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Original Article

Role of circadian rhythm disruption and dietary polyphenols in the prognosis of neoadjuvant therapy for locally advanced colorectal cancer

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Abstract: Objective: To explore the influence of circadian rhythm disruption and dietary polyphenols on the prognosis of neoadjuvant therapy in patients with locally advanced colorectal cancer (CRC). Methods: A retrospective case-control study was conducted involving 262 patients with locally advanced CRC who received neoadjuvant therapy. Patients were categorized into good prognosis (n = 121) and poor prognosis (n = 141) groups based on Tumor Regression Grading. Data collected included demographic characteristics, work schedules, dietary intake, blood biomarkers, circadian rhythm assessments, and sleep quality metrics. Statistical analyses included chi-square tests, Pearson and Spearman correlations, and Receiver Operating Characteristic curve analysis to identify significant prognostic indicators. Results: Favorable prognostic factors included younger age, better Eastern Cooperative Oncology Group performance status, lower Tumor-Node-Metastasis stage, absence of night shift work, regular work schedules, and greater exposure to natural light. Higher dietary polyphenol intake - primarily from fruits, vegetables, and plant-based foods - was significantly associated with improved treatment response. In contrast, disrupted cortisol rhythms and poor sleep quality predicted worse outcomes. Total polyphenol intake demonstrated strong predictive power (Area Under the Curve [AUC] = 0.847), as did cortisol rhythm disruption (AUC = 0.810). Conclusion: Stability of circadian rhythms and higher dietary polyphenol intake were associated with improved responses to neoadjuvant therapy in patients with locally advanced CRC.

Keywords: Colorectal cancer, neoadjuvant therapy, circadian rhythm, dietary polyphenols, prognosis, lifestyle factors

Introduction

Colorectal cancer (CRC) remains one of the most prevalent malignancies globally and a leading cause of cancer-related morbidity and mortality [1]. Advances in therapeutic strategies, particularly neoadjuvant therapy, have significantly improved outcomes for patients with locally advanced CRC. Neoadjuvant therapy targets micrometastases at an early stage by delivering chemotherapy directly to the primary tumor while the vasculature remains intact [2]. It typically includes chemotherapy and/or radiation therapy to reduce tumor burden, enhance the likelihood of complete surgical resection, and improve overall survival [3, 4]. Recent studies have shown that neoadjuvant chemotherapy offers better prognosis than the conventional sequence of radiotherapy, surgery, and adjuvant chemotherapy, with improved disease-free survival, reduced toxicity, and better treatment tolerance [2]. However, treatment responses vary widely among patients, indicating the need to explore additional influencing factors.

A critical but often overlooked regulator of human health and disease is the circadian rhythm, an intrinsic 24-hour biological cycle that governs numerous physiological processes [5]. Circadian disruption - common among individuals with irregular work schedules - has been implicated in the development of various cancers, including CRC [6]. Epidemiological evidence links circadian misalignment with elevated cancer risk, likely due to altered hormone secretion, immune dysregulation, and disrupted cell cycle control [7-9]. One key circadian hor-

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mone, cortisol (COR), follows a diurnal rhythm and plays a role in immune modulation; its dysregulation may contribute to a pro-tumorigenic microenvironment by suppressing immune surveillance and promoting cancer cell survival [10, 11].

Concurrently, lifestyle factors, especially diet, have attracted growing attention in CRC prevention and management [12]. Among dietary components, polyphenols - naturally occurring compounds in fruits, vegetables, and plant-based foods - have demonstrated promising anti-cancer effects [13]. These compounds exert antioxidant, anti-inflammatory, and anti-proliferative activities by modulating molecular pathways central to tumor progression [14]. Notably, polyphenols influence key signaling cascades such as PI3K/Akt, Wnt/β-catenin, and NF-κB, which regulate cancer cell proliferation, apoptosis, and metastasis [15, 16]. Additionally, they may enhance endogenous antioxidant defenses and reduce therapy-related oxidative stress and inflammation, both of which are known to impact cancer outcomes [17-21]. Despite this potential, the role of dietary polyphenols in augmenting the efficacy of neoadjuvant therapy in CRC remains underexplored, particularly when considered alongside circadian rhythm disturbances [22].

Current literature predominantly examines circadian disruption or polyphenol intake in isolation [15, 16], with few studies investigating their combined influence on neoadjuvant treatment outcomes in locally advanced CRC. Emerging evidence suggests that polyphenols may interact with the circadian clock and contribute to the prevention of chronic diseases, including cancer and cardiovascular conditions [23]. However, research specifically addressing this interaction in CRC - and its mechanistic implications - remains limited [24].

In this context, we conducted a case-control study to examine the joint effects of circadian rhythm disruption and dietary polyphenol intake on the prognosis of patients undergoing neoadjuvant therapy for locally advanced CRC. We particularly focused on the influence of shift work and related lifestyle factors, aiming to clarify how these variables impact treatment efficacy and survival. By investigating the interplay between circadian biology and diet, our goal is to inform personalized strategies that optimize neoadjuvant therapy and improve clinical outcomes for CRC patients.

Materials and methods

Research design

A retrospective case-control study was conducted, including 262 patients with locally advanced colorectal cancer who received neoadjuvant therapy at our hospital from June 2011 to May 2024. Comprehensive demographic and clinical data were systematically collected, including general patient information, laboratory test results, nutritional assessments, dietary patterns, circadian rhythm evaluations, and sleep quality metrics. The study was approved by the Ethics Committee of Shanghai First People's Hospital Jiuquan Hospital (Jiuquan People's Hospital), and conducted in accordance with the Declaration of Helsinki.

Inclusion and exclusion criteria

Inclusion criteria: ① Patients aged 40 to 75 years, representing a high-risk population. Patients over 75 were excluded due to potential comorbidities or organ dysfunction that may compromise chemotherapy tolerance. Excluding patients under 40 minimizes the influence of hereditary or early-onset CRC, which may exhibit distinct pathological features; ② Histologically confirmed diagnosis of locally advanced colorectal cancer; ③ Completion of two cycles of neoadjuvant chemotherapy. Two cycles provide a standardized timeframe for evaluating early therapeutic response while reducing the risk of treatment-related toxicity or patient dropout [25]; ④ Normal cognitive function and the ability to cooperate with examinations and treatments; ⑤ Availability of complete medical records.

Exclusion criteria: Patients were excluded if they had comorbid heart, liver, or kidney diseases; were unable to tolerate intravenous chemotherapy; or had other severe medical conditions. Additional exclusions included individuals with impaired communication ability; those with thyroid disorders, respiratory or infectious diseases, other malignancies, or major organ dysfunction. The flow chart is presented in **Figure 1**.

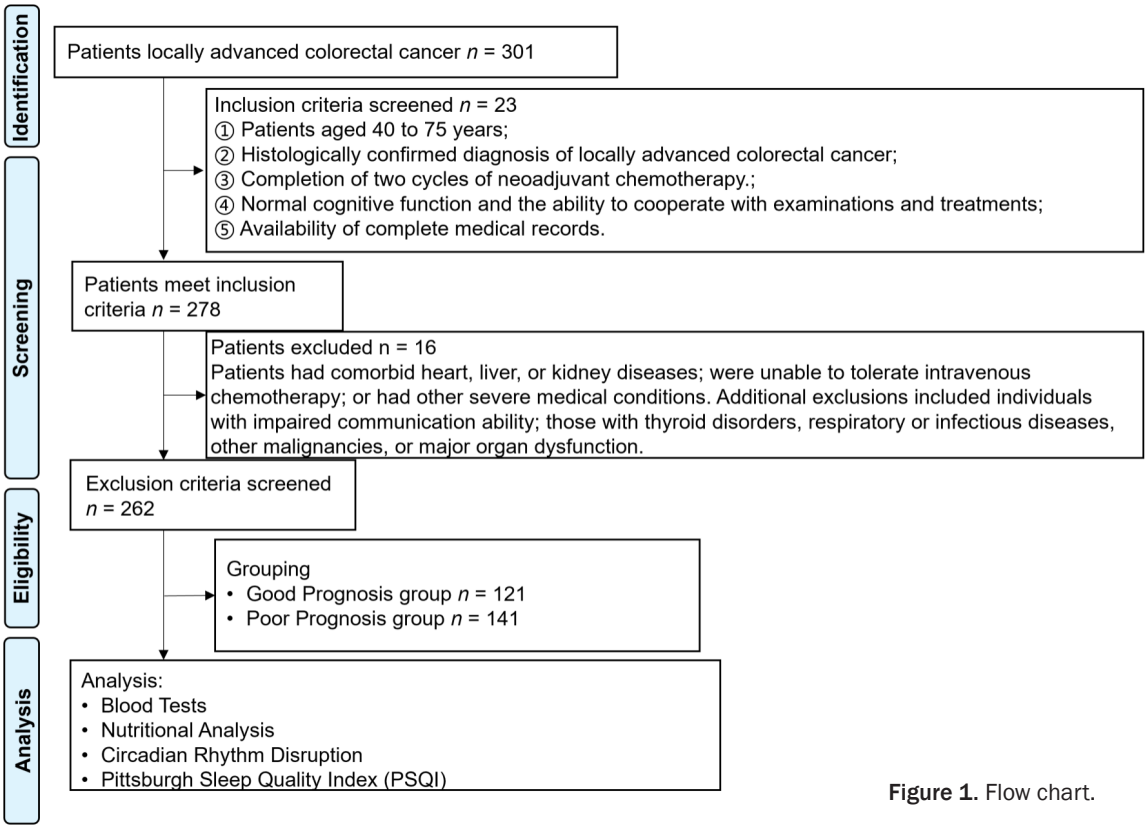

Figure 1. Flow chart.

Grouping criteria

Prognostic classification following neoadjuvant therapy was based on Tumor Regression Grading (TRG), according to the American Joint Committee on Cancer (AJCC) and College of American Pathologists (CAP) guidelines:

TRG 0: No residual tumor cells (complete pathological response); TRG 1: Single or few residual tumor cells; TRG 2: Significant fibrosis with residual tumor cells; TRG 3: Minimal or no tumor regression, with abundant viable tumor cells.

Following completion of two standardized neoadjuvant chemotherapy cycles, patients were categorized based on treatment response. Those with TRG 0-2 were classified as the favorable prognosis group (n = 121), while patients with TRG 3 were assigned to the poor prognosis group (n = 141).

Treatment protocol

All patients received a standardized neoadjuvant chemotherapy regimen. On days 1, 3, and 5, Etoposide was administered intravenously at a dose of 100 mg/m^2 (Qilu Pharmaceutical Co., Ltd., Batch No.: 113768). From days 1 to 5, 5-Fluorouracil was infused at 1000 mg/m^2 daily (Hainan Zhonghe Pharmaceutical Co., Ltd., Batch No.: 113795). On day 1, Cisplatin was given intravenously at 100 mg/m^2 (Shandong Luoxin Pharmaceutical Group Co., Ltd., Batch No.: 0129803). Each treatment cycle spanned four weeks, and patients underwent two consecutive cycles.

Eastern cooperative oncology group (ECOG) performance status

The ECOG Performance Status scale was used to evaluate patients' overall health and treatment tolerance based on their physical activity. The scale includes six levels:

0: Fully active, no restrictions compared to pre-disease activity. 1: Restricted in strenuous activities but ambulatory and capable of light work. 2: Ambulatory and capable of self-care but unable to work; active more than 50% of waking hours. 3: Limited self-care; confined to bed or chair for more than 50% of waking hours.

4: Completely disabled; entirely confined to bed or chair and unable to perform any self-care. 5: Deceased.

The reliability of the ECOG scale was supported by a Cohen's κ coefficient of 0.486 [20].

Blood tests

Within 24 hours of admission, 5 mL each of fasting venous and arterial blood was collected. White blood cell (WBC) count, absolute lymphocyte count (ALC), hemoglobin (HB), and albumin (ALB) levels were measured using an automated hematology analyzer (Mindray BC6800, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China). The monocyte-to-lymphocyte ratio (MLR) and platelet-to-lymphocyte ratio (PLR) were subsequently calculated. An automatic biochemical analyzer (AU5811, Kehua Bio-Engineering Co., Ltd., Shanghai, China) was used to measure plasma levels of interleukin-6 (IL-6), interleukin-22 (IL-22), high-sensitivity C-reactive protein (CRP), and procalcitonin (PCT).

Nutritional analysis

To reduce the inherent limitations of a retrospective design, enhanced 24-hour dietary recall questionnaires were used, alongside rigorous data curation to ensure accuracy and reliability [25, 26]. These questionnaires recorded all food and beverages consumed in the past 24 hours, including portion sizes and cooking methods. Two physicians were responsible for data entry and nutritional counseling records, cross-validating each other's inputs to ensure data integrity. Dietary intake was converted into average daily consumption (g/day), and nutrient composition was assessed using the Chinese Food Composition Table [27].

Circadian rhythm disruption

After a 12-hour fast, 5 mL of venous blood was drawn from the antecubital vein at 08:00, 16:00, and 24:00. Plasma adrenocorticotropic hormone (ACTH) and COR levels were measured using the Siemens IMMULITE 2000 chemiluminescent immunoassay system with standard reagent kits. Circadian rhythm disruption was defined as follows: ACTH or COR levels at 16:00 ≥ 50% of the 08:00 level, or ACTH or COR levels at 24:00 ≥ 50% of the 08:00 or 16:00 levels [26].

Pittsburgh sleep quality index (PSQI)

The PSQI was employed to assess sleep quality, covering seven components including subjective sleep quality and use of sleep medications [27, 28]. Each component was scored from 0 to 3, with higher total scores indicating poorer sleep. The scale demonstrated split-half reliability of 0.833, internal consistency of 0.767, and a Cronbach's alpha of 0.723.

Statistical analysis

Data analysis was conducted performed using SPSS version 29.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as counts and percentages [n (%)]. Normally distributed data were reported as mean ± standard deviation ($\bar{x}$ ± s). Variations between groups were computed using a t-test for continuous variables and chi-square tests for categorical variables. Pearson correlation was applied to continuous variables, while Spearman correlation was used for ordinal or non-normally distributed data. A predictive model was developed using Receiver Operating Characteristic (ROC) curve analysis. A *P*-value < 0.05 was considered statistically significant.

Results

Comparison of demographic and disease characteristics

Patients in the good prognosis group were significantly younger, with a mean age of 46.63 ± 8.54 years, compared to 51.66 ± 9.57 years in the poor prognosis group (P < 0.001) (**Table 1**). ECOG performance status also differed significantly: 85.12% of patients in the good prognosis group had a score of 0, versus 73.05% in the poor prognosis group (P = 0.017). TNM staging showed a similar pattern, with 51.24% of patients in the good prognosis group at stage ≤ II, compared to 39.01% in the poor prognosis group (P = 0.047). There were no significant differences between groups regarding sex, ethnicity, body mass index (BMI), smoking or alcohol history, comorbidities (e.g., hypertension, diabetes), marital status, education level, residence type, tumor location, disease duration, or tumor size (all P > 0.05).

Comparison of work and economic situation

Night shift work (18.18% vs. 42.55%; P < 0.001) and irregular working hours (22.31% vs.

Table 1. Comparison of demographic and disease characteristics between two groups

Parameter	Good Prognosis (n = 121)	Poor Prognosis (n = 141)	t/χ^2	P
Age (years)	46.63 ± 8.54	51.66 ± 9.57	4.453	< 0.001
Female/Male	56 (46.28%)/65 (53.72%)	68 (48.23%)/73 (51.77%)	0.099	0.753
Ethnicity (Han/Other)	99 (81.82%)/22 (18.18%)	111 (78.72%)/30 (21.28%)	0.392	0.531
BMI (kg/m^2)	23.64 ± 2.55	24.14 ± 2.84	1.482	0.140
ECOG performance status (0/≥ 1)	103 (85.12%)/18 (14.88%)	103 (73.05%)/38 (26.95%)	5.649	0.017
Smoking history (Yes/No)	45 (37.19%)/76 (62.81%)	50 (35.46%)/91 (64.54%)	0.084	0.772
Drinking history (Yes/No)	30 (24.79%)/91 (75.21%)	41 (29.08%)/100 (70.92%)	0.605	0.437
Hypertension (Yes/No)	41 (33.88%)/80 (66.12%)	52 (36.88%)/89 (63.12%)	0.255	0.613
Diabetes (Yes/No)	43 (35.54%)/78 (64.46%)	48 (34.04%)/93 (65.96%)	0.064	0.800
Biliary tract disease	24 (19.83%)/97 (80.17%)	22 (15.6%)/119 (84.4%)	0.806	0.369
Coronary heart disease	18 (14.88%)/103 (85.12%)	26 (18.44%)/115 (81.56%)	0.592	0.442
Education level (High school and below/Bachelor degree and above)	103 (85.12%)/18 (14.88%)	123 (87.23%)/18 (12.77%)	0.245	0.621
Marital Status (Single/Married/Divorced)	31 (25.62%)/64 (52.89%)/26 (21.49%)	39 (27.66%)/78 (55.32%)/24 (17.02%)	0.853	0.653
Place of residence [n/(%)]			0.077	0.781
Rural area	57 (47.11%)	64 (45.39%)		
Urban area	64 (52.89%)	77 (54.61%)		
TNM stage (≤ II/> II)	62 (51.24%)/59 (48.76%)	55 (39.01%)/86 (60.99%)	3.943	0.047
Tumour size (cm)	3.38 ± 0.95	3.52 ± 1.09	1.096	0.274
Tumor site [n/(%)]			0.183	0.669
Segmented colon	75 (61.98%)	91 (64.54%)		
Rectum	46 (38.02%)	50 (35.46%)		
Disease duration			1.828	0.401
< 3 months	39 (32.23%)	50 (35.46%)		
3-6 months	41 (33.88%)	54 (38.3%)		
> 6 months	41 (33.88%)	37 (26.24%)		

BMI: Body Mass Index; ECOG: Eastern Cooperative Oncology Group performance status; TNM: tumor node metastasis classification.

50.35%; P < 0.001) were significantly less frequent in the good prognosis group (**Table 2**). Patients in this group also had greater average daily daylight exposure (3.32 ± 1.17 hours vs. 1.94 ± 0.95 hours; P < 0.001). No significant differences were observed in physical activity levels, monthly income, healthcare payment methods, or family income-to-poverty ratio (all P > 0.05).

Comparison of blood tests

Compared with the poor prognosis group, patients with good prognosis had a slightly lower ALC: 1.84 ± 0.16 × 10^9/L vs. 1.89 ± 0.17 × 10^9/L; P = 0.029) and ALB: 35.25 ± 6.35 g/L vs. 36.98 ± 6.92 g/L; P = 0.038), but a higher PLR: 134.63 ± 17.44 vs. 129.74 ± 19.65; P = 0.036) (**Table 3**). Inflammatory markers were significantly lower in the good prognosis group, including IL-6 (0.31 ± 0.07 pg/mL vs. 0.35 ± 0.14 pg/mL; P = 0.005), IL-22 (0.17 ± 0.07 pg/mL vs. 0.19 ± 0.09 pg/mL; P = 0.013), and CRP (9.54 ± 1.73 mg/L vs. 9.87 ± 0.56 mg/L; P = 0.044). No significant differences were observed in WBC counts, HB levels, MLR, or procalcitonin levels (all P > 0.05).

Comparison of dietary patterns

The good prognosis group consumed significantly higher amounts of fruits, nuts, vegetables, legumes, and cereals (all P < 0.05), along with slightly higher fish intake (P = 0.027). They had lower intake of edible oils, meat, and alcohol (all P < 0.05). Dairy intake showed no significant difference (P = 0.062). See **Figure 2**.

Comparison of energy composition

Patients in the good prognosis group had lower total energy and protein-derived energy intake (P < 0.05), especially from animal sources (P = 0.036), and higher vegetable protein intake (P = 0.010). Fat intake was lower overall (P = 0.019), particularly saturated fats (P = 0.011), while monounsaturated fatty acid (MUFA) intake was higher (P = 0.033). Carbohydrate intake was higher (P = 0.031), although added sugar intake was lower (P = 0.018). Cholesterol intake was significantly reduced (P = 0.006), and polyphenol intake was markedly higher (P < 0.001). Fiber intake showed no significant difference (P = 0.066). See **Table 4**.

Comparison of trace elements composition

Patients in the good prognosis group had significantly lower intake of calcium (736.30 ± 218.47 mg vs. 817.20 ± 265.27 mg; P = 0.007) and sodium (1729.20 ± 472.39 mg vs. 1864.70 ± 513.80 mg; P = 0.028) (**Figure 3**). Zinc intake was also reduced in this group (9.37 ± 2.36 mg vs. 10.01 ± 2.34 mg; P = 0.029). Conversely, selenium intake was higher (45.02 ± 6.39 μg vs. 47.26 ± 6.77 μg; P = 0.007), as were vitamin C (90.79 ± 13.79 mg vs. 85.75 ± 15.67 mg; P = 0.007), vitamin D (702.47 ± 109.37 IU vs. 733.14 ± 124.8 IU; P = 0.037), and vitamin E (15.40 ± 2.39 mg vs. 16.19 ± 2.67 mg; P = 0.013). No significant differenwas considered statisticallyces were observed in potassium, iron, or vitamin A intake between groups (all P > 0.05).

Comparison of circadian rhythm disturbances

Analysis revealed a significantly higher prevalence of COR rhythm disturbances in the poor prognosis group (75.18%) compared to the good prognosis group (64.46%) (χ^2 = 101.729, P < 0.001) (**Table 5**). Although ACTH rhythm disturbances were also more common in the poor prognosis group (64.46% vs. 75.18%), this difference did not reach statistical significance (χ^2 = 3.575, P = 0.059).

Comparison of sleep parameters

The good prognosis group had a longer average sleep duration (7.17 ± 1.06 hours) than the poor prognosis group (6.62 ± 1.10 hours; P < 0.001) (**Table 6**). They also had lower PSQI scores, indicating better sleep quality (10.94 ± 2.13 vs. 12.17 ± 2.08; P < 0.001), shorter sleep onset latency (18.93 ± 5.44 minutes vs. 21.15 ± 6.79 minutes; P = 0.004), and lower rates of daytime sleepiness (18.18% vs. 39.72%; P < 0.001). Use of sleep aids was also less frequent in the good prognosis group (12.4% vs. 29.79%; P < 0.001).

Correlation analysis

Age positively correlated with poorer prognosis (rho = 0.277, P < 0.001), as did higher ECOG performance status (rho = 0.147, P = 0.017) and more advanced TNM stage (rho = 0.123, P = 0.047) (**Figure 4**). Night shift work (ρ = 0.262, P < 0.001) and irregular work hours (rho =

Table 2. Comparison of work and economic situation between two groups

Index	Good Prognosis (n = 121)	Poor Prognosis (n = 141)	t/χ^2	P
Physical activity (hours/week)	4.69 ± 2.22	4.69 ± 1.93	0.012	0.991
Monthly average income (< 3000/3000-6000/> 6000)	25 (20.66%)/61 (50.41%)/35 (28.93%)	24 (17.02%)/60 (42.55%)/57 (40.43%)	3.785	0.151
Treatment payment method [n/(%)]			4.706	0.095
Insurance	86 (71.07%)	114 (80.85%)		
Self-paying	18 (14.88%)	10 (7.09%)		
Other	17 (14.05%)	17 (12.06%)		
RIP (< 1/1-3/3)	31 (25.62%)/50 (41.32%)/40 (33.06%)	9 (27.66%)/68 (48.23%)/34 (24.11%)	2.635	0.268
Night Shift Workers (%)	22 (18.18%)	60 (42.55%)	17.988	< 0.001
Irregular Work Hours (%)	27 (22.31%)	71 (50.35%)	21.868	< 0.001
Daylight Exposure (hours/day)	3.32 ± 1.17	1.94 ± 0.95	10.356	< 0.001

RIP: the ratio of family income to poverty.

Table 3. Comparison of blood test between two groups

	Good Prognosis (n = 121)	Poor Prognosis (n = 141)	t	P
WBC (× 10^9/L)	13.52 ± 2.54	13.68 ± 2.58	0.498	0.619
ALC (× 10^9/L)	1.84 ± 0.16	1.89 ± 0.17	2.200	0.029
HB (g/L)	123.63 ± 10.63	122.75 ± 11.25	0.642	0.522
ALB (g/L)	35.25 ± 6.35	36.98 ± 6.92	2.090	0.038
MLR	0.25 ± 0.12	0.26 ± 0.07	0.084	0.933
PLR	134.63 ± 17.44	129.74 ± 19.65	2.113	0.036
IL-6 (pg/mL)	0.31 ± 0.07	0.35 ± 0.14	2.833	0.005
IL-22 (pg/mL)	0.17 ± 0.07	0.19 ± 0.09	2.511	0.013
CRP (mg/L)	9.54 ± 1.73	9.87 ± 0.56	2.035	0.044
PCT (μg/L)	0.19 ± 0.07	0.20 ± 0.07	1.129	0.260

WBC: white blood cell; ALC: absolute lymphocyte count; HB: hemoglobin; ALB: albumin; MLR: monocyte to lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; IL-6: Interleukin-6; IL-22: cInterleukin-22; CRP: hypersensitive C-reactive protein; PCT: Procalcitonin.

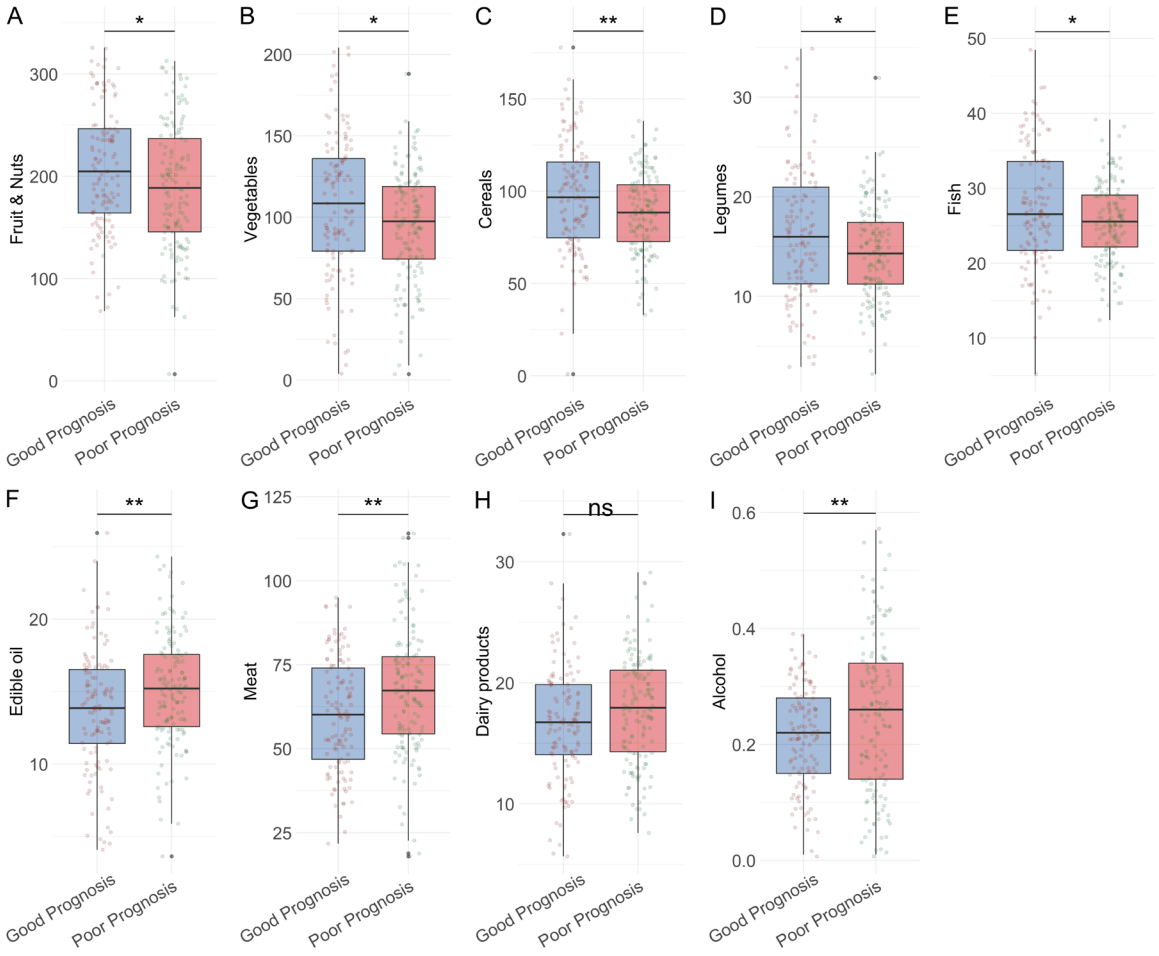

Figure 2. Comparison of dietary patterns between the two groups. A: Fruit & Nuts; B: Vegetables; C: Cereals; D: Legumes; E: Fish; F: Edible oil; G: Meat; H: Dairy products; I: Alcohol. ns: no statistically significant difference; *: $P < 0.05$; **: $P < 0.01$.

0.289, P < 0.001) were strongly associated with poorer outcomes. Reduced daylight exposure had a strong inverse correlation with prognosis (rho = -0.561, P < 0.001). Higher intake of

Table 4. Comparison of energy composition of the diet between study groups

Variable	Good Prognosis (n = 121)	Poor Prognosis (n = 141)	t	P
Total Energy (kcal/day)	1759.7 ± 452.07	1883.12 ± 504.5	2.071	0.039
Proteins (% TE)	18.36 ± 3.74	19.37 ± 3.14	2.362	0.019
Proteins Animal sources (% TE)	12.40 ± 2.13	13.10 ± 3.19	2.104	0.036
Proteins Vegetable sources (% TE)	6.67 ± 1.58	6.21 ± 1.21	2.595	0.010
Lipids (% TE)	36.20 ± 6.75	38.45 ± 8.62	2.369	0.019
SFA (% TE)	9.78 ± 2.13	10.63 ± 3.16	2.570	0.011
MUFA (% TE)	19.40 ± 4.82	18.09 ± 4.97	2.146	0.033
PUFA (% TE)	4.60 ± 1.19	4.40 ± 1.26	1.344	0.180
Cholesterol (mg/die)	276.37 ± 73.55	303.17 ± 81.79	2.770	0.006
Carbohydrates (% TE)	46.72 ± 8.73	44.32 ± 9.13	2.165	0.031
Added sugars (% TE)	2.13 ± 0.85	2.41 ± 1.03	2.385	0.018
Fiber (g/1000 kcal/day)	12.28 ± 3.12	11.57 ± 3.06	1.847	0.066
Total Polyphenols (mg)	841.45 ± 111.7	692.17 ± 106.78	11.531	< 0.001

SFA: Saturated Fatty Acids; MUFA: Monounsaturated Fatty Acids; PUFA: Polyunsaturated Fatty Acids; TE: Total Energy.

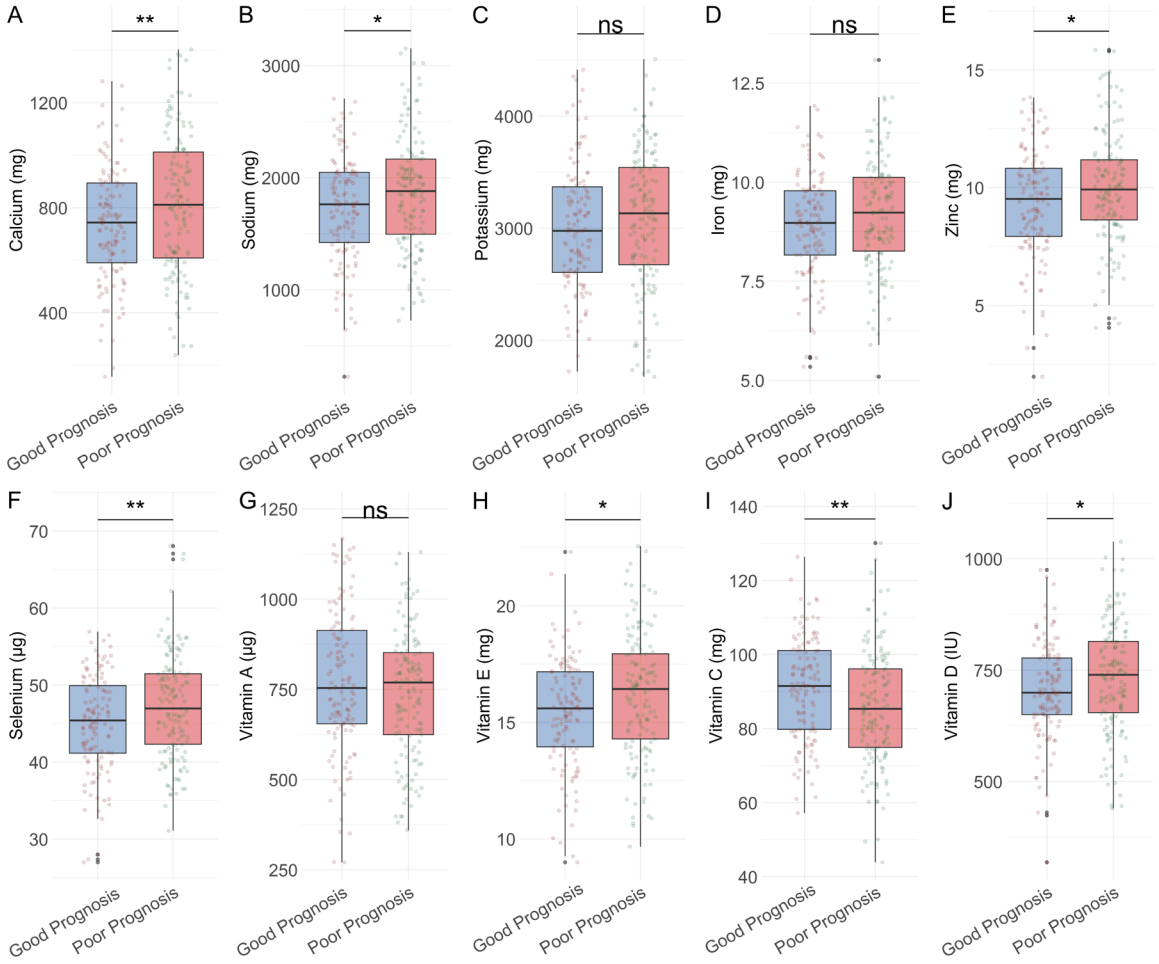

Figure 3. Compare of Trace elements composition of the diet between study groups. A: Calcium (mg); B: Sodium (mg); C: Potassium (mg); D: Iron (mg); E: Zinc (mg); F: Selenium (µg); G: Vitamin A (µg); H: Vitamin E (mg); I: Vitamin C (mg); J: Vitamin D (IU). ns: no statistically significant difference; *: $P < 0.05$; **: $P < 0.01$.

Table 5. Comparison of circadian rhythm disturbances between the two groups

Variable	Good Prognosis (n = 121)	Poor Prognosis (n = 141)	χ^2	P
ACTH rhythm disorder	78 (64.46%)	106 (75.18%)	3.575	0.059
COR rhythm disorder	93 (76.86%)	21 (14.89%)	101.729	< 0.001

ACTH: Adrenocorticotropic Hormone; COR: Cortisol.

Table 6. Comparison of sleep parameters between the two groups

Variable	Good Prognosis (n = 121)	Poor Prognosis (n = 141)	t/χ^2	P
Average Sleep Duration (hours)	7.17 ± 1.06	6.62 ± 1.10	4.090	< 0.001
PSQI	10.94 ± 2.13	12.17 ± 2.08	4.704	< 0.001
Sleep Onset Latency (minutes)	18.93 ± 5.44	21.15 ± 6.79	2.932	0.004
Daytime Sleepiness	22 (18.18%)	56 (39.72%)	14.443	< 0.001
Use of Sleep Aids (%)	15 (12.4%)	42 (29.79%)	11.569	< 0.001

PSQI: Pittsburgh Sleep Quality Index.

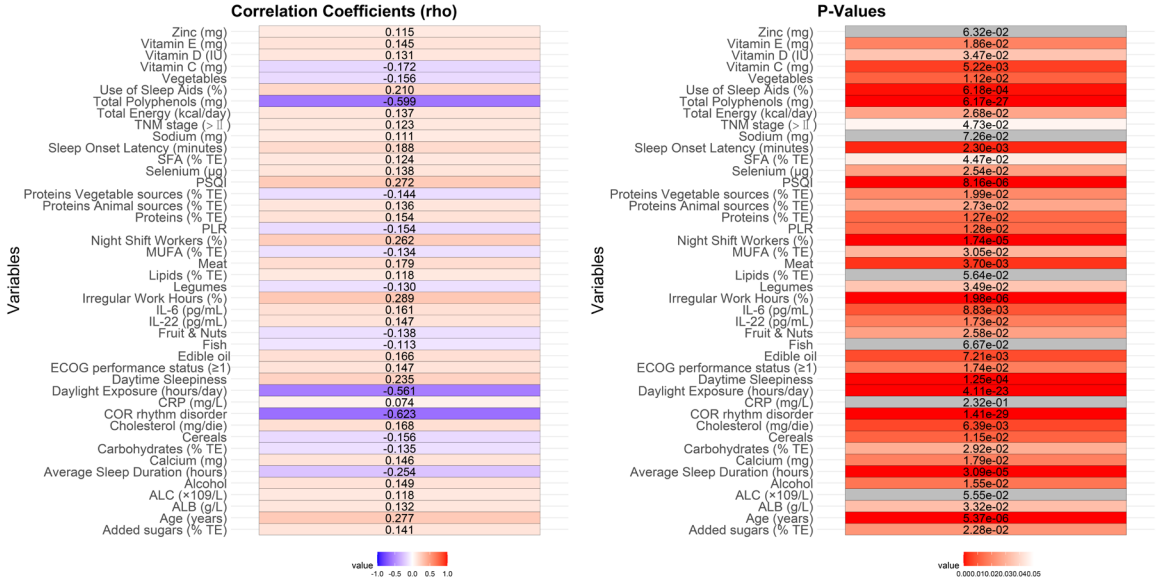

Figure 4. Correlation Analysis of Factors Associated with Poor Prognosis in Neoadjuvant Therapy for locally advanced colorectal cancer. ECOG: Eastern Cooperative Oncology Group performance status; TNM: tumor node metastasis classification; ALC: absolute lymphocyte count; ALB: albumin; PLR: platelet-to-lymphocyte ratio; IL-6: Interleukin-6; IL-22: cInterleukin-22; CRP: hypersensitive C-reactive protein; TE: Total Energy; SFA: Saturated Fatty Acids; MUFA: Monounsaturated Fatty Acids; COR: Cortisol; PSQI: Pittsburgh Sleep Quality Index.

total polyphenols (rho = -0.599, P < 0.001) and plant-based foods (fruits, vegetables, legumes, cereals) were positively associated with better outcomes. Conversely, higher intake of meat (rho = 0.179, P = 0.004), edible oils (rho = 0.166, P = 0.007), and alcohol (rho = 0.149, P = 0.015) correlated with worse prognosis. COR rhythm disturbances also showed a strong negative correlation with prognosis (rho = -0.623, P < 0.001). Sleep-related variables such as shorter sleep duration (rho = -0.254, P < 0.001), higher PSQI scores (rho = 0.272, P < 0.001), and greater reliance on sleep aids (ρ = 0.210, P < 0.001) further supported the relevance of lifestyle and circadian health to patient outcomes.

ROC analysis

Key variables demonstrated varied predictive capacities for poor prognosis (**Table 7**). COR rhythm disorder (AUC = 0.810) and total polyphenol intake (AUC = 0.847) exhibited strong predictive value, with high sensitivity (0.851

Table 7. Predictive value of various factors for poor prognosis in neoadjuvant therapy for locally advanced colorectal cancer

	Best threshold	Sensitivities	Specificities	AUC	Youden index	F1 score
Age (years)	53.255	0.468	0.810	0.660	0.278	0.574
ECOG performance status	0.500	0.270	0.851	0.560	0.121	0.386
TNM stage	0.500	0.610	0.512	0.561	0.122	0.601
Night Shift Workers (%)	0.500	0.426	0.818	0.622	0.244	0.538
Irregular Work Hours (%)	0.500	0.504	0.777	0.640	0.281	0.594
Daylight Exposure (hours/day)	2.655	0.794	0.744	0.825	0.538	0.223
ALC (× 10^9/L)	1.775	0.716	0.405	0.569	0.121	0.643
ALB (g/L)	39.275	0.397	0.769	0.576	0.166	0.498
PLR	128.175	0.511	0.669	0.589	0.180	0.474
IL-6 (pg/mL)	0.415	0.319	0.893	0.593	0.212	0.452
IL-22 (pg/mL)	0.185	0.596	0.554	0.585	0.150	0.602
CRP (mg/L)	9.135	0.922	0.413	0.543	0.335	0.760
Fruit & Nuts	173.915	0.440	0.702	0.580	0.142	0.518
Vegetables	122.23	0.801	0.446	0.591	0.247	0.251
Legumes	21.210	0.936	0.248	0.575	0.184	0.100
Cereals	100.480	0.709	0.479	0.590	0.188	0.342
Fish	33.470	0.943	0.264	0.566	0.207	0.088
Edible oil	15.105	0.518	0.645	0.596	0.163	0.568
Meat	54.170	0.766	0.413	0.603	0.179	0.675
Alcohol	0.325	0.298	0.901	0.586	0.199	0.431
Total Energy (kcal/day)	1917.195	0.482	0.669	0.579	0.151	0.546
Proteins (% TE)	19.510	0.532	0.645	0.589	0.177	0.579
Proteins Animal sources (% TE)	14.900	0.319	0.901	0.579	0.220	0.455
Proteins Vegetable sources (% TE)	7.675	0.901	0.273	0.583	0.174	0.149
Lipids (% TE)	41.765	0.348	0.785	0.568	0.133	0.454
SFA (% TE)	11.155	0.447	0.769	0.572	0.216	0.543
MUFA (% TE)	18.300	0.511	0.653	0.577	0.164	0.478
Cholesterol (mg/die)	261.210	0.716	0.463	0.597	0.179	0.658
Carbohydrates (% TE)	43.185	0.461	0.702	0.578	0.163	0.503
Added sugars (% TE)	3.315	0.227	0.934	0.581	0.161	0.354
Total Polyphenols (mg)	789.815	0.865	0.736	0.847	0.601	0.153
Calcium (mg)	943.505	0.319	0.860	0.585	0.179	0.443
Sodium (mg)	1801.22	0.574	0.554	0.564	0.128	0.587
Zinc (mg)	8.315	0.809	0.331	0.567	0.140	0.679
Selenium (μg)	47.835	0.489	0.661	0.58	0.150	0.550
Vitamin E (mg)	16.26	0.532	0.645	0.584	0.177	0.579
Vitamin C (mg)	89.465	0.617	0.587	0.600	0.204	0.406
Vitamin D (IU)	739.16	0.511	0.661	0.576	0.172	0.567
COR rhythm disorder	0.500	0.851	0.769	0.810	0.620	0.165
Average Sleep Duration (hours)	6.805	0.631	0.636	0.647	0.267	0.385
PSQI	11.270	0.709	0.562	0.657	0.271	0.680
Sleep Onset Latency (minutes)	24.780	0.333	0.884	0.609	0.217	0.465
Daytime Sleepiness	0.500	0.397	0.818	0.608	0.215	0.511
Use of Sleep Aids (%)	0.500	0.298	0.876	0.587	0.174	0.424

ECOG: Eastern Cooperative Oncology Group performance status; TNM: tumor node metastasis classification; ALC: absolute lymphocyte count; ALB: albumin; PLR: platelet-to-lymphocyte ratio; IL-6: Interleukin-6; IL-22: cInterleukin-22; CRP: hypersensitive C-reactive protein; TE: Total Energy; SFA: Saturated Fatty Acids; MUFA: Monounsaturated Fatty Acids; COR: Cortisol; PSQI: Pittsburgh Sleep Quality Index.

and 0.865, respectively) and specificity (0.769 and 0.736). Daylight exposure (AUC = 0.825) and sleep indicators - such as average sleep duration (AUC = 0.647) and PSQI score (AUC = 0.657) - showed moderate predictive power. Age (AUC = 0.660) and irregular work hours (AUC = 0.640) demonstrated modest accuracy, while ECOG status (AUC = 0.560), TNM stage (AUC = 0.561), and CRP (AUC = 0.543) showed limited predictive utility. Dietary factors such as vegetable protein and cholesterol intake had weak to moderate predictive performance. These results highlight the predictive significance of circadian rhythm stability and dietary polyphenol intake in neoadjuvant therapy outcomes. See **Figure 5**.

Discussion

In the context of locally advanced colorectal cancer, the prognosis following neoadjuvant therapy is shaped by a complex interplay of lifestyle factors, dietary patterns, and biological rhythms. Among these, COR rhythm disruption demonstrated a strong association with poor prognosis, emphasizing the clinical relevance of circadian regulation. This finding contributes to a growing body of evidence linking circadian misalignment to cancer development and treatment resistance. COR, a glucocorticoid hormone, typically follows a diurnal pattern, peaking in the early morning and declining throughout the day [29]. Disruption of this rhythm may impair immune surveillance and alter cell cycle regulation, fostering a tumor-permissive environment. Mechanistically, COR dysregulation can interfere with key signaling pathways involved in apoptosis and cellular proliferation, potentially reducing the efficacy of chemotherapeutic agents [30]. Our results underscore the importance of circadian rhythm stability and suggest that interventions aimed at restoring normal COR dynamics could improve therapeutic outcomes.

Moreover, the strong predictive value of total dietary polyphenol intake highlights its potential role in enhancing treatment responsiveness. These bioactive compounds - abundant in fruits, vegetables, legumes, and whole grains - exhibit diverse anticancer properties, including anti-inflammatory, antioxidant, and immunomodulatory effects [31]. Polyphenols strengthen the body's oxidative defense systems, potentially mitigating therapy-induced oxidative damage and suppressing systemic inflammation [32, 33]. Mechanistically, polyphenols such as resveratrol and quercetin, which are common in plant-based diets, target key oncogenic pathways:

NF-κB Suppression: Resveratrol inhibits nuclear translocation of NF-κB, thereby counteracting glucocorticoid receptor (GR)-mediated inhibition of apoptosis.

ROS Modulation: Quercetin scavenges chemotherapy-induced reactive oxygen species (ROS) in healthy cells while promoting oxidative stress in CRC cells via p53 pathway activation [34].

These actions may contribute to the improved pathological responses observed in patients receiving neoadjuvant therapy. The favorable dietary profile in these patients was characterized by increased intake of plant-based foods and reduced consumption of meat, alcohol, and edible oils. This dietary pattern may provide therapeutic advantages via several mechanisms. A diet rich in plant-based foods is generally associated with higher fiber intake, which supports beneficial shifts in gut microbiota composition and increases production of short-chain fatty acids - compounds known for their anti-inflammatory and immunomodulatory properties [35, 36]. Additionally, plant-rich diets offer a broad spectrum of micronutrients and bioactive phytochemicals that enhance immune function and metabolic resilience - both crucial for favorable cancer outcomes [37, 38].

In contrast, meat and alcohol consumption were negatively associated with treatment response, likely due to their pro-inflammatory and carcinogenic properties. Red and processed meats contain heme iron and nitrates, which can promote oxidative stress, DNA damage, and colorectal carcinogenesis [39, 40]. Alcohol, meanwhile, has been shown to impair immune function, reduce treatment tolerance, and increase the risk of cancer progression [40, 41].

Non-responders exhibited significantly lower daylight exposure and poorer sleep quality [41, 42]. These factors likely contribute to the dysregulation of melatonin secretion, a circadian hormone that plays dual anti-tumor roles: inhibiting lactate dehydrogenase A to suppress the Warburg effect and enhancing CD8+ T-cell infil-

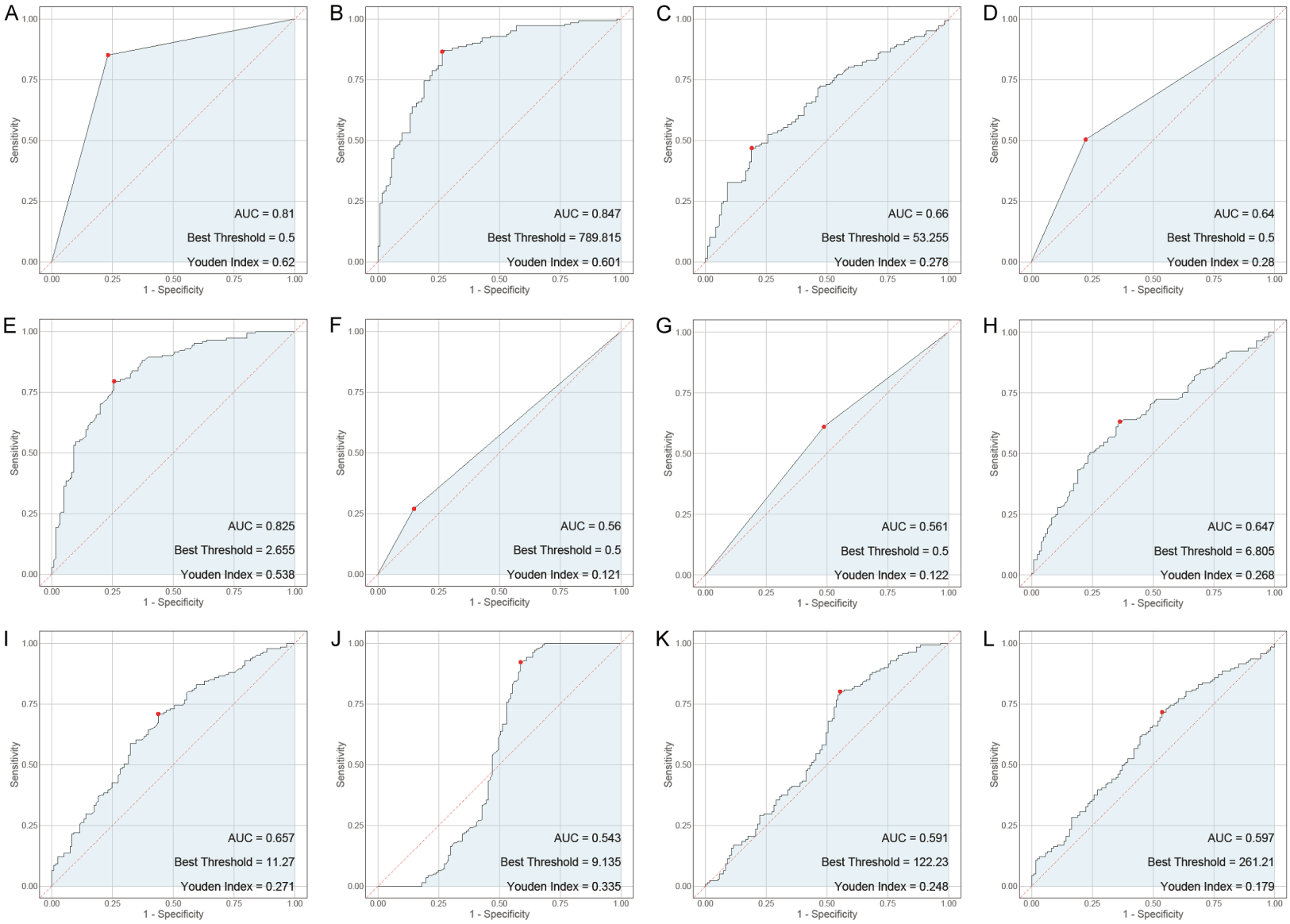

Figure 5. ROC Curves for Key Factors Predicting Poor Prognosis: A: COR rhythm disorder; B: Total polyphenols; C: Age; D: Irregular work hours; E: Daylight exposure time; F: ECOG performance status; G: TNM stage; H: Average sleep; I: PSQI score indicating; J: CRP; K: Vegetable; L: Cholesterol. COR: Cortisol; ECOG: Eastern Cooperative Oncology Group performance status; TNM: tumor node metastasis classification; PSQI: Pittsburgh Sleep Quality Index; CRP: hypersensitive C-reactive protein.

tration through upregulation of CXCL10. Sleep deprivation concurrently elevates systemic COR levels, creating a feedback loop that exacerbates GR signaling. These findings suggest the potential benefit of multimodal interventions combining light therapy, sleep hygiene protocols, and polyphenol supplementation to disrupt pro-tumorigenic cycles [43, 44].

Additionally, blood test results further support the connection between inflammation and cancer prognosis. The good prognosis group exhibited lower levels of inflammatory markers such as IL-6 and CRP, which are critical mediators of cancer-related inflammation. Reduced systemic inflammation enhances immune surveillance and mitigates tumor-promoting effects, potentially contributing to a more favorable response to chemotherapy [45, 46]. This underscores the importance of managing inflammation as part of a comprehensive cancer treatment strategy.

Our correlation and ROC analyses highlight the multifactorial nature of cancer prognosis, illustrating how circadian rhythm, dietary habits, and lifestyle factors interact to influence therapeutic outcomes. The establishment of a predictive model integrating these variables emphasizes the potential for personalized interventions targeting lifestyle modifications to optimize cancer care. Future research should explore intervention strategies that integrate chronotherapy - timing treatments to align with individual circadian rhythms - and dietary interventions emphasizing polyphenol-rich foods. Such approaches could enhance the effectiveness of neoadjuvant therapy and improve clinical outcomes. Additionally, the molecular pathways through which circadian disruptions and dietary factors exert their effects warrant further investigation to uncover novel therapeutic targets.

While this study provides valuable insights into the interplay between circadian rhythm disruptions, dietary polyphenols, and prognosis in neoadjuvant therapy for colorectal cancer, several limitations must be acknowledged. First, the observational nature of this case-control study prevents the establishment of causality, and reliance on self-reported data for lifestyle habits introduces the potential for recall bias. Moreover, the sample size, while adequate for preliminary findings, limits the generalizability of the results to larger populations. Variability in individual metabolic responses to polyphenols and differences in circadian rhythm resilience may also confound the results, highlighting the need for controlled interventional studies to validate these associations. Future research should incorporate more objective measures of circadian rhythms and dietary intake, as well as expand to diverse populations and further explore different subgroups to strengthen the robustness of these findings.

Conclusion

This study emphasizes the importance of a holistic approach to cancer treatment, one that considers the broader lifestyle and environmental factors influencing patient health. By understanding and integrating these aspects, clinicians can develop more personalized and effective treatment plans that extend beyond conventional pharmaceutical interventions, ultimately improving the quality of life and therapeutic efficacy for patients with locally advanced colorectal cancer.

Disclosure of conflict of interest

None.

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