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ORIGINAL RESEARCH

Psychometric and Molecular Profiling to Predict Outcomes of Spinal Cord Stimulation for Chronic Pain: A Pilot Study

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Purpose: Spinal cord stimulation (SCS) is a well-established intervention for chronic pain, but the factors predicting treatment success remain unclear. This pilot study investigated psychometric and inflammatory biomarkers associated with clinical outcomes in patients undergoing SCS for chronic low back pain.

Patients and Methods: Twenty-two eligible patients were enrolled. Clinical evaluations, psychometric assessments, and blood samples were collected at baseline and at 1-, 3-, and 6-month post-implantation. Pain intensity, psychological status, and quality of life were assessed using validated questionnaires. Inflammatory markers were analyzed in peripheral blood mononuclear cells (PBMCs) at both mRNA and protein levels.

Results: Nineteen patients completed the trial and received definitive SCS implantation (Trial Completed, TC group), while three were discontinued (Trial Failed, TF group). In the TC group, pain intensity and its interference with emotional and work life significantly improved. Psychometric scores also improved: pain catastrophizing decreased below the clinical threshold, and anxiety and depression scores were significantly reduced, alongside enhanced quality of life. Greater pain relief at follow-up was associated with lower pre-implant anxiety and depression levels. Cytokine analysis revealed downregulation of pro-inflammatory IL-1β and upregulation of anti-inflammatory IL-10 and IL-4 post-SCS. In the TF group, baseline depression was higher compared to the TC group. SCS trial implantation in these patients induced only IL-4 upregulation, without broader cytokine modulation.

Conclusion: SCS significantly improved clinical and psychometric outcomes and positively modulated inflammatory profiles in patients with chronic low back pain. High baseline depressive symptoms may predict poorer SCS outcomes, suggesting the importance of psychological assessment in patient selection.

Keywords: spinal cord stimulation, chronic pain, psychometric variables, quality of life, inflammatory markers, cytokines

Introduction

Spinal Cord Stimulation (SCS) is an advanced medical procedure designed to address chronic pain conditions that have not responded to conventional treatment methods.[1] It is primarily used for pain management in Persistent Spinal Pain Syndrome (PSPS, also known as failed back surgery syndrome - FBSS), complex regional pain syndrome (CRPS) and peripheral neuropathies.[2] Despite SCS is a widely used technique, the factors that could influence its success are still being investigated.[3] Indeed, not all patients derive the same benefits from the implant, and not all maintain them in the long term. Among the prognostic variables considered for treatment success, it is believed that patients' psychological state may play a key role, although this topic remains much debated. Both PSPS that affects up to 5–10% of patients after spine surgery and CRPS, with a prevalence of 20–90 per 100,000 individuals are associated with high healthcare

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utilization and indirect costs.[4–7] Recent economic evaluations demonstrate that spinal cord stimulation (SCS) is a more cost-effective intervention compared with conventional medical management, especially when considering medium-long term time horizons.[8–10] Current estimates indicate that tens of thousands of spinal cord stimulation (SCS) devices are implanted worldwide each year, with figures ranging between ~34,000 and 50,000 annually.[11,12] Moreover, over the past decade, there has been a growing demand for SCS in major European healthcare systems.[13–15] These observations underscore the widespread adoption of SCS in Europe and globally. Success rates and complications have been reported in large national registries and databases, with long-term efficacy of SCS remaining variable, as approximately 50–60% of patients maintain significant pain relief after implantation,[16–21] underscoring the importance of improving candidate selection to maximize clinical benefit and healthcare sustainability. However, in the literature there is no unanimous consensus regarding the predominant underlying psychopathological conditions.[22] It is known that various components of pain subjective experience, such as cognitive, affective, motivational, and sociocultural factors, can amplify or inhibit pain perception.[23] Therefore, the evaluation of psychopathological comorbidities, particularly mood alterations within the depressive spectrum and anxiety disorders, is of great importance as they are strongly associated with chronic pain.[24] Personality traits, such as neuroticism, harm avoidance, and self-directedness, have also been investigated in relation to chronic pain persistence. Fear-avoidance belief and pain catastrophizing have been found to contribute to the maintenance of chronic pain.[25] The presence of alexithymia, a psychological trait characterized by difficulties in identifying and expressing emotions, has been also associated with pain exacerbation and disability in patients with chronic pain.[26] To date, few studies have been conducted to consider psychological state as a predictor of SCS treatment outcomes. Some of these studies suggest that the evaluation of anxiety and depression, using appropriate rating scales, could predict the success of the stimulator trial phase.[27] In contrast, other studies have not found correlations among anxiety, depression, perceived pain-related disability with SCS outcomes.[28] Nevertheless, recent recommendations from neuromodulation scientific societies suggest excluding patients with "significant levels of psychological comorbidities using validated tools", although it is unclear which validated tools should be preferred.[29] Therefore, further research to identify correlations between SCS implant outcome and psychological factors is needed. Moreover, in addition to psychological assessments, it would also be important to identify biomarkers related to chronic pain whose changes during SCS trials might better predict long-term treatment success. In particular, the relevance of the interactions between pain and the immune system has been recently recognized, indicating the involvement of immunological mechanisms, inflammatory state and neuroinflammation in pain onset and maintenance.[30] Consequently, the assessment of immune biomarkers, before and after SCS implantation, could provide information of inflammation influence on treatment outcomes. Based on these premises, we undertook a pilot study to investigate psychometric variables and inflammatory markers as potential predictors of clinical outcomes in patients receiving SCS for chronic pain management. Our study aimed to evaluate the feasibility and efficacy of approach before proceeding with a larger multicenter trial.

Materials and Methods

Study was approved by the local ethics committee (Comitato Etico Unico dell'Area Vasta Emilia Nord, Italy; protocol number 29867 on 16/07/2019) and conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent prior to enrollment.

Steps Clinical Trial Process

Patients with chronic neuropathic pain eligible for SCS were contacted for consent to participate. The recruitment was carried out between April 2019 and March 2021. Patients who were unable or unwilling to participate in all parts of the study, as well as those undergoing active treatment for any psychiatric condition, were not recruited. Additionally, institutional exclusion criteria for SCS trialing included presumed inability to manage the SCS device, coagulation disorders and suspected surgical site(s) infection. In total, 25 patients were screened for eligibility, 22 were enrolled, 19 completed the trial and 3 withdrew before the permanent implant. Briefly, eligible patients (n=22), at time 0 (t0), underwent surgery for the application of the temporary SCS device. After 4 weeks (t1), patients who had shown clinical improvement with the SCS device were implanted with the definitive SCS device (n=19, 86%), whereas in cases where clinical improvement was deemed insufficient (n=3, 14%), the temporary SCS device was removed, and the study was

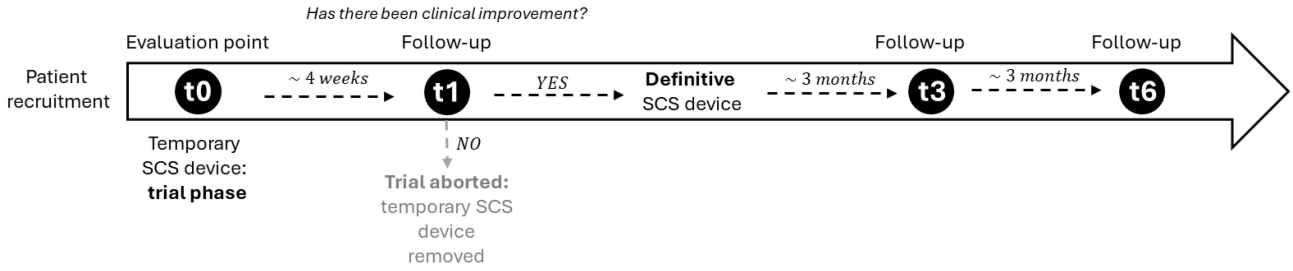

Figure 1 Study flowchart.
Abbreviation: SCS, spinal cord stimulation.

discontinued. Subsequently, after 3 (t3) and 6 (t6) months from the definitive implantation of the SCS device, the patients underwent follow-up checks (Figure 1). At all evaluation points, i.e. t0 and t1 (i.e. before temporary and permanent implantation, respectively), and t3 and t6 (i.e. follow-ups) the clinical condition of the patients was assessed by self-completion of questionnaires, and a blood sample was taken for subsequent immune analyses (see below).

Surgical Procedure

SCS device trial procedures were carried out according to institutional practice.[31,32] Surgery was performed under monitored anesthesia care. Briefly, after applying standard monitoring, patients were placed prone on the operating table; the externalized portion of the lead extensions used during the trial were excised; a line was drawn 3–5 cm below the edge of the iliac crest, on the side chosen by the patient; sedation was induced with midazolam ~0.03 mg/kg and dexmedetomidine 0.1–0.3 µg/kg/h after a loading dose of 1 µg/kg over 15 minutes. The skin was prepped using chlorhexidine in isopropyl alcohol. Local anesthesia along the incisions was given with lidocaine 2% up to 20 mL. The first skin incision was at the level of the connector(s) between the lead(s) and the trial extension(s). The internal portion of the extension(s) were removed. A second incision was then performed along the pre-drawn line below the iliac crest, and a subcutaneous pocket was created by blunt dissection followed by accurate hemostasis. The pocket, as well as the space below the first incision were abundantly washed with saline. The lead or leads were then tunneled to the subcutaneous pocket, where the implantable pulse generator was connected, tested and sited. Wounds were sutured by layers with absorbable monofilament material. The temporary SCS device was maintained for about 4 weeks (ie from t0 to t1). The decision to proceed with a permanent SCS implant was made according to clinical criteria discussed by patients with their clinician. However, at least a 50% reduction in pain was required.

Clinical Data Collection and Outcome Assessment

Pain intensity was assessed with both the Visual Analogue Scale (VAS, 0–100 mm) and the Brief Pain Inventory (BPI) questionnaire.[33] In detail, by BPI the pain intensity (BPI-1, score: 0–10) and the pain impact on daily life and mood (BPI-3, score: 0–10) were evaluated. Psychometric evaluations were performed using the Pain Catastrophizing Scale (PCS, pathological score: ≥ 30 | max score: 52) and the Hospital Anxiety-Depression Scale (HADS, physiological score: 0–7 | borderline score: 8–10 | pathological score: > 10) questionnaires.[34] In particular, the HADS-A (physiological score: 0–5 | borderline score: 6 | pathological score: ≥ 7) aims to investigate anxiety-related symptoms, while the HADS-D those related to depression (physiological score: 0–4 | borderline score: 5–7 | pathological score: ≥ 8).[35] Quality of life was assessed using the EuroQoL EQ-5D-3L scale (score: 0–1).[36]

Blood Sample Collection and PBMC Cultures

For all patients, at each visit/follow-up (ie t0, t1, t3 and t6), 20 mL of peripheral blood was collected in a K3-EDTA vacutainer (BD, Thermo Fisher Scientific, USA). Peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation using Ficoll-Paque™ Plus Medium (Sigma-Aldrich, Italy) at 1200g for 20 minutes, at room temperature.[37,38] PBMCs were collected and washed in Phosphate-Buffered Saline Solution (PBS) through centrifugation at 1500 rpm for 15 minutes at 4°C using sterile methods. The supernatant was discarded and PBMCs pellets were

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resuspended in Roswell Park Memorial Institute (RPMI)-1640 medium supplemented with 10% fetal calf serum (FCS). The viability of cells was checked by trypan blue exclusion test. Cells at the final concentration of 2×10^6 cells were dispensed in 24-well plates (500 µL/well). PBMCs were incubated with or without 10 µg/mL phytohemagglutinin (PHA – Roche, Italy) to evaluate cytokine secretion. Phytohemoagglutinin (PHA) was added to cultures (500 µL/well) in RPMI-1640 plus 10% FCS, 1% glutamine, 2% streptomycin solution and 0.1% 2-mercaptoethanol. After 24 hours of culture at 37°C and 5% CO2, the supernatants were collected and stored at −80°C until analysis.[37] Additionally, a PBMCs aliquot ($4x10^6$ cells) was stored at −80°C for gene expression analyses.

Cytokine Protein Level Analysis

Protein levels of a broad panel of analytes released in culture media were assessed in PBMCs supernatant by MILLIPLEX® MAP Human Cytokine Panel A Magnetic Bead Panel 96-Well Plate Assay (Millipore Corporation Service, Merck Group, Germany). The results are reported as delta % of baseline data (t0).

mRNA Expression Levels and RT-qPCR

The pellet of PBMCs was homogenized with TRIzol® reagent (Invitrogen, USA) for RNA extraction. CDNA was obtained using LunaScript™ Reverse Transcriptase Kit (BioLabs, UK). mRNA levels of interest genes were measured with quantitative RT-PCR by CFX Connect Real-Time PCR System (Biorad, Italy) using TaqMan® Gene Expression Assays (Applied Biosystems™, USA - TNF-α, Hs00174128_m1; IFN-γ, Hs00989291_m1; IL-1β, Hs01555410_m1; IL-4, Hs00174122_m1; IL-6, Hs00174131_m1; IL-10, Hs00961622_m1) and Luna® Universal Probe qPCR Master Mix (BioLabs, UK). The mRNA levels obtained were normalized to GAPDH (Hs02786624_g1) and expressed as $2^{-\Delta\Delta CT}$ vs t0. Each sample was run in duplicate alongside non-template controls (NTC).

Statistical Analysis

GraphPad Prism 10 (v3, USA) was used for statistical analysis. Data distribution was assessed using the Shapiro–Wilk test and found to be normal. All correlations were determined using the Pearson correlation coefficient. The analysis between clinical indices and sex and between trial success and failure, reported as violin plots, were performed by unpaired *t*-test. The variations of clinical outcomes over time and biochemical evaluations were reported as median (IQR) or Mean ± SEM and analysed by One-way ANOVA followed by Tukey post-test. OriginPro (v10.2 - OriginLab Corp, USA) was used for the matrix correlation plots: data were analysed using Pearson correlation coefficients for all possible pairs of parameters of the matrix. For all analyses, differences were considered significant at $p \leq 0.05$.

Results

Twenty-five patients were approached and screened for study inclusion. Twenty-two patients were enrolled and underwent temporary spinal cord stimulation (SCS) device implantation (t0). In 86% of cases (n=19), temporary SCS resulted in a pain reduction ≥ 50% at follow-up (t1), and these patients proceeded to permanent SCS implantation (Trial Completed - TC group). In 14% of cases (n=3), pain reduction ≥ 50% was not achieved, and these patients did not proceed with the permanent implantation (Trial Failed - TF group). Demographic and clinical characteristics of patients in the TC group are presented in Table 1.

Baseline Correlation

For each patient in the TC group, age, gender, and baseline clinical outcomes (t0) were subjected to statistical analysis. No significant associations were found between patient age and any of the clinical outcomes evaluated (Supplementary Figure 1A–I). Additionally, no gender-based differences were observed in pain measures (VAS, BPI, BPI-1, BPI-3), mood alterations (HADS, HADS-A, HADS-D), or quality of life (EQ-5D-3L) (panels J–M, O–R). However, female patients exhibited significantly higher pain catastrophizing scores (PCS) compared to male patients (panel N, $p<0.01$). Subsequently, correlations among clinical outcomes were assessed to evaluate potential interrelations between different pain dimensions and associated comorbidities, with the aim of identifying predictive factors for SCS treatment outcome (Figure 2). A negative correlation was identified between quality of life and: pain intensity (panel A, EQ-5D-3L and BPI-

Table 1 Clinical Outcomes of Patients

Gender	
Female Male	9 (47%) 10 (53%)
Age	
Median (IQR)	60 (20)
Diagnosis	
FBSS (Failed Back Surgery Syndrome) Degenerative Disease	16 (84%) 3 (16%)
Visual Analog Scale (VAS)	
Median (IQR)	80 (18)
Brief Pain Inventory (BPI)	
Severity - Median (IQR) Interference - Median (IQR)	7 (2) 7 (3)
Hospital Anxiety-Depression Scale (HADS)	
Total - Median (IQR) Anxiety - Median (IQR) Depression - Median (IQR)	18 (10) 9 (4) 9 (5)
Pain Catastrophizing Scale (PCS)	
Total - Median (IQR) Clinically relevant Normal	32 (10) 15 (79%) 4 (21%)
Euro Quality of Life Scale (EQ-5D-3L)	
Median (IQR)	0.49 (0.13)

Note: The data referred to 19 patients before the temporary Spinal Cord Stimulation (SCS) device implant.

1), pain interference in daily activities (panel B, EQ-5D-3L and BPI-3), and depressive symptoms (panel C, EQ-5D-3L and HADS-D), indicating that lower quality of life was associated with higher scores on these variables. Positive correlations were found between pain intensity and: pain severity (panel D, BPI-1 and VAS), pain interference (panel E, BPI-1 and BPI-3), and depressive symptoms (panel F, BPI-1 and HADS-D). Furthermore, anxiety and depression scores were positively correlated (panel G, HADS-A and HADS-D), as were pain interference and anxiety levels (panel H, BPI-3 and HADS-A). No additional significant correlations were detected among the other clinical variables (Supplementary Table 1).

Modulation of Post-Implant Clinical Outcomes

Regarding clinical outcomes, a progressive reduction in pain intensity was observed post-implantation (Figure 3A, VAS), reaching statistical significance at t6 compared to baseline (t0 vs t6, $p<0.05$). The total BPI score showed a significant reduction at all time points following SCS implantation (panel B, $p<0.01$). Specifically, both pain intensity (BPI-1, panel C, $p<0.05$) and pain interference in emotional and occupational domains (BPI-3, panel D, $p<0.01$) were significantly decreased. Pain catastrophizing was also significantly reduced after implantation (PCS, panel E, $p<0.01$), consistently remaining below the clinical threshold through the final follow-up. Mood disturbances associated with pain (HADS, panel F) decreased significantly, with a median reduction of 7 points between t0 and t6 (Median (IQR): 18(8) vs 11(8); $p<0.01$). Analysis of

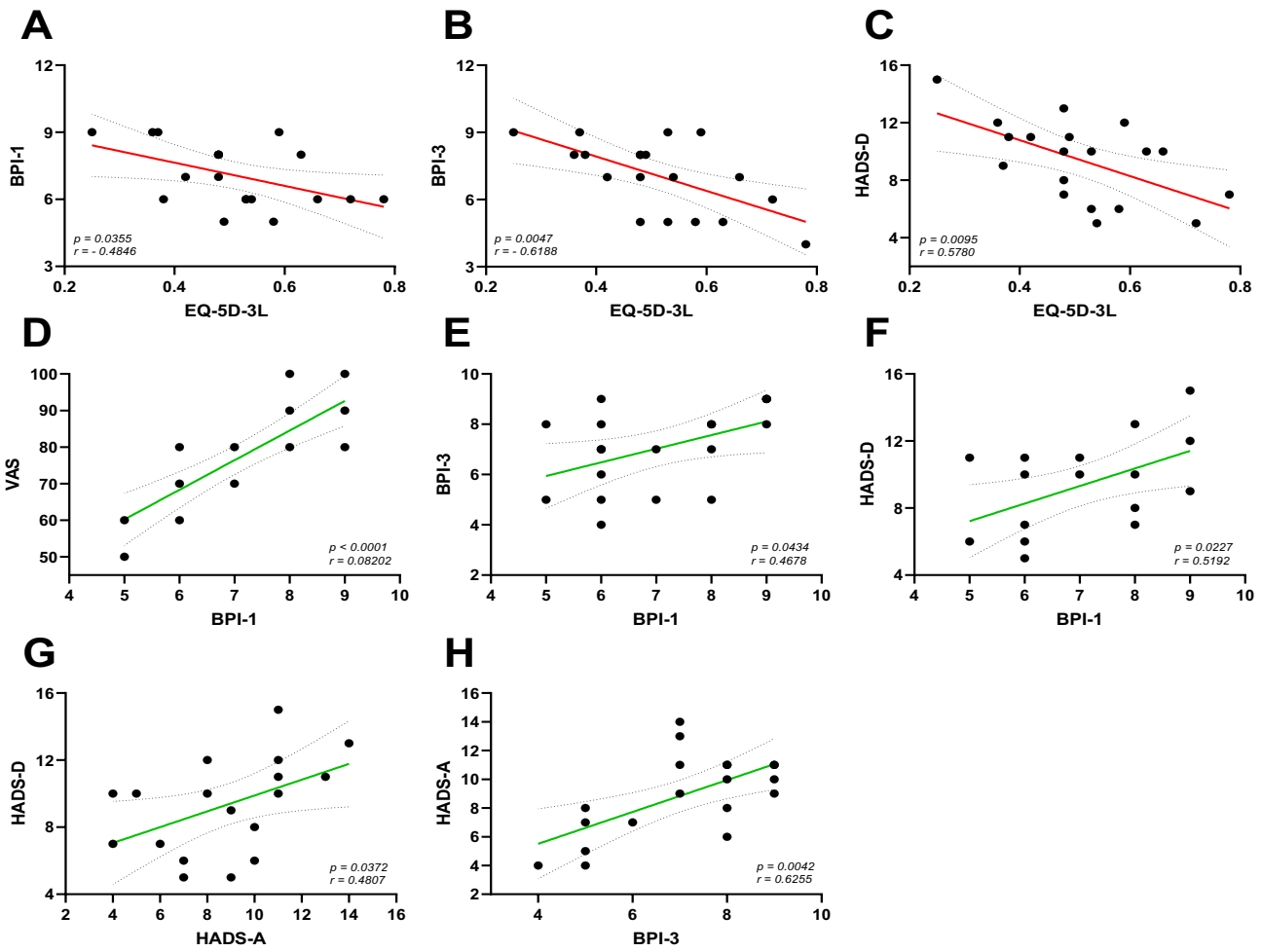

Figure 2 Baseline clinical outcomes correlations. (**A**–**C**) Negative (red line) and (**D**–**H**) positive (green line) correlations between the outcomes were reported. Data from 19 patients were reported. Statistical analysis was performed by Pearson's correlation coefficients. p, p-value; r, Pearson's correlation coefficient.
Abbreviations: VAS, Visual analogue scale (pain severity); BPI, Brief Pain Inventory (which includes BPI-1 – intensity and BPI-3 - interference); HADS, Hospital Anxiety-Depression Scale (which includes HADS-A – anxiety and HADS-D - depression); EQ-5D-3L, Euro Quality of Life Scale.

individual HADS subscales revealed significant reductions in both anxiety (HADS-A, panel G) and depression (HADS-D, panel H) scores ($p<0.05$). Although the most pronounced improvements in pain (BPI), pain catastrophizing (PCS), and mood (HADS) were observed at the short-term follow-up (t1) (panels B, E, F; t0 vs t1, $p<0.0001$), a significant benefit persisted at t6 (t0 vs t6, $p<0.01$), with stabilization of symptoms over time. Quality of life (EQ-5D-3L, panel I) improved significantly immediately after implantation (t1, $p<0.0001$) and this improvement was sustained through the final follow-up (t6, $p<0.0001$), mirroring the VAS trend. Longitudinal correlations among clinical outcomes from t0 to t6 were assessed (Figure 4). Pain interference in daily life positively correlated with both pain intensity (panel A, BPI-3 and BPI-1) and pain catastrophizing (panel B, BPI-3 and PCS). Depressive symptoms were positively associated with pain interference (panel C, HADS-D and BPI-3), pain catastrophizing (panel D, HADS-D and PCS), and anxiety (panel E, HADS-D and HADS-A). Negative correlations were observed between quality of life and pain catastrophizing (panel F, EQ-5D-3L and PCS), depression (panel G, EQ-5D-3L and HADS-D), and anxiety (panel H, EQ-5D-3L and HADS-A). No additional significant correlations were found (Supplementary Table 2). Subsequently, a correlation matrix was generated to compare baseline clinical parameters (t0) with those at study completion (t6) (Figure 5A). A significant negative correlation was found between baseline quality of life and depressive symptoms at t6 (EQ-5D-3L t0 vs HADS-D t6, $p<0.05$), indicating that lower pre-implant quality of life could predict higher depression levels at final follow-up. Finally, another correlation matrix was constructed to assess the relationship between baseline emotional status and final pain relief (defined as Δ = t0 value − t6

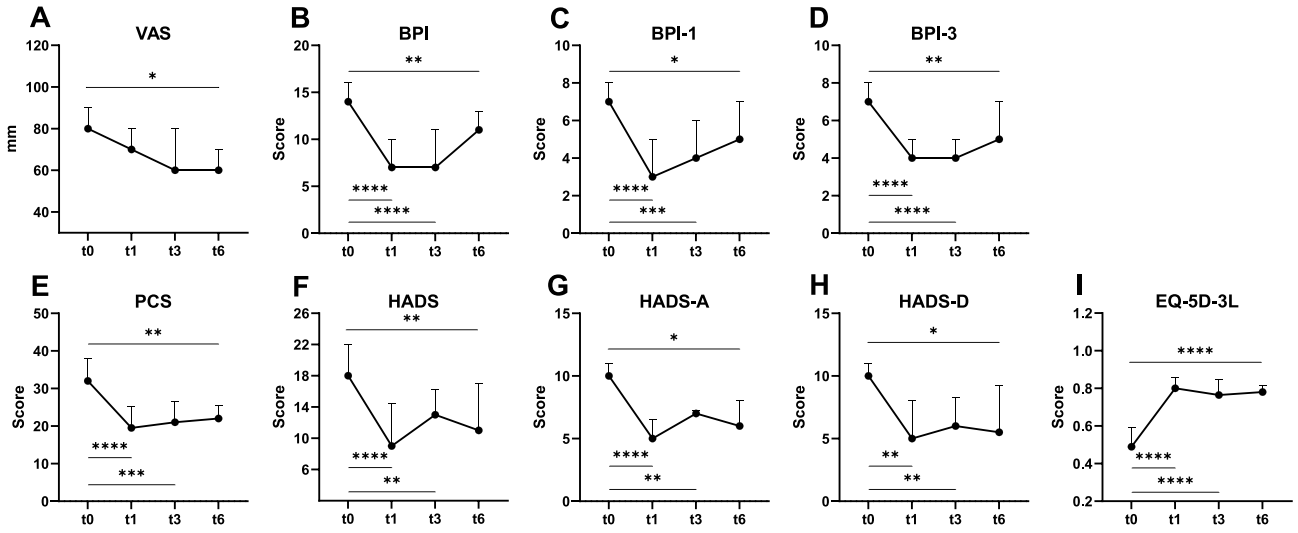

Figure 3 Trends in clinical parameters after SCS device implantation. Clinical and psychometric results of patients enrolled at baseline (t0) and after 1-month (t1) from temporary SCS implant as well as after 3 (t3) and 6 (t6) months of definitive SCS implant. (**A**) VAS, Visual analogue scale (pain severity); (**B**) BPI, Brief Pain Inventory (which includes (**C**) BPI-1 – intensity and (**D**) BPI-3 - interference); (**E**) PCS, Pain Catastrophizing Scale; (**F**) Hads, Hospital Anxiety-Depression Scale (which includes (**G**) HADS-A – anxiety and (**H**) HADS-D - depression); (**I**) EQ-5D-3L, Euro Quality of Life Scale. Data are expressed as median (IQR) of 19 patients. Statistical analysis was performed by means of One-way ANOVA followed by Bonferroni's post-test. ****p<0.0001, ***p<0.001, **p<0.01, *p<0.05 vs t0. mm, millimeters.

value for pain-related parameters) (panel B). Negative correlations were identified, indicating that higher baseline anxiety, depression, or both were associated with reduced pain relief ($p<0.05$).

Biochemical Assessment of Cytokine Levels in Peripheral Blood Mononuclear Cells

Cytokine levels were assessed at all observation time points (t0, t1, t3, and t6), both at the mRNA level in unstimulated PBMCs and as protein concentrations in PHA-stimulated PBMC culture supernatants. As shown in Figure 6, SCS implantation did not significantly alter mRNA expression of TNFα (panel A) or IFNγ (panel B). IL-1β mRNA levels (panel C) showed a non-significant decreasing trend at the first follow-up (t0 vs t1, $p=0.0965$), followed by a significant downregulation at 3 months post-implantation, which was sustained through the final follow-up (t0 vs t6, $p<0.0001$). In contrast, IL-6 mRNA expression (panel D) was significantly upregulated at t1 ($p<0.05$) but returned to baseline levels at subsequent time points. A similar transient increase was observed for IL-2 mRNA (panel E). Notably, the expression of anti-inflammatory cytokines IL-10 (panel F) and IL-4 (panel G) was significantly upregulated one month after SCS implantation (t0 vs t1, $p<0.05$ and $p<0.0001$, respectively). While IL-10 levels returned to baseline by t3, IL-4 expression remained significantly elevated at both t3 and t6 (t0 vs t3/t6, $p<0.0001$). Protein levels of cytokines released in PHA-stimulated PBMC supernatants were also quantified (Figure 7). A progressive decrease in TNFα (panel A, t0 vs t6, $p=0.1723$), IL-1β (panel B, $p<0.0001$), and granulocyte colony-stimulating factor (G-CSF; panel C, $p<0.0001$) was observed following SCS implantation. No significant changes were detected in IFNγ protein levels (panel D). Transient increases in the secretion of IL-6 (panel E, $p<0.0001$), IL-2 (panel F, $p<0.01$), and IL-8 (panel G, $p<0.01$) were detected at t1, with levels returning to baseline at later time points ($p>0.05$). Anti-inflammatory cytokines IL-10 and IL-4 (panels H and I) were significantly elevated post-implantation; however, IL-10 levels returned to baseline by t6, while IL-4 remained elevated (t0 vs t6, $p<0.01$). Cytokines IL-5, IL-7, IL-12, and IL-13 were also measured, but their concentrations were below the detection threshold (values under the standard curve).

Baseline Comparison of Clinical and Biochemical Data Between Patients Who Did or Did Not Complete the Study

Three patients did not receive the definitive SCS implant due to the absence of a ≥50% reduction in pain following the temporary trial (all females; age (median (IQR)): 71 (9.5)). Although the sample size is limited for robust statistical inference, notable differences in cytokine expression profiles were observed in these patients compared to those who

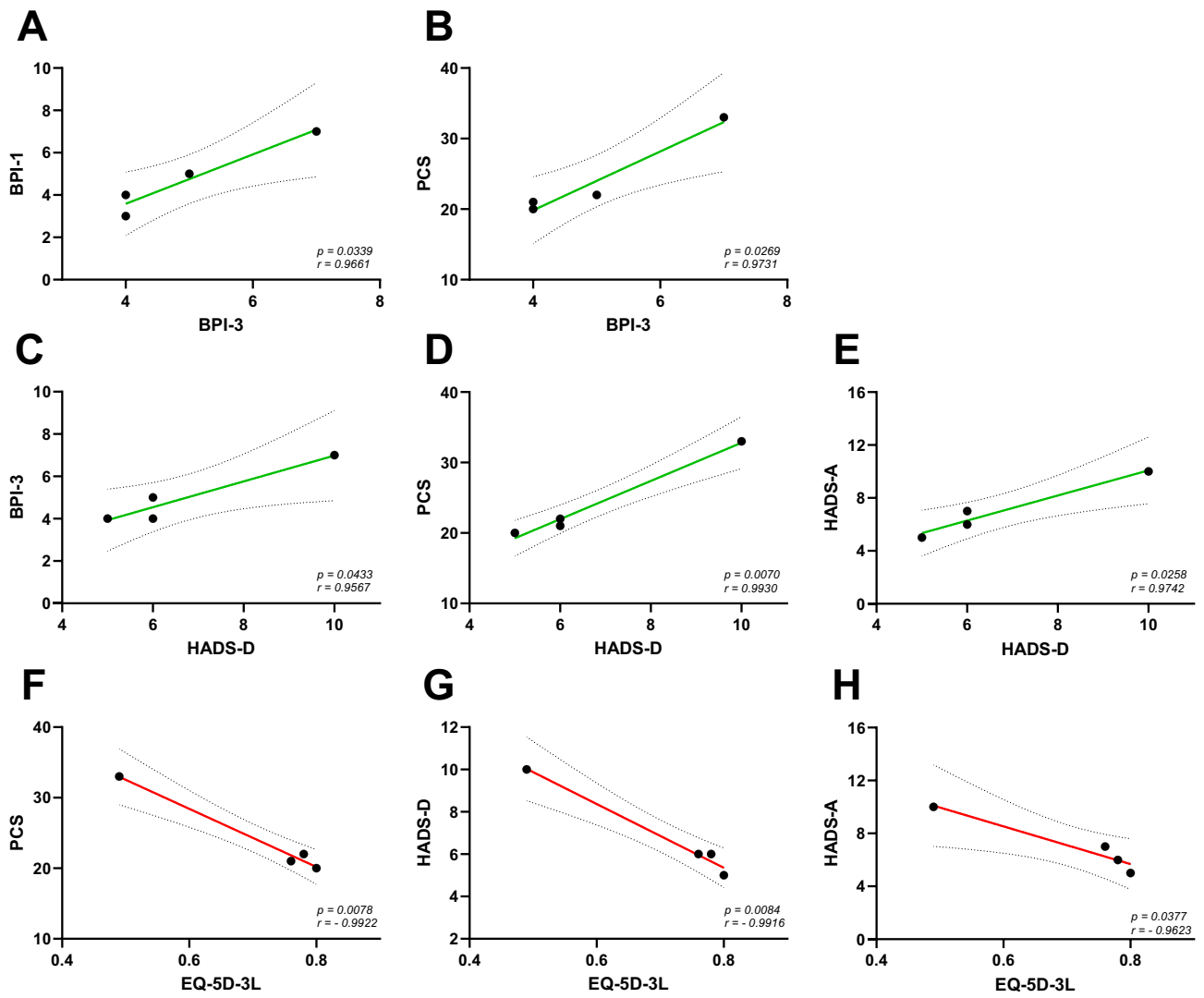

Figure 4 Timeline correlations of clinical outcomes. (**A**–**E**) Positive (green line) and (**F**–**H**) negative (red line) correlations between the outcomes were reported. Clinical data of patients were correlated each other over time. Each point represents the correlation between the two variables at the same observation time. Data from 19 patients were reported. Statistical analysis was performed by Pearson's correlation coefficients. p, p-value; r, Pearson's correlation coefficient.
Abbreviations: BPI, Brief Pain Inventory (1-intensity and 3-interference); PCS, Pain Catastrophizing Scale; HADS, Hospital Anxiety-Depression Scale (A-anxiety and D-depression); EQ-5D-3L, Euro Quality of Life Scale.

proceeded to permanent implantation. As shown in Figure 8, at baseline (t0), the trial-failed group exhibited significantly lower levels of the pro-inflammatory cytokines TNFα (panel A, p=0.0709), IL-2 (panel B, $p<0.05$), and IL-1β (panel C, $p<0.05$), and significantly higher levels of IFNγ (panel D, $p<0.05$) and IL-6 (panel E, $p<0.0001$), relative to the trial-completed group. No differences were observed in baseline expression levels of the anti-inflammatory cytokines IL-10 and IL-4 (panels F and G, respectively). At one-month post-temporary implantation (t1), cytokine mRNA levels in the trial-failed group remained largely unchanged compared to baseline, except for a significant increase in IL-4 expression (t0 vs t1, $p<0.0001$). Additionally, baseline clinical parameters (t0) were compared between patients who completed the trial and those who did not (Figure 9). A significantly higher level of depressive symptoms was observed in the trial-failed group (panel H, $p<0.05$), whereas no significant differences were found in other clinical measures.

Discussion

This pilot study aimed to investigate the relationship between baseline psychometric parameters and the outcome of spinal cord stimulation (SCS) on pain, as well as its subsequent effects on quality of life and inflammatory markers, in

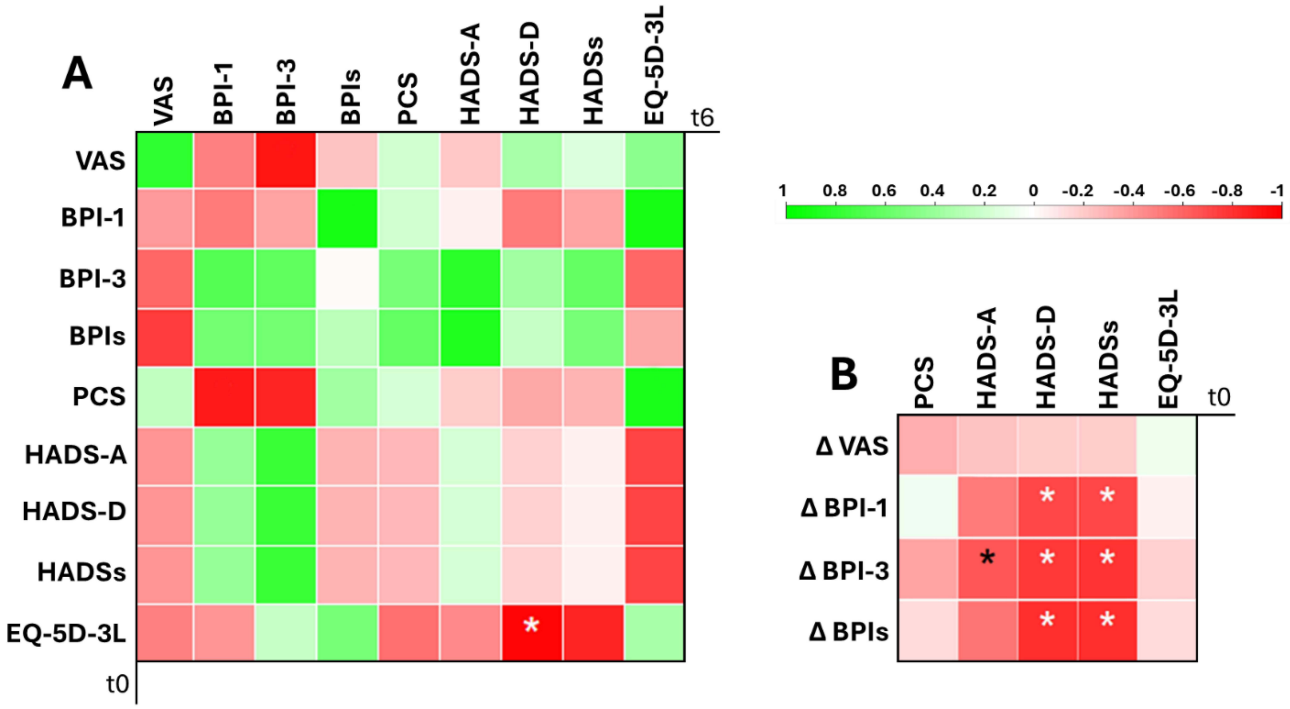

Figure 5 Correlation matrix of clinical outcomes. (**A**) Clinical data at t0 (y-axis) and at t6 (x-axis). (**B**) Pain relief (y-axis) and emotional component at t0 (x-axis). Pearson's correlation coefficients were calculated and p-value (<0.5, ie *) was shown in the plots for each pair of variables (n=19 patients). Correlation ranges from −1 to +1: where negative values (red) and positive values (green) suggest positive and negative correlations, respectively. The colour intensity indicates the correlation strength. Δ, delta.
Abbreviations: VAS, Visual Analogue Scale (pain severity); BPI, Brief Pain Inventory (1-intensity, 3-interference and Tot-intensity+interference); PCS, Pain Catastrophizing Scale; HADS, Hospital Anxiety-Depression Scale (A-anxiety, D-depression and Tot-anxiety+depression); EQ-5D-3L, Euro Quality of Life Scale.

a cohort of patients suffering from intractable low back pain. Although the sample size of patients in whom the trial was unsuccessful was relatively small (n=3, representing 14%), comparative analyses included these patients to provide preliminary insights. The primary objective was to gather valuable information to identify potential challenges and optimize our methodology for future multicenter studies. Ultimately, the goal is to personalize SCS therapy by identifying the most suitable candidates.

Previous research on the predictive value of baseline pain catastrophizing scale (PCS) scores for SCS outcomes has yielded inconsistent results. Rosenberg et al reported that higher PCS scores were associated with reduced pain relief following SCS, suggesting PCS as a potential predictor of poor response.[39] Conversely, a recent multicenter study with a three-year follow-up failed to find a significant association between PCS and pain relief post-SCS.[40] In our cohort, 19 patients experienced significant pain reduction following device implantation, allowing us to explore the interplay between clinical pain parameters and emotional factors. Moreover, our 86% success rate is at the upper end of reported rates, which generally range from 70% to 90%.[41–44] This high success rate may therefore reflect the rigorous screening criteria applied, as well as the longer-than-average duration of the temporary implant, typically 7–14 days,[45,46] which allows for a more reliable assessment of sustained pain reduction (≥50%), device tolerability and potential adverse events[47] Nevertheless, the risk of reinterventions and long-term complications remains a relevant concern in larger cohorts.[19–21] These recent insights reinforce the clinical and economic impact of SCS and provide additional context for the psychometric and molecular predictors evaluated in our study.

We first examined whether demographic variables such as age or sex influenced the clinical indices predictive of SCS success. No correlation with age was observed. However, women exhibited higher levels of pain catastrophizing compared to men, although this did not translate into differences in other clinical parameters. Baseline correlations revealed that patients with higher pain severity also reported greater pain intensity and interference, as well as elevated depressive symptoms. Additionally, higher depressive scores correlated positively with anxiety levels, which in turn were associated with increased pain interference. These findings confirm the well-established link between pain and emotional

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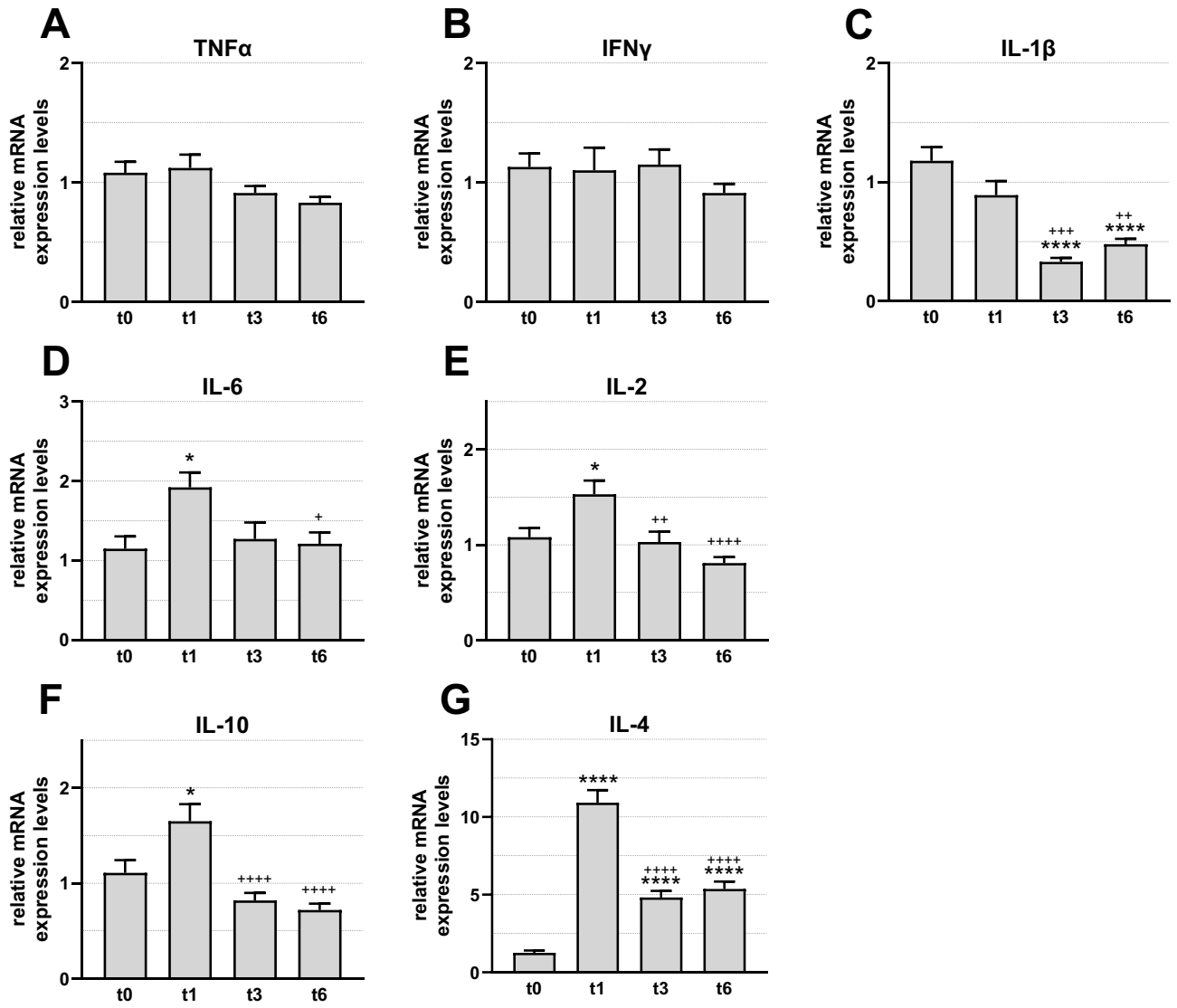

Figure 6 Cytokine expression levels. Blood samples were obtained before (t0) and after 1-month (t1) from temporary SCS implant as well as after 3 (t3) and 6 (t6) months of definitive SCS implant. In PBMC the mRNA expression levels of pro-inflammatory cytokines (**A**) TNFα, (**B**) IFNγ, (**C**) IL-1β, (**D**) IL-6 and (**E**) IL-2 as well as anti-inflammatory cytokines (**F**) IL-10 and (**G**) IL-4 were assessed by RT-qPCR. Data were normalized to GAPDH expression and presented as fold-changes over point t0. Data are expressed as mean ± SEM of 19 patients. Statistical analysis was performed by One-way ANOVA followed by Tukey's post-test. *p<0.05, ****p<0.0001 vs t0; +p<0.05, ++p<0.01, +++p<0.001, ++++p<0.0001 vs t1.

distress, indicating that patients with more severe pain also tend to experience greater depressive symptoms, impacting overall quality of life.

Longitudinal assessment revealed that, at the final follow-up, pain-related parameters showed a slight increase, whereas emotional parameters remained at minimal levels. This pattern further supports the close relationship between pain perception and psychological state. Temporal correlation analyses reinforced this connection, although further studies are necessary to clarify causality. Importantly, a significant association between preoperative psychiatric status and treatment outcome was observed: patients with higher baseline depressive scores were less likely to experience substantial pain relief. We therefore tried to identify which factors could be involved in the failure of the intervention in the 3 patients who discontinued the study. We established that the only baseline clinical parameter that was statistically different compared to the cohort of patients who successfully completed the trial was a higher depressive condition. Although this observation is very interesting, the sample under examination was relatively small (equal to 14% of enrolled patients). For this reason, we decided to set up correlation matrices to establish possible differences between the

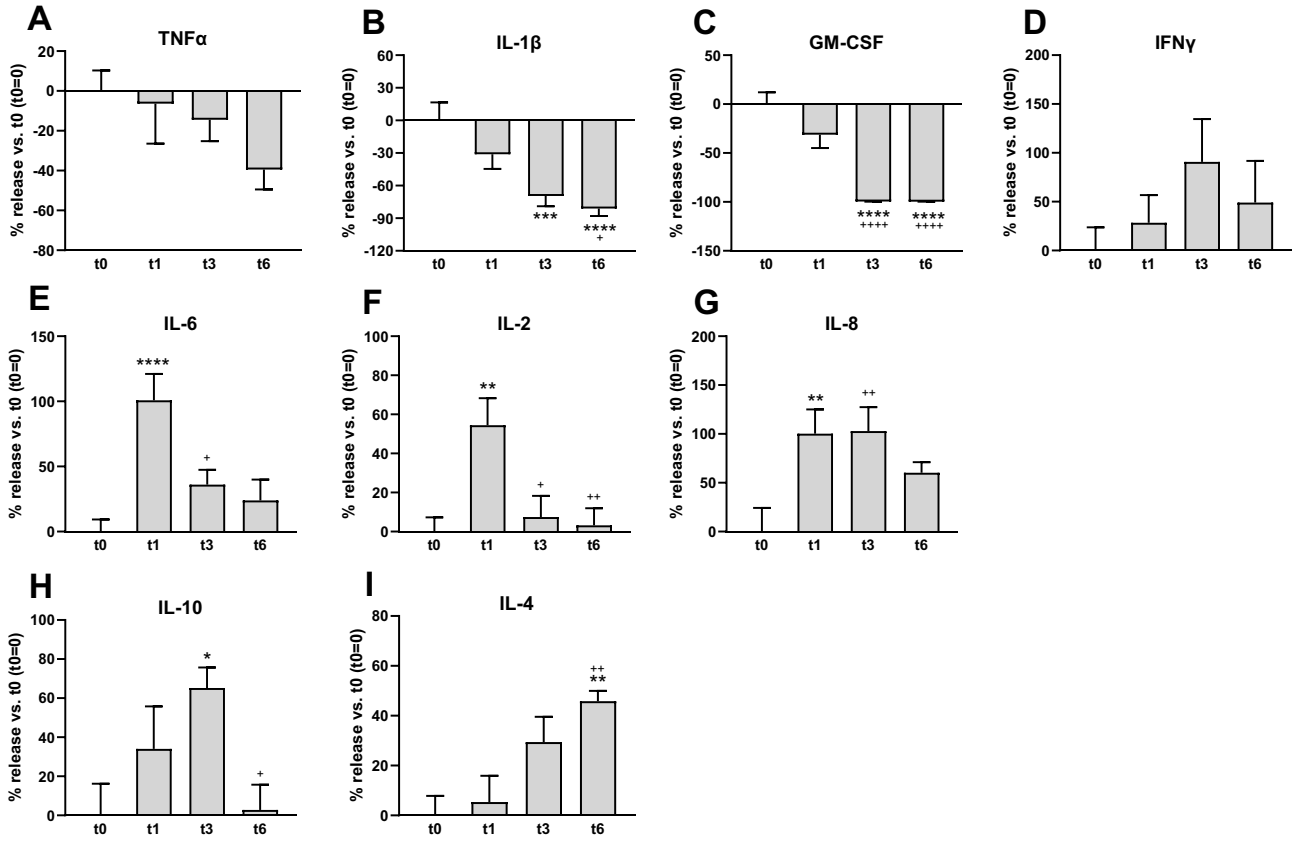

Figure 7 Cytokine release in PBMC cultures. Blood samples were obtained before (t0) and after 1-month (t1) from temporary SCS implant as well as after 3 (t3) and 6 (t6) months of definitive SCS implant. PBMCs were stimulated in vitro for 24 hours with 10 µg/mL PHA. The levels of (**A**) TNFα, (**B**) IL-1β, (**C**) GM-CSF, (**D**) IFNγ, (**E**) IL6, (**F**) IL-2, (**G**) IL-8, (**H**) IL-10 and (**I**) IL-4 released in media were evaluated by MILLIPLEX® MAP service. Data were expressed as % of release in comparison to basal values (t0), as mean ± SEM of 19 patients. Statistical analysis was performed by One-way ANOVA followed by Tukey's post-test. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs t0; +p<0.05, ++p<0.01, ++++p<0.0001 vs t1.

pre-operative and the end of the trial in the patients who completed the study. Thanks to this, we observed that, although in all patients the SCS implant had a good therapeutic effect, pain relief was significantly lower in those patients in whom the baseline depressive score was high. Although, limited by the small sample size, this finding suggests that preoperative depression may negatively influence SCS efficacy and warrants further investigation in larger cohorts.

In addition to clinical and psychometric assessments, we analyzed pro- and anti-inflammatory cytokine levels at both mRNA and protein levels in peripheral blood mononuclear cells (PBMCs). The bidirectional interaction between the immune/inflammatory and the nervous systems plays a pivotal role in the development and maintenance of chronic pain. Pro-inflammatory cytokines such as IL-1β, IL-6, and TNFα are known to facilitate peripheral and central sensitization, leading to hyperalgesia and enhanced pain perception. Conversely, anti-inflammatory cytokines like IL-10 and IL-4 exert anti-inflammatory and neuroprotective effects by dampening glial activation and restoring inhibitory control of nociceptive transmission.[48–52] SCS may influence immune and glial cell activation, thus modifying the levels of inflammatory mediators. Pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNFα are typically upregulated in chronic pain states, contributing to inflammation, neuroinflammation and associated mood disturbances.[52–55] Post-SCS, we observed transient increases in IL-2, IL-6, and IL-8, likely reflecting the surgical trauma rather than the stimulation itself, as these levels returned to baseline within a short period.

This aligns with the known immune response following surgical procedures, where activation of innate and adaptive immunity results in temporary increases in pro-inflammatory cytokines such as IL-6, IL-8, and IL-2.[56] These elevations are part of the body's natural healing process and typically normalize in the absence of complications. Interestingly, IL-1β levels showed a significant and progressive decrease over time, suggesting that SCS may modulate neuroinflammatory

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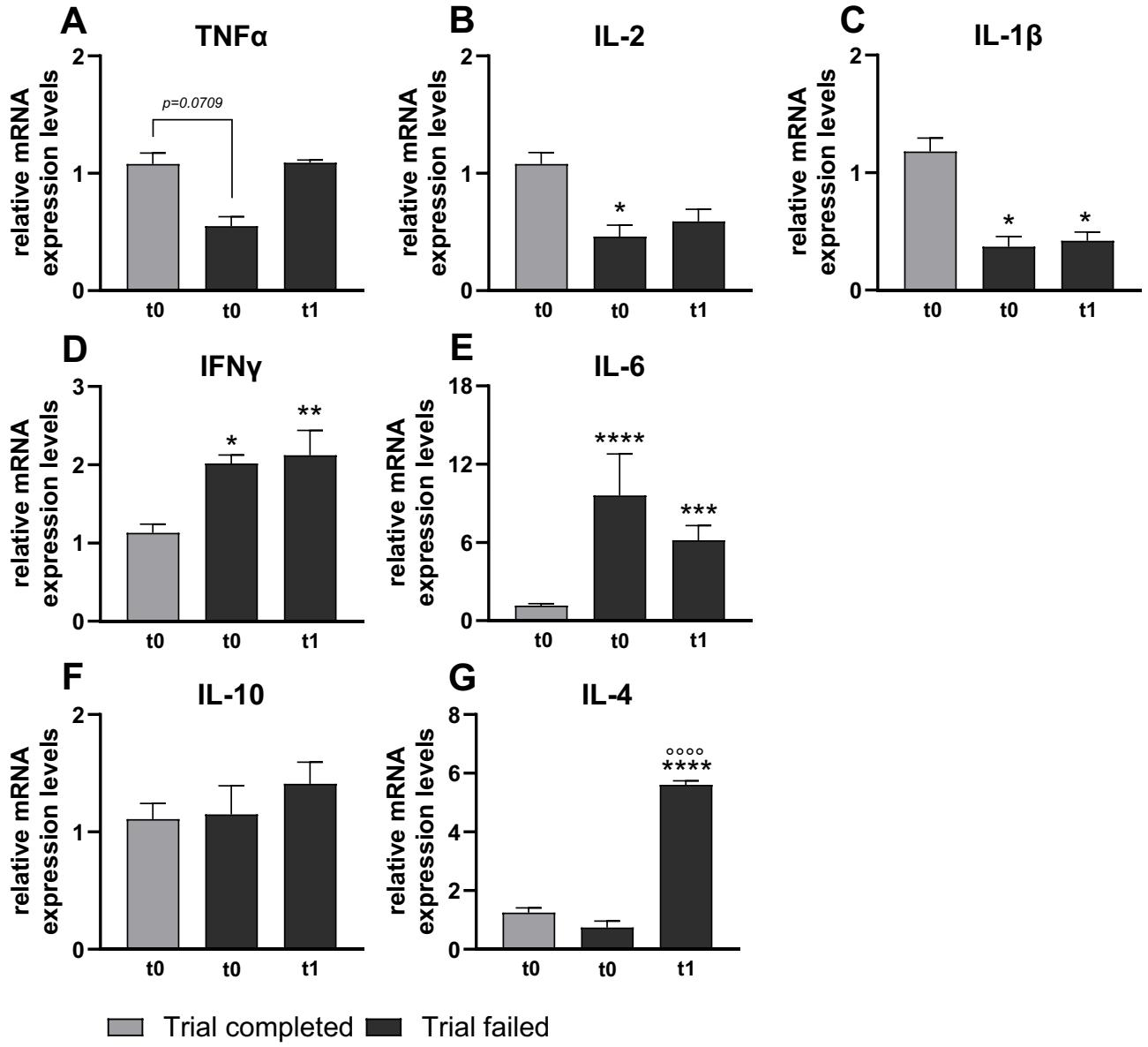

Figure 8 Patients withdrawn from the clinical trial: cytokine expression levels. Blood samples were obtained before (t0) and after 1-month (t1) from temporary SCS implant in both patients who completed the trial (trial completed, n=19) and in those who dropped out (trial failed, n=3). In PBMC the mRNA expression levels of pro-inflammatory cytokines (**A**) TNFα, (**B**) IL-2, (**C**) IL-1β, (**D**) IFNγ and (**E**) IL-6 as well as anti-inflammatory cytokines (**F**) IL-10 and (**G**) IL-4 were assessed by RT-qPCR. Data were normalized to GAPDH expression and presented as fold-changes over point t0 of the trial completed group. Data are expressed as mean ± SEM of 19 (trial completed) or 3 (trial failed) patients. Statistical analysis was performed by One-way ANOVA followed by Tukey's post-test. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs trial completed group; °°°°p<0.0001 vs trial failed group. p, p-value.

pathways. This reduction could be mediated through mechanisms involving negative feedback loops, where the body releases anti-inflammatory cytokines such as IL-10, IL-4, and TGF-β to counteract inflammation.[51] It has also been identified that SCS could hyperactivate the glial component (microglia and astrocytes), but that repeated stimulation could instead silence them, thus regulating the production of IL-1β to limit neuroinflammation. Therefore, a precise crosstalk between nervous and immune systems is important for neuroprotection and axonal plasticity. A recent study demonstrated, in a mouse model of spinal cord compression injury, that local application of recombinant IL-1β led to an increase in lesion size and a decrease in nerve fiber number, significantly worsening neurological outcome. In contrast, in IL-1β-deficient animals (KO animals), the absence of this cytokine significantly improved recovery, with reduced lesion size and astrogliosis.[57] These findings suggest that decreased IL-1β levels post-SCS could serve as a biomarker for favorable clinical response. Conversely, anti-inflammatory cytokines like IL-10 and IL-4 were upregulated following

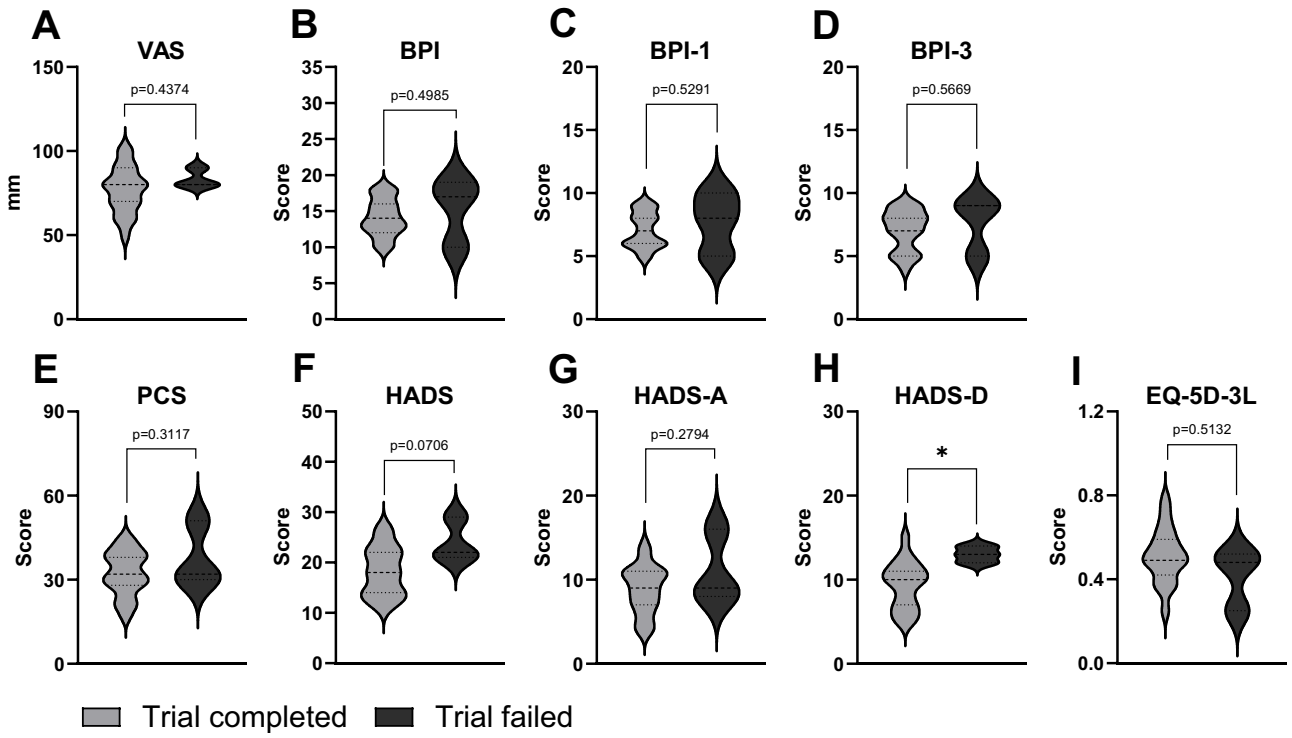

Figure 9 Patients withdrawn from the clinical trial: clinical outcomes evaluations. Baseline clinical and psychometric results of patients completed and failed trial study. Data were reported as violin plots of 19 (trial completed) or 3 (trial failed) patients. Statistical analysis was performed by unpaired *t*-test. *p<0.05 vs trial completed group. p, p-value.

Abbreviations: VAS, Visual Analogue Scale (pain severity); BPI, Brief Pain Inventory (which includes BPI-1 – intensity and BPI-3 - interference); PCS, Pain Catastrophizing Scale; HADS, Hospital Anxiety-Depression Scale (which includes HADS-A – anxiety and HADS-D - depression); EQ-5D-3L, Euro Quality of Life Scale.

SCS, indicating a shift toward an anti-inflammatory profile. The transient increase in IL-10 and sustained upregulation of IL-4 support the hypothesis that SCS promotes a balanced immune response, potentially contributing to pain relief and mood stabilization.[51,58,59]

The SCS has effects on both the nervous and immune systems, and the modulation of cytokines could induce a reduction of local and systemic inflammation and pain, by suppressing the production of pro-inflammatory cytokines on the one hand and by promoting a more balanced immune response on the other. Therefore, the SCS appears to favor a balance towards a type 2 immune response, supporting the hypothesis that SCS efficacy may partly depend on its immunomodulatory capacity.[60–62] We would like to add that since the assessment of cytokines in plasma may not represent the neuroinflammatory condition in patients, we decided to measure cytokine production in BPMC that better mirror neuroinflammation that is characterized by recruitment of circulating immune cells in the nervous system, besides activation of resident glial cells.

This immunomodulatory effect may also influence cognitive and emotional functions, as systemic inflammation has been linked to mood disorders and cognitive impairment.

Although our data suggest that SCS can modulate inflammatory markers toward an anti-inflammatory state, further research is needed to establish a direct causal relationship between cytokine changes and clinical improvements. Notably, patients who discontinued the study exhibited baseline cytokine profiles characterized by significantly lower levels of TNFα, IL-2, and IL-1β, alongside higher levels of IFN-γ and IL-6. One month after temporary implantation, these patients showed no significant biochemical changes except for an increase in IL-4, indicating a possible immune system impairment that hindered effective response to the intervention. This immune dysregulation might partly explain their lack of pain relief.

Limitations

We acknowledge the small sample size of our patients' group. Originally a formal a priori power calculation was performed, indicating a number of 70 patients for robust statistical analysis. Unfortunately, the COVID-19 pandemic limited patient recruitment However, the data of this pilot study are useful for calculating the sample size in a future study. In fact, on the basis of the results obtained we now calculated that 46 patients are sufficient for a larger multicenter study.

Few patients were free of SCS effects. Additionally, the absence of a control group, ie patients not undergoing SCS, limits the ability to draw definitive conclusions regarding the specific effects of the therapy. Other confounding factors, such as concomitant medications, comorbidities, and lifestyle variables, were not fully controlled, which could influence outcomes. Moreover, the follow-up duration was limited to six months, which may not capture long-term effects or the sustainability of observed benefits. Longer follow-up periods are necessary to assess the durability of clinical and molecular changes.

Conclusions

Despite its preliminary nature, this study highlights several important findings. Baseline correlations between pain severity and emotional disturbances were evident, yet moderate levels of anxiety, depression, and catastrophizing did not preclude positive pain outcomes, which improved alongside psychological parameters. Importantly, lower baseline depression levels appeared to predict better long-term pain relief and patients who discontinued the study showed significantly higher baseline levels of depression compared to the group who completed the study, suggesting that preoperative psychiatric assessment could help patient selection. Additionally, molecular analyses revealed that SCS modulates cytokine profiles toward an anti-inflammatory state, supporting its role in reducing neuroinflammation and associated symptoms. These results underscore the potential of combining clinical, psychometric, and molecular markers to optimize patient selection and personalize SCS therapy. Future studies with larger cohorts and extended follow-up are essential to validate these findings and fully elucidate the mechanisms underlying SCS efficacy.

Acknowledgments

The free version of ChatGPT was used to improve the quality of the English language in this manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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