Effects of yoga practice on physiological distress, fatigue and QOL in patients affected by breast cancer undergoing adjuvant radiotherapy

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A R T I C L E   I N F O

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A B S T R A C T

Background and purpose: In this study we want to evaluate the efficacy of yoga practice on dysfunctional stress, inflammation and QOL in breast cancer patients undergoing adjuvant radiotherapy.

Patients and methods: Patients with stage 0 to III breast cancer were recruited before starting radiotherapy (XRT) and were randomly assigned to yoga group (YG) two times a week during XRT or control group (CG). Self-report measures of QOL, fatigue and sleep quality, and blood samples were collected at day 1 of treatment, day 15, end of treatment and 1, 3 and 6 months later. Cortisol blood level, IL6, IL10, IL1RA, TNFα and lymphocyte-to-monocyte ratio were analyzed as measures of dysfunctional stress and inflammation.

Results: Patients started XRT and yoga classes in October 2019. Due to COVID-19 pandemic we closed the enrollment in March 2020. We analysed 24 patients, 12 YG and 12 CG. The analysis of blood cortisol levels revealed an interaction (p = 0.04) between yoga practice and time, in particular YG had lower cortisol levels at the end of XRT respect to CG (p adj = 0.02). The analysis of IL-1RA revealed an interaction effect (p = 0.04) suggesting differences between groups at some time points that post-hoc tests were not able to detect.

Conclusions: To our knowledge, this is the first study to evaluate the effects of yoga in a cancer population studying inflammation markers, cortisol trend and QOL during and until 6 months after XRT. This study suggests that yoga practice is able to reduce stress and inflammation levels over time. Besides including a larger number of patients to increase the power, future studies should consider other inflammatory or pro inflammatory factors and long-term yoga program to gain more evidence on yoga practice benefits.

Introduction

Radiotherapy (XRT) is often the final step in the multimodal treatment regimen for women with breast cancer [1]. Pain, skin changes, sleep disturbances, fatigue are the most frequent treatment-related adverse effects: they negatively affect physical, psychological, social and spiritual aspects of quality of life (QOL) [2–5]. Radiotherapy can also induce local or systemic increase in inflammation: it may result in cancer cell death through necrosis, which is a proinflammatory form of cell death. There is also growing evidence that links inflammation and fatigue both during and after cancer treatment, hypothesizing that limited physical activity of survivors as a further cause of the persistent fatigue together with the over-activation of the inflammatory network [6]. In addition, several studies have revealed that both elevated cortisol levels and a less steep diurnal cortisol production curve are associated with worse survival in women with breast cancer [1–3].

Research on yoga in patients with cancer has increased considerably in the last decade, and a variety of yoga programs studied in cancer have reported improvements in stress and QOL [7], fatigue and emotional health [8,9], pain and vitality [10]. Previous studies reported that regular exercise reduces fatigue as well as inflammation [11–14] and in particular, studies with cancer survivors suggest that yoga practice lowers fatigue and improves mood and sleep quality [15–17]. In addition, yoga may provide graded exercises that can be tailored for cancer patient conditions [15]. Chandwani et al. [1] demonstrated that yoga, associated with XRT, improves QOL, physiological changes and results

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in a steeper cortisol slope behind the benefits of an active stretching or control group.

In this study, with the introduction of a control group, we want to examine as primary goal the impact of yoga on dysfunctional stress and inflammation through the analysis of cortisol production [18], plasma levels of inflammation-related cytokines such as IL-6, IL-10, TNF-α, IL-1RA [19–21] and lymphocytes-to-monocytes ratio (LMR), a peripheral blood marker of systemic inflammation investigated by several groups for its predictive and prognostic role in several malignancies.

Notably, there is relatively limited information about inflammatory dynamics, which may reveal the patient’s actual inflammatory status during treatment more precisely than baseline evaluation. In particular, to our knowledge, very few studies have reported the association of the post-treatment LMR values and tumor response to chemo-radiotherapy [22,23].

The secondary aim of this study is to assess the efficacy of yoga practice in the improvement of QOL, physiological distress and fatigue, in order to validate the benefits of yoga as an adjuvant to XRT in patients with breast cancer.

Patients and methods

Patients

Women with stage 0-III breast cancer were recruited before XRT. Inclusion criteria were ≥ 18 years old and scheduled to undergo daily adjuvant XRT for 5 weeks at IRST’s Radiotherapy Unit. Patients with documented diagnosis of mental disorders (e.g., Schizophrenia), stage IV disease, patients with active or untreated DVT, patients with mobility problems (e.g., unable to get up from the chair), patients who have practiced yoga or are practicing yoga in the 6 months before the cancer diagnosis and patients diagnosed with just upper extremity lymphedema in association with prior breast surgery were excluded.

Ethical approval

All procedures performed in this study were in accordance with the ethical standard of the Area Vasta Romagna Ethics Committee, with the 1964 Helsinki declaration and its later amendments and with Good Clinical Practice (GCP) guidelines. Informed consent was obtained from all individual participants included in the study. No identifiable images were included in the manuscript, therefore consent for publication is not applicable. The study was registered on ClinicalTrials.gov, number NCT04775290.

Randomization and schedule

This is a randomized, non-pharmacological, interventional, prospective study. Any decision about drug administration is made by the physician based on his/her clinical judgement in the context of clinical practice, and separate from the decision to include the patient in this study. After giving written informed consent, patients were randomly assigned to one of two groups: YG (yoga group) and CG (control group). Patients randomized to the experimental arm attended a yoga class for 5 weeks from the beginning of XRT. Patients were assigned to the yoga or control arms with a random block design having a maximum block size of 10 patients. Participants in the CG received usual care and completed all the assessments following the same timeline as the active group. All participants were asked to refrain from participating in any other yoga classes while in the study.

Intervention programs

Participants in the YG attended up to two 75-minute-classes two times a week during their 5 weeks of XRT. Classes were held near the radiation treatment unit (radiotherapy unit) in a large conference-style room dedicated to meetings and congresses. The yoga program included the following: (1) preparatory warm-up synchronized with breathing; (2) breath control exercises (pranayama); (3) selected postures or asana (forward-, backward- and side-bending asanas in sitting and standing position); (4) final deep relaxation; (5) meditation. The program was taught by a Hatha Yoga trained teacher. Blood samples, QOL, sleep disturbance and fatigue questionnaires, were assessed on day 1, day 15 and on the last day of XRT, then 1, 3 and 6 months after the end of XRT. Blood samples were assessed early in the morning on empty stomach before the daily XRT. QOL (SF-36, QLQ-C30 and PSQI) and BFI were given to patients, and they filled in the questionnaires at the radiotherapy waiting area in the institute.

Immunologic assays

Four whole blood tubes per patient were obtained. One BD Vacutainer® SSD II Advance (5 mL, BD) was sent to the Hub Laboratory of the AUSL della Romagna (local health authority) for the assessment of cortisol concentration. All the other samples were processed and stored at -80 °C until assayed.

Serum cytokine analysis

Patient serum concentrations of IL-6, IL-10, IL-1RA, and TNF-α were determined using specific high sensitivity ELISA kits according to the manufacturer’s instructions (Catalog # BMS213HS, # BMS215-2, # BMS2080, # BMS223HS, Thermo Fisher Scientific). The concentration of target proteins was calculated by interpolating the calculated standard curve with GraphPad Prism (5-parameter logistic curve) (GraphPad, San Diego, CA).

Measures

General QOL was assessed by the Medical Outcomes Study 36-item short-form survey (SF-36) and by the EORTC Core Quality of Life QLQ-C30 questionnaire. The SF-36 measures eight scales: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The eight scales are used to assess an overall physical component scale (PCS) and a mental component scale (MCS) [24]. The PCS and MCS were the analyzed outcomes of SF-36. Normed-based scoring is presented with a population mean = 50 and standard deviation = 10. The QLQ-C30 assesses both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status, six single items and a summary score obtained as the mean of all the items except the global health status and the financial difficulties. The scales used as primary outcomes for QLQ-C30 were emotional functioning (EF) and the summary health score (QLQ) [25]. Missing items are completed with the mean value of available items in the same scale. Higher scores of all the outcomes selected reflect better QOL. Fatigue was assessed using the Brief Fatigue Inventory (BFI) [26], a questionnaire that evaluates the severity and the impact of fatigue on daily functioning. A global fatigue score was obtained by averaging all the items on the BFI. Lower scores reflect less fatigue. Sleep disturbances were assessed by means of the Pittsburgh Sleep Quality Index (PSQI) [27], a self-rated questionnaire which assesses sleep quality and disturbances over a 1 month time interval. The total score was used as the endpoint. Lower scores reflected fewer sleep disturbances.
Data analyses

The aim of the study was to evaluate the effect of Yoga practice during RT on blood cortisol, proinflammatory cytokines levels (IL-6, IL-10, IL-1Ra, TNF-α), LMR and on QOL and physiological distress, measured by self-reported measures (PCS, MCS, EF, QLQ, BFI, PSQI). No formal sample size was proposed for the study due to its exploratory nature. A total of 120 (60 per arm) patients were planned to be enrolled, however the study stop early due to Covid-19 pandemic. Only 12 patients randomized to YG completed the program, therefore to maintain the original 1:1 randomization and to prevent pandemic influence on the analysis we selected the first 12 patients enrolled in the control group as CG. This small sample size reduced the power of the study, nonetheless we tried to detect at least large effects.

We employed nonparametric rank-based methods for longitudinal data due to the small sample size. The main effects of time and practice and their interaction were assessed by nonparametric ANOVA-type statistics provided in the nparLD [28] package for R (version 4.0.0). In the presence of significant interaction effects, the simple main effect of time was evaluated by nonparametric ANOVA-type statistics in each practice group (YG, CG), while the simple main effect of practice was evaluated by Wilcoxon rank-sum test at each level of time. In the case of a significant simple main effect of time, multiple pairwise comparisons between time points were performed. In the presence of a significant main effect of time without interaction, multiple pairwise comparisons between time points were performed ignoring the practice factor.

The p-values < 0.05 were considered statistically significant and for multiple comparisons we adopted Benjamini-Hochberg (BH) adjustment.

All the analysis was carried out using R software (version 4.0.0).

Results

One hundred twenty patients undergoing adjuvant radiotherapy had to be enrolled in this study. We started enrollment in September 2019. Patients started XRT and yoga classes in October 2019. Due to the COVID-19 pandemic and the DPCM of the 8th of March 2020 we closed the enrollment at that time. We managed to enrol 52 patients, of which

Fig. 1. Diagram of study participants over study period.
12 in the YG and 22 in the CG had finished XRT by the 6th of March 2020. Twelve patients were randomly selected from CG in order to maintain the planned 1:1 analysis, Fig. 1. Baseline characteristics of patients are summarized in Table 1. Medians and IQRs of self-reported measures are presented in Table 2.

The observations with missing data are just a random subset of all observations, so there were no systematic differences between the missing and observed values.

**Cortisol**

The analysis of cortisol revealed a significant interaction ($p = 0.04$) between practice and time on cortisol level, Fig. 2A. In particular the YG had a lower cortisol level with respect to the CG at the end of XRT ($p_{adj} = 0.02$). Since some patients were treated with hormonal therapies that may influence cortisol level, we analysed the interaction of practice $\times$ time with hormonal therapy factor. The effect of practice $\times$ time remained significant ($p = 0.01$) without any significant interaction of the three factors. This result suggested that the interaction effect of practice $\times$ time did not depend on hormonal therapies.

The time effect on cortisol was significant ($p = 0.003$) only in the YG. In particular, cortisol levels were significantly lower the last day of XRT compared to the first day ($p_{adj} = 0.02$), at 15 days of XRT and the last day of XRT compared to 1-month follow up ($p_{adj} = 0.008$), at 15 days of XRT compared to 6 months post XRT ($p_{adj} = 0.03$) and at 3 months post XRT compared to 1 month post XRT ($p_{adj} = 0.04$), Fig. 2B.

**Proinflammatory cytokines**

TNF-$\alpha$ was never expressed. TNF-$\alpha$ is a proinflammatory cytokine with an important role in the pathogenesis of several diseases. Currently, this molecule is thought to be involved in the regulation of many important cellular processes such as proliferation, differentiation, growth, and the immune response [29]. TNF-$\alpha$ is produced by various types of cells including macrophages, monocytes, neutrophils, T cells, and NK-cells. Our data indicate that TNF-$\alpha$ is present in negligible concentrations in the serum of patients. This could be due to either the absence of disease (all patients were underwent to surgical removal of breast tumor) and the lack of stimulation by the XRT either alone or in association with yoga of the immune response as demonstrated by the lowering of the LMR.

There was no evidence of effects of yoga practice, time or their interaction on IL-6 and IL-10, Fig. 3A and B. The analysis of IL-1Ra

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**Table 1**

<table>
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<th>Patient clinical characteristics</th>
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<th>Control</th>
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**Table 2**

| Raw medians (med) and interquartile ranges (IQR) of self-report measures at each assessment. |
|----------------------------------|------|---------|
| First day of XRT | 15 days of XRT | Last day of XRT | 1 month post XRT | 3 months post XRT | 6 months post XRT |
| **YG** | | | | | | |
| **CG** | | | | | | |
| PCS | med | IQR | med | IQR | med | IQR | med | IQR | med | IQR | med | IQR | med | IQR | med | IQR |
| 44.5 | 4.5 | 39.8 | 14.3 | 39.4 | 13.3 | 89.4 | 13.3 | 89.9 | 10.7 | 88.1 | 12.2 | 91.4 | 12.1 | 90.4 | 10.1 | 91.7 | 12.5 |
| 40.4 | 8.5 | 33.8 | 7.9 | 41.8 | 8.2 | 87.5 | 8.7 | 87.5 | 8.9 | 89.9 | 8.9 | 91.4 | 8.9 | 90.4 | 8.9 | 92.5 | 8.9 |
| 39.1 | 2.3 | 38.1 | 2.6 | 38.1 | 2.6 | 38.1 | 2.6 | 38.1 | 2.6 | 38.1 | 2.6 | 38.1 | 2.6 | 38.1 | 2.6 | 38.1 | 2.6 |
| 4.0 | 1.3 | 4.0 | 1.3 | 4.0 | 1.3 | 4.0 | 1.3 | 4.0 | 1.3 | 4.0 | 1.3 | 4.0 | 1.3 | 4.0 | 1.3 | 4.0 | 1.3 |
| 4.0 | 1.3 | 4.0 | 1.3 | 4.0 | 1.3 | 4.0 | 1.3 | 4.0 | 1.3 | 4.0 | 1.3 | 4.0 | 1.3 | 4.0 | 1.3 | 4.0 | 1.3 |

XRT, radiotherapy; YG, yoga group; CG, control group; PCS-36, SF-36 Physical Component Scale; MS-36, Mental Component Scale; SF-36, SF-36 Physical Component Scale; SF-36, SF-36 Mental Component Scale; M, MS-36 Physical Component Scale; MS-36 Mental Component Scale; SF-36, SF-36 Physical Component Scale; SF-36, SF-36 Mental Component Scale; EF, QLQ-C30 Emotional Functioning Scale; QQ, QLQ-C30 Summary Health Score; BFI, Brief Fatigue Inventory; PSQI, Pittsburgh Sleep Quality Index.

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[29] Micheletti et al.
revealed an interaction effect ($p = 0.04$), but the Wilcoxon test did not show practice effect at any assessment time. The effect of time on the IL-1Ra level was significant in both YG and CG ($p < 0.001$, $p = 0.008$). In particular, in the YG IL-1Ra was lower at day one of XRT, at 15 days of XRT, the last day of XRT and at 1-month follow up with respect to 3-months follow up ($p_{adj} < 0.001$, $p_{adj} < 0.001$, $p_{adj} < 0.001$, $p_{adj} = 0.003$), and at the last day of XRT compared to 6-months follow up ($p_{adj} = 0.001$) and higher values at 3 and 6 months post XRT compared to 1-month post XRT ($p_{adj} = 0.006$, $p_{adj} < 0.001$), Fig. 3C. In CG, instead, the values of IL-1Ra were lower at the first day of XRT, last day of XRT, 1-month follow up and 3-months follow up compared to 6-months follow up ($p_{adj} = 0.02$, $p_{adj} < 0.001$, $p_{adj} < 0.001$, $p_{adj} < 0.001$), Fig. 3D.

There was no evidence of practice $\times$ time interaction on LMR, while the main effect of time was significant ($p < 0.001$). In particular, LMR was lower at 15 days of RT, at the last day of XRT and at 1 month post XRT with respect to the first day of XRT ($p_{adj} < 0.001$, $p_{adj} < 0.001$, $p_{adj} = 0.002$). Lower values were found also at 15 days of XRT compared to 3 and 6 months post XRT ($p_{adj} = 0.009$, $p_{adj} < 0.001$) and at the last day of XRT compared to 15 days of XRT ($p_{adj} = 0.002$). From the last day of XRT the LMR had increased with higher values at 3 months post XRT and 6 months post XRT compared to the last day of XRT ($p_{adj} < 0.001$, $p_{adj} < 0.001$) and higher values at 3 and 6 months post XRT compared to 1 month post XRT ($p_{adj} = 0.006$, $p_{adj} < 0.001$), Fig. 4. No other effect reached significance.

There was no evidence of significant effects of yoga practice, time or interaction on PCS, MCS, BFI and PSQI. No main effect or interaction effect was shown for QLQ, while a significant main effect of time ($p = 0.03$) was revealed for EF. Multiple comparisons showed a significant increase of EF between the first day of XRT and 15 days of XRT ($p_{adj} = 0.04$), Table 2.

**Complete blood count**

There was no evidence of practice $\times$ time interaction on LMR, while the main effect of time was significant ($p < 0.001$). In particular, LMR was lower at 15 days of RT, at the last day of XRT and at 1 month post XRT with respect to the first day of XRT ($p_{adj} < 0.001$, $p_{adj} < 0.001$, $p_{adj} = 0.002$). Lower values were found also at 15 days of XRT compared to 3 and 6 months post XRT ($p_{adj} = 0.009$, $p_{adj} < 0.001$) and at the last day of XRT compared to 15 days of XRT ($p_{adj} = 0.002$). From the last day of XRT the LMR had increased with higher values at 3 months post XRT and 6 months post XRT compared to the last day of XRT ($p_{adj} < 0.001$, $p_{adj} < 0.001$) and higher values at 3 and 6 months post XRT compared to 1 month post XRT ($p_{adj} = 0.006$, $p_{adj} < 0.001$), Fig. 4. No other effect reached significance.

**Self-reported measures**

There was no evidence of significant effects of yoga practice, time or interaction on PCS, MCS, BFI and PSQI. No main effect or interaction effect was shown for QLQ, while a significant main effect of time ($p = 0.03$) was revealed for EF. Multiple comparisons showed a significant increase of EF between the first day of XRT and 15 days of XRT ($p_{adj} = 0.04$), Table 2.
Discussion

To our knowledge, this is the first study to compare the effects of YG against a control group in a cancer population studying inflammation markers, blood cortisol trend and QOL during and up until 6 months after XRT.

The enrollment in this study did not imply an alteration of standard breast cancer medical or radiotherapy therapies.

Although the study was closed well in advance due to Covid19, it generated great interest and participation in patients affected by breast cancer who had to undergo adjuvant radiotherapy. We had enrolled 52 patients by the 6th March but only 33 patients were able to complete XRT and yoga classes. To keep the original 1:1 randomization and prevent pandemic influence, we analysed the 12 patients in YG and the first 12 enrolled in CG.

The current study examined an objective measure of stress by assessing the blood cortisol levels. There was evidence that the YG had lower levels of cortisol compared with the CG at the end of XRT, with a trend in the YG of lower cortisol values during XRT and yoga practice with respect to the period post XRT. These findings suggest that yoga has a positive effect on the stress hormone cortisol. The present findings are consistent with Chandwani et al [11] Study in which salivary cortisol daily slope was examined. Participants in the YG had, in fact, a significantly steeper cortisol slope than the other groups at the end of XRT.

To date, the therapeutic effect of XRT has been considered to be mainly local and to occur via the direct or indirect DNA damage of irradiated cancer cells. However, accumulating preclinical and clinical evidence now indicates that XRT has systemic antitumor effects that are exerted through changes in the immune environment. This result is of particular relevance since there is evidence that widespread inflammation promotes invasiveness and concomitantly also inhibits anti-tumor immune responses [30]. To support the assumption that yoga practice exerted an anti-inflammatory effect on our cancer patients, we investigated the circulating level of cytokines. Despite the low number of patients recruited, our study highlighted a significant interaction between yoga practice and time on circulating levels of the IL-1 receptor antagonist (IL-1Ra). IL-1Ra is a physiological inhibitor of IL-1 that binds to its receptor without the transmission of activation signals and thus serves as a decoy target. IL-1 is one of most abundant and inflammatory cytokines in the tumor microenvironment, which is produced by the tumor cells, stromal cellular elements or infiltrating leukocytes. It is involved in all phases of the malignant process, such as tumorigenesis, tumor invasiveness and progression, as well as in activation/suppression of anti-tumor immunity [30-35]. Different FDA-approved agents that neutralize IL-1, including the same IL-1Ra and specific antibodies, exist on the market and have been widely and successfully used in patients with Rheumatoid arthritis, autoinflammatory diseases and various other diseases that have an inflammatory component. Currently, regarding cancer disease, there is only preclinical evidence that the use of anti-IL-1 agents combined with conventional therapies could exert antitumor effects [36]. In the present work, for the first time to our knowledge, we reported the suppressive effect of yoga practice on circulating levels of IL-1Ra. In particular, our data showed that in the YG the IL-1Ra levels were lower during XRT up to 1 month post XRT respect to 3 months post XRT, while in CG IL-1Ra levels were lower from the end of XRT up to 3 months post XRT respect to 6 months post XRT. These findings suggest that yoga practice may anticipate the beneficial effect of XRT and may reduce the secondary effects of XRT inflammation.

Lastly, our study also evaluated the dynamic changes of the lymphocyte–monocyte ratio (LMR), a blood marker of systemic inflammation. Currently, there is still great uncertainty on prognostic value of LMR as highlighted in recent studies conducted in breast cancer patients treated with neoadjuvant chemotherapy [37–39]. Furthermore, to our knowledge, there are no studies reporting data on the modulation of LMR during combined chemotherapy and radiation therapy in breast cancer patients and its correlation with the patient’s inflammatory status during or after treatment. In this work, we observed a decrease in LMR respect to baseline values in breast cancer patients after radiotherapy. Moreover, we reported that this reduction of LMR exerted by XRT could probably be amplified by yoga practice, but the reduced patient enrolment due to Covid-19 pandemic allows us only to hypothesize it. This effect of YG, if confirmed, could have important implications for the prevention of the side effects of radiotherapy. Literature data strongly suggest taking into account the immune repertoire of the breast cancer patients such as the modulation of lymphocyte recruitment or proliferation before and after XRT, for the prevention of adverse late effects of XRT to normal tissues [40–42]. This is particularly important, because late or chronic effects including radiation-induced fibrosis and myocardial infarction are typically expressed after latent periods of months to years and are highly relevant as they tend to be irreversible or even progressive in severity. The data reported in the present work, support a potential protective effect of YG on inflammation status induced by XRT in breast cancer patients and its usefulness to optimize therapeutic strategies for the prevention of late side effects of irradiation treatment.

This study did not show any effects of YG on subjective measure of QOL, in contrast with (1) where yoga revealed benefit on PCS scores. The small sample size surely mines significant differences, but it is noteworthy that this study and (1) propose different yoga programs in terms of duration and classes, which is likely to influence subjective QOL assessment [43–46].

The main limitation of this research was, however, the small sample size due to the pandemic restrictions. These numbers forced the use of nonparametric procedures without the possibility to correct for covariates (such as baseline values) or to perform properly designed post-hoc tests. Significant differences, therefore, should be interpreted with caution.

In conclusion, the current study found that, for some outcomes, the YG yielded better values of physiological distress markers than the CG according to the program proposed. Besides a greater sample size to have enough power, future studies should consider long-term yoga programs, should start from the moment of diagnosis, and measure other inflammatory or proinflammatory factors to confirm or strengthen the yoga effects and to examine the benefit of practice on patients’ prognosis.

Author contribution

Conception and design: SM, PS, AT and VA. Provision of study material or patients: SM. Collection and assembly of data: SM, IA, PS and VA. Data analysis and interpretation: AT and IA. Manuscript writing: SM, AT, IA and PS. Final approval of manuscript: All authors.

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Data Sharing Statement

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.
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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