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Naturally nutrient rich (NNR) score and the risk of colorectal cancer: a case-control study

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ABSTRACT

Background The association between colorectal cancer (CRC) and nutrients has been studied frequently. However, the association of nutrient density of diets with the risk of CRC has been less studied. This study aimed to investigate the association between CRC and naturally nutrient rich (NNR) score in Iranian adults.

Method This case-control study included 160 patients with colorectal cancer and 320 controls aged 35–70 years in Tehran, Iran. Dietary intake was assessed using a 168-item food frequency questionnaire. The NNR score was obtained by calculating the average daily value of 14 nutrients including protein, vitamins A, C, D, E, B_1, B_2, B_{12}, calcium, zinc, iron, folate, potassium and unsaturated fatty acids.

Results Regarding dietary intake of the components of NNR score, the case group had a lower intake of polyunsaturated fat (15.41±4.44 vs 16.54±4.20 g/day, p=0.01), vitamin E (10.15±4.16 vs 13.1±5.33; p=0.001), vitamin B_1 (2±0.86 vs 2.19±0.84 mg/day, p=0.03) and folate (516.45±96.59 vs 571.05±80.31; p=0.001) and a higher intake of oleic acid (8.21±5.46 vs 5.59±3.17 g/day, p=0.01) compared with the control group. Colorectal cancer risk was inversely associated with the NNR score after adjusting for the confounders (OR 0.92; 95% CI 0.88 to 0.97; p=0.03).

Conclusion Low NNR scores may be linked to CRC. If confirmed by future longitudinal research, this result may help prevent CRC by recommending nutrient-rich diets.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Colorectal cancer (CRC) is the third most common cancer and the second major cause of cancer-related death worldwide.

⇒ The evidence regarding diet, and particularly the association of specific foods and nutrients with CRC, is inconsistent with few exceptions.

⇒ Dietary nutrient density score (naturally nutrient rich (NNR)) is a widely accepted nutrient-to-calorie ratio that can be calculated as a percentage of the average daily value for 16 nutrients.

WHAT THIS STUDY ADDS

⇒ The results of this study will help us to adjust a suitable diet for people at risk of colon cancer or to predict its prognosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings suggested lower NNR scores which reflect low consumption of some macronutrients and micronutrients may be related to the risk of CRC.

⇒ If confirmed with future longitudinal studies, the findings of this study will be beneficial in providing dietary recommendations for the prevention of CRC.

INTRODUCTION

Colorectal cancer (CRC) is the third most frequent cancer and the second major cause of cancer mortality.[1] The prevalence of CRC has been dramatically growing at an alarming rate globally in recent years and 1.93 million new CRC cases and 0.94 million CRC-caused deaths were reported in 2020 worldwide, representing 10% of the global cancer incidence.[2] Several risk factors such as environmental (modifiable) and genetics (non-modifiable) factors have been linked to CRC progression.[3] There are some evidence on the association of specific foods and nutrients with CRC through different mechanisms.[4–6] For example, consumption of nutrients that diminish colonic exposure to bile acids and microbial bile acid metabolites may be an effective method for lowering CRC risk.[7] Moreover, anti-inflammatory effects of short-chain fatty acids (SCFAs) and omega-3 polyunsaturated fatty acids (PUFAs) have been considered as possible factors to prevent gut microbiota imbalance and reduce the risk of CRC.[8] The higher intake of fibre associated with lower consumption of meat and consumption of fruit and vegetables may reduce the incidence of CRC.[9] Some other dietary components such as vitamins D, E and C, selenium and curcumin may also reduce the risk of CRC.[10–15]

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As mentioned above, the effect of nutrients has been evaluated separately on CRC. However, the association of nutrient-rich diets with the risk of CRC has been less studied. The naturally nutrient rich (NNR) score is a nutrient-to-calorie ratio that is calculated as the average of the per cent daily value (%DV) of 16 nutrients.[16] Without focusing on a specific food or nutrient, the NNR score evaluates the adequacy and quantity of some beneficial nutrients in the diet.[17] A higher NNR score indicates a diet with greater nutrient density. Several studies have demonstrated the usefulness of the NRS in evaluating nutrient density across different populations.[18 19] NNR score examines the quantity of micronutrients based on guidelines and its primary purpose is to ensure adequate intake of micronutrients to improve the quality of diet.[20] Due to the significance of energy intake in the assessment of the association between diseases and diet, in addition to nutrients, the total energy intake is taken accounted for in the NNR score calculation.[21]

Recently, some studies have been conducted on the relationship between the health outcomes and NNR score.[16 20 22] However, few studies have been done on the association between different types of cancer and NNR score. Therefore, the present study aimed to investigate the relationship between NNR score and CRC in Iranian adults. The results may help us recommend a proper diet for people at risk for CRC.

METHODS

This hospital-based case-control study was carried out between the summer of 2020 and June 2021 on 480 rendomly selected participants including 160 patients with CRC in stages 3 and 4 as the case group and 320 age-matched non-cancer patients as the control group in Tehran, Iran. The sample size was determined using OPENEPI online software.[23] The patients with CRC were histologically diagnosed with primary CRC and underwent surgery at Firoozgar Hospital in Tehran, Iran. Since all patients were recruited from the same hospital, were at the same stage of cancer and had surgery, they were treated with similar medicines, including adjuvant chemotherapy with the 5-fluorouracil, leucovorin and oxaliplatin method after the surgery. The control group was randomly selected among non-cancer indiviuals referring to Firoozgar hospital for general check-up. The inclusion criteria of the case group were willingness to participate in the study, histological confirmation of CRC, a maximum of 3 months after the first diagnosis of CRC and age between 35 and 70 years. The inclusion criteria for the control group were willingness to take part in the study, no malignancies and age between 35 and 70 years. Also, patients receiving supplements were not included in the study. The exclusion criteria were inability to collect the required data (n=9), drugs and supplement affecting dietary intake (n=2), total energy intake <800 kcal/day or >4200 kcal/day for men and<600 kcal/day or >3500 kcal/day for women (n=10). There were ultimately 480 participants including 160 cases and 320 controls.

DATA COLLECTION

Anthropometric status, food intake and physical activity were all assessed for each individual. Face-to-face interviews were used to collect data on sociodemographic factors such as age, gender, marital status, ethnicity, smoking and alcohol consumption. A patient's medical background including diabetes, inflammatory bowel disease and a family history of CRC in first-degree relatives (father, mother, children, brothers and sisters) and second-degree relatives (grandfather, grandmother, aunt, uncle and grandchild) was collected through face-to-face interviews.

The height and weight were measured by professionals using a standard SECA stadiometer and scale with an accuracy of 0.5 cm and 100 g, respectively. In the case group, the possible weight change of the patients in the last 1 year was investigated and if there was a significant weight change (>10%), the weight before the disease was considered. The body mass index (BMI) of the participants was calculated by dividing their weight in kg by their height squared in m^2. The information regarding the physical activity level was collected through the International Physical Activity Questionnaire, the validity and reliability of which have already been confirmed in Iran.[24] The amount of participants' activity at home, during exercise, commuting and sedentary activities in 1 week (before the disease in the case group) was determined via this questionnaire, and their activity level was compared according to the metabolic equivalent of task.

ASSESSMENT OF DIETARY INTAKE AND NNR SCORE

The participants' food intake was assessed by filling out a 168-item food frequency questionnaire (FFQ), whose validity and reliability have already been confirmed.[25] The information on dietary intake during the year before the diagnosis of the disease was collected by FFQ, and the intake of macronutrients and micronutrients were assessed using Nutritionist IV software. The NNR score is based on a nutrient-to-calorie ratio that examines the quantity of micronutrients based on guidelines.[17] In

Table 1 The characteristics of study participants

	Cases (n=160)	Controls (n=320)	P value
Age (year)	52.36±17.060	47.8±10.82	0.06
Males n (%)	81 (51%)	32 (10%)	0.001
BMI (kg/m^2)	27.59±3.25	28.76±3.97	0.001
Low activity level n (%)	136 (85%)	314 (98%)	0.25
Smoking n (%)	9 (6%)	32 (10%)	0.004
Drink alcohol n (%)	22 (14%)	30 (9%)	0.12

BMI, body mass index.

order to estimate the NNR index, the DV of each nutrient was determined for each 2000 kcal energy intake based on the US dietary reference intakes. For this purpose, dietary intake of 14 nutrients including protein, vitamins A, C, D, E, B_1, B_2, B_{12}, calcium, zinc, iron, folate, potassium and unsaturated fatty acids was compared with reference intake amounts of these foods in a 2000-calorie diet recommended by the Food and Nutrition Board. After calculating the DV, the NNR value was obtained through calculating the average DV of these 14 nutrients as follows:

NNR score=∑%DV 2000 kcal/14.

STATISTICAL ANALYSIS

The daily intake of nutrients in the case and control groups were compared using the independent t-test. The binomial logistic regression analysis method was applied in order to investigate the relationship between CRC and NNR. The regression models comprised crude (model 1), adjusted for age and sex, smoking and alcohol consumption (model 2) and additionally adjusted for BMI and calorie intake (model 3). Statistical analysis was performed using SPSS software V.21 (SPSS, Chicago, Illinois, USA), and a p value <0.05 was considered statistically significant in all analyses.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

This study was conducted on patients with CRC. The patients with CRC were histologically diagnosed with primary CRC and underwent surgery at Firoozgar Hospital in Tehran, Iran . Dietary intake was assessed using a 168-item FFQ. The NNR score was obtained by calculating the average DV of 14 nutrients. Patients were involved in the recruitment to and conduct of the study. The study information was summarised and provided to the participants at the end of the study.

RESULTS

The characteristics of the participants are presented in table 1. The cases had a lower BMI (27.59±3.25 vs 28.76±3.97 kg/m^2, p=0.001), and a higher tobacco consumption (65% vs 87%, p=0.004) compared with the controls. There was no significant difference between age, alcohol consumption and physical activity level of the cases and controls.

A comparison of the intake of macronutrients and micronutrients in the case and control groups is shown in table 2. Regarding dietary intake of the components of NNR score, the case group had a lower intake of polyunsaturated fat (15.41±4.44 vs 16.54±4.20 g/day, p=0.01), vitamin E (10.15±4.16; p=0.001), vitamin B_1 (2±0.86 vs 2.19±0.84 mg/day, p=0.03) and folate (516.45±96.59; p=0.001) and a higher intake of oleic acid (8.21±5.46 vs 5.59±3.17 g/day, p=0.01) compared with the control group. There was no significant difference regarding the intake of vitamin C, vitamin D, iron, calcium, zinc, copper, potassium, vitamin B_2 and vitamin B_{12}.

Table 3 compares the intake of macronutrients and micronutrients based on the NNR score median. The participants with the NNR score >99.53 had higher intake of fibre (26.27±5.22 vs 24.40±6.37 g/day, p=0.002), crude fibre (9.93±2.76 vs 9.25±3.73 g/day, p=0.04), magnesium (349.20±43.49 vs 335.52±82.10 mg/day, p=0.04), zinc (11.48±2.67 vs 9.82±3.65 mg/day, p=0.001), potassium (4052.51±561.88 vs 3882.29±1018.90 mg/day, p=0.04), beta-carotene (2480.63±800.08 vs 2218.05±1032.69 µg/day, p=0.005), vitamin B_1 (2.30±0.79 vs 1.97±0.84 mg/day, p=0.001), vitamin B_2 (3.68±0.99 vs 1.98±1.18 mg/day, p=0.001), vitamin E (13.37±3.9 vs 11.23±6.43 mg/day, p=0.001), vitamin B_{12} (4.92±1.72 vs 3.76±2.83 mg/day, p=0.001), biotin (29.11±0.68 vs 27.10±8.57 µg/day, p=0.007), vitamin C (159.17±64.16 vs 139.22±34.63 mg/day, p=0.001) and vitamin D (1.28±0.73 vs 1.08±0.70 mg/day, p=0.005) compared with the participants with lower than median of NNR score.

The association between CRC and NNR score is shown in table 4. There was a negative association between NNR score and CRC (OR 0.96, 95% CI 0.97 to 0.99, p=0.04). The association remained significant after adjusting for age and sex, smoking and physical activity (model 2) and after additional adjustment for BMI and calorie intake (model 3) (OR 0.92; 95% CI 0.88 to 0.97; p=0.03) (figure 1).

DISCUSSION

According to our knowledge, this is the first study to examine the connection between NNR score and CRC. There was an inverse connection between NNR score and CRC, and the association remained significant after adjusting for age and sex, smoking and physical activity and after additional adjustments for BMI and calorie intake. In addition, regarding dietary intake of the components of NNR score, the case group had a lower intake of polyunsaturated fat, vitamin E, vitamin B_1, and folate and a higher intake of oleic acid compared with the control group. There was no significant difference regarding the information on vitamin C, vitamin D, iron, calcium, zinc, copper, potassium, chromium, molybdenum, tocopherol, vitamins B_2, B_3, B_6, B_{12}, pantothenic acid and phosphorus. In line with the present study, a recent prospective cohort study in China indicated that a higher nutrient-rich food index was related to improved recovery in patients with ovarian cancer.[26] Furthermore, Streppel *et al* reported that there was an association between the nutrient-rich food score and a lower risk of all-cause mortality.[27]

While the effect of nutrients has been assessed in several studies separately, few studies have focused on how the whole diet affects CRC. Bradbury *et al*[9] reported that a higher intake of fibre is associated with a lower intake of meat, and the consumption of fruit and vegetables may reduce the incidence of CRC. Also, several studies found

Table 2 Comparison of dietary intake of nutrients among the case and control groups

	Cases (n=160) Mean±SD	Controls (n=320) Mean±SD	P value
Calorie (kcal/day)	2493.39±176.02	2568.76±404.48	0.03
Protein (g/day)	85.77±9.17	85.4±19.85	0.83
Carbohydrate (g/day)	354.28±33.72	368.89±51.49	0.03
Fat (g/day)	88.90±10.62	90.15±20.15	0.31
Cholesterol (g/day)	273.07±53.63	257.17±61.12	0.02
SFA (g/day)	31.68±6.05	31.19±10.04	0.59
MUFA (g/day)	28.17±4.83	28.79±6.38	0.31
PUFA (g/day)	15.41±4.44	16.54±4.20	0.01
Oleic acid (g/day)	8.21±5.46	5.59±3.17	0.001
Linolenic acid (g/day)	0.83±0.80	0.99±0.73	0.052
Linoleic acid (g/day)	7.02±4.08	6.03±3.44	0.08
EPA (g/day)	0.26±0.25	0.28±0.26	0.30
DHA (g/day)	0.68±0.56	0.63±0.59	0.42
Fibre (g/day)	23.77±4.86	26.01±6.17	0.001
Soluble fibre (g/day)	0.99±0.65	1.08±0.79	0.23
Insoluble fibre (g/day)	5.08±1.80	5.28±2.31	0.38
Crude fibre (g/day)	9.08±2.42	9.85±3.44	0.01
Sugar (g/day)	116.06±20.64	126.79±31.57	0.001
Iron (mg/day)	18.71±3.19	18.62±2.88	0.77
Calcium (mg/day)	1206.96±118.71	1230.07±498.98	0.59
Magnesium (mg/day)	332.03±42.90	348.88±73.66	0.01
Phosphors (mg/day)	1396.36±172.87	1412.65±461.03	0.68
Zinc (mg/day)	10.75±2.44	10.59±3.43	0.64
Copper (mg/day)	1.56±0.66	1.68±0.69	0.11
Manganese (mg/day)	4.83±1.74	5.24±1.09	0.003
Selenium (mg/day)	51.54±25.96	68.70±20.13	0.001
Fluoride (mg/day)	1583.32±9773.24	10820.81±3431.17	0.001
Chromium (µg/day)	0.12±0.17	0.99±0.15	0.15
Molybdenum (µg/day)	50.89±9.35	50.75±4.70	0.87
Sodium (mg/day)	6355.03±1523.70	6085.03±1059.26	0.03
Potassium (mg/day)	3921.24±389.23	3990.76±886.81	0.28
Vitamin A (µg/day)	691.08±158.84	842.47±288.87	0.001
Beta-carotene (µg/day)	2076.30±591.56	2468.07±936.27	0.001
Vitamin E (mg/day)	10.15±4.16	13.10±5.33	0.001
Alpha-tocopherol (mg/day)	9.14±5.02	9.06±3.74	0.20
Vitamin B_1 (mg/day)	2±0.86	2.19±0.84	0.03
Vitamin B_2 (mg/day)	2023±0.99	2.34±1.18	0.33
Vitamin B_3 (mg/day)	21.44±2.53	21.75±3.14	0.32
Vitamin B_6 (mg/day)	1.93±0.80	1.92±0.84	0.88
Folate (µg/day)	516.45±96.59	571.05±80.31	0.001
Vitamin B_{12} (mg/day)	4.47±1.9	4.27±2.56	0.40
Pentatonic acid (mg/day)	5.51±1.77	5.36±1.93	0.43
Biotin (µg/day)	26.90±4.58	28.76±8.04	0.002
Vitamin C (mg/day)	145.16±21.75	150.97±56.75	0.24
Vitamin D (mg/day)	1.04±0.82	1.01±1.77	0.17
Vitamin K (mg/day)	161.73±48	144.01±26.35	0.001

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

Table 3 Comparison of macronutrients based on NNR score levels

	Higher than 99.53	Lower than 99.53	P value
Calorie (kcal/day)	2552.06±223.71	2535±485.42	0.67
Protein (g/day)	86.84±10.41	84.44±23.9	0.20
Carbohydrate (g/day)	365.51±36.19	362.60±59.94	0.56
Fat (g/day)	89.97±11.30	90.24±24.43	0.89
Cholesterol (g/day)	264.47±41.02	256.76±78.97	0.22
Saturated fat (g/day)	31.29±5.80	31.51±12.19	0.82
MUFA (g/day)	28.75±4.35	28.44±7.74	0.62
PUFA (g/day)	16.26±3.60	16.27±5.26	0.97
Oleic (g/day)	6.24±3.07	6.47±5.06	0.60
Linoleic (g/day)	6.23±3.08	6.43±4.47	0.61
Linolenic (g/day)	1±0.79	0.99±0.74	0.16
EPA (g/day)	0.290±0.26	0.26±0.25	0.36
DHA (g/day)	0.69±0.59	0.59±0.57	0.09
Fibre (g/day)	26.27±5.22	24.40±6.37	0.002
Soluble fibre (g/day)	1.06±0.72	2.01±0.79	0.35
Insoluble fibre (g/day)	5.25±1.85	5.24±2.66	0.97
Crude fibre (g/day)	9.93±2.76	9.25±3.73	0.04
Sugar (g/day)	125.33±19.79	121.36±38	0.19
Iron (mg/day)	18.71±2.5	18.56±3.4	0.61
Calcium (mg/day)	1236.26±143.63	1212.87±624.73	0.61
Magnesium (mg/day)	349.20±43.49	335.52±82.10	0.04
Phosphorus (mg/day)	1422.52±169.25	1390.59±575.43	0.45
Zinc (mg/day)	11.48±2.67	9.82±3.65	0.001
Copper (mg/day)	1.70±0.720	1.59±062	0.08
Manganese (mg/day)	5.06±1.51	5.10±1.77	0.79
Selenium (mg/day)	64.10±13.17	61.77±28.38	0.30
Fluoride (mg/day)	12086.28±4866.50	12600.99±8602.55	0.46
Chromium (µg/day)	0.11±0.15	0.93±0.14	0.18
Molybdenum (µg/day)	–	50.8±7.60	0.90
Sodium (mg/day)	6183.58±864.77	6152.17±1647.69	0.81
Potassium (mg/day)	4052.51±561.88	3882.29±1018.90	0.04
Vitamin A (µg/day)	749.46±170.99	726.69±281.88	0.32
Beta-carotene (µg/day)	2480.63±800.08	2218.05±1032.69	0.005
Vitamin E (mg/day)	13.37±3.9	11.23±6.43	0.00
Alpha-tocopherol (mg/day)	9.22±3.2	9.77±5.19	0.38
Vitamin B_1 (mg/day)	2.30±0.79	1.97±0.84	0.001
Vitamin B_2 (mg/day)	3.68±0.99	1.98±1.18	0.001
Vitamin B_3 (mg/day)	21.63±2.58	21.66±3.32	0.92
Vitamin B_6 (mg/day)	1±0.81	1.91±0.85	0.48
Folate (mg/day)	560.80±71.03	547±113.70	0.15
Vitamin B_{12} (mg/day)	4.92±1.72	3.76±2.83	0.00
Pantothenic acid (mg/day)	5.55±1.68	5.25±2.11	0.11
Biotin (µg/day)	29.11±0.68	27.10±8.57	0.007
Vitamin C (mg/day)	159.17±64.16	139.22±34.63	0.00
Vitamin D (mg/day)	1.28±0.73	1.08±0.70	0.005
Vitamin K (mg/day)	151.7±829.61	147.03±44.79	0.21

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MUFA, monounsaturated fatty acid; NNR, naturally nutrient rich; PUFA, polyunsaturated fatty acid.

Table 4 Crude and multivariable-adjusted ORs and 95% CIs for colorectal cancer with a median of NNR

	OR	95% CI	P value
Model 1	0.96	0.97 to 0.99	0.04
Model 2	0.91	0.30 to 0.98	0.03
Model 3	0.92	0.88 to 0.98	0.03

Model 1: crude; model 2: adjusted for age and sex, smoking and physical activity; model 3: additional adjustments for BMI and calorie intake.
BMI, body mass index; NNR, naturally nutrient rich.

that curcumin, vitamins D, E and C and selenium may reduce the risk of CRC.[10–15] Furthermore, Gheorghe *et al*[8] found that SCFA and omega-3 fatty acids may reduce the risk of CRC through anti-inflammatory effects.

The results of the present study also indicated that dietary intake of some other nutrients such as magnesium, manganese, selenium, fluoride, beta-carotene and biotin was lower in the case group compared with the control group. Diets containing fruits, vegetables and whole grains may reduce the risk of CRC due to their antioxidant properties. Wedlake *et al* found that dietary fibre may play a significant role in the prevention of CRC.[28] The NNR score, which is based on mean percentage DVs for 14 nutrients in 2000 kcal food, can be used to assign nutrient density values to foods within food groups.[17] So, the NNR score may predict the ability of diet to prevent chronic diseases such as inflammatory diseases and cancer.

However, this study has some limitations, including the fact that it was conducted in the Iranian population without considering racial differences and genetic influences. Also, retrospective studies are based on participants' memory and may be associated with overestimation and underestimation of dietary intakes. In order to minimise biases in this study, a validated FFQ was used to evaluate food intake, and in cases where sufficient information was not obtained from the participants, first-degree relatives were asked to confirm and complete the data. It is crucial to conduct more studies in larger populations and different racial groups considering the genetic backgrounds to confirm the results and to set a proper diet for people at risk for CRC.

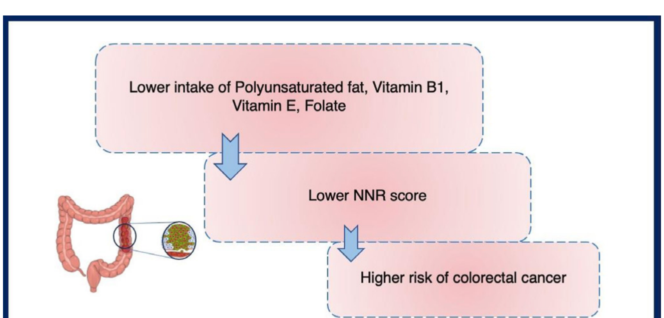

Figure 1 Colorectal cancer risk was inversely associated with the naturally nutrient rich (NNR) score.

CONCLUSION

Lower NNR scores which reflect low consumption of some macronutrients and micronutrients may be related to the risk of CRC. If confirmed with future longitudinal studies, the findings of this study will be beneficial in providing dietary recommendations for the prevention of CRC. Further longitudinal studies on different racial and age groups are needed to confirm these findings and discover the underlying mechanisms of the association of CRC with NNR score.

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Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval This research has been approved according to the code IR.SBMU.CRC.REC.1402.003 on 23 July 2019 by the Ethics Committee at the Cancer Research Center of Shahid Beheshti University of Medical Sciences, Tehran, Iran. The details of the present study were explained sufficiently to all participants, and they filled out a consent form before collecting the data. Also, the condition of not imposing the cost of blood sampling or testing on the patients and paying the cost of transportation for them was explained prior to the study.

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