Original Article

Relationship between pre-treatment nutritional status, serum glutamine, arginine levels and clinicopathological features in Taiwan colorectal cancer patients

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Background and Objectives: To examine the relationship between malnutrition criteria, serum glutamine and arginine concentrations, and clinicopathological features in Taiwan colorectal cancer patients. **Methods and Study Design:** Three malnutrition criteria (body weight loss >5% over past 6 months, body mass index (BMI) <18.5 kg/m^2, and hypoalbuminemia) and serum levels of glutamine and arginine were measured in 164 colorectal patients. Malnutrition status and serum glutamine and arginine concentrations were tested for their association with each other, as well as with the clinicopathological variables. **Results:** Of the 164 patients, 38 (23.5%) had body weight loss, 19 (11.9%) had low BMI, and 57 (35.8%) had hypoalbuminemia. The univariate analysis showed hypoalbuminemia was correlated with advanced tumour stage, lower concentrations of glutamine, higher C-reactive protein level, and progression-free survival rate. Univariate analysis also showed glutamine levels were lower in advanced tumour stage, but arginine levels were not associated with any clinicopathologic variables. Neither the nutrition criteria used in this study nor glutamine and arginine levels were correlated with hospital stay or progression-free survival rate in multivariate analysis. **Conclusions:** Different nutrition assessment criteria produced different malnutrition rates in colorectal cancer patients; however, pre-treatment malnourished status and low serum glutamine and arginine concentrations were not correlated with hospital stay and progression-free survival rate.

Key Words: body weight loss, low BMI, hypoalbuminemia, glutamine, arginine

INTRODUCTION

Malnutrition is a common and recurrent problem in colorectal cancer (CRC) patients. Malnutrition is defined as body weight loss of more than 5% of body weight over the past 6 months,[1] body mass index (BMI) less than 18.5 kg/m^2,[2] or hypoalbuminemia (serum albumin level lower than 3.5 g/dL).[3] Malnutrition results in longer hospital stays, reduced treatment efficacy, increased treatment complications, and higher care cost. It also makes patients hesitate or defer advanced interventions.[1] Intriguingly, some studies have reported that there is no association between nutritional status and incidence of postoperative morbidity or treatment-related adverse events in CRC patients;[3] however, other evidence suggests that aggressive nutrition support for CRC patients with poor nutrition status reduces treatment-related adverse effects, improves treatment response, and offers better survival.[4-6] These observations suggest that pre-treatment malnutrition status in CRC patients is manageable and reversible if the appropriate nutritional intervention is administered.

Glutamine is the most abundant amino acid in the body,

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Manuscript received 26 July 2014. Initial review completed 19 October 2014. Revision accepted 22 December 2014.
doi: 10.6133/apjcn.2015.24.4.23

but it is often depleted during periods of stress such as malignancies.[7] The marked glutamine depletion observed in cancer malnutrition results in a negative impact on the function of host tissue that relies on adequate glutamine store for optimal function.[8] Some studies have reported that glutamine supplementation efficiently prevents treatment-induced side effects,[8-10] but one double-blind randomized trial showed that glutamine supplementation did not have the response benefit or secondary effect of chemotherapy for cancer patients.[11]

A similar scenario occurs with arginine, a dibasic and cationic amino acid involved in numerous biosynthetic pathways that influence both tumour development and host immunity.[12] Decreased availability of arginine is characteristic of cancer. Lower circulating arginine levels or abnormal arginine metabolism are commonly found in different types of cancer, that possibly contributing to cancer progression and impaired immunity.[12-14] However, some cancers can be controlled by arginine restriction, and arginine supplementation may not promote tumour progression.[12,15] It is unclear whether the extent of glutamine and arginine depletion at time of diagnosis is associated with nutritional status and with clinicopathologic variables of cancer patients.

We carried out a retrospective study to examine malnutrition status of CRC patients. We also assessed the relationship between serum glutamine and arginine, nutrition status, and clinicopathologic parameters, particularly for hospital stay for patients undergoing curative surgery, as well as for progression-free survival.

METHODS

Study participants

Data were retrospectively collected from 164 patients with CRC who visited Chang Gung Memorial Hospital in Keelung, Taiwan from January 2007 to December 2009. The following parameters were recorded and analyzed for all study patients: age, sex, body height (BH), body weight (BW), BMI, tumour location, tumour-node metastasis (TNM) stage, histological grading, hemoglobin level (Hb), white blood cell count (WBC), total lymphocyte count (TLC), albumin level, hepatic function as measured by aspartate aminotransferase (AST), C-reactive protein (CRP), plasma carcinoembryonic antigen (CEA) levels, hospital stay duration after curative surgery for stage I to III patients, and 3-year progression-free survival rate (PFSR). PFSR was defined as the percentage of patients who had no imaging evidence of disease progression 3 years after diagnosis. As shown in Table 1, the patients' ages ranged from 18 to 94 years (average age 64.9 years). There were 108 men and 56 women. The tumour was located in the colon in 109 cases (66.5%) and in the rectum in 55 cases (33.5%). Tumours were reclassified retrospectively according to the 7th edition American Joint Committee on Cancer Staging System (AJCC) based on physical examination, routine laboratory tests, chest radiography, and computerized tomography (CT) of the abdomen. Using these criteria, 37 patients (22.6%) had TNM stage I, 45 patients (27.4%) had TNM stage II, 56 patients (34.1%) had TNM stage III, and 26 patients (15.9%) had TNM stage IV. All patients had adenocarcinoma histology at the time of diagnosis. The histological grade was assessed by World Health Organization criteria: 50 tumours (30.5%) were well differentiated, 104 tumours (63.4%) were moderately differentiated, and 10 tumours (6.1%) were poorly differentiated and undifferentiated. The pathological diagnoses of all enrolled specimens were reviewed and confirmed by the CRC committee atour institute. The committee members included 2 colorectal surgeons, 3 medical oncologists, 2 radiation oncologists, and 2 pathologists. This study was approved by the Institutional Review Board at Chang Gung Memorial Hospital in Taiwan.

Measurements of serum glutamine and arginine concentrations

Blood was collected from patients before treatment and centrifuged at 1,500 rpm for 15 minutes. All serum samples were stored at −80°C until analysis. We determined serum glutamine and arginine concentration using an Enzy Chrom^{TM} Glutamine Assay Kit (EGLN-100, Bio Assay Systems, CA, USA), and an L-arginine enzyme-linked immunosorbent assay kit (K7733, Immunodiagnostik AG, Bensheim, Germany), respectively (manufacturer instructions were followed by both). All samples were thawed only once and assayed in triplicate.

Statistical analysis

Statistical analyses were performed using the SPSS statistical package, version 140 (SPSS, Inc., Chicago, IL, USA). Analysis of variance (ANOVA) using Bonferroni adjustments (for age, BH, BW, BMI, WBC, TLC, Hb, Albumin, CRP, AST, glutamine, arginine, and CEA) or chi-square test (for sex, stage, location, and histologic differentiation) was used for multiple comparisons in Table 1. For the different malnutrition criteria presented in Table 2, the p value was determined by independent Student's t test (for age, BH, BW, BMI, WBC, TLC, Hb, Albumin, CRP, AST, glutamine, arginine, and CEA) or chi-square test (for sex, stage, location, histologic differentiation, and 3-year PFSR). All p values were derived from two-tailed statistical tests. Correlation between glutamine and arginine concentrations and sex, tumour location, tumour stage, histologic differentiation, and survival rate were tested by Kendall's tau (τ) coefficient. Correlations between glutamine and arginine concentrations and age, BH, BW, BMI, WBC, TLC, Hb, Albumin, CRP, AST, and CEA were tested by Spearman's rho (ρ). A p value of <0.05 was considered statistically significant.

RESULTS

The average levels of WBC, CRP, and CEA in the entire group at time of diagnosis were higher than normal limits (Table 1). Mean serum glutamine and arginine concentrations were 95±121 ng/mL and 121±77 ng/mL, respectively. When patients were stratified by TNM stage, we found that advanced stage was associated with higher histologic grading, CRP levels, AST levels, and longer hospital stay, but lower albumin level and 3-year PFSR (Table 1). Advanced-stage patients also showed a trend for lower Hb, higher CEA levels and more tumours in the rectum ($0.05<p<0.1$). Tumour stages were not significantly associated with sex, age, BH, BMI, WBC, or TLC (Table 1). Glutamine level was lower in advanced stage disease and

Table 1. Demographic and clinicopathologic data for 164 CRC patients

Variables expressed as number (%) or mean±SD	ALL	Stage I	Stage II	Stage III	Stage IV	*p* value*
Patient number (%)	164 (100)	37 (22.6)	45 (27.4)	56 (34.1)	26 (15.9)	
Sex						
Men	108 (65.9)	30 (81.1)	27 (60.0)	36 (64.3)	15 (57.7)	0.10
Women	56 (34.1)	7 (18.9)	18 (40.0)	20 (35.7)	11 (42.3)	
Age	64.9±13.7	62.8±10.5	67.6±15.8	64.1±13.9	65.0±13.5	0.42
Location						
Colon	109 (66.5)	29 (78.4)	34 (75.6)	32 (57.1)	14 (53.8)	0.05
Rectum	55 (33.5)	8 (21.6)	11 (24.4)	24 (42.9)	12 (46.2)	
Histologic grade differentiations						
1	50 (30.5)	19 (51.4)	14 (31.3)	12 (24.1)	5 (19.2)	0.02*
2	104 (63.4)	18 (48.6)	29 (64.4)	39 (69.6)	18 (69.2)	
3	10 (6.1)	0 (0)	2 (4.4)	5 (8.9)	3 (11.5)	
BH (cm)	161±8.8	162±9.3	159±8.3	162±8.2	161±9.9	0.41
BW before diagnosis (kg)†	61.8±11.2	63.8±11.8	60.8±11.6	62.0±10.2	60.1±11.7	0.55
BW at diagnosis (kg)	60.3±12.2	61.9±11.4	58.7±11.5	61.7±13.6	57.5±10.8	0.34
BMI before diagnosis (kg/m^2)†	23.9±3.9	24.3±3.6	23.9±4.6	24.0±3.4	23.2±4.1	0.77
BMI at diagnosis (kg/m^2)	24.4±14.1	23.5±3.5	23.3±4.6	26.8±23.5	22.2±3.5	0.46
WBC (cells/μL)	10,517±4,392	10,851±4,405	10,026±3,997	9,882±3,930	12,261±5,574	0.11
TLC (cells/mm^3)	1,424±733	1,618±850	1,399±369	1,434±721	1,174±696	0.13
Hb (g/dL)	12.0±1.9	12.5±2.2	11.5±1.9	12.2±1.9	11.9±1.3	0.08
Albumin (g/dL)	3.6±0.7	3.9±0.4	3.5±0.8	3.7±0.6	3.2±0.7	<0.0001*
CRP (mg/dL)	24.6±48.0	4.9±6.5	27.8±42.5	21.6±52.6	51.7±64.2	0.01*
AST (U/L)	27.6±22.9	26.7±6.7	27.3±13.8	23.1±9.2	40.9±55.2	0.04*
Glutamine (ng/mL)	94.6±121	123±134	105±130	96.2±119	29.9±53.1	0.04*
Arginine (ng/mL)	122±77.2	118±76.6	142±86.5	112±73.1	113±66.9	0.28
CEA (ng/mL)	1,425±733	2.3±2.1	6.0±9.8	7.9±10.9	298±1,313	0.08
Hospital stay after curative surgery (days)	19.2±17.6	13.5±7.8	18.9±13.2	23.1±23.6	NA	0.03*
3-year progression-free survival rate (%)	76.2	100	93.3	73.2	19.2	<0.001*

*p value was determined by ANOVA using Bonferroni adjustments (for age, BH, BW, BMI, WBC, TLC, Hb, albumin, CRP, AST, glutamine, arginine, CEA, and hospital stay) or chi-square test (for sex, stage, location, histologic differentiation, and progression-free survival rate) for multiple comparisons.

†BW or BMI of patients was obtained at 6 months before diagnosis.

AST: aspartate aminotransferase; BH: body height; BMI: body mass index; BW: body weight; CEA: carcinoembryonic antigen; CRC: colorectal cancer; CRP: C-reactive protein; Hb: hemoglobin; NA: not available; TLC: total lymphocyte count; WBC: white blood cell.

correlated with serum albumin levels. Arginine level was not associated with tumour stage (Table 1). There was no significant correlation between glutamine or arginine concentrations and age, sex, tumour location, histologic differentiation, BH, BW, BMI, WBC, TLC, Hb, CRP, AST, CEA, hospital stay or survival rate (p>0.05 for all correlations).

We evaluated if there was a relationship between malnutrition status of CRC patients (stratified by body weight loss >5%, BMI <18.5, and albumin level <3.5 g/dL) and clinicopathologic parameters, serum glutamine and arginine levels (Table 2). Of 164 CRC patients, 38 patients (23.5%) had body weight loss >5%. These 38 patients had a significantly higher histologic grading (p<0.05), and a trend for higher WBC count, lower albumin and glutamine concentrations (0.05<p<0.1) as compared with those without body weight loss >5%. CRC patients with BMI <18.5 represented 11.9% of the entire group. The low BMI patients had lower albumin level than those with BMI >18.5; however, the frequency of malnutrition increased to 35.8% when albumin <3.5 g/dL was used as a cut-off. Serum albumin level <3.5 g/dL showed a significant association with older age, advanced tumour stage, lower concentrations of Hb and glutamine, and higher CRP level. There was no difference in serum arginine levels for CRC patients with or without malnutrition.

We further analyzed whether malnutrition status, clinicopathologic parameters, serum glutamine and arginine levels were associated with hospital stay and 3-year PFSR. Albumin level <3.5 g/dL had a significantly lower 3-year PFSR in univariate analysis; however, the PFSR benefit did not remain after adjusting for age, sex, tumor stage and other clinicopathologic variables. Neither nutrition stratification criteria used in this study nor serum glutamine and arginine levels were correlated with hospital stay or PFSR.

DISCUSSION

Various malnutrition rates of CRC patients, ranging from 10% to 70%, have been previously reported. This broad spectrum of malnutrition rates may result from varying definitions of malnutrition, which use different measurements to determine a patient's nutrition status.[3-6,16] Consequently, the inconsistent evaluation tools made it difficult to compare malnutrition status and treatment endpoints between studies. For example, Mauricio et al prospectively analyzed 70 CRC patients and found significant variation in nutritional status based upon different measurements (e.g., BMI, triceps skinfold, and midarm circumference), none of which were associated with complications from anti-cancer treatment.[16] Thoreson et al studied a homogeneous group of 77 stage IV CRC patients and found a lack of concordance in malnutrition status among different assessment criteria; however, patients with malnutrition had shorter survival.[17] Additionally, some factors may confound the analysis of the effects of malnutrition at time of CRC diagnosis on clinical outcomes and its association with demographic parameters. In particular, co-existing medical illness, other than cancer itself, and early nutrition intervention usually precipitate or abate (respectively) the harmful effect of malnutrition on cancer treatment endpoints.[6,18] Selection bias (i.e., homogeneity of groups enrolled, sample size of patients studied, and clinical outcome assessed) also contribute to this controversy. The current study analyzed the nutrition status of CRC patients by 3 malnutrition criteria commonly and conveniently used in daily practice: body weight loss >5%, BMI <18.5 kg/m^2, and serum albumin level <3.5 g/dL. Our results reinforce the notion that different assessment criteria produce inconsistent determinations of one's nutritional status, which may consequently affect the association with treatment outcomes.

Several studies, including ours, showed hypoalbuminemia is a relatively reliable indicator for malnutrition for CRC patients as compared to body weight loss or low BMI.[18-21] CRC-related malnutrition is characterized by protracted inflammation involving several pro-inflammatory cytokines, such as interleukin-6 and tumour necrosis factor which interfere with protein metabolism and induce protein-calorie imbalance in patients.[22] The present study found that low albumin concentration was strongly correlated with high CRP level, suggesting that hypoalbuminemia may reflect inflammation-related, prolonged malnourishment in CRC patients. In contrast, pretreatmenthypoalbuminemia was not an independentprognosticfactor for 3-year PFSR in our multivariate analysis after adjusting for demographic variables. It is likely because we offered intensive nutritional support, including scheduled counselling, prompt nasogastric tube feeding, and parental nutrition throughout the treatment course. In addition, certain comorbid conditions, such as diabetes mellitus and liver cirrhosis, that have been associated with hypoalbuminemia in CRC patients,[18] were not taken into consideration in this study. Last, patient-generated subjective global assessment or mini-nutritional assessment, rather than a single indicator like serum albumin level, is a better way to reflect nutrition status for colorectal cancer patients.

The other salient feature presented in this study is the relationship between serum glutamine and arginine concentrations and clinicopathologic parameters of CRC patients. In the past decade, metabolomic profiles of CRC patients found perturbation of the metabolism of certain amino acids.[23,24] Although the results were inconsistent, since methodology and tissue samples used were not the same among studies, glutamine and arginine levels in both tissue and serum were changed among CRC patients.[23,24] The present findings showed pre-treatment glutamine levels were decreased and correlated with tumour stage, CRP and serum albumin levels, but arginine levels were unrelated to any clinicopathologic parameters of CRC patients. Thus, our data supports the notion that certainamino acid metabolism could dramatically change upon CRC onset;[7] increased amino acid uptake by tumours may contribute to low serum glutamine concentrations.[25] Perhaps the alterations of amino acid profiles within tumour cells rather than serum offers a prognostic and therapeutic potential.[24]

In this retrospective study, we conclude that different nutrition assessment criteria produced different rates of malnutrition in CRC patients. Regardless, hospital stay and progression-free survival were not correlated with pre-treatment malnourished status or low serum glutamine and arginine concentrations.

Table 2. The association between clinicopathologic features and different malnutrition criteria for 164 CRC patients

Variables expressed as	Body weight >5%		*p*	BMI <18.5 kg/m^2		*p*	ALB <3.5 g/dL		*p*
number (%) or mean±SD	Yes	No	value*	Yes	No	value*	Yes	No	value*
Patient number (%)	38 (23.5)	124 (76.5)		19 (11.9)	141 (88.1)		57 (35.8)	102 (64.2)	
Sex									
Men	24 (63.2)	82 (66.1)	0.736	15 (78.9)	90 (63.8)	0.193	36 (63.2)	67 (65.6)	0.749
Women	14 (36.8)	42 (33.9)		4 (21.1)	51 (36.2)		21 (36.8)	35 (35.4)	
Age	65.7±11.8	64.6±14.2	0.664	68.2±19.7	64.1±12.6	0.446	69.1±4.5	63.2±13.0	0.007*
Location									
Colon	27 (71.1)	80 (64.5)	0.457	6 (31.6)	48 (34.1)	0.809	39 (68.4)	66 (64.7)	0.635
Rectum	11 (28.9)	44 (35.5)		13 (68.4)	93 (65.9)		18 (31.6)	36 (35.3)	
TNM stage									
I	9 (23.6)	28 (22.6)	0.633	3 (15.7)	33 (23.4)	0.555	6 (10.5)	29 (28.4)	0.005*
II	8 (21.1)	36 (29.0)		5 (26.3)	38 (26.9)		16 (28.1)	28 (27.4)	
III	13 (34.2)	43 (34.6)		6 (31.7)	50 (35.5)		19 (33.3)	35 (34.3)	
IV	8 (21.1)	17 (13.8)		5 (26.3)	20 (12.5)		16 (28.1)	10 (9.9)	
Histologic grade differentiations									
1	5 (13.1)	45 (36.2)	0.019*	5 (26.3)	43 (30.5)	0.903	17 (29.8)	30 (29.4)	0.956
2	29 (76.3)	73 (58.8)		13 (68.4)	89 (63.1)		36 (63.1)	66 (64.7)	
3	4 (10.6)	6 (5.0)		1 (5.3)	9 (6.4)		4 (7.1)	6 (5.9)	
WBC (cells/L)	11,542±4,604	10,110±4,148	0.073	11,468±4,848	10,256±4,153	0.244	11,187±5,306	10,187±3,818	0.213
TLC (cells/mm^3)	1,430±875	1,429±691	0.993	1,221±623	1,458±741	0.185	1,275±675	1,475±736	0.092
Hb (g/dL)	12.2±1.9	11.9±1.9	0.484	12.2±1.3	12.0±2.0	0.471	11.4±1.7	12.3±1.9	0.002*
Albumin (g/dL)	3.5±0.8	3.7±0.6	0.066	3.2±0.8	3.7±0.6	0.007*	2.9±0.5	4.0±0.3	<0.0001*
CRP (mg/dL)	35.3±57.9	21.2±44.1	0.207	36.6±55.6	23.1±47.1	0.283	52.2±69.3	7.1±8.8	<0.0001*
AST (U/L)	35.4±42.9	25.3±11.4	0.205	22.5±11.4	27.9±23.9	0.422	33.5±38.0	25.1±9.0	0.156
Glutamine (ng/mL)	65.5±94.2	103±127	0.071	56.1±88.7	97.7±123	0.115	63.7±100	107±127	0.028*
Arginine (ng/mL)	120±72.4	122±79.2	0.881	118±52.0	121±78.9	0.855	122±74.4	121±80.1	0.959
CEA (ng/mL)	13.4±31.4	64.1±604	0.607	375±1539	9.4±19.3	0.314	138±889	6.6±12.8	0.269
Hospital stay after curative surgery (days)	27.2±29.3	16.9±11.7	0.069	22.6±14.8	18.8±18.1	0.448	19.6±15.0	19.1±19.1	0.877
3-year progression-free survival rate (%)	71.1	78.2	0.361	63.2	78.0	0.160	63.1	83.4	0.004*

*p value was determined by independent Student's t-test (for age, BH, BW, BMI, WBC, TLC, Hb, albumin, CRP, AST, glutamine, arginine, CEA, and hospital stay) or chi-square test (for sex, stage, location, histologic differentiation, and progression-free survival rate) for different malnutrition criteria.

ALB: albumin; AST: aspartate aminotransferase; BH: body height; BMI: body mass index; BW: body weight; CEA: carcinoembryonic antigen; CRC: colorectal cancer; CRP: C-reactive protein; Hb: hemoglobin; NA: not available; TLC: total lymphocyte count; TNM: tumour-node metastasis; WBC: white blood cell.

ACKNOWLEDGEMENTS

This study was supported by grants (CMRPG2C0161, CMRPG2A0351 and CMRPG2A0352) from the Chung Gang Memorial Hospital, Keelung.

AUTHOR DISCLOSURES

We declared no conflict of interest in employment (other than primary affiliations), commercial grant, other commercial research support, ownership interest, consultant/advisory board, or honoraria from speakers' bureau.

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Original Article

Relationship between pre-treatment nutritional status, serum glutamine, arginine levels and clinicopathological features in Taiwan colorectal cancer patients

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台湾地区大肠直肠癌病人治疗前营养状况、血清谷氨酰胺与精氨酸值和临床病理特征之间的关系

背景与目的：本研究的目的是探讨台湾地区大肠直肠癌病人治疗前营养不良情形、血清谷氨酰胺与精氨酸值和临床病理特征之间的关系。**方法与研究设计：**对 164 位直肠癌病人运用三种营养不良诊断标准，包含六个月内体重下降超过百分之五、身体质量指数小于 18.5 kg/m^2 及低蛋白血症，评估治疗前营养不良状况，同时测量治疗前血清中谷氨酰胺与精氨酸浓度，来测试它们之间的关系，及其与临床病理参数的关系。**结果：**164 位患者中，有 38 位（23.5%）病人体重下降、19 位（11.9%）病人有较低的身体质量指数及 57 位（35.8%）病人有低蛋白血症。单因素分析发现低蛋白血症与肿瘤前期、低谷氨酰胺浓度、高 C 反应蛋白值和无进展存活率有关。单因素分析还显示肿瘤前期时谷氨酰胺浓度低，但没有发现精氨酸浓度与临床病理参数有关。在多变量分析中，无论是营养不良诊断标准或是血清中谷氨酰胺与精氨酸浓度都与住院时间和无进展存活率无关。**结论：**台湾地区大肠直肠癌病人治疗前营养不良发生率因不同营养不良诊断标准而有所差异，但治疗前营养不良状况及低血清中谷氨酰胺与精氨酸浓度与住院时间和无进展存活率无关。

关鍵词：体重下降、低体质指数、低蛋白血症、谷氨酰胺、精氨酸