

## Significance of the CONUT Score in the Prognosis of Colorectal Cancer Patients

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Abbreviations:

CONUT: The Controlling Nutritional Status;

CRC: colorectal cancer;

OS: overall survival;

DFS: disease-free survival;

LOS: length of stay.

### Rezumat

#### *Semnificația scorului CONUT în prognosticul pacienților cu cancer colorectal*

*Introducere/Obiective:* Prognosticul pacienților cu cancer colorectal este corelat cu statusul nutrițional al acestora. Scorul CONUT (The Controlling Nutritional Status) este un marker nutrițional recent descoperit. Acest studiu și-a propus să examineze asocierea scorului CONUT preoperator cu supraviețuirea globală și supraviețuirea fără boală, în timp ce scopul secundar a fost acela de a evalua importanța stării nutriționale preoperatorii pentru dezvoltarea complicațiilor postoperatorii.

*Metode:* Numărul total de pacienți cu cancer colorectal incluși în studiu a fost de 111. Tuturor pacienții li s-au efectuat analize de laborator cu o săptămână înainte de intervenția chirurgicală. Datele medicale au fost colectate din datele arhivate la Centrul Medical al Universității Zvezdara. Scorul CONUT a fost analizat în raport cu supraviețuirea globală și supraviețuirea fără boală.

*Rezultate:* Folosind curba de supraviețuire Kaplan-Meier și testul Log-rank, a fost observată o diferență semnificativă statistic în supraviețuirea globală și supraviețuirea fără boală între grupurile de pacienți cu scoruri CONUT diferite. Pacienții cu scoruri CONUT mai mari au o durată mai lungă de spitalizare după intervenția chirurgicală, o durată totală mai mare a spitalizării și un grad mai sever de complicații postoperatorii.

*Concluzie:* Scorul CONUT se corelează cu rezultatele tratamentului pe termen scurt, precum durata tratamentului intraspitalicesc și frecvența și severitatea complicațiilor postoperatorii, dar și de

Received: 17.06.2023

Accepted: 13.08.2023

parametrii de prognostic pe termen lung. Screeningul nutrițional precoce poate avea o semnificație prognostică.

Cuvinte cheie: cancer colorectal, scor CONUT, supraviețuirea globală, supraviețuire fără boală, clasificarea Clavien-Dindo

## Abstract

*Introduction/Objective:* Nutritional status is related to the prognosis of colorectal cancer (CRC) patients. The CONUT (The Controlling Nutritional Status) score is a recent nutritional marker. This study aimed to examine the association of preoperative CONUT score with overall survival (OS) and disease-free survival (DFS), while the secondary aim was to assess the importance of preoperative nutritional status for the development of postoperative complications.

*Methods:* The total number of CRC patients included in the study was 111. All patients underwent laboratory analyses within a week before surgery. Medical data were collected from archived data at the Zvezdara University Medical Centre. The CONUT score was analyzed in relation to the OS and DFS.

*Results:* Using the Kaplan-Meier survival curve and Log-rank test, a statistically significant difference in OS and DFS between groups of patients with different CONUT scores was observed. Patients with higher CONUT scores have a longer duration of hospitalization after surgery, a longer total length of stay, and a more severe degree of postoperative complications.

*Conclusion:* The CONUT score is related to short-term treatment outcomes, such as the length of intrahospital treatment and frequency and severity of postoperative complications, but also to long-term prognostic parameters. Early nutritional screening may be of prognostic significance.

Key words: colorectal cancer, CONUT score, overall survival, disease-free survival, Clavien-Dindo classification

## Introduction

Colorectal cancer represents a significant public health problem. Colorectal cancer is the third most common and the second most deadly malignancy worldwide with an estimated 1.9 million incidence cases and 0.9 million deaths during 2020, according to the GLOBOCAN (1). This means that on a global level, every tenth newly diagnosed person and person who died from a malignant disease had colorectal cancer (1).

Although operative treatment is the main modality of CRC treatment (2), the multidisciplinary approach to the treatment of CRC has reduced the frequency of relapse and improved overall survival (1). In the therapeutic sense, it is necessary to identify patients with a

poorer prognosis or an increased risk of recurrence of the disease to adjust the surgical technique and/or optimize (neo)adjuvant chemoradiotherapy (3). The immune response specifically associated with malignancy represents a critical control point in the process of disease progression (4). The results of numerous studies have indicated that the importance of the standard preoperative value of hematological/biochemical parameters and their mutual integration into indexes and scores are good indicators of the prognosis of colorectal cancer (5). In this respect, the CONUT (The Controlling Nutritional Status) score is a recent nutritional marker based on the values of serum albumin, the absolute number of lymphocytes, and the value of serum of cholesterol (6). Simple calculation

from data collected from routine biochemical analyses and complete blood counts and effectiveness in assessing nutritional status make it potentially widely applicable (7).

Results of studies examining the significance of the CONUT score on potentially curative outcomes resection in patients with colorectal cancer were first published in 2015. However, most studies were limited by small numbers of subjects, variability in disease stage, and results were not uniform (8). In this regard, the primary aim of our study was to examine preoperative nutritional status, expressed through the CONUT score, in relation to overall survival (OS) and disease-free survival (DFS). The secondary aim of our study was assessment the importance of the preoperative nutritional status of CRC patients for postoperative complication development.

## Material and Method

The retrospective study was carried out at the Surgical Clinic Nikola Spasic, Zvezdara University Clinical Center in Belgrade. Exclusion criteria were: 1) The existence of other malignancies treated for less than 5 years at the time of surgery for CRC; 2) Incomplete medical documentation; 3) Insufficient postoperative monitoring. The study group consisted of 111 patients. The study was approved by the ethics board of the Zvezdara University Medical Centre in Belgrade, and all patients gave their written consent to participate in the research.

Blood samples were routinely collected within a week before the operative treatment.

Standard biochemical and hematological analyses were performed in the hospital laboratory on a Roche analyzer Cobas 6000 (c501 and e601) (Roche Diagnostics GmbH, Mannheim, DE) and Sysmex XN-1000 (Sysmex Europe SE, Norderstedt, DE).

The CONUT (The Controlling Nutritional Status) score, a nutritional marker based on values of serum albumin, serum cholesterol, and absolute lymphocyte count, was calculated based on formulas from existing studies (6). The values of these parameters were scored according to the limit values, and the sum of the results was evaluated as the CONUT score. Based on the CONUT score patients were divided into 4 groups: group Normal (0-1) CONUT score; group Light (2-4) CONUT score; group Moderate (5-8) CONUT score and group Severe (9-12) CONUT score (*Table 1*).

Postoperative surgical complications are presented through the Clavien-Dindo grading system (grade of complications: I, II, IIIa, IIIb, IVa, IVb, V) (9). Due to the relatively small number of subjects in our study, postoperative complications were regrouped and presented to patients as follows: Group I (patients with I, II degree of complications); Group II (patients with IIIa, IIIb degree of complications); Group III (patients with IVa, IVb, V degree of complications).

In addition to intrahospital mortality, data on the exact date of death were obtained by examining the death registers for the territory of the Republic of Serbia. At the Nikola Spasić Clinic of Surgery, KBC Zvezdara, where the study was carried out, the strategy of postoperative monitoring of

**Table 1.** The CONUT scoring system<sup>10</sup>

Parameters		Values			
Serum albumin (g/dL)	≥ 3.5	3.0-3.49	2.5-2.9	< 2.5	
Score	1	2	4	6	
Absolute lymphocyte count (/mm <sup>3</sup> )	≥ 1600	1200-1599	800-1199	< 800	
Score	0	1	2	3	
Cholesterol (mg/dL)	≥ 180	140-180	100-139	< 100	
Score	0	1	2	3	
CONUT score	0-1	2-4	5-8	9-12	
CONUT Score Groups	Normal	Light	Moderate	Severe	

patients operated on for CRC is based on the National Guide for colorectal cancer issued by the Ministry of Health of the Republic of Serbia (10). Relapse was defined as any clinically, biochemically, or radiologically manifest relapse of the disease during the follow-up period.

### Statistical Analysis

In the statistical analysis, the primarily obtained data were analyzed using descriptive statistical methods, like measurements of central tendency (mean value, median), measurements of variability (standard deviation), and indicators of structure expressed in percentages, while the Spearman correlation test was used to assess the significance of the correlation. The overall survival and disease-free survival period were analyzed using the Kaplan-Meier method and compared using the Log-rank test. SPSS 23.0 software was used for statistical data processing.

### Results

The retrospective study was conducted on 111 patients, mostly undergoing elective operative treatment. Of the total number of patients, there were 48 (43.2%) females and 63 (56.8%) males. Most of the patients included in the study were with ASA (American Society of Anesthesiology) scores 2 and 3. The median age was 67 (32-88) years. Intra-hospital mortality was recorded in 6 (5.4%) patients. The median duration of postoperative treatment was 10 (8-12) days and the total length of hospitalization for 13 (11-21) days. In our study, the median follow-up was 42 (24-48) months after surgery, while the median survival without disease recurrence was 39 (10-45) months. Basic clinical and biochemical analyses of examined populations are given in *Table 2*.

Based on the Kaplan-Meier survival curve, the average survival time for patients in the group Normal was  $44.45 \pm 1.37$  months, in the group Light  $34.74 \pm 2.4$  months, in the group

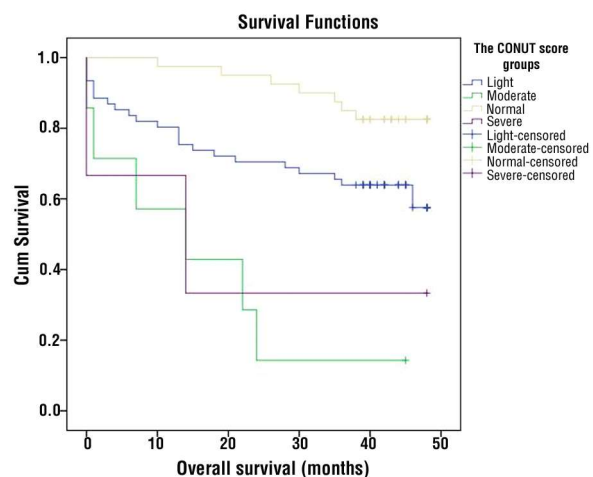
**Table 2.** Basic clinical and laboratory characteristics of the studied population

Characteristics of Patients	n (%)
Sex	
Male	63 (56,8%)
Age*	67 (62-75)
ASA Score**	
1	18 (16.2)
2	50 (45.0)
3	43 (38.7)
4	0 (0)
5	0 (0)
Hematological/Biochemical Values***	
Lymphocyte absolute count (109/l)	1.47 (1.14-1.94)
Serum albumin (g/dl)	3.9 (3.5-4.2)
Cholesterol (mg/dl)	174 (146.95-204.95)
Colorectal Cancer Patients	
Right colon	40 (36)
Left colon	35 (31.5)
Rectum	34 (30.9)
Synchronous adenocarcinomas of the colon	2 (1.8)
TNM Stage	
I/II	60 (54.05)
III/IV	51 (45.95)

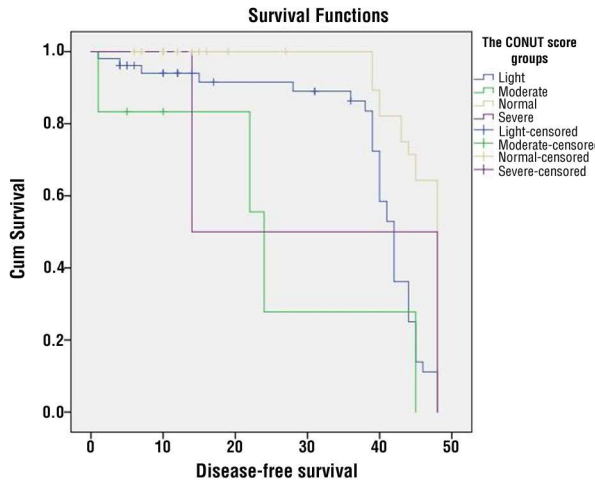
\*Data are shown as Median (min-max); \*\*ASA (American Society of Anesthesiologists) skor\*\*\*; Data are shown as Median (25-75 percentiles);

Moderate was  $16.14 \pm 5,54$  months, while for patients in the group Severe was  $20.67 \pm 11.64$  months. Using the Log-rank test a statistically significant difference in survival was observed between different groups of patients ( $p < 0.001$ ) (*Fig. 1*).

Also, the Kaplan-Meier survival curve shows that the DFS period in group Normal was  $45.75 \pm 0.64$  months, in the group Light

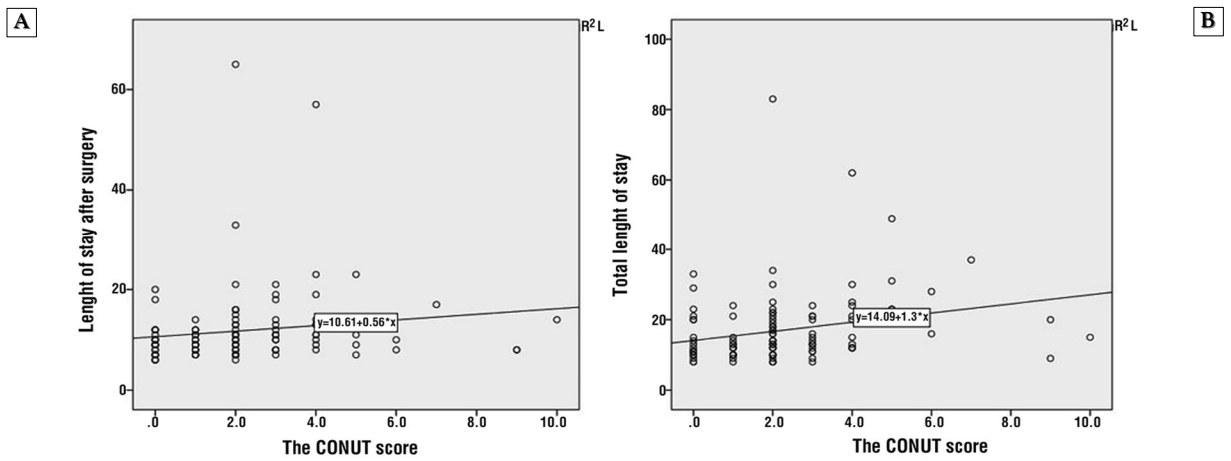


**Figure 1.** The Kaplan-Meier curve of overall survival in relation to the CONUT score

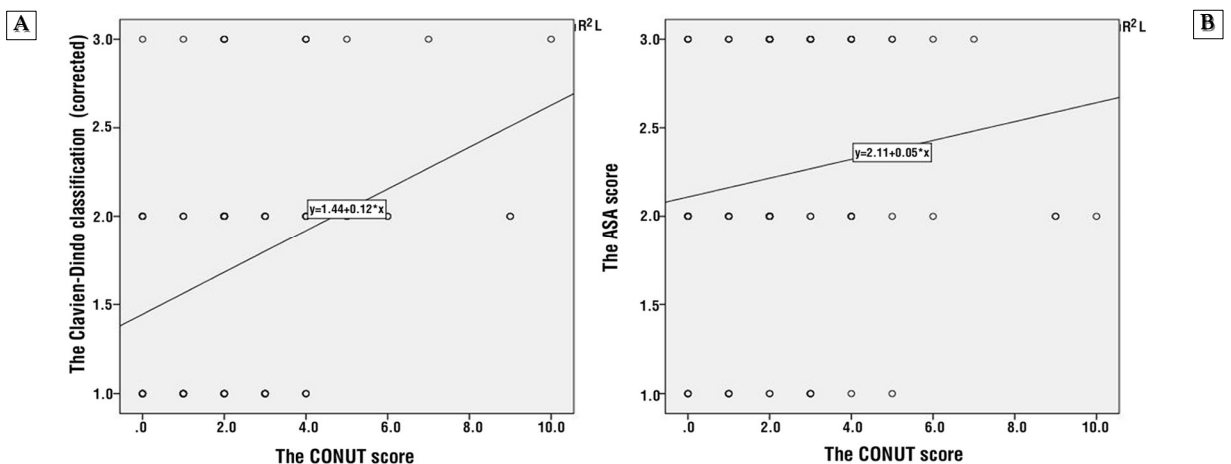


**Figure 2.** The Kaplan-Maier curve of the DFS period in relation to the CONUT score

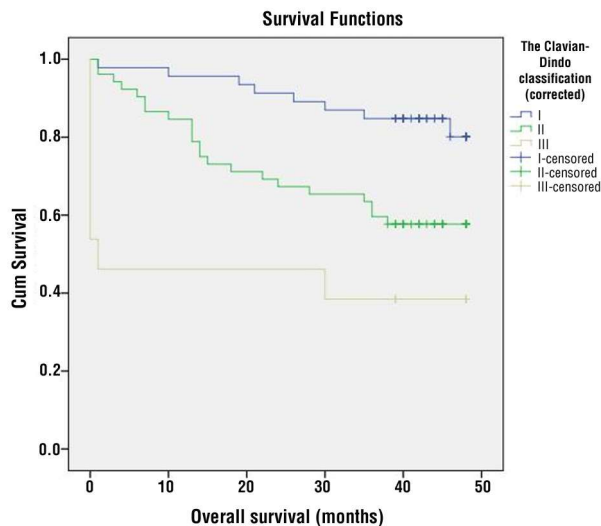
39.1±1.57 months, in the group Moderate was 25.44±7.74 months, while for patients in the group Severe was 31±17 months. Using the Log-rank test a statistically significant difference in the DFS period was observed ( $p < 0.001$ ) (Fig. 2). Analyzing the correlation between variables, it was found that patients with higher CONUT scores have a longer duration of hospitalization after surgery ( $\rho = 0.26$ ;  $p < 0.01$ ) (Fig. 3A) and a longer total duration of hospitalization ( $\rho = 0.35$ ;  $p < 0.01$ ) (Fig. 3B). It was observed that patients with higher CONUT scores have a more severe degree of postoperative complications ( $\rho = 0.32$ ;  $p < 0.001$ ) (Fig. 4A) and higher ASA scores ( $\rho = 0.221$ ;  $p = 0.02$ ) (Fig. 4B).



**Figure 3.** (A) The correlation between the CONUT score with length of stay after surgery. (B) The correlation between the CONUT score with the total length of stay



**Figure 4.** (A) The correlation between the CONUT score with The Clavien-Dindo classification of postoperative complications. (B) The correlation between the CONUT score with the ASA score



**Figure 5.** The Kaplan-Maier curve of overall survival (OS) in patients with colorectal cancer in relation to the severity of post-operative complications

Using the Kaplan-Meier survival curve, the average survival time of patients classified in group I of the Clavian-Dindo classification of postoperative complications was  $43.69 \pm 1.59$  months, in group II  $34.58 \pm 2.41$  months, while in group III was  $20.84 \pm 6.33$  months. By applying the Log-rank test, statistically significant differences in survival between different groups of patients ( $p < 0.001$ ) were evaluated (Fig. 5).

## Discussion

The CONUT (The Controlling Nutritional Status) score is a nutritional marker based on serum albumin values, the absolute number of lymphocytes, and serum values of cholesterol (6). The value of serum albumin represents the nutritional status and is a non-specific marker of the inflammation process, so hypoalbuminemia can be related to worse outcomes in patients suffering from malignant diseases (11). Serum cholesterol values are related to tumor progression and length of survival and the results of some studies indicate that can act protectively (12). Lower values of lymphocytes are associated with pre-existing immunosuppression as well as poor long-term prognosis of these patients

(13). The CONUT score, combining these three parameters, can potentially overcome the individual shortcomings of each of them.

Analyzing the relationship between the CONUT score values and the survival time expressed in months after the operation, the association of higher score values with shorter ones was noted. The Kaplan-Meier survival curve results showed that between the studied groups there was a statistically significant difference in overall survival and disease-free survival period, which was the primary aim of our research. Differences in the length of overall survival between the groups Moderate and Severe can also be explained by the fact that only 3 patients were included in the group Moderate, which represents the limitation of our study. The results of our study are supported by the findings of other studies in which the CONUT score was marked as a prognostic factor for OS and DFS period (8). Research by Yasuhiro Fukui et al. also showed that the CONUT score has independent significance for overall survival in various groups, especially for the groups with higher values of the CONUT score (14). Ultimately, Takagi et al., in a meta-analysis that included 6 studies with a total of 2,601 patients showed that the CONUT score is a practical prognostic factor associated with prognosis in patients undergoing surgery for colorectal cancer, despite the heterogeneity of different research (15). By analyzing the results of our research and comparing them to the published results of other studies, we conclude that it would be desirable to include the CONUT score in the standard preoperative nutritional status examination. Since the median age of our group of patients was 67 years old, the CONUT score could also be a good screening method for the assessment of nutritional status in the elderly population, which is in line with other studies that examined the significance of CONUT score in the population of elderly patients (16).

Individual nutritional status measured preoperatively is related to short-term prognosis parameters, such as frequency and severity of postoperative complications, but

also the length of hospitalization (17,18), which is supported by the results of our research. Namely, the results of our research show that patients with higher values of the CONUT score have had an increased length of intrahospital treatment after surgery, but also the total hospital length of stay (LOS).

The results of our study show that the severity of postoperative complications measured by the Clavien-Dindo classification affects the survival time after resection. Namely, in groups of patients who had milder postoperative complications, overall survival time was longer. A recent study conducted by Duraes et al. (19) demonstrated a correlation between the severity of postoperative complications with a shorter five-year survival, a shorter DFS period, and shorter cancer-specific survival. In our study, we showed that there is a statistically significant association between higher values of the CONUT score at the level of the complete sample, with the degree of postoperative complications. The findings of our study stay in line with research conducted by Tokunaga R et al. where they conclude that the CONUT score correlates positively with the degree of postoperative complications in the 417 patients who underwent potentially curative resection of CRC. The rates of all complications, as well as severe complications (Clavien–Dindo  $\geq$ III), were higher in the moderate/severe groups than in the normal or light status groups (20). Also, research by Bojesen RD et al. demonstrates that screening for nutritional status and prehabilitation on the outcomes for CRC can decrease the risk for postoperative complications (21).

The ASA score is used to assess the patient's general health condition and comorbidities (22). The results of our study indicate the association of higher ASA score values with a higher complication rate and higher CONUT score values. Results of our study suggest that patients with a higher ASA score have a higher risk of preoperative nutritional deficiency deficit, but vice versa, those with higher values of the CONUT score would potentially have a higher risk for the

development of nutritional deficit in the perioperative period of treatment. In this regard, Novello M et al. conclude that combined preoperative nutritional status and comorbidities should be strongly considered as exclusion criteria for elective surgery treatment due to their influence on postoperative mortality (23).

The limitations of our study were the retrospective study design of a single center, the relatively small number of patients, the observation of colon cancer in different locations and rectal cancer.

## Conclusion

The CONUT score measured preoperatively can be of prognostic significance in patients with colon and rectal cancer who underwent potentially curable resections.

The CONUT score is related to short-term treatment outcomes, such as length of intrahospital treatment and the frequency and severity of postoperative complications, but also to long-term prognosis parameters, overall survival and disease-free survival period.

Early nutritional screening and nutritional support may be of prognostic significance, but also for monitoring the response to therapeutic interventions. Simplicity, accessibility, and ease of interpretation of the results make it broadly applicable.

## Conflict of Interest and Source of Funding

The authors declared no potential conflicts of interest and no funding.

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