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Advancing the integration of biosignal-based automated pain assessment methods into a comprehensive model for addressing cancer pain

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Abstract

Background Tailoring effective strategies for cancer pain management requires a careful analysis of multiple factors that influence pain phenomena and, ultimately, guide the therapy. While there is a wealth of research on automatic pain assessment (APA), its integration with clinical data remains inadequately explored. This study aimed to address the potential correlations between subjective and APA-derived objectives variables in a cohort of cancer patients.

Methods A multidimensional statistical approach was employed. Demographic, clinical, and pain-related variables were examined. Objective measures included electrodermal activity (EDA) and electrocardiogram (ECG) signals. Sensitivity analysis, multiple factorial analysis (MFA), hierarchical clustering on principal components (HCPC), and multivariable regression were used for data analysis.

Results The study analyzed data from 64 cancer patients. MFA revealed correlations between pain intensity, type, Eastern Cooperative Oncology Group Performance status (ECOG), opioids, and metastases. Clustering identified three distinct patient groups based on pain characteristics, treatments, and ECOG. Multivariable regression analysis showed associations between pain intensity, ECOG, type of breakthrough cancer pain, and opioid dosages. The analyses failed to find a correlation between subjective and objective pain variables.

Conclusions The reported pain perception is unrelated to the objective variables of APA. An in-depth investigation of APA is required to understand the variables to be studied, the operational modalities, and above all, strategies for appropriate integration with data obtained from self-reporting.

Trial registration This study is registered with ClinicalTrials.gov, number (NCT04726228), registered 27 January 2021, https://classic.clinicaltrials.gov/ct2/show/NCT04726228?term=nct04726228&draw=2&rank=1

Keywords Pain, Cancer Pain, Automatic Pain Assessment, Opioids, Breakthrough Cancer Pain, Palliative Care, Artificial Intelligence, Pain Management, Oncology, Quality of Life

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Background

Cancer pain is a prevalent concern among cancer patients. Significantly, according to the World Health Organization (WHO), 55% of individuals undergoing anti-cancer treatment suffer from moderate to severe pain. Furthermore, an even larger percentage, potentially reaching 70%, of those facing advanced or terminal illnesses, experience pain [1, 2].

The challenge of pain management lies in tailoring effective strategies that address the unique nature of each individual's pain experience while considering factors such as pain intensity, underlying causes, and personal responses to treatments [3–5]. The pain experience often reflects an intricate interplay of multiple factors, such as psychosocial elements, levels of distress, tumor attributes, disease advancement, and the underlying pain pathophysiology[4]. In this complex scenario, pain assessment is the cornerstone for planning effective pain management. Nevertheless, this crucial step is often challenging. The subjective nature of pain presents one of the most intricate aspects. The description of pain can vary significantly among individuals, highlighting the importance of employing methods that can accurately capture this diversity. Additionally, cultural influences play a role in how pain is expressed and communicated, leading to potential misunderstandings or underreporting [6]. Furthermore, certain populations, such as children [7, 8] or those with cognitive impairments [9], present unique challenges, requiring specialized approaches to accurately assess their pain experiences [10, 11].

Self-report measurement instruments, including the visual analog scale (VAS) and the numeric rating scale (NRS), are frequently employed to evaluate the intensity of pain. These scales heavily rely on the individual's ability to accurately recall and convey their pain intensity, which can be affected by memory biases, emotional states, and cognitive impairments. Hence, due to the susceptibility of subjective methods to individual interpretations and biases, they fall short of fully encompassing the intricate complexity of pain [12].

Automatic Pain Assessment (APA) is focused on objective measures for the assessment of pain intensity, offering a more unbiased substitute to subjective pain scales [13]. APA methodologies encompass a variety of behavioral and physiological approaches. Behavioral approaches include the analysis of facial expressions [14], linguistic patterns using qualitative and quantitative analyses [15], and the observation of non-verbal physical behaviors such as body movements and gestures [16]. On the other hand, physiological indicators concern the study of biosignals such as electrocardiogram (ECG) and electrodermal activity (EDA), as well as advanced brain imaging techniques such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), for addressing pain-related brain activity [17]. In particular, biosignals like EDA and ECG could also offer the potential of being used in continuously monitoring settings and easily available as wearable devices, thus allowing implementing systems that can register objective physiological variables reflecting both the sympathetic and parasympathetic activity in daily situations and conditions. This would enable the long-term monitoring of subjective autonomous nervous system responses, as reflected by specific sympathetic and parasympathetic indicators that can be derived from galvanic skin responses and variability of cardiac rhythm.

Nevertheless, while APA methods have the potential to offer more objective insights into pain intensity, it is crucial to acknowledge their limitations. These mostly include the lack of high-quality validation studies, uncertainty about which parameters should be implemented in different settings, and technical issues such as timing of utilization [18]. Consequently, a comprehensive pain assessment approach should ideally combine both subjective self-reporting and objective measures to provide a more holistic understanding of pain experiences and enable better-informed pain management strategies.

Given these premises, the objective of this study was to explore potential correlations between subjective and objectively derived variables using APA modalities in cancer patients, as an initial step towards establishing a comprehensive pain assessment pathway.

Methods

Study design and population

The investigation was granted approval by the local Ethics Committee of Istituto Nazionale Tumori, Fondazione Pascale, Naples, Italy (protocol code 41/20 Oss; approval date: 26 November 2020), and all participants provided written informed consent. All methods were performed following the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards and it was registered with ClinicalTrials.gov, number (NCT04726228). The study employed a prospective observational design, utilizing medical records as its primary data source. The cohort for this study comprised adult patients undergoing treatment for cancer-related pain at the Istituto Nazionale Tumori, Fondazione Pascale, Italy. Clinical-instrumental assessments and collection of anamnestic data were conducted during a single outpatient visit at the pain therapy clinic. The process of recording biosignals was executed spanning a timeframe of approximately 5 min.

Variables considered

The analysis involved the examination of numerous variables, including demographic factors such as age, and body mass index (BMI). Clinical measurements included the number of comorbidities (categorized as "None" and at least one), Eastern Cooperative Oncology Group (ECOG) performance status (categorized as low ≤ 2, high > 2), metastases (yes/no), bone metastases (yes/no). Other clinical data concerned the type of anticancer therapy (chemotherapy, immunotherapy, surgery, and radiotherapy). Pain-related variables were pain type (nociceptive, neuropathic) and intensity (0–10 NRS), breakthrough cancer pain (BTcP) [19], and its features (type: nociceptive or neuropathic; 0–10 NRS intensity). Pain therapy included opioids, calculated as morphine equivalent dose (MED) for background pain, rapid onset opioids for BTcP, and pain adjuvants (corticosteroids, antidepressants, anticonvulsants, muscle relaxants, and anti-anxiety medications).

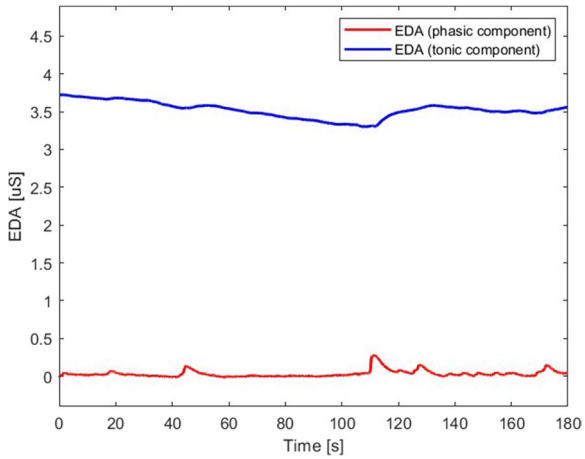

Fig. 1 Phasic and tonic components of the electrodermal activity (EDA) signal over time. Legend: The signal is recorded in microsiemens (µS)

Biosignals

The objective variables were obtained from the analysis of the EDA and ECG biosignals. EDA reflects the sympathetic nervous system activity and serves as a valuable indicator for evaluating pain-induced neurocognitive stress. It detects alterations in the skin's electrical properties, triggered by sweat gland activation, ultimately resulting in increased skin conductance [20]. The continuous variations in skin conductance are termed the Skin Conductance Level (SCL), while the rapid responses occurring within seconds are identified as the Galvanic Skin Response (GSR). Both SCL and GSR play roles in the tonic and phasic components (Fig. 1).

For acquiring and analyzing biosignals, we employed a previously validated approach [21]. Regarding EDA biosignals, two EDA-derived analyses have been performed including the continuous decomposition analysis (CDA), and the trough-to-peak (TTP) analysis, both conducted in accordance to [22–24]. For the analysis, the mean amplitude of all above-threshold GSRs was calculated for both CDA and TTP analyses and adopted as a representative parameter of the EDA signal since it provides an overall synthetic measure of the average amplitude of registered skin conductance responses.

Concerning the ECG signal, temporal changes in inter-beat intervals offer a gauge of heart rate variability (HRV), closely associated with the autonomic nervous system (ANS) activity. These fluctuations can also signal physiological reactions to stressful or painful situations. Following our previous study [21], we focused on the R-R series of interbeat intervals, defined as the time between successive R waves of the QRS complex on the ECG waveform, [25], and then used it to extract time-domain parameters of the HRV. In particular, as reported in [21], R peaks were detected using a modified version of the Pan-Tompkins technique based on the ECG envelope and subsequent flattening of the signal to enhance the QRS-complexes as proposed in [26–28], and the raw series of differences between consecutive peaks was obtained (R-R). Then, using a recursive filtering process, the ECG-derived R-R time series were filtered to remove outliers and intervals that deviated most from the mean of the nearby RR intervals. Subsequently, from the ECG-derived R-R time series (Fig. 2), the heart rate (HR) time series has been obtained, and the standard deviation (SD) of both R-R and HR series has been calculated and used as a reference time-domain indicator of the variability of the heart rhythm.

As we described in a previous study [21], EDA and ECG signals have been acquired by using a BITalino device equipped with sensors for the recording of ECG and EDA signals. The BITalino platform is a hard-ware-affordable and open-source biosignals platform developed for physiological computing. Signals have been collected at a 1000 Hz sampling rate.

Statistical analyses

The sensitivity analysis tests were conducted using the Li and Yu [29] and Raikov test [30] on the continuous variables for assessing the potential Missing Not At Random (MNAR) process presence. Therefore, based on the information obtainable from the data and 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.

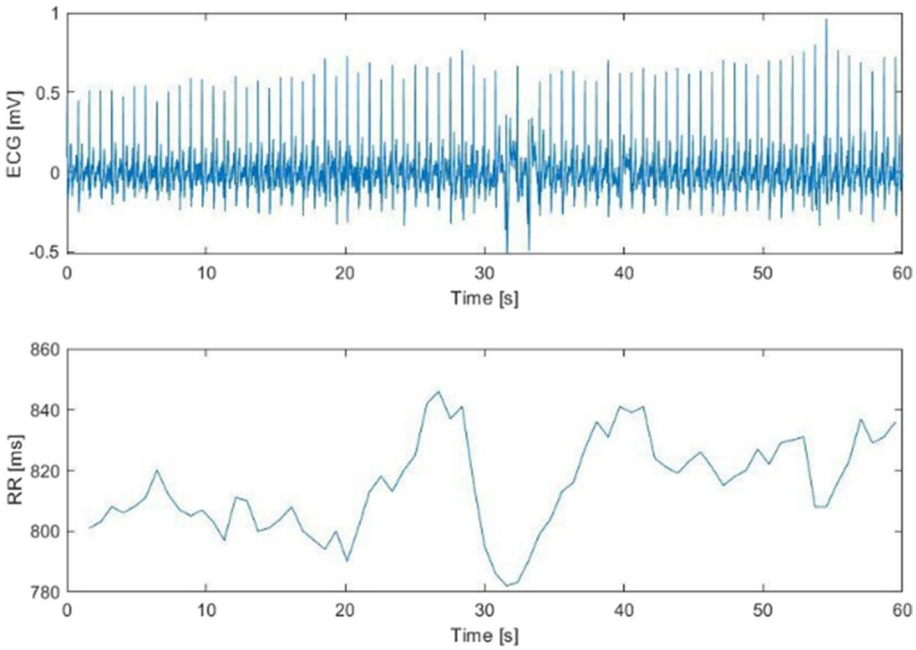

Fig. 2 Plot of the ECG and R-R intervals over time

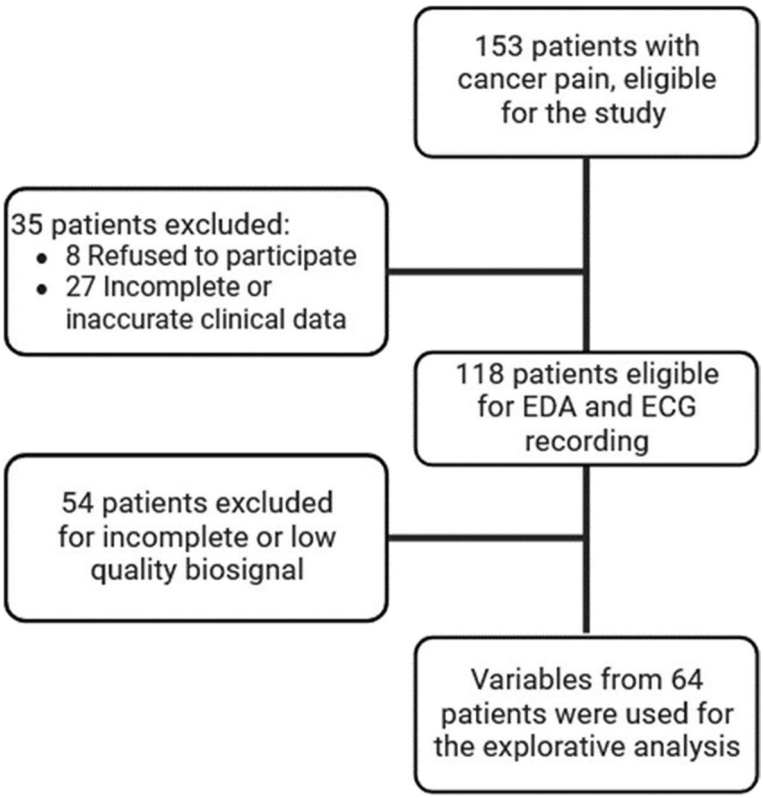

Fig. 3 Flowchart of the study. Abbreviations: EDA, electrodermal activity; ECG electrocardiogram

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 [31]. 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 [32]. 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 [33]. 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, metastases (No, Yes, bone metastases), chemotherapy, radiotherapy, and surgery, as well as drug therapy including 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. The graphics packages included ggplot2 and factoextra. Biosignal processing and analysis were conducted using MatLab v. R2021b from The Math-Works Inc.

Results

Among 153 patients deemed eligible for the study, biosignals were recorded from 118 individuals. Data from 54 patients were excluded from the analysis due to issues with signal quality or incomplete information. Ultimately, the exploratory statistical analysis incorporated clinical, demographic, and biosignal variables from 64 patients (Fig. 3).

Table 1 Demographic data and variables ($n=64$)

Variable (n/%)			
Age		**ECOG**	
Mean (SD)	60.6 (13.3)	< 3	44 (69%)
BMI		> 2	20 (31%)
Mean (SD)	25 (4.5)	**Metastases**	
Comorbidities		No	30 (47%)
None	31 (48%)	Yes	13 (20%)
≥ 1	33 (52%)	Bone metastases	21 (33%)
BTcP		**Chemotherapy**	
No	36 (56.2%)	No	36 (56%)
Yes	28 (43.8%)	Yes	28 (44%)
Type of BTcP		**Immunotherapy**	
None	37 (58%)	No	61 (95%)
Neuropatic	7 (11%)	Yes	3 (5%)
Nociceptive	20 (31%)	**Surgery**	
BTcP Intensity		No	55 (86%)
No BTcP	36 (56%)	Yes	9 (14%)
NRS 4–8	14 (22%)	**Radiotherapy**	
NRS > 8	14 (22%)	No	47 (73%)
Adjuvants		Yes	17 (27%)
No	40 (63%)	**Mean CDA**	
Yes	24 (38%)	Mean (SD)	0.1 (0.1)
Opioids		**Mean TTP**	
No	14 (22%)	Mean (SD)	0.1 (0.1)
Yes	50 (78%)	**SDRR**	
Type of Tumor		Mean (SD)	56.9 (59.1)
Other	23 (36%)	**SDHR**	
Gastro-intestinal	11 (17%)	Mean (SD)	6.5 (7.1)
Breast	6 (9%)		
Bone/soft tissue	13 (20%)		
Lung	11 (17%)		

Abbreviations: *BMI* body mass index, *ECOG* Eastern Cooperative Oncology Group performance status, *BTcP* Breakthrough cancer pain, *NRS* Numeric Rating Scalem, *CDA* Continuous Decomposition Analysis, *TTP* Trough-To-Peak, *SDRR* standard deviation R-R (interbeat intervals), *SDHR* standard deviation heart rate

Demographic data, clinical variables, as well as subjective and objective data are reported in Table 1.

Multiple factorial analysis for BTcP analysis

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) (Fig. 4a). 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%) (Fig. 4b).

Moreover, poor correlations were found for Metastases with FA1 ($cos^2 = 0.05$); concerning FA2, strong indicators were found for both SDHR and SDRR (both contributed > 42% and > 0.8 cos^2'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 cos^2'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 (Fig. 5).

The results of the univariable group analysis for BTcP are presented in Table 2.

Clustering on principal components for BTcP

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, $p < 0.01$) (Fig. 6).

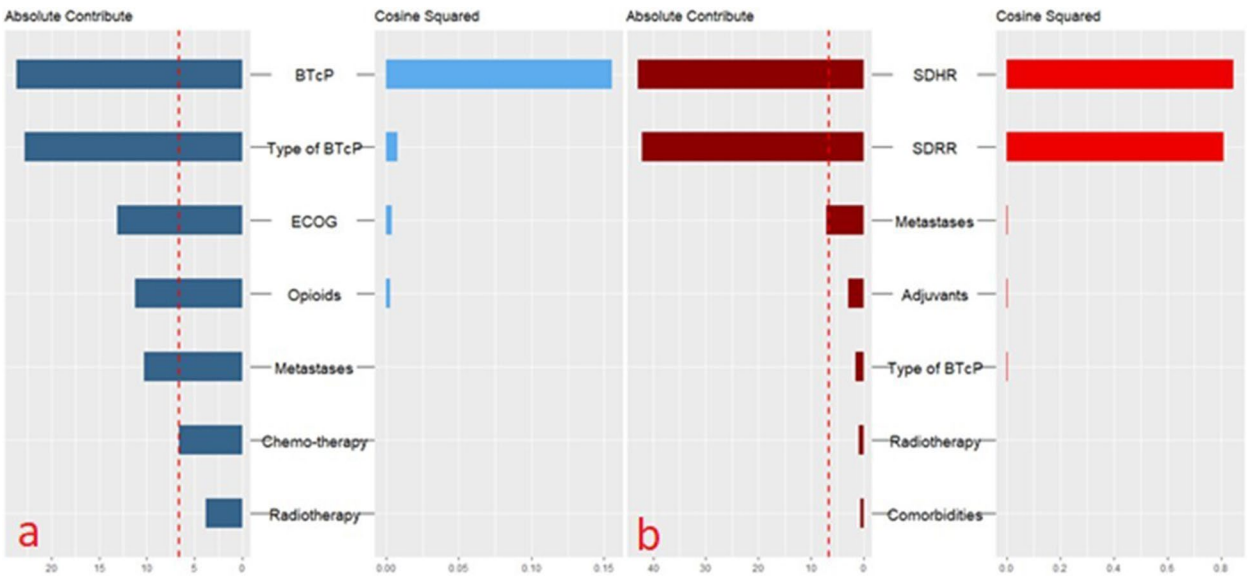

Fig. 4 The main absolute contributes and main squared cosines to the factorial axes: Factorial Axes (FAs): FA1 (**a**) and FA2 (**b**)

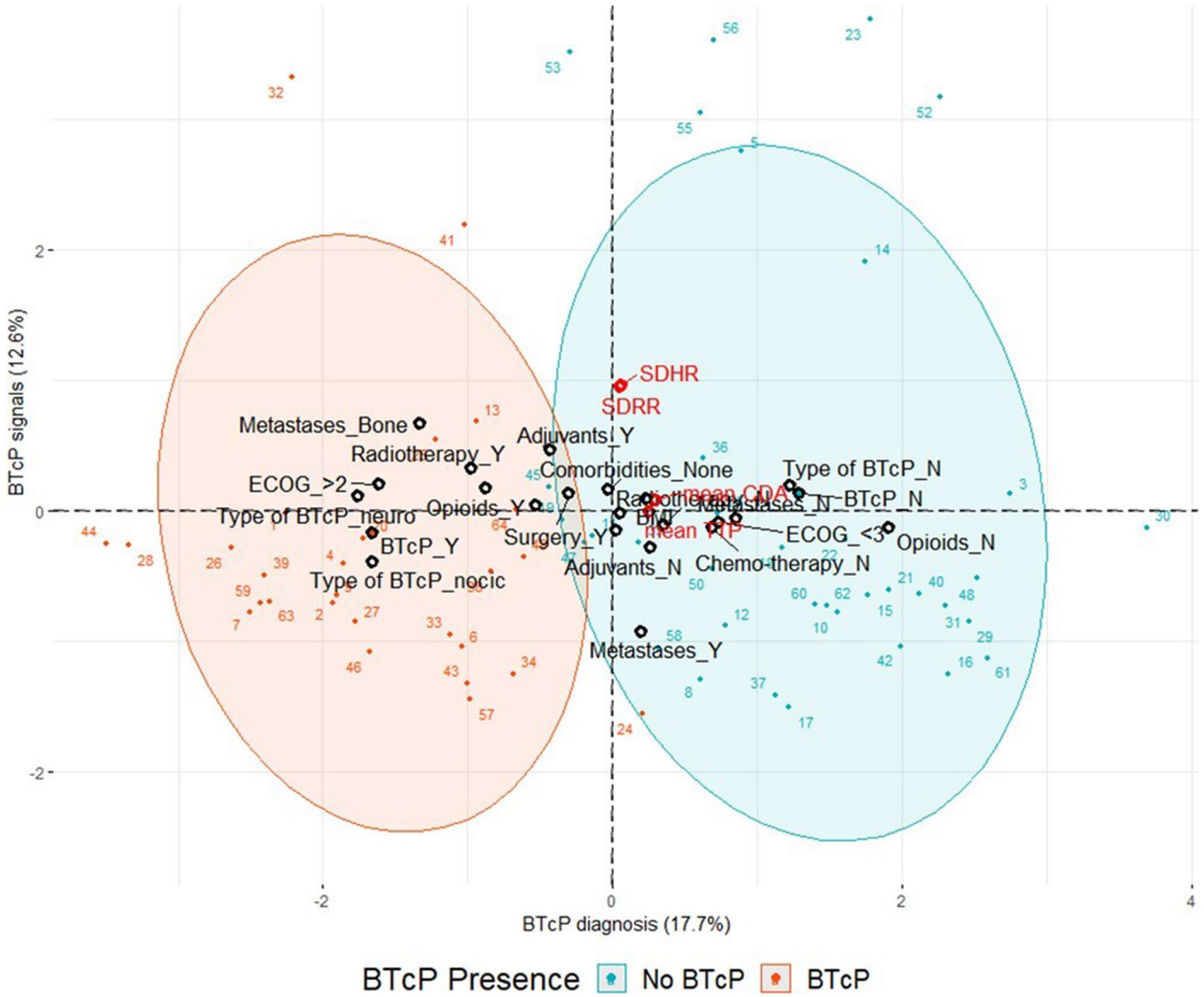

Fig. 5 Multiple Factorial Analysis. Factorial planes for modalities and individuals. Legend: The first two dimensions were considered. Strong components were given by the type of BTcP, the intensity of BTcP, ECOG, Opioids, and metastases. Very poor contributions were finally detected for objective pain variables (red spots and labels): TTP, CDA SDHR, SDNN. 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: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group performance status; BTcP, Breakthrough cancer pain; CDA, Continuous Decomposition Analysis; NRS, Numeric Rating Scale; TTP, Trough-To-Peak; SDRR, standard deviation R-R (interbeat intervals); SDHR, standard deviation heart rate; MED, Morphine Equivalent Dose

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.

Results from the k-mean were reported in Table 3. Comparing clusters with BTcP measures 87% of cancer patients, in cluster 1 were not affected by BTcP while cluster 3 was characterized by higher NRS pain (85% vs. 17%, $p < 0.01$). Mean CDA, mean TTP, SDNN (defined as the normal R-R intervals standard deviation, after

Table 2 Analysis of BTcP groups

Variable	No BTcP *n* = 36	BTcP *n* = 28	No BTcP vs. BTcP[a]
Age			0.760
Mean (SD)	59.7 (14.8)	61.7 (11.1)	
BMI			0.180
Mean (SD)	25.7 (4.2)	24.1 (4.8)	
Comorbidities			0.636
None	16 (44%)	15 (54%)	
≥ 1	20 (56%)	13 (46%)	
ECOG			**< 0.001**
< 3	32 (89%)	12 (43%)	
> 2	4 (11%)	16 (57%)	
CDA			0.808
Mean (SD)	0.1 (0.2)	0.1 (0.1)	
TTP			0.556
Mean (SD)	0.1 (0.1)	0.1 (0.1)	
SDRR			0.962
Mean (SD)	59.3 (64.2)	53.7 (52.7)	
SDHR			0.984
Mean (SD)	6.9 (7.8)	5.9 (6.3)	
Metastasis			0.117
No	20 (56%)	10 (36%)	
Yes	8 (22%)	5 (18%)	
Bone	8 (22%)	13 (46%)	
Chemotherapy			0.099
No	24 (67%)	12 (43%)	
Yes	12 (33%)	16 (57%)	
Surgery			> 0.999
No	31 (86%)	24 (86%)	
Yes	5 (14%)	4 (14%)	
Radiotherapy			0.544
No	28 (78%)	19 (68%)	
Yes	8 (22%)	9 (32%)	
Adjuvants			> 0.999
No	22 (61%)	18 (64%)	
Yes	14 (39%)	10 (36%)	
Opioids			**0.027**
No	12 (33%)	2 (7%)	
Yes	24 (67%)	26 (93%)	
Cancer Type			0.842
Other	15 (42%)	8 (29%)	
Gastrointestinal	5 (14%)	6 (21%)	
Breast	3 (8%)	3 (11%)	
Bone/soft tissue	7 (19%)	6 (21%)	
Lung	6 (17%)	5 (18%)	

Abbreviations: *BMI* body mass index, *ECOG* Eastern Cooperative Oncology Group performance status, *CDA* Continuous Decomposition Analysis, *TTP* Trough-To-Peak, *SDRR* standard deviation R-R (interbeat intervals), *SDHR* standard deviation heart rate

[a] Wilcoxon rank sum test; Pearson's Chi-squared test

outliers removal from R-R series), and SDHR were not found as significantly different among clusters.

Multivariable regression analyses for opioid therapy

In multivariable analysis, age and BMI were not associated with opioid therapy (see Model 1, Table 4). Similarly, no significant differences based on SDNN, SDHR, and adjuvant therapy were detected; the opioid amount was significantly and positively associated with ECOG as cancer patients with higher ECOG meanly received 72.4 MED more (95% CI: [12.1,133.0], $p = 0.02$). A positive correlation was found with the type of BTcP ($p < 0.01$): neuropathic pain likely received more opioids (147 units of MED) compared with No pain. Mean TTP showed a non-significant trend with the MED therapy ($p = 0.09$). In the logistic analysis (Model 2, Table 4) a significant association with higher MED assumption was given by the Intensity of BTcP, as expected: in particular, cancer patients with high pain (> 8 NRS) were 8 times more likely to receive higher opioid dosages (MED > 60) (OR = 8.3, 95%CI = [1.8, 48.4], $p = 0.02$). A borderline association was detected for SDHR (OR = 1.5, 95%CI = [0.98, 2.39], $p = 0.06$).

Discussion

To effectively manage pain, a thorough assessment of the various components that characterize different pain manifestations is essential [34]. This is particularly crucial for oncological pain, which exhibits complex and distinctive features [35]. For instance, BTcP is a sudden, intense flare-up of pain that occurs in cancer patients who are already receiving pain medication for their chronic pain. It is a pain phenomenon with a complex pathophysiology that has yet to be fully characterized [36]. In this convoluted situation, integrating objective data in a multidimensional model and analyzing clinical and therapeutic elements can yield significant insights for tailoring the therapy [17].

While research on APA processes is a rapidly advancing field [17, 18, 37], to our knowledge, this study represents one of the first attempts to integrate data derived from biosignal analysis and subjective, patient-reported, elements. For this aim, we followed a multidimensional exploratory statistical pathway. In the MFA, variability is condensed into a few components (dimensions) by creating FAs. This approach is employed to clarify the general pattern of data when there is a large number of statistical relations among a set of numerous variables [32]. The obtained latent variables (i.e., FA1 and FA2) are linear combinations of the data variables. They collect the sample's variability in a descending manner with the first being the most significant, followed by the second, and so on. These latent variables are uncorrelated with each

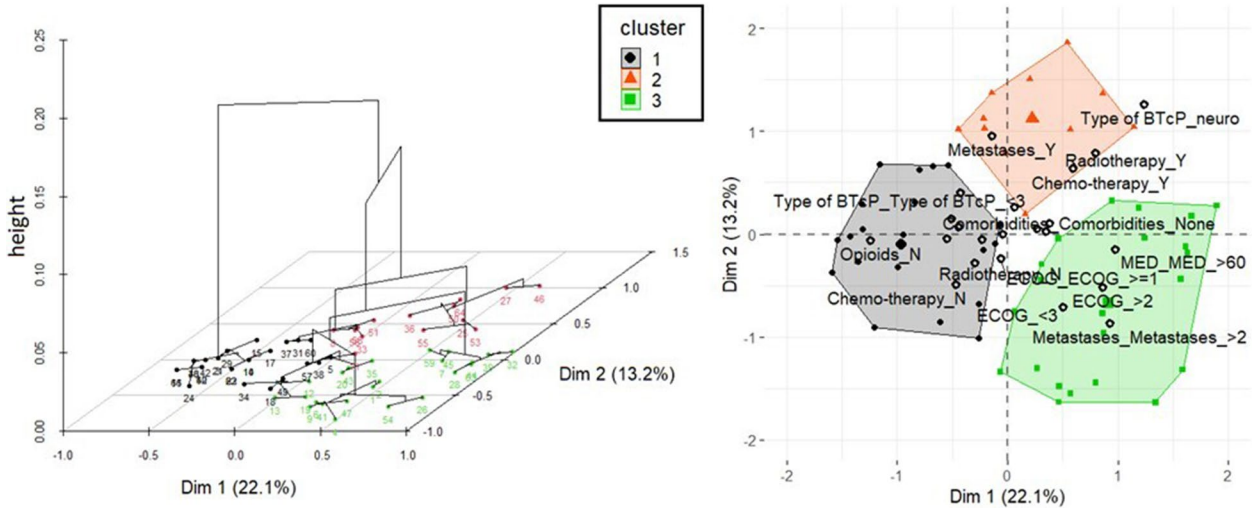

Fig. 6 Cluster analysis for opioid therapy. Legend: The study identified three distinct clusters through principal component analysis. Multiple Correspondence Analysis (MCA) explained 35.2% of global variability across 10 categorical variables and 22 modalities. Cluster 1 (27 patients) had no medication, mostly low Eastern Cooperative Oncology Group (ECOG) performance status scores, no chemotherapy, and no metastases, with no or minimal pain reported. Cluster 2 (14 patients) consisted of patients all on chemotherapy, with low ECOG scores, and some experiencing neuropathic pain. Cluster 3 (23 patients) showed 100% opioid usage, high ECOG scores, MED > 60, and a high prevalence of bone metastases breakthrough cancer pain (BTcP)

other and reflect distinct aspects of the whole set of variables. The analysis showed that the presence or not of BTcP, and BTcP type are mainly projected onto the first dimension (FA1). Notably, they represent "subjective" variables. This result suggests that clinical and subjective factors, including patients' overall health, strongly describe BTcP features. On the other hand, statistical measures (contributions and squared cosines) demonstrated that the objective APA-extracted variables are not correlated with the other clinical factors. Therefore, although as expected, patients with BTcP had worse clinical conditions, for example in terms of ECOG and metastases [38], the analysis failed to find a correlation between subjective and objective pain variables to explain the BTcP phenomenon. These findings were confirmed by the clustering analysis as well as in the multivariate analysis conducted for therapeutic profile characterization (MED). Remarkably, the results indicated that performance status and the type of pain are correlated with a higher demand for opioid analgesics, objective variables alone did not provide a clear or comprehensive explanation for the overall opioid dosage.

The lack of statistical correlation between APA variables and pain features and management can be attributed to the inherent complexity of pain, the individual nature of pain perception, and the limitations of measurement methods. Objective pain measures are based on physiological or clinical indicators, such as HR, blood pressure, or the presence of specific physical symptoms. Subjective pain assessments, on the other hand, rely on patients' self-reported experiences, including pain intensity, quality, and emotional aspects. These two approaches may capture different aspects of pain, making them less likely to correlate. Besides the barrier between objective and subjective measures, the lack of significance of quantitative physiological parameters based on EDA and ECG should be investigated from a broader and more complex perspective as it can be affected by other measuring and technical factors, such as the duration of the recordings and the type of features considered, which is limited to the most widespread and simple indicators GSRs and HR variations and does not still consider frequency-domain parameters that could better enlighten the role of sympathovagal balance as well as more complex and sophisticated measures of nonlinear and chaotic dynamics (e.g., entropy indices, fractal analysis) that may be involved in physiological control systems in pathological states. As mentioned in the Introduction section, by elucidating the role of biosignals in cancer pain assessment, the potential of such sources of information to be used in continuously monitoring settings could then be fully exploited, such as through the integration of pain indicators within wearable platforms for long-term patients' monitoring. Moreover, pain is a complex and highly individual experience [39]. The variability in pain perception can make it challenging to establish a direct relationship between objective physiological changes and subjective pain reports. Furthermore, pain perception is influenced by

Table 3 Cancer pain clusters

	Cluster			*p*-values	
Variable	**1, *n* = 27**	**2, *n* = 14**	**3, *n* = 23**	**C1 vs C2[a]**	**C1 vs C3[b]**
Age				0.601	0.238
Mean (SD)	57.7 (15.2)	62.1 (8.8)	63.0 (12.9)		
BMI				0.063	0.243
Mean (SD)	26.1 (4.4)	23.6 (3.7)	24.6 (5.1)		
Comorbidities				0.381	> 0.999
None	12 (44%)	9 (64%)	10 (43%)		
≥ 1	15 (56%)	5 (36%)	13 (57%)		
ECOG-PS				0.780	**< 0.001**
< 3	25 (93%)	14 (100%)	5 (22%)		
> 2	2 (7%)	0 (0%)	18 (78%)		
BTcP				0.405	**< 0.001**
No	22 (81%)	9 (64%)	5 (22%)		
Yes	5 (19%)	5 (36%)	18 (78%)		
BTcP Pain				**0.012**	**< 0.001**
No pain	22 (81%)	9 (64%)	6 (26%)		
Neuropathic	0 (0%)	4 (29%)	3 (13%)		
Nociceptive	5 (19%)	1 (7%)	14 (61%)		
BTcP Intensity				0.303	**< 0.001**
No BTcP	23 (85%)	9 (64%)	4 (17%)		
Moderate (NRS 4–8)	1 (4%)	1 (7%)	12 (52%)		
Severe (NRS 9–10)	3 (11%)	4 (29%)	7 (30%)		
Mean CDA				0.762	0.397
Mean (SD)	0.1 (0.2)	0.1 (0.2)	0.1 (0.1)		
Mean TTP				0.640	0.220
Mean (SD)	0.1 (0.2)	0.1 (0.1)	0.1 (0.1)		
SDRR				0.281	0.386
Mean (SD)	55.4 (59.7)	69.0 (62.0)	51.3 (58.2)		
SDHR				0.211	> 0.999
Mean (SD)	6.2 (7.2)	7.9 (7.7)	6.0 (6.8)		
Metastases				**0.038**	**< 0.001**
No	20 (74%)	5 (36%)	5 (22%)		
Yes	6 (22%)	6 (43%)	1 (4%)		
Bone metastases	1 (4%)	3 (21%)	17 (74%)		
Chemotherapy				**< 0.001**	**0.010**
No	24 (89%)	0 (0%)	12 (52%)		
Yes	3 (11%)	14 (100%)	11 (48%)		
Surgery				0.835	> 0.999
No	23 (85%)	13 (93%)	19 (83%)		
Yes	4 (15%)	1 (7%)	4 (17%)		
Radiotherapy				**< 0.001**	**0.029**
No	26 (96%)	5 (36%)	16 (70%)		
Yes	1 (4%)	9 (64%)	7 (30%)		
Adjuvants				0.232	0.314
No	20 (74%)	7 (50%)	13 (57%)		
Yes	7 (26%)	7 (50%)	10 (43%)		
Opioids Therapy				**0.023**	**< 0.001**
No	13 (48%)	1 (7%)	0 (0%)		
Yes	14 (52%)	13 (93%)	23 (100%)		

Table 3 (continued)

Variable	Cluster			*p*-values	
	1, *n* = 27	2, *n* = 14	3, *n* = 23	C1 vs C2[a]	C1 vs C3[b]
MED				**0.005**	**< 0.001**
≤ 60	27 (100%)	9 (64%)	8 (35%)		
> 60	0 (0%)	5 (36%)	15 (65%)		

Abbreviations: *BMI* body mass index, *ECOG* Eastern Cooperative Oncology Group performance status, *BTcP* Breakthrough cancer pain, *CDA* Continuous Decomposition Analysis, *NRS* Numeric Rating Scale, *TTP* Trough-To-Peak, *SDRR* standard deviation R-R (interbeat intervals), *SDHR* standard deviation heart rate, *MED* Morphine Equivalent Dose

[a] Wilcoxon rank sum test; Wilcoxon rank sum exact test, Pearson's Chi-squared test

[b] Wilcoxon rank sum test, Pearson's Chi-squared test

Table 4 Multivariable regression analyses

Variable	Model 1			Model 2		
	Beta[a]	95% CI	*p*-value	OR[b]	95% CI	*p*-value
Age			0.991			0.370
≤ 60	—	—		—	—	
> 60	-0.32	-58, 57		1.90	0.47, 8.65	
BMI			0.335			0.890
< 25	—	—		—	—	
≥ 25	27	-28, 82		1.10	0.29, 4.15	
ECOG			**0.020**	*		
< 3	—	—				
> 2	72	12, 133				
BTcP Intensity^	*			—	—	**0.024**
No BTcP						
NRS ≤ 8				2.13	0.45, 10.7	
NRS > 8				8.30	1.78, 48.4	
Type of BTcP			**0.003**	*		
No BTcP	—	—				
Neuropathic	147	65, 229				
Nocicieptive	50	-12, 113				
Mean TTP	-21	-46, 3.2	0.086			
SDRR	-1.4	-3.5, 0.68	0.183	0.96	0.91, 1.01	0.108
SDHR	13	-3.8, 31	0.122	1.47	0.98, 2.39	0.063
Adjuvants			0.410	*		
No	—	—				
Yes	-24	-81, 34				

Abbreviations: *BMI* body mass index, *ECOG* Eastern Cooperative Oncology Group performance status, *BTcP* Breakthrough cancer pain, *NRS* Numeric Rating Scale, *TTP* Trough-To-Peak, *SDRR* standard deviation R-R (interbeat intervals), *SDHR* standard deviation heart rate

[a] Referred to Gaussian multivariable regression model (Model 1)

[b] Referred to logistic multivariable regression model (Model 2)

* not entered the model; ^0–10 Numeric Rating Scale

psychological factors, such as anxiety, depression, and coping strategies [40]. These aspects can significantly impact a person's subjective pain experience but may not be reflected in objective measures. Another key element is the clinical setting adopted for APA recording. Objective measures may be more reliable in acute pain situations, such as post-surgery, where there is a clear physiological response. In chronic pain conditions, the relationship between objective and subjective measures may be less straightforward due to long-term adaptations

and psychosocial factors [41]. Consequently, serious challenges arise for the analysis of acute cancer pain phenomena such as BTcP. More importantly, for an effective physiological characterization, objective measures should capture the phenomenon in real time. It would require almost continuous recording of physiological data. Likely, the availability of detection systems with wearable platforms and more complex feature extraction approaches for biosignal analysis may provide us with more reliable data. In this initial investigation, the purpose was to understand the potential for integrating data to subsequently enhance both data collection and analysis strategies.

Study limitations

While the study aims to offer insights into the multimodal assessment of cancer pain, its limitations underscore the need for cautious interpretation of its findings. For example, the study's sample size might not be representative of the broader population of cancer patients. Moreover, the investigation was conducted at a single medical institution, which could limit the generalizability of the findings to other healthcare settings and diverse populations. Biosignal measurement represents the main limitation of the study. For example, the timing and methods of recording are crucial aspects to be defined to calibrate a model. The accuracy and reliability of these signals in assessing pain can be influenced by factors such as noise, signal artifacts, and individual variability in physiological responses. Furthermore, additional biosignals-based features derived from time- and frequency-domain approaches as well as time–frequency analysis and newly proposed deep learning-based features for both ECG and EDA have not been considered in this study but will be adopted in future works to widen the range of quantitative physiological parameters that could provide new descriptors and predictors of pain, thus yielding higher sensitivity in quantifying cancer pain. Finally, the study lacked extensive validation of its biosignal-based pain assessment methods against established pain measurement techniques. Notably, the absence of high-quality validation studies could limit the reliability of these methods.

Conclusions

Recognizing the significance of thorough pain assessment is a pivotal step in enhancing pain management strategies. Although subjective pain assessment modalities are widely used to understand and manage pain, they are not without limitations. Striking a balance between patient reports and objectivity in pain assessment can offer incredible opportunities to provide optimal care. Nevertheless, achieving a cohesive integration between the objective physiological parameters assessed through APA and the subjective insights gathered from self-reporting is a complex endeavor. It is crucial to recognize the significance of each considered feature and thoughtfully harmonize them to derive comprehensive conclusions that truly capture the essence of pain phenomena. Future research with larger and more diverse samples, rigorous validation of biosignal-based methods, and controlled experimental designs could provide a more comprehensive understanding of pain assessment and management strategies.

Abbreviations

ANS	Autonomic nervous system
APA	Automatic pain assessment
BMI	Body mass index
BTcP	Breakthrough cancer pain
CDA	Continuous decomposition analysis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDA	Electrodermal activity
EEG	Electroencephalography
FA	Factorial Axis
fMRI	Functional magnetic resonance imaging
GSR	Galvanic Skin Response
HCPC	Hierarchical clustering on principal components
HR	Heart rate
HRV	Heart rate variability
MCA	Multiple Correspondence Analysis
MED	Morphine Equivalent Dose
MFA	Multiple factorial analysis
MNAR	Missing Not At Random
NRS	Numeric rating scale
PCA	PC analysis
SCL	Skin Conductance Level
SDHR	Heart rate standard deviation
SDNN	Normal RR intervals standard deviation
SDRR	RR intervals standard deviation
SDs	Standard deviations
VAS	Visual Analogic Scale
WHO	World Health Organization

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Authors' contributions

Conceptualization, M.C., P.D.G., A.V. and S.C.; methodology, M.C., P.D.G., A.C., A.V., E.P., S.S., F.M., A.M.P., M.R., C.O., A.O., F. S., F.P., O.P. and S.C.; software, M.C., P.D.G., A.C., A.V., A.M.P., M.R., C.O., O.P. and S.C; validation, M.C., P.D.G., A.C., AV., A.M.P., M.R., C.O., O.P. and S.C.; formal analysis, M.C., P.D.G., A.C., AV., A.M.P., M.R., C.O., O.P. and S.C.; investigation, M.C., P.D.G., A.C., AV., A.M.P., M.R., C.O. and S.C.; resources, M.C., A.V. and F.M.; data curation, M.C., P.D.G., A.C., AV., A.M.P., M.R., C.O., O.P. and S.C.; writing-original draft preparation, M.C., P.D.G., A.C., A.V. and S.C.; writing-review and editing, M.C., P.D.G., A.C., A.V., E.P., S.S., F.M., A.M.P., M.R., C.O., A.O., F. S., F.P.,F.S., O.P. and S.C.; visualization, M.C., A.V., O.P. and S.C.; supervision, M.C., O.P. and S.C.; project administration, M.C., A.V., F.M., and O.P. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from Marco Cascella on reasonable request.

Declarations

Ethics approval and consent to participate

The investigation was granted approval by the local Ethics Committee of Istituto Nazionale Tumori, Fondazione Pascale, Naples, Italy (protocol code 41/20 Oss; approval date: 26 November 2020), and all participants provided written informed consent. All methods were performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication

Not competent.

Competing interests

The authors declare no competing interests.

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