

Randomized clinical trial of the efficacy of the EmoLED medical device in the treatment of stage 2 and stage 3 pressure ulcers: The RISE_UP study

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ABSTRACT

Aim of the study: Pressure ulcers are an important public health issue, impacting quality of life and causing health deterioration. Blue light photobiomodulation has been shown promoting wound healing in vascular, diabetic, rheumatologic ulcers and lesions in spinal cord injury patients. Based on these preliminary results, this study was developed to assess the effectiveness of blue light therapy in second and third stage pressure ulcers.

Materials and methods: This study was a randomized controlled trial enrolling hospitalized patients with poor mobility. The intervention group included blue light treatment in addition to standard care, three times a week, for 4 consecutive weeks. The primary objective is the difference in the healing process by measuring the average difference of the lesion's PUSH score between the first and the last visit.

Results: The analysis shows that the mean PUSH reduction and the probability of belonging to responder patients were higher in the treatment group. A latent profile analysis that identifies two trajectory classes based on treatment response, shows an association in the probability of following best trajectory for the treatment group (30 % vs 2 %).

Conclusions: The result shows that blue light photobiomodulation promotes recovery of tissue repair in pressure ulcers, and in stabilizing wounds that would otherwise worsen despite standard of care treatment. This therapy may be a valuable contribution to the daily management of pressure lesions since it has an excellent safety profile and the addition of this therapy to a treatment program may speed healing, improving the quality of life.

([Clinicaltrials.gov](https://clinicaltrials.gov) Ref. numb.: NCT05130814)

1. Introduction

Pressure ulcers (PU), also known decubitus ulcers and pressure injuries, represent in an important public health issue, for example, a recent systematic review reports that the global incidence of PUs in inpatients is 12 % [1], with an annual prevalence of approximately 2–3 million individuals admitted in hospitals and nursing homes [2,3].

A typical pressure ulcer forms when a skin area is damaged due to pressure impairing blood flow and, therefore, oxygen supply to the

underlying tissue. As a result, this leads to hypoxia and eventual necrosis within the tissue. Pressure ulcers often occur in areas with a bony prominence such as the sacrum and heel [4], and are caused by external forces such as pressure, friction or shear, or a combination of these [5].

Individuals with spinal cord injuries and those immobilized or with limited mobility [6], such as elderly people and those with acute or chronic conditions are prone to the risk of pressure ulceration [7]. The consequence of having a PU is severe, with patients often suffering from pain and discomfort, having longer hospitalization and rehabilitation

Abbreviations: EPUAP, (European Pressure Ulcer Advisory Panel); (GLM), Generalized linear models); IT, (Intention to Treat); LED, (Light Emitting Diode); LLLT, (Low Level Laser Therapy); LOS, (Length Of Stay); NPUAP, (National Pressure Ulcer Advisory Panel); PP, (Per Protocol); PU, (Pressure Ulcer); PUSH, (Pressure Ulcer Scale for Healing); RCT, (Randomized Controlled Trial); SoC, (Standard of Care); (VLUs), venous leg ulcers.

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times compared to the general population, and requiring prolonged ulcer treatment in long-term care facilities outside the hospital [8,9]. Prolongation of PU care results in \$15,400 per person each year [10], with an overall spending for the US healthcare system estimated at over \$26.8 billion annually. About 59 % of these costs are attributable to stages 3 and 4 PUs, which predominantly occupy clinician time and hospital resources [8,11].

Recently, blue light has raised interest for its potential as a wound healing treatment strategy [12]. The therapeutic effect of light on skin tissues is the result of a photophysical and photochemical process elicited by the direct interaction of light with endogenous photoacceptors. This therapeutic mechanism has been defined as photobiomodulation therapy [13].

In a recent study, 40 patients with venous leg ulcers (VLUs) were treated once a week with standard of care (SoC) or SoC and blue light. After 10 weeks, VLUs treated with blue light had a smaller residual wound area compared to those treated only with SoC and the mean wound area reduction was 66.7 % [14]. Pezzuto et al. [15] implemented blue light photobiomodulation on a total of 32 PUs which did not show signs of healing and had been present for more than 90 days. This approach restarted the healing process in 69 % of the treated lesions. These encouraging preliminary studies were from case series without control groups and established enrollment criteria, so, we designed a randomized controlled clinical trial (R.I.S.E._U.P. study) to assess the effectiveness of blue light photobiomodulation on the healing process of PUs developed by patients admitted to a rehabilitation hospital.

2. Materials and methods

2.1. Study design

The R.I.S.E._U.P. study was a monocentric prospective, parallel, open label, controlled, randomized clinical trial conducted at a rehabilitation hospital situated in Italy. The regional Ethics Committee for Clinical Research of the Area Vasta Centro (Florence, Italy) approved the trial protocol on June 29, 2021 (Ref. 188813_spe), which was registered at [Clinicaltrials.gov](https://clinicaltrials.gov) (Reference number: NCT05130814) before the enrollment of participants. In September 2021, a substantial amendment regarding enrollment criteria (change in Braden scale score at the enrollment time) was approved by Ethical Committee (Ref. CEAVC Em. 2021-418_18813_spe), before the first patient enrollment.

Participants were recruited by the medical staff participating in the study and, after signing the informed consent form, were randomly assigned to two groups (Treatment: EmoLED device, and Control: standard care protocol) based on the randomization grid generated by the trial sponsor with the online software available on the website “randomization.com”. The randomization procedure was stratified based on presence of stage 2 and stage 3 lesions and diabetic disease. It was a 1:1 randomization with 4 blocks of 10 patients distributed in the two groups (Treatment and Control). To eliminate bias, investigators were blinded to the randomization scheme and, upon contacting the Clinical Trial Office of the study center, they received an indication on the patient’s assigned group and the enrollment number.

2.2. Ethical considerations

This trial was conducted in Italy in accordance with the international standards of Good Clinical Practice and the ethical principles of the Declaration of Helsinki. All participants and relatives were informed about the RCT, both verbally and in written form, and provided their consent before the enrollment. A relative or legal tutor provided consent when participants were incapable of decision-making.

2.3. Participants and setting

Because of the absence of clinical trials with clear results combining



Fig. 1. The medical device EmoLED v.1 during the therapy delivery on a sacral lesion.

blue light treatments with the standard care of PUs, and the lack of reliability about any inference based on clinical studies associating this type of treatment with other types of skin lesions, the sample size was based on empirical considerations concerning the recruitment capacity and the percentage of patients with PUs entering the trial center. Therefore, it was determined to enroll 40 patients, 20 with stage 2 and 20 with stage 3 PUs, who were “evaluable” at the end of the observation, namely, those who attended regularly the temporal sequence of treatments as indicated in the study protocol. Patients who did not receive treatment with the EmoLED device and/or the standard dressings more than two times within the 4-week observation period were not considered “evaluable” for the analysis of the results. Enrolled subjects were hospitalized in the study center.

Eligible patients were screened using the following inclusion criteria: stage 2 and 3 pressure ulcers located on lower limbs/sacrum; lesion area $\geq 2 \text{ cm}^2$; ≥ 50 years old; length of stay (LOS) ≥ 30 days; Braden scale score ≥ 11 . Patients were excluded from the trial for any of the following reasons: recruitment in other clinical trials; history of self-harm; pregnant or breastfeeding; stage 3 PUs with undermining, tunneling or eschar; manifest systemic or superficial infection requiring systemic antibiotic therapy; intravenous therapy of corticosteroids ($>40 \text{ mg/day}$); neoplasia; cytostatic drugs therapy; skin photosensitivity; life expectancy of less than 30 days.

2.4. Intervention

Patients in both groups received SoC treatment three times a week for consecutive weeks, including wound cleansing, debridement as indicated, and dressing changes. During each dressing change, wounds were cleansed with saline or ringer’s lactate and covered with hyaluronic acid gauze plus polyurethane foam. In addition, zinc cream or hyaluronic acid sodium salt/metallic silver spray was applied to prevent or treat the skin maceration of the surrounding area.

The experimental group, in addition to the standard treatment, received treatment of the lesion with the medical device EmoLED v.1 three times a week, contextually with the dressing change, for 4 consecutive weeks. The treatment consists of irradiation with blue light for 60 s on the lesion area, after cleansing and before dressing.

2.5. Experimental device

The device EmoLED v.1 (Emoled srl, Florence, IT) is a phototherapy medical device (Fig. 1) for the treatment of skin lesions of subjects more than 16-year-old (CE marking n. G1 099242 0002 Rev.01). It is a class IIA non-invasive and non-contact portable device. EmoLED emits light in the blue range (between 410 and 430 nm, Optical Power Density 120 mW/cm²) and the treatment distance from the target is 40 ± 10 mm. A single application is performed over a circular area with a diameter of 50 mm. In the case of wounds larger than 50 mm, the subsequent applications of a treatment shall be repeated on adjacent areas until the whole wound is covered. The blue light emitted by the device interacts with the endogenous chromophores of the skin triggering reactions that lead to the activation of the cellular pathways required for tissue repair [16–18].

2.6. Variables

The primary endpoint is the comparison of the average difference of the lesion's PUSH score between the first and the last visit in the treatment versus control group. The secondary endpoints were the lesion area variation (average percentage of lesion area reduction) and the level of safety of EmoLED treatment (adverse events related to the device or study procedure).

Demographic and clinical variables were collected at baseline. The recorded demographic characteristics were age (years) and gender. The clinical variables were time since ulcer onset, location and ulcer grade according to the NPUAP/EPUAP [19], presence of infection in the site, pressure ulcer risk according to the Braden scale, diabetes and other comorbidities. Baseline characteristics were used as covariates in the statistical analysis to evaluate their influence on the results of the study.

Before enrollment began, nurses involved in the trial were trained on the study protocol and wound assessment by PUSH scale. The group of nurses was coordinated by a wound care specialist nurse.

Patients were evaluated by nurses three times a week for up to 4 weeks by recording data on digital CRF. At baseline and each week, lesions were recorded by photographs.

Since pressure ulcers do not usually close completely within 4 weeks [20], complete wound closure assessment was deemed unlikely, so, at each visit, the ulcer healing progress was measured with the Pressure Ulcer Scale for Healing (PUSH) [21] that evaluates ulcers by considering three parameters: lesions dimensions, exudate amount and tissue type on bed wound.

Another healing-related variable was the wound area, measured by the image analysis of the photographs. Possible adverse events were recorded at each visit.

2.7. Statistical analysis

Both Per Protocol (PP) and Intention-to-Treat (IT) analysis were conducted. The last available score was employed when data were missing due to dropouts. Demographic and clinical data were described by frequencies and percentages for categorical variables, and means and standard deviations, medians and interquartile ranges for continuous variables.

At a first analysis, a qualitative comparison was carried out between the treatment groups (improvement or no improvement), both general and differentiated for 2 and 3 stage lesions through the χ^2 test or Fisher's exact test for counts of less than 5. A quantitative comparative statistic between the treatment groups was then performed by comparing the outcome variables (percentage reduction of the lesion area and reduction of the PUSH index) through the non-parametric test of Mann-Whitney. To analyze time-related differences between groups, Friedman's non-parametric test for the outcome variables was performed. The same statistical methods were used to analyze the data in different subgroups according to the diabetes presence or the lesion stage.

Table 1

Descriptive table of the sample at baseline.

Variables	Group		p-value
	Control n = 24	Treated n = 24	
Age (median (range))	75.50 (50.00, 91.00)	75.00 (55.00, 89.00)	0.910
Sex (%)	F	7 (29.2)	8 (33.3)
	M	17 (70.8)	16 (66.7)
Braden (median (range))	13.00 (11.00, 19.00)	14.00 (12.00, 17.00)	0.609
Initial PUSH score (median (range))	9.50 (6.00, 14.00)	10.00 (6.00, 15.00)	0.155
Lesion stage (%)	Second	12 (50.0)	13 (54.2)
	Third	12 (50.0)	11 (45.8)
Lesion position (%)	Left malleolus	1 (4.2)	0 (0.0)
	Left trochanter	1 (4.2)	3 (12.5)
	Right gluteus	0 (0.0)	1 (4.2)
	Right heel	1 (4.2)	0 (0.0)
	Right ischiatic spin	1 (4.2)	0 (0.0)
	Right ischium	0 (0.0)	1 (4.2)
	Right outer tibia	0 (0.0)	1 (4.2)
	Right trochanter	1 (4.2)	0 (0.0)
	Sacrum	18 (75.0)	18 (75.0)
	V metatarsus right	1 (4.2)	0 (0.0)

Generalized linear models (GLM) were used to investigate whether the differences between the two groups are influenced in a confounding way by demographic and clinical covariates, pre-treatment measurement, and to measure their impact, allowing us to understand which variables affect the outcome and to analyze the differences between groups being equal for these covariates.

In this study, the high variability observed in PUSH scale levels led to prefer a longitudinal clustering technique (Latent Profile Analysis - LPA) over a linear model. LPA is a statistical technique used in Latent Profile Analysis within mixture modelling because it identifies unobserved (latent) subgroups within a population based on continuous observed variables. The number of clusters was determined using goodness-of-fit indices, such as the Akaike Information Criterion (AIC), and entropy. The probability of an individual belonging to a specific cluster, given the variables of interest, was modeled using generalized linear models, such as logistic regression.

3. Results

3.1. Patients' characteristics

The study center recruited the participants from December 2021 to February 2024. A total number of 48 patients were screened, enrolled in the trial and randomized in 4 blocks (diabetic/not diabetic; stage 2/stage 3). Among the 48 patients included in the study, 40 patients were considered "evaluable". Eight patients were withdrawn from the study because five dropped out for reasons other than ulcer treatment (one cardiac arrest; two transfers to other wards; two premature resignation) and three did not respect inclusion criteria. The baseline demographics and characteristics of the patients and the lesions are showed in Table 1.

3.2. Pressure ulcer healing

The IT analysis shows that the mean PUSH reduction in the control group was 2.29 (25.96 %), from 9.54 to 7.25, and the mean PUSH reduction in the treated group was 3.29 (34.33 %), from 10.02 to 6.73 (Mann-Whitney $p = 0.221$).

Similarly, the PP analysis shows that the mean PUSH reduction in the

Table 2

PUSH reduction between groups.

	Group	N	Mean	Median	p
PUSH reduction (IT analysis)	Control	24	2.29	1.50	0.221
	Treated	24	3.29	3.00	
PUSH reduction (PP analysis)	Control	20	2.10	1.50	0.103
	Treated	20	3.70	3.50	

Abbreviations: N: number of patients.

control group was 2.10 (23.10 %), from 9.43 to 7.33, and the mean PUSH reduction in the treated group was 3.70 (39.10 %), from 9.85 to 6.15 (Mann-Whitney $p = 0.103$) (Table 2).

In both types of analysis, the treated group demonstrated a greater reduction on the PUSH scale score, although not significant, equivalent to an improved wound healing trend (Fig. 2).

To analyze whether the absolute reduction in the PUSH scale was influenced by confounding demographic and clinical variables, a linear regression model was constructed on the PP sample but failed to generate any significant results, with the exception of the stage 2 lesions that are significantly associated with a greater reduction on the PUSH scale. An interesting $p = 0.115$ in the Treated-Control association emerged from the model, although once again a higher effect was observed in the Treated group.

In both randomization groups, four patients achieved complete healing, all with an initial PUSH scale score ≥ 10 . Since not all the 40 patients who completed the study protocol had a reduction of the PUSH scale score, the responding patients (or “Responders”, having an improvement >0 on the PUSH scale) in the two allocation groups were analyzed (18 Treated patients and 12 Control patients). The distributions of respondents between the two treatment groups on the PP sample were compared using Fisher’s exact test achieving a $p = 0.065$ (Fig. 3).

To minimize the influence of confounding variables on the probability of belonging to Responders in the two treatment groups, a logistic regression model was constructed. This model showed that the probability of belonging to Responders is higher in the treated group (97.2 % vs 56.1 %), and this value is statistically significant ($p = 0.018$) (Fig. 4) (see Fig. 5).

To better analyze the phenomenon of the time course of the PUSH scale in the 4 weeks period of observation, a latent profile analysis was carried out on the PP sample. This analysis identifies two trajectory classes based on treatment response (Fig. 4), one formed by highly responding subjects (class 1) and one formed by poorly responding subjects (class 2).

Subsequently the probability of belonging to one of the two trajectory classes in the presence of confounders was analyzed with a binomial logistic regression analysis. The analysis also shows the statistically significant association ($p = 0.036$) in the probability of following type 1 trajectory (responsive) if the subject belongs to the treated group (30 %)

instead of the control group (2 %) (Fig. 6A). Unsurprisingly, having a stage 2 PU ($p = 0.013$) (Fig. 6B) or a lower starting PUSH level ($p = 0.011$) (Fig. 6C) leads to a higher probability of having a type 1 trajectory (responsive); as shown in the figure, belonging to the treated group increases this probability of association with the better trajectory.

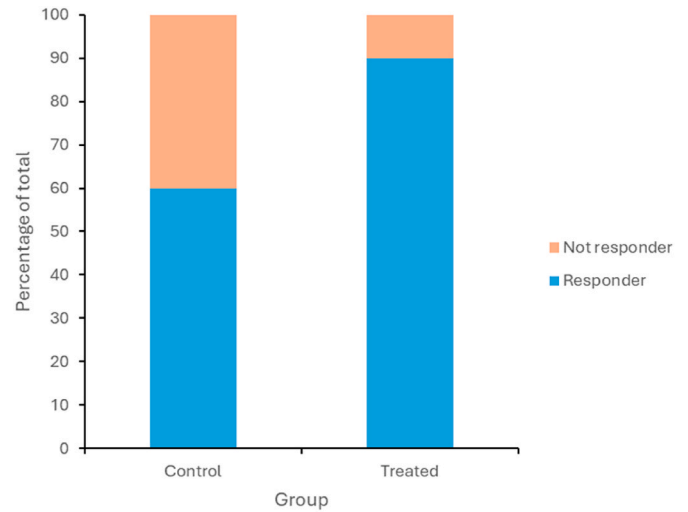


Fig. 3. Percentages of “Responder” between groups ($p = 0.065$).

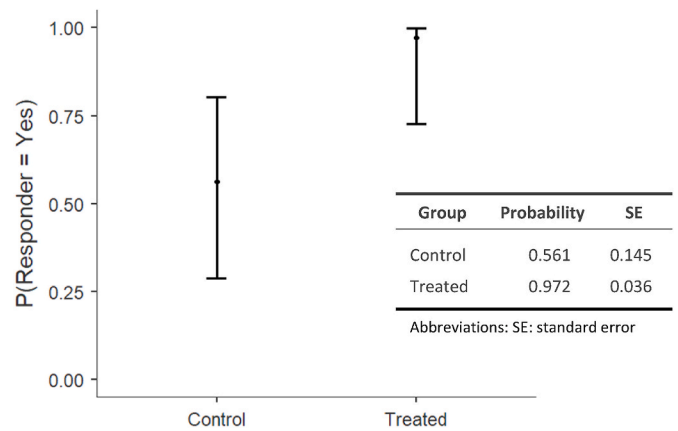


Fig. 4. Probability of belonging to the “Responders” category between groups ($p = 0.018$).

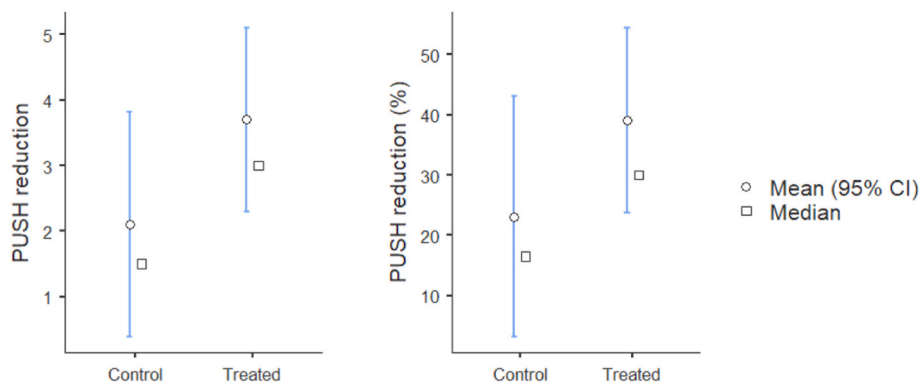


Fig. 2. Mean and median of PUSH reduction between the two groups (PP analysis).

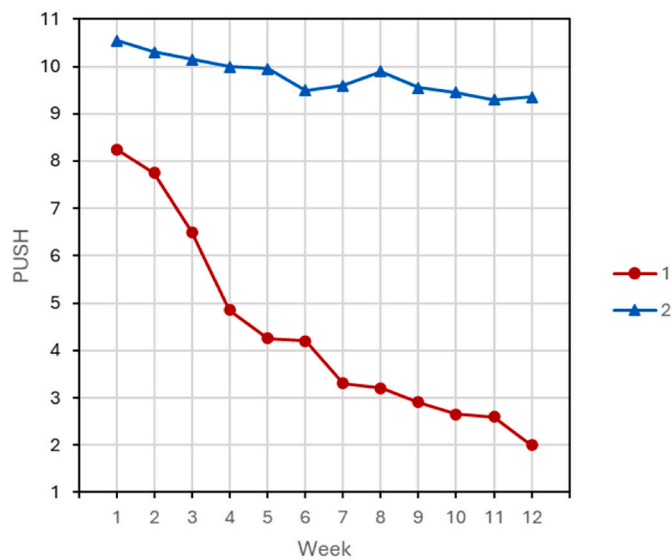


Fig. 5. Latent profile analysis. Line plot of two trajectories of the highly responding patients (class 1, red line) and poorly responding patients (class 2, blue line).

3.3. Wound area reduction

The image analysis of the lesions photographs was performed on 28 patients (15 treated and 13 control) whose initial and final photographs were available. The mean area reduction of the control group was 29.83 %, while the mean area reduction of the treated group was 52.46 % showing a greater trend to reduce the wound area in the treated group compared to the control group. To compare the percentage reduction of the wound area, the Mann-Whitney test was performed; due to the small

number of available photographs, the statistical analysis did not yield significant results.

3.4. Adverse events

An adverse event (cardiac arrest) was reported in a patient during the study period, but it was considered unrelated to the EmoLED treatment or any other study procedure. The patient discontinued the study due to this adverse event.

4. Discussion

Blue light treatment has recently collected evidence in wound healing. Due to the safety of blue light photobiomodulation [22], specialized healthcare personnel have used this therapy to treat wounds of various etiologies, particularly of vascular or diabetic origin [23–26], giving patients greater chance to achieve healing. Blue light therapy proved to be effective not only in accelerating but also in unlocking the re-epithelialization process of wounds that often does not progress despite the application of a proper standard of care [27–29]. Recent studies have shown that blue light therapy can increase the healing speed of chronic wounds of venous origin and increase the healing probability within 10 weeks [14], as well as improve the re-epithelialization trend in Systemic Sclerosis Skin Ulcers [30].

The efficacy of phototherapy, especially Low Level Laser Therapy (LLLT), in the treatment of PUs has been evaluated in the last 20 years by clinical studies with variable samples and different results [31–34]. To the best of our knowledge, this study is the first one evaluating photobiomodulation with LED blue light in PUs and one of the few that used LED therapies [34–36] in this type of lesions that require a multidisciplinary approach and often do not respond to therapies.

This prospective, randomized controlled clinical trial showed that the efficacy of the EmoLED v.1 device was confirmed in promoting

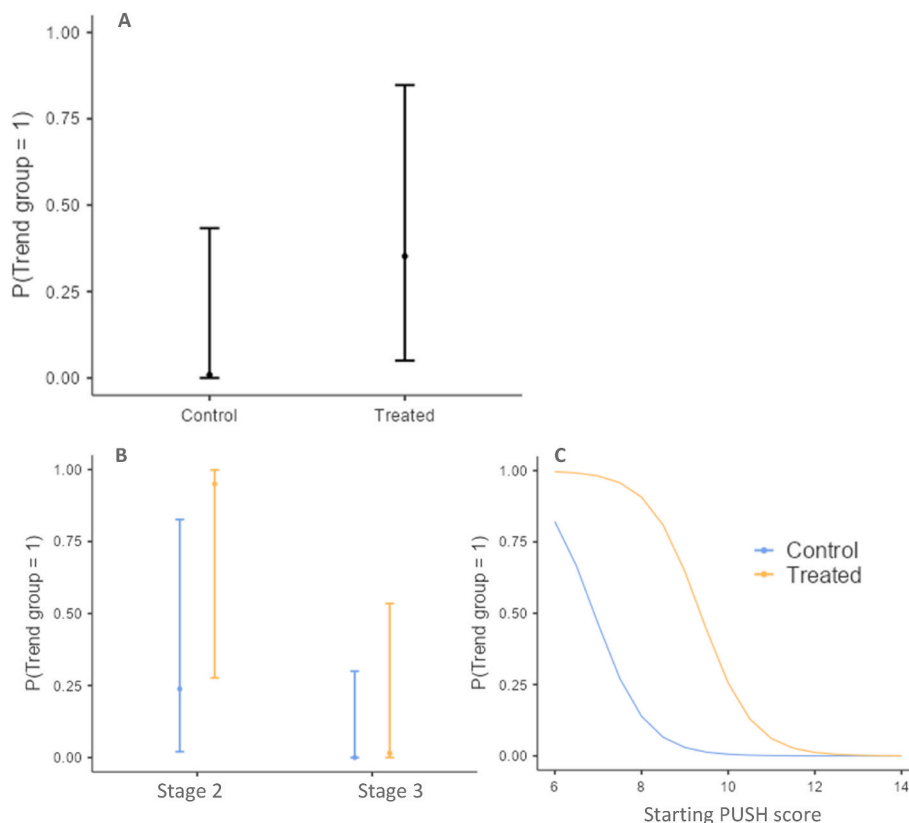


Fig. 6. Probability of belonging to the responsive trajectory according to group (A), lesion stage between group (B), and starting PUSH score between group (C).

healing of second and third stage pressure ulcers, as patients treated with blue light were significantly more likely to be in the group of subjects who experienced wound improvement, according to the PUSH scale, than patients treated only with standard therapy (97.2 % vs 56.1 %), over the 4-week observation period. Thus, the result shows that the medical device EmoLED v.1 is effective in promoting recovery and advancement of tissue repair towards complete wound healing in pressure ulcers. The presence of more responding patients in the treated group shows that blue light treatment appears to be effective in stabilizing wounds that would otherwise worsen despite standard of care treatment.

The above is also confirmed by the other performed analyses, which produced results supporting the positive trend. In fact, the reduction of the PUSH scale showed a better trend in the group of treated patients even after analyzing the data with a linear regression to avoid confounding variables. The mean reduction of the PUSH scale in the patients in the treatment group was 76 % greater than in the control group with a median of the treatment group twice that of the control group. The recovery and improvement of the treated group, which accelerated tissue healing, also supported the rehabilitation pathway of these patients.

In addition to these results, a trajectory analysis defined two classes of patients, those responding poorly to treatment and those responding well. Confirming the action of blue light on the progression of PUs healing, the group that performed the EmoLED device treatment was found to be associated with the trajectory of patients who have a better PUSH score trend thus being more likely to achieve complete healing.

The limitations of this study were the restricted sample and the involvement of a single center, that may have contributed to the failure to achieve statistical significance, the short observation time (4 weeks) for the type of lesion, usually healing in a longer time, which was imposed by the standard LOS of the study center. Another trial limitation was the lack of wound age which is important to determine the chronicity of the lesion; this deficiency results from the inability to know the past data of the ulcer prior to the patient arrival at the rehabilitation center. To mitigate this limitation, blue light photobiomodulation has been shown in previous studies to reactivate healing of lesions with high chronicity [14,24,29].

5. Conclusion

The results of this study suggest that, within a rehabilitation setting, treatment with blue light of chronic pressure ulcers three times per week can effectively promote improvement of the pressure lesion toward healing. This easy-to-administer therapy may be a valuable contribution to the daily management of these lesions. The EmoLED device has an excellent safety profile and the addition of this therapy to a treatment program may speed healing, improving the quality of life of patients, and supporting the rehabilitation pathway assigned.

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Declaration of competing 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jtv.2025.100895>.

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