spontaneous BTcP, remain largely unknown. The potential to conduct investigations through multidimensional and multimodal strategies, employing AI techniques, could herald a significant breakthrough in research in this field. This aspect is of fundamental importance, especially in the context of targeted therapy, considering that the different pain phenomena are managed with drugs that have distinct pharmacokinetic and, above all, dynamic properties.

2.3. Study Framework

The PASCALE study involves the collection and analysis of clinical data, including mono and multidimensional subjective pain assessment instruments, as well as the analysis of objective elements relevant to pain research. In this context, quantitative assessment of different biosignals has been integrated with data from behavioral studies, particularly focusing on facial expressions and language analysis for emotional analysis. The multiparametric data collection utilizes a dedicated dashboard, wearable platform, and various processing software tools.
The study was performed in accordance with the Declaration of Helsinki and the patients provided written informed consent. The Medical Ethics Committee of the Istituto Nazionale Tumori, Fondazione Pascale

(Napoli, Italy) approved the research (Pascale study, Pain ASsessment in CAncer Patients by Machine Learning). Protocol code 41/20 Oss (26 November 2020).
The study includes in-person assessments as well as remote evaluations conducted through telemedicine.

The study framework is shown in Figure 4.

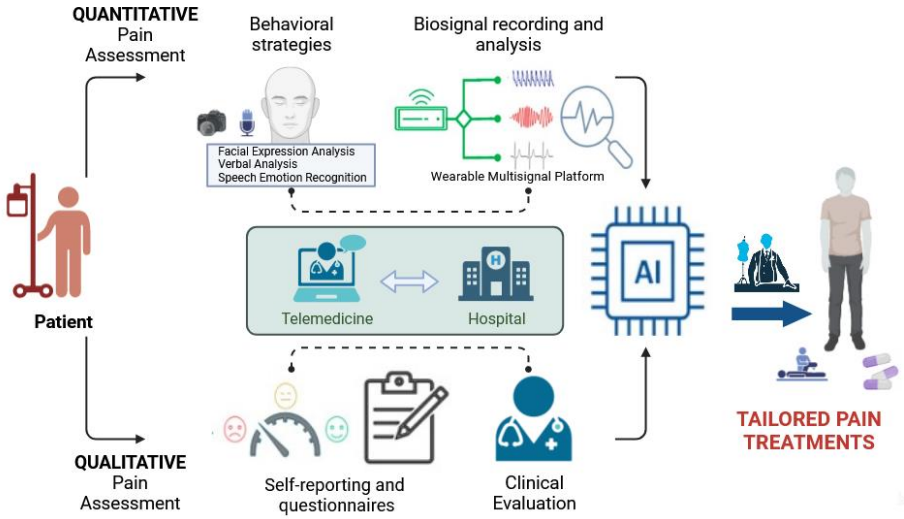

Figure 4. *Framework for multimodal and multidimensional quantitative and qualitative cancer pain assessment.*

2.4. Methods

2.4.1. Qualitative Pain Assessment. Clinical assessment and data collection

The enrolled patients were clinically assessed, and demographic data were collected, including age, gender, height, and weight. Data pertaining to the oncological disease were also gathered, including tumor type, stage, presence of metastases, and bone metastases. Comorbidities, such as cardiovascular, renal, neurological, pulmonary, and others, were documented. Pain-related information included the type of baseline pain (nociceptive, neuropathic, mixed), intensity (0-10

NRS), location of baseline pain, and breakthrough pain (BTcP), including intensity (0-10 NRS), quality (nociceptive, neuropathic, mixed), duration (0-30 minutes; > 30 minutes), and location. Information about oncological therapy, including chemotherapy, radiation therapy, and surgery, was also collected. Analgesic therapy details encompassed opioids (dose and molecule) and other medications (neuropathic pain drugs, NSAIDs, paracetamol, and others). Lastly, data regarding the patient's performance status and quality of life were recorded. The obtained dataset is available in [65].

2.4.2. Telemedicine and Quantitative Pain Study

Among the patients enrolled in the study, a portion was chosen to complete the assessment remotely, and their consent was obtained for asynchronous telemedicine monitoring. Patients were selected based on their ability to use the study's technology.
The patients were trained to use an app (APA Pascale) for entering data. These selected volunteers agreed to wear a smartwatch to measure and store physiological data such as body temperature, oxygen saturation, and heart rate. The smartwatch dialogues with an Android app that collects all the data and sends them to a remote server. Supplemental device-generated data were manually inserted in the app by the patient who was required to take a measurement through a push notification generated within the app. Diary drug supply is also memorized in the app and the patient was alerted to assume her medicines. Moreover, the app was developed to provide data entry of a quality-of-life questionnaire and to record video diaries at least twice a day, or at any moment the volunteer needs to communicate the clinical status. These video recordings are centered around the description of the patient’s status, the development of pain perception during the day, and the self-evaluation of the patient’s general conditions. At least three times per day the app lets a notification start and a prompt asks the patient to select an NRS value for the degree of the perceived pain in that time.
The mobile app is a software client feeding a server-side running on a remote cloud system. Specialists can monitor the arrival of the data and operate on the patients’ reports by using a software dashboard.

2.4.3. Interview and video recording

During the in-hospital routine clinical evaluation, a brief interview lasting approximately two minutes was conducted with oncology patients, and video recordings were taken during the session. The video footage served to gain insights into the emotional and physical aspects of pain experienced by the subjects. It was employed to conduct automated analysis of facial expressions associated with pain and, by processing the audio content within the videos, to capture and analyze the verbal expressions and vocal cues to provide further context and understanding in the realm of speech recognition analysis. This comprehensive approach allowed us to explore both the visual and auditory dimensions of pain assessment, contributing to a more holistic and accurate evaluation of the participants' pain responses (Figure 5).

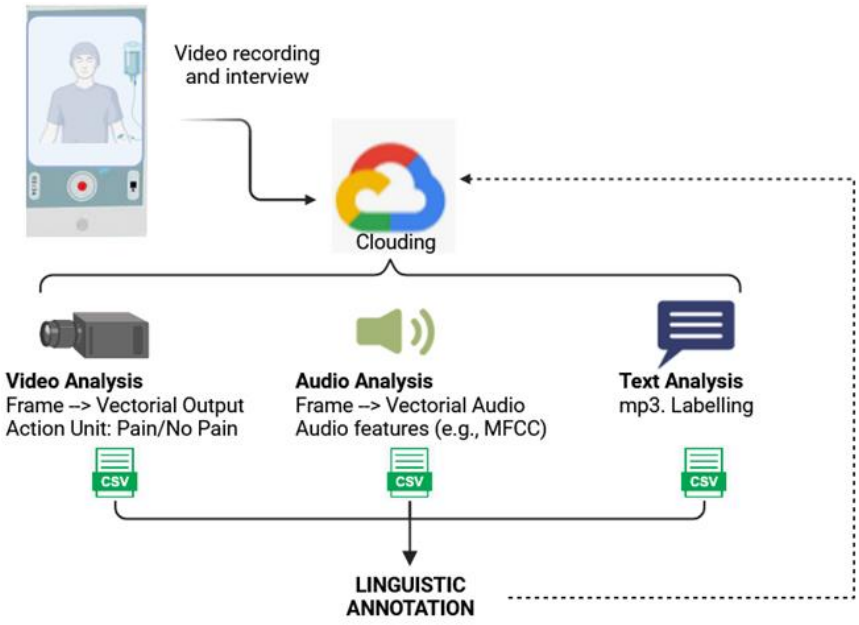

Figure 5. *Video recording, storage, and processing.*

The interview is presented in Table 1.

DEMOGRAPHICS
How old are you?
What is your occupation?
Are you married?
How many people are in your family? / Do you have children? / How old are your children?
CLINICAL INFORMATION
When were you diagnosed?
What type of therapy are you currently undergoing or have undergone?
PAIN FEATURES
Can you try to describe your pain?
Where in your body do you feel pain? Where is it localized?
Can you try to describe the episode in which you experienced the worst pain (when it happened, what type of pain it was, how long it lasted)?
What does it resemble? Could you describe it using a word, an adjective, a symbol, or an object?
If we could describe your pain using a color, what color would it be?
FINAL QUESTIONS
Do you have any hobbies?
What do you enjoy doing in your free time?
What would you like to do today?
Thank you for the information provided.

Table 1. Interview "Expression of Pain" used for video recording. The Italian version was translated and validated by researchers of the Urban Eco (DIETI).

The interview was used to obtain a "corpus" of pain. Subsequently, starting from the assumption that the produced statement (i.e., the stimulus) can be associated with emotional status, we have implemented the Kubler-Ross model to correlate pain and emotions. The Kubler-Ross, also known as the Five Stages of Grief, is a psychological model introduced by psychiatrist Elisabeth Kubler-Ross in her 1969 book "On Death and Dying" [66]. The model outlines five emotional stages that

individuals may go through when dealing with grief and terminal illness. While originally developed in the context of coping with death, the model has been applied more broadly to various forms of emotional adjustment and change. The five stages are denial, anger, bargaining, depression, and acceptance. Denial is the initial stage where individuals may have difficulty accepting the reality of the situation. As the reality of the situation sets in, individuals may experience anger, manifesting as frustration, resentment, or irritation. The third stage is bargaining, where people may try to negotiate or make deals to change the situation. Depression is a deep sense of sadness and hopelessness with a profound emotional low when individuals confront the reality of their situation. Acceptance represents the final stage characterized by a state of relative peace and understanding, with acceptance of the inevitable or the changed circumstances. The model is a general framework to understand the emotional responses to difficult situations, and its application has extended beyond the realm of grief to various aspects of life changes and challenges. Moreover, the five stages may not occur in a linear sequence as patients can move back and forth between stages, skip stages, or experience them in a different order [67].
As shown in Figure 5, the audiovisual files are anonymized, labeled, and stored (on Google Cloud). Video, audio, and text tracks can be extracted in CSV format and used for linguistic annotation. For audiovisual files, each frame corresponds to a vectorial output that represents the associated feature. For videos, the output is the pain/no pain classification (from the AUs analysis); for audio files, the output of the frame is the collection of the vectorial features. Outputs are also stored in the cloud.

2.4.4. Biosignal investigations

In this study, we specifically selected EDA and ECG signals due to their innovative and pivotal roles in pain assessment. Notably, preliminary findings have already indicated rapid responses elicited by specific stimuli, whether sensory or emotional, in EDA signals [53]. Conversely, we assessed RR intervals based on ECG signals, as there exists well-documented literature establishing the correlation between heart rate variability (HRV) and pain or stress [54-57].

EDA and ECG signals were acquired using a BITalino device equipped with sensors for ECG and EDA signal recording. The BITalino platform

is a cost-effective, open-source biosignal platform designed for physiological computing. As reported in the literature, data collected with this device exhibit reliability for quantitative analysis [57,58]. The signals were sampled at a rate of 1000 Hz (Figure 6).

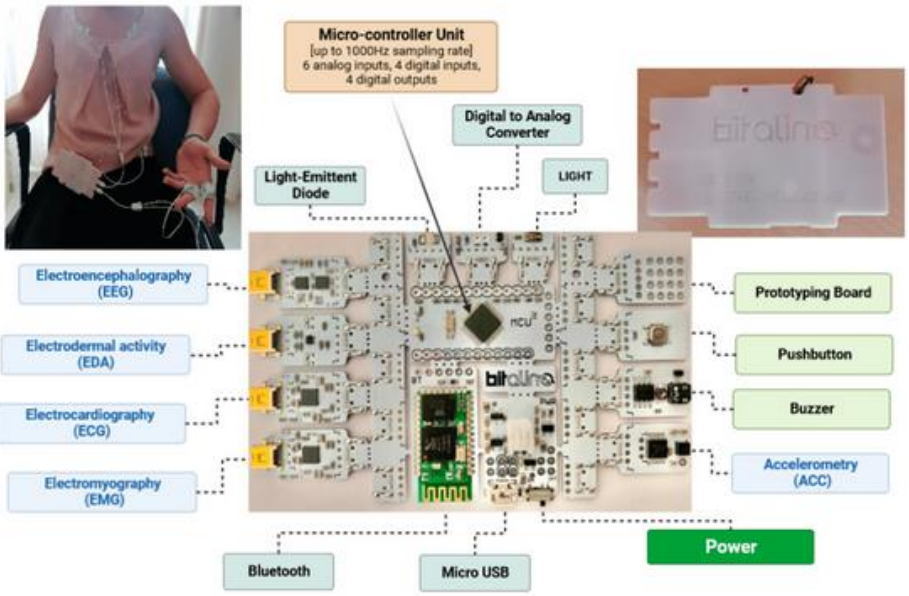

Figure 6. *BITalino anatomy. Board and plugged channel mapping, 3D printed casing, and application; data and signals were acquired from 2 sensors, namely electrocardiography (ECG) and electrodermal activity (EDA).*

2.5. Data Collection

2.5.1. Demographic and clinical data collection

Demographic and clinical data were collected from patients either during hospitalization, or during ambulatory visits, and synchronous and asynchronous telemedicine processes. Table 2.

Table 2. Demographic and clinical data

Type of Data	Variable
Demographic	Age Weight Height Gender
Clinical	Hospitalization Type of primary tumor Therapy Presence of metastases Presence of bone metastases ECOG (Performance Status) Presence of comorbidities Type of comorbidities
Pain-related information	Base cancer pain type Base cancer pain intensity Main site of cancer pain Opioid treatment for base cancer pain Adjuvants for base cancer pain Dose of opioids for base cancer pain Breakthrough cancer pain (BTcP) BTcP type BTcP maximum duration BTcP intensity Main site of BTcP BTcP treatment

Abbreviations: ECOG, Eastern Cooperative Oncology Group Performance status; BTcP, Breakthrough cancer pain

2.5.2. Biosignal collection

As far as the EDA signal, two types of analyzes have been performed: (i) the Trough-To-Peak analysis (TTP), or min-max analysis, aimed at

measuring the difference between the Skin Conductance (SC) at the peak of a response and its previous minimum within pre-established time-windows; (ii) the Continuous Decomposition Analysis (CDA), aimed at performing a decomposition of SC data into continuous signals of tonic (basic level of conductance) and phasic (short-duration changes in the SC) activity.
Before applying the TPP analysis or the CDA, the signal was filtered by means of a fifth-order Butterworth low-pass filter with a cutoff frequency of 1 Hz and downsampled up to 10 Hz to reducing the computational burden of the analysis. The application of TPP and CDA allowed the detection and measurement of SC Responses (SCR) and the following parameters have been calculated for both TPP and CDA methodologies:

- Total number of detected SCRs (N)
- Maximum value of SCRs [measured in μS]:

$$max(SCR_i), \quad i = 1 \dots N \text{ and } SCR_i \text{ denoting the value of the } i-th \text{ SCR}$$

- Minimum value of SCRs [measured in μS]:

$$min(SCR_i), \quad i = 1 \dots N \text{ and } SCR_i \text{ denoting the value of the } i-th \text{ SCR}$$

- Arithmetic means of the SCRs [measured in μS]:

$$\frac{1}{N}\sum_{i=1}^{N} SCR_i, \quad i = 1 \dots N \text{ and } SCR_i \text{ denoting the value of the } i-th \text{ SCR}$$

- Maximum interval between SCRs [measured in ms]:

$$max(t_{i+1} - t_i), \quad i = 1 \dots N-1 \text{ and } t_i \text{ denoting the time of occurrence of the } i-th \text{ SCR}$$

- Minimum interval between SCRs [measured in ms]:

$$min(t_{i+1} - t_i), \quad i = 1 \dots N-1 \text{ and } t_i \text{ denoting the time of occurrence of the } i-th \text{ SCR}$$

- Arithmetic means of the intervals between SCRs [measured in ms]:

$$\frac{1}{N}\sum_{i=1}^{N} (t_{i+1} - t_i), \quad i = 1 \dots N-1 \text{ and } t_i \text{ denoting the time of occurrence of the } i-th \text{ SCR}$$

As far as the ECG, The RR series of interbeat intervals (i.e., the time between successive R waves of the QRS complex on the ECG waveform) has been computed to extract time-domain parameters of the HRV. The R peak detection was carried out by adopting the Pan–Tompkins algorithm for QRS detection and R peak identification. The corresponding RR series of interbeat intervals were derived as the difference between successive R peaks in the ECG.

The ECG-derived RR time series was then filtered by means of a recursive procedure to remove the intervals differing most from the mean of the surrounding RR intervals. Then, both the Time-Domain Analysis (TDA) and Frequency-Domain Analysis (FDA) of the HRV have been carried out to extract the main features characterizing the variability of the heart rhythm.
Time-domain parameters are obtained from statistical analysis of the intervals between heartbeats and are used to describe how much variability in the heartbeats is present at various time scales.
The parameters computed through the TDA include the following:

- Arithmetic means of the RR time series [measured in ms]:

$$\overline{RR} = \frac{1}{n}\sum_{i=1}^{n} RR_i$$

with n denoting the number of interbeat intervals and RR_i denoting the value of the *i*-th interbeat interval.

- The standard deviation of the RR time series [measured in ms], which reflects the cyclic components responsible for heart rate variability during the recording period:

$$SDRR = \left[\frac{1}{n-1}\sum_{i=1}^{n}(RR_i - \overline{RR})^2\right]^{1/2}$$

where n is the number of interbeat intervals and $\overline{RR}$ is the mean of the RR intervals.

- Mean value of heart rate [measured in bpm]:

$$\overline{HR} = \frac{1}{n}\sum_{i=1}^{n} HR_i$$

with n denoting the number of heartbeats and HR_i denoting the value of the *i*-th heartbeat, derived from the RR series according to the following

formula: $HR_i = \frac{60}{RR_i} * 1000$ with RR_i denoting the value of the *i*-th interbeat interval.

- Standard deviation of the heart rate [measured in bpm]:

$$SDHR = \left[\frac{1}{n-1}\sum_{i=1}^{n}(HR_i - \overline{HR})^2\right]^{1/2}$$

where n is the number of heartbeats and $\overline{HR}$ is the mean of the HR series.

- Root Mean Square of Successive Differences of RR intervals [measured in ms], which is sensitive to high-frequency heart period fluctuations in the respiratory frequency range and has been used as an index of vagal cardiac control:

$$RMSSD = \left[\frac{1}{n-1}\sum_{i=1}^{n-1}(RR_{i+1} - RR_i)^2\right]^{1/2}$$

with n denoting the number of interbeat intervals and RR_i denoting the value of the *i*-th interbeat interval.

- Number of successive RR intervals whose difference is higher than 50 ms ($NN50$).
- Percentage of successive RR intervals > 50 ms:

$$pNN50 = \frac{NN50}{n-1} * 100$$

with n denoting the number of interbeat intervals and $NN50$ denoting the

- Number of successive RR intervals whose difference is higher than 50 ms.

Frequency-domain parameters reflect the distribution of spectral power across different frequency bands and are used to assess specific components of HRV (e.g., thermoregulation control loop, baroreflex control loop, and respiration control loop, which are regulated by both sympathetic and vagal nerves of the ANS). The parameters computed through the FDA have been computed by adopting Welch's Fourier periodogram method based on the Discrete Fourier Transform (DFT), which allows the expression of the RR series in the discrete frequency domain. However, due to the non-stationarity of the RR series, the Welch's Fourier periodogram method is used for dealing with non-

stationarity. Welch's periodogram breaks the signal into specific periods of constant length and applies the Fast Fourier Transform (FFT) transform individually on each of these parts of the signal. s. The periodogram, extension of the DFT, is a basic method of estimating power spectral density of a time series and is given by:

$$P_M(f) = \frac{1}{MU}\left|\sum_{n=0}^{M-1} X(n)w(n)e^{-i2\pi fn}\right|^2 \quad \text{i=0,1,...,L-1} \quad \text{where } U = 1/M\sum_{n=0}^{M-1} w^2(n)$$

In the above formula, the signal to be transformed X(n) is multiplied by a windowing function w(n) (usually a Hanning function), and the resulting signal is locally transformed as the windowing function shifts along the time axis. Finally, in an effort to reduce the variance of the periodogram estimation, the Welch method separates the data series into N overlapping segments and an averaged PSD is calculated using all segments:

$$P_W(f) = \frac{1}{N}\sum_{i=0}^{N-1} P_{M,i}(f)$$

The following table report summarizes all the features calculated through the analysis of EDA and ECG signals, including FDA parameters (Table 3).

Type of Signal	Features
Electrodermal Activity (EDA)	**Features from Continuous Decomposition Analysis (CDA)** • Number of significant skin conductance responses (nTTP) [a.u.] • Maximum value of skin conductance responses (maxCDA) [µS]

	• Minimum value of skin conductance responses (minCDA) [μS] • Mean value of skin conductance responses (meanCDA) [μS] • Maximum interval between skin conductance responses (maxDiffTTP) [ms] • Minimum interval between skin conductance responses (minDiffTTP) [ms] • Mean interval between skin conductance responses (meanDiffTTP) [ms] **Features from Trough-To-Peak Analysis (TTP)** • Number of significant skin conductance responses (nTTP) [a.u.] • Maximum value of skin conductance responses (maxTTP) [μS] • Minimum value of skin conductance responses (minTTP) [μS] • Mean value of skin conductance responses (meanTTP) [μS] • Maximum interval between skin conductance responses (maxDiffTTP) [ms] • Minimum interval between skin conductance responses (minDiffTTP) [ms] • Mean interval between skin conductance responses (meanDiffTTP) [ms]
Electrocardiography (ECG)	**Features from Time Domain Analysis (TDA) of Heart Rate Variability (HRV)**

	• Mean value of RR intervals (mRR) [ms] • Standard deviation of RR intervals (SDRR) [ms] • Mean value of heart rate (mHR) [bpm] • Standard deviation of HR (SDHR) [bpm] • Root Mean Square of Successive Differences of RR intervals (RMSSD) [ms] Number of successive RR intervals < 50 ms (NN50) [a.u.] Percentage of successive RR intervals < 50 ms (pNN50) [%] **Features from Frequency Domain Analysis (FDA) of Heart Rate Variability (HRV)** • Peak value in the Very Low-Frequency Band of the HRV power density spectrum (peakVLF) [Hz] • Peak value in the Low-Frequency Band of the HRV power density spectrum (peakLF) [Hz] • Peak value in the High-Frequency Band of the HRV power density spectrum (peakHF) [Hz] • Power in the Very Low-Frequency Band of the HRV power density spectrum (powVLF) [ms^2] • Power in the Low-Frequency Band of the HRV power density spectrum (powLF) [ms^2] • Power in the High-Frequency Band of the HRV power density spectrum (powHF) [ms^2] • Total Power of the HRV power density spectrum (Ptot) [ms^2]

	• Percentage power in the Very Low-Frequency Band of the HRV power density spectrum with respect to the total power (%VLF) [%] • Percentage power in the Low-Frequency Band of the HRV power density spectrum with respect to the total power (%LF) [%] • Percentage power in the High-Frequency Band of the HRV power density spectrum with respect to the total power (%HF) [%] • Normalized power in the Low-Frequency Band of the HRV power density spectrum with respect to the sum of LF and HF power (nLF) [a.u.] • Normalized power in the High-Frequency Band of the HRV power density spectrum with respect to the sum of LF and HF power (nHF) [a.u.] • Sympathovagal balance measured as the ratio between power in LF and power in the LF band (LF/HF) [a.u]

2.6. Telemedicine Pathway

Selected volunteers agreed to wear a smartwatch to measure and store physiological data such as body temperature, oxygen saturation, and heart rhythm. The smartwatch dialogues with an Android app that collects all the data and sends them to a remote server. The supplemental device-generated data are manually inserted in the app by the patient who is required to take a measurement through a push notification generated within the app. Diary drug supply is also memorized in the app and the patient can choose to be remembered to assume her medicines. Moreover, the app requires to enter data in a questionnaire

and to record video diaries at least twice a day or at any moment the volunteer needs to communicate their status. These video recordings are centered around the description of the patient's status, the development of pain perception during the day, and the self-evaluation of the patient's general conditions. At least three times per day the app lets a notification start and a prompt asks the patient to select an NRS value for the degree of the perceived pain at that time.
The mobile app is a software client feeding a server-side running on a remote cloud system. Specialists can monitor the arrival of the data and operate on the patients' reports by using a software dashboard which will be shortly described in the next subsection.

2.6.1. Dashboard development

The collection of multimodal information including physiological data, audiovisual material (e.g., video diaries), and questionnaires for pain and quality of life needs to be channeled to a database. Data storage must follow criteria that facilitate writing and reading operations. Consequently, a graphical interface is essential for the easy use of the data and to make the most of all the information available. For this purpose, a dashboard must be as complete as it is simple to use.

The definition of the data visualization dashboard requirements involves the integration of functional and non-functional prerequisites.

Functional requirements include:

- Log in to the dashboard.
- Log out.
- View the list of patients registered on the platform.
- View the summary patient's information.
- View the history of the collected data:
    - NRS values entered.
    - vital signs collected.
    - recorded video diaries (with or without sentiment analysis).
    - completed questionnaires.
    - crisis reports.
    - activities entered.

- View the patient's current therapy.

- Assign a new therapy to a patient.
- View the list of drugs on the platform.
- Insert, modify, or delete a drug.

Concerning non-functional prerequisites, the dashboard was developed as a web app (APA Pascale App). In this way, there was no need to install software and it enables quick access from any device with an internet browser. For this aim, the web app supports Chrome, Firefox, Microsoft Edge, and Safari. Furthermore, the web app is responsive and can be adapted to the various types of screens, while maintaining a graphical interface oriented to a desktop or tablet view. The system guarantees a start-up time of fewer than 4 seconds in 90% of cases and a response time to any search of fewer than 5 seconds in 90% of cases. Finally, it ensures that the user is able to understand the entire set of platform functions after a very short time of use.

In Figure 7 the block diagram of the dashboard facilities is depicted.

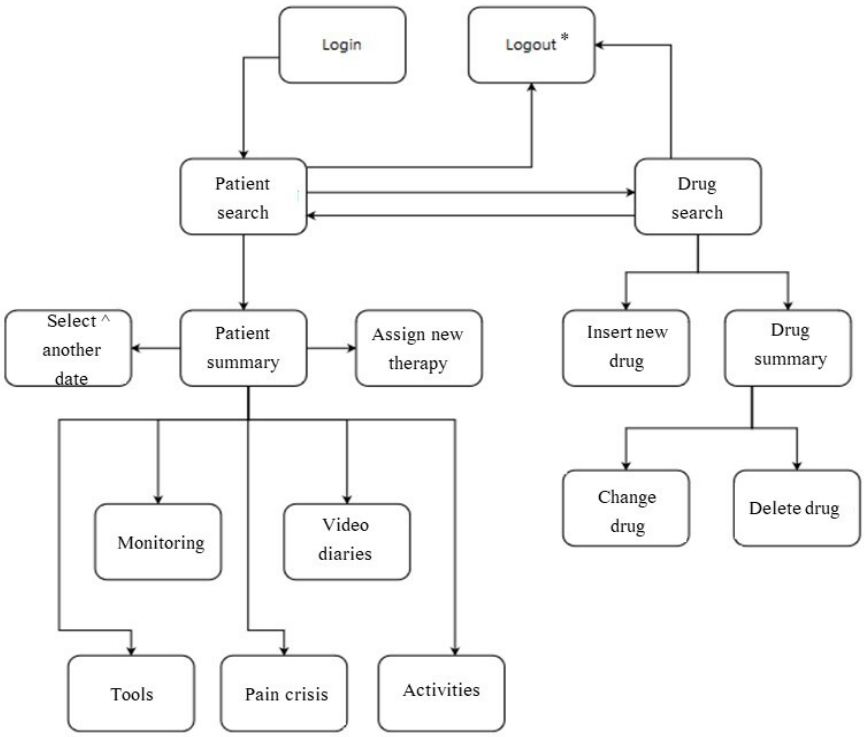

Figure 7. *Tree graph created by implanting the Draw.io web app. Legend: *The logout is always reachable, but to simplify the graph it has been reached after two screens; ^The "Patient summary" subtree shows information from the last available date, by default.*

2.6.1.1. High-fidelity mock-ups.

High-fidelity mock-ups represent software in the late stages of design. They go beyond placeholders and wireframe “lorem ipsum” and include actual content, fonts, colors, images, and branding.
For the creation of the mock-ups, the Figma web app was implemented. It is an extremely complete and easy-to-use web app. Figure 8 shows the login and logout views.

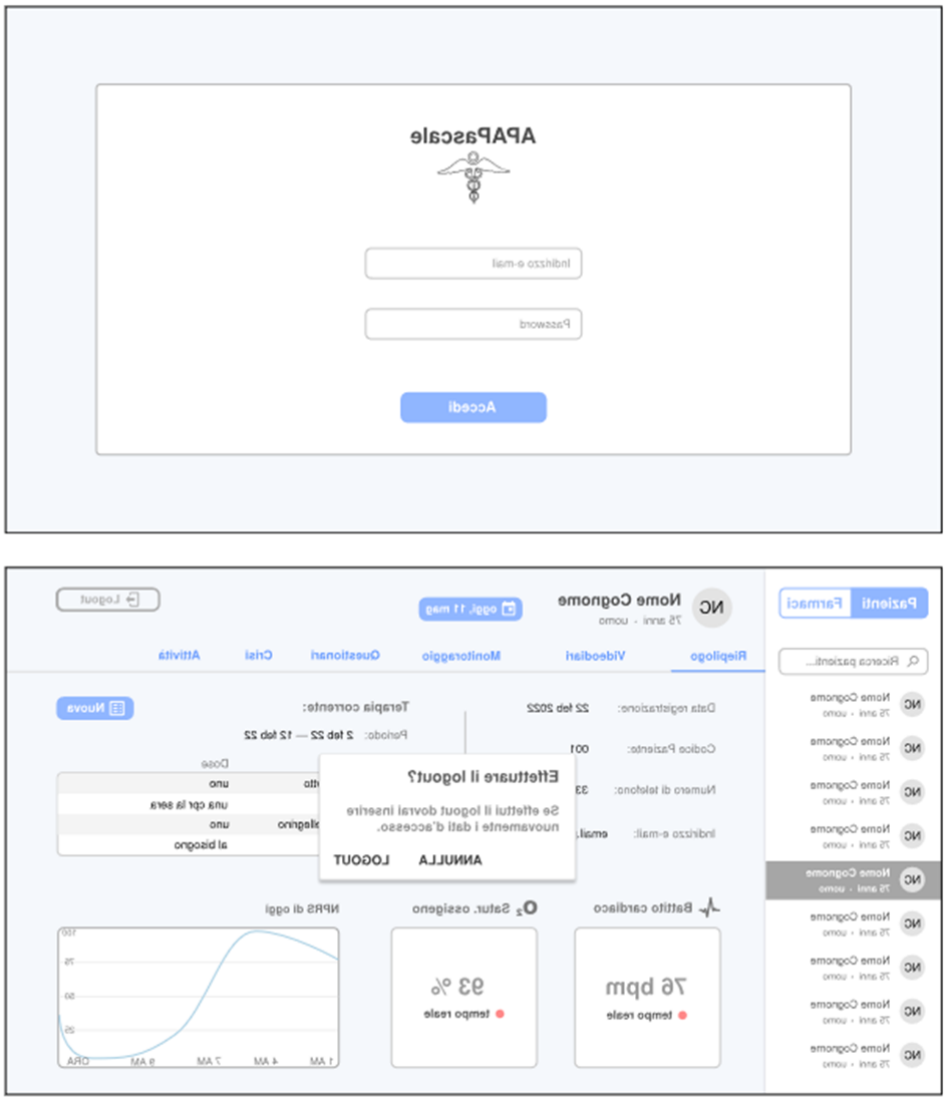

Figure 8. *Login and Logout views*

The patient's monitoring view is shown in Figure 9.

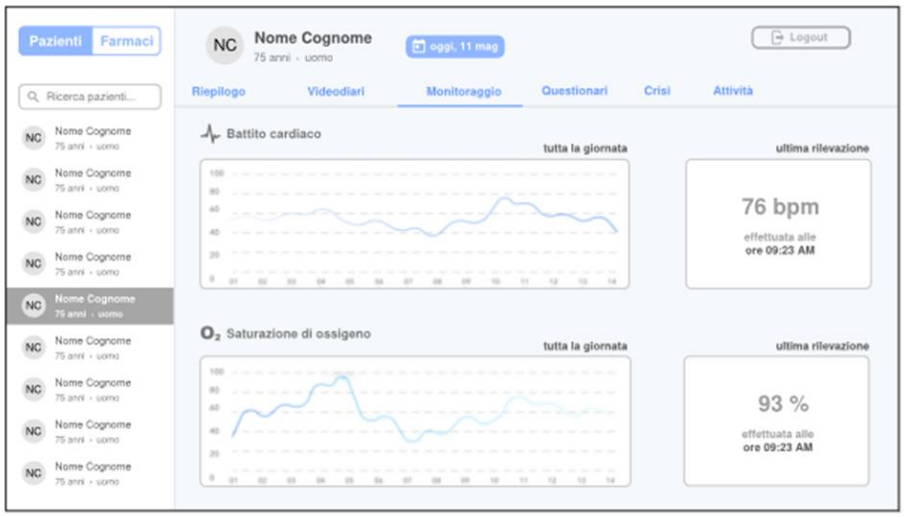

Figure 9. *Physiological monitoring*

2.6.1.2. Interface design according to UX design criteria

When crafting the interface, every decision was meticulously aligned with established principles of user experience design. Specifically, we adhered to Shneiderman's eight golden rules [68] of interface design and Nielsen's ten heuristics [69], all with the ultimate goal of ensuring the dashboard's clarity and user-friendliness.

The Shneiderman Golden Rules include:

- Rule 1. Strive for consistency.
- Rule 2. Seek universal usability.
- Rule 3. Offer informative feedback.
- Rule 4. Design dialogs to yield closure.
- Rule 5. Prevent errors.
- Rule. Permit easy reversal of actions.
- Rule 7. Keep users in control.
- Rule 8. Reduce short-term memory load.

In accordance with the first rule, for example, we have maintained a consistent light blue color scheme for most clickable elements and

confirmation buttons. Additionally, to prevent user errors such as omitting a dosage when adding a drug to the therapy, the system proactively displays a message prompting the user to input the required dose (Rule 5).

The Nielsen Usability Heuristics consist of ten overarching principles that guide interaction design. They are referred to as "heuristics" because they are broad, general rules rather than specific usability guidelines. The principles include:

- Principle 1. Visibility of system status.
- Principle 2. Match between the system and the real world.
- Principle 3. User control and freedom.
- Principle 4. Consistency and standards.
- Principle 5. Error prevention.
- Principle 6. Recognition rather than recall.
- Principle 7. Flexibility and efficiency of use.
- Principle 8. Aesthetic and minimalist design.
- Principle 9. Help users recognize, diagnose, and recover from errors.
- Principle 10. Help and documentation.

For instance, when an operator adds a drug to the therapy but later decides to remove it, the process is made effortless by the presence of a red "X" icon conveniently located near the list of drugs, adhering to principle 3. Furthermore, the design embraces minimalism to its fullest extent. Each window is meticulously curated, containing only essential elements required for the specific task at hand. In simplifying data entry, we've incorporated "hints" within text fields, following principle 8. These hints are predefined text prompts within the fields, which vanish as soon as the user begins typing and reappears if the user clears the text field, enhancing usability.

2.6.1.3. Flutter implementation

The platform was developed as a web app using the unconventional Flutter framework. It is an open-source framework developed by Google for creating high-performance native interfaces. This framework allows development for almost any device, from the desktop (Windows, Mac, or Linux) to the web, from iOS to Android, with a single code base. It

can also import external packages and allows the transition from a web app to a desktop or mobile app, through minimal or no code changes.
Flutter uses the programming language Dart. Since Flutter is written specifying what must be done and not how it must be done, it is based on declarative programming. These features mainly concern the way the graphical interface is built and populated. Flutter is provided with the status of the application (i.e., the data), and how to display them, and the framework creates the user interface to reflect the current state of the application. It can be imagined as a mathematical formula:

$$UI=f(state)$$

Where UI is the graphical interface, f is the method construction of the graphical interface and state is the status of the application.

When the status of the app changes (for example, the user changes an option in the settings screen), Flutter is notified of the modification and triggers a refresh of the user interface. It is not necessary to change the interface as required by mandatory programming, for example by executing the widget.setText ("new text") instruction as, when the state changes, the user interface is rebuilt from scratch.

2.6.1.4. Usability assessment

The usability of a system is the extent to which users succeed in using it to achieve specific objectives effectively and efficiently, while at the same time deriving satisfaction from the process.
Usability assessment involves different activities depending on the method used. Among methods, the most common are data acquisition, data analysis, and criticism.

Data acquisition concerns the collection of usability data combined with usability tests and subjective evaluations. These usability tests can be divided into two macro-categories namely task test and scenario test. To evaluate the usability of the dashboard, we decided to carry out only task tests, observing and analyzing user behavior in order to understand if, where, and why they encountered difficulties. in particular, task tests are a series of tests in which users perform individual tasks that allow exercising multiple system functions. Task tests are very useful as they simulate real situations in which the user will find himself. Despite the

user being engaged to reach a certain purpose, he does not know what intermediate steps must be followed.

The tasks selected to carry out the tests are:

- Search for a patient and view their monitoring.
- Enter a new drug on the platform.
- Delete a drug from the platform.
- Log off the platform.

A time limit of 5 minutes was imposed for each task. The selected users (n=5) were randomly chosen among clinicians from the Cancer Institute of Naples, Italy. To familiarize users with the application, a test session was launched. In this preliminary step, clinicians were able to use it for 2 minutes without any specific task and without knowing what had to be done for the purpose of the test, thus avoiding influences. Results are shown in Table 4.

Table 4. Test results

	Search for a patient and view their monitoring	Enter a new drug on the platform	Delete a drug from the platform	Log off the platform
User 1	S	P	S	S
User 2	S	S	S	S
User 3	F	F	F	P
User 4	S	S	S	S
User 5	S	S	S	S

Legend: S, success; F, failure; P, partial success

The calculation of the average success rate can be done with the following formula:

((N_(success) • P_success) + (N_(partial success) • P_(partial success)))/N_(total performed test)

Where N is the number of events and P is the weight. By evaluating the weight of a full success as 1 and that of a partial success as half success (i.e., 0.5), the application of the formula is a success rate of (15 + (2 x 0.5))/20=80%. This result gives a significant indication of the usability

of the system. In other words, users are able to successfully complete almost all tasks in a short time.

Concerning the interpretation of collected data to identify problems (data analysis), all the difficulties encountered by various users in interacting with the system during the execution of tasks have been grouped. In particular, no serious usability problems were highlighted; only User 3 reported failures in the execution of tasks, but he was a user accustomed to analog tools and not to the use of computer systems. User 1, on the other hand, correctly carried out all the operations in the pre-established time, except for the one concerning the insertion of a new drug in the system.

Criticism concerns suggestions for solutions or improvements to mitigate the problems identified. The criticality analysis concerned the two users who encountered problems:

- Criticality 1. One of the users was not able to use computer systems, he had problems with all the tasks that were entrusted to him.
  Possible solution: add an initial tutorial for less experienced users.

- Criticality 2: a user was unable to complete the task of inserting a drug into the system in the set time.
  Possible solution: highlight the fields or fields more clearly.

2.6.2. Retrieving and data processing flow

The audiovisual material is uploaded to Firebase Cloud Storage through the APA Database dashboard. Every 4 hours all unprocessed videos are downloaded from Firebase Cloud Storage and processed, generating a .zip file with the results inside. When customers utilize Firebase, Google typically acts as a data processor in accordance with the General Data Protection Regulation (GDPR), processing personal data on their behalf. Similarly, when customers employ Firebase, Google generally functions as a service provider under the CCPA/CPRA, managing personal information on their behalf [70]. The script uploads this .zip file to Firebase Cloud Storage.

Subsequently, the APA Database dashboard displays the previously uploaded .zip file, allowing it to be downloaded to the user's computer in use. For this aim, the ELAN (Eudico Linguistic Annotator) software version 6.4 was implemented [71]. It is a software tool designed for the annotation and analysis of multimedia data, including video, audio, and text. ELAN is a versatile tool used by researchers and professionals to investigate various aspects of language, communication, and human behavior. It has applications in fields such as linguistics, psychology, anthropology, and beyond, where the detailed analysis of multimedia data is essential for gaining insights into complex phenomena (Figure 10).

Figure 10. *ELAN File loading*

A PHP 7.2.0 web server has been set up to upload patient videos for subsequent analysis. It is a server configuration that runs the PHP programming language, specifically version 7.2.0. PHP is a server-side scripting language commonly used for web development to create dynamic content and interact with databases. In this context, the server is set up to handle PHP scripts and facilitate the upload and subsequent analysis of patient videos. (Figure 11).

```php
$storage = $factory->createStorage();
$storageClient = $storage->getStorageClient();
$defaultBucket = $storage->getBucket();


$UPLOADDIR = 'upload';

$currTime = new DateTime();
$currTime = $currTime->format('YmdHi');

$allowedExts = array("mp4");
$extension = pathinfo($_FILES['file']['name'], PATHINFO_EXTENSION);
if ((($_FILES["file"]["type"] == "video/mp4")) && in_array($extension, $allowedExts)){
        if ($_FILES["file"]["error"] > 0){
                header("Location: index.php?status=0");
                //echo "Return Code: " . $_FILES["file"]["error"] . "<br />";
        } else {
                //echo "Upload: " . $_FILES["file"]["name"] . "<br />";
                //echo "Type: " . $_FILES["file"]["type"] . "<br />";
                //echo "Size: " . ($_FILES["file"]["size"] / 1024) . " Kb<br />";
                //echo "Temp file: " . $_FILES["file"]["tmp_name"] . "<br />";


                $ok = move_uploaded_file($_FILES["file"]["tmp_name"], "upload/" .$_POST['name'].$_POST['surname'].$currTime.".mp4");
                //echo "test: ".$ok;
                  //echo "Stored in: " . "upload/" . $_FILES["file"]["name"];
                  //$command = escapeshellcmd('python uploader.py '.$_POST['name'].$_POST['surname']);
                  //$output = shell_exec($command);
                  //echo $output;

                $pathName = $UPLOADDIR."/".$_POST['name'].$_POST['surname'].$currTime.".mp4";
                $file = fopen($pathName, 'r');

                $fileToWrite = $_POST['name'].$_POST['surname'].$currTime;
                $object = $defaultBucket->upload($file, [
          'name' => $fileToWrite."/".$fileToWrite.".mp4",
          'predefinedAcl' => 'publicRead'
                        ]);
                unlink($UPLOADDIR."/".$_POST['name'].$_POST['surname'].$currTime.".mp4");
                header("Location: index.php?status=1");
        }
} else {
        header("Location: index.php?status=0");
}
```

Figure 11. *Script PHP 7.2.0 for video uploading.*

An authentication mechanism criterion has been implemented to prevent unauthorized access. (Figure 12).

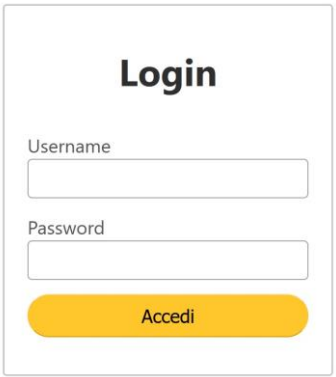

Figure 12. *Authentication Process*

Finally, the file is uploaded to a folder labeled with the patient's identifier.

3. Chapter:

Results of APA investigations

3.1. Behavioral-based APA

3.1.1. Facial expressions of pain: the binary classifier

Based on videos collected from cancer patients, a binary classifier capable of distinguishing between "pain" and "no-pain" was developed. The training process utilized the publicly available Delaware Pain Database [72] and the UNBC-McMaster Shoulder Pain dataset [73]. The Delaware Pain Database comprises photographs capturing painful expressions. It was created with 240 individuals (127 females and 113 males) posing with neutral facial expressions, followed by expressions representing their reactions to five potentially painful scenarios. Different levels of pain were induced for each scenario. The collected images were processed to assess emotional features and apply the FACS, resulting in 229 distinct painful expressions.
The UNBC-McMaster Shoulder Pain dataset contains video recordings featuring 129 participants (66 females and 63 males) experiencing shoulder pain. These recordings document active and passive range-of-motion tests performed on both affected and unaffected limbs during two separate sessions. Certified FACS coders analyzed the participants' facial expressions frame by frame, rating AU intensities. To complement the visual data, self-reported and observer-based assessments of pain and discomfort were recorded at the sequence level. For our analysis, we converted the video dataset into images, selecting one image out of every thirty and labeling them with pain or no-pain tags.
From the information gleaned from these datasets, the images were categorized into two groups: "pain" (marked as 'p' in the Delaware dataset) and "no-pain" (neutral) images.
For AU analysis, we employed OpenFace 2.0, a free and open-source toolkit for facial recognition and landmark detection using Deep Neural

Networks (DNN). This toolkit can be used for various tasks, including facial recognition, facial tracking, and facial expression analysis [74,75]. The neural network classifier focused on the intensities (represented as 'r') of 17 specific AUs. These intensities are measured on a five-point scale, with “1” indicating minimal presence, “5” indicating maximum presence, and “0” indicating no presence at all. We selected AUs related to key actions of pain expression, including brow lowering (AU4), orbital tightening (AU6 and AU7), nose wrinkling (AU9), upper lip raising (AU10), and eye closure (AU43). Additionally, we incorporated eleven AUs from Littlewort's study on spontaneous pain expressions, covering inner brow raiser (AU01), outer brow raiser (AU02), upper lid raiser (AU05), lip corner puller (AU12), dimpler (AU14), lip corner depressor (AU15), chin raiser (AU17), lip stretcher (AU20), lip tightener (AU23), lips part (AU25), and jaw drop (AU26) (Figure 13).

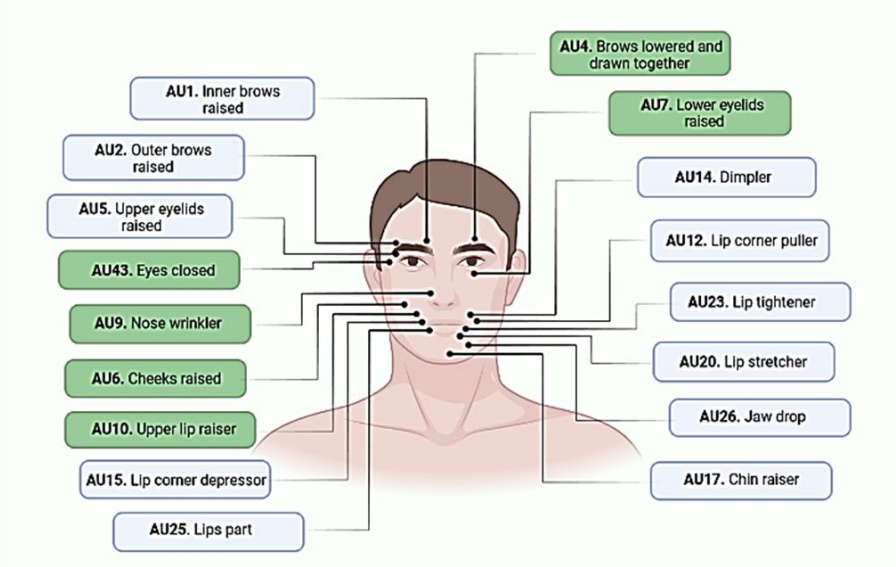

Figure 13. *The action units (AUs) employed. The “core” set of six pain expressions (AU4, AU6, AU7, AU9, AU10, and AU43) [41,42] (green boxes) was extended with eleven selected AUs (light blue boxes), including inner brow raiser (AU1), outer brow raiser (AU2), upper lid raiser (AU5), lip corner puller (AU12), dimpler (AU14), lip corner depressor (AU15), chin raiser (AU17), lip stretcher (AU20), lip tightener (AU23), lips part (AU25), and jaw drop (AU26). Created with BioRender.com (Accessed on 25 April 2023).*

For each image, OpenFace extracted the relevant AUs frame by frame. The collected data were divided into training and test sets, with 80% allocated to training and 20% to testing. Within the training set, 20% was reserved for validation.

The developed neural network classifier followed a Shallow Network architecture, typically consisting of two layers. This architecture has proven effective for small-scale datasets [76]. The dataset used for model training and validation, including parameters, and extracted AUs from the OpenFace toolkit, is accessible at reference [77].

The first layer of the classifier incorporated the 17 AU intensity values as input for each image, using a ReLU/sigmoid activation function. The final layer employed a sigmoid activation function to produce a classification label, indicating either pain (1) or no-pain (0). Figure 14.

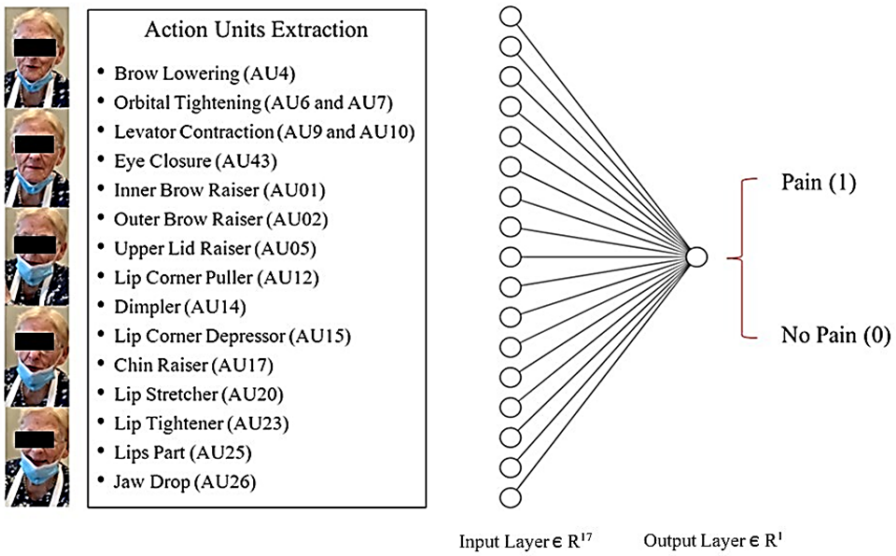

Figure 14. *The binary classifier model. The classifier is made up of two dense layers. The first layer consists of 17 nodes associated with the facial Action Units (AUs) extracted by OpenFace for each image. The final layer (i.e., output layer), uses a sigmoid activation function to output a classification label of either "pain" (1) or "no-pain" (0), based on the outputs from the neurons in the previous layer. Patient consent*

was acquired for the study (ClinicalTrials.gov Identifier: NCT04726228) and scientific divulgation of personal identifiable information.

Subsequently, in order to perform continuous estimation, the entire patient video, along with its corresponding frame prediction values ranging from 0 (no-pain) or 1 (pain), was imported into ELAN. Time-aligned annotations enabled the assessment of temporal relationships between events. Figure 15.

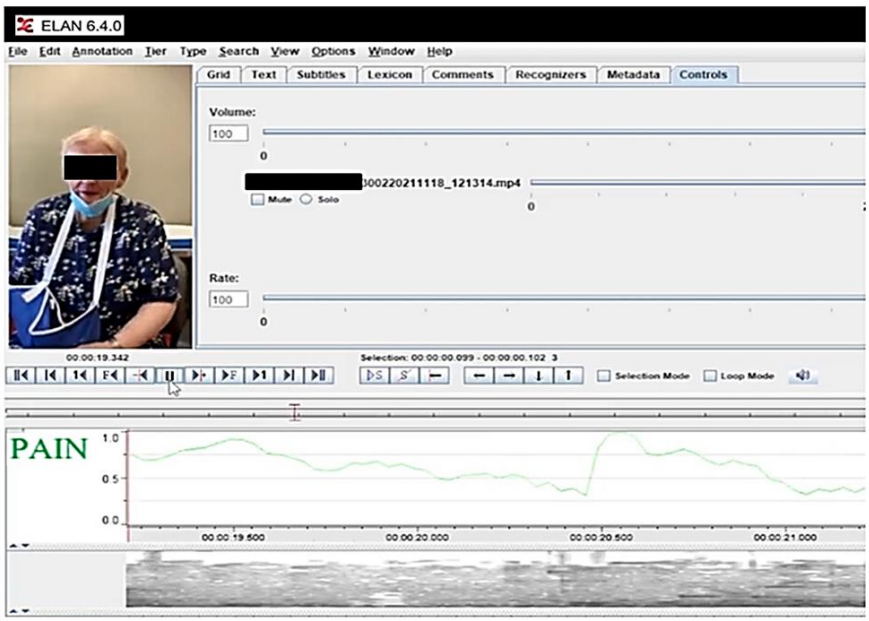

Figure 15. *Frame prediction values of "pain" ranging from 0 to 1 (red line). The annotation tool for audio and video recordings ELAN 6.4 was implemented. Patient consent was acquired for the study (ClinicalTrials.gov Identifier: NCT04726228) and scientific divulgation of personally identifiable information.*

Regarding the strategy employed for frame extraction, training, and validation of the neural network, as well as the approach used to create the image dataset for testing the neural network on cancer patients, the following steps were taken:

- For the McMaster dataset, the pre-processed version, already divided into frames, comprising a total of 48,398 images, was utilized. Subjects appeared in only one of the three phases, with a balanced gender ratio in each phase.
- For the Delaware dataset, a similar approach was followed, preserving the proportion of different ethnicities.
- For data collected by our team, high-definition videos were recorded at 30 frames per second, and AUs were extracted for each frame.

Concerning model evaluation, all samples underwent OpenFace processing and were converted into AU intensities. The processed datasets, containing AUs, were combined and shuffled using the standard Keras framework. The classifier was trained with a maximum of 10,000 epochs, implementing early stopping based on validation loss with a patience of 200 epochs.

The performance of the binary classifier was evaluated using various metrics, including the Receiver Operating Characteristic (ROC) curve, the Area Under the ROC Curve (AUROC), accuracy, precision, recall, and binary cross-entropy. The AUROC value of approximately 0.98 indicated strong performance in distinguishing between pain and no-pain. Figure 16.

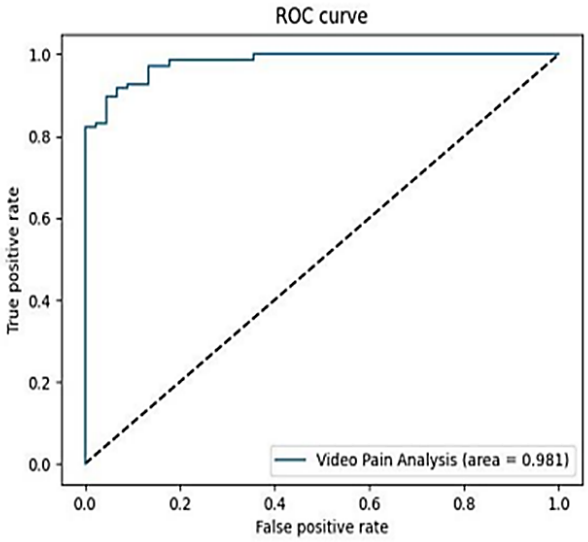

Figure 16. *The area under the receiver operating characteristic (ROC) curve (AUC) of the considered model.*

The classifier achieved an accuracy of 0.9448 after approximately 400 training epochs, with a binary cross-entropy error of 0.1581 on the validation set. Precision and recall measures were 0.9528 and 0.968, respectively. Table 5.

Table 5. Performance of the Binary Classifier model.

	Validation Loss	Accuracy	Precision	Recall
Performance	0.1581	0.9448	0.9528	0.968

3.1.2. Speech analysis

The second dimension of our multimodal dataset is speech analysis. For this aim, we conducted an automatic emotion recognition based on prosodic and textual analysis. For this goal, the pain corpus was implemented (interview in Table 1).

3.1.2.1. Automatic emotion recognition

The leading idea is that prosody and speaking features can significantly express pain as a set of complex emotions according to the classical VAD multidimensional analysis. Nevertheless, the difficulties hidden in this approach lie in the scarce availability of speech data annotated along any pain scale.
Following the same approach pursued in the facial expression analysis, we used previously collected data for building the Audio Signal Analysis Classifier (Multi-Layer Perceptron: 181,588 -> 1,7).
In particular, we adopted the EMOVO dataset, a repository created from the voices of 6 actors replicating 14 phrases to simulate 6 emotional states (disgust, fear, anger, joy, surprise, and sadness), along with a neutral state. Each audio clip has a duration of 3 seconds.
The required libraries are Librosa for extracting prosodic features from audio files (extracted features include chroma, mfcc, and mel spectrogram) and Sklearn for defining the neural network. Moreover, reLU was implemented for the activation function, and Adam for weight optimization.
Concerning Pre-Normalization, the audio source is normalized to a sampling frequency of 16 kHz. Prosodic features are extracted, and the neural network evaluates them.
The obtained Neural Network is composed of a network input of 181 prosodic features and an output of distribution over six emotional states (disgust, joy, fear, anger, surprise, sadness) plus a neutral state. There are three hidden layers of 300, 200, and 100 nodes respectively. The resulting emotional state is the one with the highest probability.

For Model Training, 25% of the available data was reserved for the test set. Model evaluation is based on the test set and measured by accuracy. Therefore, 100 models are created, each trained on a different training set. The best model is returned by the concluding procedure. The obtained accuracy was 0.8435. The model performances are shown in Figure 17.

	precision	recall	f1-score	support
anger	0.87	0.80	0.83	25
disgust	0.69	0.85	0.76	13
fear	0.82	0.86	0.84	21
joy	0.71	0.63	0.67	19
neutral	1.00	0.88	0.93	24
sadness	0.90	1.00	0.95	26
surprise	0.84	0.84	0.84	19
accuracy			0.84	147
macro avg	0.83	0.84	0.83	147
weighted avg	0.85	0.84	0.84	147

Figure 17. *Audio Signal Analysis Classifier (Multi-Layer Perceptron: 181,588 -> 1,7) performances.*

An example of the model's real-world application is shown in Figure 18.

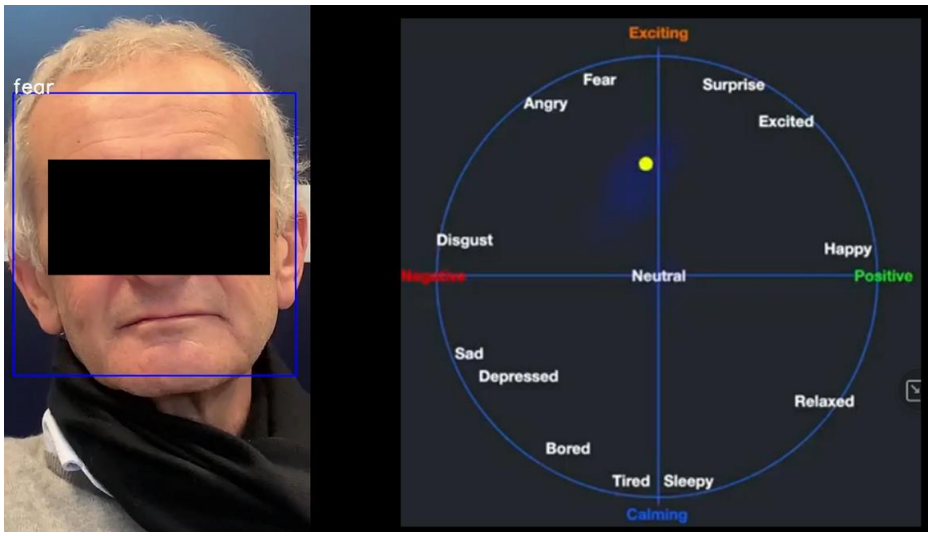

Figure 18. *Automatic emotion recognition in a cancer patient. Patient consent was obtained both for the study (registered under clinicaltrials.gov identifier: NCT04726228) and for the dissemination of scientific findings.*

3.1.2.2. Linguistic analysis from the “corpus” of pain

Given the collected interview (Table 1), the dataset of embedding vectors is presented in [78].
After trascription (Figure 19), the text was manually grouped into sentences (rather than word by word) and annotated in a dedicated channel in ELAN. A channel has been created for the interviewer (SPEAKER channel) to conduct further analysis (video, text, audio).

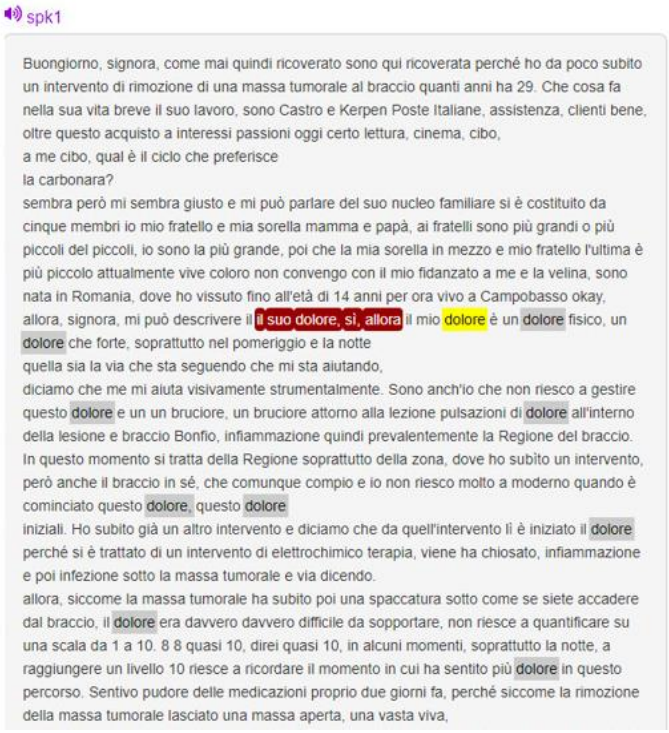

Figure 19. *Text transcription (Speech Developer).*

The ELAN annotator was thus implemented to assemble, frame-by-frame, different behavioral features including textual phonetic and prosodic analysis, sentiment analysis, and arousal. Figure 20.

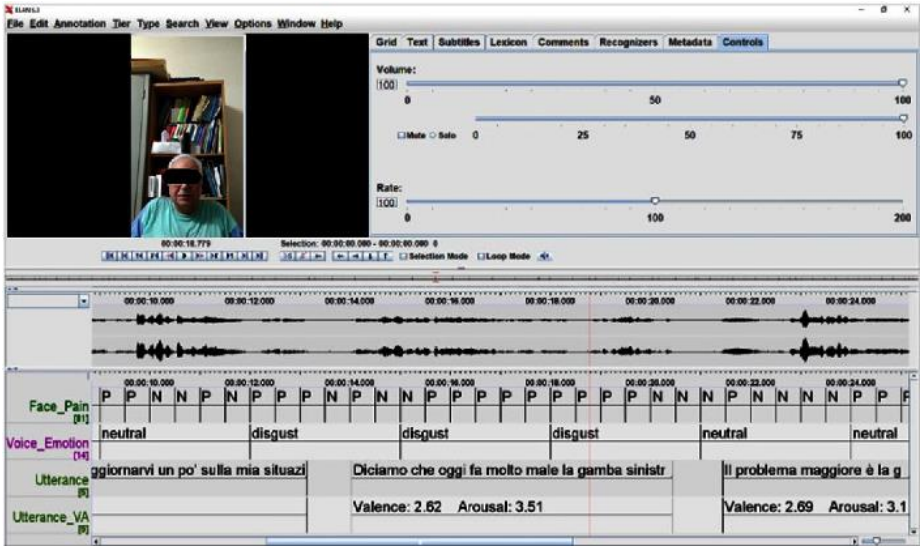

Figure 20. *The ELAN tool is utilized to integrate and analyze frame-by-frame facial expressions (pain/no-pain) in conjunction with language analysis, encompassing textual phonetic and prosodic analysis, sentiment analysis (including categories such as neutral and disgust), and arousal. Patient consent was obtained both for the study (registered under clinicaltrials.gov identifier: NCT04726228) and for the dissemination of scientific findings.*

The linguistic analysis of the pain corpus was conducted at different levels. The first level considered the categories of pain/no pain. In the second level, labels referencing the characteristics of pain according to the five stages of Kubler-Ross were applied.
The corpus and the first two levels can be used for advanced-level linguistic analyses. Given the corpus, once the pain stage is identified (first level), and the correlation pain-emotion validated (second level), a valid tool for proceeding with an in-depth study of the linguistic act (providing examples related to the past or contrast) is provided. The idea is the linguistic translation of the sentences. In other words, from the second level, a series of hidden pragmatic linguistic labels (e.g., depression expressed in different ways, as well as acceptance) related to pain can be obtained (Figure 21).

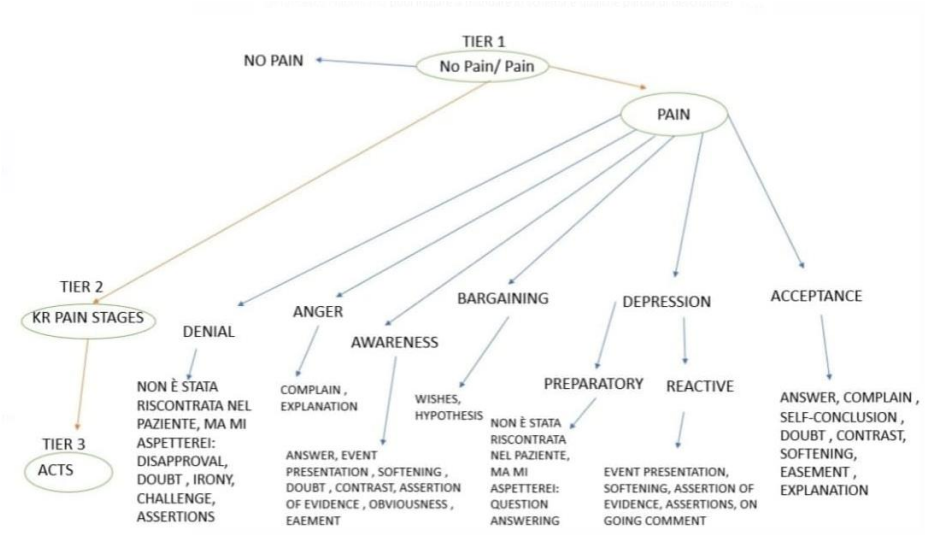

Figure 21. *Three-level linguistic analysis. Abbreviation: KR, Kubler-Ross.*

Undoubtedly, the limitation is that these stages pertain to illnesses and not pain specifically. However, pain is connected to the disease progression stages, and these are not just progressive phases but can be integrated [2,3,5]. In the context of discourse, there is a sudden shift in the stages (the stages are evoked).

3.1.3. Perspectives

In the context of pain, linguistic analysis faces two main obstacles: the scarcity of data available for training models and the need to reference datasets that align with the research objectives.
Text analysis could be performed using lemmatization and stemming techniques, and as a vector metric TF-idf on a reviewed dataset (pain/no pain). For this purpose, the Medical Speech database [79] could be adopted. It contains 8.5 hours of audio utterances paired with text for common medical symptoms. Following a semantic axis method [80], negative and positive phrases related to pain could be obtained. In other words, it would be possible to hypothesize a quantization of pain expressed through text analysis. In these preliminary stages, we are attempting to categorize sentences into two groups: pain and no pain. This has resulted in 25 classes (15 pain, 10 no pain), with one

specifically related to purely emotional aspects. The fundamental concept is that the rarer the term, the more significant it is. After its training and validation, the model will be tested on the pain corpus dataset.
Another fascinating perspective regards the implementation of fusion engine strategies: the aim is to develop a unique vector which considers all the three modalities (text, video, and audio). Such vector should be composed selecting only the relevant information across video, text and audio and this goal could be achieved by using self-attention techniques. Nevertheless, the fusion of embeddings is highly complex, requiring vector-type data for each dimension. An alternative may involve using a vector database, such as leveraging Milvus, for the three dimensions (video, audio, text) related to pain.
For video embedding, several strategies can be used. The open-source pre-trained 3D RESNET model [81] can be easily utilized. An 'N' hyperparameter is chosen, where N identifies the number of frames to process for the video associated with the phrase. If the video has more than N frames, exactly N frames are taken, evenly distributed. If the video has fewer than N frames, additional padding frames are added as needed to reach N. Additionally, Bidirectional Encoder Representations from Transformers (BERT) can be adopted for text. It is a state-of-the-art pre-trained natural language processing model developed by Google. BERT typically generates word embeddings in a high-dimensional space, often 768 dimensions. Notably, this transformer architecture — allows for efficient parallel processing and captures long-range dependencies in the data — produces contextualized word embeddings, meaning that the representation of a word can vary depending on its context within a sentence. Finally for audio embedding extraction wav2vec2 can be used. It is a validated framework for self-supervised learning of speech representations [82].

3.2. Biosignal investigations

3.2.1. Biosignal processing

To process and analyze the EDA signals, we applied a fifth-order Butterworth low-pass filter with a cutoff frequency of 1 Hz, following

the methodology outlined elsewhere [83]. Subsequently, we employed a deconvolution approach, as recommended in prior studies [84], to segregate the signals into their tonic (representing the fundamental conductance level [53]) and phasic components (capturing short-duration changes in response to stimuli [53]). To reduce the computational load during analysis, we downsampled the signal by a factor of 100, as advised in [85].
For the EDA features extraction, we temporally marked the onset of pain episodes during recording, as reported by the patient during the session (NRS ≥ 4). This information was considered for subsequent analysis and EDA feature extraction.
Regarding the ECG signal, we performed R peak detection using a modified version of the Pan–Tompkins algorithm [86], as recommended in [87]. Subsequently, we derived the RR series of interbeat intervals, calculated as the difference between successive R peaks. We then applied a recursive procedure, as described in [88], to filter the ECG-derived RR time series, eliminating intervals that deviated significantly from the mean of the surrounding RR intervals. Subsequently, we computed both the mean and the standard deviation (SD) of the resulting RR series, with the latter serving as a time-domain indicator of HRV. Features extracted from the EDA and ECG data were used to obtain quantitative metrics reflecting the overall pain experience of the patients.
Finally, in the accelerometer data analysis, we calculated the magnitude of acceleration (referred to as the Acc magnitude) from the raw XYZ acceleration signals acquired. This unified acceleration metric reflects significant changes in overall acceleration, irrespective of the device's orientation. Specifically, we calculated the acceleration vector magnitude using the equation provided below:

$$Acc\ magnitude = \sqrt{a_x^2 + a_y^2 + a_z^2}$$

where, ax, ay, and az represent the acceleration on the x-, y-, and z-axis, respectively. The final vector magnitude of the acceleration was obtained by subtracting the mean to discard any constant effect, such as gravity. The resultant acceleration signal was then filtered using a third-order Butterworth bandpass filter with 0.25 Hz and 2.5 Hz cut-off frequencies, as suggested in [89], aiming at removing extraneous accelerations that were not due to human movement and high-frequency

noise, as it has been proven to be a simpler and less operation-intensive procedure to achieve a filtered signal.

3.2.2. Statistics

Statistical analysis was carried out to assess the EDA response associated with the patient's motion during the experimental acquisition. Before applying any statistical tests to compare the results, the data distribution shape must be assessed. Specific tests, often referred to as parametric, are well suited only for Gaussian distributions. The Shapiro–Wilk test is generally employed with this aim. After checking the kind of distribution, it is possible to choose the most adequate test. Our data were non-normally distributed; hence,
a Wilcoxon signed-rank test (the most used non-parametric test) was chosen. This is used to check whether there are any significant differences between representative parameters of two situations (e.g., before and after treatment). In our case, it was carried out to compare the median values of the EDA signals during motion and rest phases, with a significance level equal to 0.05. Furthermore, in order to examine the temporal trends in EDA and HRV parameters and their relationships, a bivariate regression and correlation analysis was carried. The Pearson correlation coefficient and the determination coefficient (R2) were calculated to characterize the relationship between EDA and HRV parameters, and a non-parametric Spearman correlation coefficient was calculated to characterize the association between the discrete pain event onsets (marked by the patients during the experimental acquisition) and the calculated biosignal parameters.
Biosignal processing and analysis were carried out in MatLab v. R2021b (The Math-Works Inc., Natick, MA, USA) for EDA, ECG, and accelerometer signals. Normality tests (Shapiro–Wilk) and hypothesis tests (Wilcoxon rank sum) were performed, and correlation coefficients (Pearson and Spearman correlation) were determined using SPSS Statistics v. 28 (IBM Corp., Armonk, NY, USA). To compare the EDA values during rest and motion, a Wilcoxon signed-rank test, chosen as a non-parametric alternative to the Student's t-test (due to the non-normal data distributions), was carried out.
For investigations on pain phenomena, we implemented the multiparametric Dataset_Pascale [65]. The sensitivity analysis tests were conducted using the Li and Yu [90] and Raikov test [91] on the continuous variables for assessing the potential Missing Not At Random

(MNAR) process presence. Therefore, on the basis of the information obtainable from the data and from the context, the best conclusion on the mechanism generating the missing data will be reached. A Multiple Imputation analysis was finally performed on data to preserve the sample size.

A Multiple Factorial Analysis (MFA) was performed on data to detect multi-correlations and associations between numerical and categorical variables within the context of subjective and objective pain features. It is a statistical technique used for analyzing databases with large sets of variables that are suspected of being statistically related and describe the same set of observations or individuals. This strategy is often implemented for addressing different types of variables (e.g., numerical, categorical) and for analyzing their relationships in a single analysis by creating principal components (PCs) which are assigned as a part of data behavior and variability. MFA allows analysts to explore patterns, similarities, and differences between the different sets of variables and observations [92]. In our analysis, a focus was applied to the main interest variables namely EDA and ECG derivates and BTcP presence (groups: No BTcP, BTcP), by reading 2D-projected modalities in the factorial plane respect with the BTcP intensity groups.

Within the realm of MFA, when dealing with complex multidimensional datasets featuring numerous categorical variables, the utilization of Multiple Correspondence Analysis (MCA) proves to be a valuable strategy. It enables the condensation of dataset dimensions into a selected set of categorical variables, effectively capturing the most essential information. Therefore, we adopted a data-driven approach known as Hierarchical Clustering on Principal Components (HCPC). This approach harmoniously integrates three established methods including MCA, or PC analysis (PCA) for numerical variables, hierarchical clustering, and the k-means algorithm, to derive a refined and enhanced cluster solution [93]. Through this amalgamation of techniques, we aimed to extract a more robust and accurate representation of patterns and relationships present within the data. Operatively, the HCPC method provides a PCA and, subsequently, a hierarchical clustering by implementing an agglomerative hierarchical tree; the ideal number of groups is obtained by a pruning approach; then k-means was performed on data by setting the number of groups, obtained as described above. Thus, different variables were inserted in the routine to find the BTcP-related risk groups. They included BTcP type, ECOG-PS, metastases (No, Yes, bone metastases), chemotherapy,

radiotherapy, and surgery, as well as drug therapy including morphine equivalent dose, MED (≤ 60 mg; > 60 mg) and adjuvants. Finally, a multivariable linear regression analysis was conducted to assess the main associations between MED (treated as a number and binary variable) and potentially related variables. The data were analyzed using the R software version 4.2.3 (R Core Teams, R Foundation for Statistical Computing, Vienna, Austria). The toolkit included car, purr, boot, snow, misty, and naniar. The Mice package was adopted for the imputation of the missing data. FactoMineR was used for the implementation of factor analysis methods. Moreover, graphical packages were adopted for the visualization of the plots.

3.2.3. Case Studies

The first case study regards the measurement of EDA and ECG-derived signals on a 66-year-old female patient affected by lung cancer and suffering from post-thoracotomy pain. The signal recording was carried out for a 13-minute duration in static conditions (i.e., patient at rest). Pain-related events were reported by the patient, who indicated the occurrence time of the pain episode (signatures).
In Figure 22, the unprocessed EDA signal (in microsiemens, μS), and the RR time series (in milliseconds, ms) are presented. The RR time series was obtained by analyzing the recorded ECG signal after detecting the R peaks.

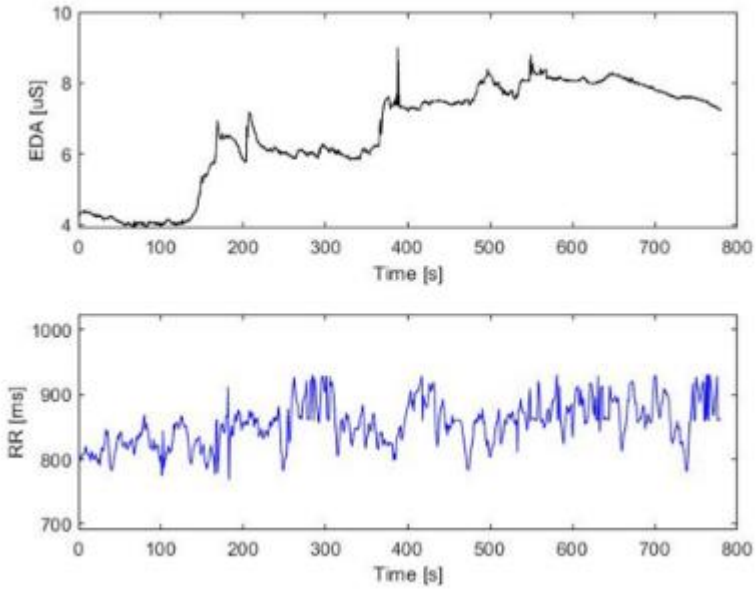

Figure 22. *Biosignal acquisitions (EDA, and ECG-derived signals).*

To accentuate signal variations attributed to an escalation in pain, we have delineated time intervals encompassing these occurrences. Specifically, these intervals delineate an initial segment, extending for approximately 160 seconds, during which the tonic component of the EDA signal remained stable. Subsequently, in the subsequent segment, extending until the conclusion, a noticeable increase in the EDA signal coincided with the emergence of pain. Simultaneously, changes in the RR series were monitored within the same time frame. As elucidated in further detail below, there existed a temporal gap between the onset of the pain event and the commencement of the EDA elevation.
Therefore, we conducted a decomposition of the EDA signal into its tonic and phasic components. Following this, we paired and analyzed both the EDA and ECG signals (i.e., RR intervals) in accordance with the pain events reported by the patient (NRS $\geq$ 4). (Figure 23).

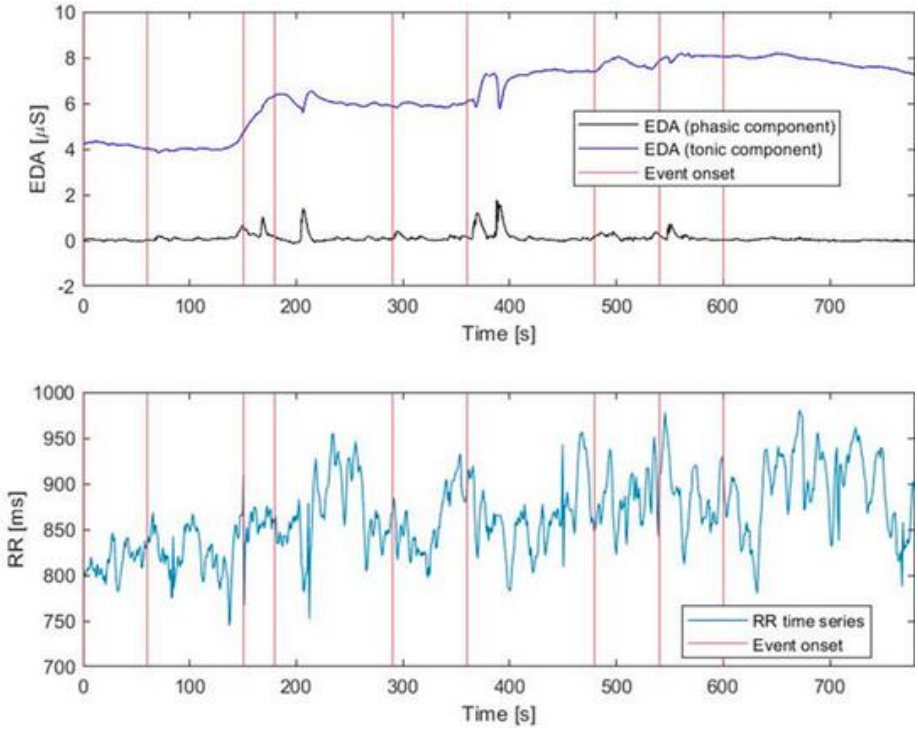

Figure 23. *The original EDA signal was deconstructed into its tonic and phasic constituents, with pain event onsets marked by straight vertical red lines. Correspondingly, the RR interbeat interval time series was displayed below, also denoting pain event onsets with straight vertical red lines. In this depiction, the red lines signify instances of pain events, as defined by a numeric rating scale (NRS) score of ≥ 4. The measurement unit for EDA is expressed in microsiemens (μS).*

For each pain event occurring within a predefined 40-second time window following the event onset, we computed the following skin conductance response (SCR) features:

- SCR Latency: This represents the time delay from the event onset to the detection of the first SCR with an amplitude above the 0.01 μS threshold.
- SCR Sum: This quantifies the cumulative sum of the amplitudes of all detected SCRs within the specified time window.

- SCR Average: This signifies the mean value of the phasic activity observed in the EDA signal during the predetermined time window.
- Integrated SCR (ISCR): This metric reflects the total area encompassed by the detected phasic activity in the EDA signal within the specified time window.

Regarding HRV signals, while a multitude of approaches and metrics for HRV analysis exist, and various factors such as age, gender, and circadian cycle can influence them, we focused on the following time-domain HRV features for this pilot study:

- Mean RR: This is the average value of the RR intervals.
- SD RR: This represents the standard deviation of the RR intervals and serves as an indicator of short-term HRV.

These specific parameters were chosen due to their reliability as health markers and their sensitivity to fluctuations in the ANS. Additionally, mean RR is a straightforward and rapidly responsive parameter that can be visually assessed, while SD RR reflects the influence of both the sympathetic and parasympathetic nervous systems.
The analysis of the trends showed a discernible upward trajectory in the SD RR as the data collection process advanced, coinciding with the intensification of the EDA signal. This pattern suggests an augmentation in HRV concurrent with the onset of pain. The correlation analysis using the Spearman correlation coefficient revealed a strong and statistically significant relationship between SD RR and the onset of pain (Spearman correlation coefficient = 0.733, p-value = 0.025). In contrast, the ISCR parameter displayed a less pronounced variation with a weaker correlation (Spearman correlation coefficient = 0.217) and lacked statistical significance (p-value = 0.576). Despite these observable increasing trends, the statistical examination unveiled only a feeble correlation between EDA and HRV parameters. Specifically, the Pearson correlation coefficient between SD RR and ISCR was 0.179, and no statistical significance was discerned (p-value = 0.644)(Figure 24).

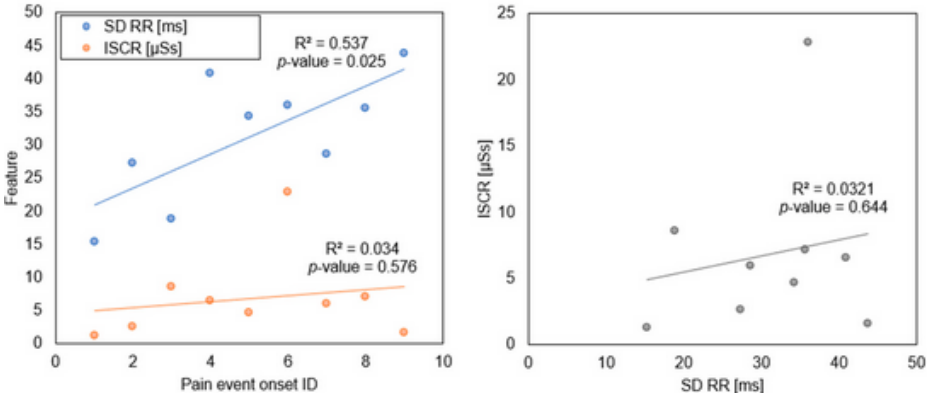

Figure 24. *(Left) Depicts the values of ISCR and SD RR at the occurrence of successive pain events. (Right) Features a scatter plot designed to evaluate the correlation between ISCR and SD RR. Both figures include a linear fitting curve, accompanied by its corresponding determination coefficient (R2). Abbreviations: ISCR - integrated skin conductance response; SD RR - standard deviation of the RR intervals.*

A second case study was addressed for studying mechanisms of different cancer pain phenomena including background and BTcP. It focuses on the simultaneous measurement of both EDA and accelerometer signals on a 74-year-old male patient with prostate cancer and cancer-related pain. In this case, the objective was to assess the motion-associated pain (i.e., incident BTcP). Although the patient's baseline pain was effectively managed with drug therapy, his pain became more pronounced during movement. Therefore, the patient experienced episodes of severe cancer-induced incident pain with intensity levels ranging from 7 to 8 on the NRS.
To this aim, a 13-minute EDA and accelerometer signal acquisition was carried out during both the motion and the rest phase. The biosignal analysis demonstrated that movement served as a pain trigger, as indicated by higher EDA values, corresponding to increased acceleration magnitudes. Nonetheless, the EDA signal required some time to gradually revert back to its baseline values (Figure 25).

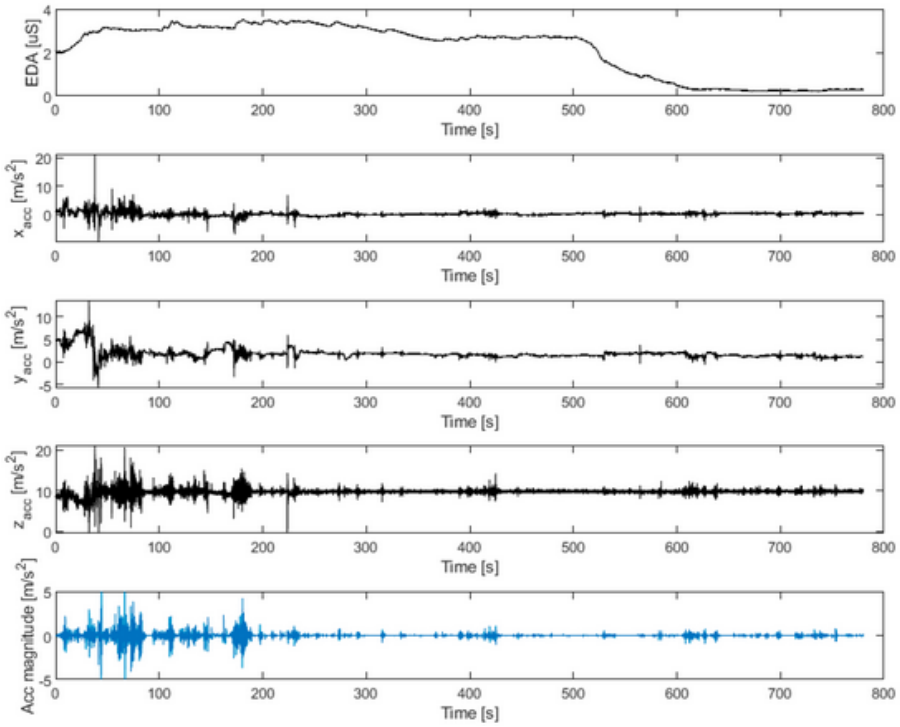

Figure 25. *Simultaneous registration of electrodermal activity (EDA), x–y–z acceleration, and acceleration magnitude after gravity subtraction.*

The simultaneous registration of EDA and acceleration magnitude with the indication of motion and rest phases during the acquisition is presented in Figure 26.

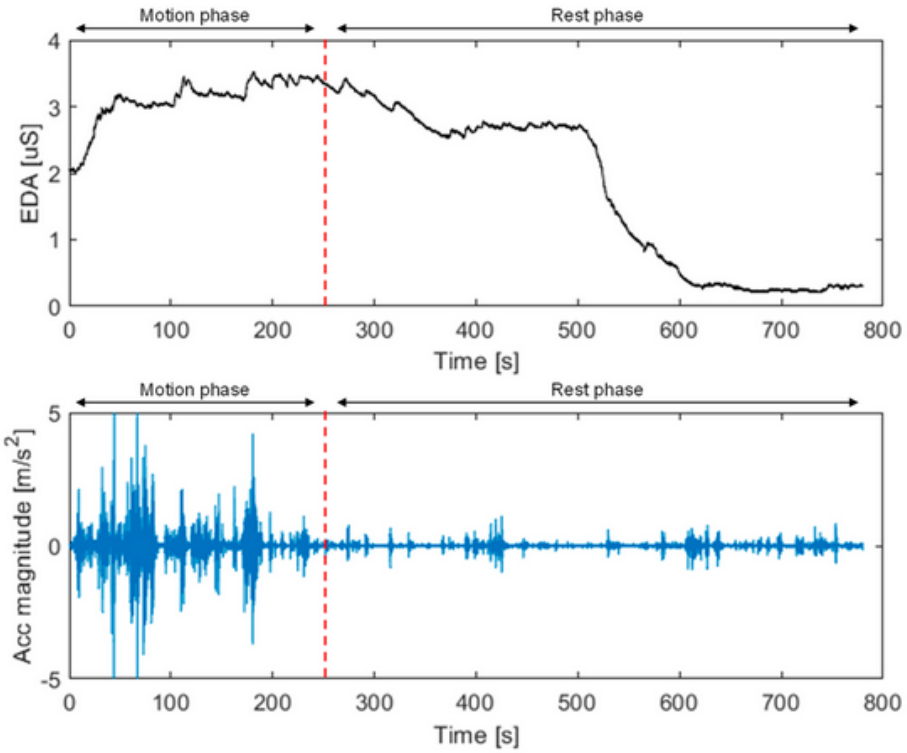

***Figure 26**. Simultaneous registration of electrodermal activity (EDA) and acceleration magnitude with an indication of motion and rest phases during the acquisition; the EDA signal demonstrates a gradual return to its baseline values, requiring a certain amount of time for recovery.*

The EDA signal exhibited a significant increase during the motion phase in comparison to the rest phase of the experimental acquisition. This statistical significance was confirmed by a p-value < 0.001 obtained from the Wilcoxon signed-rank test. Likewise, heart rate values showed significant differences between the motion and rest phases (p-value < 0.001 for the Wilcoxon signed-rank test), with a higher mean heart rate and increased variability observed during the motion phase compared to the rest phase (Figure 27)

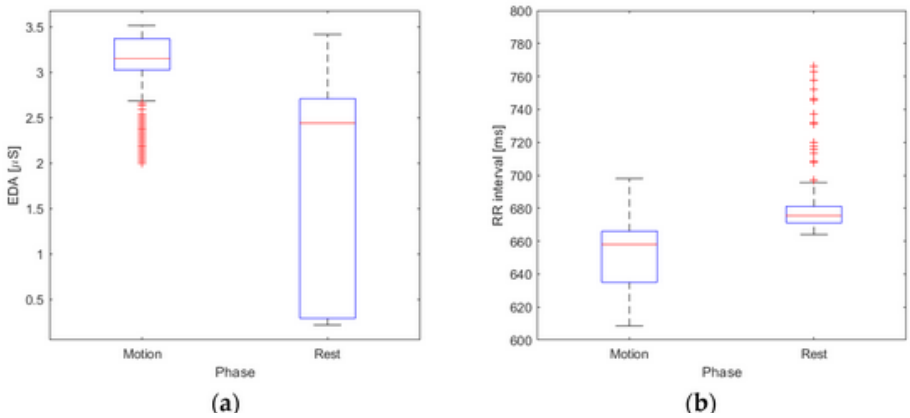

Figure 27. *Boxplots of (a) electrodermal activity (EDA) values and (b) ECG-derived RR values during both the motion and rest phases.*

3.2.4. Investigations on pain phenomena

Out of the initial pool of 153 eligible patients, biosignals were successfully recorded from 118 individuals. Unfortunately, data from 54 patients had to be excluded from the analysis due to signal quality issues or incomplete information. Consequently, the exploratory statistical analysis was conducted using data from a final cohort of 64 patients, which included clinical, demographic, and biosignal variables. From the multiparametric Dataset_Pascale [65], we considered two EDA-derived parameters including the continuous decomposition analysis (CDA), and the trough-to-peak (TTP) analysis, The former decomposes the SCL data into continuous signals of phasic and tonic activity. The TTP is a standard valley-to-peak or min-max analysis and quantifies the difference between the skin conductance at the peak of a response. For the analysis, the means of CDA and TTP were examined. Concerning the ECG-derived signals, the R-R series of interbeat intervals (i.e., the time between successive R waves of the QRS complex on the ECG waveform) has been computed to extract time-domain parameters of the HRV. The ECG-derived R-R time series has been then filtered by means of a recursive procedure to remove those intervals differing most from the mean of the surrounding R-R intervals. Finally, the variables under consideration were R-R intervals, and heart rate (HR). The standard deviations (SDs) of both parameters have been calculated afterward as they are a better time-domain indicator of the variability of the heart rhythm.

Table 6 reports the main descriptive statistics regarding the demographic and clinical variables present in the dataset [62].

Table 6. Descriptive statistics

Variable	**Main descriptive statistics** *(mean and standard deviation, SD)*
Age	
Age (mean)	60.6
Age (SD)	13.3
Gender	
Women	23
Men	41
Weight (kg)	
Weight (mean)	70.5
Weight (SD)	15.0
Height (cm)	
Height (mean)	167.6
Height (SD)	8.9
Variable	**Distribution frequencies** *(N)*
Gender	
Women	23
Men	41
Hospitalization	
Yes	13
No	51
Type of primary tumor	
Lung	11
Pancreas	3
Bone / Soft tissues	13
Breast	6
Colon / Colon rectum/ Lung and colon	4
Head and neck	10
	1

Stomach	7
Urogenital	3
Liver	6
Other	
Therapy	
Radio	17
Chemo	28
Immuno	3
Surgery	9
Presence of metastases	
Yes	34
No	30
Presence of bone metastases	
Yes	23
No	41
ECOG	
1	33
2	11
3	7
4	13
Presence of comorbidities	
Yes	32
No	32
Type of comorbidities	
Diabetes	5
Hypertension	21
Kidney failure	3
Hyperthyroidism	1
COPD	3
Ischemic heart disease	1
Base cancer pain type	
Nociceptive	41
Neuropathic	14
Mixed	9
Base cancer pain intensity	
1	0
2	5
3	6
4	9
5	4

6	6
7	6
8	19
9	4
10	5
Main site of cancer pain	
Lung	9
Pancreas	3
Bone	2
Breast	4
Sarcoma	9
Prostate	2
Desmoid	2
Liver	2
Pelvis	2
Shoulder	1
Chest	3
Head and neck	9
Melanoma	1
Larynx	1
Bladder	2
Opioid treatment for base cancer pain	
Yes	50
No	14
Adjuvants for base cancer pain	
Yes	24
No	40
Dose of opioids for base cancer pain	
dose <= 100	34
100 < dose < 200	20
dose > 200	10
Breakthrough cancer pain (BTcP)	
Yes	28
No	36
BTcP type	
Incident	7
Spontaneous	17
Violent	1

Nociceptive	0
Neuropathic	1
Mixed	1
Not Defined	1
BTcP maximum duration	
0-30 min	16
30-60 min	5
60-90 min	5
Not relevant	1
Not Defined	1
BTcP intensity	
1	0
2	0
3	0
4	1
5	1
6	0
7	2
8	10
9	4
10	10
Main site of BTcP	
Back	5
Abdomen	7
Leg	3
Chest	6
Head and neck	4
Face	1
Kidney	1
Not Defined	1
BTcP treatment	
Rapid onset opioid (ROO) >100 mcg	16
Rapid onset opioid (ROO) < 100 mcg	1
Other (no ROO)	7

Abbreviations: ECOG, Eastern Cooperative Oncology Group Performance status; BTcP, Breakthrough cancer pain; COPD, chronic obstructive pulmonary disease.

The flowchart of the study is presented in Figure 28.

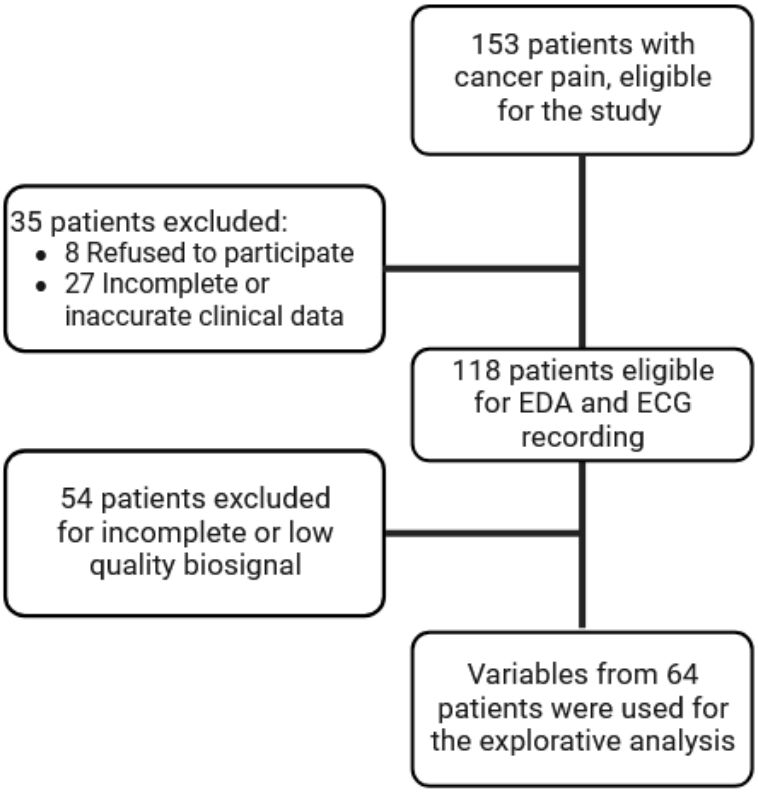

Figure 28. *Flowchart of the study on pain phenomena.*

The MFA focused on the main two components or dimensions of variables correlation, expressed as Factorial Axes (FA1 and FA2). The total explained variance was 30.3% (17.7% on FA1, 12.6% on FA2) for the complete set of variables. The first dimension (FA1) was mainly described by BTcP presence (23.6%) and Type of BTcP (22.8%), followed by ECOG, Opioids, and Metastases (13.1%, 11.2%, and 10.3%, respectively). The second dimension (FA2) was strongly characterized by the objective variables SDHR and SDRR (42.9% and 42.0%, respectively), followed by metastases (7.1%). Moreover, poor correlations were found for Metastases with FA1 (cos2 = 0.05);

concerning FA2, strong indicators were found for both SDHR and SDRR (both contributed > 42% and > 0.8 cos2's, and almost null values were calculated for other variables); mean TTP and CDA were mainly collected into the third dimension (absolute contributes: 26.2% and 24.5%, and similar cos2 's).
The factorial plane highlighted the characteristics of the BTcP groups. Patients without BTcP tended to be treated with lesser opioid dosages (MED) for background pain (67% vs 93%, p = 0.03) and, although not significantly, they were less prone to undergo chemotherapy (33% vs 57%, p = 0.1), and radiotherapy (22% vs 32%, p = 0.54) compared to BTcP affected cancer patients. Patients with BTcP were more likely to have metastases (64% vs. 22%, p = 0.18, not shown in table), especially bone metastases (46% vs. 22%, p = 0.12) compared with no BTcP group. Moreover, the BTcP group was characterized by a higher ECOG (57% vs. 11%, p<0.01). MFA detected no potential correlations between subjective variables (BTcP presence) and objective ones (Figure 29).

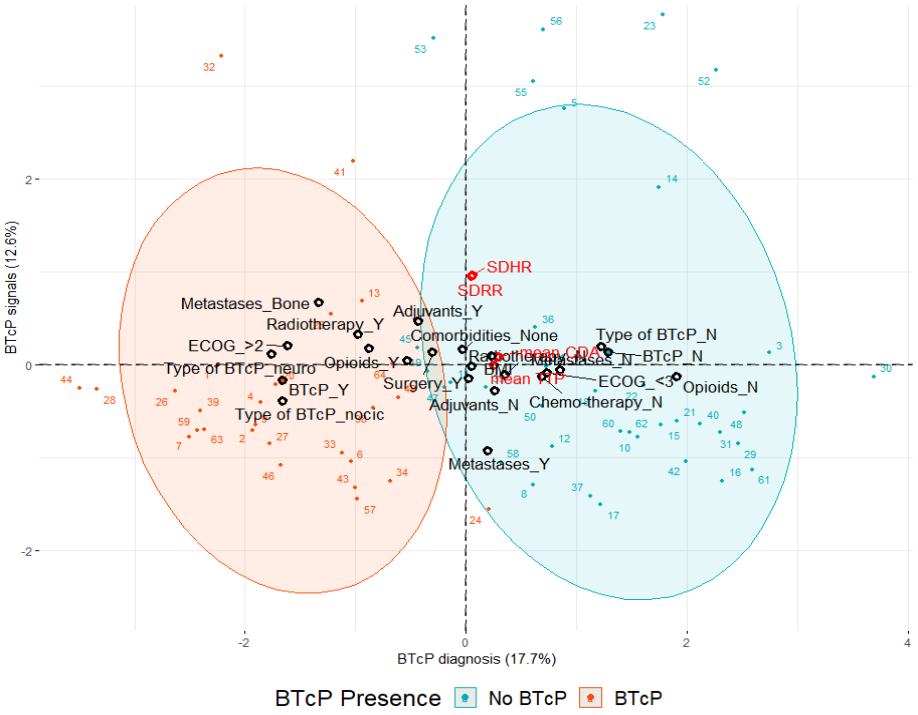

Figure 29. *Multiple Factorial Analysis. Factorial planes for modalities and individuals. The first two dimensions were considered. Strong*

components were given by the type of BTcP, the intensity of BTcP, ECOG, Opioids, and metastases. Very poor contributions were finally detected for objective pain variables (red spots and labels): TTP, CDA SDHR, SDRR. The projection from the center to the variable's point revealed two key aspects including an orthogonal alignment with the existing variables' cloud pattern and a predominantly centralized contribution to FA2. Therefore, null correlations were confirmed between subjective variables (BTcP Intensity as NRS measure) and objective ones. The red arrow (zoomed mean of coordinates from the objective variables) points out the variable cloud shape, stating that poor correlations were detected. Each black point represents a variable modality which was plotted as "name of the variable"-underscore-modality: "N" = "No", "Y" = "Yes", "neuro" = "neuropathic", "nocic" = "nociceptive". Abbreviations: FA, Factorial Axis; BTcP, Breakthrough cancer pain; ECOG, Eastern Cooperative Oncology Group Performance status; SDRR, RR intervals standard deviation; SDHR, heart rate standard deviation.

Regarding the cluster analysis, the optimal partition based on principal components yielded 3 distinct clusters. MCA reported a global variability explanation of 35.2% on 10 categorical variables and 22 modalities. None of the cancer patients belonging to Cluster 1 (27 cancer patients) had MED ($p<0.01$), almost 93% of them had a low ECOG ($p<0.01$), more than 88% did not have chemotherapy ($p<0.01$), 96.3% radiotherapy ($p<0.01$), did not present metastases (74.1%, $p<0.01$). This cluster was mainly characterized by no pain nor nociceptive pain (0% and 18.5%, respectively, $p<0.01$); 59.4% of cancer patients with no pain belong to cluster 1. Cluster 2 was composed of 14 cancer patients, all of whom had chemotherapy ($p<0.01$) and was characterized by a low ECOG ($p<0.01$). An amount of 57% of them suffered from neuropathic pain ($p= 0.04$), only one had nociceptive pain, and another one did not assume opioids. Cluster 3 (23 individuals) was characterized by opioids assumption (100%, $p<0.01$), high ECOG (90% of them belonged to cluster 3, $p<0.01$, 78.3% of cluster 3), had MED > 60 (65%; corresponding to the 75% of the whole set of patients with MED > 60, $p<0.01$); moreover, cancer patients of cluster 3 were affected by bone metastases BTcP (81% of all bone metastases belonged to cluster 3, of them the 73.9% was bone metastases, $p<0.01$) (Figure 30).

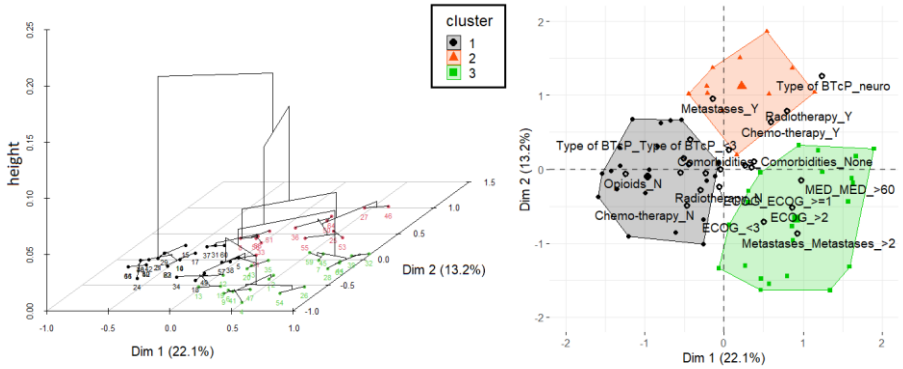

Figure 30. *Cluster analysis for opioid therapy. The principal component analysis identified three distinct clusters. Multiple Correspondence Analysis (MCA) explained 35.2% of global variability across 10 categorical variables and 22 modalities. Cluster 1 (27 patients) had no MED, predominantly low ECOG, no chemotherapy, and no metastases. It was characterized by the absence of pain, with 59.4% of pain-free patients belonging to this cluster. Cluster 2 (14 patients) had all patients on chemotherapy, low ECOG, and some experiencing neuropathic pain. Cluster 3 (23 patients) had 100% opioid usage, high ECOG, MED > 60, and a high prevalence of bone metastases BTcP.*

4. Chapter:

Discussion

The research presented in this PhD thesis delves into various aspects of APA, encompassing an array of investigations across multiple domains. Remarkably, the study successfully amalgamated three distinct datasets, each contributing unique perspectives to the comprehensive understanding of pain in oncological patients. These datasets include clinical and demographic information alongside biosignals [65], videos utilized for the binary classifier [77], and a linguistic corpus [78]. Each of the datasets generated throughout the course of this research is available for use in further research investigations. Researchers interested in delving deeper into the intricacies of pain assessment in oncological patients can request access to these datasets for extended analysis and exploration. This ensures that the valuable information collected in this study remains accessible to the scientific community, fostering collaboration and contributing to advancements in the broader field of APA.

Since in the realm of APA, the examination of facial expressions holds paramount significance, a pivotal component of the research lies in the development and application of a binary classifier for pain/non-pain categorization within the oncological context [28-30,54]. This pioneering experiment marks a significant stride in the field of APA, with implications for enhancing the accuracy and efficiency of pain assessment in cancer patients. The classifier, an outcome of meticulous investigation, represents a noteworthy advancement, substantiated by the publication of the first experiment on this subject [60]. Two datasets were employed to construct the model capable of discerning between the categories "pain=1" and "non-pain=0". The complete patient video, along with its associated frame prediction values (0 and 1), was integrated into ELAN [71]. This process facilitated a more granular analysis of the video, utilizing frame prediction values as a quantitative measure of pain levels in each frame. This approach enabled a more precise estimation of overall pain levels, capturing specific moments and durations of pain throughout the video. Notably, this study represents the first application of APA using AUs in the context of cancer patients. The

systems, initially trained with an expanded set of AUs for enhanced pain expression capture, were subsequently tested on real-world scenarios involving individuals suffering from cancer pain syndromes. In contrast to other classifiers relying on shallow network architecture [94], our proposed model utilized meaningful features without extracting them through a feature processing layer trained alongside the classification layer. The model demonstrated high accuracy in validation (∼94%). This outcome aligns with expectations, as error rates tend to decrease on smaller datasets when employing shallow networks.

Additional experiments were conducted to extract pain characteristics from videos through AU analysis. For instance, Lucey et al. [73] utilized the UNBC-McMaster Shoulder Pain database, implementing an active appearance model to detect frames depicting patient pain. Visual features were extracted, and 3D parameters were derived, classifying individual AUs through a linear SVM. Linear logistic regression was then employed to merge SVM outputs, allowing supervised calibration of scores into log-likelihood scores. The study also incorporated a CNN and RNN combination for spatial and temporal analysis of video frames, followed by a regression model to estimate pain intensity scores.

The FACS, a comprehensive system describing facial movements resulting from individual muscle activation, is widely used in psychology to study various aspects related to emotions [31]. While FACS doesn't inherently provide emotion-specific descriptors, its utility in pain research, especially regarding "pain relevant AUs," and the choice between automated and semi-automated systems remains to be determined. In our study, the ability to analyze video frame-by-frame proves crucial for detecting pain fluctuations, particularly in cancer pain phenomena like BTcP [60].

The integration of linguistic analysis into the study framework further expands the dimensions of APA [43]. The linguistic corpus, eventually coupled with clinical data, can add a qualitative layer to the investigation, enabling a more comprehensive understanding of pain experiences [44]. The pain corpus encompasses the rich tapestry of language used by individuals to describe their pain and becomes a valuable source of information. It not only adds depth to the investigation but also enables a more nuanced understanding of the diverse ways in which individuals articulate and express their cancer-related pain. This multifaceted approach contributes to the richness of insights derived from the study. It is important to note that, in this field of APA, research is in the early stages, and numerous limitations need to

be addressed. For instance, the corpus refers to the disease rather than specifically focusing on pain. However, pain, emotions, and disease are intricately interconnected [95]. Similarly, the adopted strategy, which involves the use of the Kubler-Ross model, requires further exploration and refinement.

Furthermore, a cutting-edge aspect of the research involves the development of a neural network dedicated to sentiment analysis. This innovative approach explores the emotional nuances embedded in linguistic expressions related to pain. The incorporation of sentiment analysis not only enhances the depth of understanding but also introduces a novel dimension to the field of APA.

Another contribution of the study is the clinical investigation dedicated to acquiring and analyzing biosignals. This segment is aimed to provide a deeper insight into the physiological responses associated with pain in oncological patients. By combining clinical data with biosignals, the research sought to unravel predictive clusters, laying the foundation for more nuanced pain assessments. Our framework introduces a novel approach by processing the EDA signal into tonic and phasic components and integrating it with motion activity data from a three-axis accelerometer, as well as elements obtained from ECG analysis. The objective is to amalgamate parameters derived from multiple biosignals, creating distinct pain signatures in different clinical scenarios, including rest and movement (incident pain) [96]. According to other research in the field [97], a commercially available low-cost multisensory wearable platform facilitated the simultaneous acquisition of various physiological signals during pain-monitoring sessions. The EDA signal was processed, decomposed into tonic and phasic components, and integrated with accelerometer data to assess incident pain. Additionally, raw ECG data analysis provided time-domain parameters related to HRV, a novel exploration in cancer pain management combined with other biosignals like EDA and accelerometer data. Despite the preliminary and experimental nature of this study, the results obtained are highly promising, showcasing the feasibility and potential impact of our approach. Notably, the registration and analysis of EDA signals effectively identified and characterized important skin conductance responses, providing indicators of the patient's pain experience. Figures 21 and 22 highlight that an increase in the EDA signal corresponds to higher acceleration magnitude during motion, whereas during rest, lower acceleration magnitude is associated with lower EDA responses. This dynamic relationship between the ANS activity and motor dynamics in

response to painful stimuli underscores the intricate interplay between sensory perception and motor responses. Incorporating both autonomic and motor assessments offers a more comprehensive understanding of pain mechanisms and aids in developing targeted interventions. The decomposition of the EDA signal into tonic and phasic components, coupled with HRV analysis, establishes a vital foundation for model validation. Separating the EDA signal into baseline sympathetic activity (tonic) and rapid changes associated with emotional arousal or stress (phasic) provides valuable physiological insights. HRV analysis contributes information about pain-related ANS functioning and the patient's overall physiological state. Future studies will aim to build a comprehensive dataset for different cancer patients, correlating clinical and biosignal features.

Integrating objective data in a multidimensional model and analyzing clinical and therapeutic elements can yield significant insights for tailoring the therapy. This study represents a pioneering effort to integrate biosignal analysis with subjective, patient-reported elements in the context of APA. The multidimensional exploratory statistical approach involved MFA to condense variability into a few components [93]. The analysis revealed that the presence or absence of BTcP and its type are predominantly projected onto the first dimension, representing subjective variables related to patients' overall health. Objective APA-extracted variables showed no correlation with clinical factors. Despite patients with BTcP having worse clinical conditions, the analysis failed to establish a clear link between subjective and objective pain variables to explain the BTcP phenomenon. The lack of statistical correlation is probably due to the complexity of pain, individual variations in pain perception, and the limitations of measurement methods [58,98].

5. Chapter:

Conclusion

Appreciating the importance of a comprehensive pain assessment is a critical step in advancing pain management techniques. Pain management in oncology, indeed, is a specialized field that requires a tailored approach to meet the unique needs and preferences of each patient. Nevertheless, while subjective pain assessment methods are widely employed to comprehend and address pain, they have inherent limitations. Striking a balance between patient self-reports and the objective evaluation of pain offers valuable opportunities for delivering optimal care. The combination of clinical and instrumental elements and an investigation based on multiple statistical and predictive approaches can lead to extraordinary results and lay the foundation for new research processes. In other words, the ability to refer to specific clinical and instrumental data for this study population is an incredible opportunity to define the various phenomena of oncological pain, which, although well-studied clinically, have knowledge gaps regarding their origin and processing.

Notably, despite research on APA processes is a rapidly advancing field, to our knowledge, our investigations represent one of the first attempts to integrate data derived from biosignal analysis, behavioral findings, and subjective, patient-reported, elements, in the setting of cancer-related pain.

On the other hand, seamlessly integrating the objective physiological parameters measured through APA with the subjective insights obtained from self-reports poses a complex challenge. It is essential to acknowledge the significance of each feature under consideration and carefully harmonize them to draw comprehensive conclusions that genuinely encompass the intricacies of pain experiences. Future research, involving larger and more diverse participant samples, rigorous validation of biosignal-based approaches, and controlled experimental designs, holds the potential to yield a deeper understanding of pain assessment and management strategies.

Finally, research in APA for cancer pain management faces several challenges, with multimodal data collection being a key aspect.

Combining language and text analysis with physiological data holds promise for developing more accurate predictive models, acknowledging pain as a multidimensional experience influenced by physiological, psychological, and emotional factors. Integrating these diverse data types could lead to more targeted and effective treatment plans in cancer pain management.

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