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ORIGINAL ARTICLE

# EXPLORING AUTONOMIC NERVOUS SYSTEM RESPONSES DURING COGNITIVE STRESS TEST FOR AUTOMATIC PAIN ASSESSMENT IN CANCER PATIENTS

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**ABSTRACT:** Despite progress in guideline-driven cancer pain management, crucial challenges persist. Automatic Pain Assessment (APA) investigates behavioral aspects and biosignals, such as electrodermal activity (EDA) and heart rate (HR) variability (HRV), for providing objective and context-aware pain evaluation and monitoring. In this prospective, single-center study on cancer pain, we recorded EDA and HRV during a 3-block cognitive Stroop task and stratified patients by 0-10 Numeric Rating Scale (NRS) pain (<6 *vs* ≥6). Since chronic pain can induce cognitive and attentional alterations, the aim is to assess the performance of the autonomic nervous system during a cognitive stress test, investigating the links between nociception (the encoding of noxious stimuli through autonomic or behavioral responses) and the neurobiological consequences of pain. We extracted tonic and phasic electrodermal activity (EDA) features, including skin conductance level (SCL), skin conductance response (SCR), recovery times, and time/frequency-domain HR/HRV indices, and then we compared groups across Stroop phases. Patients with lower pain intensity showed consistently higher SCL and stronger phasic SCR components across test phases (SCL mean $p \leq 0.05$; SCR mean and SCR integral $p \leq 0.01$), whereas rise/recovery times did not differ; peak counts normalized by phase duration diverged modestly (significant in Stroop phases 1 and 3). HRV differences were limited, with a notable increase in HF power during the incongruent (phase III) block only. These exploratory findings provide initial evidence that cognitive stress–evoked autonomic responses may contribute to distinguishing pain phenotypes in cancer patients. Pipeline and results can be used for developing a multimodal APA framework aimed at personalizing cancer pain treatment.

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## INTRODUCTION

Pain is one of the most common and debilitating symptoms in cancer patients. However, despite advances in pain management in oncology, many patients still report poorly controlled pain (1). The prevalence of pain during anticancer treatment is estimated to range from 40% to 70%, reaching up to 90% in terminal stages (2). Therefore, in this vulnerable group, understanding the mechanisms and exact pathophysiology of pain is essential for developing research approaches and personalized treatment strategies (3).

Pain assessment is commonly performed using unidimensional or multidimensional scales. These approaches, however, present several limitations, especially in individuals who are unable to properly express pain, such as newborns (4), and non-communicative patients with cognitive impairment (5) or under sedation, including those in intensive care units (6). The automatic pain assessment (APA) refers to the evaluation of pain through the application of behavioral techniques and biosignal analysis. This approach usually integrates objective physiological data, such as heart rate variability (HRV), electrodermal activity (EDA), and electroencephalography (EEG), with behavioral observations such as facial expressions and body movements, to detect and quantify pain in a standardized way (7). The aim is to provide continuous, real-time, and unbiased pain monitoring across different clinical settings (8).

Different applications of APA strategies in cancer patients have been proposed. They focus on biosignals (9, 10), facial expressions and other behaviors (11), singularly considered or through multimodal processes (12). However, several aspects still need to be clarified. These include the specific clinical setting of analysis and its correlation with the underlying oncological condition, the varying impact and reliability of measurements in acute *versus* chronic pain scenarios, the optimal model design, the reference datasets to be used, and the integration of biosignal data with clinical and instrumental information. Existing studies, for example, are often conducted in controlled laboratory settings. They address mainly acute pain and lack external validity for real-world cancer care (7). Furthermore, most APA models rely on single-modality inputs, while multimodal models, although more accurate, are not standardized for clinical deployment (12). Importantly, no consensus exists on which markers best capture objectively acute or chronic pain–related phenomena, including autonomic dysregulation (13).

Additionally, APA strategies should capture the multifaced and dynamic features of chronic pain, also acknowledging that it reflects maladaptive neuroplastic changes involving multiple brain regions, particularly those within the limbic system (14, 15). For example, the prefrontal cortex often shows impairments in cognitive processes related to top-down regulation, contributing to altered pain modulation and emotional processing (16, 17). Chronic pain, indeed, is associated with neurocognitive issues, including attention, inhibition, and executive control. This reduced inhibitory control may amplify the physiological cost of cognitive interference (18). Research suggested that cognitive stressors such as the Stroop task, which engages prefrontal executive control networks, may represent a valuable method for assessing pain-induced neurophysiological dysfunction (19).

The impact of chronic pain on the regulation and balance of the sympathetic–vagal axis is a key area that warrants further investigation. Chronic cancer pain involves not only peripheral nociceptive and central sensitization processes, but also dysregulation of the autonomic nervous system (ANS), particularly in the balance between sympathetic and parasympathetic activity. This autonomic dysfunction may modulate pain experience, prognosis, and response to stressors (9, 20). Consequently, investigation in this area is crucial for defining appropriate study pathways on which to base APA analyses as well as for better addressing neurocognitive aspects of pain perception (21-23).

On these premises, as part of a research project on artificial intelligence (AI) and pain in cancer patients, we investigated the phenomenology of the ANS in individuals with chronic cancer pain undergoing cognitive assessment. We assumed that the integration of a cognitive challenge with biosignal monitoring would enhance the sensitivity to detect autonomic reactivity patterns and provide a reliable approach to characterize pain-related ANS alterations. Specifically, we investigated whether EDA and HRV differ according to pain intensity across Stroop task phases. We hypothesized that patients with higher pain levels would exhibit blunted autonomic reactivity compared with those reporting lower pain, reflecting impaired sympathetic–parasympathetic modulation during cognitive interference. Ultimately, this work represents an attempt to shed light on the links between nociception (the encoding of noxious stimuli through autonomic or behavioral responses) and the neurobiological consequences of pain.

## MATERIAL AND METHODS

### Study design and Ethics

This investigation was carried out within the "*Refining multiple artificial Intelligence strategies for automatic pain assessment investigations (RUGGI)*" study, designed for exploring the integration of AI in chronic pain evaluation at the AOU San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy. The study was conducted in accordance with the Declaration of Helsinki (2013 amendment) and ICH-GCP guidelines. Ethical approval for this study (Comitato Etico Territoriale Campania 2, N°2024/28590) was provided by the Ethical Committee Campania 2 (Chairperson Prof. C. Napoli) on the 3rd of April 2025. Written informed consent was obtained from all participants before enrollment.

## Participants

Patients were consecutively recruited from the oncology and palliative care units of our institution. Inclusion criteria were age ≥18 years, diagnosis of solid cancer, presence of chronic pain (≥3 months), ability to communicate and provide informed consent, and completion of the full Stroop test while wearing biosignal sensors. Exclusion criteria were severe cognitive impairment, psychiatric or neurological disorders affecting autonomic function, inability to complete the cognitive task, implanted cardiac devices, arrhythmias, or medications with major autonomic impact (*e.g.*, β-blockers at unstable dosage).

## Stroop Test

In this study, the Stroop test was used as a tool to evaluate the impact of stress (here, pain) on patients' cognitive functions and emotional responses. The test, developed by John Ridley Stroop in 1935, is commonly employed in cognitive research and measures an individual's ability to suppress automatic responses while maintaining selective attention. Evidence indicates that it is an effective method to examine attentional bias in chronic pain patients (19, 24, 25). Specifically, since the test induces cognitive interference and engages executive control, it can be used to investigate pain-related attentional and inhibitory dysfunction.

The test typically involves three conditions (blocks): neutral, congruent, and incongruent conditions. Each phase lasted approximately 2 minutes, for a total Stroop duration of about 6 minutes. Specifically, the test starts with a 3-minute resting baseline with eyes closed, followed by a 2-minute open-eyes resting condition. Subsequently, in the neutral block, participants are asked to quickly read a list of words that are names of colors, but all printed in black on a white background. This portion of the test serves as a baseline control for measuring speed and accuracy in word reading. In the congruent condition, participants read color-word names printed in the same color (for example, the word "red" printed in red). This measures the speed and accuracy when the word meaning and ink color align. In the incongruent condition, participants must read color words printed in a color that does not match the meaning of the word (for example, the word "red" printed in blue). This last block is considered the most challenging, as it requires inhibiting the automatic response to read the word and instead responding to the ink color. After the task, a 3-minute eye-closed recovery period and a final 2-minute open-eyes condition were recorded.

During the Stroop task, each block consisted of 60 stimuli (180 trials in total). Each stimulus remained on screen for 1.5 seconds, followed by a 0.5-second interstimulus interval. Behavioral performance was assessed through accuracy (%) and reaction times (ms), which were automatically recorded.

In the text, "Stroop phases" refer to the three sequential blocks of the Stroop task: neutral, congruent, and incongruent.

## Biosignals

During the execution of the Stroop color-word test, we implemented the BITalino device with sensors for capturing ECG and EDA signals, as reported in (26). It is an open-source, hardware-affordable biosignal platform designed for physiological computing. Data collected with this instrument shows dependability for quantitative analysis (27). A sample rate of 1000 Hz was used to measure the signals. For EDA assessment, a fifth-order Butterworth low-pass filter with a cutoff frequency of 1 Hz was used for the processing and analysis of the signals and, after downsampling the signal by a factor of 100 to lessen the computational load of the analysis, the signals were further examined using a deconvolution approach to separate the tonic (basic level of conductance) and phasic components (short-duration changes in the presentation of a stimulus) (26). The following parameters were then considered for further analysis: tonic response (SCL), phasic response (SCR), SCR integral (*i.e.*, the mean area of the SCR peaks), number of phasic peaks normalized by the experiment duration (peaks/minute), mean rise time (measured in seconds), and recovery time (measured in seconds). Concerning HRV, a modified version of the Pan–Tompkins method was used to detect an R peak in the ECG signal; the accompanying RR series of interbeat intervals was then calculated as the difference between subse-

quent R peaks (26, 27). For the HRV assessment, both time-domain features (average HR, standard deviation of RR intervals (SDNN), and Root Mean Square of Successive Differences of the RR, RMSSD) and frequency-domain features (power in low, LF: 0.04-0.15 Hz, and high, HF: 0.15-0.40 Hz, frequency bands as well as the LF/HF ratio representing the sympatho-vagal balance) were analyzed.
Therefore, selected EDA and HRV indices were chosen because they represent well-established markers of sympathetic (EDA, LF) and parasympathetic (HF, RMSSD) function (26, 27). Tonic SCL reflects baseline sympathetic arousal, whereas phasic SCR amplitude, integral, and peak frequency capture transient sudomotor responses to stimuli. HRV parameters were included as they reflect cardiac autonomic modulation and have been associated with chronic pain and stress reactivity, and the LF/HF ratio is useful for addressing the dynamic sympatho-vagal equilibrium. Processing was carried out in Python language using the Spyder software version 4.1.5, while ECG processing was carried out in MATLAB v2023a.

### Pain Assessment

Pain intensity was assessed using the 0–10 Numeric Rating Scale (NRS), a validated unidimensional tool widely used in cancer pain assessment, where 0 = “no pain” and 10 = “worst imaginable pain”. Scores 0–3 are generally considered mild, 4–6 moderate, and ≥7 severe pain (28). For the analyses, in line with previous research on cancer pain, patients were categorized into two groups: NRS <6 *vs* NRS ≥6 (moderate *vs* severe pain phenotypes) (28).

### Statistical Analysis

Analyses were stratified according to pain intensity (0-10 numeric rating scale, NRS) in two independent groups based on an empirically established threshold (NRS = 6) for identifying a “high pain” category and a “low pain” category (NRS <6 and NRS ≥6). After grouping the patients, Shapiro-Wilk test was adopted to check the normality of the data distributions in the two groups and, given the non-normality of the distributions (p <0.05), a Mann Whitney U test was carried out as an alternative to the Student’s t test for independent samples in order to assess statistical differences in the median values of the biosignals’ signatures across the two groups. Level of significance alpha was set to 0.05 (Confidence Level 95%) for all the statistical analyses performed in this study. All statistical tests were carried out in Python language using the Spyder software version 4.1.5.

## RESULTS

The analysis included data from 45 patients enrolled between May and August 2025. No participants were excluded after enrollment (**Table 1**).

**Table 1.** *Demographic characteristics (n = 45).*

| VARIABLE | N (%) OR MEAN ± SD |
|---|---|
| Age (years) | 64.5 ± 14 |
| Gender | Male: 22 (48.9%); Female: 23 (51.1%) |
| BMI (kg/m²) | 27.1 ± 5.3 |
| Cancer type | Pancreatic 11 (24.4%)<br>Breast 8 (17.8%)<br>Lung 6 (13.3%)<br>Colorectal 6 (13.3%)<br>Prostate 3 (6.7%)<br>Gastric 2 (4.4%)<br>Others 9 (20%) |
| Metastasis | Yes: 32 (71.1%)<br>No: 13 (28.9%) |
| Bone metastasis | Yes: 17 (37.8%)<br>No: 28 (62.2%) |
| ECOG-PS | 0: 8 (17.8%)<br>1: 11 (24.4%)<br>≥2: 26 (57.8%) |
| Pain intensity (NRS) | 5.8 ± 2.7 |
| Pain type | Nociceptive: 8 (17.8%)<br>Neuropathic: 8 (17.8%)<br>Mixed: 29 (64.4%) |

Across all Stroop phases, patients in the low-pain group (NRS <6) showed higher median SCL values (*e.g.*, Stroop I: median 0.67 μS *vs* 0.41 μS; Stroop II: 0.72 μS *vs* 0.45 μS; Stroop III: 0.80 μS *vs* 0.48 μS). In this subgroup, a stronger phasic SCR component in the Stroop phases was found compared to patients with NRS ≥6. Significant differences were observed in SCL mean (p ≤0.05 across phases), SCR mean (p ≤0.01), and SCR integral (p ≤0.01), indicating a more pronounced autonomic response in the low-pain group. In contrast, rise time and recovery time did not significantly differ between groups, suggesting that magnitude rather than temporal dynamics of sudomotor responses distinguished between the two groups. The frequency of SCR peaks normalized by phase duration showed only modest differences between groups and was significant in phases I and III, indicating that pain intensity may influence the strength rather than the frequency of sympathetic reactivity during cognitive interference (**Figure 1**).

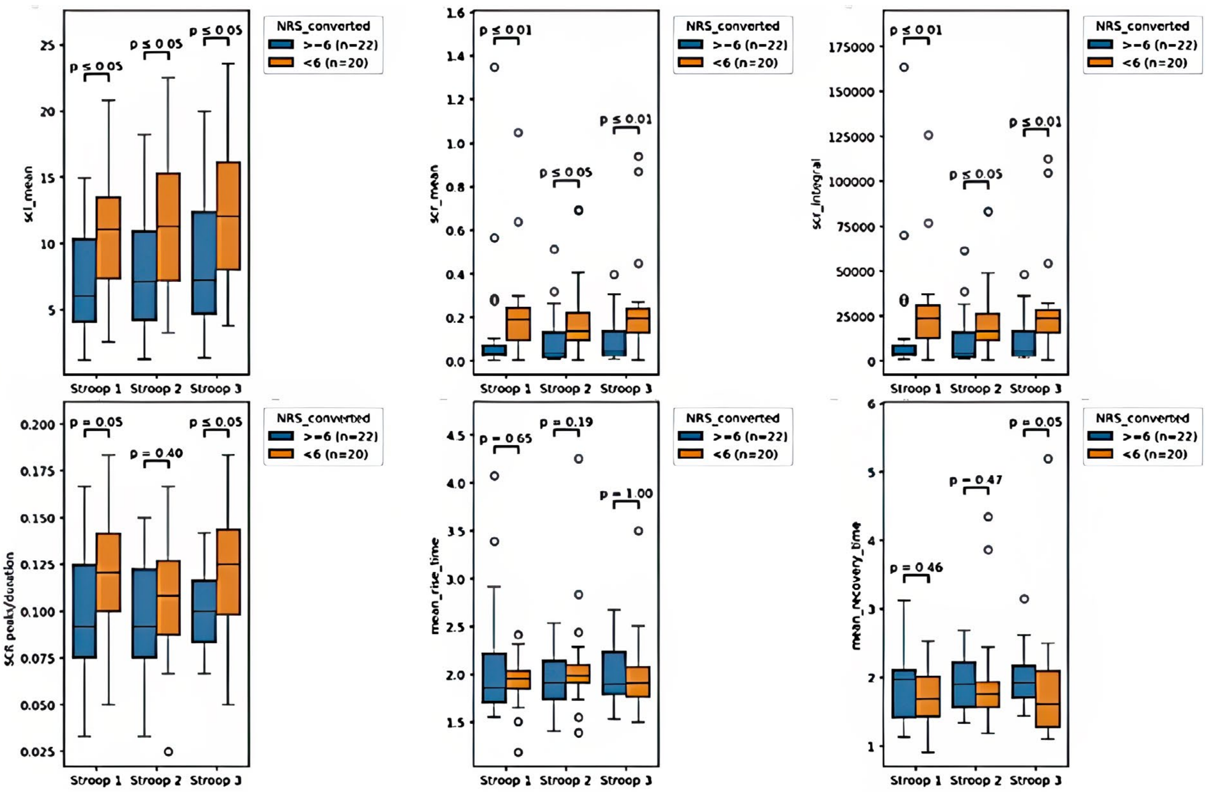


**Figure 1.** *Electrodermal activity (EDA) features across Stroop test phases in patients with different pain intensity levels. Boxplots show the distribution of EDA-derived features during the three phases of the Stroop task (Stroop 1 to 3) for patients with high pain intensity (NRS ≥6, n = 22) and low pain intensity (NRS <6, n = 20). EDA parameters (from the top): mean skin conductance level (scl_mean), mean skin conductance response amplitude (scr_mean), integrated SCR signal (scr_integral), ratio between the number of SCR peaks and phase duration (num_peaks/timing), mean SCR rise time, and mean SCR recovery time. Horizontal bars indicate statistically significant differences between groups (Mann–Whitney U tests), with p-values reported above each comparison. Patients with mild to moderate pain (NRS <6) showed more pronounced tonic and phasic EDA activity. Response times (peaks) did not differ, but the amplitude of the response was more evident.*

Concerning HRV parameters, median average HR values were slightly higher in the high-pain group throughout the task (*e.g.*, Stroop I: median 83 bpm *vs* 78 bpm), although these differences did not reach significance. Time-domain HRV markers (SDNN and RMSSD) also showed a consistent trend toward reduced variability in the high-pain group (*e.g.*, RMSSD Stroop I: median 16 ms *vs* 22 ms; Stroop III: 14 ms *vs* 20 ms), without significant divergence across phases. Frequency-domain indices displayed comparable patterns in phases I and II, whereas during the incongruent block (phase III), HF power was significantly higher in the low-pain group (*e.g.*, median 402 $ms^2$ *vs* 255 $ms^2$, Mann–Whitney $p < 0.05$), indicating more preserved parasympathetic regulation under maximal cognitive interference. LF power and LF/HF ratio did not show meaningful between-group differences in any phase. No other statistically significant differences were found between the high- and low-pain groups across Stroop phases (**Figure 2**).

## DISCUSSION

This study explored autonomic responses during a cognitive interference task in cancer patients with chronic pain. The main finding of this study was the clear differential sensitivity between EDA-derived features and HRV indices in detecting pain-related autonomic alterations during cognitive interference. Specifically, while tonic and phasic EDA components (SCL, SCR amplitude, and SCR integral) consistently distinguished between pain groups across all Stroop phases, HRV separation was modest and limited to a single phase (HF power during the incongruent block, phase III). Therefore, the sympathetic-sudomotor reactivity during cognitive interference may better reflect chronic pain phenotypes than cardiac variability alone in this context. Notably, a feasibility work in ambulatory cancer patients reported that machine-learning models trained on physiological signals achieve approximately 70% accuracy for pain state discrimination (9). Our EDA-forward pattern is

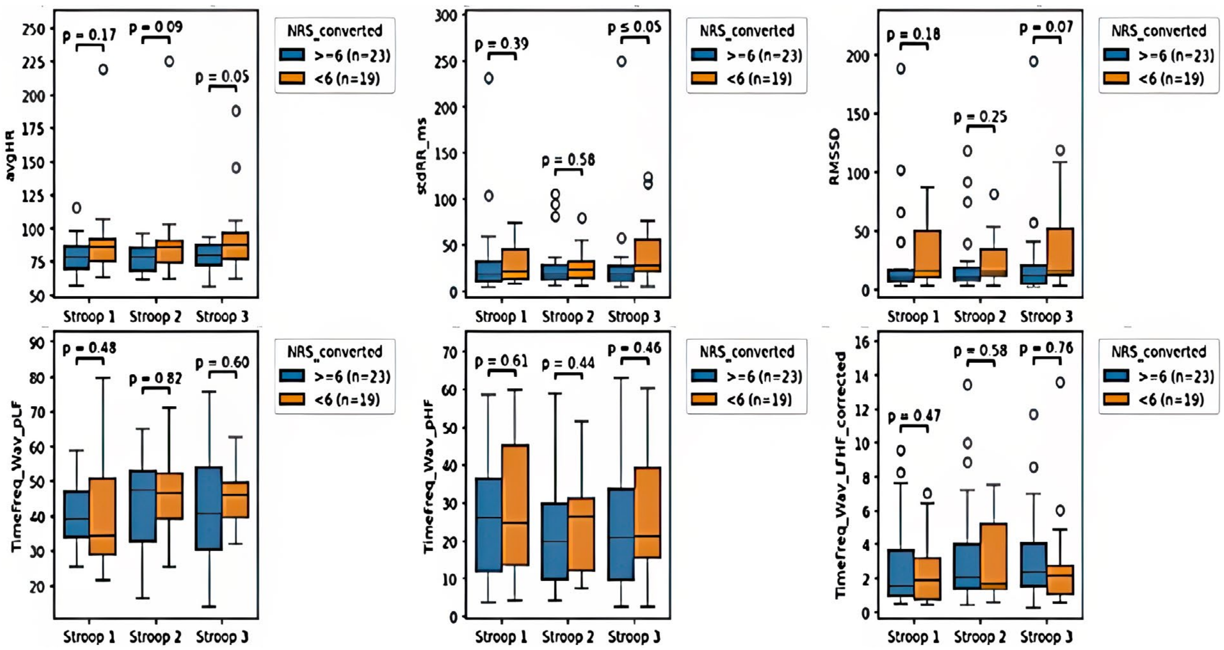

**Figure 2.** *Heart rate and heart rate variability (HRV) features across Stroop test phases in patients with different pain intensity levels. Boxplots display the distribution of cardiovascular features recorded during the three Stroop task phases (Stroop 1 to 3) for patients with high pain intensity (NRS ≥6, n = 23) and low pain intensity (NRS <6, n = 19). HRV parameters (from the top): average heart rate (avgHR), standard deviation of RR intervals (stdRR_ms), root mean square of successive differences (RMSSD), low-frequency power (TimeFreq_Wav_pLF), high-frequency power (TimeFreq_Wav_pHF), and LF/HF ratio corrected (TimeFreq_Wav_LFHF_corrected). Horizontal bars indicate statistically significant differences between groups (Mann–Whitney U tests), with p-values shown above each comparison.*

consistent with those observations and extends them with phase-resolved Stroop probing. This approach can better highlight the relationship between pain and its impact on cognitive functions. Although the finding requires confirmation, it can have meaningful implications for APA development and for capturing pain-related autonomic signatures, particularly when contextualized within cognitive or emotional load.

Autonomic dysfunction has been documented in patients with advanced cancer, where it is associated with fatigue, worse quality of life, and reduced survival. For example, Stone *et al.* (29) found that autonomic dysregulation is highly prevalent in advanced cancer, suggesting that cancer itself or its treatment may injure autonomic pathways. Furthermore, Ben-David *et al.* (30) observed that cancer patients exhibit lower HRV compared to healthy controls. The prognostic importance of autonomic measures has also been demonstrated. For example, reduced HRV seems to be associated with shorter survival (31). Probably, cardiac autonomic dysfunction is an underrecognized feature in oncology (32). In our analysis, the EEG-derived parameters showed less pronounced results compared to EDA. It emerged that HR increased and HRV decreased with pain; nevertheless, effect sizes vary across tasks, diagnoses, and sensors, explaining why our HRV separation was limited outside the most demanding Stroop block. Methodological syntheses further emphasize wearable-first, multimodal, and interpretable designs, again consonant with our findings that EDA is an informative anchor modality but benefits from fusion. The relationship between ANS evaluations and pain intensity is particularly interesting because it can allow for to identification of the variables to be investigated within a multimodal model. In patients with bone metastases, an initial study aimed to define an HRV-based objective method for assessing metastatic pain, reporting promising associations between HRV measures and pain status (33). From the perspective of pain modulation, there is evidence that lower parasympathetic function may be linked to heightened pain sensitivity. For example, in patients suffering from chemotherapy-induced polyneuropathy, Nahman-Averbuch *et al.* (34) demonstrated that lower Valsalva ratios and diminished HRV, indicative of reduced parasympathetic tone, correlated with higher ratings of experimental pain stimuli. Interestingly, we found that in chronic oncologic pain, the analysis of the ANS in relation to cognitive tasks highlights different patterns depending on pain intensity. Patients with lower pain levels exhibit an active and functional system.

However, in subjects reporting severe pain, the system appears less active and less functional.

## LIMITATIONS AND PERSPECTIVES

This analysis is exploratory, single-center, and modest in size (n = 45), limiting power for subgroup analyses by tumor type, therapy line, or comorbidities. Medication effects (opioids, adjuvants), metastasis distribution (including bone), performance status, and mood/sleep could confound autonomic readouts. Moreover, in cancer patients, the autonomic effects of systemic inflammation, metabolic derangements, treatment toxicity (*e.g.*, anthracyclines, taxanes), and microvascular injury may further distort baseline autonomic tone and responsiveness (29-34). We acknowledge that, given the small sample size, dividing participants into two groups impaired statistical power. Moreover, adopting the NRS as a continuous variable within a single group would be more appropriate. Nevertheless, we followed the methodology of prior cancer-pain research in treating the NRS as a categorical variable rather than a continuous one (35). Specifically, several studies in oncology pain categorize NRS scores into mild, moderate, and severe pain bands (for example, ≤3, 4-6, ≥7) because these thresholds are strictly linked to clinical decision-making and analgesic escalation protocols (28, 36). Therefore, we used the cut-off of NRS ≥6 to separate two categories of pain (moderate to severe pain).
Concerning methods for sympatho-vagal investigations, while we focused on EDA and HRV, additional modalities such as EEG, EMG, PPG, skin temperature, and accelerometry were not assessed here. Furthermore, the temporal dynamics of autonomic change in response to pain or cognitive stress may be subtle and transient, requiring high-resolution recording and careful signal processing (time-, frequency-, and nonlinear domains). Finally, we did not perform external validation or causal modeling, as multiple comparisons across features and phases also raise a risk of type I error.
Future work should integrate these findings into multimodal APA models. Importantly, machine learning techniques can be implemented to classify pain levels based on combined physiological, clinical, and behavioral features. In this direction, feature fusion, temporal modelling (*e.g.*, using recurrent deep learning architectures or transformers), and explainability methods may enhance performance and clinical trust. From an ethical standpoint, the development of APA systems must ensure transparency, patient autonomy, and equitable access. Therefore, future APA frameworks must be developed to support safe clinical decision-making and to safeguard patient rights and well-being (37).

## CONCLUSIONS

Biosignal can be implemented for phenotyping chronic cancer pain. Nevertheless, further research is needed for developing multimodal APA systems in oncology. Prospective, interpretable, and context-aware models should integrate EDA and other selected biosignals with clinical data. This step is mandatory for improving assessment and, ultimately, personalizing pain management in cancer patients.

## COMPLIANCE WITH ETHICAL STANDARDS

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### Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Authors' contributions

FS, AMP, OP and MC initiated and supervised the project. VS and CG collected the data. MR, DE and MPB performed the data analysis. FA, LS, RD, VC, SP and OP interpreted the experimental data and prepared figures. MC wrote the manuscript with input from all Authors. All Authors have been involved in the Manuscript's revisions.

### Availability of data and materials

The data underlying this article are available in the public domain.

### Publications ethics

#### *Plagiarism*

The article provides a comprehensive review of the latest studies in the field, with accurate citations.

*Data falsification and fabrication*

The writing and contents of the article are entirely original and were developed entirely by the authors. The article provides a comprehensive review of the latest studies in the field, with accurate citations. The writing and contents of the article are entirely original and were developed entirely by the authors.

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