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Changes in Serum Tryptophan Levels and Chemotherapy-related Cognitive Impairment in Older Patients with Colon Cancer: A Prospective Pilot Study

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Abstract

Objectives: Chemotherapy-related cognitive impairment (CRCI) significantly affects quality of life among older adults with cancer. Despite its prevalence, reliable biomarkers for CRCI risk assessment and monitoring are lacking. This study proposes and evaluates the hypothesis that alterations in serum tryptophan levels, influenced by systemic inflammation, may be associated with CRCI in older patients with colon cancer undergoing chemotherapy.

Methods: A prospective pilot study was conducted involving older patients with stage II-III colon adenocarcinoma who received adjuvant mFOLFOX6 chemotherapy. Serum tryptophan and C-reactive protein (CRP) levels were measured at baseline, after six cycles of chemotherapy, and at the three-month post-chemotherapy follow-up. Cognitive function was assessed using the mini-mental state examination (MMSE), and patients were classified according to the presence of CRCI.

Results: Baseline tryptophan levels were significantly lower in cancer patients than in healthy controls ($p<0.001$). However, no significant baseline differences were found between CRCI and non-CRCI subgroups. Notably, follow-up tryptophan levels were significantly lower in the CRCI group, with a marked decrease in Δ tryptophan ($p<0.001$). Receiver operating characteristic analysis demonstrated promising discriminatory performance for follow-up and Δ tryptophan levels (area under the curve=0.874 and 0.904, respectively). These findings are exploratory and require external validation. Follow-up tryptophan levels were inversely correlated with CRP and positively correlated with MMSE scores.

Conclusion: Declining serum tryptophan levels during chemotherapy, especially in the context of systemic inflammation, may reflect increased vulnerability to CRCI. These findings support the potential utility of tryptophan as a non-invasive candidate biomarker associated with CRCI. Further large-scale studies are warranted to validate its clinical application and explore preventive interventions.

Keywords: Chemotherapy-related cognitive impairment, tryptophan metabolism, inflammation, older cancer patients, biomarker, cognitive dysfunction, neuroinflammation, colon cancer

Introduction

Chemotherapy-related cognitive impairment (CRCI), colloquially known as “chemo brain”, encompasses a range of cognitive deficits including impairments in memory, attention, processing speed, and executive function (1). It is especially prevalent among older cancer patients and survivors (2). Despite the growing recognition of CRCI in clinical oncology, its mechanisms remain insufficiently understood, and a robust, accessible biomarker is lacking (1-3).

Current hypotheses implicate neuroinflammation, oxidative stress, cytokine dysregulation, and neurotransmitter imbalances (4-6). One emerging candidate that intersects these pathways is tryptophan; an essential amino acid involved in both serotonin and kynurenine metabolic pathways (7-9). The balance between these pathways is influenced by

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inflammatory stimuli, notably cytokines such as interferon-γ and tumor necrosis factor-α, which drive tryptophan metabolism away from serotonin production toward the kynurenine pathway, yielding neurotoxic metabolites (10). This biochemical shift is believed to affect neuroplasticity, mood, and cognition (10,11).

Furthermore, aging and systemic inflammation, both prevalent in oncology populations, may exacerbate this shift (2,12-14). Thus, evaluating serum tryptophan as a peripheral indicator of cognitive vulnerability during chemotherapy is a timely and potentially transformative approach.

This study aimed to investigate whether changes in serum tryptophan levels were associated with CRCI in older patients with colon cancer undergoing adjuvant chemotherapy.

Material and Methods

Patients and Methods Study Design

This prospective observational pilot study with a matched control group was conducted after approval by the Muğla Sıtkı Koçman University Institutional Ethics Committee (approval no: 14/X, date: 24.08.2022) and in accordance with the Declaration of Helsinki. Data were collected in the Department of Medical Oncology at a tertiary oncology center between September 6, 2022, and August 2, 2024. Prior to enrollment, all participants were provided with comprehensive verbal and written information about the study, and written informed consent was obtained from each individual who voluntarily agreed to participate.

Study Population

The study group consisted of male and female patients aged 65 years and older who had undergone surgical resection for stage II or stage III colon adenocarcinoma and who were deemed eligible to receive adjuvant chemotherapy with the modified FOLFOX6 (mFOLFOX6) regimen administered biweekly. Only patients with preserved cognitive function, as demonstrated by a mini-mental state examination (MMSE) score of 25 or higher, were included in the study.

Patients were excluded if they had prior systemic anticancer therapy for other malignancies; previous neurosurgery or cranial radiotherapy; psychiatric disorders requiring ongoing treatment or follow-up (including psychosis, major depression, or personality disorders); neurodegenerative or cerebrovascular diseases; diabetes mellitus; myocardial infarction within the past six months; significant renal dysfunction or the need for dialysis; decompensated chronic liver disease; neurological involvement in rheumatologic or connective tissue disorders; clinical hypothyroidism; megaloblastic anemia due to vitamin B12 or folic acid deficiency; chronic alcoholism; substance dependence; alcohol withdrawal syndrome; significant electrolyte disturbances (such as hyponatremia, hypokalemia, hypercalcemia, or hyperkalemia); insufficient proficiency in reading and understanding Turkish; significant hearing impairment; or a history of symptomatic, polymerase chain reaction (PCR)-confirmed coronavirus disease-2019 (COVID-19) requiring hospitalization or home-based treatment.

Patients in the study group were scheduled to receive a total of 12 cycles of adjuvant chemotherapy every two weeks, according to the mFOLFOX6 regimen, which consisted of 5-fluorouracil (400 mg/m^2 bolus plus 2400 mg/m^2 46-hour continuous infusion), leucovorin (400 mg/m^2 infusion), and oxaliplatin (85 mg/m^2 infusion). After completion of six cycles of chemotherapy, computed tomography scans were performed to assess recurrence or metastasis.

Patients without evidence of disease progression continued treatment up to the planned 12 cycles. Following treatment completion, patients were monitored every three months for two to three years for disease surveillance. During the study, patients who developed significant clinical complications precluding further participation were excluded, and additional eligible patients were enrolled to achieve the planned sample size. Ultimately, the study group included 30 patients who completed the planned treatment protocol and were confirmed to be free of recurrence or metastasis at the three-month follow-up after completion of chemotherapy.

Control Group

The control group was recruited after completion of patient enrollment and comprised healthy volunteers who were matched to the study group in terms of age and sex. Volunteers were primarily selected from healthy caregivers of patients under follow-up in the oncology department. Exclusion criteria for the control group were inadequate proficiency in reading and understanding Turkish and a history of symptomatic, PCR-confirmed COVID-19 requiring hospitalization or home-based care.

Data Collection Tools

Data collection was conducted using a specifically developed case follow-up form alongside validated instruments, including the MMSE and the functional assessment of cancer therapy-general (FACT-G) questionnaire.

The case follow-up form captured demographic and personal information, such as age, sex, occupation, education level, marital status, socioeconomic status, smoking status, height,

weight, body mass index (BMI), and body surface area (BSA). For the study group, additional clinical information was recorded, including details of the colon cancer diagnosis, the chemotherapy regimen, and chemotherapy-related adverse events, which were assessed and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events.

Laboratory evaluations were conducted at three time points for the study group: prior to the initiation of chemotherapy, after the completion of the sixth cycle, and three months after the completion of all twelve chemotherapy cycles. Parameters measured included complete blood count, C-reactive protein (CRP) levels (reference range: 0-2 mg/L), and serum tryptophan concentrations. For the control group, these measurements were collected only at baseline.

MMSE

Cognitive function was assessed using the MMSE, which has been validated for use in the Turkish population. An MMSE score of 25 or higher was considered indicative of normal cognitive function, while scores between 19 and 24 suggested mild impairment, scores between 10 and 19 indicated moderate impairment, and scores below 10 reflected severe cognitive decline (15). For the purposes of this study, CRCI was defined as a decline of total MMSE score to below the normal-range threshold (<25) at the post-chemotherapy assessment in a patient who had scored within the normal range (≥25) at baseline. Although the MMSE is a widely used and validated screening instrument, it is primarily designed to detect global cognitive impairment and may have limited sensitivity for the subtle deficits in executive function, attention, processing speed, and working memory that characterize CRCI. This limitation is further addressed in the discussion section.

FACT-G

Quality of life was evaluated using the FACT-G, a 27-item questionnaire validated in Turkish, encompassing four domains: physical well-being, social/family well-being, emotional well-being, and functional well-being. Higher scores on the FACT-G correspond to better perceived quality of life (16).

Data Collection Process for the Study Group

Eligible patients were enrolled following screening based on inclusion and exclusion criteria. Participants who provided informed consent and scored within the normal range on the MMSE were scheduled to begin the study assessments on the first day of chemotherapy.

On the initial day of chemotherapy, fasting blood samples were collected to measure serum tryptophan and CRP levels and promptly transported to the biochemistry laboratory for processing and storage. The FACT-G was administered prior to chemotherapy to assess baseline quality of life.

Assessments performed after six cycles of chemotherapy included clinical evaluations, imaging studies to detect metastasis or recurrence, repeat administration of the MMSE and FACT-G, and collection of additional blood samples for serum tryptophan and CRP measurements. Patients without evidence of disease progression proceeded to complete the full chemotherapy regimen.

At the three-month post-chemotherapy follow-up, patients underwent imaging, MMSE and FACT-G assessments, and further blood sampling for tryptophan and CRP levels.

Data Collection Process for the Control Group

Recruitment of the control group commenced after enrollment of the patient group had been finalized. A matching process ensured demographic and clinical comparability between groups, that smoking status was not included in the matching criteria because the controls were healthy.

Healthy volunteers underwent cognitive screening using the MMSE, and only individuals with scores of 25 or higher were included. Fasting blood samples were collected once to measure serum tryptophan and CRP levels and stored until batch analysis.

Measurement of Blood Samples

All collected blood samples were analyzed in batches at the medical biochemistry research laboratory after completion of data collection. Fasting venous blood samples were drawn into red-top biochemistry tubes, centrifuged at 1500×g for 15 minutes to separate serum, and transferred into Eppendorf tubes for storage at -80 °C until analysis. Serum tryptophan levels were measured using a commercially available enzyme-linked immunosorbent assay kit, with all analyses performed in duplicate according to the manufacturer's instructions. The procedure involved incubation of samples in antibody-coated wells, followed by sequential steps including incubation with biotinylated antibody, addition of enzyme conjugate, chromogenic substrate reaction, and measurement of optical density at 450 nm using a microplate reader. Sample concentrations were determined from a standard calibration curve.

Serum CRP levels were measured by a high-sensitivity nephelometric method on an automated analyzer, and results were expressed in mg/L.

Statistical Analysis

Sample size calculations were performed using G*Power software, based on an assumed effect size of 0.5, a significance level of 0.05, and a power of 0.80, yielding a target sample size of 30 patients and 30 controls.

To reduce potential confounding between the study and control groups, frequency matching was applied during recruitment of the control group to ensure comparable group-level distributions of the matching variables across the two groups. Patients and controls were matched on age and sex; smoking status was not included among the matching variables, given the health status of the control group. Standardized mean differences were calculated for each matching variable, with values <0.1 considered acceptable. Statistical comparisons employed independent samples t-tests for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed continuous variables, and chi-square or Fisher's exact tests for categorical variables. Longitudinal changes in variables such as serum tryptophan levels, MMSE scores, and FACT-G scores were analyzed using paired-sample t-tests or appropriate non-parametric alternatives, with Bonferroni correction applied to account for multiple repeated-measures comparisons across the three assessment time points.

Receiver operating characteristic (ROC) analysis was performed to evaluate the ability of serum tryptophan levels to discriminate CRCI. The resulting cut-off values are reported as exploratory findings derived from this pilot cohort and require external validation. All statistical analyses were conducted using SPSS v24, with significance set at $p<0.05$.

Results

Comparison Between Study and Control Groups

A total of 30 patients with stage II-III colon adenocarcinoma and 30 age- and sex-matched healthy controls were included (Supplementary Figure 1). Demographic characteristics such as educational level, marital status, economic status, occupation, body weight, height, BMI, and BSA did not differ significantly between groups (all $p>0.05$).

However: a higher proportion of active smokers was observed in the patient group than in controls (50% vs. 20%, $p=0.014$; Supplementary Table 1).

Baseline cognitive function, assessed by the MMSE total score, was slightly lower in patients than in controls (28.59±1.02 vs. 28.69±1.01), although this difference did not reach statistical significance ($p=0.492$). However, baseline serum tryptophan levels were significantly reduced in the patient group (49.37±28.62 ng/mL) compared with controls (97.97±47.75 ng/mL; $p<0.001$) (Supplementary Table 2).

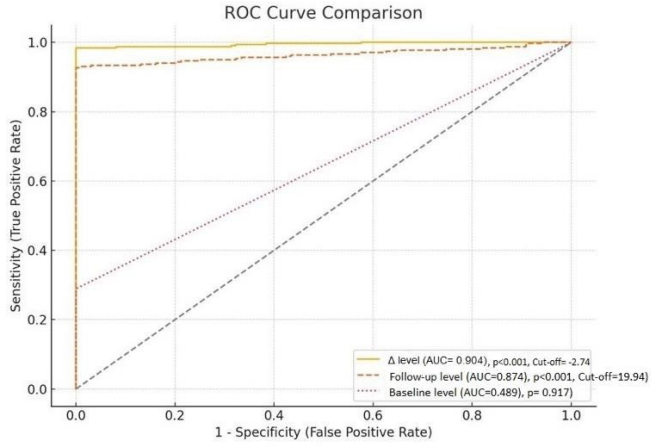

Figure 1. ROC curve for CRCI of tryptophan levels during the study period

ROC: Receiver operating characteristic, CRCI: Chemotherapy-related cognitive impairment, AUC: Area under the curve

Cognitive Changes during Chemotherapy

Among patients, MMSE subscale scores showed significant declines over the course of chemotherapy. From baseline to the final assessment, three months after completing 12 chemotherapy cycles, significant reductions were observed in orientation ($p<0.001$), registration memory ($p<0.001$), recall ($p<0.001$), language ($p<0.001$), and attention-calculation ($p<0.001$) subdomains. The MMSE total score also significantly decreased from baseline (26.91±1.02) to follow-up (23.67±2.78; $p<0.001$) (Supplementary Table 2).

Quality of Life Changes

FACT-G total scores declined significantly during chemotherapy, dropping from 88.8±2.45 at baseline to 73.2±1.76 after six cycles ($p<0.001$). However, by the three-month post-chemotherapy follow-up, FACT-G total scores recovered to baseline levels (88.7±2.41, $p=0.618$ compared to baseline). A similar pattern of temporary decline and subsequent recovery was observed across all FACT-G subdomains, including physical, social/family, emotional, and functional well-being (all $p<0.001$ for decline during treatment and all $p>0.05$ for recovery at follow-up) (Supplementary Table 3).

Tryptophan Levels and Cognitive Impairment

Within the study group, 16 patients developed cognitive impairment based on MMSE scores, whereas 14 maintained normal cognitive function. Patients with cognitive impairment exhibited significantly lower hemoglobin levels at both baseline and follow-up ($p<0.001$) and higher CRP levels at follow-up ($p=0.033$) (Table 1).

Table 1. Comparison of demographic, clinical, laboratory, and chemotherapy side effects between patients with and without cognitive impairment in the study group

Characteristics	Patients with cognitive impairment	Patients without cognitive impairment	p-value[α]
n	**(n=16)**	**(n=14)**	
Qualitative variables			
Gender; n (%) Male Female	11 (69) 5 (31)	8 (57) 6 (43)	0.345
Educational status; n (%) Primary or middle school High school Undergraduate or above	7 (44) 6 (37) 3 (19)	4 (29) 3 (21) 7 (50)	0.137
Economic level; n (%) Lower income Middle income Higher income	4 (25) 7 (44) 5 (31)	4 (29) 6 (42) 4 (29)	0.616
Occupation; n (%) Housewife Retired worker Retired officer	3 (19) 6 (37) 7 (44)	4 (29) 6 (42) 4 (29)	0.314
Marital status; n (%) Married Single	11 (69) 5 (31)	9 (64) 5 (36)	0.469
Smoking habits; n (%) Never smoking Quit smoking (>10 years) Active smoker	2 (12) 4 (25) 10 (63)	4 (28) 5 (36) 5 (36)	**0.037**
Disease stage; n (%) Stage 2 Stage 3	5 (31) 11 (69)	4 (29) 10 (71)	0.433
Chemotherapy-related oral mucositis; n (%) Absent Grade 1 Grade 2	4 (25) 8 (50) 4 (25)	5 (36) 7 (50) 2 (14)	0.494
Chemotherapy-related fatigue; n (%) Absent Grade 1 Grade 2	2 (13) 9 (56) 5 (31)	1 (7) 8 (57) 5 (36)	0.174
Chemotherapy-related diarrhea; n (%) Absent Grade 1 Grade 2	8 (50) 8 (50) 0	7 (50) 6 (43) 1 (7)	0.396
Chemotherapy-related chronic neuropathy; n (%) Absent Grade 1 Grade 2	7 (44) 9 (56) 0	4 (29) 8 (57) 2 (14)	0.096
Chemotherapy-induced anemia; n (%) Absent Grade 1 Grade 2	0 13 (81) 3 (19)	6 (43) 7 (50) 1 (7)	**<0.001**
Chemotherapy-induced neutropenia; n (%) Absent Grade 1 Grade 2	2 (13) 12 (74) 2 (13)	2 (14) 11 (79) 1 (7)	0.348
Chemotherapy-induced thrombocytopenia; n (%) Absent Grade 1 Grade 2	6 (38) 9 (56) 1 (6)	5 (36) 8 (57) 1 (7)	0.597

Table 1. Continued

Characteristics	Patients with cognitive impairment	Patients without cognitive impairment	p-value[α]
n	**(n=16)**	**(n=14)**	
Quantitative variables			
Weight (kg); median (min-max)	72 (52-82)	77 (56-88)	0.324
Height (cm); median (min-max)	167 (148-178)	168 (148-178)	0.245
BMI (kg/m²); median (min-max)	**20.1 (17.2-24.4)**	21.9 (18.4-24.2)	0.316
BSA (m²); median (min-max)	1.74 (1.54-2.01)	1.76 (1.54-2.21)	0.654
Leukocyte count (µL); median (min-max) Baseline Follow-up*	 9137 (6974-11241) 6937 (5374-8766)	 8648 (5474-8335) 6344 (4274-7037)	**<0.001** 0.412
Neutrophil count (µL); median (min-max) Baseline Follow-up*	 7964 (4837-9474) 4169 (3433-6274)	 6219 (3798-5964) 4296 (3374-5974)	**<0.001** 0.374
Lymphocyte count (µL); median (min-max) Baseline Follow-up*	 2954 (975-4125) 1978 (742-3148)	 2845 (918-3945) 2055 (908-3214)	0.245 0.494
Platelet count (x10³/µL); median (min-max) Baseline Follow-up*	 496 (337-674) 248 (137-407)	 414 (294-537) 234 (137-407)	**<0.001** 0.415
Hemoglobin level (g/dL); median (min-max) Baseline Follow-up*	 9.2 (8.9-10.6) 8.9 (8.6-9.4)	 10.4 (8.4-12.7) 9.6 (9.1-12.1)	**<0.001** **<0.001**
Serum CRP level (mg/L); median (min-max) Baseline Follow-up*	 3.7 (2.8-5.7) 2.9 (1.9-3.6)	 3.3 (1.9-4.2) 2.6 (1.4-3.4)	<0.001 0.033
Serum tryptophan level (ng/mL); mean ± SD Baseline Follow-up* Difference	 41.19±33.92 36.64±24.51 -4.55±9.81	 43.37±32.21 42.19±32.62 -1.22±0.41	0.496 <0.001 <0.001
Δ Baseline-follow-up FACT-G scores (mean ± SD)			
Physical score			
Baseline Follow-up* Difference	13.19±1.17 21.75±3.26	13.78±1.12 15.21±1.76	0.165 <0.001
Social-family support			
Baseline Follow-up* Difference	24.37±1.02 23.68±0.87	24.93±1.07 23.57±1.16	0.160 0.757
Emotional			
Baseline Follow-up* Difference	19.31±1.53 14.44±1.51	19.14±1.46 14.21±1.31	0.760 0.670
Functional			
Baseline Follow-up* Difference	19.44±1.86 24.56±0.89	20.21±1.76 24.07±1.38	0.252 0.252
Total score			
Baseline Follow-up* Difference	76.32±1.58 84.44±3.83	78.07±2.37 77.07±2.76	0.22 <0.001

*: Follow-up: at control after 3 months completed 12-cycles treatment, α: Statistical significance is indicated by p-values in bold. Chi-square test and Fisher's exact test were used for comparing categorical variables, and Mann-Whitney U test were used for continuous variables with non-normal distributions. The Student's t-test was used for normally distributed variables. Mean and standard deviations were presented for normally distributed variables, and medians and ranges were given for non-normally distributed variables, Δ: Difference between, BMI: Body mass index, BSA: Body surface area, FACT-G: Functional assessment of cancer therapy-general, CRP: C-reactive protein, SD: Standard deviation

Serum tryptophan levels declined significantly in patients with cognitive impairment, decreasing from 41.19±33.92 ng/mL at baseline to 36.64±24.51 ng/mL at follow-up (p<0.001).

In contrast, patients without cognitive impairment showed no significant change in serum tryptophan levels over time (43.37±32.21 ng/mL at baseline vs. 42.19±32.62 ng/mL at follow-up; p=0.496) (Table 1).

Factors Associated with Cognitive Impairment

In univariate logistic regression analysis, baseline BMI below 22 kg/m^2, elevated CRP levels at follow-up, and follow-up serum tryptophan levels below 19.94 ng/mL were each significantly associated with cognitive impairment (all p<0.001). In multivariate analysis, low baseline BMI [odds ratio (OR): 2.96; 95% confidence interval (CI): 1.656-3.274], elevated follow-up CRP levels (OR: 1.89; 95% CI: 1.578-3.148), and low follow-up serum tryptophan levels (OR: 1.83; 95% CI: 1.637-3.513) remained associated with cognitive impairment (p<0.001) (Table 2). Given the limited sample size and number of cognitive impairment events relative to the number of covariates, these multivariate findings should be interpreted with caution, as the model may be susceptible to overfitting; this limitation is further discussed below.

ROC analysis was performed to evaluate the diagnostic performance of serum tryptophan levels in predicting CRCI. The analysis identified a follow-up serum tryptophan cut-off value of 19.94 ng/mL, which yielded an area under the curve (AUC) of 0.874 (p<0.001). These exploratory findings require external validation. At the follow-up cut-off of 19.94 ng/mL, the sensitivity and specificity were 86% and 74%, respectively. These cut-off values should be regarded as exploratory findings derived from a pilot cohort and therefore require external validation in larger samples before clinical application. Additionally, changes in serum tryptophan levels (Δ level) demonstrated even higher discriminative performance, with an AUC of 0.904 (p<0.001) and an exploratory cut-off of -2.74 ng/mL. In contrast, baseline serum tryptophan levels showed no significant discriminatory ability (AUC=0.489, p=0.917). These results are illustrated in Figure 1.

Correlation Analyses

Correlation analysis revealed a significant inverse relationship between the reduction in serum tryptophan levels and the decline in MMSE total scores over the course of treatment (r=-0.654, p<0.001), suggesting that greater decreases in serum tryptophan levels were associated with more pronounced cognitive decline. No significant correlations were observed between changes in tryptophan levels and other clinical or laboratory parameters, including leukocyte, neutrophil, lymphocyte, or platelet counts (all p>0.05). Although both MMSE and FACT-G scores declined during chemotherapy, their recovery patterns diverged: FACT-G scores returned to baseline by the three-month follow-up, whereas MMSE scores remained reduced. This dissociation suggests that the transient decline in FACT-G largely reflects treatment-related physical and emotional burden, while the persistent MMSE decline is more specifically related to cognitive impairment; no significant correlation was observed between changes in MMSE and FACT-G scores (Supplementary Table 3).

Discussion

This study suggests that reductions in serum tryptophan levels during chemotherapy may represent a candidate biomarker for CRCI in older patients with colon cancer. While baseline tryptophan levels were significantly lower in patients than in healthy controls, this baseline difference cannot be causally attributed to chemotherapy exposure, nor was it the primary focus of this study; rather, our findings indicate that the trajectory of tryptophan levels over the course of treatment, rather than baseline levels alone, better reflects CRCI risk. Notably, patients who developed cognitive impairment experienced greater declines in serum tryptophan and had elevated CRP levels, supporting a link between systemic inflammation and cognitive vulnerability.

Table 2. Factors associated with the presence of cognitive impairment

Variables	Univariate analysis				Multivariate analysis			
	p-value	OR	95% CI lower	95% CI upper	p-value$^{\alpha}$	OR	95% CI lower	95% CI upper
Baseline low BMI* (<cut-off)	<0.001	2.74	1.768	3.749	<0.001	2.96	1.656	3.274
Follow-up** CRP (>UNL vs. other)	<0.001	1.94	1.592	3.137	<0.001	1.89	1.578	3.148
Follow-up** tryptophan (<cut-off)*	<0.001	1.91	1.673	2.969	<0.001	1.83	1.637	3.513

*: Cut-off for BMI=22 kg/m^2 (AUC=0.764, p<0.001). Cut-off for follow-up tryptophan=19.94 ng/mL (AUC=0.874, p<0.001). **: Follow-up: at control after 3 months completed 12-cycles treatment, $^{\alpha}$: These models included multiple ordinal and nominal variables. Initially, the probability of predicting cognitive impairment was 59.6%, but with the developed model, this rate increased to 82.9% (p<0.001, the Nagelkerke R^2=0.719), OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein, UNL: Upper normal limit, AUC: Area under the curve, BMI: Body mass index

These results align with existing evidence that systemic inflammation can alter tryptophan metabolism through activation of indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase, shifting tryptophan away from serotonin synthesis toward the kynurenine pathway. This metabolic diversion increases neurotoxic metabolites, such as quinolinic acid, while reducing neuroprotective compounds, contributing to neuroinflammation and cognitive dysfunction (13,17). Similar metabolic disturbances have been implicated in neurocognitive disorders such as depression and Alzheimer's disease, which share clinical features with CRCI (18,19).

Our data extend this mechanistic hypothesis by demonstrating an inverse correlation between declining tryptophan levels and worsening MMSE scores. This supports the notion that tryptophan may be a candidate biomarker for CRCI. Previous studies have shown that cancer patients, particularly those undergoing chemotherapy, frequently display sustained disruptions in tryptophan metabolism, especially in the presence of elevated inflammatory markers like CRP (20-24). In this context, CRP is best regarded as an inflammatory biomarker associated with both CRCI and alterations in tryptophan metabolism, rather than as evidence of a direct causal pathway linking inflammation, tryptophan, and cognitive decline.

Study Limitations

Nevertheless, limitations exist. Not all studies have reported significant associations between baseline tryptophan levels and CRCI (25-27), highlighting the limited utility of single-point measurements. As a pilot investigation, this study was limited by a modest sample size that constrained statistical power, generalizability, and causal inference; the observational design further precludes conclusions about causality. Cognitive assessments relied on the MMSE, which, despite its widespread clinical use and validation in the Turkish population, may not detect subtle deficits, particularly in executive functions, attention, processing speed, and working memory. Future studies should consider more sensitive instruments such as the Montreal Cognitive Assessment and comprehensive neuropsychological batteries. Moreover, serum tryptophan levels may not perfectly reflect central nervous system availability due to blood-brain barrier dynamics and competition with other amino acids. Additionally, factors such as dietary intake, nutritional status, circadian variation, and medications, as well as hepatic and renal function, were not systematically controlled (2,10,22). The control group was not followed longitudinally and was assessed only at a single baseline time point, precluding comparison of within-group changes over time. In addition, smoking status differed significantly between the study and control groups and was not included among the matching variables. Because smoking can influence systemic inflammation and tryptophan metabolism, this imbalance may have confounded comparisons between groups. Finally, although Bonferroni correction was applied to the repeated-measures analyses, multiple comparisons across variables and time points may still increase the risk of type I error, and our regression findings in particular should be interpreted with caution given the limited number of events relative to the number of covariates examined.

If validated in larger cohorts, monitoring serum tryptophan levels may facilitate early identification of patients at high risk of CRCI, enabling timely interventions. Strategies such as anti-inflammatory therapies, lifestyle modifications, or direct modulation of the kynurenine pathway (e.g., IDO or kynurenine 3-monooxygenase inhibitors) are potential avenues for future research (28-31). Given mechanistic overlaps with neurodegenerative conditions, oncology may benefit from biomarker models established in neuropsychiatric disorders (32-35).

Importantly, our findings revealed that, even before chemotherapy, cancer patients had significantly lower serum tryptophan levels than controls. This suggests that cancer-related metabolic stress, inflammation, or malnutrition may predispose patients to lower tryptophan reserves, potentially increasing vulnerability to cognitive decline once chemotherapy is initiated (36). Early nutritional or metabolic interventions might help mitigate this risk (37).

Future studies should include larger, multicenter cohorts and more sensitive neurocognitive assessments. Investigating sex differences, microbiome interactions, and neuroimaging correlates may further clarify the role of tryptophan in CRCI and improve biomarker specificity (2,10,22). Additionally, exploring cerebrospinal fluid metabolites could help link peripheral changes to central neurobiology.

Conclusion

Serum tryptophan emerges as a biologically plausible candidate biomarker associated with CRCI and requires validation in larger prospective studies. Our findings suggest that decreases in tryptophan levels during chemotherapy are associated with cognitive decline and systemic inflammation. Integrating tryptophan monitoring into oncology care could enable earlier detection of cognitive risks and inform preventive strategies.

Beyond its diagnostic potential, maintaining tryptophan levels during chemotherapy might help protect against neuroinflammation and cognitive impairment. Preclinical data and our pilot results support investigating tryptophan supplementation or modulation of its metabolic pathways as a topic for future research. Future randomized clinical trials are needed to determine whether preserving physiological tryptophan levels can reduce CRCI incidence and severity and potentially improve quality of life and survivorship outcomes.

In summary, serum tryptophan offers promise as a candidate biomarker associated with CRCI, meriting further rigorous clinical evaluation.

Ethics

Ethics Committee Approval: This study with a matched control group was conducted after approval by the Muğla Sıtkı Koçman University Institutional Ethics Committee (approval no: 14/X, date: 24.08.2022) and in accordance with the Declaration of Helsinki.

Informed Consent: Prospective observational pilot study.

Footnotes

Authorship Contributions

Surgical and Medical Practises: Ö.T., Concept: Ö.T., Ü.Ö.T., Design: Ö.T., Data Collection or Processing: Ö.T., Analysis or Interpretation: Ö.T., Ü.Ö.T., Literature Search: Ö.T., Ü.Ö.T., Writing: Ö.T., Ü.Ö.T.

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Supplementary Tables 1-3: https://d2v96fxpocvxx.cloudfront.net/e3bb5c55-588b-4d9b-90a5-1da04e1a25d8/content-images/2cced50b-4ca6-4bcd-9cde-2895776ac590.pdf

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Reader Questions

Based on the manuscript: "Changes in Serum Tryptophan Levels and Chemotherapy-related Cognitive Impairment in Older Patients with Colon Cancer: A Prospective Pilot Study"

1. Which chemotherapy regimen was administered to all patients in this study?

A. CAPOX

B. FOLFIRI

C. mFOLFOX6

D. FOLFIRINOX

Correct Answer: C. mFOLFOX6

2. Which biomarker showed the strongest association with chemotherapy-related cognitive impairment during follow-up?

A. Baseline CRP

B. Baseline tryptophan

C. Follow-up serum tryptophan level

D. White blood cell count

Correct Answer: C. Follow-up serum tryptophan level

3. Which cognitive assessment tool was used to evaluate chemotherapy-related cognitive impairment in this study?

A. Montreal cognitive assessment (MoCA)

B. FACT-Cog

C. Mini-mental state examination (MMSE)

D. Trail making test

Correct Answer: C. Mini-Mental State Examination (MMSE)

4. According to the proposed biological mechanism, inflammatory activation shifts tryptophan metabolism toward which pathway?

A. Dopamine pathway

B. Glutamate pathway

C. Kynurenine pathway

D. GABA pathway

Correct Answer: C. Kynurenine pathway

5. What was the primary conclusion of this pilot study?

A. Baseline serum tryptophan predicts CRCI with high accuracy.

B. Declining serum tryptophan during chemotherapy may serve as a candidate biomarker associated with CRCI.

C. CRP alone is sufficient to diagnose CRCI.

D. Tryptophan supplementation prevents CRCI.

Correct Answer: Correct Answer: B. Declining serum tryptophan during chemotherapy may serve as a candidate biomarker associated with CRCI.