Original Article

Fatigue and Its Related Factors Among Iranian Cancer Survivors

Musab Ghaderi[1] , **Arman Azadi**[2] , **Azad Rahmani**[3*] , **Zohreh Sanaat**[4] , **Hosein Nazemiyeh**[5] , **Afzal Shamsi**[6] , **Leila Nabiolahi**[7]

[1]Department of Medical-Surgical Nursing, Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Medical-Surgical Nursing, Faculty of Nursing and Midwifery, Ilam University of Medical Sciences, Ilam, Iran
[3]Department of Medical-Surgical Nursing, Hematology and Oncology Research Center, Faculty of nursing and midwifery, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Department of Hematology and Oncology, Medical Oncologiest, Hematology and Oncology Research Center, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[5]Department of Pharmacognosy, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
[6]Department of Anesthesiology, Nursing and Midwifery Care Research Center, Tehran University of Medical Sciences, Tehran, Iran
[7]Department of Medical-Surgical Nursing, Shohada Hospital, Tabriz University of Medical Sciences, Tabriz, Iran

Abstract

Introduction: Cancer-related fatigue (CRF) is one of the major problems experienced by cancer patients. Identifying the prevalence and factors associated with CRF may be effective in designing appropriate interventions to reduce this problem. This study aimed to examine the prevalence of CRF and its related factors among Iranian cancer survivors.
Methods: The samples of this descriptive cross-sectional study included 131 cancer survivors referred to outpatient clinic of Shahid Gazi Hospital affiliated to Tabriz University of Medical Sciences. Brief fatigue inventory (BFI) questionnaire was used for data collection. The data were analyzed using SPSS software version 13, descriptive statistics, and regression analysis.
Results: The mean (SD) fatigue score was 6.41 (1.68) and 89% of survivors reported that they had suffered from CRF. The factors affecting CRF included blood pressure, diabetes mellitus, anemia, serum levels of blood urea nitrogen (BUN), marital status, type of cancer, and physical activity.
Conclusion: High level of CRF in cancer survivors requires special attention and designing effective interventions through considering the identified factors associated with CRF.

Introduction

Cancer is one of the leading causes of death worldwide.[1] The number of cancer survivors has increased because of the advances in early detection and cancer treatments over the past three decades.[2] It is estimated that the number of cancer survivors in the United States will increase from 14 million in 2014 to 19 million in 2024.[2] It is expected that most cancer survivors can return to their normal life after completion of the treatments.[3] However, symptoms caused by cancer or its treatment are the most important reasons that prevent cancer survivors from returning to a normal life.[4]

Cancer-related fatigue (CRF) is one of the most common and distressing symptoms experienced by cancer patients, with a prevalence of 59%-96%.[5-7] In a study by Sharifi Rizi et al., 59% of cancer patients under treatment reported significant levels of fatigue.[8] Another study by Zeighami Mohammadi et al., reported that 95% of Iranian cancer patients suffer from fatigue.[9] CRF is a distressing, persistent, and subjective sense of physical, emotional, and/or cognitive tiredness related to cancer or cancer treatment, that is not proportional to recent physical activity and interferes with the patient's functioning.[10] CRF is a multifactorial phenomenon in cancer patients and may be influenced by numerous factors including demographics, medical, psychosocial, behavioral, and biological factors.[11]

The experiences of cancer survivors have shown that CRF is more severe, longer, and more debilitating than normal fatigue caused by insomnia or excessive rest.

In addition, it cannot be relieved by sleep or sufficient rest, and no effective and definitive therapies have been identified for it so far.[12] CRF may lead to the creation or exacerbation of numerous complications, such as insomnia, stress, depression, and mental impairment due to changes in organ function and duration of the disease.[13,14] Hence, CRF is considered as an important factor as mortality caused by cancer from the perspective of public health.[15]

Despite the importance of treating CRF, the results of several studies have showed that CRF is less diagnosed or not treated properly.[16,17] One of the main barriers to proper management of CRF is the lack of accurate identification of CRF-related factors.[18] Thus, the existing literature have suggested that further studies are needed to better identify these factors.[19,20] Although the prevalence of CRF has been studied in Iranian cancer patients under treatment, it has not been studied in Iranian cancer survivors. Therefore, the current study aimed to examine the prevalence of CRF and its related factors among Iranian cancer survivors.

Materials and Methods

This descriptive cross-sectional study was conducted on 131 cancer patients referred to Shahid Ghazi hospital in Tabriz, Iran. Data were collected from January 21 to July 23, 2018. The inclusion criteria were: age over 18 years, final diagnosis of cancer by a clinical oncologist, not receiving blood or blood components in the last 60 days, and without suffering from fatigue one year before the diagnosis of cancer according to the patients' medical records. Based on the previous study,[20] the sample size was calculated as 131 participants for the study. Finally, by considering 10% of attrition and using the convenience sampling method, 145 survivors were invited to participate in the study. In the initial review, 15 patients were not willing to participate in the study, and finally, 131 patients' data were gathered (response rate = %90). The sampling method was such that the researcher was present daily in the research environment and selected the patients who met the inclusion criteria and were willing to participate in the study. After explaining the objectives of the research to the patients and obtaining their consent to participate in the study, the questionnaires were completed by them.

The instrument used in this study consisted of two parts. The first part was a checklist that collected the demographic characteristics and specifications related to the disease. Some information was obtained from patients, and others were extracted from patients' records by obtaining the necessary permissions. Anemia in patients was determined based on hemoglobin (Hb) level and physician's confirmation (Hb < 13 in males vs. Hb < 12 in females).[21] The patient's physical activity was recorded based on the amount of exercise per day in minutes. The second part of the questionnaire used the 10-item brief fatigue inventory (BFI). The first item assessed the existence of fatigue in the past week. If the response was yes, the other 9 items (the amount of current fatigue, usual fatigue in past 24 hours, the highest amount of fatigue and severity in the past day, the fatigue impact in past 24 hours on the general activity, mood, walking ability, relations with other people, and enjoyment of life) were responded by the participants. The answer to the items was scored on a 10-point Likert scale, in which the zero scores represented the absence of fatigue and the score of 10 represented the highest score that indicated severe fatigue. In this questionnaire, the total score of fatigue was obtained from total scores of 9 items of the second part divided by 9. The score of 0 represented no fatigue, a score between 0.1-3.9 mild fatigue, a score between 4-6.9 moderate fatigue, a score between 7-9.9 severe fatigue, and score of 10 represented very severe fatigue.[22] This questionnaire has been used in studies in Iran[22] and other countries.[23]

In current study, face validity and content validity were assessed and verified by an expert panel including 10 faculty members of Tabriz University of Medical Sciences, Iran. The final version of the questionnaire was tested for reliability in a pilot study involving 30 cancer patients. The Cronbach's alpha value for 9 items of BFI questionnaire was 87%.

To perform data collection, first, this research project was approved by the Regional Ethics Committee at the Tabriz University of Medical Sciences (Ethics code: IR.TBZMED. REC.1396.345). Then, the necessary permissions were obtained from the research environment (oncology clinic of Shahid Ghazi hospital in Tabriz). The first author attended the hospital clinic during the sampling period and identified eligible patients who were referred to the clinic for the follow-up visit. After providing the necessary information to the patients regarding the aims of the study, the patients were invited to participate in the study. Moreover, after providing verbal consent, a written informed consent was obtained from all participants. Since most of the participants were illiterate (55.4%), their data were collected through an interview in a private room in the hospital's clinic.

Data were analyzed using SPSS software version 13. The normality of data was examined using the Kolmogorov-Smirnov normality test. Mean, standard deviation, frequency, and percent were used for describing the variables. Furthermore, inferential statistics, including independent-sample t-test, chi-squared test, and ANOVA were used to identify the factors to be included in regression model. Linear regression was used to examine factors associated with fatigue. Finally, $P = 0.05$ was considered as statistically significant.

Results

The mean (SD) age of the patients was 53.76 (12.72) years. Other demographic characteristics of participants are presented in Table 1. The mean (SD) of blood urea nitrogen (BUN) and creatinine was 24.18 (1.32) and 1.11

Table 1. The demographic characteristics of participants (N = 131)

Variable	N (%)
Gender	
Male	72(55)
Female	59(45)
Marital status	
Single	17 (13)
Married	114(87)
Employment status	
Housewife	37(28.2)
Self-employed	33(25.2)
Retired	25(19.1)
Unemployed	25(19.1)
Employee	11(8.4)
Level of education	
Under the diploma	66 (50.4)
Diploma	44 (33.6)
College degree	21 (16)
Type of disease	
Colorectal cancer	64 (48.9)
Gastric cancer	26 (19.8)
CML[a]	19 (14.5)
MM[b]	6 (4.6)
ALL[c]	4 (3.1)
Breast cancer	7 (5.3)
Bladder cancer	5 (3.8)
Age	
≤39	20 (15.3)
40-59	62 (47.3)
≥60	49 (37.4)
Anemia	
Yes	93 (71)
No	38 (29)
Diabetes	
Yes	16 (12.2)
No	115 (87.8)
Hypertension	
Yes	48 (36.6)
No	83 (63.4)
Smoking[d]	
Yes	3(25.1)
No	98 (74.9)
Physical activity (minutes per day)	
No activity	90 (68.7)
Less than 60	17 (13)
60-120	18 (13.7)
More than 120	6 (6.4)

[a] Chronic myeloid leukemia; [b] Multiple myeloma; [c] Acute lymphoblastic leukemia. [d] Some participants did not respond.

(0.44).

According to the analysis of the first question of the BFI questionnaire, 89.23% of survivors reported that they had suffered from fatigue. The mean (SD) score of fatigue in patients was 6.41 (1.68). Moreover, 14 (10.77%) were without fatigue, 10 (7.70%) had mild fatigue, 58 (44.61%) had moderate fatigue, and 48 (36.92%) had severe fatigue.

Based on the results of primary statistical tests, including independent-sample *t* test, chi-square test, and ANOVA, being single, presence of anemia, diabetes mellitus, hypertension, increased level of BUN, and the level of physical activity (less than 30 minutes per day or more than 2 hours per day) were significant factors for the presence of CRF. Then, the linear regression model was used to determine the factors affecting fatigue and the effect of each factor. All variables were significant with regards to the Pearson test, independent-sample *t* test, and ANOVA or they were significant based on the review of previous studies. Variables including marital status, anemia, blood pressure, diabetes, smoking, physical activity, BUN, and type of disease were included in the regression model. The results showed that factors of hypertension, marital status, anemia, urea-creatinine ratio, and activity levels, respectively, were the factors affecting fatigue in cancer patient. (Table 2)

Discussion

In current study, the prevalence of fatigue in patients with cancer was 89%. In a study by Berger et al., the overall prevalence of fatigue was 48%, though it was higher during treatment and reduced following treatment.[24] In another study, the prevalence of fatigue exceeded 70% but decreased significantly following completion of cancer treatment.[25] The significant decrease in the prevalence of fatigue following treatment (to 50%) has also been confirmed in another study.[26] In the current study, both the prevalence and severity of fatigue were higher compared to other studies, such that 82% of participants had moderate and severe fatigue. Zeighami Mohammadi et al., reported that the prevalence of fatigue in patients with cancer undergoing chemotherapy was 95%,[9] which

Table 2. Factors affecting fatigue in cancer patients

Variable	B	SE	β
Constant	8.64	0.46	-
Marital status (single = 0)	-1.64	0.18	-0.43[a]
Anemia (anemia = 0)	-1.81	0.19	-0.47[a]
Hypertension (yes = 0)	-1.61	0.20	-0.39[a]
Diabetes (yes = 0)	-0.13	0.29	-0.01[b]
Smoking (yes = 0)	0.04	0.16	0.01[c]
Activity	-0.09	0.09	-0.04[a]
BUN/Cr	0.01	0.005	0.20[a]

Adjusted R2 = 0.93; f = 120.94; [a] P < 0.001; [b] P = 0.65; [c] P = 0.80.

was higher than our study. In some other studies, the prevalence of fatigue in patients undergoing treatment was equivalent to our study.[8,9] The differences between the results of fatigue rate in these studies and the current study may be due to cultural differences. While our study was conducted in Tabriz with a Turkish culture, the studies by Sharifi Rizi et al.,[8] and Zeighami Mohammadi et al.,[9] had been conducted in Isfahan and Tehran, respectively, with a Persian culture. A difference in the endorsement of positive effect appears to be consistent across cultures, languages, and types of mood assessments.[27]

The results also showed that factors associated with fatigue were related to anemia disorders, blood pressure, diabetes, and low physical activity. In current study, anemia was the only factor associated with fatigue. As previous studies have shown, the presence of anemia is an important factor associated with fatigue in cancer patients.[28,29] Moreover, some studies have shown that the presence of anemia is an important factor in cancer patients' survival. Studies have reported that mild anemia treatment contributes to improving quality of life in cancer patients.[30] In the current study and a previous study,[31] the high level of fatigue in patients with colorectal cancer and leukemia cancer is justifiable concerning the presence of anemia.

Our results showed that some chronic disorders, such as blood pressure and diabetes, lead to increased fatigue in patients, which is consistent with the results of some other studies. In addition, some studies confirmed such an association between blood pressure and fatigue.[32,33] It seems that high blood pressure, directly and indirectly through the effects of antihypertensive drugs, is an important factor in the incidence and severity of fatigue in patients.[34] Furthermore, many studies have confirmed the relationship between BUN and fatigue, which regarding the relationship between BUN and protein metabolism and body muscle mass can be investigated.[31,35] Urea plays an important role in the metabolism of nitrogen-containing compounds. As a result, increased BUN levels indicate protein breakdown, which strongly affects muscle contraction and leads to fatigue. When the body lacks energy, protein is consumed and BUN levels increase in response to fatigue. Hence, this issue has given rise to BUN, which is an important factor in fatigue assessment.[36]

The analysis in current study showed that fatigue level in single patients was higher compared to married ones. This can be attributed to the lower social support in single patients than married ones, because married people receive support from their spouse, children, and relatives, as well as their parents.[37,38] Since fatigue is a multidimensional phenomenon and psychological factors can exacerbate it in patients, the findings of current research corroborate this case.

Moreover, fatigue level was higher in patients with physical activity for less than 30 minutes a day or more than 2 hours a day. Previous studies have shown the significant role of physical activity in the management of fatigue-related cancer.[39] The results showed that moderate physical activity can reduce fatigue, and higher and lower levels of activity can have reverse effects on fatigue. The results of a systematic review by Cramp & Byron-Daniel are compatible with the results of current study; they showed that physical activity is an important factor in decreasing fatigue in patients with cancer. However, more studies are needed regarding the intensity and the amount of physical activity.[40] Therefore, the findings of current research showed that 1-2 hours of daily activity a day could decrease fatigue in patients with cancer.

In addition, the results showed that a high percentage of cancer survivors had moderate and severe fatigue. Given the findings from previous studies, the fatigue rate in cancer patients whose active treatment has been completed should be significantly reduced. However, the findings of the current study showed that many cancer survivors experience a moderate to high level of fatigue. Although much evidence and findings have been provided about CRF in recent decades, it has not been reported, diagnosed, or understood precisely yet.[16] One of the barriers to the evaluation and management of fatigue may be the lack of knowledge of the mechanisms underlying these symptoms, risk factors, and effective treatments.[18] Thus, adopting supportive care programs is necessary to reduce this annoying problem in cancer survivors. Furthermore, current study showed that physical factors such as anemia, blood pressure, BUN level, and physical activity level, along with psycho-social factors like marital status have a substantial effect on patients' fatigue level. Accordingly, supportive care programs to control the fatigue of cancer survivors should focus on the mentioned factors.

The main limitation of this study was that it was conducted in a governmental center located in East Azerbaijan province, which is a referral center for two neighboring provinces with a similar culture. However, we should be careful when generalizing the results to other cities of the country with different cultures. Finally, it is suggested that similar studies be conducted on patients from both governmental and private centers.

Conclusion
The prevalence of fatigue in cancer survivors is high. The CRF is related to such factors as blood pressure, diabetes mellitus, anemia, serum levels of the BUN, marital status, and levels of physical activity. Accordingly, there is an urgent need to develop supporting programs for CRF management and related factors in cancer survivors. Management of any medical conditions including anemia, diabetes, and hypertension and some lifestyle modifications such as quitting smoking and diet adjustments should be included in such supportive programs.

Research Highlights

What is the current knowledge?
Cancer-related fatigue (CRF) is one of the major problems experienced by cancer patients. Identifying the prevalence and factors associated with CRF may be effective in designing appropriate interventions to reduce this problem.

What is new here?
The CRF is related to such factors as blood pressure, diabetes mellitus, anemia, serum levels of the BUN, marital status, and levels of physical activity.

References
1. Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin. 2019;69(5):363-85. doi: 10.3322/caac.21565
2. de Moor JS, Mariotto AB, Parry C, Alfano CM, Padgett L, Kent EE, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. Cancer Epidemiol Biomarkers Prev. 2013;22(4):561-70. doi: 10.1158/1055-9965.epi-12-1356
3. Rolke HB, Bakke PS, Gallefoss F. HRQoL changes, mood disorders and satisfaction after treatment in an unselected population of patients with lung cancer. Clin Respir J. 2010;4(3):168-75. doi: 10.1111/j.1752-699X.2009.00171.x
4. Young KE, White CA. The prevalence and moderators of fatigue in people who have been successfully treated for cancer. J Psychosom Res. 2006;60(1):29-38. doi: 10.1016/j.jpsychores.2005.03.011
5. de Santiago A, Portela MA, Ramos L, Larumbe A, Urdiroz J, Martínez M, et al. A new palliative care consultation team at the oncology department of a university hospital: an assessment of initial efficiency and effectiveness. Support Care Cancer. 2012;20(9):2199-203. doi: 10.1007/s00520-012-1476-x
6. Delgado-Guay MO, Parsons HA, Li Z, Palmer LJ, Bruera E. Symptom distress, interventions, and outcomes of intensive care unit cancer patients referred to a palliative care consult team. Cancer. 2009;115(2):437-45. doi: 10.1002/cncr.24017
7. Dhillon N, Kopetz S, Pei BL, Fabbro ED, Zhang T, Bruera E. Clinical findings of a palliative care consultation team at a comprehensive cancer center. J Palliat Med. 2008;11(2):191-7. doi: 10.1089/jpm.2007.0094
8. Sharifi Rizi M, Ghanbari Khanghah A, Adib M, Kazem Nejad Leili E. The assessment of fatigue and its related factors in patients with cancer. J Holist Nurs Midwifery. 2017;27(2):75-83. doi: 10.18869/acadpub.hnmj.27.2.75
9. Zeighami Mohammadi S, Houshmand P, Jafari F, Esmaily H, Kooshyar MM. The relationship between anemia and severity of fatigue and quality of life in cancer patients undergoing chemotherapy. Medical Sciences Journal of Islamic Azad University. 2011;20(4):265-72. (Persian).
10. Berger AM, Mooney K, Alvarez-Perez A, Breitbart WS, Carpenter KM, Cella D, et al. Cancer-related fatigue, version 2.2015. J Natl Compr Canc Netw. 2015;13(8):1012-39. doi: 10.6004/jnccn.2015.0122
11. Mitchell SA. Cancer-related fatigue: state of the science. PM R. 2010;2(5):364-83. doi: 10.1016/j.pmrj.2010.03.024
12. Poulson MJ. Not just tired. J Clin Oncol. 2001;19(21):4180-1. doi: 10.1200/jco.2001.19.21.4180
13. Meeske K, Smith AW, Alfano CM, McGregor BA, McTiernan A, Baumgartner KB, et al. Fatigue in breast cancer survivors two to five years post diagnosis: a HEAL Study report. Qual Life Res. 2007;16(6):947-60. doi: 10.1007/s11136-007-9215-3
14. Heydarnejad MS, Hassanpour DA, Solati DK. Factors affecting quality of life in cancer patients undergoing chemotherapy. Afr Health Sci. 2011;11(2):266-70.
15. Üstün TB, Kostanjsek N, Chatterji S, Rehm J. Measuring Health and Disability: Manual for WHO Disability Assessment Schedule WHODAS 2.0. United States: World Health Organization; 2010.
16. Passik SD, Kirsh KL, Donaghy K, Holtsclaw E, Theobald D, Cella D, et al. Patient-related barriers to fatigue communication: initial validation of the fatigue management barriers questionnaire. J Pain Symptom Manage. 2002;24(5):481-93. doi: 10.1016/s0885-3924(02)00518-3
17. Horneber M, Fischer I, Dimeo F, Rüffer JU, Weis J. Cancer-related fatigue: epidemiology, pathogenesis, diagnosis, and treatment. Dtsch Arztebl Int. 2012;109(9):161-71; quiz 72. doi: 10.3238/arztebl.2012.0161
18. Bower JE. Cancer-related fatigue--mechanisms, risk factors, and treatments. Nat Rev Clin Oncol. 2014;11(10):597-609. doi: 10.1038/nrclinonc.2014.127
19. Farajollahi M, Alikhani M, Farmani F, Hosseini F. Fatigue in cancer patients receiving chemotherapy. Iran Journal of Nursing. 2004;16(36):47-52. (Persian)
20. Safaee A, Moghimi-Dehkordi B, Reza Tabatabaee H, Zeighami B. Cancer related fatigue: a focus on breast cancer patients under chemotherapy. Open Breast Cancer J. 2009;1:14-7. doi: 10.2174/1876817200901010014
21. Ferrari M, Manea L, Anton K, Bruzzone P, Meneghello M, Zamboni F, et al. Anemia and hemoglobin serum levels are associated with exercise capacity and quality of life in

chronic obstructive pulmonary disease. BMC Pulm Med. 2015;15:58. doi: 10.1186/s12890-015-0050-y

22. Rejeh N, Heravi-Karimooi M, Bahrami T, Raeesi R, Tadrisi SD. The assessment of factors affecting fatigue in older people with hemodialysis. Iran J Nurs Res. 2015;10(3):108-17. (Persian)

23. Conley CC, Kamen CS, Heckler CE, Janelsins MC, Morrow GR, Peppone LJ, et al. Modafinil moderates the relationship between cancer-related fatigue and depression in 541 patients receiving chemotherapy. J Clin Psychopharmacol. 2016;36(1):82-5. doi: 10.1097/jcp.0000000000000442

24. Berger AM, Gerber LH, Mayer DK. Cancer-related fatigue: implications for breast cancer survivors. Cancer. 2012;118(8 Suppl):2261-9. doi: 10.1002/cncr.27475

25. Portenoy RK, Itri LM. Cancer-related fatigue: guidelines for evaluation and management. Oncologist. 1999;4(1):1-10. doi: 10.1634/theoncologist.4-1-1

26. Campos MPO, Hassan BJ, Riechelmann R, Del Giglio A. Cancer-related fatigue: a practical review. Ann Oncol. 2011;22(6):1273-9. doi: 10.1093/annonc/mdq458

27. Iwata N, Buka S. Race/ethnicity and depressive symptoms: a cross-cultural/ethnic comparison among university students in East Asia, North and South America. Soc Sci Med. 2002;55(12):2243-52. doi: 10.1016/s0277-9536(02)00003-5

28. Gascón P, Rodríguez CA, Valentín V, Mata JG, Carulla J, Cassinello J, et al. Usefulness of the PERFORM questionnaire to measure fatigue in cancer patients with anemia: a prospective, observational study. Support Care Cancer. 2013;21(11):3039-49. doi: 10.1007/s00520-013-1862-z

29. Savina S, Zaydiner B. Cancer-related fatigue: some clinical aspects. Asia Pac J Oncol Nurs. 2019;6(1):7-9. doi: 10.4103/apjon.apjon_45_18

30. Rades D, Kuhn H, Schultze J, Homann N, Brandenburg B, Schulte R, et al. Prognostic factors affecting locally recurrent rectal cancer and clinical significance of hemoglobin. Int J Radiat Oncol Biol Phys. 2008;70(4):1087-93. doi: 10.1016/j.ijrobp.2007.07.2364

31. Huang LZ, Huang BK, Liang J, Zheng CJ, Han T, Zhang QY, et al. Antifatigue activity of the liposoluble fraction from *Acanthopanax senticosus*. Phytother Res. 2011;25(6):940-3. doi: 10.1002/ptr.3346

32. Vissers PA, Falzon L, van de Poll-Franse LV, Pouwer F, Thong MS. The impact of having both cancer and diabetes on patient-reported outcomes: a systematic review and directions for future research. J Cancer Surviv. 2016;10(2):406-15. doi: 10.1007/s11764-015-0486-3

33. Wright F, Hammer MJ, D'Eramo Melkus G. Associations between multiple chronic conditions and cancer-related fatigue: an integrative review. Oncol Nurs Forum. 2014;41(4):399-410. doi: 10.1188/14.onf.41-04ap

34. Segerstedt J, Lundqvist R, Eliasson M. Patients with type 1 diabetes in Sweden experience more fatigue than the general population. J Clin Transl Endocrinol. 2015;2(3):105-9. doi: 10.1016/j.jcte.2015.06.001

35. Wang J, Sun C, Zheng Y, Pan H, Zhou Y, Fan Y. The effective mechanism of the polysaccharides from Panax ginseng on chronic fatigue syndrome. Arch Pharm Res. 2014;37(4):530-8. doi: 10.1007/s12272-013-0235-y

36. Li J, Sun Q, Meng Q, Wang L, Xiong W, Zhang L. Anti-fatigue activity of polysaccharide fractions from *Lepidium meyenii* Walp. (maca). Int J Biol Macromol. 2017;95:1305-11. doi: 10.1016/j.ijbiomac.2016.11.031

37. Bower JE. Cancer-related fatigue--mechanisms, risk factors, and treatments. Nat Rev Clin Oncol. 2014;11(10):597-609. doi: 10.1038/nrclinonc.2014.127

38. Moghaddam Tabrizi F, Alizadeh S. Cancer related fatigue in breast cancer survivors: in correlation to demographic factors. Maedica (Bucur). 2017;12(2):106-11.

39. Thong MSY, van Noorden CJF, Steindorf K, Arndt V. Cancer-related fatigue: causes and current treatment options. Curr Treat Options Oncol. 2020;21(2):17. doi: 10.1007/s11864-020-0707-5

40. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev. 2012;11(11):CD006145. doi: 10.1002/14651858.CD006145.pub3