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# Controlling Nutritional Status (CONUT) Score Is a Prognostic Marker in Metastatic Colorectal Cancer Patients Receiving First-line Chemotherapy

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**Abstract.** *Background/Aim: The Controlling Nutritional Status (CONUT) score is a useful nutritional evaluation, that is calculated from serum albumin, total cholesterol concentrations, and total lymphocyte count. This study aimed to investigate the association between the CONUT score and prognosis in patients with metastatic colorectal cancer (mCRC). Patients and Methods: The CONUT score was retrospectively calculated in 211 patients with mCRC receiving first-line chemotherapy. The patients were divided into three groups: the CONUT low-group (0-1), intermediate-group (2-4), and high-group (5-). The associations of the CONUT score with clinicopathological factors and survival outcomes were evaluated. Results: The higher CONUT score was significantly associated with synchronous metastases, and no primary tumor resection. The higher CONUT score group showed a significant shorter progression-free survival (log-rank p<0.05) and overall survival (log-rank p<0.001). Conclusion: The CONUT score is a useful prognostic marker for predicting survival outcomes of patients with mCRC.*

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths worldwide (1). Over the past decades, treatment outcomes for metastatic CRC (mCRC) patients have improved remarkably (2). This has been driven to a large extent by the approval of new drugs, including irinotecan, oxaliplatin, capecitabine, several humanized monoclonal antibodies, and most recently, regorafenib and trifluridine/tipiracil (TAS-102) (3, 4). The clinical benefit from these drugs is now well established for mCRC patients, with the median overall survival (OS) increasing to over 30 months (2); however, more reliable and specific biomarkers are needed.

Patients' nutritional status has recently been associated with prognosis in mCRC (5). The nutritional condition of mCRC patients is an important factor because it allows an estimation of treatment tolerability and cancer progression. A poor nutritional condition is reported to be associated with tumor progression (6), and may reflect elevated metabolism caused by the cancer, an immunocompromised status due to tumor progression, or treatment intolerance (7). A systemic immunological condition is also reported to be associated with cancer prognosis (8). Blood neutrophil, lymphocyte, monocyte, and platelet counts are reported to reflect systemic and local inflammation associated with cancer progression and prognosis (7).

Controlling Nutritional Status (CONUT) score is a new scoring system for patients' nutritional status (9), similar to the modified Glasgow Prognostic Score (mGPS) and the neutrophil-to-lymphocyte ratio (NLR) (10). CONUT score is easily calculated and has been reported to be a predictor for postoperative gastrointestinal cancers (11-15), liver disease (16-18) and heart failure (19-21). CONUT score is calculated from three clinical parameters: serum albumin, total cholesterol, and total lymphocyte count. These are readily obtained parameters from routine blood examinations during hospital stays. Previously, we reported that CONUT score may predict survival and severe complications after curative CRC surgery (15). However, associations between CONUT score and mCRC patient outcomes have not been examined. Therefore, this study aimed to evaluate the efficacy of CONUT score for predicting the outcomes of mCRC patients.

## Patients and Methods

*Patients and CONUT scoring*. We retrospectively assessed 211 consecutive mCRC patients who received systemic first-line chemotherapy between January 2005 and March 2014 at Kumamoto

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University (Kumamoto, Japan). The eligibility criteria included histologically confirmed CRC and measurable metastatic disease according to Response Evaluation Criteria in Solid Tumors (RECIST), and no previous exposure to systemic chemotherapy for metastatic disease. The exclusion criteria included patients who lacked full blood counts or serum albumin and/or total cholesterol levels measured one month before first-line chemotherapy. We collected the following data from inpatient and outpatient records for clinical characteristics: sex, age, body mass index (BMI), carcinoembryonic antigen (CEA) levels (ng/ml), CA19-9 levels (U/ml), metastasis (synchronous or metachronous, single or multiple), liver metastasis (only or not only), primary tumor location (right-side or left-side), whether the primary was resected or not, and *KRAS* status. BMI was calculated from the pretreatment patient heights and weights, which were measured by our medical staff a few days before chemotherapy began. All patients were evaluated for progression-free survival (PFS) and OS.

In this study, CONUT score was used as an indicator of nutritional status and prognosis. Serum albumin and total cholesterol levels, and total lymphocyte count were measured to calculate CONUT score (Table I). All patient blood samples were obtained within one month before they received first-line chemotherapy. Patients were divided into three groups according to their CONUT score: the low score (0-1), intermediate score (2-4), and high score (5-) groups. The use of clinical data in this study was approved by the human ethics review committee of the Graduate School of Medicine, Kumamoto University and the Helsinki Declaration of 1964. Informed consent was obtained from all patients before they were included in this study. This study was conducted in adherence to the REporting recommendations for tumor MARKer prognostic studies (REMARK) (22).

*Statistical analyses*. All statistical analyses were performed using JMP (version 13; SAS Institute, Cary, NC, USA). The log-rank test was used to determine statistical differences between groups. Cox proportional hazard analyses were performed to determine prognostic factors. A *p*-value of less than 0.05 was considered significant. Univariate analyses were performed to investigate the correlation between CONUT score and clinicopathological factors. Categorical variables were analyzed by the chi-square test or Fisher's exact test, and continuous variables were analyzed by Student's *t*-test. The Kaplan–Meier method and log-rank test were used for survival analyses. Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

## Results

*Correlations between CONUT scores and clinicopathological factors*. Baseline characteristics of the patients are shown in Table II. Among the 211 CRC patients included in this study, 126 (59.7%) were male and 85 (40.3%) were female; their median age was 63.0 years (range=34-86 years). The patients were divided into three groups: patients with a CONUT score of 1 or less were defined as the CONUT-low group, patients with a score of 2-4 were defined as the CONUT-intermediate group, and those with a score of 5 or more were defined as the CONUT-high group for analyses of correlations with clinicopathological factors (Table III). CONUT score was significantly associated with several clinicopathological factors; metastasis (synchronous or metachronous, $p<0.001$) and primary tumor resection ($p<0.001$) were significantly lower in the CONUT-high group than in the CONUT-low group. There were no other significant differences between the three groups regarding these clinical parameters.

Table I. *Definition of CONUT score*.

| Parameters | Normal | Light | Moderate | Severe |
|---|---|---|---|---|
| Serum albumin (g/dl) | ≥3.5 | 3.0-3.49 | 2.5-2.9 | <2.5 |
| score | 0 | 2 | 4 | 6 |
| Total lymphocyte (count/mm$^3$) | ≥1600 | 1200-1599 | 800-1199 | <800 |
| score | 0 | 1 | 2 | 3 |
| Total cholesterol (mg/dl) | ≥180 | 140-180 | 100-139 | <100 |
| score | 0 | 1 | 2 | 3 |
| CONUT score (total) | 0-1 | 2-4 | 5-8 | 9-12 |
| Assessment | Low | Intermediate | High | |

CONUT: Controlling nutritional status.

Table II. *Baseline characteristics of the patients*.

| | n=211 |
|---|---|
| Age, years (range) | 63.0 (34-86) |
| Male/Female | 126/85 |
| Body mass index, kg/m$^2$ (range) | 22.8 (15.3-33.2) |
| Time to metastases, synchronous/metachronous | 162/49 |
| Number of metastases, single/multiple | 103/108 |
| Liver only metastases, yes/no | 80/131 |
| Primary tumor location, right-side/left-side | 60/151 |
| Primary tumor resection, yes/no/unknown | 95/107/9 |
| KRAS status, wild type/mutant/unknown | 101/53/57 |
| CEA, ng/ml (range) | 497.9 (0.5-18021) |
| CA19-9, U/ml (range) | 1587.0 (0.1-67200) |

CEA: Carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

*Correlations between CONUT score and survival outcomes*. Figure 1 shows the Kaplan–Meier analysis for OS and PFS according to CONUT score. The median 5-year OS and PFS were 24.5 and 6.9 months. Five-year OS rates in the low, intermediate, and high groups were 22.4%, 21.4%, and 9.1%, respectively ($p<0.001$). Both OS and PFS survival curves were better in patients with low or intermediate status than for those with CONUT-high status (OS; $p<0.001$, PFS; $p<0.05$). In Cox hazard analyses, univariate analysis showed that CA19-9 concentration (>37.0 U/ml, $p<0.05$), metastasis (synchronous, $p<0.05$), metastatic lesions (multiple, $p<0.05$), liver metastasis (not only, $p<0.05$), primary tumor location (right-side, $p<0.001$), primary resection (no, $p<0.05$), and CONUT score (high, $p<0.001$) were significantly associated with worse OS

Table III. *Clinical characteristics of the three groups according to the CONUT score.*

| | Low (n=89) | Intermediate (n=90) | High (n=32) | *p*-Value |
|---|---|---|---|---|
| Male/Female | 58/31 | 51/39 | 17/15 | 0.30 |
| Age, years (range) | 63.1 (35-85) | 62.3 (34-81) | 64.5 (49-86) | 0.57 |
| Body mass index, kg/m$^2$ (range) | 23.8 (16.8-32.5) | 22.0 (15.9-33.2) | 22.2 (15.3-29.5) | 0.20 |
| CEA, ng/ml (range) | 281.8 (0.5-6319) | 468.0 (0.6-11210) | 1184.9 (1.8-18021) | 0.25 |
| CA19-9 (U/ml), range | 1256.8 (0.1-67200) | 1019.9 (0.1-30860) | 4082.6 (0.6-47050) | 0.16 |
| Metastasis, synchronous/metachronous | 64/25 | 66/24 | 32/0 | <0.001 |
| Metastatic lesions, single/multiple | 48/41 | 43/47 | 12/20 | 0.27 |
| Liver metastasis, only/not only | 39/50 | 34/56 | 7/25 | 0.08 |
| Primary tumor location, right-side/left-side | 22/67 | 29/61 | 9/23 | 0.54 |
| Primary tumor resection, yes/no/unknown | 45/40/4 | 48/38/4 | 2/29/1 | <0.001 |
| KRAS status, wild type/mutant/unknown | 42/20/27 | 41/22/27 | 18/11/3 | 0.14 |
| White blood cell count, /μl (range) | 6742.7 (3100-14400) | 6381.1 (2200-26600) | 8459.4 (2900-19800) | 0.08 |
| Total lymphocyte count, /μl (range) | 1878.5 (1210-4423) | 1416.0 (445-3382.5) | 1258.1 (509-3524) | <0.001 |
| Albumin, g/dl (range) | 4.0 (3.5-4.8) | 3.75 (3.0-4.9) | 2.6 (1.8-3.1) | <0.001 |
| Total cholesterol, mg/dl (range) | 207.2 (142-391) | 191.8 (116-397) | 190.4 (111-350) | 0.04 |

Low: Low CONUT score (0-1) group; Intermediate: intermediate CONUT score (2-4) group; High: high CONUT score (5-) group; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

(Table IV). Multivariate analysis showed that CONUT score was an independent prognostic factor for OS (high *vs.* intermediate/low, HR=2.01, 95%CI=1.26-3.12, $p<0.05$).

## Discussion

CONUT score is a nutritional evaluation system that is easy to calculate from serum albumin, total cholesterol, and total lymphocyte count. This study showed that CONUT score is an independent scoring system that can predict outcomes in patients who received first-line chemotherapy for mCRC. We retrospectively assessed 211 consecutive mCRC patients receiving systemic first-line chemotherapy and found that CONUT score was significantly associated with PFS and OS. In addition, multivariate analysis indicated that CONUT score was an indicated prognostic factor for OS; higher CONUT score was significantly associated with worse prognoses. To our knowledge, this is the first study to show that CONUT score is an independent prognostic factor for mCRC patients receiving systemic chemotherapy.

CONUT score was first reported by Ignatio *et al*. (9), and is useful for evaluating the nutritional and immune status of patients. Additionally, CONUT score is a prognostic factor for patients with chronic diseases such as end-stage liver disease (16), heart failure (21), and several cancers (23, 24, 25). Several previous reports have shown that CONUT scores are useful for estimating postoperative complications and prognosis in cases of esophageal cancer (12), gastric cancer (14) and intrahepatic cholangiocarcinoma (26). CONUT score has also proven to be a promising scoring system for predicting outcomes in CRC patients undergoing surgery (15, 23). However, there have not been any studies that assessed the relationship between CONUT score and mCRC patient prognoses.

Cancer progression has been shown to not only be affected by the malignant features of tumor cells themselves, but by the nutritional status of the patient (7). Furthermore, patient nutritional status has been associated with short- and long-term outcomes in CRC (5). Serum albumin concentration is one of the common nutritional indicators; however, albumin concentrations can be affected by patient status, such as liver function and body fluid volume. So, some reports have proposed adding plasma cholesterol levels to optimize the evaluation of nutritional status (23, 24). Hypocholesterolemia influences cell membrane fluidity, decreasing the mobility of cell surface receptors and their ability to transmit signals (27). Immune responses are dependent on lymphocytes; high numbers of infiltrating lymphocytes are associated with a good prognosis, whereas low lymphocyte levels are a recognized predictor of poor outcomes. CONUT scoring system includes plasma cholesterol levels, serum albumin and lymphocyte concentrations. Thus, CONUT score may be a good indicator of nutritional and inflammatory status.

Patient systemic inflammation and nutritional status may change during cancer progression (28). Several reports have shown that patient nutritional status is associated with short- and long-term outcomes in CRC (23, 27). Previously, Lu *et al*. reported the prognostic role of the platelet to lymphocyte ratio in CRC including mCRC (29). The platelet to lymphocyte ratio may reflect the patient's inflammatory and nutritional status. Kim *et al*. reported that a continuously high NLR or the change to a high NLR was also associated with poor OS and PFS in mCRC patients (28). The NLR is

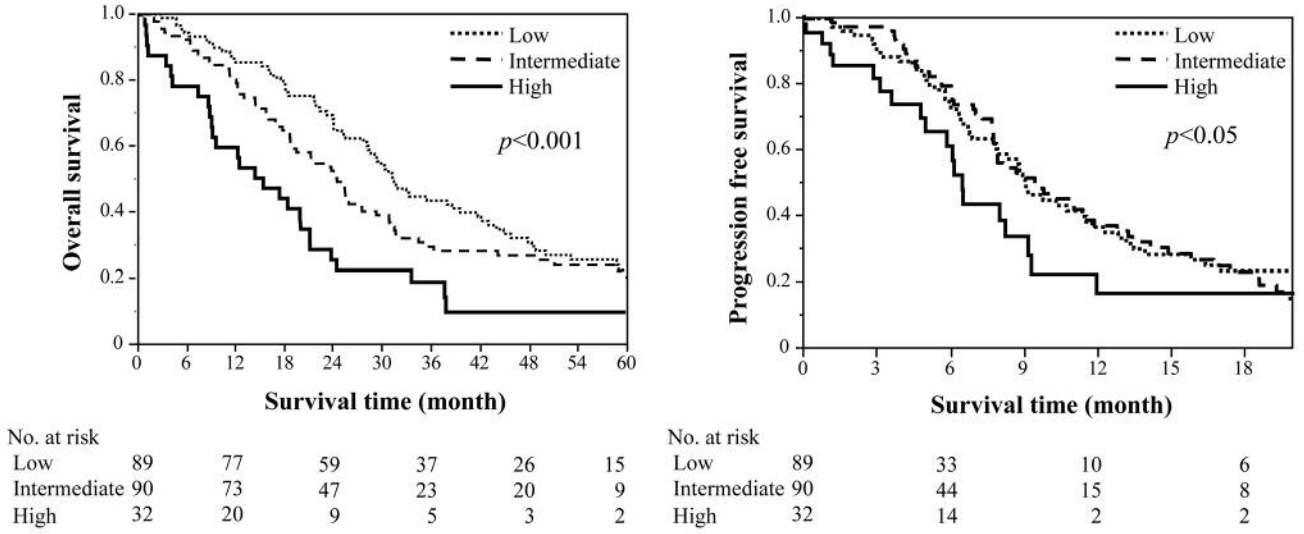


Figure 1. *Overall survival and progression-free survival according to the CONUT score. Low: Low CONUT score (0-1) group; Intermediate: intermediate CONUT score (2-4) group; High: high CONUT score (5-) group.*

Table IV. *Univariate and multivariate analyses of prognostic factor for OS of this study.*

| Variables | Univariate analyses | | | Multivariate analyses | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | *p*-Value | HR | 95%CI | *p*-Value |
| Age (≥75 years) | 1.44 | 0.91-2.18 | 0.11 | | | |
| Gender (male) | 0.90 | 0.66-1.23 | 0.51 | | | |
| Body mass index (<18.5 kg/m$^2$) | 1.07 | 0.61-1.75 | 0.80 | | | |
| CEA (>3.4ng/ml) | 1.44 | 0.96-2.24 | 0.08 | | | |
| CA19-9 (>37.0U/ml) | 1.45 | 1.08-1.97 | <0.05 | 1.29 | 0.95-1.77 | 0.10 |
| Metastasis (synchronous) | 1.54 | 1.08-2.25 | <0.05 | 1.55 | 1.02-2.43 | <0.05 |
| Metastatic lesions (multiple) | 1.57 | 1.16-2.14 | <0.05 | 1.15 | 0.76-1.74 | 0.51 |
| Liver metastasis (not only) | 1.53 | 1.12-2.12 | <0.05 | 1.38 | 0.88-2.18 | 0.16 |
| Primary Tumor location (right-side) | 1.94 | 1.40-2.68 | <0.001 | 2.21 | 1.57-3.10 | <0.001 |
| Primary resection (no) | 1.56 | 1.15-2.13 | <0.05 | 1.17 | 0.82-1.67 | 0.40 |
| KRAS status (wild type/mutant) | 1.15 | 0.77-1.76 | 0.81 | | | |
| CONUT score (High/Low+Intermediate) | 2.14 | 1.39-3.17 | <0.001 | 2.01 | 1.26-3.12 | <0.05 |

OS: Overall survival; HR: hazard ratio; CI: confidence interval; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

also a nutritional indicator. In this study, we assessed the prognosis of mCRC patients and their CONUT score. No previous studies have reported correlations between CONUT score and mCRC patient outcomes. Despite advances in therapy, mCRC still has a poor prognosis. Nagata *et al*. reported that mCRC patients with a high CONUT score had lower skeletal muscle mass (30). These patients had a shorter period of chemotherapy and lead to poor prognosis. Identifying patient status before chemotherapy could have several uses in clinical practice, including prognostic stratification and treatment aggressiveness. Early detection and the improvement of malnutrition may result in better patient outcomes.

This study had certain limitations; first, this was a retrospectively designed single-center study. Thus, the significance of CONUT score needs to be validated in other individual cohorts. Second, this study did not exclude several factors that may affect inflammation and nutritional status, such as non-steroidal anti-inflammatory drugs (NSAIDs) or lipid-lowering agents. However, we believe that these results will provide customized first-line therapy and improve mCRC patient outcomes.

## Conclusion

In conclusion, CONUT score is a useful prognostic marker for predicting long-term PFS and OS in mCRC patients.

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