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The prognostic value of the controlling nutritional status (CONUT) score on patients undergoing nephrectomy for upper tract urothelial carcinoma or renal cell carcinoma: a systematic review and meta-analysis

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Abstract

Background & aims: In recent years, the controlling nutritional status (CONUT) score has increasingly became an effective indicator associated with tumor prognosis. This study was conducted to synthesise data on the prognostic value of CONUT score on patients with upper tract urothelial carcinoma (UTUC) or renal cell carcinoma (RCC) undergoing nephrectomy.

Methods: We designed and performed a systematic analysis of studies that verified the correlation between preoperative CONUT score and prognosis for UTUC and RCC using PubMed, Web of Science and Embase. The conclusion was clarified by pooled hazard ratios (HR) and 95% confidence intervals (95% CI). Subgroup analysis were further conducted in accordance with different primary tumor.

Results: Six studies involving 3529 patients were included in this evidence synthesis, which revealed that the CONUT score had a potential role to predict the survival of UTUC and RCC patients accepting surgery. Pooled analysis showed that the overall survival (OS, HR 2.32, p<0.0001), cancer-special survival (CSS, HR 2.68, p<0.0001) and disease-free survival (DFS, HR 1.62, p<0.00001) were inferior in the high CONUT score group when compared with low score group. Subgroup analysis revealed that this result was in line with UTUC (OS: HR 1.86, P=0.02; CSS: HR 2.24, P=0.01; DFS: HR 1.54, P<0.00001) and RCC (OS: HR 3.05, P<0.00001; CSS: HR 3.47, P<0.00001; DFS: HR 2.21, P=0.0005) patients respectively.

Conclusion: The CONUT score is a valuable preoperative index to predict the survival of patients with UTUC or RCC undergoing nephrectomy.

Keywords: Upper tract urothelial carcinoma, Renal cell carcinoma, Controlling nutritional status score, Prognosis, Nephrectomy

Abbreviations

CONUT: controlling nutritional status

UTUC: upper tract urothelial carcinoma

RCC: renal cell carcinoma

95% CI: 95% confidence intervals

HR: hazard ratios

OS: overall survival

CSS: cancer-special survival

DFS: disease-free survival

1. Introduction

Nutritional status is a significant indicator for physical conditions, especially for cancer patients. Several nutritional assessment indexes including nutritional risk index (NRI), prognostic nutritional index (PNI) and the modified Glasgow prognostic score (mGPS) have been applied to predict outcomes of cancers[1-4]. Similarly, the preoperative controlling nutritional status (CONUT) score is known as a relatively objective, validated and emerging index to assess patients' nutritional status, which is derived from serum albumin level, total lymphocyte count, as well as total cholesterol concentration[5]. A series of retrospective cohort studies had demonstrated that CONUT score was closely related with the prognosis of some type of cancers, including gastric carcinoma[6], hepatocellular carcinoma[7], esophageal carcinoma[8], colorectal carcinoma[9], breast carcinoma[10], ovarian carcinoma[11], lymphoma[12] and lung carcinoma[13]. In addition, the systematic review and meta-analysis about gastric carcinoma, hepatocellular and colorectal cancer have also been released recent years[14-16].

The utility of the CONUT score on survival outcomes of patients accepting nephrectomy due to upper tract urothelial carcinoma (UTUC) or renal cell carcinoma (RCC) was first reported in 2017[17]. Since then, this effect has been further examined by clinicians all over the world. However, the value of the preoperative CONUT score in urinary system tumors has not been proved with evidenced-based medicine until now.

Consequently, the first systematic review and meta-analysis, which is about the relationship between the CONUT score and prognosis of patients with UTUC or RCC, was performed by our team to provide more valid evidence.

2. Material and methods

2.1 Search strategy

This study was designed and conducted on the basis of the Preferred Reporting Items for Systematic Reviewers and Meta-Analyses (PRISMA) guidelines[18]. Major public medical and scientific database including PubMed, Embase along with Web of science were systematically searched to seek out all original articles, which examined the association between the preoperative CONUT score and prognosis of patients with UTUC or RCC. Search terms were as follows: kidney neoplasm OR kidney cancer OR kidney cancers OR renal neoplasm OR renal neoplasms OR renal cancer OR renal cancers OR neoplasm, kidney OR neoplasm, renal OR neoplasms, renal OR neoplasms, kidney OR cancer of kidney OR cancer, renal OR cancers, renal OR cancer of the kidney OR cancer, kidney OR cancers, kidney OR upper tract urothelial carcinoma AND the Controlling Nutritional Status Score OR CONUT Score AND nephrectomy. The systematic search was performed on the February, 2021.

2.2 Study selection

Inclusion criteria were presented as follows: (1) patients undergoing radical or partial nephrectomy for UTUC or RCC; (2) the CONUT score of patients was assessed before surgical operation; (3) prognosis indicators including overall survival (OS), cancer-special survival (CSS) as well as disease-free survival (DFS) were reported.

Exclusion criteria were shown as follows: (1) Human studies on other cancers were excluded. (2) Patients treated with non-operation therapy were excluded as well. (3) Reviews, case reports, comments, letters, as well as meeting abstracts were also excluded.

2.3 Data extraction

After deleting same articles, the titles, abstracts and full text of the remaining records were independently checked and approved by two authors. If there existed disagreement, the divergence was resolved by the third investigator. Using a unified form, variables including study type, issuing time, publishing country of study, essential information of patients, cut-off value of the CONUT score, as well as long-term survival outcomes were extracted.

2.4 Quality assessment

A quality assessment system which was on the basis of the Newcastle-Ottawa Scale (NOS) for cohort studies were applied to evaluate methodological quality of all included articles[(19)]. The minimum and maximum score for NOS of included studies were 6 and 9 respectively, and the study would be considered as high-quality study if total score was 6 or higher [(20)]. The quality and level of evidence for all included studies were evaluated independently by two authors and the results were presented in supplementary Table S1.

2.5 Statistical analysis

The value of the CONUT score on survival was examined by using Review Manager 5.4 (Cochrane Collaboration, 2014). The pooled hazard ratios (HR) with 95% confidence interval (95%CI) were calculated for dichotomous variables by applying the inverse variance method. To assess heterogeneity among studies, we calculated the I^2 values and the Chi-square test. P value <0.05 was regarded as statistical significance and I^2 values >50% indicated that there was heterogeneity among included studies. The random effects meta-analysis was used if the I^2 values >50%, otherwise, we conducted the fixed effects models.

3. Results

Study selection was performed according to the procedures of Figure 1. After deleting the duplications, 95 relevant articles in total were acquired initially using the search strategy above. Then we reviewed the titles and abstracts, and 84 studies were further excluded on account of reporting the CONUT score of non-urinary tumors or for that the content has nothing to do with the CONUT score. The full text of the remaining 11 articles were screened next and 5 studies of them were excluded for that these articles were examining the prognostic significance of CONUT score on prostate and bladder carcinoma and the intervention of one article was not surgery.

Finally, 6 full-text articles were regarded as qualified and included for the pooled analysis, as represented in Table 1[21-26]. The survival rates for patients in all included studies were showed in Table 2. Four studies reported that 5-year OS, CSS and DFS in the low CONUT group were better than that in the high CONUT group. These articles came from different countries including China, Japan as well as Germany and were released from 2017 to 2020. All selected articles were single-center retrospective study and 3529 patients altogether were enrolled with sample sizes ranged from 107 to 1046 cases. All patients included were treated with nephrectomy. Six studies included were considered as high-quality due to the NOS score was more than 6.

3.1 Impact of the CONUT score on OS

Prognostic value of the CONUT score on OS were examined by all included studies with 3529 patients. Pooled analysis revealed that the CONUT score was related to OS and the OS of high CONUT score group was inferior than that of low score group (HR 2.32, 95%CI 1.58-3.41, $p<0.0001$, $I^2=68\%$, $p=0.008$). Subgroup analysis was further performed in accordance with various primary tumors. In the subgroup analysis, the preoperative CONUT score was found to be associated with OS of UTUC (HR 1.86, 95%CI 1.13-3.08, $p<0.02$, $I^2=74\%$, $p=0.02$) and RCC (HR 3.05, 95%CI 2.07-4.49, $p<0.0001$, $I^2=0\%$, $p=0.93$) respectively (Figure 2A).

3.2 Impact of the CONUT score on CSS

Six studies involving 3529 patients demonstrated the connection between the preoperative CONUT score and CSS. Pooled analysis confirmed the statistically significant predictive role of the CONUT score on CSS, and the CSS was better for the low CONUT score group when compared with the high score group (HR 2.68, 95%CI 1.69-4.26, $p<0.0001$, $I^2=68\%$, $p=0.009$). Subgroup analysis revealed that the

COUNT score had a potential value to predict the CSS of UTUC (HR 2.24, 95%CI 1.17-4.26, p=0.01, I^2=79%, p=0.009) and RCC (HR 3.47, 95%CI 2.12-5.68, p<0.00001, I^2=0%, p=0.81) (Figure 2B).

3.3 Impact of the CONUT score on DFS

Data about the effect of preoperative CONUT score on DFS were synthesized from 5 studies including 2894 patients. Our evidence synthesis revealed that the higher CONUT score was associated with reduced DFS, in other words, the high CONUT score group were more likely to relapse than the low score group (HR 1.62, 95%CI 1.37-1.92, p<0.00001, I^2=26%, p=0.25). In the subgroup analysis, this result was also applied to UTUC (HR 1.54, 95%CI 1.28-1.84, p<0.00001, I^2=5%, p=0.35) and RCC (HR 2.21, 95%CI 1.42-3.45, p=0.0005, I^2=11%, p=0.29) respectively (Figure 2C).

4. Discussion

This systematic review and meta-analysis was conducted to reveal the impact of CONUT score on the survival of patients with UTUC or RCC undergoing nephrectomy. The relationship between the CONUT score and OS had been demonstrated previously, however, the value of CONUT score on CSS and DFS remained controversial on account of discrepancy in reported articles. Multivariable analyses were performed by all selected studies respectively, and the evidence that the high CONUT score was an independent risk factor for OS, CSS, and DFS was demonstrated by most of included studies. However, Bao et al. found that there was no critical association between the CONUT score and CSS[21]. Ishihara et al. reported that the preoperative CONUT score had little significance in predicting DFS. Therefore, a systematic review and meta-analysis was needed urgently to guide clinical diagnosis and treatment. Our pooled analysis revealed that UTUC and RCC patients with high CONUT score had inferior OS, CSS and DFS when compared with those having low score. The same conclusion was also demonstrated by other tumors such as gastric carcinoma, hepatocellular carcinoma and colorectal cancer[14-16].

As we all know, the CONUT score is assessed by the level of serum albumin, peripheral lymphocyte and total blood cholesterol. Each index of preoperative CONUT score had been reported to be related to the prognosis of different tumors. There exist a lot of reasons to account for the predictive effect of the CONUT score on the prognosis of UTUC and RCC. First of all, albumin, a major element of serum total proteins, plays a great role in reflecting nutrition status and metabolic status[3, 27]. On the other hand, albumin was strongly related to the extent of the systemic inflammatory response by regulating concentrations of C-reactive protein[28, 29]. For patients with renal cancer, serum albumin has been proved as an independent prognostic factor [30]. In addition, low albuminemia could lead to poor prognosis of patients with cancer by affecting immune response[28]. Secondly, lymphocyte count can reflect the level of immunological and systematic inflammatory reaction[31]. In the tumor microenvironment, the high lymphocyte count indicates the body's immunoreaction against tumor. The anti-tumor effect of lymphopenia is achieved by promoting cell apoptosis, restraining the growth and migration of tumor cell, and mediating cytotoxicity reaction[32]. Lymphopenia was reported to be independently correlated with the inferior survival outcomes of clear cell renal cancer[33]. What' s more, neutrophil to lymphocyte (NLR) and platelet to lymphocyte ratio (PLR), two kind of indexes based on the lymphocyte count, had been reported to be prognostic factor for UTUC[34, 35]. Finally, cholesterol, an essential component of cell membrane, plays a crucial role in maintaining the cellular function by affecting the organization, dimensions and fluidity of plasma membrane[36]. Previous study demonstrated that low cholesterol level was connected with worse outcomes of patients with renal cell carcinoma[37]. A recent study has shown that high serum cholesterol levels can enhance the anti-tumor effect of natural killer cells in mice[38]. In addition, the higher level of serum cholesterol also indicates the lower overall cancer risk[39]. However, the mechanism was unclear. Although in an initial cancer process the expected immunological reaction would be an increase of total lymphocytes, in the case of more serious situation, the nutritional deficit in albumin and cholesterol will prevent the development of the immunological reaction which would be required for the regeneration of the cell membranes. This is also what happens with the caloric and protein needs that are covered by the albumin: In fact, it is the latter one that is in charge of the energetic and protein substrates that are required for cell development as well as lymphocyte proliferation. As a consequence, nutrient deficiency affects all three parameters and is reflected in the controlling nutritional prognostic and clinical risk index. Patients with high CONUT score had low albumin, lymphocyte count and serum cholesterol level. Consequently, it's not difficult for us to understand that the survival rates of high CONUT score group was worse than the low score group.

What's more, malnutrition is a common clinical feature of cancer patients and even can evolve into cachexia especially in advanced cancer patients. Previous evidence supported that malnutrition could influence progression and survival of patients with tumor(40). In addition, nutritional intervention of perioperative period has the effect of increasing treatment tolerance and improving prognosis of cancer patients(41). However, it has not been confirmed that the perioperative nutritional intervention can affect the long-term outcomes of oncological patients. The present study indicates that the perioperative nutritional support is of importance for survival of patients with RCC and UTUC. The CONUT score of patients is easily to assess and it can help clinicians to identify patients who need nutritional support during the perioperative period.

We should acknowledge that there exist some limitations in the present study. Firstly, although the study included the up to date and the most complete articles, there were only six studies involved in the pooled analysis. Secondly, all articles included were retrospective single center research and we can only get the effective data of long-term outcomes without short-term outcomes. In addition, the cut-off values of dividing high CONUT score and low CONUT score were different for included studies. Consequently, further studies are needed to demonstrated the value of preoperative CONUT score on prognosis of RCC and UTUC. The association between CONUT and prognosis is not necessarily causal. The CONUT score could be a proxy for another aspect of illness. However, CONUT is clinically useful in that it predicts outcomes.

5. Conclusions

The first systematic review and meta-analysis that examined the role of preoperative CONUT score on prognosis of patients accepting nephrectomy for UTUC or RCC was performed by our team. Our pooled analysis revealed that the CONUT score was an effective and convenient index to predict survival of UTUC and RCC patients undergoing surgery, which could provide a reliable reference for clinician.

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Conflict of interest

None.

Authorship

JC and DC contributed to the study conception and design, and the drafting of the manuscript. ZP and PS were responsible for data extraction. ZL and LY were responsible for data analysis and interpretation. Data integrity and accuracy was confirmed by LW and JZ. QW and QD contributed to the critical revising of the final draft. All authors read and approved the final manuscript.

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Figure legends

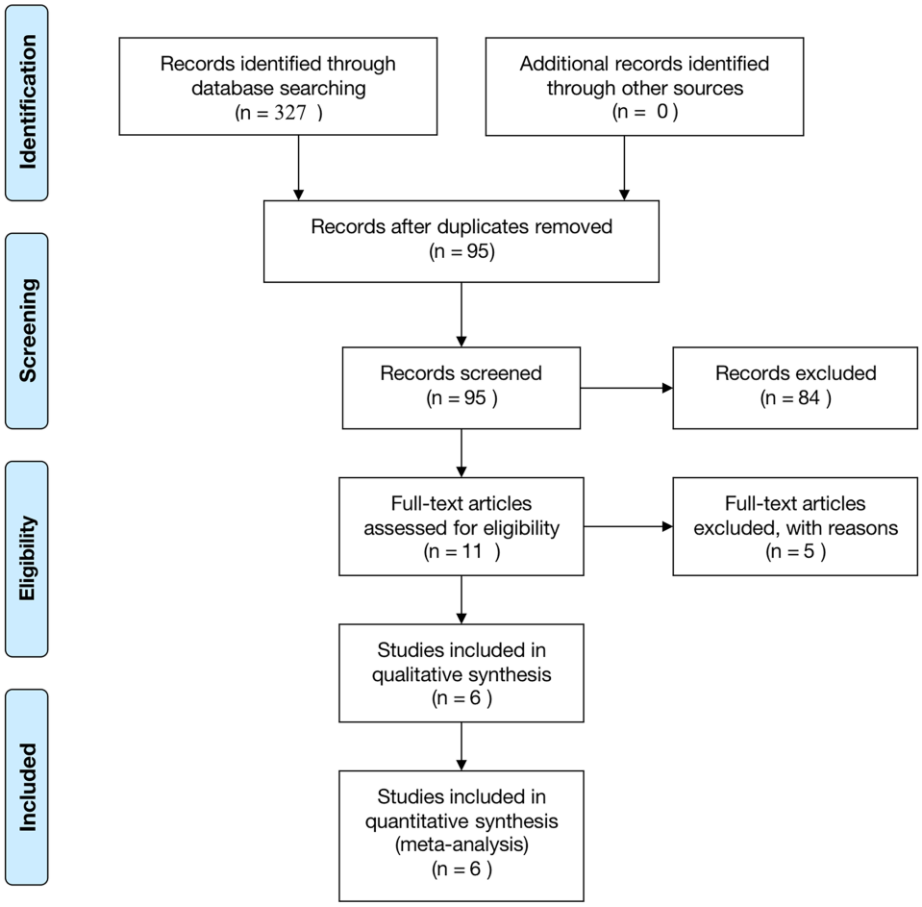

Figure 1. Flow diagram of evidence acquisition.

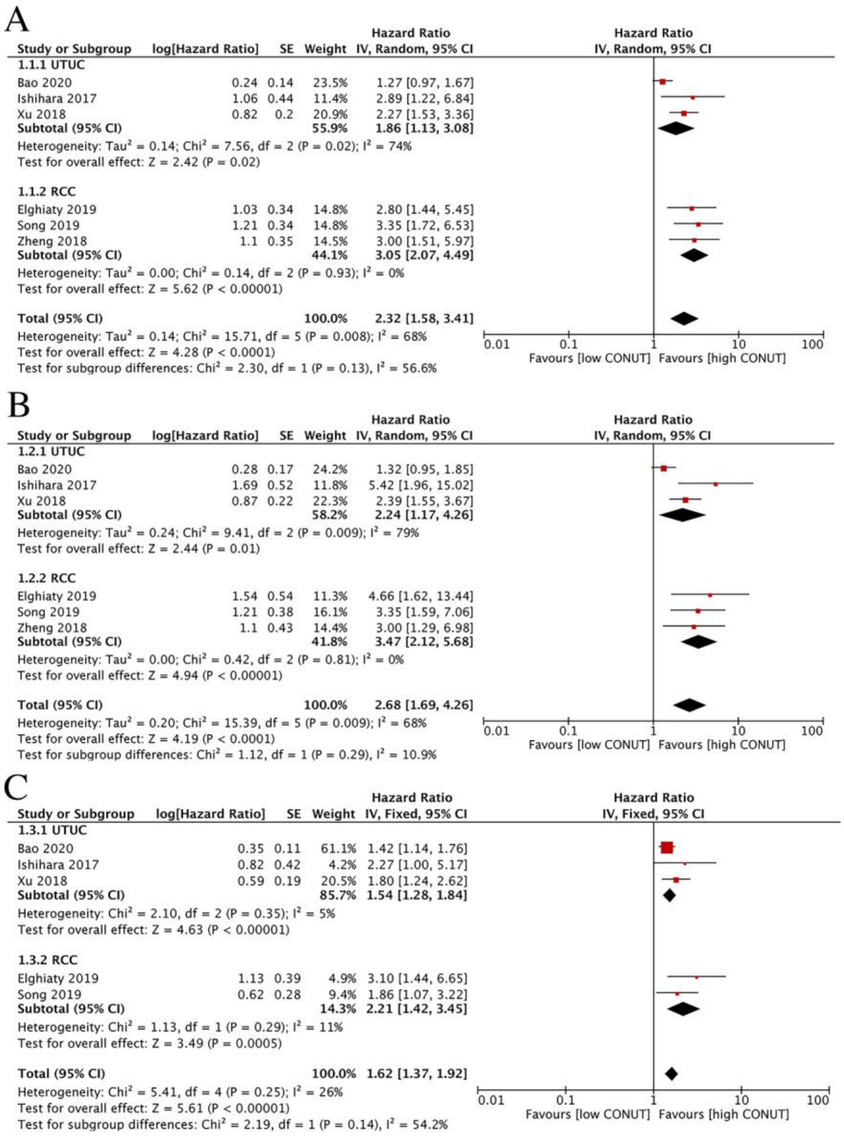

Figure 2. Forest plots demonstrating long-term outcomes in terms of low CONUT versus high CONUT score. (A) Overall survival; (B) Cancer-special survival; (C) Disease-free survival.

Table 1. Literatures about the impact of the CONUT score on patients undergoing nephrectomy for UTUC or RCC

Study	Year	Country	Study design	Number (Male)	Tumor	Cut-off for high CONUT group	Prevalence of high CONUT score	End points	Follow-up (median,months)	Quality[a]
Bao (21)	2020	China	Retrospective Single center	754 (342)	UTUC	≥4	27.1%	OS/CSS/DFS	61	7
Elghiat (22)	2019	Germany	Retrospective Single center	1046 (745)	RCC	>2	11.0%	OS/CSS/DFS	63	6
Song (23)	2019	China	Retrospective Single center	325 (231)	RCC	≥3	21.5%	OS/CSS/DFS	64	8
Xu (24)	2018	China	Retrospective Single center	662 (376)	UTUC	0-1(normal) 2-4(light) 5-12(moderate or severe)	40.8% 45.6% 13.6%	OS/CSS/DFS	41	9
Zheng (25)	2018	China	Retrospective Single center	635 (400)	RCC	≥2	55.0%	OS/CSS	48.4	7
Ishihara (26)	2017	Japan	Retrospective Single center	107 (68)	UTUC	≥3	22.4%	OS/CSS/DFS	n.a.	8

CONUT, controlling nutritional status; OS, overall survival; CSS, cancer-special survival; DFS, disease-free survival; n.a., not available.

[a] Score from a maximum of 9 evaluated by the Newcastle-Ottawa quality assessment scale for cohort studies.

Table 2. Studies investigating the impact of the CONUT score on survival in patients with UTUC or RCC

Study	Overall survival	Cancer-special survival	Disease-free survival
Bao (21)	HR 1.273 (0.960-1.686) p=0.093*	HR 1.328 (0.954-1.847) p=0.092*	HR 1.418 (1.132-1.776) p=0.002*
Elghiaty (22)	5-year: 90.9% vs 96.5% (p=<0.001) HR 2.812 (1.437-5.502), p=0.003*	5-year:96.2% vs 98.8% (p=0.006) HR 4.664 (1.625-13.391), p=0.004*	5-year: 88.2% vs 97.1% (p<=0.001) HR 3.092 (1.450-6.593), p=0.003*
Song (23)	5-year: 67.8% vs 93.7% HR 3.36 (1.73-6.56), p<0.001*	5-year: 72.9% vs 94.9% HR 3.34 (1.59-6.98), p=0.001*	5-year: 58.8% vs 87% HR 1.85 (1.07-3.21), p=0.029*
Xu (24)	5-year: 49.7% vs 66.5% (Light vs normal) (p<0.0001) HR 1.58 (1.18-2.11) p=0.002* 37.3% vs 66.5% (Moderate/severe vs normal) (p<0.0001) HR 2.26 (1.53-3.34) p<0.0001*	5-year: 55.7% vs 72.6% (Light vs normal) (p<0.0001) HR 1.69 (1.21-2.34) p=0.002* 46.1% vs 72.6% (Moderate/severe vs normal) (p<0.0001) HR 2.39 (1.55-3.68) p<0.0001*	5-year: 44.8% vs 58.5% (Light vs normal) (p<0.0001) HR 1.43 (1.10-1.86) p=0.008* 36.3% vs 58.5% (Moderate/severe vs normal) (p<0.0001) HR 1.80 (1.24-2.60) p=0.002*
Zheng (25)	HR 3.012 (1.525-5.948) p=0.001*	HR 3.001 (1.290-6.984) p=0.011*	n.a
Ishihara (26)	5-year: 26.4% vs 66.8% (p=0.0140) HR 2.90 (1.18-6.75) p=0.0214*	5-year: 28.1% vs 71.7% (p=0.0041) HR 5.44 (1.95-14.8) p=0.0016*	5-year: 50.1% vs 66% (p=0.0395) HR 2.26 (0.97-4.94) p=0.0581*

Data are shown for high CONUT group versus low CONUT group unless otherwise indicated. HR is shown with 95% confidence interval.

* Multivariable analysis. CONUT, Controlling nutritional status; HR, Hazard ratio; n.a., not available.