Integrative Cancer Therapies
Volume 21: 1–13

DOI: 10.1177/15347354221105485
journals.sagepub.com/home/ict
SAGE

Milk and Egg Are Risk Factors for Adverse Effects of Capecitabine-Based Chemotherapy in Chinese Colorectal Cancer Patients

Jinrong Xu, MD[1*], Zeshuai Lin, MD[2,3*], Jiani Chen, BD[3*], Jian Zhang, PhD[3], Wanqing Li, BD[4], Rui Zhang, BD[4], Jin Xing, BD[5], Zhihuan Ye, BD[5], Xiaoping Liu, BD[5], Qianmin Gao, BD[3], Xintao Chen, BD[3], Jingwen Zhai, BD[3], Houshan Yao, PhD[3], Mingming Li, PhD[3], and Hua Wei, PhD[3,6]

Abstract

Background: Chemotherapy-induced adverse effects (CIAEs) remain a challenging problem due to their high incidences and negative impacts on treatment in Chinese colorectal cancer (CRC) patients. We aimed to identify risk factors and predictive markers for CIAEs using food/nutrition data in CRC patients receiving post-operative capecitabine-based chemotherapy. **Methods:** Food/nutrition data from 130 Chinese CRC patients were analyzed. Univariate and multivariate analyses were used to identify CIAE-related food/nutrition factors. Prediction models were constructed based on the combination of these factors. The area under the receiver operating characteristic curve (AUROC) was used to evaluate the discrimination ability of models. **Results:** A total of 20 food/nutrition factors associated with CIAEs were identified in the univariate analysis after adjustments for total energy and potential confounding factors. Based on multivariate analysis, we found that, among these factors, dessert, eggs, poultry, and milk were associated with several CIAEs. Most importantly, poultry was an overall protective factor; milk and egg were risk factors for hand-foot syndrome (HFS) and bone marrow suppression (BMS), respectively. Developed multivariate models in predicting grade 1 to 3 CIAEs and grade 2/3 CIAEs both had good discrimination (AUROC values from 0.671 to 0.778, 0.750 to 0.946 respectively), which had potential clinical application value in the early prediction of CIAEs, especially for more severe CIAEs. **Conclusions:** Our findings suggest that patients with high milk and egg intakes should be clinically instructed to control their corresponding dietary intake to reduce the likelihood of developing HFS and BMS during capecitabine-based chemotherapy, respectively.
Trial registration: ClinicalTrials.gov Identifier: NCT03030508.

Keywords

anemia, bone marrow suppression, capecitabine, chemotherapy-induced adverse effects, chemotherapy-induced nausea and vomiting, colorectal cancer, food/nutrition factor, hand-foot syndrome

Submitted January 7, 2022; revised April 21, 2022; accepted May 20, 2022

[1]Taiyuan Institute of Technology, Taiyuan, Shanxi, China
[2]Shanxi Medical University, Taiyuan, Shanxi, China
[3]Second Affiliated Hospital of Naval Medical University, Shanghai, China
[4]Chengdu Medical College, Chengdu, China
[5]Shanghai University of Medicine & Health Sciences, Shanghai, China
[6]905th Hospital of PLA Navy, Naval Medical University, Shanghai, China

*These authors contributed equally to this work.

Corresponding Authors:
Houshan Yao, Department of General Surgery, Second Affiliated Hospital of Naval Medical University, 415 Fengyang Road, Shanghai 200003, China.
Email: Yao-hs@hotmail.com

Mingming Li, Department of Pharmacy, Second Affiliated Hospital of Naval Medical University, 415 Fengyang Road, Shanghai 200003, China.
Email: limingming@smmu.edu.cn

Hua Wei, Department of Pharmacy, Second Affiliated Hospital of Naval Medical University, 415 Fengyang Road, Shanghai 200003, China.
Email: weihua@smmu.edu.cn

Introduction

Capecitabine is a prodrug of 5-fluorouracil (5-FU). It has been widely used in the treatment of various solid tumors, such as colon, rectum, breast, and gastric cancers in both adjuvant and neoadjuvant settings.[1] Capecitabine can be applied alone or combined with other cytotoxic agents, including oxaliplatin, irinotecan, or cisplatin. The National Comprehensive Cancer Network (NCCN) guidelines of the US recommend capecitabine-based chemotherapy as a first-line chemotherapy regimen for stage II, III, and IV colorectal cancer (CRC),[2] which is one of the most common malignant tumors worldwide. CRC ranks third in incidence and second in mortality rate worldwide.[3]

Despite its promising treatment outcomes, capecitabine-based chemotherapy can also induce many adverse effects (chemotherapy-induced adverse effects, CIAEs). Nausea and vomiting (NV), hand-foot syndrome (HFS), and bone marrow suppression (BMS) are the 3 common adverse effects caused by capecitabine according to literatures and our ongoing observational clinical trial.[4-10] These CIAEs hamper the successful completion of anti-cancer treatment, bringing a highly burdensome condition for patients, and even threaten life if left untreated.[11]

In order to facilitate clinicians to develop personalized treatment strategies through CIAE prediction, it is urgent to identify all the important risk factors for CIAEs. Increasing evidence points out that nutrition factors are related to the CIAE susceptibility. Our previous study confirmed the association between variations in endogenous metabolites and the CIAE susceptibility.[12] For example, there was a positive relation between pre-operative urine 4-pyridoxic acid and HFS, which is an indicator of vitamin B6 catabolism during inflammation.[13,14] The level of vitamin B6 is remarkably dependent on dietary intake. Our earlier studies have also found a series of potential valuable hematological/body parameters to predict CIAEs in CRC patients,[15] some of which have been reported as predictors of CIAE risk in various cancer patients.[16,17] These parameters are also under the influence of nutrition factors in both short and long terms.[18-21] What's more, Kim et al showed that nutritional supplements can elicit beneficial effects on pancreatic and bile duct cancer patients receiving chemotherapy.[22] Therefore, we propose that food/nutrition factors are potential markers for CIAEs.

In this study, we performed a nutrition survey based on a modified and simple Food-Frequency Questionnaire 25 (FFQ25) for middle-aged and elderly residents in Shanghai, China.[23] FFQ25 showed reasonable reproducibility and validity of the major dietary patterns, compared with the full-length Food-Frequency Questionnaire.[23,24] And it is considered easier to use with convenience. The purpose of this study was to test the hypothesis that food/nutrition factors exert influence on the susceptibility to certain CIAEs and even can be used as predictive markers in CRC patients receiving post-operative capecitabine-based chemotherapy.

Materials and Methods

Patient Enrollment

Patients with recorded food/nutrition data and CIAE(s) per cycle who received capecitabine after radical surgery were enrolled in this study. They were selected from a registered ongoing clinical trial (registered at www.clinicaltrials.gov, NCT03030508) at Shanghai Changzheng Hospital from January 2018 to June 2019. Recruited subjects in CRC patients were (1) over 18 years old and (2) diagnosed with CRC by biopsy examination. The exclusion criteria were: (1) pregnant and lactating women, (2) patients with hypersensitivity to fluorouracil or severe metabolic failure, (3) patients with severe infection, (4) patients with cancers other than CRC within the first 5 years of CRC surgery, and (5) patients with any pre-operative anti-neoplastic medication.[12] This study was approved by Biomedical Research Ethics Committee of Shanghai Changzheng Hospital (No. 2016SL007), and written informed consent was obtained from every patient.

CIAEs were assessed according to Common Terminology Criteria for Adverse Events (CTCAE v4.03), based on which the CIAEs were graded from grade 0 (no symptom of a certain CIAE) to grade 4 (the most severe symptom of a certain CIAE). The occurrence of all incidences (grade 1-3) and severe incidences (grade 2/3) of each CIAE were studied. The clinical characteristics (sex, age, height, weight, and body mass index [BMI]) for all the enrolled patients were also collected.

Nutritional Status Assessment

The 25 food-item FFQ25 questionnaire about diet in the past 1 year was issued to patients after their radical surgery and was completed before the start of adjuvant chemotherapy (See detailed explanation on FFQ25 in Supplemental Methods). Patient's daily dietary intake amount of each food and total energy intake was calculated according to the collected data on the frequency and amount of food intake, referred to China Food Composition Tables 2002[25] and 2004.[26] Combining these 2 elements and the nutrition content of each food, the daily amount of various nutrient intake (protein, fat, carbohydrate, dietary fiber, cholesterol, vitamin A [VA], vitamin B1 [VB1], vitamin B2 [VB2], vitamin C [VC], vitamin E [VE], calcium, iron, and zinc) was also calculated. The frequency of food intake was defined as follows: "never," "less than once a month," "1-3 times per month," "1-2 times per week," "3-4 times per week," "5-6 times per week," "once a day," "2 times per day," "≥3 times per day," and their corresponding conversion factors are: 0.00, 0.03,

0.07, 0.21, 0.50, 0.79, 1.00, 2.00, 3.00. The weight of each food per serving is expressed in terms of "Liang" that is a traditional weight unit commonly used in Chinese, and 1 Liang equals to 50 g.[23] The amount of daily food intake was calculated from the FFQ25 using the following formula:

$$\text{food intake} = \text{conversion factor for frequency of food intake} \times \text{serving size} \times \text{total number of servings} \times \text{weight (or volume) of food per serving.}$$

Based on this, the amount of daily total energy, and nutrition content of food was calculated according to formulas (1) and (2), respectively. Patients with implausible total energy intake (<600 or above 4000 kcal) were excluded. The specific flow chart of participation is shown in Supplemental Figure S1.

$$\text{Total energy intake} = \sum_{n=1}^{i} \left(f1_i \times f2_i \times E_i \right) \quad (1)$$

$$\text{nutrition content of food} = \sum_{n=1}^{i} \left(f1_i \times f2_i \times N_i \right) \quad (2)$$

in which, f1 is the conversion factor for frequency, f2 is the conversion factor for intake, E is the energy from each food, N is the nutrition content from each food, and i equals to 1 to 25 food items (25 items in total).

Plasma Metabolome Profile

In order to further prove the existence of the changes in food/nutrition factors, the correlation between CIAE-related food/nutrition factors and CIAE-related plasma metabolome profile from 36 out of the 130 enrolled patients were analyzed. The plasma metabolome data of the 36 patients was acquired from published data.[7] To put it briefly, an UHPLC system coupled to a quadruple time-of-flight mass spectrometer was utilized for the metabolome assays. All the samples were screened separately under both positive and negative ionization modes, and the detailed methods of data pre-processing about metabolome were described in our previous study.[7]

Statistical Analysis

Descriptive statistics were conducted to investigate the demographic characteristics of patients as well as the information of CIAEs. Principal variance component analysis (PVCA)[27] was applied to study the influence of potential confounding factors of age, body weight, height, BMI on food/nutrition data, and those with continuous values were converted to discrete variables. Total energy intake has been proven to be related to intakes of food and nutrients.[28] Subsequently, the residual method was used to adjust the impact of total energy intake on food/nutrition data. Further, in order to remove the effect of the identified potential confounding factors, our data were then adjusted through the removeBatchEffect method in the "limma" package.

The univariate logistic regression analysis was employed for 2 different conditions: grade 1 to 3 versus grade 0, and grade 2/3 versus grade 0 to identify potential factors associated with all CIAEs and severe CIAEs respectively. On the basis of these significant relative food/nutrition factors, multivariate logistic regression analysis was then performed to further identify independent factors and construct a prediction model for each CIAE. The discrimination ability of each model was determined by the area under the receiver operating characteristic curve (AUROC) using "pROC" package. The best cut-off values for their predictive probabilities were determined by the maximum value of the Youden index (in the range of 0.6 sensitivity and 0.6 specificity). The "limma" package was applied for differential metabolome analysis. Spearman correlation was utilized to assess associations between food/nutrient intake and differentially expressed metabolites in plasma samples using cor. test () function. All statistical analyses were performed using R software (version 4.0.4), and $P < .05$ was considered to indicate statistical significance.

Results

Patient and CIAE Characteristics

Amongst 139 participants initially enrolled in this study, a total of 130 CRC patients from 31 to 88 years old, with the diagnosis of advanced CRC (stages II, III, and IV), were included in this study for final analysis; 83 (63.8%) patients were males, and 47 (36.2%) were females. They all received 3-week-cycle capecitabine-based adjuvant XELOX (capecitabine plus oxaliplatin) chemotherapy. During each cycle, patients received oxaliplatin (0.16-2 g/day) intravenously on day 1 and capecitabine (1.5 g/day) per oral for the first 2 weeks. The demographic characteristics and observed CIAEs during chemotherapy of these patients are described in Supplemental Table S1. The variations of these clinical covariates on our data are shown in Figure 1A.

Figure 1B displays the incidence of each CIAE. HFS had the highest incidence (64.6%), followed by CINV (54.6%), nausea (51.5%), BMS (43.8%), and vomiting (35.4%); and the incidences of the other CIAEs were all lower than 30%. In addition, the majority of patients suffered from CIAEs with grade 1 to 2. Higher incidences of grade 2/3 CIAEs were observed in CINV, nausea, HFS, and BMS, all of which were higher than 10% than the other CIAEs. It is noteworthy that the total incidences of CINV and nausea were approximately 50%, and grade 2/3 accounted for at least 20%. Thus, an understanding of these CIAEs and their related food/nutrition factors is crucial. The correlation clustering results of the CIAE grades showed the relationship among the CIAEs (Figure 1C).

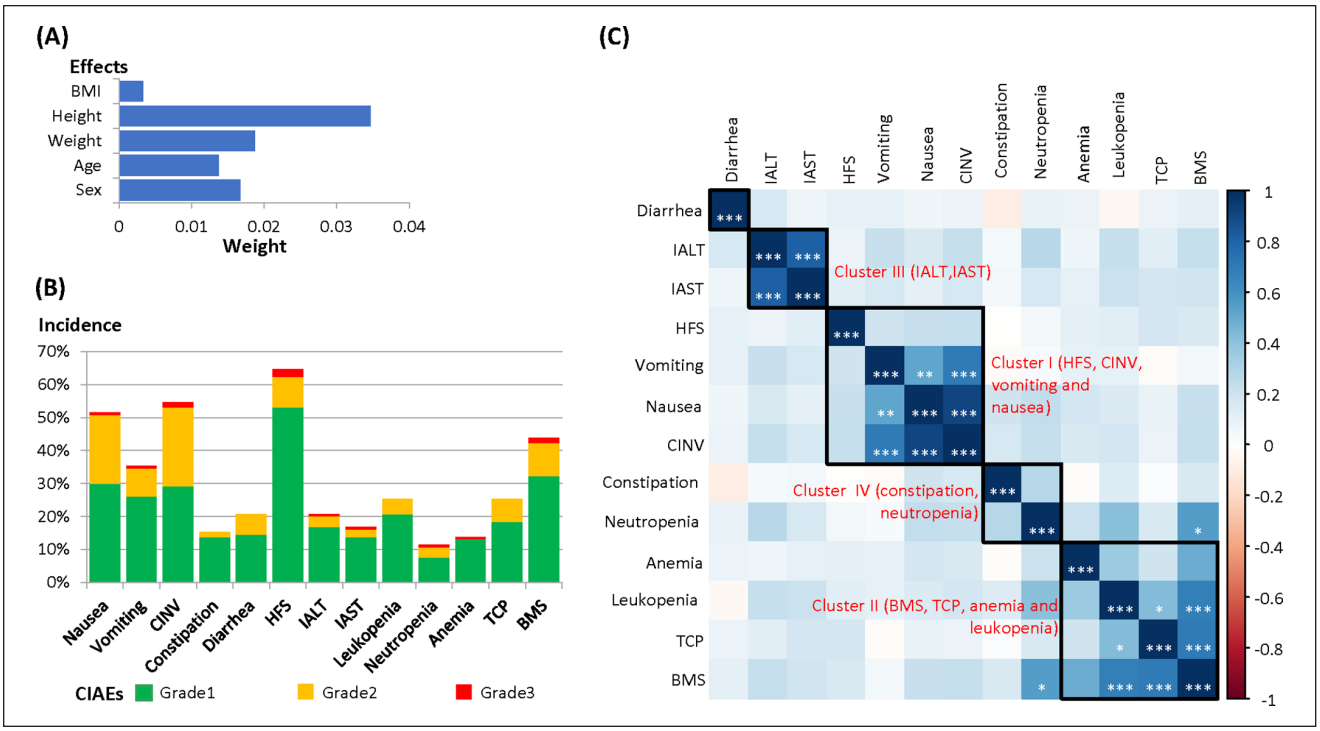

Figure 1. The characteristics of CIAEs. (A) The effects of patient clinical covariates on food/nutrition data. (B) Incidence rate of CIAEs. (C) The Pearson correlations across CIAEs. The CIAEs were subject to hierarchical clustering order using the agglomeration method with "hclust" by R package corrplot. Statistical significance: ***$P < .001$. **$P < .01$. *$P < .05$.
Abbreviations: BMS, bone marrow suppression; CINV, chemotherapy-induced nausea and vomiting; HFS, hand-foot syndrome; IALT, aspartate aminotransferase increased; IAST, aspartate aminotransferase increased; TCP, thrombocytopenia.

Adjustment for Confounding Factors and Univariate Analysis

Traditionally, food and nutrition factors were adjusted for the total energy intake via the residual method alone. Therefore, we first applied this normalization method and then performed univariate analysis (Supplemental Table S3). We found that a total of 15 factors were associated with CIAEs. Association of HFS with dessert, milk, VB2, and calcium were observed; besides, BMS was influenced by eggs, VB2, and nuts. Milk, VB2, and calcium were risk factors for grade 1 to 3 HFS, and dessert was a protective factor for grade 1 to 3 HFS. For grade 1 to 3 BMS, eggs, and VB2 were risk factors; for grade 2/3 BMS, nuts were a risk factor. In terms of food/nutrition factors, eggs were risk factors for BMS, leukopenia, TCP, and anemia. On the other hand, milk was a risk factor for HFS, diarrhea, and anemia.

The potential confounding factors exert influence on food consumption and nutrition factors (Figure 1A), the effects of which were further eliminated using the removeBatchEffect method after the residual method. Then we repeated the univariate analysis (Table 1). Among all the 20 factors in relation to CIAEs, HFS was influenced by dessert, milk, VB2, calcium, and poultry; CINV was influenced by dessert and poultry; the only influential factor for nausea was dessert; BMS was influenced by eggs, VB2, dessert, poultry, and nuts. Milk, VB2, and calcium were risk factors for HFS, and dessert and poultry were protective factors for HFS; for CINV, both dessert and poultry were protective factors; nausea negatively correlated with dessert; eggs, VB2, and nuts were risk factors for BMS, and dessert and poultry were protective factors. Overall, eggs were risk factors for BMS, leukopenia, TCP, and anemia. Poultry, on the other hand, was a protective factor for HFS, CINV, BMS, leukopenia, TCP, IALT, and IAST. Dessert was a protective factor for HFS, CINV, nausea, BMS, and diarrhea.

In general, the results of the 2 normalization methods were very similar to each other. Poultry was an overall protective factor; milk and eggs were risk factors for HFS and BMS, respectively. However, we found that the additional normalization for confounding factors gave more CIAE-related food/nutrition factors (20 relative factors) than normalization only for total energy intake (15 relative factors). On top of this, the number of statistically significant associations between food/nutrition factors and CIAEs based on confounding factor-normalized data (29 associations with grade1-3 CIAEs and 23 associations with grade 2/3 CIAEs) were also higher than

Table 1. Univariate Analysis of Factors Significantly Associated With CIAEs Using Data Normalized by the Combination of the Residual Method and Confounding Factors.

CIAEs	Food and nutrition factors	Grade 1-3 vs Grade 0		Grade 2/3 vs Grade 0	
		OR (95% CI)	*P*	OR (95% CI)	*P*
HFS	Calcium	1.004 (1.001-1.007)	.0115	—	—
	Dessert	0.113 (0.015-0.589)	.0204	—	—
	Milk	1.782 (1.099-3.029)	.0246	2.707 (1.296-6.124)	.0107
	Poultry	—	—	0 (0-0.022)	.0026
	VB2	8.899 (1.874-49.443)	.0085	—	—
CINV	Dessert	0.126 (0.016-0.671)	.0297	—	—
	Poultry	—	—	0.037 (0.001-0.75)	.0446
Nausea	Dessert	0.151 (0.02-0.782)	.0430	—	—
BMS	Dessert	0.103 (0.011-0.644)	.0298	—	—
	Eggs	2.901 (1.552-5.755)	.0013	5.26 (1.518-23.795)	.0164
	Nuts	—	—	11.468 (1.385-114.434)	.0258
	Poultry	—	—	0.005 (0-0.325)	.0254
	VB2	4.895 (1.182-23.078)	.0348	—	—
Vomiting	Beers	—	—	0 (0-0)	.0034
Leukopenia	Eggs	2.668 (1.332-5.736)	.0078	—	—
	Poultry	0.05 (0.002-0.738)	.0483	—	—
TCP	Eggs	3.313 (1.611-7.433)	.0019	—	—
	Poultry	—	—	0.001 (0-0.226)	.0240
	Tubers	—	—	13.582 (1.141-149.01)	.0300
Diarrhea	Calcium	1.004 (1.001-1.007)	.0131	1.006 (1.001-1.011)	.0238
	Dessert	0.041 (0.002-0.573)	.0329	—	—
	Manufactured meat	0 (0-0)	.0210	—	—
	Milk	1.753 (1.055-2.957)	.0309	2.787 (1.277-6.662)	.0121
	VB2	5.521 (1.053-33.297)	.0487	—	—
IALT	Beers	0 (0-0.035)	.0239	0 (0-0)	.0033
	DGV	0.577 (0.325-0.948)	.0432	—	—
	FWS	0.056 (0.002-0.72)	.0496	0 (0-0.052)	.0139
	Iron	0.827 (0.683-0.981)	.0393	—	—
	Poultry	0.01 (0-0.252)	.0090	0 (0-0.009)	.0092
	Sweet drinks	—	—	0 (0-0)	.0154
	Tubers	—	—	0 (0-0.132)	.0492
	VA	0.998 (0.996-1)	.0138	—	—
IAST	Beers	0 (0-0.132)	.0346	0 (0-0.004)	.0250
	Cholesterol	—	—	1.011 (1-1.023)	.0433
	Poultry	0.005 (0-0.191)	.0075	—	—
	Red meat	—	—	9.188 (0.838-102.457)	.0489
	Zinc	—	—	1.844 (0.97-3.5)	.0477
Constipation	Nuts	8.048 (1.147-58.644)	.0333	—	—
Anemia	Eggs	2.399 (1.028-6.01)	.0492	—	—
Neutropenia	FWS	0.005 (0-0.264)	.0189	0 (0-0.195)	.0275
	Rice	1.552 (0.996-2.426)	.0496	—	—
	Seafood	—	—	0 (0-0.578)	.0476
	Sweet drinks	—	—	0 (0-0.194)	.0415

Univariate logistic analysis was performed using data normalized by the combination of the residual method and confounding factors. The data were firstly normalized by the residual method, and then it was further normalized by the potential confounding factors (sex, age, height, weight, and body mass index [BMI]) by removeBatchEffect method in limma. In brief, after applying the residual method and removeBatchEffect method to the original data, we obtained a new expression matrix, with the same dimensions as our original dataset. This new expression matrix has been adjusted for both total energy intake and potential confounding factors of age, body weight, height, BMI. Further analyses were performed on the adjusted data. CIAEs are sorted in descending order based on their incidence rate. "—" values that are not statistically significant.

Abbreviations: BMS: bone marrow suppression; CI: confidence interval; CIAEs: chemotherapy-induced adverse effects; CINV: chemotherapy-induced nausea and vomiting; DGV: dark green vegetables; FWS: food with stuffing; HFS: hand-foot syndrome; IALT: alanine aminotransferase increased; IAST: aspartate aminotransferase increased; OR: odds ratio; TCP: thrombocytopenia; VA: vitamin A; VB2: vitamin B2.

Table 2. Multivariate Analysis of Factors Associated With CIAEs Using Data Normalized by the Combination of the Residual Method and Confounding Factors.

CIAEs	Food and nutrition factors	Grade 1-3 vs Grade 0		Grade 2/3 vs Grade 0	
		OR (95% CI)	*P*	OR (95% CI)	*P*
HFS	Milk	1.431 (0.727-2.916)	—	2.711 (1.195-6.816)	.0221
	Poultry	—	—	0 (0-0.028)	.0047
BMS	Dessert	0.113 (0.011-0.8)	.0497	—	—
	Eggs	3.346 (1.419-8.692)	.0085	9.673 (2.291-60.385)	.0056
	Nuts	—	—	16.542 (1.563-231.354)	.0239
	Poultry	—	—	0.004 (0-0.383)	.0320
Leukopenia	Eggs	2.65 (1.315-5.756)	.0090	—	—
	Poultry	0.048 (0.002-0.771)	.0483	—	—
TCP	Poultry	—	—	0.001 (0-0.342)	.0326
Diarrhea	Manufactured meat	0 (0-0.01)	.0469	—	—
IALT	Beers	0 (0-0.195)	.0451	0 (0-712.577)	—
IAST	Beers	0 (0-0.744)	—	0 (0-0.065)	.0385
	Poultry	0.007 (0-0.261)	.0129	—	—
Neutropenia	FWS	0.007 (0-0.459)	.0349	0.001 (0-0.298)	—

Statistically significant factors in univariate logistic analysis using data normalized by the combination of the residual method and confounding factors were entered in the multivariate logistic analysis. In brief, after applying the residual method and removeBatchEffect method to the original data, we obtained a new expression matrix, with the same dimensions as our original dataset. This new expression matrix has been adjusted for both total energy intake and potential confounding factors of age, body weight, height, BMI. Further analyses were performed on the adjusted data.
Abbreviations: BMS: bone marrow suppression; CI: confidence interval; CIAEs: chemotherapy-induced adverse effects; FWS: food with stuffing; HFS: hand-foot syndrome; IALT: alanine aminotransferase increased; IAST: aspartate aminotransferase increased; OR: odds ratio; TCP: thrombocytopenia.

the residual-normalized data (15 associations with grade1-3 CIAEs and 12 associations with grade 2/3 CIAEs) as shown in Table 1 and Supplemental Table S3. Besides these, the results generated from confounding factor-normalized data were more consistent with the result of CIAE clustering analysis. For example, HFS, CINV, nausea, and vomiting were clustered into cluster I. On the basis of normalization for confounding factors, univariate factor analysis revealed that dessert was the common protective factor for HFS, CINV, and nausea, which was in line with the result of cluster analysis (Figure 1C; Table 1). On the other hand, this type of similarity was not observed based on the residual-normalized data. Taken together, we decided to use the confounding factor-normalized data for subsequent analysis.

Multivariate Analysis

Multivariate analysis further showed that dessert, milk, eggs, FWS, manufactured meat, poultry, nuts, and beers were independent factors for CIAEs (Table 2). Amongst them, poultry, and eggs were common factors for several CIAEs. Poultry was a general protective factor for HFS, BMS, leukopenia, TCP, and IAST; dessert was a protective factor for BMS. On the contrary, milk was a risk factor for HFS, and eggs were a risk factor for BMS and leukopenia.

Correlation Between CIAE-Related Food/ Nutrition Factors and Plasma Metabolome

Correlation analysis demonstrated the remarkable association between the potential nutritional markers of CIAEs and multiple CIAE-related endogenous plasma metabolites (Figure 3), which further validated the effects of dietary intake. A single food factor, milk, retained in the multivariate analysis, was related to significantly altered 7 metabolites for HFS susceptibility, and all 4 food/nutrition factors (dessert, eggs, nuts, and poultry) showed significant association with 18 metabolites for BMS susceptibility.

Development of CIAE Prediction Models

We developed combined prediction models for CIAEs, which ultimately retained the significantly relevant nutrition predictors from the univariate analysis. Results showed that the AUROC of the developed models ranges from 0.574 to 0.946. Of these, the AUROC of 9 models were less than 0.7, 7 were between 0.7 and 0.8, 5 were greater than 0.8, and two were greater than 0.9. We identified that 12 of the grade 1 to 3 (leukopenia, diarrhea, IALT, IAST, and neutropenia) and grade 2/3 (HFS, BMS, TCP, diarrhea, IALT, IAST, and neutropenia) CIAEs in total had relatively modest predictive performances (AUROC higher than 0.7), which account for a third of the total prediction models

(Supplemental Table S4 and Figure S2). More importantly, there were 5 models in predicting grade 2/3 (HFS, BMS, IALT, IAST, and neutropenia) demonstrating excellent performance with AUROC values higher than 0.8, implying better accuracy than models in predicting grade 1 to 3 CIAEs. On the other hand, CINV's prediction model had a lower AUROC (0.671), which was also relatively acceptable. Similarly, the AUROC of the grade 1 to 3 models of HFS and BMS were 0.671 and 0.696, respectively. This indicated that the grade 1 to 3 model for HFS and BMS was not as accurate as the models for grade 2/3 ones (Figure 2 and Supplemental Table S4).

Utilizing the analysis of AUROC, we found that the best cut-off value for the food/nutrient factors to identify the grade 2/3 HFS risk of these patients was milk (100 ml/day) $>$ 0.950, poultry (100 g/day) $<$ 0.077; regarding identifying the grade 2/3 BMS risk of these patients was eggs (100 g/day) $>$ 1.058, Nuts (100 g/day) $>$ 0.108, and Poultry (100 g/day) $<$ 0.018 (Table 3).

Discussion

In this study, we investigated the contribution of dietary intakes on CIAE susceptibility in Chinese CRC patients receiving capecitabine-based chemotherapy for the first time. Our findings support our hypothesis that food/nutrition factors affect the susceptibility to certain CIAEs and they can also be used as predictive markers in predicting CIAEs. Milk and eggs were identified as common risk factors for the most frequent CIAEs.

As reported by previous studies, HFS, CINV, nausea, and BMS were the most common types of CIAEs among CRC patients.[6,29] Correlation-based clustering analysis of CIAE occurrence divided CIAEs into different clusters. There were 2 relatively large clusters, one of which comprised HFS, vomiting, nausea, and CINV (cluster I). The cluster II included anemia, leukopenia, TCP, and BMS (Figure 1C). CIAEs in the same cluster may bear similarities in pathological mechanism, including risk and protective factors from food/nutrition factors. Published studies have reported the association between mucosal toxicities involving stomatitis/mucositis, diarrhea, and HFS, as well as the association between BMS and arrested cell proliferation,[30] which was almost consistent with our result.[31] We hypothesize that CIAEs in cluster I (including HFS) are primarily caused by abnormal inflammatory responses, and CIAEs in cluster II (including BMS) are primarily associated with cell cycle arrest.[31] Notably, the incidence of each CIAE from the cluster I was above 30.0%.

Based on the CIAE data we have collected, we found that HFS, CINV, and BMS were the 3 types of CIAEs with the highest incidence. We also found that eggs, milk, poultry, and dessert were associated with the most frequent CIAEs. Based on the risk and protective factors from the univariate and multivariable analyses, we suggested a potential scientific explanation of how these food/nutrition factors affected the susceptibility to CIAEs.

The most apparent factor was poultry intake, which was found to be a general protective factor for types of CIAEs including HFS, CINV, and BMS. According to published literatures and our previous metabolomic analysis, we believe that the variation in inflammation response and wound regeneration amongst individuals are potential susceptible factors for CIAEs. As nutrition deficiency is associated with poor health state,[32] we considered it as a general risk factor for CIAEs. Therefore, poultry, as a good resource of the 3 main types of nutrition (ie, carbohydrates, proteins, and fats), can serve as a reasonably protective factor for CIAEs. What is interesting is why poultry was a better protective source of meat than the other types of meat. Marangoni et al[33] have produced a good summary of the beneficial effects of poultry on maintaining health and well-being, but also discussed the potential scientific reason. Poultry has a variable but moderate energy content: digestible proteins, unsaturated lipids, B-group vitamins (mainly thiamin, vitamin B6, and pantothenic acid), and minerals (like iron, zinc, and copper). Epidemiological studies performed across the world have also constructed a solid association between poultry consumption on a balanced diet, and reduced risk of developing overweight and obesity, cardiovascular diseases, type 2 diabetes mellitus, and cancer risk. Therefore, we believe that the protective effects of poultry on CIAEs also come with its balanced nutrition. Particularly, compared with the red meats (pork and beef), poultry has more unsaturated fatty acids and less reactive oxygen species.[34]

The mechanism of HFS remains elusive. The widely accepted one is considered as a type of inflammation response mediated by cyclooxygenase-2 over-expression in the palm and plantar area.[35] Consistently, our previous work has also identified several pro-inflammatory metabolites associated with HFS susceptibility.[12] However, a prospective study reported that pyridoxine, which suppresses inflammation, cannot effectively prevent HFS.[5] Herein we found that milk was a risk factor for HFS. The association between milk intake and HFS was also consistent with the HFS-related plasma metabolome. A remarkably negative correlation between the milk intake and altered "lipids and lipid-like molecules" metabolites, including 2 downregulated steroid hormones (5α-dihydrotestosterone [DHT] sulfate, and epiandrosterone sulfate) in HFS group was observed (Figure 3A). As the steroid hormones are synthesized from cholesterol in human body, our result was in agreement with the well-known fact that milk intake can decrease the absorption of cholesterol.[36] Furthermore, our recent study showed that HFS-related transcriptome changes of normal colorectal tissue had an overall suppressed inflammation profile.[7] Our food/nutritional

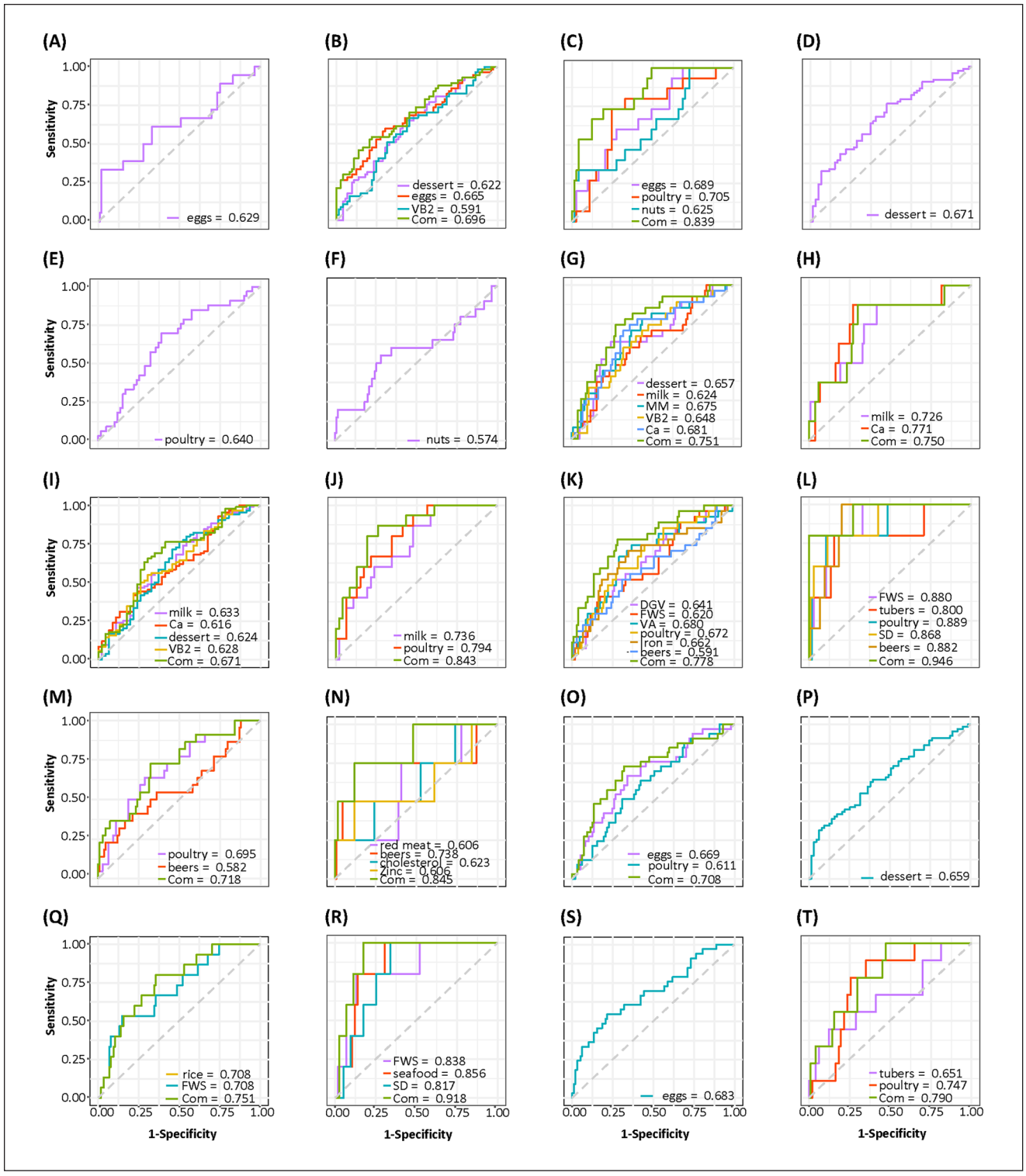

Figure 2. Receiver operating characteristic (ROC) curve for the developed models using relevant food and nutrition factors to predict CIAEs. (A) to (T) show the ROC curves for the models of anemia 1-3 vs 0, BMS 1-3 vs 0, BMS 2/3 vs 0, CINV 1-3 vs 0, CINV 2/3 vs 0, constipation 1-3 vs 0, diarrhea 1-3 vs 0, diarrhea 2/3 vs 0, HFS 1-3 vs 0, HFS 2/3 vs 0, IALT 1-3 vs 0, IALT 2/3 vs 0, IAST 1-3 vs 0, IAST 2/3 vs 0, leukopenia 1-3 vs 0, nausea 1-3 vs 0, neutropenia 1-3 vs 0, neutropenia 2/3 vs 0, TCP 1-3 vs 0, TCP 2/3 vs 0, respectively. "Com" indicates the multivariate models incorporating significantly relevant nutrition predictors from univariate analysis. Abbreviations: Ca, calcium; Com, combination; DGV, dark green vegetables; FWS, food with stuffing; MM, manufactured meat; SD, sweet drinks; VA, vitamin A; VB2, vitamin B2.

Table 3. The Best Cut-Off Values of Food/Nutrition Factors for Predicting HFS and BMS.

CIAEs	Food and nutrition factors (unit)	Grade 2/3 vs Grade 0
		Cut-off value
HFS	Milk (100 ml/day)	>0.950
	Poultry (100 g/day)	<0.077
BMS	Eggs (100 g/day)	>1.058
	Nuts (100 g/day)	>0.108
	Poultry (100 g/day)	<0.018

The normalized data by the combination of the residual method and confounding factors was used here. In brief, after applying the residual method and removeBatchEffect method to the original data, we obtained a new expression matrix, with the same dimensions as our original dataset. This new expression matrix has been adjusted for both total energy intake and potential confounding factors of age, body weight, height, BMI. Further analyses were performed on the adjusted data. Only the cut-off values of food/nutrition factors for grade 2/3 HFS and BMS were listed here.

Abbreviations: BMS: bone marrow suppression; HFS: hand-foot syndrome.

findings are also in accordance with the well-established function of milk in anti-inflammation. The fat content and fermentation effect do not affect the anti-inflammation effect.[37-40] In addition, DHT sulfate is a sulfate derivative of DHT. Both DHT and its precursor cholesterol have pro-inflammatory effect.[41,42] Therefore, our results suggest that, as the overall inflammation is suppressed in patients susceptible to HFS, patients with a high risk of developing grade 2 or even more severe HFS may benefit from reducing the everyday milk consumption below 95 ml.

For BMS, it comprises 4 types of CIAEs, namely, leukopenia, neutropenia, anemia, and TCP. The direct cause of BMS is the suppressed synthesis and (or) elevated consumption of mature blood cells, which can be induced by chemotherapy and environmental stimuli.[43,44] Mature blood cell formation is a complex multistep process that starts from the differentiation of pluripotent hematopoietic stem cells and ends with the formation of types of mature blood cell formation. It is tightly regulated by types of signaling mediators, growth factor receptors, and transcriptional factors.[45,46]

The association between food intakes (egg, dessert, nuts, and poultry) and BMS was also consistent with the BMS-related plasma metabolome, with the largest molecular group being "lipids and lipid-like molecules." Egg has a complicated effect on plasma lipid profile. On one hand, daily egg consumption can increase serum TC and LDL-C concentrations in women.[47] On the other hand, egg-yolk sphingomyelin and phosphatidylcholine had a negative effect on cholesterol absorption.[48] Consistently, we observed that egg intake was positively related to PC(34:2) and plasmenyl-PC(36:2), but negatively related to PC(42:9) and docosahexaenoic acid.[49,50] These lipids exert influence on regulating hematopoietic stem progenitor cell.[51] Nuts are enriched with types of lipids and lipid-like molecules. Consistently, our data showed that nut intake was positively associated with SM(d40:2), 9,10-epoxyoctadecanoic acid, and FAHFA(32:4). In addition, high dessert intake mainly affected the levels of glycerophospholipids (Figure 3B). Desserts vary in ingredient, production method, and even appearance, but sugar is always one of the most common and abundant ingredients. Glucose can suppress the plasma level of choline[52,53] which is the key precursor for lipid metabolism, especially for phosphatidylcholine synthesis. Consistently, we observed that dessert intake was negatively correlated with types of phosphatidylcholines. Therefore, we speculate that food/nutrition factors may induce BMS by disrupting one's lipid and fatty acid homeostasis, since disrupted lipid metabolism is also associated with nearly every aspect of cellular molecular functions from membrane formation to cell differentiation.[54,55] Disrupted lipid metabolism is one of the main risk factor for anemia,[56] TCP,[57] and leukopenia.[58,59]

Amongst the 4 BMS-related food (egg, dessert, nuts, and poultry), eggs were a common risk factor for all BMS-related adverse effects except neutropenia that had the lowest incidence rate (12%) amongst cluster II. Therefore, we considered eggs as the common and most important risk factor for all BMS-related adverse effects. Our result was in agreement with one previous report in which dietary egg sphingomyelin prevented aortic root plaque accumulation in apolipoprotein-E knockout mice.[57] Excessive accumulation of platelet is one of the most important contributing factors toward aortic root plaque accumulation. Therefore, our results suggest that, as the overall disrupted lipid homeostasis is a characteristic for patients susceptible to BMS, patients with a high risk of developing grade 2 or even more severe BMS may benefit from reducing the everyday egg consumption to 105.8 g. Considering moderate discrimination in CRC patients with grade 2/3 CIAEs and the prediction model for HFS2/3 patients used in clinical practice is of greater importance, herein we focused on discussing the cut-off value of food/nutrition factors for patients at the risk of the most common CIAEs with severe grade.

The susceptibility to CIAEs is affected by various factors from internal genomic background to exogenous stimuli. Our previously developed CIAE prediction models based on urinary metabolome exhibited great potential in predicting the occurrence of 5 types of CIAEs (grade 1-3) with AUROC values higher than 0.7, namely, HFS, anemia, neutropenia, TCP, and BMS.[12] Comparatively, based on our food/nutrition data, the constructed prediction models demonstrated good discrimination accuracies for 5 types of CIAEs (leukopenia, diarrhea, IALT, IAST, and neutropenia) with AUROC values higher than 0.7. This suggested that the direct measurement of metabolites was more relevant to the susceptibility to HFS. One reasonable explanation is

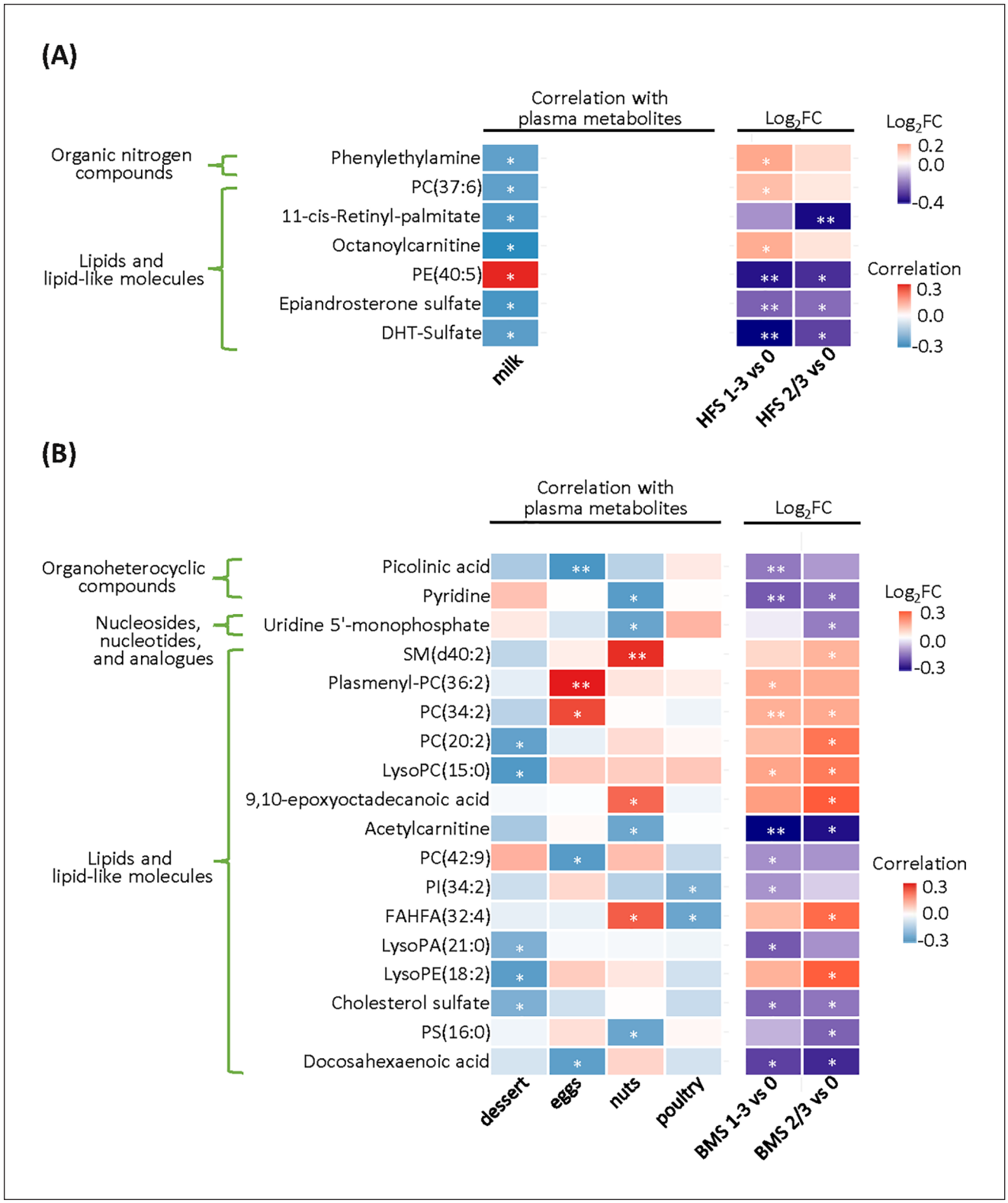

Figure 3. CIAE-related food/nutrition factors and plasma metabolites. Correlations between HFS-related (A) and BMS-related (B) food/nutrition factors and plasma metabolome (left), and selected average levels of related metabolites for the CRC patients in groups 1 to 3 versus 0, and groups 2/3 versus 0 (right).

Abbreviations: DHT, 5α-dihydrotestosterone; FAHFA, fatty acid ester of hydroxyl fatty acid; LysoPC, lysophosphatidylcholines; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; SM, sphingomyelin.

that metabolites are influenced by all possible HFS-related factors and food/nutrition are parts of these factors. We also tried to use blood/body parameters acquired before chemotherapy to predict CIAEs, but only the prediction model for anemia achieved AUROC higher than 0.7.[8] Both urinary metabolites and food/nutrition factors showed much better predictive performances than body/blood parameters. Furthermore, food/nutrition factors gave an overall better prediction for more severe CIAEs (grade 2/3) compared with the onset of CIAEs (grade 1-3). We could predict 7 severe CIAEs (namely, HFS, BMS, TCP, IALT, IAST, and neutropenia) with AUROC values higher than 0.7 (Figure 2). The prediction models for patients with more severe CIAEs are of greater importance. This further confirmed that food/nutrition factors did influence the susceptivity to CIAEs, and the contribution weighted more for more severe CIAEs as such patients have a more prominent clinical phenotype and are less likely to be misjudged.

This study had several limitations. First, as the causes of CIAEs may involve types of factors ranging from intrinsic DNA mutation to exogenous material consumption, and even environmental variations. Therefore, relative factors other than food/nutrition factor should also be considered together to give the best individualized chemotherapy. Second, it was a single-center study, and the sample size was small. External validation based on a larger sample size is warranted in the future. Finally, considering this is merely an observational study, only suggestions could be given to patients to avoid CIAEs. More efforts need to be done to develop a practical individualized chemotherapy including prospective clinical trials.

Conclusions

In summary, we confirmed that food/nutrition factors were important contributing factors for types of CIAEs. Poultry intake was an overall protective factor; milk and egg intakes were risk factors for HFS and BMS, respectively. The prediction models based on food/nutrition factors were constructed with modest performance, which can provide reference for Chinese CRC patients with chemotherapy. Patients prone to HFS and BMS consumed more milk and egg than the control groups, respectively. In order to reduce the prevalence of HFS and BMS, patients with higher milk and egg intakes should be clinically instructed to control their corresponding dietary intake. Our findings advocate that dietary control may be a promising tool in personalized chemotherapy to prevent CIAEs.

Acknowledgments

The authors appreciate the supports from Shanghai Science and Technology Commission Research Project of China (Grant No. 13DZ1930600), the International Scientific and Technological Cooperation Project of China (Grant No. 2015DFA31810), the Clinical Science and Technology Innovation Project of Shanghai Shenkang Hospital Development Center of China (Grant No. SHDC12015120), National Major Scientific and Technological Special Project for "Significant New Drugs Development" (Grant No. 2020ZX09101001), and National Natural Science Foundation of China (Grant No. 31771043). The authors also thank all the participants in this study the staff of Department of General Surgery of Shanghai Changzheng Hospital of China for assistance with the data collection.

Author Contributions

Hua Wei, Mingming Li, and Houshan Yao designed and supervised the study. Jinrong Xu, Zeshuai Lin, and Jiani Chen analyzed and interpreted the data, and wrote the original draft. Jian Zhang, Wanqing Li, Rui Zhang, Jin Xing, Zhihuan Ye, Xiaoping Liu, Qianmin Gao, Xintao Chen, and Jingwen Zhai collected the data. Jinrong Xu, Zeshuai Lin, and Jiani Chen visualized the data. All authors contributed to the writing of this manuscript. All authors read and approved of the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Shanghai Science and Technology Commission Research Project of China (Grant No. 13DZ1930600), the International Scientific and Technological Cooperation Project of China (Grant No. 2015DFA31810), the Clinical Science and Technology Innovation Project of Shanghai Shenkang Hospital Development Center of China (Grant No. SHDC12015120), National Major Scientific and Technological Special Project for "Significant New Drugs Development" (Grant No. 2020ZX09101001), and National Natural Science Foundation of China (Grant No. 31771043). None of the funders had a role in study design, data collection and analysis, decision to publish, or manuscript preparation.

Ethics Approval

Patients in this study were selected from a registered clinical trial (registered at www.clinicaltrials.gov, NCT03030508) at Shanghai Changzheng Hospital from January 2016 to June 2019.The ethics of this study was approved by Biomedical Research Ethics Committee of Shanghai Changzheng Hospital (No. 2016SL007).

Consent to Participate

Written informed consent was obtained from all individual participants included in the study.

ORCID iD

Hua Wei https://orcid.org/0000-0002-3852-7276

Data Availability

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

Code Availability

All codes for data cleaning and analysis associated with the current study are available from the corresponding author on reasonable request.

Supplemental Material

Supplemental material for this article is available online.

References

1. Lam SW, Guchelaar HJ, Boven E. The role of pharmacogenetics in capecitabine efficacy and toxicity. *Cancer Treat Rev*. 2016;50:9-22.
2. Benson AB, Venook AP, Al-Hawary MM, et al. NCCN guidelines insights: colon cancer, version 2.2018. *J Natl Compr Canc Netw*. 2018;16:359-369.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
4. Newman NB, Sidhu MK, Baby R, et al. Long-term bone marrow suppression during postoperative chemotherapy in rectal cancer patients after preoperative chemoradiation therapy. *Int J Radiat Oncol Biol Phys*. 2016;94:1052-1060.
5. Yap YS, Kwok LL, Syn N, et al. Predictors of hand-foot syndrome and pyridoxine for prevention of capecitabine-induced hand-foot syndrome: a randomized clinical trial. *JAMA Oncol*. 2017;3:1538-1545.
6. Chan SL, Chan AWH, Mo F, et al. Association between serum folate level and toxicity of capecitabine during treatment for colorectal cancer. *Oncologist*. 2018;23:1436-1445.
7. Li M, Chen J, Liu S, et al. Spermine-related DNA hypermethylation and elevated expression of genes for collagen formation are susceptible factors for chemotherapy-induced hand-foot syndrome in Chinese colorectal cancer patients. *Front Pharmacol*. 2021;12:2267.
8. Li M, Chen J, Deng Y, et al. Risk prediction models based on hematological/body parameters for chemotherapy-induced adverse effects in Chinese colorectal cancer patients. *Support Care Cancer*. 2021;29:7931-7947.
9. Li M, Sun X, Yao H, et al. Genomic methylation variations predict the susceptibility of six chemotherapy related adverse effects and cancer development for Chinese colorectal cancer patients. *Toxicol Appl Pharmacol*. 2021;427:115657.
10. Yao H, Xu H, Qiu S, et al. Choline deficiency-related multi-omics characteristics are susceptible factors for chemotherapy-induced thrombocytopenia. *Pharmacol Res*. 2022;178:106155.
11. López-Pousa A, Rifà J, Casas de Tejerina A, et al. Risk assessment model for first-cycle chemotherapy-induced neutropenia in patients with solid tumours. *Eur J Cancer Care*. 2010;19:648-655.
12. Deng Y, Yao H, Chen W, et al. Profiling of polar urine metabolite extracts from Chinese colorectal cancer patients to screen for potential diagnostic and adverse-effect biomarkers. *J Cancer*. 2020;11:6925-6938.
13. Ueland PM, Ulvik A, Rios-Avila L, Midttun Ø, Gregory JF. Direct and functional biomarkers of vitamin B6 status. *Annu Rev Nutr*. 2015;35:33-70.
14. Zuo H, Ueland PM, Eussen SJP, et al. Markers of vitamin B6 status and metabolism as predictors of incident cancer: the Hordaland Health study. *Int J Cancer*. 2015;136:2932-2939.
15. Chen W, Li M, Yao H, et al. Application values of tumor markers and inflammatory markers in diagnosis of colorectal cancer and prediction of chemotherapy-related adverse effects. *Tumori*. 2018;38:1038-1047.
16. Xu R, Li J, Yuan Y, Wang J, Chen B, Zhao J. Preliminary study on prediction model of adverse reactions in patients with lymphatic tumors after chemotherapy with high dose methotrexat. *Chin J Mod Appl Pharm*. 2018;35:878-883.
17. Moreau M, Klastersky J, Schwarzbold A, et al. A general chemotherapy myelotoxicity score to predict febrile neutropenia in hematological malignancies. *Ann Oncol*. 2009;20:513-519.
18. Razzaghdoust A, Mofid B, Moghadam M. Development of a simplified multivariable model to predict neutropenic complications in cancer patients undergoing chemotherapy. *Support Care Cancer*. 2018;26:3691-3699.
19. Seo SH, Kim SE, Kang YK, et al. Association of nutritional status-related indices and chemotherapy-induced adverse events in gastric cancer patients. *BMC Cancer*. 2016;16:900.
20. He Y, Jian Z, Ou Yang M, Peng W, Zhang M. Using mini-nutritional assessment to investigate the nutritional status of the aged hospitalized patients. *Chin J Clin Nutr*. 2004;2004:20-23.
21. Lei B, Zheng G. Chemotherapy-induced myelosuppression of non-small cell lung cancer: clinical analysis of risk factors and development of a predictive model. *J Clin Med Lit*. 2015;2:7378-7379.
22. Kim SH, Lee SM, Jeung HC, et al. The effect of nutrition intervention with oral nutritional supplements on pancreatic and bile duct cancer patients undergoing chemotherapy. *Nutrients*. 2019;11:E1145.
23. Gao J, Fei J, Jiang L, Yao W, Lin B, Guo H. Assessment of the reproducibility and validity of a simple food-frequency questionnaire used in dietary patterns studies. *Acta Nutr Sin*. 2011;33:452-456.
24. Zang J, Luo B, Chang S, et al. Validity and reliability of a food frequency questionnaire for assessing dietary intake among Shanghai residents. *Nutr J*. 2019;18:30.
25. Yang Y, Wang G, Pan X. *China Food Composition Table*. Peking University Medical Press; 2002.
26. Yang, Y *China Food Composition Table*. 1st ed. Peking University Medical Press; 2004.
27. Bushel P *PVCA: Principal Variance Component Analysis (PVCA)*. R Package Version 1.30.0. 2020. doi:10.18129/B9.bioc.pvca
28. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr*. 1997;65:1220S-1228S; discussion 1229S.
29. Miller KK, Gorcey L, McLellan BN. Chemotherapy-induced hand-foot syndrome and nail changes: a review of clinical

presentation, etiology, pathogenesis, and management. *J Am Acad Dermatol*. 2014;71:787-794.
30. Isoardi KZ, Harris K, Carmichael KE, Dimeski G, Chan BSH, Page CB. Acute bone marrow suppression and gastrointestinal toxicity following acute oral methotrexate overdose. *Clin Toxicol*. 2018;56:1204-1206.
31. Hu W, Sung T, Jessen BA, et al. Mechanistic investigation of bone marrow suppression associated with palbociclib and its differentiation from cytotoxic chemotherapies. *Clin Cancer Res*. 2016;22:2000-2008.
32. Szewczuk M, Gasiorowska E, Matysiak K, Nowak-Markwitz E. The role of artificial nutrition in gynecological cancer therapy. *Ginekol Pol*. 2019;90:167-172.
33. Marangoni F, Corsello G, Cricelli C, et al. Role of poultry meat in a balanced diet aimed at maintaining health and wellbeing: an Italian consensus document. *Food Nutr Res*. 2015;59:27606. doi:10.3402/fnr.v59.27606
34. Kim SR, Kim K, Lee SA, et al. Effect of red, processed, and white meat consumption on the risk of gastric cancer: an overall and dose–response meta-analysis. *Nutrients*. 2019;11:826. doi:10.3390/nu11040826
35. Zhang RX, Wu XJ, Wan DS, et al. Celecoxib can prevent capecitabine-related hand-foot syndrome in stage II and III colorectal cancer patients: result of a single-center, prospective randomized phase III trial. *Ann Oncol*. 2012;23:1348-1353.
36. Vors C, Joumard-Cubizolles L, Lecomte M, et al. Milk polar lipids reduce lipid cardiovascular risk factors in overweight postmenopausal women: towards a gut sphingomyelin-cholesterol interplay. *Gut*. 2020;69:487-501.
37. Ulven SM, Holven KB, Gil A, Rangel-Huerta OD. Milk and dairy product consumption and inflammatory biomarkers: an updated systematic review of randomized clinical trials. *Adv Nutr*. 2019;10:S239-S250.
38. Benmoussa A, Diallo I, Salem M, et al. Concentrates of two subsets of extracellular vesicles from cow's milk modulate symptoms and inflammation in experimental colitis. *Sci Rep*. 2019;9:14661.
39. Redondo N, García-González N, Diaz-Prieto LE, et al. Effects of ewe's milk yogurt (whole and semi-skimmed) and cow's milk yogurt on inflammation markers and gut microbiota of subjects with borderline-high plasma cholesterol levels: a crossover study. *Eur J Nutr*. 2019;58:1113-1124.
40. Bordoni A, Danesi F, Dardevet D, et al. Dairy products and inflammation: a review of the clinical evidence. *Crit Rev Food Sci Nutr*. 2017;57:2497-2525.
41. Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. *Nat Rev Immunol*. 2015;15:104-116.
42. Shi H, Lo TH, Ma D, et al. Dihydrotestosterone (DHT) enhances wound healing of major burn injury by accelerating resolution of inflammation in mice. *Int J Mol Sci*. 2020;21:6231.
43. Forbes CA, Worthy G, Harker J, et al. Dose efficiency of erythropoiesis-stimulating agents for the treatment of patients with chemotherapy-induced anemia: a systematic review. *Clin Ther*. 2014;36:594-610.
44. Grimes CN, Fry MM. Nonregenerative anemia: mechanisms of decreased or ineffective erythropoiesis. *Vet Pathol*. 2015;52:298-311.
45. Seita J, Weissman IL. Hematopoietic stem cell: self-renewal versus differentiation. *Wiley Interdiscip Rev Syst Biol Med*. 2010;2:640-653.
46. Mendelson A, Frenette PS. Hematopoietic stem cell niche maintenance during homeostasis and regeneration. *Nat Med*. 2014;20:833-846.
47. Baumgartner S, Kelly ER, van der Made S, et al. The influence of consuming an egg or an egg-yolk buttermilk drink for 12 wk on serum lipids, inflammation, and liver function markers in human volunteers. *Nutrition*. 2013;29:1237-1244.
48. Lemos BS, Medina-Vera I, Blesso CN, Fernandez ML. Intake of 3 eggs per day when compared to a choline bitartrate supplement, downregulates cholesterol synthesis without changing the LDL/HDL ratio. *Nutrients*. 2018;10:E258.
49. Billah MM, Anthes JC. The regulation and cellular functions of phosphatidylcholine hydrolysis. *Biochem J*. 1990;269:281-291.
50. Kabarowski JH, Xu Y, Witte ON. Lysophosphatidylcholine as a ligand for immunoregulation. *Biochem Pharmacol*. 2002;64:161-167.
51. Liu C, Han T, Stachura DL, et al. Lipoprotein lipase regulates hematopoietic stem progenitor cell maintenance through DHA supply. *Nat Commun*. 2018;9:1310.
52. Obeid R, Awwad HM, Knell AI, Hübner U, Geisel J. Glucose and fat tolerance tests induce differential responses in plasma choline metabolites in healthy subjects. *Nutrients*. 2018;10:E1209.
53. Chen M, Zheng H, Wei T, et al. High glucose-induced PC12 cell death by increasing glutamate production and decreasing methyl group metabolism. *Biomed Res Int*. 2016;2016:4125731.
54. Hannun YA, Obeid LM. Principles of bioactive lipid signalling: lessons from sphingolipids. *Nat Rev Mol Cell Biol*. 2008;9:139-150.
55. Niazi H, Zoghdani N, Couty L, et al. Murine platelet production is suppressed by S1P release in the hematopoietic niche, not facilitated by blood S1P sensing. *Blood Adv*. 2019;3:1702-1713.
56. Marks PW. Hematologic manifestations of liver disease. *Semin Hematol*. 2013;50:216-221.
57. Millar CL, Norris GH, Vitols A, et al. Dietary egg sphingomyelin prevents aortic root plaque accumulation in apolipoprotein-E knockout mice. *Nutrients*. 2019;11:E1124. doi:10.3390/nu11051124
58. Dorninger F, Wiesinger C, Braverman NE, Forss-Petter S, Berger J. Ether lipid deficiency does not cause neutropenia or leukopenia in mice and men. *Cell Metab*. 2015;21:650-651.
59. Estrela GR, Arruda AC, Torquato HFV, et al. Gemfibrozil induces anemia, leukopenia and reduces hematopoietic stem cells via PPAR-α in mice. *Int J Mol Sci*. 2020;21:E5050. doi:10.3390/ijms21145050