中国临床研究 Chin J Clin Res, February 2024, Vol.37, No.2
Cite as: Li MZ, Tan RM, He SH, et al. Preoperative controlling nutritional status on the prognosis of postoperative gastric cancer patients:Meta-analysis [J]. Chin J Clin Res, 2024,37(2) 223-229:
DOI: 10.13429/j.cnki.cjcr.2024.02.012

Preoperative controlling nutritional status on the prognosis of postoperative gastric cancer patients: a Meta-analysis

LI Mingzhen[1], TAN Ruiming[2], HE Shaohua[1], LIU Huan[1], CHEN Cheng[1], ZHANG Yuanyi[1], YAO Bolan[1], TAN Liming[3]

1.Precision Medicine Centre, the Second People's Hospital of Huaihua, Huaihua, Hunan 418000, China

2. Department of Gastroenterology, the Second People's Hospital of Huaihua, Huaihua, Hunan 418000, China

3. Huaihua Key Laboratory of Cancer Prevention and Treatment, Huaihua, Hunan 418000, China

Corresponding author: TAN Liming, E-mail: tanliming1973@126.com

Abstract: Objective To evaluate the prognostic value of controlling nutritional status (CONUT) score in patients undergoing gastrectomy for gastric cancer. **Methods** CNKI, Wanfang, China Biomedical Literature Library, VIP, PubMed, Web of Science, CocHRane Library, and Embase databases were electronically searched for collecting relevant studies on the application of preoperative CONUT scores to the prognosis of gastric cancer patients after surgery. The search period was from database establishment to April 20, 2023. Data extraction and quality assessment were performed followed by Meta-analysis using the RevMan 5.3 and Stata 15 software. **Results** A total of 17 studies involving 9 233 patients were included. The results of meta-analysis showed that, compared with the low CONUT group, patients in the high CONUT group had poorer overall survival [*HR*=1.70, *95%CI* (1.54, 1.87), *P*<0.01], tumor specific survival [*HR*=2.55, *95%CI* (1.23, 5.27), *P*=0.01], and progression free survival [*HR*=1.53, *95%CI* (1.29, 1.82), *P*<0.01]. The CONUT score was significantly correlated with complications [*OR*=2.10, *95%CI* (1.53,2.90), *P*<0.01], nerve infiltration [*OR*=1.54, *95%CI* (1.02,2.32), *P*=0.04], mortality [*OR*=2.24, *95%CI* (1.25,4.01), *P*=0.006], T3/4 [*OR*=2.06, *95%CI* (1.73,2.46), *P*<0.01], N2/3 [*OR*=1.76, *95%CI* (1.51,2.05), *P*<0.01], Stage III [*OR*=1.62, *95%CI* (1.39,1.90), *P*<0.01], but not with tumor differentiation [*OR*=0.88, *95%CI* (0.75,1.04), *P*=0.13]. **Conclusion** Preoperative CONUT score is an independent prognostic indicator of postoperative complications and survival in patients with gastric cancer, and is correlated with clinicopathological parameters.

Keywords: Gastric cancer, Controlling nutritional status (CONUT) Score, Gastrectomy, Survival; Meta-analysis

Fung program: Hunan Province natural science Foundation Project (2022JJ30462); Huaihua Technology Innovation Platform (2021R2206)

The incidence of gastric cancer is the fifth highest in the world, with an estimated 1 099 103 cases in the Global Cancer Statistics 2020, ranking third among cancer-related causes of death [1]. For patients with early-stage gastric cancer, surgical resection is still the most important treatment. Although surgical techniques and adjuvant therapy have made great progress, the prognosis of patients with gastric cancer after surgery is not ideal [2]. At present, TNM staging is considered to be the most commonly used survival prediction method, but it cannot provide complete clinical information, and more efficient predictive indicators are needed to identify whether surgery can benefit patients [3]. Perioperative systemic nutrition and inflammation of patients can affect the progression and metastasis of tumors, which are closely related to the occurrence of postoperative complications, and to a certain extent affect the overall survival rate of patients [4]. Controlling nutritional status (CONUT) score is a newly proposed nutritional scoring system in recent years, which evaluates nutritional status based on serum albumin, total cholesterol and lymphocyte counts [5]. By delimiting the scoring range of these indicators, the nutritional score of patients can be calculated simply and efficiently. It has been reported that it has been widely used in breast cancer, lung cancer, colorectal cancer and other fields, which not only has outstanding nutritional evaluation performance, but also has a significant correlation with the evaluation of postoperative complications and survival time [4, 6]. However, whether it has the same applicability in patients with gastric cancer still needs further exploration. The purpose of this study was to evaluate the association between CONUT score and short-term prognosis and long-term survival in patients with gastric cancer after surgery, in order to provide reference for relevant clinical applications.

1. Data and methods

1.1 Literature search

CNKI, Wanfang, China Biomedical Literature Library, VIP, PubMed, Web of Science, CocHRane Library, Embase database were searched. The literature published in English and Chinese from the establishment of the database to April 20, 2023 was searched. The search terms were "controlling nutritional status score", "stomach neoplasms", gastrectomy, etc. The method of combining subject words and free words is used to search, and the relevant documents are collected by manual search and document tracing.

1.2 Inclusion and exclusion criteria

Inclusion criteria:(1) Patients with gastric cancer confirmed by pathology and underwent surgical treatment;(2) Preoperative CONUT score was performed;(3) Postoperative prognosis was reported, including short-term efficacy and long-term survival rate.

Exclusion criteria:(1) Studies where data is not available or cannot be converted;(2) Language is not Chinese or English.

1.3 Literature screening and data extraction

Literature was screened independently by two researchers, data were extracted, and cross-checked. In case of disagreement, it was resolved through discussion or by a third party. In the literature selection process, the title and abstract were read first, and then the full text, in order to determine whether the final inclusion was included. Data extraction included: (1) Basic information of the included study, including first author, publication year, sample size, CONUT cut-off score, etc.; (2) Relevant elements of literature quality evaluation; (3) Outcome indicators.

1.4 Quality evaluation

The quality of literature was evaluated using the Newcastle-Ottawa Scale (NOS), with a total score of 9 points. The higher the score, the higher the quality of the literature [7].

1.5 Statistical methods

RevMan 5.3 and Stata 15.0 software were used for analysis. The HR value and 95%CI were processed by using the reciprocal variance method. The odds ratio (*OR*) of bitaxonomic variables was used as the statistic of effect analysis, and 95%*CI* was provided for each effect size. The I^2 and chi-square test statistics were used for statistical heterogeneity. If I^2<50% and *P*>0.1, the fixed-effect model was used to combine the effect size; otherwise, the random-effect model was used. Subgroup analysis was performed on the sources of heterogeneity, and they were grouped according to CONUT score truncation value and source country. Funnel plots were drawn for the included studies and Egger tests were conducted to assess publication bias. *P*<0.05 was considered statistically significant.

2 Results

2.1 Literature screening process

A total of 322 related literatures were obtained at the initial examination, and 17 studies were finally included after layer-by-layer screening. The literature screening process and results are shown in **Figure 1.**

2.2 Basic features of included studies

A total of 17 studies [3, 6,8-22] were included, with a total of 9 233 patients. Only one study [17] was a prospective single-center study, and the rest were retrospective single-center studies.

There were 16 studies with NOS quality score ≥7. The basic characteristics of the included studies and literature quality evaluation are shown in **Table 1**.

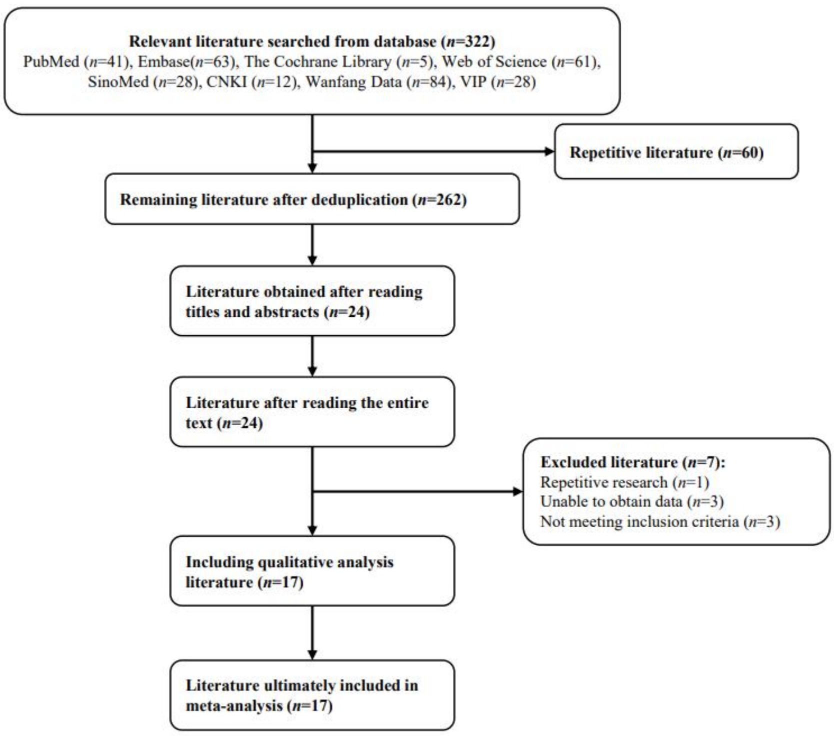


Fig. 1 Literature screening process

Tab.1 General characteristics of included literatures

Author	Year	Country	Sample size (male)	Tumor Stage	CONUT cut-off value	Percentage of high COUNT	Outcome indicators	Follow up time (months)	NOS
Hu[3]	2021	China	218(164)	I:61, II:57, III:100	>2	48.00%	complication, OS	60	7
Du[6]	2021	China	239(174)	I:54, II:48, III:137	>2	36.40%	OS	52(1-75)	6
Suzuki[8]	2019	Japan	211(141)	I:132, II:53, III:26	≥5	17.06%	CSS, OS, complication	47(5-185)	8
Hirahara[9]	2019	Japan	368(254)	I:217, II:65, III:86	≥3	28.50%	OS, complication	35.3(4-97)	7
Lin[10]	2020	China	2 182(1643)	I:632, II:526, III:1024	>2	21.90%	complication, OS	52(1-118)	7
Sun[11]	2021	China	1 479(1083)	I:505, II:366, III:592, IV:16	≥2	57.60%	complication	-	7
Liu[12]	2018	China	697(457)	II:194, III:503	≥3	31.10%	CSS, complication	36(3-162)	8
Qian[13]	2021	China	309(228)	I:102, II:51, III:148, IV:8	>2.5	30.74%	complication	-	7
Xiao[14]	2022	China	106(84)	I:17, II:20, III:57, IV:12	≥5	59.43%	complication, OS	30(7-64)	7
Xie[15]	2019	China	536(372)	II:112, III:424	≥3	29.10%	OS, complication	61(3-162)	7
Zheng[16]	2018	China	532(403)	I:291, II:183, III:58	Normal (0-1); mild (2-4); moderate and severe (≥5)	54.7%, 34.4%, 10.9%	OS, RFS	60	7
Huang[17]	2019	China	357(275)	I:119, II:87, III:151	Normal (0-1); mild (2-4); moderate and severe (≥5)	42.85%, 47.05%, 10.1%	complication	12	8
Zhao[18]	2020	China	231(-)	-	≥3	27.70%	DFS	60	7
Zhou[19]	2021	China	454(334)	I:185, II:63, III:188, IV:18	>2	33.04%	complication	-	7
Ryo[20]	2019	Japan	626(435)	II:281, III:345	≥2	46.17%	OS, complication, DFS	49.2	8
Kuroda[21]	2018	Japan	416(267)	I:275, II:81, III:60	≥4	14.90%	OS, CSS, RFS, complication	60	7
Jin[22]	2021	China	272(201)	-	≥4	31.80%	OS, PFS, complication	60	7

Note：-，Not obtained or reported; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; DFS, disease-free survival; CSS, cancer-specific survival.

2.3 Association between preoperative CONUT score and survival prognosis

There were 11 studies [3, 6, 8-10, 14-16, 20-22] reported the correlation between CONUT score and overall survival of patients with gastric cancer after surgery. Results showed that patients in the high CONUT group had a worse prognosis in terms of overall survival compared with those in the low CONUT group [*HR*=1.70, 95%CI (1.54, 1.87), *P*<0.01] (**Figure 2A**).

There were 3 studies [8, 12, 21] reported the association between CONUT score and tumor-specific survival of patients. Results showed that patients in the high CONUT group had worse prognosis in terms of tumor-specific survival than those in the low CONUT group [*HR*=2.55, *95%CI* (1.23, 5.27), *P*=0.01] (**Figure 2B**).

There were 5 studies [16, 18, 20-22] reported the association between CONUT score and progression-free survival. Results showed that patients in the high CONUT group had a worse prognosis in terms of progression-free survival than those in the low CONUT group [*HR*=1.53, *95%CI* (1.29, 1.82), *P*<0.01] (**Figure 2C**).

2.4 Association between preoperative CONUT score and secondary outcome indicators

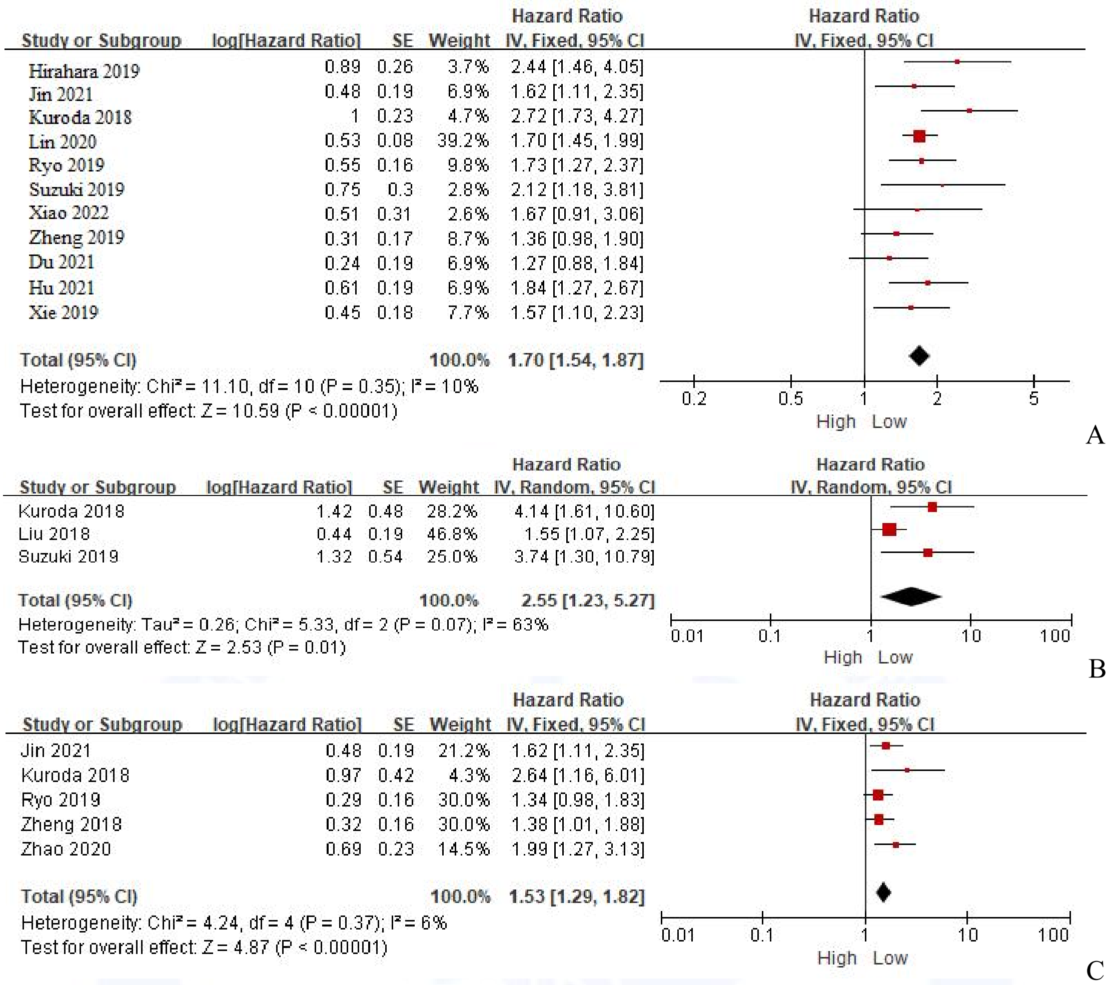
Preoperative CONUT score was associated with postoperative complications, nerve infiltration, mortality, T3/4, N2/3, and Stage III. **See Table 2** for details.

2.5 Subgroup analysis

Subgroup analysis was performed according to different cut-off values and different source countries. The results show that the source of heterogeneity is not found when grouping by truncation value. When the cutoff value was 2, 3, 4, or 5, all subgroups showed that patients in the high CONUT group had worse OS outcomes than those in the low CONUT group (**Figure 3A**). When they were grouped by country of origin, it was found that the source was probably heterogeneous (χ^2=4.60, *P*=0.03, I^2=78.2). All subgroups showed that patients in the high CONUT group had worse OS outcomes than those in the low CONUT group (**Figure 3B**).

2.6 Publication bias

Funnel plots were drawn for 11 studies that reported OS, and the results showed that the scatter distribution was roughly symmetrical, and the P-value of Egger test was 0.451, suggesting a small possibility of publication bias. See Figure 4 for details.

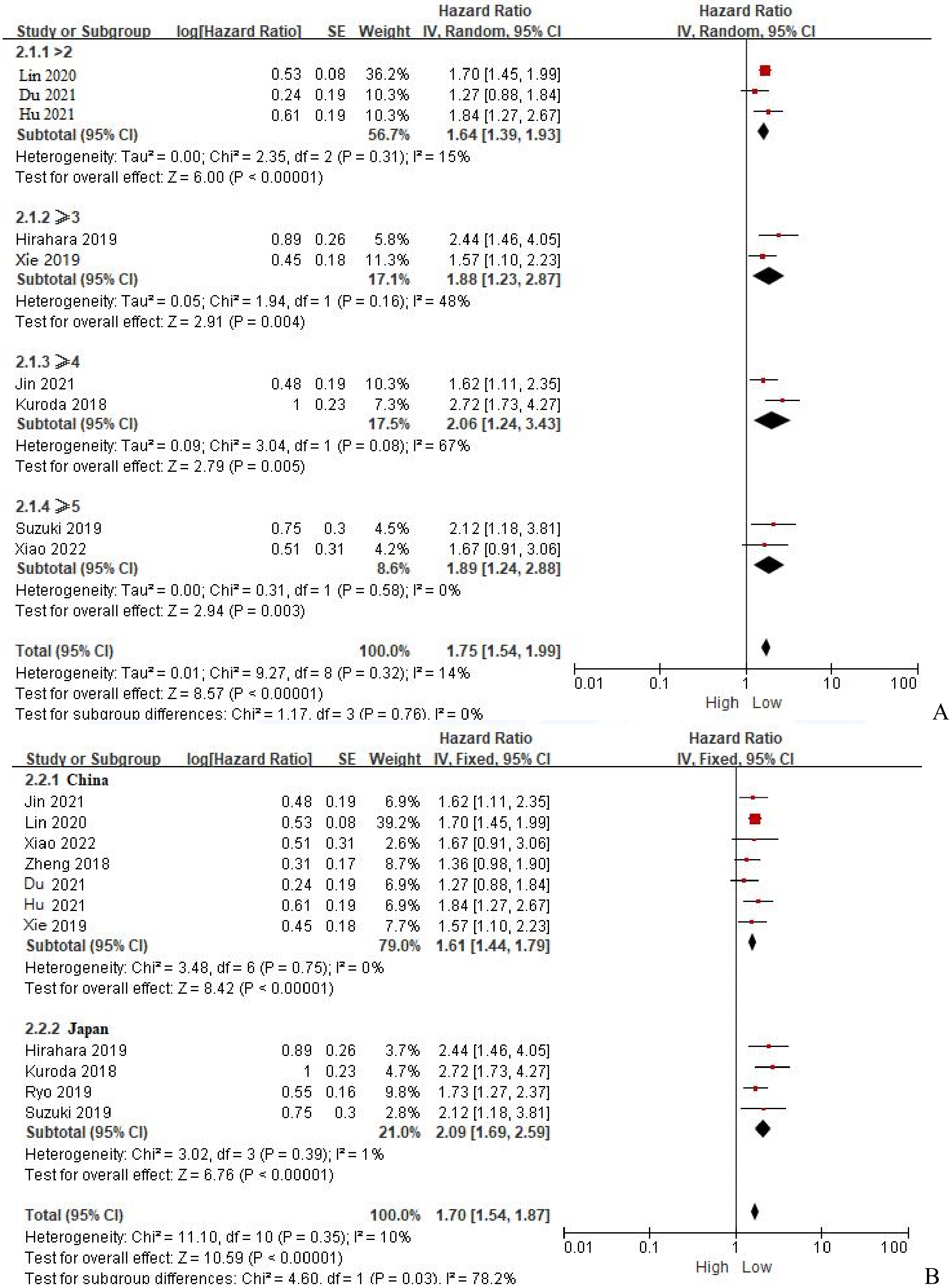


Note: A, CONUT score and overall survival; B, CONUT score and tumor-specific survival; C, CONUT score and progression-free survival.

Fig. 2 Correlation between CONUT score and survival prognosis

Tab.2 Comparison of secondary outcome between CONUT high and low groups

Outcome indicators	Number of obtained studies	Heterogeneity test		Effects model	Meta analysis	
		I^2 value	*P* value		*OR (95%CI)*	*P* value
Complications	14	83	<0.01	random	2.10(1.53,2.90)	<0.01
Neuronal Infiltration	2	23	0.25	fixed	1.54(1.02,2.32)	0.04
Mortality	5	12	0.34	fixed	2.24(1.25,4.01)	0.06
T3/4	9	0	0.69	fixed	2.06(1.73,2.46)	<0.01
N2/3	8	10	0.35	fixed	1.76(1.51,2.05)	<0.01
Stage Ⅲ	14	25	0.19	fixed	1.62(1.39,1.90)	<0.01
Low Differentiation	9	0	0.57	fixed	0.88(0.75,1.04)	0.13



Note: A, grouped by cut-off value of CONUT score; B, grouped by country.

Fig. 3 Subgroup analysis of the correlation between CONUT score and OS

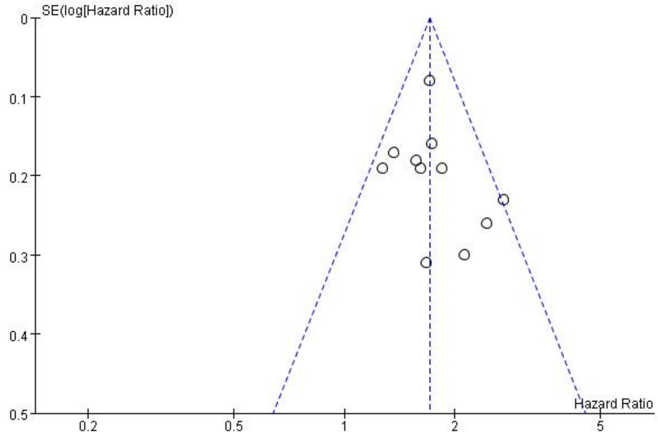


Fig. 4 Publication bias funnel diagram

3 Discussion

The results of this study suggest that CONUT score is a potential nutritional screening tool, which can be used to predict the short-term prognosis and long-term survival prognosis of patients with gastric cancer after radical gastrectomy, and is correlated with clinicopathological parameters.

Patients with gastric cancer are often complicated with malnutrition of varying degrees, mainly due to reduced intake, increased consumption, gastrointestinal insufficiency and metabolic changes caused by the primary disease and treatment [23]. Malnutrition not only affects the patients' tolerance to surgical treatment, but also negatively affects the smooth implementation of adjuvant treatment. After radical gastrectomy for gastric cancer, the continuous catabolic state of the body will last for several months or even longer, increasing the incidence of postoperative complications and affecting the long-term prognosis [24]. In addition, immune status is also regarded as a prognostic indicator for patients with gastric cancer [25]. Therefore, the selection of simple and efficient predictive indicators has important guiding significance for perioperative management of gastric cancer patients. In recent years, the prognostic value of CONUT score in patients with gastric cancer has been gradually concerned and reported. CONUT scoring system was first proposed by Ignacio et al. [5] in 2005. Compared with the internationally recognized nutrition evaluation system NRS 2002, CONUT scoring can effectively reduce the interference of human factors by conducting objective evaluation through laboratory detection of nutrition and inflammation indicators. The CONUT score ranges from 0 to 9, and the higher the score, the worse the nutritional status. CONUT score can more accurately reflect the nutritional and immune status of patients, and help to manage perioperative patients and customize diagnosis and treatment plans [14]. The results of this study found that patients with higher CONUT score showed higher TNM stage, which was consistent with the results of previous studies that malnutrition was positively correlated with tumor progression [26]. Sun et al. [11] collected preoperative CONUT score of 1 479 patients with gastric cancer for analysis, and found that preoperative CONUT score was a powerful independent predictor of short-term complications after gastrectomy. Patients with high CONUT score have a higher incidence of total postoperative complications and major complications, a longer hospital stay, and a higher total cost [11]. In addition, a large number of studies have confirmed that patients with high CONUT score have worse prognosis in terms of overall survival and progression-free survival than patients with low CONUT score [9,22].

The biological mechanism of CONUT score correlation with the prognosis of tumor patients is still unclear. This paper attempts to explain the correlation from each parameter of CONUT score. Systemic nutritional status is an important part of the tumor microenvironment and plays an important role in the process of tumor occurrence, development and metastasis [27]. The CONUT score includes objective laboratory measures of serum albumin, total cholesterol, and lymphocyte counts, representing host protein reserve, energy reserve, and immunoinflammatory status, respectively. Serum albumin reflects nutritional status and immune response level [28]. Hypoalbuminemia suggests low nutritional status and elevated levels of inflammation, which may negatively affect survival in patients with stomach cancer. In addition, hypoalbuminemia can reduce the transport of substances such as fatty acids and cholesterol, as well as the removal of oxygen free radicals, which has adverse effects on patient survival [2]. As an important part of cell membrane, cholesterol has many biological functions, which not only reflects the energy reserve of the host, but also affects the occurrence and development of tumors through multiple signaling pathways [29]. Studies have reported that low cholesterol level may be an important risk factor for gastric cancer in Chinese Han population [30]. Lymphocyte count reflects the immune defense function of patients, and patients with low lymphocyte level will weaken the anti-tumor immune response, resulting in tumor cell growth and proliferation [26]. The scoring system based on the combination of these three indexes can better reflect the nutritional and immune status of the host.

The results of subgroup analysis showed a worse overall survival in the high CONUT group when the cut-off value was 2, 3, 4 or 5, consistent with the findings reported by You *et al.* [31]. Although a large number of studies on CONUT scoring have been reported, no consensus was reached on the cut-off value of the scoring system. At present, the truncation value of CONUT score fluctuates between 2 and 5. Some studies select the optimal critical value according to the ROC curve for grouping [21], and some studies use previous literature reports as the basis for grouping [3,18]. Different threshold values still have a certain impact on the prognosis, and more evidence may be needed to accurately determine the boundary values of nutritional indicators in the future.

There are some limitations in this study: (1) The cut-off values of CONUT scores among different studies have not been unified and need to be further standardized in the future; (2) The included literature is from China and Japan, and its applicability to other countries or ethnicities is not clear; (3) Except for 2 studies reported as prospective or multi-center studies, all the other studies were retrospective single-center studies; (4) Due to the number of included studies, subgroup analysis of disease stage and follow-up duration cannot be conducted, and evidence support from future studies is still needed.

Gastric cancer is digestive system tumor, which is closely related to nutritional status. Preoperative nutritional index monitoring can reflect the body status of patients, effectively predict their tolerance to subsequent treatment and clinical outcome, and provide evidence and reference for clinicians to formulate individualized diagnosis and treatment strategies, which is of great significance in the clinical management of tumors throughout the whole process.

Conflict of Interest: None

Reference

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Submission received: 2023-06-26/**Revised:** 2023-08-21

·论　著·

术前控制营养状态评分对胃癌术后患者预后影响的 Meta 分析

李明珍[1]，谭瑞明[2]，何韶华[1]，刘欢[1]，陈成[1]，张沅懿[1]，姚波兰[1]，谭力铭[3]

1. 怀化市第二人民医院精准医学中心，湖南 怀化 418000；2. 怀化市第二人民医院消化内科，湖南 怀化 418000；3. 肿瘤防治怀化市重点实验室，湖南 怀化 418000

摘要：目的　系统评价术前控制营养状态(CONUT)评分在胃癌术后患者预后中的价值。**方法**　计算机检索中国知网、万方、中国生物医学文献图书馆、维普、PubMed、Web of Science、Cochrane Library、Embase 数据库，收集将术前 CONUT 评分应用于胃癌术后患者预后的相关研究，检索时间为建库至 2023 年 4 月 20 日。按照纳排标准筛选文献、提取数据、质量评价后，采用 RevMan 5.3 和 Stata 15.0 软件进行 Meta 分析。**结果**　共纳入 17 项研究，总计患者 9 233 例。Meta 分析结果显示，与 CONUT 低分组相比，CONUT 高分组患者总生存期[HR=1.70，95%CI（1.54，1.87），P<0.01]、肿瘤特异性生存期[HR=2.55，95%CI（1.23，5.27），P=0.01]、无进展生存期[HR=1.53，95%CI（1.29，1.82），P<0.01]更差。同时，CONUT 评分与并发症[OR=2.10，95%CI（1.53，2.90），P<0.01]、神经浸润[OR=1.54，95%CI（1.02，2.32），P=0.04]、死亡率[OR=2.24，95%CI（1.25，4.01），P<0.01]、T3/4[OR=2.06，95%CI（1.73，2.46），P<0.01]、N2/3[OR=1.76，95%CI（1.51，2.05），P<0.01]、Ⅲ期[OR=1.62，95%CI（1.39，1.90），P<0.01]显著相关，但与肿瘤分化无关[OR=0.88，95%CI（0.75，1.04），P=0.13]。
结论　术前 CONUT 评分与胃癌患者术后并发症和临床病理参数相关是患者预后的独立预测指标。

关键词：胃癌；控制营养状态评分；胃切除术；生存期；Meta 分析

中图分类号：R735.2　**文献标识码：**A　**文章编号：**1674-8182(2024)02-0223-07

Preoperative controlling nutritional status on the prognosis of postoperative gastric cancer patients: a Meta-analysis

LI Mingzhen*, TAN Ruiming, HE Shaohua, LIU Huan, CHEN Cheng, ZHANG Yuanyi, YAO Bolan, TAN Liming

** Precision Medicine Centre, The Second People's Hospital of Huaihua, Huaihua, Hunan 418000, China*

Corresponding author: TAN Liming, E-mail: tanliming1973@126.com

Abstract: Objective　To evaluate the prognostic value of controlling nutritional status score (CONUT) in patients undergoing gastrectomy for gastric cancer. **Methods**　CNKI, Wanfang, China Biomedical Literature Library, VIP, PubMed, Web of Science, Cochrane Library, and Embase databases were electronically searched for collecting relevant studies on the application of preoperative CONUT scores to the prognosis of gastric cancer patients after surgery. The search period was from database establishment to April 20, 2023. After screening literature, extracting data, and assessing quality assessment, Meta-analysis was performed using the RevMan 5.3 and Stata 15.0 software. **Results**　A total of 17 studies involving 9 233 patients were included. The results of Meta-analysis showed that, compared with the low CONUT group, patients in the high CONUT group had poorer overall survival [HR=1.70, 95%CI (1.54, 1.87), P<0.01], tumor specific survival [HR=2.55, 95%CI (1.23, 5.27), P=0.01], and progression free survival [HR=1.53, 95%CI (1.29, 1.82), P<0.01]. The CONUT score was significantly correlated with complications [OR=2.10, 95%CI (1.53, 2.90), P<0.01], nerve infiltration [OR=1.54, 95%CI (1.02, 2.32), P=0.04], mortality [OR=2.24, 95%CI (1.25, 4.01), P<0.01], T3/4 [OR=2.06, 95%CI (1.73, 2.46), P<0.01], N2/3 [OR=1.76, 95%CI (1.51,

DOI: 10. 13429/j. cnki. cjcr. 2024. 02. 012
基金项目：湖南省自然科学基金面上项目（2022JJ30462）；怀化市科技创新平台（2021R2206）
通信作者：谭力铭，E-mail：tanliming1973@126.com
出版日期：2024-02-20

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2.05), $P<0.01$], Stage Ⅲ [$OR=1.62$, 95%CI (1.39, 1.90), $P<0.01$], but not with tumor differentiation [$OR=0.88$, 95%CI (0.75, 1.04), $P=0.13$]. **Conclusion**　Preoperative CONUT score is an independent prognostic indicator of gastric cancer patiem associated with clinicopathological parameters of gastric cancer.

Keywords: Gastric cancer; Controlling nutritional status score; Gastrectomy; Survival; Meta-analysis

Fund program: Hunan Province Natural Science Foundation Project(2022JJ30462); Huaihua Technology Innovation Platform(2021R2206)

胃癌发病率居世界第五位,2020 年全球癌症统计数据显示约有 1 089 103 人患病。同时,在癌症相关死亡病因中排名第三[1]。对早期胃癌患者而言,手术切除仍是最主要的治疗方式。虽然手术技术及辅助治疗已经有了很大的发展,但胃癌术后患者的预后并不理想[2]。目前,TNM 分期系统被认为是最常用的生存预测手段,但其并不能提供完整的临床信息,需要更高效的预测指标来识别手术是否能让患者从中获益[3]。患者围手术期的全身营养及炎症状况可以影响肿瘤的进展与转移,与术后并发症的发生密切相关,并在一定程度上影响患者的整体生存率[4]。控制营养状态(controlling nutritional status, CONUT)评分是近年来新提出的一种营养评分系统,基于血清白蛋白、总胆固醇和淋巴细胞计数指标来评估营养状况[5]。通过划定这些指标的评分范围,可以简便高效的计算出患者的营养评分。已有研究报道其在乳腺癌、肺癌、结直肠癌等领域广泛应用,不仅具有突出的营养评价表现,甚至对术后并发症及生存时间的评估也有显著相关性[4,6]。但其在胃癌患者中是否存在同样的适用性仍需进一步的探索。本研究旨在评估 CONUT 评分对胃癌术后患者的短期预后及长期生存之间的关联,以期为相关临床应用提供参考。

1　资料与方法

1.1　*文献检索*　计算机检索中国知网、万方、中国生物医学文献图书馆、维普、PubMed、Web of Science、Cochrane Library、Embase 数据库,检索从建库至 2023 年 4 月 20 日公开发表的中、英文文献。中文检索词为"胃癌"、"胃切除"、"控制营养"等;英文检索词为"controlling nutritional status score"、"stomach neoplasms"、"gastrectomy"等。采用主题词与自由词相结合的方式进行检索,同时辅以手工检索和文献追溯法收集相关文献。

1.2　*纳入与排除标准*　纳入标准:(1) 研究对象为病理确诊的胃癌患者,并接受手术治疗;(2) 术前行 CONUT 评分;(3) 术后报道预后情况,包括短期疗效及长期生存率。排除标准:(1) 无法获取或无法转换数据的研究;(2) 语言非中文、英文。

1.3　*文献筛选和资料提取*　由两名研究者独立筛选文献、提取资料,并交叉核对,如遇分歧,则通过讨论或由第三方解决。文献筛选时首先阅读文题和摘要,在排除明显不相关的文献后,进一步阅读全文,以确定最终是否纳入。资料提取内容包括:(1) 纳入研究的基本信息,包括第一作者、发表年份、样本量、CONUT 评分截断值等;(2) 文献质量评价的相关要素;(3) 结局指标。

1.4　*质量评价*　文献质量评价采用 Newcastle-Ottawa Scale(NOS)量表评分,总分为 9 分,分数越高,文献质量越高[7]。

1.5　*统计学方法*　采用 RevMan 5.3 和 Stata 15.0 软件分析。采用倒方差法对 HR 值及 95%CI 进行数据处理。二分类变量采用比值比(odds ratio, OR)为效应分析统计量,各效应量均提供其 95%CI。统计学异质性采用 I^2 和 χ^2 检验统计量,若 $I^2<50\%$,且 $P>0.1$,采用固定效应模型合并效应量,反之,则采用随机效应模型。对异质性来源进行亚组分析,按 CONUT 评分截断值、来源国家进行分组。对纳入研究绘制漏斗图及进行 Egger 检验评估发表偏倚。$P<0.05$为差异有统计学意义。

2　结　果

2.1　*文献筛选流程及结果*　初检获得 322 篇相关文献,经逐层筛选,最终纳入 17 项研究。文献筛选流程及结果见图 1。

2.2　*纳入研究的基本特征*　共纳入 17 项[3,6,8-22]研究,总计 9 233 例患者,只有一项研究[17]为前瞻性单中心研究,其余均为回顾性研究。16 项研究 NOS 质量评分≥7 分。纳入研究的基本特征和文献质量评价见表 1。

2.3　*术前 CONUT 评分与生存预后的关联*　11 项研究[3,6,8-10,14-16,20-22]报道了 CONUT 评分与胃癌术后患者总生存期(overall survival, OS)的相关性。结果显示,与 CONUT 低分组相比,CONUT 高分组患者在 OS 方面的预后更差[$HR=1.70$, 95%CI (1.54, 1.87), $P<$

0.01］（图 2A）。3 项研究［8,12,21］报道了 CONUT 评分与患者肿瘤特异性生存期（cancer-specific survival，CSS）的相关性。结果显示，与 CONUT 低分组相比，CONUT 高分组患者在 CSS 方面的预后更差［HR = 2.55，95%CI（1.23，5.27），P = 0.01］（图 2B）。5 项研究［16,18,20-22］报道了 CONUT 评分与患者无进展生存期（progression-free survival，PFS）的相关性。结果显示，与 CONUT 低分组相比，CONUT 高分组患者在 PFS 方面的预后更差［HR = 1.53，95% CI（1.29，1.82），P<0.01］（图 2C）。

2.4　术前 CONUT 评分与次要结局指标的关联　术前 CONUT 评分与术后并发症、神经浸润、死亡率、T3/4、N2/3、Ⅲ期具有相关性。见表 2。

2.5　亚组分析　本研究根据不同截断值和不同来源国家进行亚组分析。结果显示，按截断值进行分组时，结果尚未发现异质性来源；当截断值为 2、3、4 或 5 时，各亚组均显示 CONUT 高分组较低分组患者在 OS 方面的预后更差（图 3A）；按来源国家进行分组时，结果发现其可能为异质性来源（χ^2 = 4.60，P = 0.03，I^2 = 78.2）；各亚组均显示 CONUT 高分组较低分组患者在 OS 方面的预后更差（图 3B）。

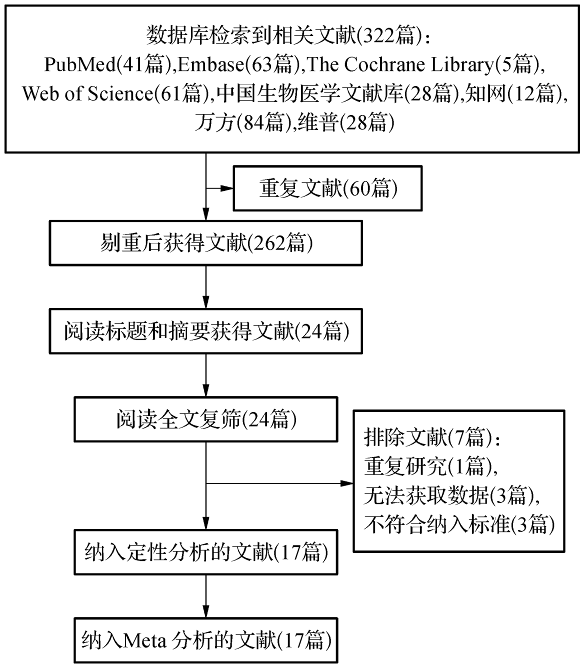
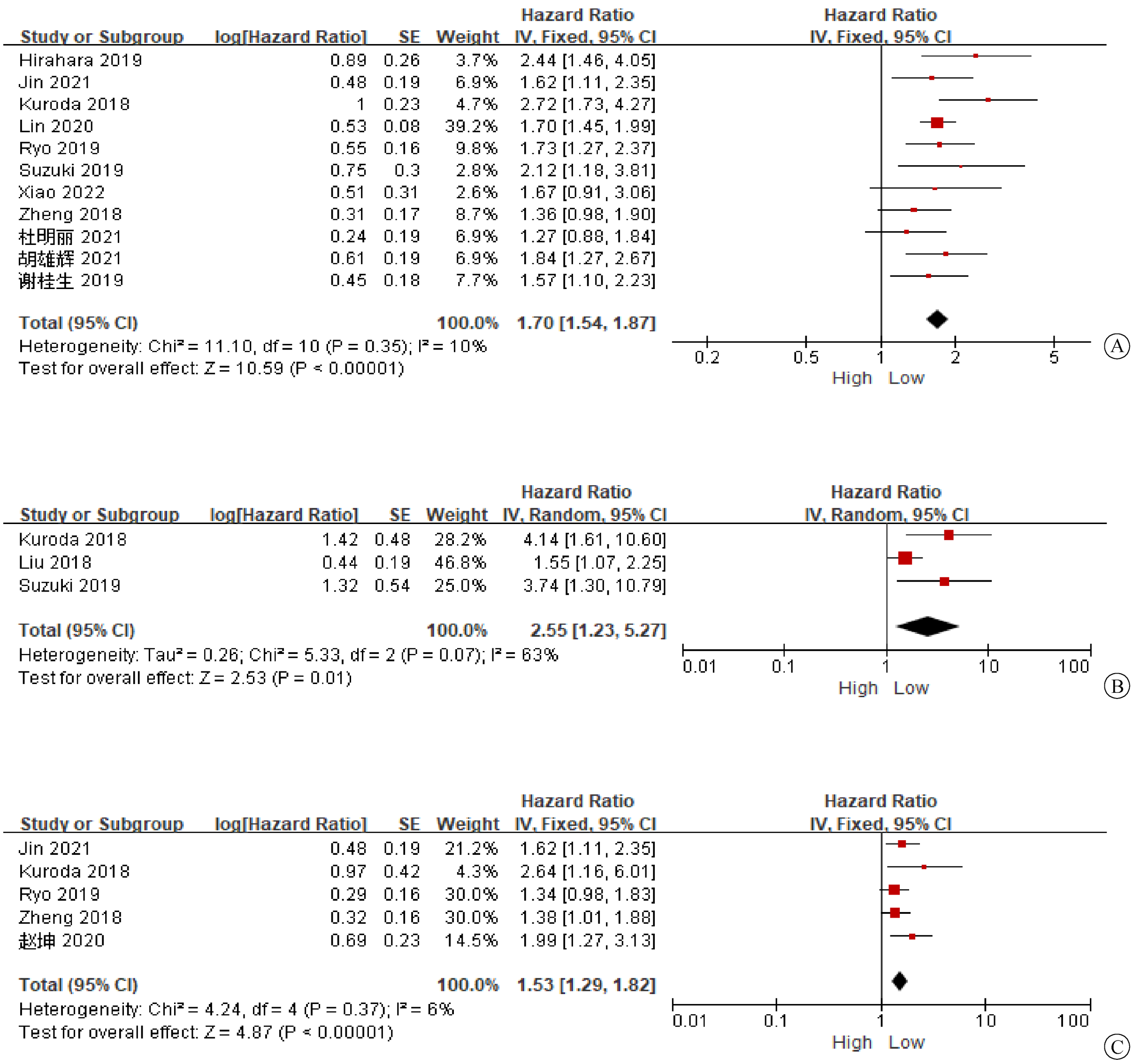


图 1　文献筛选流程图
Fig. 1　Literature screening process

表 1　纳入文献的一般特征
Tab. 1　General characteristics of included literature

作者	年份	国家	样本量（男）	肿瘤分期	CONUT 截断值	高 CONUT 组患者比例（%）	结局指标	随访时间（月）	NOS 得分
胡雄辉［3］	2021	中国	218（164）	Ⅰ，61；Ⅱ，57；Ⅲ，100	>2	48.00	并发症、OS	60	7
杜明丽［6］	2021	中国	239（174）	Ⅰ，54；Ⅱ，48；Ⅲ，137	>2	36.40	OS	52（1~75）	6
Suzuki［8］	2019	日本	211（141）	Ⅰ，132；Ⅱ，53；Ⅲ，26	≥5	17.06	CSS、OS、并发症	47（5~185）	8
Hirahara［9］	2019	日本	368（254）	Ⅰ，217；Ⅱ，65；Ⅲ，86	≥3	28.50	OS、并发症	35.3（4~97）	7
Lin［10］	2020	中国	2 182（1 643）	Ⅰ，632；Ⅱ，526；Ⅲ，1 024	>2	21.90	并发症、OS	52（1~118）	7
Sun［11］	2021	中国	1 479（1 083）	Ⅰ，505；Ⅱ，366；Ⅲ，592；Ⅳ，16	≥2	57.60	并发症	—	7
Liu［12］	2018	中国	697（457）	Ⅱ，194；Ⅲ，503	≥3	31.10	CSS、并发症	36（3~162）	8
Qian［13］	2021	中国	309（228）	Ⅰ，102；Ⅱ，51；Ⅲ，148；Ⅳ，8	>2.5	30.74	并发症	—	7
Xiao［14］	2022	中国	106（84）	Ⅰ，17；Ⅱ，20；Ⅲ，57；Ⅳ，12	≥5	59.43	并发症、OS	30（7~64）	7
谢桂生［15］	2019	中国	536（372）	Ⅱ，112；Ⅲ，424	≥3	29.10	OS、并发症	61（3~162）	7
Zheng［16］	2018	中国	532（403）	Ⅰ，291；Ⅱ，183；Ⅲ，58	正常（0~1）； 轻度（2~4）； 中重度（≥5）	54.70 34.40 10.90	OS、RFS	60	7
Huang［17］	2019	中国	357（275）	Ⅰ，119；Ⅱ，87；Ⅲ，151	正常（0~1）； 轻度（2~4）； 中重度（≥5）	42.85 47.05 10.10	并发症	12	8
赵坤［18］	2020	中国	231（-）	—	≥3	27.70	DFS	60	7
周庆森［19］	2021	中国	454（334）	Ⅰ，185；Ⅱ，63；Ⅲ，188；Ⅳ，18	>2	33.04	并发症	—	7
Ryo［20］	2019	日本	626（435）	Ⅱ，281；Ⅲ，345	≥2	46.17	OS、并发症、OFS	49.2	8
Kuroda［21］	2018	日本	416（267）	Ⅰ，275；Ⅱ，81；Ⅲ，60	≥4	14.90	OS、CSS、RFS、并发症	60	7
Jin［22］	2021	中国	272（201）	—	≥4	31.80	OS、PFS、并发症	60	7

注：—，未获得或未报告；RFS，无复发生存时间（recurrence-free survival）；DFS，无病生存期（disease-free survival）。



注：A，CONUT 评分与 OS 的相关性；B，CONUT 评分与 CSS 的相关性；C，CONUT 评分与 PFS 的相关性。

图 2　CONUT 评分与生存预后的相关性

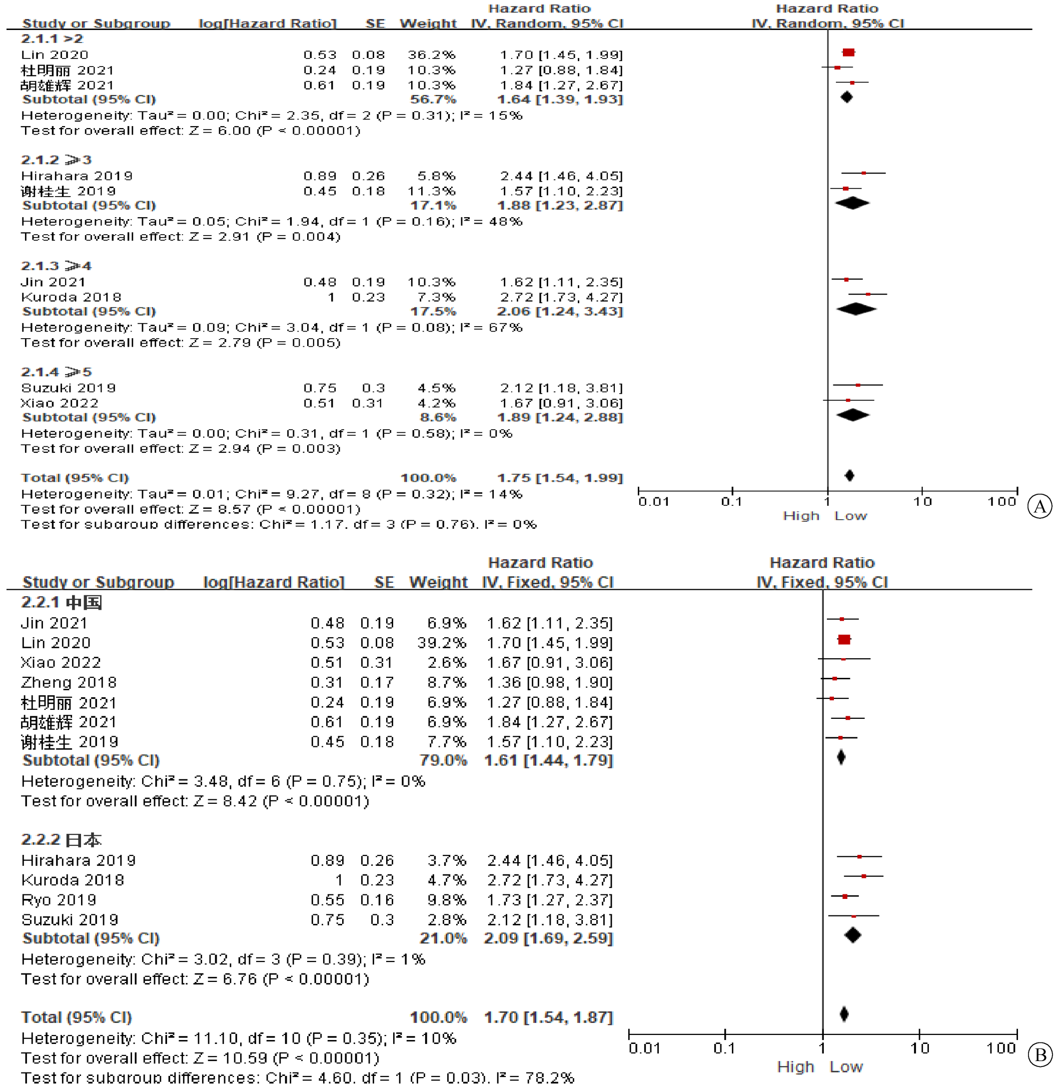
Fig. 2　Correlation between CONUT score and survival prognosis

表 2　CONUT 高分组及低分组次要结局指标的比较

Tab. 2　Comparison of secondary outcome between CONUT high and low groups

结局指标	纳入研究数量	异质性检验结果		效应模型	Meta 分析结果	
		I^2 值	*P* 值		*OR*(95%*CI*)	*P* 值
并发症	14	83	<0.01	随机	2.10(1.53,2.90)	<0.01
神经浸润	2	23	0.25	固定	1.54(1.02,2.32)	0.04
死亡率	5	12	0.34	固定	2.24(1.25,4.01)	<0.01
T3/4	9	0	0.69	固定	2.06(1.73,2.46)	<0.01
N2/3	8	10	0.35	固定	1.76(1.51,2.05)	<0.01
Ⅲ期	14	25	0.19	固定	1.62(1.39,1.90)	<0.01
低分化	9	0	0.57	固定	0.88(0.75,1.04)	0.13

2.6　*发表偏倚*　针对报道了 OS 的 11 项研究绘制漏斗图，结果显示散点分布大体对称，且 Egger 检验 *P* = 0.451，提示存在发表偏倚的可能性小。见图 4。



注：A，按 CONUT 评分截断值进行分组；B，按文献来源国家进行分组。

图 3　CONUT 评分与 OS 相关性的亚组分析

Fig. 3　Subgroup analysis of the correlation between CONUT score and OS

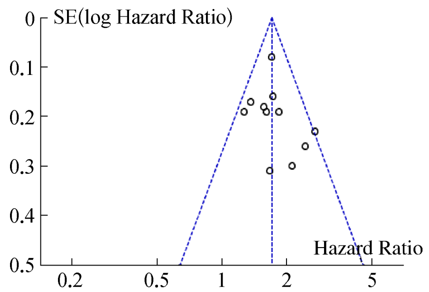


图 4　发表偏倚漏斗图

Fig. 4　Publication bias funnel diagram

3 讨　论

本研究结果提示 CONUT 评分是一种潜在的营养筛查工具，可用于预测胃癌术后患者的短期预后和长期生存预后，且与临床病理参数具有相关性。

胃癌患者多合并程度不一的营养不良，主要原因是原发疾病状况及治疗引起的摄入减少、消耗增加、胃肠功能不全及机体代谢变化等[23]。营养不良不仅会影响患者对手术治疗的耐受性，而且对辅助治疗方案的顺利实施造成负面影响。患者行胃癌根治术后，机体的持续分解代谢状态会持续数月甚至更长时间，增加术后并发症的发生率，同时影响远期预后[24]。此外，免疫状态也被视为胃癌患者的预后指标[25]。因此，选择简便高效的预测指标对胃癌患者围手术期管理具有重要的指导意义。近年来，CONUT 评分在胃癌患者中的预后价值逐渐被关注和报道。CONUT 评分系统由 Ignacio 等[5]在 2005 年首次提出，与国际公认的营养评价系统 NRS 2002 相比，CONUT 评分通过实验室检测营养及炎症指标进行客观评价，可以有效减少人为因素的干扰。CONUT 评分范围为 0～9，评分越高，营养状况越差，它能较准确的反映患者的

营养免疫状况,有助于对围手术期患者进行管理及定制诊疗计划[14]。本研究结果发现 CONUT 评分越高的患者表现出更高的 TNM 分期,这与之前的研究结果一致,即营养不良与肿瘤进展呈正相关[26]。Sun 等[11]收集 1 479 例胃癌患者的术前 CONUT 评分进行分析,研究发现术前 CONUT 评分是胃癌切除术后短期并发症强有力的独立预测因子。CONUT 评分高的患者术后总并发症及主要并发症的发生率更高,患者住院时间更长,总费用也更高[11]。此外,大量研究证实 CONUT 评分高的患者在总生存期、无进展生存期方面的预后明显比 CONUT 评分低的患者差[9,22]。

CONUT 评分与肿瘤患者预后相关的生物学机制尚不清楚,本文试图从 CONUT 评分的每个参数来解释其间的关联性。全身营养状态是肿瘤微环境的重要组成部分,在肿瘤发生、发展及转移过程中起着重要作用[27]。CONUT 评分细则包括血清白蛋白、总胆固醇和淋巴细胞计数的客观实验室指标,分别代表宿主蛋白储备、能量储备和免疫炎症状态。血清白蛋白反映营养状况及免疫反应水平[28]。低白蛋白血症提示营养状况低,炎症水平升高,可能对胃癌患者的生存产生负面影响。此外,低白蛋白血症可减少脂肪酸和胆固醇等物质的运输,以及对氧自由基的清除,这对患者生存造成不良影响[2]。胆固醇作为细胞膜的重要组成部分,具有许多生物学功能,不仅反映宿主的能源储备,而且通过多条信号通路影响肿瘤的发生发展[29]。有研究报道,低胆固醇水平可能是中国汉族人群胃癌发生的重要危险因素[30]。淋巴细胞计数则反映了患者的免疫防御功能,低淋巴细胞水平的患者会因抗肿瘤的免疫应答反应减弱从而导致肿瘤细胞生长、增殖[26]。通过这三种指标组合的评分系统能更好的反映宿主的营养及免疫状况。

本研究中的亚组分析结果显示,当截断值为 2、3、4 或 5 时,CONUT 高分组较低分组患者在总生存期方面的预后更差。这与游慧慧等[31]报道的研究结果一致。尽管报道了大量关于 CONUT 评分的研究,但评分系统的截断值仍未达成共识。目前,CONUT 评分的截断值在 2~5 之间波动,有些根据 ROC 曲线选择最佳临界值进行分组[21],有些研究根据既往的文献报道作为分组依据[3,18]。不同临界值对预后的判断能力还是会产生一定的影响,未来可能需要更多证据来准确确定营养指标的分界值。

本研究尚存在一些局限性:(1) 各研究间 CONUT 评分的截断值尚未统一,未来需进一步规范;(2) 本研究纳入的文献均来自中国及日本,对于其他国家或种族的适用性并不清楚;(3) 除 2 篇文献报道为前瞻性或多中心研究外,其余研究均为回顾性的单中心研究;(4) 受限于纳入研究的数量,无法对疾病分期、随访时长进行亚组分析,仍需未来研究的证据支持。

胃癌属于消化系统肿瘤,与营养状况密切相关,术前营养指标监测能反映患者的机体状态,可以有效预测其对后续治疗的耐受性及临床结局,能为临床医生制定个体化的诊疗策略提供依据和参考,这在肿瘤全程临床管理中具有重要意义。

利益冲突　无

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收稿日期:2023-06-26 **修回日期**:2023-08-21 **编辑**:李方