The Effect of a Single Session of 30-Minute Mindful Breathing in Reducing Fatigue Among Patients With Haematological Cancer – A Randomised Controlled Trial.

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Research Article

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Abstract

Background:

Patients with haematological cancer had considerable symptom burden, in which fatigue was the most prevalent. Almost 70% of haematological cancer patients reported fatigue.

Methods:

We conducted a parallel-group, non-blinded, randomised control trial at the haemato-oncology unit of University Malaya Medical Centre, from 1st October 2019 to 31st May 2020. Patients included were ≥ 18 years, had histopathological diagnosis of haematological cancer, and fatigue score of ≥ 4 based on the fatigue subscale of Edmonton Symptom Assessment System (ESAS). Patients allocated to the intervention group received standard care plus a guided 30-minute mindful breathing session, while those in control group received standard care. The study outcomes include fatigue severity according to the fatigue subscale of ESAS, visual analogue scale of 0 – 10, and Functional Assessment of Chronic Illness Therapy Fatigue Scale Version 4, at minute 0 and minute 30.

Results:

Of 197 patients screened, 80 were eligible and they were equally randomised into 30-minute mindful breathing versus standard care. Lymphoma (58.9%) was the commonest haematological malignancy, followed by multiple myeloma (13.8%), acute leukaemia (11.3%), myeloproliferative neoplasm (6.3%), chronic leukaemia (5.0%) and myelodysplastic syndrome (5.0%). There was no difference in the demographic and clinical characteristics between the 2 groups.

At minute 0, both arms of patients had similar ESAS-fatigue score (median, 5) and FACIT-fatigue score (mean ± SD, 24.7 ± 10.6 for intervention group versus 24.7 ± 9.7 for control group). At minute 30, intervention group had lower ESAS-fatigue score (median, 3 versus 5) and FACIT-fatigue score (mean ± SD, 17.1 ± 10.5 versus 24.8 ± 11.3) compared to control group. Both the ESAS-fatigue score reduction (median, -2 versus 0, p = 0.002) and FACIT-fatigue score reduction (mean ± SD, -6.7 versus +0.8; p < 0.001) for the intervention group were statistically significant. The calculated effect size Cohen’s d was 1.4 for between-group comparison of differences in total FACIT-fatigue score.

Conclusions:

Our results provide evidence that a single session of 30-minute mindful breathing was effective in reducing fatigue in haematological cancer patients. On top of all the currently available methods, 30-minute mindful breathing can prove a valuable addition.

Background
Haematological cancers include leukaemia, lymphoma, multiple myeloma, myeloproliferative neoplasms and myelodysplastic syndrome.(1, 2) They accounted for 10% of all malignancies and 9.5% of malignancies-related mortality.(3) Patients with haematological cancers have considerable symptom burden, with an average of 8.8 symptoms per patient according to one cross-sectional study.(4) Among the symptoms, fatigue was the most prevalent. Almost 70% of haematological cancer patients reported fatigue.

The National Comprehensive Cancer Network defined cancer-related fatigue (CRF) as a distressing, persistent and subjective sense of physical, emotional, or cognitive tiredness or exhaustion associated with cancer or cancer-related treatment, that is disproportional to recent activity, and interferes with usual functioning.(5) Fatigue was not only the most prevalent symptom of haematological cancer,(6-10) it was also the commonest side-effect of haematological cancer treatments such as cytotoxic chemotherapy or marrow suppressive agents.(11) Fatigue might persist for many years or remain for life in patients who had successfully achieved haematological cancer remission, post cytotoxic chemotherapy or haematopoietic stem-cell transplantation.(12-15) CRF had significant negative impact on patients' quality of life, daily activities, employment, social relationships and mood.(16)

Management of CRF in patients with haematological cancer remained challenging despite studies reporting non-pharmacological measures, particularly exercise and psychological interventions might significantly improve CRF.(17, 18) First, exercise was contraindicated in patients with anaemia, thrombocytopenia, active infection, bone lesion and risk of falls.(19) Second, attending psychological interventions such as cognitive-behavioural therapy, psycho-educational therapy, supportive-expressive therapy and mindfulness-based stress reduction therapy in outpatient setting could be tiring, as well as time-consuming and expensive because these interventions are delivered in multiple sessions over months. Third, pharmacological treatments such as methylphenidate, modafinil and corticosteroid in CRF are still lacking strong evidence, and are not without side-effects.(18)

Mindfulness involves paying attention on purpose, in the present moment and non-reactively.(20) It has been shown to reduce fatigue, stress, anxiety, depression and improve sleep.(21-25) However, most evidence on the benefits of mindfulness are based on conventional 6-8 weeks mindfulness programme. Brief mindfulness practices of 5-30 minutes duration warrant more research. Recent studies have shown that a single session of 20-minute mindful breathing significantly reduced dyspnoea in patients with chronic lung disease and decompensated heart failure,(26, 27) as well as palliating multiple symptoms in patients with terminal cancer.(28) Brief mindfulness practices require less energy and time from patients, and have the potential advantage of more sustainable habit-formation, when it is practiced regularly. But the evidence for such practices in reducing fatigue is still lacking. In this study, we aim to determine the efficacy of a single session of 30-minute mindful breathing in reducing fatigue among patients with haematological cancers.

Methodology
Study design:

We conducted a parallel-group, non-blinded, randomised control trial at the haemato-oncology unit of University Malaya Medical Centre (UMMC), a tertiary university hospital with 1,617 beds in Kuala Lumpur, capital of Malaysia, from 1st October 2019 to 31st May 2020. Patients included were aged 18 years and above, had a histopathological diagnosis of haematological cancer according to World Health Organisation classification, and a fatigue score of $\geq 4$ based on the fatigue subscale of Edmonton Symptom Assessment System (ESAS). Patients were excluded if they had impaired conscious level, cognitive impairment or any psychiatric illness that would prevent them from giving informed consent or participate fully in the study; active or past history of cancer of other system, or a haemoglobin level of $<8$g/dl.(29)

Procedure:

Patients with haematological cancer attending the haematology clinic or admitted to the haematology ward of UMMC were consecutively screened for eligibility. The demographic and clinical data of the eligible patients, which include age, gender, ethnicity, religion, occupation, education level, marital status, type of haematological cancer, current status of cancer, types of cancer treatment, duration of cancer, blood parameters and other co-morbidities were obtained from the hospital Electronic Medical Record System. Any missing information was obtained by face-to-face interview with patients or relatives.

Patients who satisfied the inclusion criteria and agreed to participate in the study were randomly assigned into 2 groups based on computer-generated random numbers, in blocks of 10, with a one-to-one allocation ratio. Allocation sequence was concealed with sealed envelopes to prevent selection bias. Patients allocated to the intervention group received standard care plus a guided 30-minute mindful breathing session which consisted of four breathing exercises done consecutively. The four exercises included identifying the in-and out-breath, following the entire length of the breath, bringing the mind back to the body and relaxing the whole body.(30) Each exercise lasted 7.5 minutes. Guidance was given by one of the two research assistants, who were medical doctors. They were trained by one of the co-investigators, who was a palliative care physician, certified in mindfulness training.

The training included a brief introduction to the basic concepts of mindfulness, followed by a 30-minute mindful breathing session guided by the trainer. Guidance on delivering the intervention with attention to paralanguage (intonation, rate and rhythm of speech, pitch, articulation, use of silence, etc.) and body language (eye contact, facial expression, posture and bodily movement), followed by supervision of the actual delivery of the 30-minute mindful breathing session by each research assistant were performed. The instructions for the 30-minute mindful breathing are presented in Table 1. Patients in the control group received standard care alone. They were allowed to resume their usual activities 30 minutes prior to further assessment.

The study outcomes were assessed at minute 0 (before intervention – T0) and minute 30 (after intervention – T30). The outcomes at T0 and T30 include fatigue severity according to the fatigue
Subscale of ESAS, a unidimensional visual analogue scale (VAS) of 0 – 10, and the score of Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale Version 4, a multidimensional fatigue scale. At the end of the study, patients in the intervention group were asked about their feedback, any harm, and asked if they were satisfied and willing to practise 30-minute mindful breathing in their daily life.

The ESAS is a valid and reliable tool to assess nine common symptoms experienced by cancer patients. (31) The nine symptoms assessed include: pain, tiredness, nausea, depression, anxiety, drowsiness, loss of appetite, wellbeing and shortness of breath. An additional blank scale is given to assess each patient’s ‘other problems’ as needed. The severity for each symptom upon assessment has a rating from 0 to 10 on a numerical scale; with 0 indicating absence of the symptom and 10 indicating the worst symptom severity. For this study, the tiredness subscale was chosen to assess participants’ fatigue severity.

The FACIT Fatigue Scale is a 13-item multidimensional assessment tool to measure individual’s fatigue level during their normal daily activities over the past 7 days. (32) It has high internal validity (Cronbach’s alpha = 0.96) and high test-retest reliability (ICC = 0.95). Each participant’s level of fatigue is rated on a five point Likert scale (0 = not at all fatigued to 4 = very much fatigued). The total FACIT-fatigue score ranges from 0 to 52, with a higher score reflecting more fatigue.

The medical ethics approval was obtained from the Medical Ethic Committee of the UMMC (Ethics no: 201971-7588). Written informed consent were obtained from all the participants. The study was conducted according to the Declaration of Helsinki.

Statistical analysis:

The sample size was calculated based on the formula for a randomised control trial for continuous variables with statistical superiority design, \[ n = \frac{2 \text{SD}^2(\frac{Z_{\alpha/2}}{2} + Z_{\beta})^2}{d^2}\] (33) in which \( n \) was sample size in each group; \( \text{SD} \) was standard deviation from previous study; \( Z_{\alpha/2} \) was desired level of statistical significance, typically 1.96 for type-1 error of 0.05; \( Z_{\beta} \) was desired power, typically 0.842 for 80% power; \( d \) was effect size, the difference in means. In this study, we took the SD of 1.58 and \( d \) of 1. (21) Therefore, the minimum sample size was 78 (39 for each arms).

Results for continuous variables were expressed as mean ± standard deviation (SD), median or inter-quartile range depending on normality of the variable distributions; while results for categorical variables were expressed as percentages. Between-groups differences for continuous data was compared by using independent t-test or Mann-Whitney U test, as applicable; while between-group differences for categorical data was compared by using Chi-Square test or Fisher-Exact test, as applicable. A 2-sided p-value of less than 0.05 was considered as significant in this study. Statistical analyses were performed using the software package, Statistical Package for the Social Sciences (SPSS for windows version 25.0, SPSS Inc, Chicago, IL, USA).

Results
Of 197 patients screened, 80 were eligible and randomised into 30-minute mindful breathing (intervention group, n = 40) versus standard care (control group, n = 40) (Figure 1). The patients’ gender was almost equally distributed, with mean age of 54.6 ± 15.4 years (Table 2). Lymphoma (58.9%) was the commonest haematology malignancy, followed by multiple myeloma (13.8%), acute leukaemia (11.3%), myeloproliferative neoplasm (6.3%), chronic leukaemia (5.0%) and myelodysplastic syndrome (5.0%). There was no difference in terms of age, gender, ethnicity, marital status, religion, education level, occupation, type of haematological malignancy, disease status, comorbid or haemoglobin level between the 2 groups.

At minute 0, both arms of patients had similar ESAS-fatigue score (median, 5) and FACIT-fatigue score (mean ± SD, 24.7 ± 10.6 for intervention group versus 24.7 ± 9.7 for control group) (Table 3). At minute 30, intervention group had lower ESAS-fatigue score (median, 3 versus 5) and FACIT-fatigue score (mean ± SD, 17.1 ± 10.5 versus 24.8 ± 11.3) compared to control group. Both the ESAS-fatigue score reduction (median, -2 versus 0, p = 0.002) and FACIT-fatigue score reduction (mean ± SD, -6.7 versus +0.8; p < 0.001) for the intervention group were statistically significant (Table 4). The calculated effect size Cohen's d was 1.4 for between-group comparison of differences in total FACIT-fatigue score.

Analysis of FACIT fatigue subscales showed that patients receiving 30-minute mindful breathing experienced significant reduction in symptoms 1 (generalised fatigue), 3 (feeling wash-out), 4 (tiredness), 5 (difficulty to initiate work), 6 (difficulty to finish work), 10 (tiredness to eat), 12 (frustration), and 13 (difficulty in social activities), compared to standard care patients (all p < 0.05) (Table 5).

Regarding the feedback from patients in the intervention group, the majority of them found the 30-minute mindful breathing useful in reducing their fatigue. The mindful breathing script was good. They felt calm and peaceful as they focused on their breathing, and were able to forget their worrying thoughts. Many slept during the session due to their extreme tiredness and felt better on waking up. Some patients reported that they would continue to practice themselves. A few asked for more guided sessions. Duration wise, some said it could be longer; some said it was too long. No harm was reported by any of the participants in the intervention group.

**Discussion**

The results showed that a single session of 30-minute mindful breathing was effective in reducing fatigue rapidly in hematological cancer patients. The strength of the fatigue reduction was large with a Cohen's d effect size of 1.4. To date, two other clinical trials have shown beneficial effects of mindfulness-based interventions on cancer-related fatigue.(34, 35) However, the intervention period of both studies was longer. The first was a 9-week mindfulness-based cognitive therapy (MBCT).(34) The second was an 8-week mindfulness-based stress reduction (MBSR).(35)

Although conventional mindfulness practice could potentially produce a longer lasting effect on fatigue reduction, a single session of brief mindfulness practice offers an immediate bedside option to palliate fatigue in hematological cancer patients. The script of the guided 30-minute mindful breathing is simple
and the practice is easy to deliver. The instructors for the brief mindfulness practice need only a single session of mindfulness training. This has the potential of making the intervention easily available to cancer patients.

Other non-pharmacological interventions that improved cancer-related fatigue included home-based walking exercise program and relaxation therapy. As for pharmacological interventions, psychostimulants such as methylphenidate and modafinil, and dexamethasone have shown promise in reducing cancer-related fatigue. Thirty minutes mindful breathing could be a useful complement to the above-mentioned interventions.

Conducting the guided 30-minute mindful breathing in the ward setting was not without its challenges. Approaching newly-admitted fatigued patients was difficult because most of them were unwell to undergo the session. Patients who had been admitted for some time or were near hospital discharge were more receptive for participation in the study. Other challenges were interruption from staff for checking vital signs, serving meals or medications, and cleaning. A quiet environment will be more conducive to practice. Few patients expressed difficulty concentrating for 30 minutes and suggested a shorter session tailored to patient’s energy. For the clinic patients, delivering the session in a private room was commendable.

The study has several limitations. This is a single center study. We were unable to blind the patients because their active participation was required. There was a lack of an active control. The outcome measures were subjective. We did not include any objective measurement of fatigue. We explored the immediate effect of the intervention and not the sustained effect. Multiple sessions may be necessary to produce a longer lasting effect. There were also those who requested for audio recordings for home-practice.

**Conclusion**

To conclude, our results provide evidence that a single session of 30-minute mindful breathing was effective in reducing fatigue in haematological cancer patients. Fatigue, disabling and the most prevalent symptom in hematological malignancies, warrants the development of better methods of management. On top of all the methods, 30-minute mindful breathing can prove a valuable addition.

**Abbreviations**

CRF, cancer-related fatigue; UMMC, University Malaya Medical Centre ESAS, Edmonton Symptom Assessment System; T0, minute 0 - before intervention; T30, minute 30 - after intervention; VAS, visual analogue scale; FACIT, Functional Assessment of Chronic Illness Therapy; n, sample size in each group; SD, standard deviation; Z α/2, desired level of statistical significant; Zβ, desired power; d, effect size; SPSS, Statistical Package for the Social Sciences; MBCT, mindfulness-based cognitive therapy; MBSR, mindfulness-based stress reduction; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia;
CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; Hb, Haemoglobin; ESAS-F, Edmonton Symptom Assessment System-Fatigue component; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue component; IQR, Interquartile Range

Declarations

Ethic Approval and Informed Consent:

Ethical approval for this study was obtained from the Medical Ethic Committee of the UMMC with Ethics no: 201971-7588. Written informed consent was obtained from all the study patients.

Consent for publication:

Not applicable.

Availability of Data and Materials:

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

Competing Interest:

The authors declare no potential conflicts of interest in respect to the research, authorship, and publication of this article.

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Authors Contributions:

Diana-Leh-Ching Ng, Gin-Gin Gan, Nur Adila Bt Anuar, Yu-Zhen Tung, Natalie-Zi Lai, Yi-Wen Tan, Siti Norazilah Bt Mohd Said, Amalia Bt Madhilie, Chee-Shee Chai, and Seng-Beng Tan had contributed substantially to this study, which includes:

1. Substantial contributions to conception and design, data acquisition, or data analysis and interpretation;
2. Drafting the article or critically revising it for important intellectual content;
3. Final approval of the version to be published; and
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of the work are appropriately investigated and resolved.

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References

1. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al. The World Health Organization classification of hematological malignancies report of the Clinical Advisory Committee Meeting, Airlie House, Virginia, November 1997. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2000;13(2):193-207.

2. Arber DA, Orazi A, Hassuerjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391.

3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA: a cancer journal for clinicians. 2018;68(1):7-30.

4. Manitta V, Zordan R, Cole-Sinclair M, Nandurkar H, Philip J. The symptom burden of patients with hematological malignancy: a cross-sectional observational study. Journal of pain and symptom management. 2011;42(3):432-42.

5. Berger AM, Mooney K, Alvarez-Perez A, Breitbart WS, Carpenter KM, Cella D, et al. Cancer-Related Fatigue, Version 2.2015. Journal of the National Comprehensive Cancer Network : JNCCN. 2015;13(8):1012-39.

6. Courneya KS, Sellar CM, Stevinson C, McNeely ML, Peddle CJ, Friedenreich CM, et al. Randomized controlled trial of the effects of aerobic exercise on physical functioning and quality of life in lymphoma patients. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(27):4605-12.

7. Else M, Smith AG, Cocks K, Richards SM, Crofts S, Wade R, et al. Patients' experience of chronic lymphocytic leukaemia: baseline health-related quality of life results from the LRF CLL4 trial. British journal of haematology. 2008;143(5):690-7.

8. Gulbrandsen N, Hjermstad MJ, Wisloff F. Interpretation of quality of life scores in multiple myeloma by comparison with a reference population and assessment of the clinical importance of score differences. European journal of haematology. 2004;72(3):172-80.

9. Johnsen AT, Tholstrup D, Petersen MA, Pedersen L, Groenvold M. Health related quality of life in a nationally representative sample of haematological patients. European journal of haematology. 2009;83(2):139-48.

10. Persson L, Larsson G, Ohlsson O, Hallberg IR. Acute leukaemia or highly malignant lymphoma patients' quality of life over two years: a pilot study. European journal of cancer care. 2001;10(1):36-47.

11. Zittoun R, Achard S, Ruszniewski M. Assessment of quality of life during intensive chemotherapy or bone marrow transplantation. Psychooncology. 1999;8(1):64-73.
12. Heinonen H, Volin L, Uutela A, Zevon M, Barrick C, Ruutu T. Quality of life and factors related to perceived satisfaction with quality of life after allogeneic bone marrow transplantation. Annals of hematology. 2001;80(3):137-43.

13. Ruffer JU, Flechtner H, Tralls P, Josting A, Sieber M, Lathan B, et al. Fatigue in long-term survivors of Hodgkin's lymphoma; a report from the German Hodgkin Lymphoma Study Group (GHSG). European journal of cancer (Oxford, England : 1990). 2003;39(15):2179-86.

14. Sherman AC, Coleman EA, Griffith K, Simonton S, Hine RJ, Cromer J, et al. Use of a supportive care team for screening and preemptive intervention among multiple myeloma patients receiving stem cell transplantation. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2003;11(9):568-74.

15. Wettergren L, Bjorkholm M, Axdorph U, Bowling A, Langius-Eklof A. Individual quality of life in long-term survivors of Hodgkin's lymphoma--a comparative study. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2003;12(5):545-54.

16. Curt GA, Breitbart W, Cella D, Groopman JE, Horning SJ, Itri LM, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. The oncologist. 2000;5(5):353-60.

17. Hilfiker R, Meichtry A, Eicher M, Nilsson Balfe L, Knols RH, Verra ML, et al. Exercise and other non-pharmaceutical interventions for cancer-related fatigue in patients during or after cancer treatment: a systematic review incorporating an indirect-comparisons meta-analysis. British journal of sports medicine. 2018;52(10):651-8.

18. Mustian KM, Alfano CM, Heckler C, Kleckner AS, Kleckner IR, Leach CR, et al. Comparison of Pharmaceutical, Psychological, and Exercise Treatments for Cancer-Related Fatigue: A Meta-analysis. JAMA oncology. 2017;3(7):961-8.

19. Baumann FT, Kraut L, Schüle K, Bloch W, Fauser AA. A controlled randomized study examining the effects of exercise therapy on patients undergoing haematopoietic stem cell transplantation. Bone Marrow Transplantation. 2009;45:355.

20. Jacobson E, Dreaver J, Miller R, Martin D. *Wherever You Go There You Are: Mindfulness Meditation in Everyday Life – Jon Kabat-Zinn *How Yoga Works: An Introduction to Somatic Yoga – Elenor Criswell *Vanda Scaravelli on Yoga – Esther Meyers *Grace Unfolding: Psychotherapy in the Spirit of the Tao-Te Ching – Greg Johanson & Ron Kurtz *Interview with Ron Kurtz – Donna Martin *30 Scripts for Relaxation, Imagery and Inner Healing Volumes I & 2 – Julie T. Lusk. International Journal of Yoga Therapy. 1995;6(1):46-59.

21. Johns SA, Brown LF, Beck-Coon K, Monahan PO, Tong Y, Kroenke K. Randomized controlled pilot study of mindfulness-based stress reduction for persistently fatigued cancer survivors. Psycho-oncology. 2015;24(8):885-93.

22. Carlson LE, Garland SN. Impact of mindfulness-based stress reduction (MBSR) on sleep, mood, stress and fatigue symptoms in cancer outpatients. International journal of behavioral medicine. 2005;12(4):278-85.
23. Ando M, Morita T, Akechi T, Ito S, Tanaka M, Ifuku Y, et al. The efficacy of mindfulness-based meditation therapy on anxiety, depression, and spirituality in Japanese patients with cancer. Journal of palliative medicine. 2009;12(12):1091-4.

24. Yook K, Lee SH, Ryu M, Kim KH, Choi TK, Suh SY, et al. Usefulness of mindfulness-based cognitive therapy for treating insomnia in patients with anxiety disorders: a pilot study. The Journal of nervous and mental disease. 2008;196(6):501-3.

25. Shennan C, Payne S, Fenlon D. What is the evidence for the use of mindfulness-based interventions in cancer care? A review. Psycho-oncology. 2011;20(7):681-97.

26. Tan SB, Liam CK, Pang YK, Leh-Ching Ng D, Wong TS, Wei-Shen Khoo K, et al. The Effect of 20-Minute Mindful Breathing on the Rapid Reduction of Dyspnoea at Rest in Patients with Lung Diseases: A Randomized Controlled Trial. J Pain Symptom Manage. 2019.

27. Ng DL-C, Chai C-S, Tan K-L, Chee K-H, Tung Y-Z, Wai S-Y, et al. The Efficacy of a Single Session of 20-Minute Mindful Breathing in Reducing Dyspnea Among Patients With Acute Decompensated Heart Failure: A Randomized Controlled Trial. American Journal of Hospice and Palliative Medicine®. 2020:1049909120934743.

28. Look ML, Tan SB, Hong LL, Ng CG, Yee HA, Lim LY, et al. Symptom reduction in palliative care from single session mindful breathing: a randomised controlled trial. BMJ Supportive & Palliative Care. 2020:bmjspcare-2020-002382.

29. Prochaska MT, Newcomb R, Block G, Park B, Meltzer DO. Association Between Anemia and Fatigue in Hospitalized Patients: Does the Measure of Anemia Matter? J Hosp Med. 2017;12(11):898-904.

30. Tung YZ, Tan SB. Mindful breathing for suffering. BMJ supportive & palliative care. 2020.

31. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): A Simple Method for the Assessment of Palliative Care Patients. Journal of palliative care. 1991;7(2):6-9.

32. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. Journal of pain and symptom management. 1997;13(2):63-74.

33. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian J Psychol Med. 2013;35(2):121-6.

34. van der Lee ML, Garssen B. Mindfulness-based cognitive therapy reduces chronic cancer-related fatigue: a treatment study. Psycho-oncology. 2012;21(3):264-72.

35. Hoffman CJ, Ersser SJ, Hopkinson JB, Nicholls PG, Harrington JE, Thomas PW. Effectiveness of mindfulness-based stress reduction in mood, breast- and endocrine-related quality of life, and well-being in stage 0 to III breast cancer: a randomized, controlled trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(12):1335-42.

36. Mock V, Pickett M, Ropka ME, Lin EM, Stewart KJ, Rhodes VA, et al. Fatigue and Quality of Life Outcomes of Exercise During Cancer Treatment. Cancer Practice. 2001;9(3):119-27.
37. Decker TW, Cline-Elsen J, Gallagher M. Relaxation therapy as an adjunct in radiation oncology. Journal of clinical psychology. 1992;48(3):388-93.

38. Minton O, Richardson A, Sharpe M, Hotopf M, Stone PC. Psychostimulants for the management of cancer-related fatigue: a systematic review and meta-analysis. Journal of pain and symptom management. 2011;41(4):761-7.

39. Yennurajalingam S, Frisbee-Hume S, Palmer JL, Delgado-Guay MO, Bull J, Phan AT, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2013;31(25):3076-82.

Tables

Table 1. Instructions for 30-minute mindful breathing
Step 1 (7.5 minutes): Identifying the in-breath and out-breath

Make yourself comfortable. Relax your body. Close your eyes gently. Take two deep breaths slowly. Then, breathe naturally. Notice the flow of air through your nose. Rest your attention gently on the breath. Breathing in, you know you are breathing in. Breathing out, you know you are breathing out. In-out, in-out, in-out. If you are distracted by any sounds, body sensations, thoughts or feelings, gently come back to your breath. Be aware of your in-breath and out-breath for the next few minutes.

Step 2 (7.5 minutes): Following the entire length of the breath

Continue to relax your body with your eyes closed. Continue to pay attention to your breath. Follow the entire length of your breath. Follow the beginning, the middle and the end of your in-breath, and the beginning, middle and the end of your out-breath. If you are breathing in a long breath, you know you are breathing in a long breath. If you are breathing in a short breath, you know you are breathing in a short breath. If you are breathing out a long breath, you know you are breathing out a long breath. If you are breathing out a short breath, you know you are breathing out a short breath. Do not force yourself to take a long or short breath. Just breathe naturally. Be aware of the entire length of the breath. In-in-in, out-out-out, in-in-in, out-out-out. If you are distracted by any sounds, body sensations, thoughts or feelings, gently come back to your breath. Follow the entire length of your breath for the next few minutes.

Step 3 (7.5 minutes): Bringing the mind back to the body

As you follow the entire length of your breath, bring your mind back to your body. Instead of thinking about the past or future, bring your mind back to now. Bring your mind and body together as one. As you breathe in, feel your whole body moving with your breathing in. As you breathe out, feel your whole body moving with your breathing out. Breathing in, you are aware of your whole body as you are breathing in. Breathing out, you are aware of your whole body as you are breathing out. Feel the different parts of your body as you breathe in and out. Then, feel the body as a whole, fully united with your mind. Feel the wholeness of yourself with each breath for the next few minutes.

Step 4 (7.5 minutes): Relaxing the body

Once your breathing is harmonious, your body will relax naturally. Feel whether there is any tension in your body. Breathe and relax the tension one by one, from the top to the bottom. Relax your head, face, neck, arms, forearms, hands, chest, abdomen, legs, and feet. Then relax your whole body all at once. Breathing in, you calm your body when you are breathing in. Breathing out, you smile. Again, breathing in, you calm your body when you are breathing in. Breathing out, you smile. In-out-calm-smile, in-out-calm-smile, in-out-calm-smile. Feel your breath flowing through your body and calming your body. Feel your breath leaving your body and smile. Continue to relax your whole body for the next few minutes.
| Demographic and Clinical Characteristics | Techniques |
|-----------------------------------------|------------|
|                                        | 30-minute mindful breathing | Control |
|                                        | \((n = 40)\) | \((n = 40)\) | p-value |
| Age, mean ± SD (years)                 | 53.4±16.2 | 55.8±14.6 | 0.493\textsuperscript{a} |
| Gender, \(n\) (%)                     |            |            |         |
| Male                                    | 20 (50.0) | 19 (47.5) | 1.000\textsuperscript{b} |
| Female                                  | 20 (50.0) | 21 (52.5) |         |
| Ethnicity, \(n\) (%)                   |            |            |         |
| Malay                                   | 21 (52.5) | 18 (45.0) | 0.792\textsuperscript{b} |
| Chinese                                 | 15 (37.5) | 17 (42.5) |         |
| Indian                                  | 4 (10.0)  | 5 (12.5)  |         |
| Marital Status, \(n\) (%)              |            |            |         |
| Single                                  | 6 (15.0)  | 7 (17.5)  | 0.992\textsuperscript{b} |
| Married                                 | 27 (67.5) | 26 (65.0) |         |
| Widowed                                 | 6 (15.0)  | 6 (15.0)  |         |
| Divorced/Separated                      | 1 (2.5)   | 1 (2.5)   |         |
| Religion, \(n\) (%)                    |            |            |         |
| Muslim                                  | 21 (52.5) | 18 (45.0) | 0.816\textsuperscript{b} |
| Buddhist                                | 12 (30.0) | 13 (32.5) |         |
| Christian                               | 5 (12.5)  | 5 (12.5)  |         |
| Hindu                                   | 2 (5.0)   | 4 (10.0)  |         |
| Education Level, \(n\) (%)             |            |            |         |
| None                                    | 1 (2.5)   | 1 (2.5)   | 0.054\textsuperscript{b} |
| Primary                                 | 2 (5.0)   | 11 (27.5) |         |
| Secondary                               | 18 (45.0) | 15 (37.5) |         |
| College/ University                     | 19 (47.5) | 13 (32.5) |         |
| Occupation, \(n\) (%)                  |            |            |         |
| None                                    | 11 (27.5) | 4 (10.0)  | 0.130\textsuperscript{b} |
| Employed | 16 (40.0) | 21 (52.5) |
| Retired  | 13 (32.5) | 15 (37.5) |
| Haematology Malignancy, n (%) |
| ALL      | 1 (2.5)   | 0 (0.0)   | 0.075c |
| AML      | 2 (5.0)   | 6 (15.0)  |
| CLL      | 0 (0.0)   | 1 (2.5)   |
| CML      | 3 (7.5)   | 0 (0.0)   |
| Lymphoma | 24 (60.0) | 23 (57.5) |
| Multiple myeloma | 4 (10.0) | 7 (17.5) |
| Myelodysplastic syndrome | 4 (10.0) | 0 (0.0) |
| Myeloproliferative disease | 2 (5.0) | 3 (7.5) |
| Remission status, n (%) |
| Yes      | 13 (32.5) | 11 (27.5) | 0.807b |
| No       | 27 (67.5) | 29 (72.5) |
| Comorbid, n (%) |
| No       | 16 (40.0) | 16 (40.0) | 1.000b |
| Yes      | 24 (60.0) | 24 (60.0) |
| Hb level (g/dL), mean ± SD | 11.9 ± 2.3 | 11.2 ± 2.1 | 0.144a |
| Baseline ESAS-Fatigue, median (IQR) | 5 (2) | 5 (2) | 0.824d |
| Baseline FACIT-Fatigue, mean ± SD | 24.0 ± 10.6 | 24.0 ± 9.7 | 0.983a |

*SD* Standard Deviation, *ALL* Acute Lymphoblastic Leukemia, *AML* Acute Myeloid Leukemia, *CLL* Chronic Lymphocytic Leukemia, *CML* Chronic Myeloid Leukemia, *Hb* Haemoglobin, *ESAS-F* Edmonton Symptom Assessment System-Fatigue component, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue component, *IQR* Interquartile Range

^p-values from Student’s t-test

^bp-values from Chi-square test

^cp-values from Fisher’s Exact test

^dp-values from Mann-Whitney U test
## Table 3. Descriptive statistic of ESAS-F and FACIT-F total score

|                      | ESAS-F Score | FACIT-F Total Score |
|----------------------|--------------|---------------------|
|                      | 30-minute mindful breathing, median (IQR) | Control, median (IQR) | 30-minute mindful breathing, mean ± SD | Control, mean ± SD |
| Minute 0             | 5 (2)        | 5 (2)               | 24.0 ± 10.6            | 24.0 ± 9.7       |
| Minute 30            | 3 (2)        | 5 (3)               | 17.1 ± 10.5            | 24.8 ± 11.3      |
| Score difference     | -2 (2)       | 0 (2)               | -6.7 ± 5.9             | 0.8 ± 4.4        |

*ESAS-F Edmonton Symptom Assessment System-Fatigue component, FACIT-F Functional Assessment of Chronic Illness Therapy-Fatigue component, SD Standard Deviation, IQR Interquartile Range*
Table 4. Changes in ESAS-F and FACIT-F total score: comparison between 30-minute mindful breathing and control arm

| Outcomes            | 30-minute Mindful Breathing | Control | t or Z  | df or U | p-value | d or r |
|---------------------|-----------------------------|---------|---------|---------|---------|--------|
|                     | Median | Mean | Median | Mean | Rank | Z | U | Rank Sum Test | r |
| ESAS-F score        |        |      |        |      |       |    |   |            |   |
| Minute 0            | 5      | 39.9 | 5      | 41.1 | -    | 0.223 | 777.5 | 0.824 |
| Minute 30           | 3      | 33.6 | 5      | 45.1 | -    | 2.285 | 534.5 | 0.022 |
| ESAS-F difference   | -2     | 31.6 | 0      | 47.0 | -    | 3.065 | 459.5 | 0.002 | 0.12 |
| FACIT-F Total score |        |      |        |      |       |    |   |            |   |
| Minute 0            | 24.0   | 10.6 | 24.0   | 9.7  | -0.022 | 78.0 | 0.983 |
| Minute 30           | 17.1   | 10.5 | 24.8   | 11.3 | -3.117 | 76.0 | 0.003 |
| FACIT-F Total difference | -6.7 | 5.9  | 0.8    | 4.4  | -6.267 | 68.4 | 0.000 | 1.42 |

SD Standard Deviation, ESAS-F difference Difference in ESAS-F score between minute 0 and minute 30, FACIT-F Total difference Difference in FACIT-F total score between minute 0 and minute 30
Table 5. FACIT-F individual item score difference: comparison between 30-minute mindful breathing and control arm

| Techniques       | 30-minute mindful breathing | Control |
|------------------|-----------------------------|---------|
|                  | Median | Mean Rank | Median | Mean Rank | U      | z      | p-value | r     |
| F1 difference**  | -1     | 32.0      | 0      | 46.7      | 473.0  | -3.049 | 0.002*  | 0.12  |
| F2 difference    | -1     | 35.2      | 0      | 43.6      | 598.0  | -1.692 | 0.091   | 0.04  |
| F3 difference    | 0      | 32.1      | 0      | 46.5      | 480.0  | -3.045 | 0.002*  | 0.12  |
| F4 difference    | -1     | 33.5      | 0      | 45.2      | 531.5  | -2.389 | 0.017*  | 0.07  |
| F5 difference    | -1     | 31.7      | 0      | 46.9      | 464.5  | -3.135 | 0.002*  | 0.13  |
| F6 difference    | -1     | 30.6      | 0      | 47.9      | 423.0  | -3.586 | 0.000*  | 0.17  |
| F7 difference    | 0      | 38.8      | 0      | 40.2      | 733.5  | -0.287 | 0.774   | 0.00  |
| F8 difference    | 0      | 36.7      | 0      | 42.2      | 653.0  | -1.133 | 0.257   | 0.02  |
| F9 difference    | 0      | 34.8      | 0      | 44.0      | 581.0  | -1.931 | 0.054   | 0.05  |
| F10 difference   | 0      | 34.7      | 0      | 44.1      | 578.0  | -2.067 | 0.039*  | 0.06  |
| F11 difference   | 0      | 36.3      | 0      | 42.6      | 637.5  | -1.465 | 0.143   | 0.03  |
| F12 difference   | 0      | 30.0      | 0      | 48.6      | 397.5  | -4.189 | 0.000*  | 0.23  |
| F13 difference   | 0      | 33.3      | 0      | 45.4      | 524.5  | -2.593 | 0.010*  | 0.09  |

*p-value <0.05

**Difference in FACIT-F individual item score between minute 0 and minute 30