# Clinical Prediction Models of Severe Cancer-Related Fatigue in Cervical Cancer Patients and Effectiveness of Mindfulness-Based Stress Reduction: A Randomized Controlled Trial

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**Abstract**

Objective To build a clinical prediction models (CPMs) for severe CRF of cervical cancer (CC) patients, and conduct online 8-week mindfulness-based stress reduction (MBSR). Design Single-centre, cross-sectional, randomized controlled trial. Setting Gynecological clinic of a tertiary hospital in Shenyang. Population 284 patients, and 100 patients with severe CRF included in randomized controlled trial. Methods Patients were divided into construction group and validation group to verify the accuracy of CPMs. All patients participated in online 8-week MBSR and were followed up for 3 and 6 months. Main outcome measures The primary outcome were the accuracy of the CPMs and effectiveness of MBSR on CRF at 6 month. Secondary outcomes included the influencing factors of CRF, effectiveness of MBSR on sense of coherence, coping style, and perceived social support. Results In the CPMs: the C-Index was 0.921; the sensitivity was 0.821; the specificity was 0.900; the accuracy was 0.857; the AUC was 0.916; the area under the ROC curve was greater than 0.8; the calibration curve fitted well ($P<0.05$); and the net benefit of applying the model to most thresholds was good in DCA. At 6 months, CRF was from 37.70 to 31.25; SOC was from 55.07 to 64.17; ways to face was from 19.20 to 20.95; and ways to yield was from 12.10 to 8.90 in MBSR group ($P<0.01$). Conclusion The CPMs could be used as a prediction and evaluation tool for severe CRF, and the online 8-week MBSR can effectively improve the CRF of CC patients.

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Running title: Study on cancer-related fatigue

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**Abstract**

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Single-centre, cross-sectional, randomized controlled trial.

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**Methods**

Patients were divided into construction group and validation group to verify the accuracy of CPMs. All patients participated in online 8-week MBSR and were followed up for 3 and 6 months.

**Main outcome measures**

The primary outcome were the accuracy of the CPMs and effectiveness of MBSR on CRF at 6 month. Secondary outcomes included the influencing factors of CRF, effectiveness of MBSR on sense of coherence, coping style, and perceived social support.

**Results**

In the CPMs: the C-Index was 0.921; the sensitivity was 0.821; the specificity was 0.900; the accuracy was 0.857; the AUC was 0.916; the area under the ROC curve was greater than 0.8; the calibration curve fitted well ($P$ <0.05); and the net benefit of applying the model to most thresholds was good in DCA. At 6 months, CRF was from 37.70 to 31.25; SOC was from 55.07 to 64.17; ways to face was from 19.20 to 20.95; and ways to yield was from 12.10 to 8.90 in MBSR group ($P$ <0.01).

**Conclusion**

The CPMs could be used as a prediction and evaluation tool for severe CRF, and the online 8-week MBSR can effectively improve the CRF of CC patients.

**Keywords**

Clinical prediction models; Cancer related fatigue; Mindfulness-based stress reduction; Cervical cancer; Health psychology

**Introduction**

Cervical cancer (CC) has ranked the fourth in the number of new cases of women in the world, and has become an important public health problem[1]. There were 600,000 new cases of CC worldwide in 2020, and the number of deaths due to CC reached 340,000[2]. In the treatment stage of cancer patients, cancer related fatigue (CRF) usually runs through all stages of patients' radiotherapy, chemotherapy and even hospice care[3]. Ma showed that the overall incidence rate of CRF among 144,813 cancer patients was 52%[4]. Gernier followed up 45 CC patients and found that the proportion of physical fatigue and mental fatigue was 45.2% and 37.8% respectively[5]. Cancer survivors reported that CRF was a serious and destructive symptom that can last for months to years after treatment[6,7]. Therefore, it is necessary for clinical workers to carry out early screening for CRF in patients with CC.

Clinical prediction models (CPMs) are used to evaluate the probability of a specific subject suffering from a certain disease or obtaining a certain clinical result in the future[8,9]. Studies showed that age, BMI, current smoking behavior, anxiety, insomnia, pain at diagnosis, peroxygenase-5, and connector protein were predictive factors of the models of CRF in patient with breast cancer[10,11]. In order to help identify high-risk groups

of CRF, we included the influencing factors of CRF, such as sociodemographic, clinical, psychological, and behavioral factors into the CPMs to provide theoretical basis for implementing intervention measures[12,13].

Mindfulness-Based Stress Reduction (MBSR) training was effective for CRF and its influencing factors according to previous studies[14-16]. But under the background of COVID-19, domestic and foreign studies have chosen to take online intervention to make up for the defect that patients cannot go to the hospital for relevant treatment. Nissen conducted 8-week therapist directed Internet-delivered Mindfulness-Based Cognitive Therapy (iMBCT)[17]. Kang conducted an 8-week Internet based Mindfulness Decompression (iMBSR) for breast cancer survivors during COVID-19 in China[18]. The results showed that the mental health of cancer patients was significantly improved. This study aimed to provide a more scientific, accurate and convenient CPMS for predicting severe CRF. At the same time, under the background of COVID-19, MBSR training based on WeChat video guidance was used to intervene in the independent influencing factors of severe CRF, so as to prevent the occurrence of CRF in CC patients or reduce the degree of CRF.

## Material and Methods

### Study design and Sample

We conducted a cross-sectional study to construct the CPMs of sever CRF. The first 70% CC case data were included in the model building group (training set=196), and the last 30% CC case data were included in the validation group (validation set=88), including 284 people. The intervention study was designed as a randomized controlled trial. The subjects were randomly assigned to the experimental group (N=40) and the control group (N=38) at a ratio of 1:1 (Figure 1). The control group received routine care, while the experimental group received online 8-week MBSR (Table 1) on the basis of routine care, and patients were followed up for 3 and 6 months.

The samples of this study were all CC patients from a tertiary hospital in Shenyang. According to the sample size, the researchers continuously collected CC patients who met the standards and completed the questionnaire survey. The inclusion criteria were: (1) patients with primary CC confirmed by pathology; (2) aged over 18; (3) communicate independently and fill in questionnaires; (4) know the illness of themselves; (5) volunteer to participate in the investigation and sign the informed consent. Exclusion criteria for study subjects: (1) patients with other malignant tumors at the same time; (2) patients with a history of psychiatric diseases or mental retardation; (3) patients who have received psychotherapy or intervention within one year. Rejection criteria of study objects: (1) no outcome indicators of patients were measured at any two time points. The abscission criteria of the subjects: (1) voluntary withdrawal from the study; (2) interruption of treatment or death.

### Demographic and Clinical Characteristics

The self-made general situation questionnaire was used, including demographic information (age, body mass index, marital status, education level, occupation, monthly income, passive smoking, exercise, dietary characteristics, etc) and clinical information (menopause, diagnosis type, tumor stage, treatment, etc).

### Measurement of CRF

The Cancer Fatigue Scale (CFS) was designed by Okuyama and validated by 307 cancer patients[19]. CFS includes 15 items, with a total score of [?]5 for no fatigue, 6-15 for mild fatigue, 16-30 for moderate fatigue, and 31-60 for severe fatigue. The scale has been used in different cancer patients. It has been verified that the scale is simple and easy to complete, even for patients with advanced cancer.

### Measurement of Uncertainty in Illness

The Medical Uncertainty in Illness Scale (MUIS) was developed by Michel and Braden under the guidance of the theory of medical uncertainty to assess the uncertainty level of adult patients in five aspects: symptoms, diagnosis, relationship with caregivers, treatment and prognosis[20]. The scale has 25 items in total and adopts the Likert five level scoring method. The scale has a score range of 25-125 points, which can be divided into three levels, namely, low level 25-58 points, medium level 59-91 points and high level 92-125 points.

### Measurement of Coping Modes

The Medical Coping Modes Questionnaire (MCMQ) was developed by Feifel and was applicable to patients with various diseases[21]. There were three dimensions: facing (8 items), avoiding (7 items) and yielding (5 items). There are 20 items in total, and the 4-level scoring method was used. The total score range was 20-80. The higher the score, the more inclined the individual was to adopt this coping style.

### Measurement of Perceived Social Support

The Multidimensional Scale of Perceived Social Support (MSPSS), developed by Zimet and included 12 items and 3 dimensions (friend support, family support, and important others support)[22].The score of each item ranged from 1 to 7 points. The total score of the scale ranged from 12 to 84 points, which were divided into three levels. 12 to 36 points were low support, 37 to 60 points were intermediate support, and 61 to 84 points were high support.

### Measurement of Sense of Coherence

The Sense of Coherence-13 (SOC-13) was a simplified version of SOC-29 by Antonovsky, which included three dimensions: comprehensibility, controllability and sense of meaning[23]. SOC-13 used a 7-level scoring method, with a total score ranged of 13˜91 points, of which 13-63 points were low, 64-79 points were medium, and 80-91 points were high. Compared with SOC-29, the simplified version of SOC-13 is more widely used.

### Statistical analysis

We used IBM SPSS Statistics 26 for statistics and analysis, and the R4.1.2 software was used to construct and verify the CPMs. The R packages used in this study included: "Rms 6.3.0 (Nomograms, Calibration curve)", "DescTools 0.99.46 (C-Index)", "ROCit 2.1.1" (ROC analysis), "ResourceSelection 0.3.5" (Hosmer-Lemeshow test), "Rmda 1.6" (DCA analysis). In the randomized controlled trial, the independent sample t-test was used to compare the data between the two groups, and the change trend and difference of the two groups of research data were compared by repeated measurement analysis of variance. We used bootstrap resampling method, the ability of AUC and C-Index evaluation models to distinguish patients with severe CRF from patients with mild CRF. The accuracy of the model was evaluated with Hosmer Lemeshow goodness of fit test and Calibration calibration curve, and the clinical practicability of the model was evaluated with DCA curve analysis results, so as to complete the internal evaluation of the model. Finally we used the established prediction model for severe CRF of CC patients to establish the prediction probability for each patient in the validation group, and then draw ROC curve, Calibration calibration curve and DCA curve according to the prediction probability and actual probability to complete the validation of the model. Inspection level: $\alpha$=0.05 (bilateral), $P$ <0.05.

The formula of CPMs is Logit($P$ )=ln($P$ /1-$P$ )=$\beta_0$+$\beta_1$ $X_1$+$\beta_2$ $X_2$+$\beta_3$ $X_3$+[?]+$\beta_i$ $X_i$.

## Results

### Single factor analysis of severe CRF

The results of single factor analysis showed that per capita monthly income ($P$ <0.001), whether long-term passive smoking ($P$ <0.001), exercise ($P$ <0.001), diagnosis type ($P$ =0.001), uncertainty in illness ($P$ =0.018), coping style ($P$ <0.001), PSS ($P$ <0.001), and SOC ($P$ <0.001) were the influencing factors of severe CRF in CC patients. Table 2 showed the details.

### Multivariate Logistic Regression Analysis of Severe CRF

Logistic regression analysis was conducted with statistically significant as independent variables in univariate analysis, and whether severe CRF occurred as a binary outcome variable to determine long-term passive smoking ($B$ =1.107, OR=3.027, $P$ =0.009), tumor recurrence ($B$ =1.392, OR=4.022, $P$ =0.032), and coping style ($B$ =1.028, OR=2.795, $P$ <0.001) were independent risk factors for severe CRF. Per monthly income ($B$ =-0.446, OR=0.640, $P$ =0.040), physical exercise ($B$ =-0.810, OR=0.445,$P$ =0.003), PSS ($B$ =-0.823,

OR=0.439, $P$ =0.015), and SOC ($B$ =-2.498, OR=0.082, $P$ <0.001) were protective factors for severe CRF. Table 3 showed the details.

**Establishment and internal evaluation of risk prediction model for severe CRF**

According the Table 3, we can draw the CPMs of severe CRF as follows:

Logit($P$ )=1.276-0.947 monthly income+0.989 long-term passive smoking -0.952 physical exercise+1.512 diagnosis type+1.040 coping style -0.726 PSS -2.350 SOC.

Visualize the model in the form of nomograms, as shown in Figure 2. The C-Index of nomogram model calculated by Bootstrap method is 0.921 (95% CI: 0.877˜ 0.958), which indicates that the model has good discrimination (Figure 2). It can be seen from the ROC curve that the best cutoff value of the prediction probability of the nomogram model is 0.412, which corresponds to the maximum Jordan index of 0.721 (Figure 3-1). At this time, the sensitivity of the model is 0.821, the specificity is 0.900, and the accuracy is 0.857. AUC is 0.916 (95% CI: 0.876˜0.957), which further indicates that the model has high discrimination. The calibration curve shows that the predicted probability of the model fits well with the actual probability. The Hosmer Lemeshow verification shows that$\chi^2$ =9.021, $P$ =0.340, greater than 0.05, further indicating that the model has good calibration (Figure 3-2). It can be seen from the DCA curve that when the prediction probability is greater than about 10%, the benefit from using this model is positive, and there is a wide threshold range, which indicates that the use of this nomogram can benefit better (Figure 3-3).

**Model validation**

The above model can be used to calculate the probability of severe CRF of each CC patient in the model validation group to form a prediction probability set. Then, based on the actual occurrence of severe CRF of each patient in the validation group, ROC curve (Figure 3-4), Calibration calibration curve (Figure 3-5) and DCA curve (Figure 3-6) can be generated in R software to evaluate the differentiation, accuracy and clinical practicability of the model respectively. Finally, the AUC of the area under the ROC curve is 0.928 (0.876˜0.980), and the best cut-off value of the prediction probability of the nomogram model is 0.444, corresponding to the maximum Youdenindex of 0.748. At this time, the sensitivity of the model is 0.889, the specificity is 0.860, and the accuracy is 0.875, indicating that the model has a high degree of differentiation; Calibration calibration curve has good consistency ($\chi^2$ =8.89,$P$ =0.340>0.05); It can be seen from the DCA curve that when the prediction probability is greater than about 12%, the benefit of using this model is positive, and it has a wide threshold range, which indicates that this model has good clinical practicability.

**ANOVA Results of Repeated Measurement of Mental Variables**

The SOC, face, yield, and CRF of the experimental group after intervention, at the 3-month follow-up and 6-month follow-up were significantly improved compared with those before intervention ($P$ <0.001). There was no significant difference in social support before and after intervention ($P$ >0.05). Table 4 showed the details. And the simple effect results of the groups are shown in Figure 4.

**Discussion**

This study showed that the incidence of CRF in CC patients was high. 283 patients had CRF of different degrees, and the incidence of CRF is as high as 99%, of which the incidence of mild and moderate CRF is 53.2%, and the incidence of severe CRF is 46.8%. The CPMs of severe CRF is Logit(P)=1.276-0.947 Monthly income+0.989 Long-term passive smoking-0.952 Physical exercise+1.512 Diagnosis type+1.040 Coping style-0.726 PSS-2.350 SOC. In addition to demographic and clinical characteristics, patients' psychological conditions were more influential in the CPMs, similar to Meglio's model of breast cancer CRF[10].

Long term passive smoking, tumor recurrence, avoidance and yielding are risk factors for severe CRF in CC patients. The concentrations of many carcinogenic and toxic chemicals in second-hand smoke are higher than those inhaled by smokers themselves, which may lead to some malignant diseases, and the patients whose husbands do not smoke have worse negative emotions and sleep quality than those who smoke[24]. When the tumor relapses, the patient will fear the disease, and the psychological defense line will collapse. Patients will

doubt the possibility of curing the disease, affecting their confidence in treatment, and their mental health will be poor[25]. CC patients who adopted avoidance and surrender coping styles had a higher risk of serious CRF than those who adopted facing coping style. They did not care about the development of the disease and did not seek help actively. These patients had no confidence in the prognosis and was resigned to fate, which might increase the their negative mood and thus aggravated CRF[26].

Monthly income, physical exercise, PSS, and SOC are protective factors for severe CRF in CC patients. After CC was diagnosed, patients usually needed to receive comprehensive treatment, and the medical cost was high. Patients with higher income had more and better treatment options and less psychological pressure, so the risk of CRF was relatively low[27]. Exercise can improve the blood oxygen content of the body, accelerate the metabolism of the body, stimulate the central nervous system, and then improve the mental state of patients, so as to eliminate fatigue[28]. The social support provided by role relationship is a valuable resource, which helps to stabilize and develop positive self-esteem and self-confidence, enhancing the patient's ability to withstand pressure, and reduce the possibility of negative extreme emotions[29]. There were physiological and psychological stressors in the diagnosis and treatment of cancer. SOC can strengthen the management of stressors, that is, use existing resources to successfully deal with stressors. Therefore, a high level of SOC can promote the good physical and mental health of cancer patients[30].

The areas under the ROC curve of both groups were greater than 0.8, indicating that the CPMs of severe CRF for CC patients constructed can better distinguish mild/moderate CRF patients from severe CRF patients[31]. In the consistency test of the two groups, the calibration curves were well fitted ($P$ <0.05), indicating that the probability of severe CRF predicted by the model was consistent with the actual probability of severe CRF in CC patients, and the accuracy of the model prediction was high. The DCA analysis showed that the net benefit of applying the model to most thresholds in the model building group and the model validation group was good. In addition, this study visualized the CPMs in the form of Nomogram, which was more intuitive and convenient for calculation, and was conducive to the practical application of the model in clinical practice. According to the best cut-off value 0.444 in ROC curve, CC patients can be divided into high-risk group and low-risk group of CRF. For patients whose prediction probability is close to or higher than the optimal threshold, early intervention can be carried out according to their coping style, social support, psychological consistency, etc.

The patients' SOC improved after MBSR (from 55.07 to 59.95), and the effect lasted until 6 months (64.17). The facing dimension score increased after MBSR (from 19.20 to 21.15), and also maintained at 6 months (20.95). At the same time, the yielding dimension score decreased after MBSR (from 12.10 to 10.85) and continuous decreased to 8.90 at 6 months. The CRF after MBSR were significantly improved (from 37.70 to 31.25), and maintained at 6 months (31.25 months). These results fully indicated that online MBSR can effectively improve the SOC, coping style, and CRF of CC patients, and the intervention effect lasted for a short time, with scores significantly lower than those of the control group. Previous studies have proved that MBSR has achieved good results in promoting positive psychology and improving negative emotions and also tried to explore the lasting effect of MBSR through longitudinal research at different time points. Salvador proved that MBSR could improve the psychological distress, general well-being, and fatigue-related quality of life[32]. Gaboury showed that up to 12 months after MBSR, anxiety, depression, emotion-oriented coping, sleep and function significantly improved[33]. Elimimian showed cancer survivors who participated in an 8-week MBSR reported persistent benefits with reduced anxiety, depression, and improved mental health over 24 months of follow-up[34]. Green indicated mindfulness meditation had the potential to decrease stress and burnout by decreasing self-judgment and over-identification with experience, and by increasing resiliency, compassion, and emotional regulation[35]. The above researches fully proved the good intervention effect of MBSR, which may be due to the mechanism of mindfulness, that is, when patients were threatened, injured or wasted by specific events beyond their ability, individuals will actively reassess stress events, redefine or construct stress events, thus triggering positive emotions that can relieve stress, and ultimately achieve internal balance and understanding[36]. Although Carlson proved social support improved to a lesser degree after MBSR[37], our study showed that MBSR had no significant impact on social support of CC patients. This may be because social support usually emphasizes the emotion and help provided by personal social

networks, and tends to external factors. MBSR, as an internal resource, requires the subject to actively explore and develop themselves.

Limitations: first, influenced by the COVID-19, the time of arrival and the way of visiting the hospital of the research objects had changed, therefore, the missed follow-up rate was lightly high; second, the tracking of the intervention effect was only 6 months, and the evaluation results cannot reflect the long-term intervention effects. Strengths: first, the model constructed in this study can help clinical workers to identify high-risk groups of CRF, and provide a reference for taking targeted intervention programs; second, we conducted an intervention study based on the model and proved the effectiveness, which was a complete study.

## Conclusions

The CPMs constructed in this study can be used as a prediction and evaluation tool for severe cases of clinical CC patients. Based on the CPMs, this study conducted a study on MBRS, which proved that MBRS can effectively improve the SOC, coping style, and CRF of CC patients, and the intervention effect was effective in the short term. The CPMs is significant for strengthening risk management, reducing or controlling the occurrence of severe CRF. It can strengthen the risk identification of severe CRF, and its independent risk factors provide scientific basis for CC patients to implement intervention measures.

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## Disclosure of Interests

The authors declare that they have no conflicts of interest.

## Authors' contributions

Data analysis was performed by ZhiHui Gu. The first draft of the manuscript was written by ZhiHui Gu. Data collection was performed by ChenXin Yang and Ke Zhang. Hui Wu contributed to the study conception and design. All authors read and approved the final manuscript.

## Details of Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of China Medical University (2020PS623K). The procedures of this study were reviewed and approved. Written informed consent for the investigation was obtained from each participant. We protected personal privacy when handling personal data and kept personal records confidential.

## Consent for publication

The author agrees to publish details of any images, videos, recordings.

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## Reference

1. Singh M, Jha RP, Shri N, Bhattacharyya K, Patel P, Dhamnetiya D. Secular trends in incidence and mortality of cervical cancer in India and its states, 1990-2019: data from the Global Burden of Disease 2019 Study. *BMC Cancer* . 2022;22(1):149. https://doi.org/10.1186/s12885-022- 09232-w.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* . 2021;71(3):209-249. https://doi.org/10.3322/ caac.21660.

3. Nowe E, Friedrich M, Leuteritz K, Sender A, Stöbel-Richter Y, Schulte T, et al. Cancer-Related Fatigue and Associated Factors in Young Adult Cancer Patients. *J Adolesc Young Adult Oncol* . 2019;8(3):297-303. https://doi.org/10.1089/jayao. 2018.0091.
4. Ma Y, He B, Jiang M, Yang Y, Wang C, Huang C, et al. Prevalence and risk factors of cancer-related fatigue: A systematic review and meta-analysis. *Int J Nurs Stud* . 2020;111:103707. https://doi.org/10.1016/j.ijnurstu. 2020.103707.
5. Gernier F, Joly F, Klein D, Mercier M, Velten M, Licaj I. Cancer-related fatigue among long-term survivors of breast, cervical, and colorectal cancer: a French registry-based controlled study.*Support Care Cancer* . 2020;28(12):5839-5849. https://doi.org/10.1007/s00520-020- 05427-8.
6. Kim S, Han J, Lee MY, Jang MK. The experience of cancer-related fatigue, exercise and exercise adherence among women breast cancer survivors: Insights from focus group interviews. *J Clin Nurs* . 2020;29(5-6):758-769. https://doi.org/10.1111/jocn.15114.
7. Abrahams HJG, Gielissen MFM, Schmits IC, Verhagen CAHHVM, Rovers MM, Knoop H. Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: a meta-analysis involving 12,327 breast cancer survivors. *Ann Oncol* . 2016;27(6):965-974. https://doi.org/10.1093/annonc/mdw099.
8. Ranstam J, Cook JA, Collins GS. Clinical prediction models. *Br J Surg* . 2016;103(13):1886. https://doi.org/10.1002/bjs.10242. PMID: 27901285.
9. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* . 2015;162(1):W1-73.*https://doi.org/10.7326/* M14-0698.
10. Di Meglio A, Havas J, Soldato D, Presti D, Martin E, Pistilli B, et al. Development and Validation of a Predictive Model of Severe Fatigue After Breast Cancer Diagnosis: Toward a Personalized Framework in Survivorship Care. *J Clin Oncol* . 2022;40(10):1111-1123. https://doi.org/10.1200/JCO.21. 01252.
11. Lee S, Deasy JO, Oh JH, Di Meglio A, Dumas A, Menvielle G, et al. Prediction of Breast Cancer Treatment-Induced Fatigue by Machine Learning Using Genome-Wide Association Data. *JNCI Cancer Spectr* . 2020;4(5): pkaa039. https://doi.org/10.1093/jncics/pkaa039.
12. Álvarez-Bustos A, de Pedro CG, Romero-Elías M, Ramos J, Osorio P, Cantos B, et al. Prevalence and correlates of cancer-related fatigue in breast cancer survivors. Support Care Cancer. 2021 Nov;29(11):6523-6534. doi: 10.1007/s00520-021-06218-5.
13. Ruiz-Casado A, Álvarez-Bustos A, de Pedro CG, Méndez-Otero M, Romero-Elías M. Cancer-related Fatigue in Breast Cancer Survivors: A Review. Clin Breast Cancer. 2021 Feb;21(1):10-25. doi: 10.1016/j.clbc.2020.07.011.
14. Reich RR, Lengacher CA, Alinat CB, Kip KE, Paterson C, Ramesar S, et al. Mindfulness-Based Stress Reduction in Post-treatment Breast Cancer Patients: Immediate and Sustained Effects Across Multiple Symptom Clusters. *J Pain Symptom Manage* . 2017;53(1),85-95. https://doi.org/10.1016/j. jpainsymman.2016.08. 005.
15. Witek Janusek L, Tell D, Mathews HL. Mindfulness based stress reduction provides psychological benefit and restores immune function of women newly diagnosed with breast cancer: A randomized trial with active control. *Brain Behav Immun* . 2019;80:358-373. https://doi.org/10.1016/j.bbi. 2019.04.012.
16. Pedro J, Monteiro-Reis S, Carvalho-Maia C, Henrique R, Jerónimo C, Silva ER. Evidence of psychological and biological effects of structured Mindfulness-Based Interventions for cancer patients and survivors: A meta-review. *Psychooncology* . 2021;30(11):1836-1848. https://doi.org/ 10.1002/pon.5771.
17. Nissen ER, Zachariae R, O'Connor M, Kaldo V, Jørgensen CR, Højris I, et al. Internet-delivered Mindfulness-Based Cognitive Therapy for anxiety and depression in cancer survivors: Predictors of treatment response. *Internet Interv* . 2021;23:100365. https://doi.org/10.1016/j.invent.2021. 100365.
18. Kang C, Sun S, Yang Z, Fan X, Yuan J, Xu L, et al. The Psychological Effect of Internet-Based Mindfulness-Based Stress Reduction on the Survivors of Breast Cancer During the COVID-19. *Front Psychiatry* . 2021;12:738579. https://doi.org/10.3389 /fpsyt. 2021.738579.
19. Okuyama T, Akechi T, Kugaya A, Okamura H, Shima Y, Maruguchi M, et al. Development and validation of the cancer fatigue scale: a brief, three-dimensional, self-rating scale for assessment of fatigue in cancer patients. *J Pain Symptom Manage* . 2000;19(1):5-14.*https://doi.org/10.1016/s* 0885-

3924(99)00138-4.

20. Mishel MH, Braden CJ. Finding meaning: antecedents of uncertainty in illness. *Nurs Res* . 1988;37(2):98-103,127. PMID: 3347527.
21. Feifel H, Strack S, Nagy VT. Coping strategies and associated features of medically ill patients. Psychosom Med. 1987;49(6),616-25. https://doi.org/10.1097/00006842-198711000-0 0007.
22. Zimet GD, Powell SS, Farley GK, Werkman S, Berkoff KA. Psychometric characteristics of the Multidimensional Scale of Perceived Social Support. *J Pers Assess* . 1990;55(3-4):610-7. https://doi.org/10.1080/00223891. 1990.9674095.
23. Antonovsky A. The structure and properties of the sense of coherence scale. *Soc Sci Med* . 1993;36(6):725-33. https://doi.org/10.1016/0277-9536 (93)90033-z.
24. An X, Wang J, Shi W, Ma R, Li Z, Lei M, et al. The Effect of Passive Smoking on Early Clinical Outcomes After Total Knee Arthroplasty Among Female Patients. *Risk Manag Healthc Policy* . 2021;14: 2407-2419. https://doi.org/10.2147/ RMHP.S309893.
25. Reed SC, Bell JF, Miglioretti DL, Nekhlyudov L, Fairman N, Joseph JG. Fear of cancer recurrence and associations with mental health status and individual characteristics among cancer survivors: Findings from a nationally representative sample. *J Psychosoc Oncol* . 2020; 38(2):125-142. https://doi.org/10.1080/0734 7332.2019.1649338.
26. Rakers SE, Timmerman ME, Scheenen ME, de Koning ME, van der Horn HJ, van der Naalt J, et al. Trajectories of Fatigue, Psychological Distress, and Coping Styles After Mild Traumatic Brain Injury: A 6-Month Prospective Cohort Study. *Arch Phys Med Rehabil.* 2021; 102(10):1965-1971.e2. https://doi.org/10.1016/j.apmr. 2021.06.004.
27. Ridley M, Rao G, Schilbach F, Patel V. Poverty, depression, and anxiety: Causal evidence and mechanisms. *Science* . 2020;370(6522):eaay0214. https://doi.org/10.1126/science. aay0214.
28. Estévez-López F, Maestre-Cascales C, Russell D, Álvarez-Gallardo IC, Rodriguez-Ayllon M, Hughes CM, et al. Effectiveness of Exercise on Fatigue and Sleep Quality in Fibromyalgia: A Systematic Review and Meta-analysis of Randomized Trials. *Arch Phys Med Rehabil* . 2021;102(4);752-761. https://doi.org/10.1016/j.apmr. 2020.06. 019.
29. Bedaso A, Adams J, Peng W, Sibbritt D. The relationship between social support and mental health problems during pregnancy: a systematic review and meta-analysis. *Reprod Health* . 2021;18(1):162. https://doi.org/ 10.1186/s12978-021-01209-5.
30. Vahaaho N, Hakamies-Blomqvist L, Blomqvist C, Kellokumpu-Lehtinen PL, Huovinen R, Saarto T, et al. Sense of Coherence as Predictor of Quality of Life in Early Breast Cancer Patients. *Anticancer Res* . 2021;41(10):5045-5052. https://doi.org/10.21873/ anticanres.15319.
31. Hong W, Earnest A, Sultana P, Koh Z, Shahidah N, Ong ME. How accurate are vital signs in predicting clinical outcomes in critically ill emergency department patients. *Eur J Emerg Med* . 2013;20(1):27-32. https://doi.org/10.1097/MEJ. 0b013e32834fdcf3.
32. Salvador C, Mark P, Hoenemeyer T, McDonald V. Prospective feasibility study of a mindfulness-based program for breast cancer patients in the southeastern US. *Complement Ther Clin Pract* . 2022;49:101639. https://doi.org/10.1016/j.ctcp.2022.101639.
33. Gaboury I, Dobkin PL, Gendron F, Roberge P, Beaulieu MC, Carrier N et al. Mindfulness-based stress reduction to improve depression, pain and high patient global assessment in controlled rheumatoid arthritis.*Rheumatol Adv Pract* . 2022;6(3),:rkac074.*https://doi.org/10.1093/rap/* rkac074.
34. Elimimian E, Elson L, Bilani N, Farrag SE, Dwivedi AK, Pasillas R, et al. Long-Term Effect of a Nonrandomized Psychosocial Mindfulness-Based Intervention in Hispanic/Latina Breast Cancer Survivors. *Integr Cancer Ther* . 2020;19:1534735419890682.*https://doi.org/10.1177/1534735* 419890682.
35. Green AA, Kinchen EV. The Effects of Mindfulness Meditation on Stress and Burnout in Nurses. *J Holist Nurs* . 2021;39(4):356-368. https://doi.org/10.1177/08980101211015818.
36. Wielgosz J, Goldberg SB, Kral TRA, Dunne JD, Davidson RJ. Mindfulness Meditation and Psychopathology. *Annu Rev Clin Psychol* . 2019;15:285-316. https://doi.org/10.1146/annurev- clinpsy-021815-093423.
37. Carlson LE, Tamagawa R, Stephen J, Drysdale E, Zhong L, Speca M. Randomized-controlled trial

of mindfulness-based cancer recovery versus supportive expressive group therapy among distressed breast cancer survivors (MINDSET): long-term follow-up results. *Psychooncology* . 2016;25(7):750-9. https://doi.org/10.1002/pon. 4150.

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