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Review

Prognostic significance of the controlling nutritional status (CONUT) score in patients with colorectal cancer: A systematic review and meta-analysis

Kosei Takagi*, Stefan Buettner, Jan N.M. Ijzermans

Department of Surgery, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

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ABSTRACT

Background: The clinical evidence of the controlling nutritional status (CONUT) score for outcomes has increased in gastroenterological surgical oncology. The aim of this study was to investigate the impact of the CONUT score on outcomes in patients with colorectal cancer (CRC).

Methods: A literature review was systematically conducted to evaluate the significance of the CONUT score in CRC patients. Meta-analyses of survival were performed to investigate the effects of the CONUT score in CRC patients.

Results: Nine studies met the inclusion criteria, and six studies with 2601 patients were included in the present meta-analyses. High CONUT score was associated with poor overall survival (HR 1.97, 95%CI = 1.40–2.77, P < 0.001), cancer-specific survival (HR 3.64, 95%CI = 1.96–6.75, P < 0.001), and recurrence/relapse-free survival (HR 1.68, 95%CI = 1.23–2.29, P = 0.001) after CRC surgery.

Conclusions: The CONUT score is a practical prognostic factor associated with prognosis of CRC. Further studies are needed to clarify the significance of the CONUT score in CRC patients.

1. Introduction

Several nutritional indexes to evaluate the nutritional status of patients and to predict outcomes of cancers have been established [1–3]. Among these, the controlling nutritional status (CONUT) score has been developed as a nutritional screening tool. Due to its simplicity and efficiency in evaluating patients' nutritional status, which is calculated using three values such as serum albumin level, total cholesterol level and total lymphocyte count [4], it is potentially broadly applicable. Recently the clinical evidence of the CONUT score for short-term and long-term outcomes has increased in gastroenterological and hepatopancreatobiliary surgical oncology [5–8]. The impact of the CONUT score on outcomes in patients undergoing surgery for colorectal cancer (CRC) was first reported in 2015 [9]. Since then, it has been further examined, and the efficiency of the CONUT score on outcomes in CRC was demonstrated [10,11]. However, most of these studies had relatively small sample sizes, variance in tumor stage and results that were not uniform. Moreover, the effect of the CONUT score in CRC has not yet been systematically investigated so far.

Herein, we performed a systematic review and meta-analysis to investigate the association between the CONUT score and outcomes in patients with CRC, in order to provide more evidence to confirm the prognostic role of the CONUT score in CRC.

2. Materials and methods

2.1. A systematic review

The present study complies with the Preferred Reporting Items for Systematic Reviewers and Meta-Analyses (PRISMA) guidelines [12]. A systematic literature search of Embase, Medline Ovid, Web of Science, Cochrane CENTRAL, and Google scholar was constructed on December 13th, 2019 to identify all available articles reporting the effect of the CONUT score on outcomes in patients with CRC. The queries were constructed using suitable terms concerning the CONUT score and CRC (Supplementary Table 1). The methods of our systematic literature review strategy have been described previously [6–8]. No ethical approval or informed consent statement was required for this review article.

Titles, abstracts, and full-text articles were screened independently by two investigators. Afterwards, the following data were extracted: year and country of studies, patient characteristics, tumor stage, cut-off value of the CONUT score, short-term and long-term outcomes in patients with CRC. The primary outcomes of this study was to investigate

* Corresponding author. Department of Surgery, Division of HPB & Transplant Surgery, Erasmus MC, University Medical Center Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.
E-mail address: kotakagi15@gmail.com (K. Takagi).

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long-term outcomes such as overall survival (OS), cancer-specific survival (CSS), and relapse/recurrence free survival (RFS). The secondary outcomes included short-term outcomes after surgery. The Newcastle-Ottawa quality assessment scale for cohort studies was used to evaluate the methodological quality of each study, considering studies with a total scores ≥6 as high-quality studies [13].

2.2. Statistical analysis

Random effects meta-analyses were used to examine the effect of the CONUT score on long-term outcomes in CRC patients using the *meta* package for R 3.5.4 (cran.r-project.org). The pooled hazard ratios (HR) for dichotomous variables with 95% confidence interval (95% CI) were calculated using the inverse variance method. Heterogeneity among studies was assessed by the inconsistency test (I^2) and the chi-square test, with $P < 0.05$ being considered statistically significant and larger I^2 values indicating higher heterogeneity. Potential publication bias for outcomes was evaluated with Funnel plots.

3. Results

The PRISMA flow diagram of articles included in the present review is shown in Fig. 1. A systematic search of the literature resulted in 247 abstracts. After screening the abstracts, 9 full-text manuscripts were assessed for eligibility and included in the present study [9–11,14–19], as represented in Table 1. All included studies were single-center retrospective series. Eight studies included patients undergoing surgery for CRC [9–11,14–18], and one included patients receiving chemotherapy for CRC [19]. The Newcastle-Ottawa quality assessment scale evaluated all the included studies as high-quality with a total score ≥6, as shown in Supplementary Table 2. The results reporting the effects of the CONUT score on outcomes in patients with CRC are summarized in Table 2. Postoperative short-term outcomes were examined in five studies, and six studies evaluated long-term outcomes after surgery.

3.1. Effect of the CONUT score on long-term outcomes after surgery

Six studies reported data on long-term outcomes in patients undergoing surgery for CRC [9–11,16–18]. OS was investigated in four studies [10,11,16,18], CSS in two studies [9,17], and RFS in four studies [9–11,17].

Iseki et al. [9] reported the low CONUT group had significantly better 5-year CSS (92.7% versus 81.0%, P = 0.0016) and the 5-year RFS (73.0% versus 53.6%, P = 0.0018). Multivariable analyses showed the CONUT score was an independent prognostic factor for CSS (HR 4.21, 95% CI = 1.22–13.4, P = 0.025), but not for RFS (HR 1.84, 95% CI = 0.84–3.71, P = 0.12).

Tokunaga et al. [10] divided 417 patients into four groups; normal

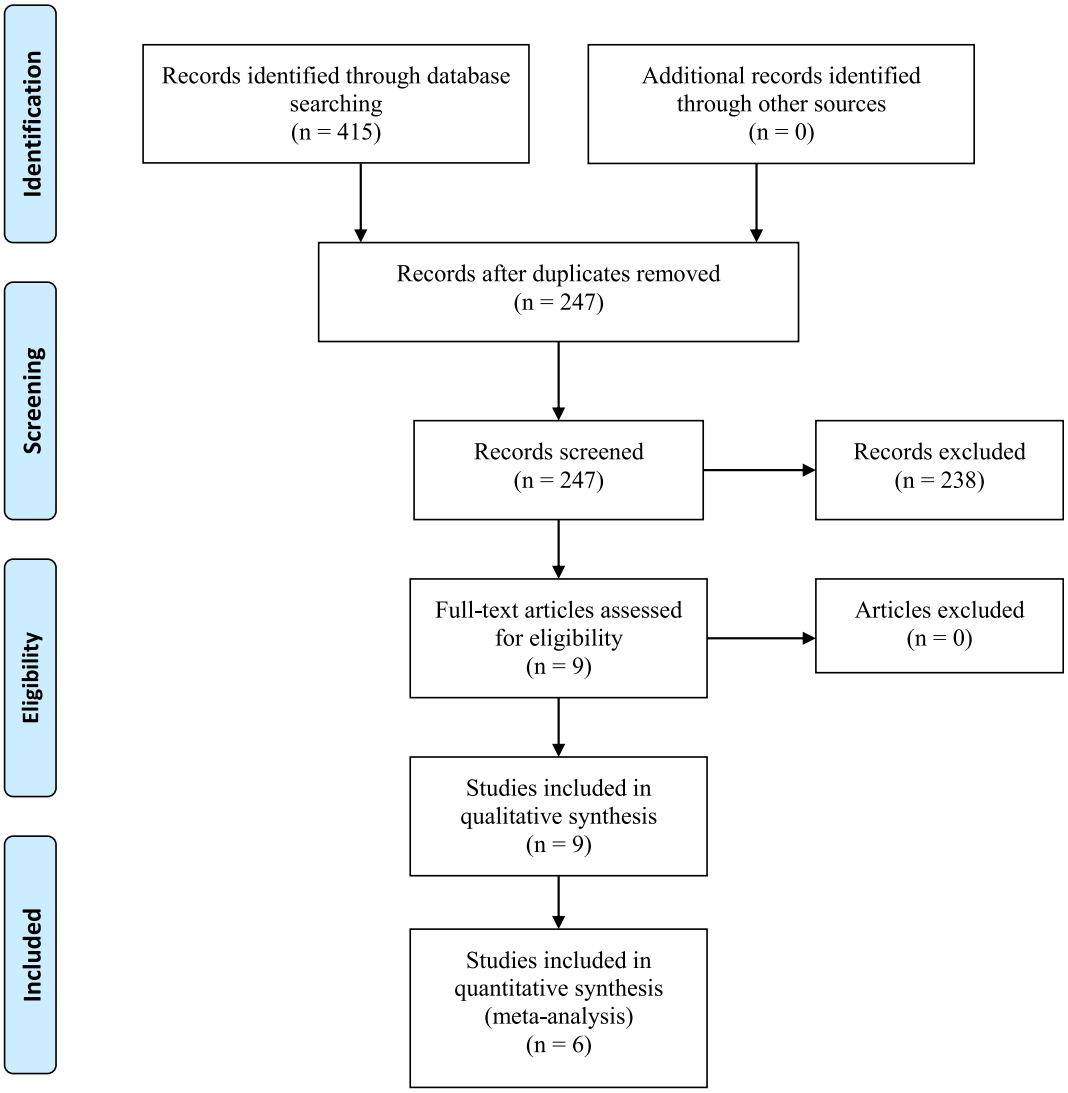

Fig. 1. PRISMA 2009 flow diagram.

Table 1
Literatures investigating the effects of the CONUT score in patients with colorectal cancer.

Study	Year	Country	Study design	Number (Male)	Tumor stage	Cut-off for high CONUT group	Prevalence of high CONUT score	Treatment	Quality[a]
Iseki [9]	2015	Japan	Retrospective Single center	204 (112)	II/III	≥3	26.5%	Curative resection	7
Tokunaga [10]	2017	Japan	Retrospective Single center	417 (247)	I: 177 II: 135 III: 105	0–1 2–4 ≥5	59% 31% 10%	Curative resection	6
Galizia [11]	2017	Italy	Retrospective Single center	562 (334)	I: 139 II: 178 III: 129 IV: 116	≥3	25.6%	Resection	8
Sagawa [14]	2017	Japan	Retrospective Single center	351 (206)	n.a.	≥2	43.0%	Curative resection	7
Sagawa [15]	2018	Japan	Retrospective Single center	351 (206)	n.a.	≥2	43.0%	Curative resection	7
Yamamoto [16]	2019	Japan	Retrospective Single center	522 (291)	I– IV	≥3	30.3%	Resection	7
Yang [17]	2019	China	Retrospective Single center	160 (90)	I/II: 91 III: 69	≥3	46.2%	Curative resection	7
Ahiko [18]	2019	Japan	Retrospective Single center	830 (470) Aged ≥75	I: 224 II: 258 III: 258 IV: 90	0–1 2–3 ≥4	61% 30% 9%	Resection	8
Daitoku [19]	2018	Japan	Retrospective Single center	211 (126)	IV	0–1 2–4 ≥5	42% 43% 15%	Chemotherapy	6

CONUT, controlling nutritional status; n.a., not available.
[a] Score from a maximum of 9 evaluated by the Newcastle–Ottawa quality assessment scale for cohort studies [13].

Table 2
Studies reporting the effects of the CONUT score on outcomes in patients with colorectal cancer.

Study	End points	Short-term	Long-term
Iseki [9]	CSS RFS Complications	18.5 vs 20.0% (P = 0.81) (CONUT ≥3 vs 0–2)	CSS: HR 4.21 (1.22–13.4), P = 0.025* RFS: HR 1.84 (0.84–3.71), P = 0.12* (CONUT ≥3 vs 0–2)
Tokunaga [10]	OS RFS Complications	Severe complications: OR 1.44 (1.70–2.91), P = 0.318* (CONUT 2–4 vs 0–1) OR 4.51 (1.89–10.7), P < 0.001* (CONUT ≥5 vs 0–1)	OS: HR 2.74 (1.30–5.87), P = 0.008* RFS: HR 1.49 (0.74–2.92), P = 0.254* (CONUT 2–4 vs 0–1) OS: HR 5.92 (2.30–14.9), P < 0.001* RFS: HR 1.93 (0.76–4.57), P = 0.16* (CONUT ≥5 vs 0–1)
Galizia [11]	OS RFS	n.a.	OS: HR 1.47 (0.95–2.28), P = 0.07* RFS: HR 1.39 (0.78–2.48), P = 0.25* (CONUT ≥3 vs 0–2)
Sagawa [14]	SSI	SSI: 13.9 vs 5.5% (P = 0.008) OR 2.78 (1.32–6.15), P = 0.008** (CONUT ≥2 vs 0–1)	n.a.
Sagawa [15]	Remote infections	Remote infections: 11.3 vs 5% (P = 0.04) OR 2.41 (1.09–5.62), P = 0.03** (CONUT ≥2 vs 0–1)	n.a.
Yamamoto [16]	OS	n.a.	5-yerar OS: 53.9 vs 76.0% (P < 0.001) (CONUT ≥3 vs 0–2)
Yang [17]	CSS RFS	n.a.	CSS: HR 3.45 (1.68–7.10), P = 0.001* RFS: HR 2.02 (1.19–3.43), P = 0.01* (CONUT ≥3 vs 0–2)
Ahiko [18]	OS Complications	Complications: OR 1.93 (1.15–3.20), P = 0.013* (CONUT ≥4 vs 0–3)	OS: HR 2.24 (1.48–3.30), P < 0.001* (CONUT ≥4 vs 0–1)
Daitoku [19]	OS PFS	n.a.	OS: HR 2.01 (1.26–3.12), P < 0.05* (CONUT ≥5 vs 0–4)

Data are shown for high CONUT group versus low CONUT group as indicated. OR and HR is shown with 95% confidence interval.
*Multivariable analysis. **Univariate analysis.
CONUT, controlling nutritional status; OS, overall survival; CSS, cancer-specific survival; RFS, recurrence/relapse-free survival; PFS, progression-free survival; HR, hazard ratio; OR, odds ratio; n.a., not available.

(n = 246), light (n = 127), and moderate (n = 33), and severe (n = 11) CONUT score, showing 5-year OS (91.1%, 81.8%, 58.3%, and 81.8%, P < 0.001) and 5-year RFS (87.0%, 84.7%, 34.9%, and 76.2%, P = 0.012). Multivariable analyses identified the CONUT score as an independent prognostic factor for OS (light versus normal, HR 2.74, 95% CI = 1.30–5.87, P = 0.008; moderate/severe versus normal, HR 5.92, 95% CI = 2.30–14.9, P < 0.001), but not for RFS.

Galizia et al. [11] explored the survival of patients after CRC surgery comparing prognostic tools such as the Naples prognostic score, the CONUT score, and systematic inflammation score. Their multivariable

analyses of OS and RFS demonstrated that the CONUT score was not significantly associated with OS (HR 1.47, 95% CI = 0.95–2.28, P = 0.07) as well as RFS (HR 1.39, 95% CI = 0.78–2.48, P = 0.25).

Yamamoto et al. [16] compared OS between the low and high CONUT groups, showing a significant difference (5-year OS: 76.0% versus 53.9%, P < 0.001). However, the significance of the CONUT score for OS was not investigated in multivariable analyses. They suggested the significance of a combination of the tumor marker carcinoembryonic antigen (CEA) and the CONT score (T-CONT) in patients with CRC.

Yang et al. [17] examined the impact of the CONUT score compared to the combination of the CONUT score and circulating tumor cell (CONUT-CTC) in CRC patients with curative resection. The CONUT score was a predictor associated with CSS (HR 3.45, 95% CI = 1.68–7.10, P = 0.001) and RFS (HR 2.02, 95% CI = 1.19–3.43, P = 0.01), however the CONUT-CTC score was a better predictor of CSS (HR 3.75, 95% CI = 2.14–6.57, P < 0.001) and RFS (HR 2.66, 95% CI = 1.79–3.96, P < 0.001).

Ahiko et al. [18] assessed effects of preoperative several biomarkers on postoperative outcomes in older patients (≥75 years) with CRC. The CONUT score was found to be associated with OS (CONUT ≥4 versus 0–1, HR 2.24, 95% CI = 1.48–3.30, P < 0.001).

Six studies with 2601 patients were included in the present meta-analyses. The results of meta-analyses comparing between high CONUT group and low CONUT group are demonstrated in Fig. 2. Meta-analyses showed that patients with high CONUT score had a significantly worse OS (HR 1.97, 95%CI = 1.40–2.77, P < 0.001, I^2 = 30%, P = 0.24, n = 1765), CSS (HR 3.64, 95%CI = 1.96–6.75, P < 0.001, I^2 = 0%, P = 0.78, n = 364), and RFS (HR 1.68, 95%CI = 1.23–2.29, P = 0.001, I^2 = 0%, P = 0.79, n = 1299) compared to those with low CONUT score. Funnel plots of meta-analyses showing no obvious asymmetry to suggest publication bias are shown in Supplementary Fig. 1.

3.2. Effect of the CONUT score on short-term outcomes after surgery

Five studies reported data on postoperative complications including overall complications in two studies [9,18], major complications in one study [10], and infectious complications in two studies [14,15].

Iseki et al. [9] found no significant difference between the low and high CONUT groups regarding the incidence of postoperative complications (20% versus 18.5%, P = 0.81). Tokunaga et al. [10] conducted multivariable analyses showing that the CONUT score was associated with the incidence of severe complications in the comparison between moderate/severe versus normal (odds ratio [OR] 4.51, 95% CI = 1.89–10.7, P < 0.001). Ahiko et al. [18] revealed that only the CONUT score was related to the incidence of overall complications in the multivariable analyses (OR 1.93, 95% CI = 1.15–3.20, P = 0.013). Sagawa et al. [14,15] reported two articles using the same cohort to identify risk factors for surgical site infections and remote infections after CRC surgery. The results demonstrated that the CONUT score was not associated with surgical site infections and remote infections in multivariable analyses.

3.3. Effect of the CONUT score on long-term outcomes after chemotherapy

One study (Daitoku et al. [19]) investigated the CONUT score as a prognostic marker in patients receiving first-line chemotherapy for metastatic CRC. The Kaplan-Meier curve showed that patients with low or intermediate CONUT score had a significantly better OS and progression-free survival (PFS) than those with high CONUT score (OS; P < 0.001, PFS; P < 0.05). In addition, the multivariable analyses demonstrated that the CONUT score was an independent predictor for OS (high vs intermediate/low, HR 2.01, 95% CI = 1.26–3.12, P < 0.05).

4. Discussion

The present study investigated the effect of the CONUT score on short-term and long-term outcomes in patients with CRC. We found that the CONUT score was an independent prognostic factor for OS, CSS, and RFS in patients undergoing surgery for CRC. The CONUT score might be associated with the incidence of postoperative complications after CRC surgery. In addition, the CONUT score could be an

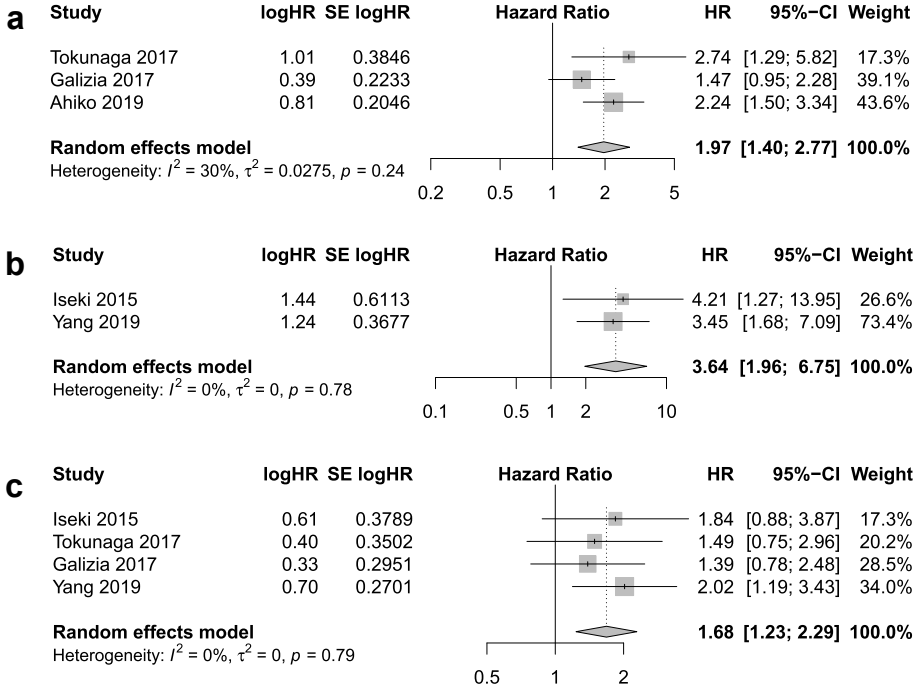

Fig. 2. Forest plots demonstrating long-term outcomes in terms of low CONUT versus high CONUT score. (a) Overall survival; (b) Cancer-specific survival; and (c) Recurrence/relapse-free survival.

independent prognostic marker in patients receiving first-line chemotherapy for metastatic CRC.

With respect to the association between the CONUT score and long-term outcomes after CRC surgery, the six included studies have shown the significance of the CONUT score as a predictor related to OS and CSS, however the reported effect on RFS was inconclusive. Our meta-analyses demonstrated the significant effect of the CONUT score on OS, CSS, and RFS without significant heterogeneity across the studies. Each of the three parameters in the CONUT score is reported to reflect cancer prognosis in various types of cancer [5,9,18,20], and there are several reasons for significant prognostic role of the CONUT score in CRC patients. Firstly, serum albumin level is influenced by nutritional status, inflammation, infection as well as hydration status [21]. Low serum albumin level is reported to be caused by the systemic inflammatory response to the tumor, and be associated with worse prognosis in CRC patients [22,23]. Secondly, total lymphocyte level reflects the immunological reaction and the systematic inflammatory response [24]. Low total lymphocyte level is reported to correlate with a poor prognosis in CRC patients [9]. Third, total cholesterol has a key role that may affect the antioxidant reserve and inflammatory reactions, therefore low cholesterol level is speculated as the result of a detrimental effect on prognosis [25]. Accordingly, the CONUT score as a combination of these factors could be a prognostic factor for long-term outcomes after CRC surgery. To the best of our knowledge, the present meta-analysis was the first to analyze the prognostic value of the CONUT score for postoperative long-term outcomes of CRC, and it could help overcome disadvantages of the included studies with small sample sizes.

The effect of the CONUT score on short-term outcomes including complications after CRC surgery remains controversial due to differently reported results. Two studies reported the association between the CONUT score and complications in multivariable analyses [10,18], in contrast no association between the CONUT score and postoperative infectious diseases was shown [14,15]. Recent meta-analyses have indicated that patients with higher CONUT score had an increased risk of complications as well as mortality after gastroenterological and hepatopancreatobiliary surgery [6–8]. Therefore, the CONUT score might be helpful in predicting complication risks in CRC surgery. Further studies with larger numbers should evaluate the impact of the CONUT score on short-term outcomes after CRC surgery.

In a clinical practice, predictive factors impaired in patients with altered nutritional status and then defecation disorders have been addressed, and the multidisciplinary approaches including rehabilitation and education can result in relevant clinical improvement for the patients [26,27]. Moreover, several nutritional biomarkers have been reported as a predictor of prognosis, showing that patients' nutritional status is associated with long-term outcomes in patients with metastatic CRC [28–30]. Patients' nutritional and systemic inflammatory status have been reported to be related to cancer progression [31,32], and the CONUT score is a biomarker which could reflect nutritional and inflammatory status. Therefore the CONUT score may predict prognosis of metastatic CRC. However, the role of the CONUT score as a predictor in patients receiving chemotherapy should be further investigated due to limited evidence.

The present study has some limitations. The number of included studies in the present meta-analyses was small, and all were retrospective series with relatively small sample sizes. In addition, the cut-off values of the CONUT scores were differently used in each studies. Moreover, no meta-analysis in terms of short-term outcomes after surgery as well as outcomes after chemotherapy was performed because of limited reported data. Accordingly, further studies with large sample sizes should be investigated to clarify the significance of the CONUT score on outcomes in patients with CRC.

5. Conclusions

The CONUT score is an independent prognostic factor associated with prognosis in patients undergoing surgery for CRC. The CONUT score might be associated with the incidence of postoperative complication, and could be an independent prognostic marker in patients receiving first-line chemotherapy for metastatic CRC. Further studies are needed to clarify the significance of the CONUT score in CRC patients.

Ethical approval

No ethical approval or informed consent statement was required for this review article.

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Author contribution

K.T. contributed to the study conception and design, the acquisition of data, the development of the protocol, and the drafting of the manuscript. S.B. contributed to the analysis and interpretation of the descriptive and the revising the final draft. J.I. contributed to the development of the protocol and the critical revising of the final draft. All authors have approved the final version.

Research registration Unique Identifying number (UIN)

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Guarantor

Kosei Takagi.

Data statement

Due to the nature of a systematic review, all data are available from previously published articles.

Declaration of competing interest

The authors declare that there are no conflicts of interest regarding this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2020.04.046.

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