Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 15 January 2021 doi:10.20944/preprints202101.0303.v1

Article

Controlling Nutritional Status (CONUT) Score is a Prognostic Indicator for Patients with Hemorrhagic Stroke: Results from a 3-month Follow-up Study

Bei-lei Zhu1*, Yan-zhi Wu2*, Zhong-ming Cai [2], Cheng-wei Liao[2], Le-qiu Sun[3], Zhi-peng Liu[2], Hao-man Chen[2], Xue-rong Huang[4], Ren-qian Feng[2], Sheng-lie Ye[2], Qun-li Lin[5], Xu-dong Zhou[6], Man-man Zhang[1#], Bo Yang[7,1#]

[1] Department of Neurology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China
[2] Department of First Clinical Medical School, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China
[3] Department of Neurology, Yueqing People's Hospital, Wenzhou, China
[4] Department of Neurology, Ruian People's Hospital, Wenzhou, Zhejiang, China
[5] Department of Neurology, Yongjia People's Hospital, Wenzhou, Zhejiang, China
[6] Department of Neurology, Pingyang People's Hospital, Wenzhou, Zhejiang, China
[7] School of Public Health and Management, Wenzhou Medical University, Wenzhou, Zhejiang, China
* The two authors contributed equally to this work
[#] Correspondence: yb@wmu.edu.cn; boyang7802@gmail.com (Y.B.), zhangmanman@wmu.edu.cn (Z.M.M.). Tel.: (86) 577-86687632 (Y.B.), (86) 577-555780166 (Z.M.M.).

Abstract: Controlling Nutritional Status (CONUT) Score is useful for the nutritional screening. We aimed to explore whether the CONUT score may predict a 3-month functional outcome in hemorrhagic stroke (AHS). Totally, 349 patients with incident AHS were consecutively recruited, and their malnutrition risks were determined using a high CONUT score of ≥ 2. Poor functional outcomes were defined as the modified Rankin Scale (mRS) score of ≥ 3 at 3 months. A total of 328 patients (mean age, 60.4 ± 12.83 years; 66.8% male) were included, 172 (52.40%) patients at malnutrition risk and 104 (31.7%) patients with a poor prognosis. High-CONUT patients had lower total lymphocyte counts and total cholesterol levels than low-CONUT patients ($p < 0.001$ and $p = 0.012$). At 3-month post discharge, patients with malnutrition risk had higher hospitalization costs ($p = 0.021$), lower Barthel Index ($p = 0.001$), and more infectious complications ($p = 0.002$) than those without, and there was a greater risk for poor functional outcomes in the high-CONUT compared with the low-CONUT patients at admission (adjusted odds ratio: 2.32, 95% confidence interval: 1.28-4.17). High-CONUT scores predict a 3-month poor prognosis in AHS, which may help identify the AHS patients who need additional nutritional managements.

Keywords: Controlling Nutritional Status Score; Hemorrhagic stroke; Nutrition screening; Prognosis; Modified Rankin Scale

1. Introduction

Stroke is increasingly recognized as a major cause of mortality and disability worldwide, leading to a high economic cost in the treatment period, especially in poor prognosis [1-3]. Clinical data showed that the nutritional status was poor in patients with stroke during several weeks after the acute onset, and the malnutrition risk was likely to be a crucial factor associated with poor prognostic outcomes [4, 5], because it may allow the prediction of treatment tolerability and functional progression [6]. Given that the malnutritional condition is an independent risk factor for poor prognosis that caused an increase in length of the average hospital stay, poor prognosis after discharge, and disability-related hospital costs [7-9], the nutritional screening tools are necessary to identify the stroke patients at a nutritional risk for developing an opportune nutrition care or medical support [10].

© 2021 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 15 January 2021 doi:10.20944/preprints202101.0303.v1

ESPEN (European Society of Clinical Nutrition and Metabolism) guideline for clinical nutrition in neurology has suggested that the risk of malnutrition should be evaluated in stroke patients within 48 hours on admission to identify prognostic factors for tailored treatments [11]. Several quantitative tools with scoring scales are developed to assess nutritional risk, postoperative complications, and long-term outcomes, such as the prognostic nutritional index (PNI) and Nutritional Risk Screening index (NRS-2002) [12, 13]. Controlling Nutritional Status (CONUT) can be calculated from two biochemical parameters (serum albumin and cholesterol levels) and one immune indicator (total lymphocyte counts) [14], which are representative markers of protein reserves, calorie deficiency, and impaired immune defenses, respectively. As Compared to the previous screening tools, the CONUT is more easily calculated from the data in blood measurements and is a newly proposed scoring system that allows the comprehensive assessment in patients in hospital settings.

Although previous studies have investigated the prognostic usefulness of the CONUT for determining the survival in patients with gastric cancer, malignant pleural mesothelioma, and colorectal cancer undergoing gastrostomy [15-17], clinical data using the CONUT score to predict stroke prognosis were scarce. Recent studies including our group's clinical epidemiological investigations showed that the CONUT score was associated with a poor prognosis and high all-cause mortality in acute ischemic stroke (AIS) [18-21]. Nevertheless, it is currently unclear whether the CONUT scores were effective for determining the 3-month functional prognosis in hemorrhagic stroke (AHS). The purpose of the current study was primarily to investigate the usefulness of the CONUT score for predicting a 3-month AHS prognosis, and secondarily to compare the prognostic accuracy of CONUT with the corresponding accuracies of NRS-2002.

2. Materials and Methods

2.1 Study design

This was a multi-center, prospective hospital-based epidemiological study. Patients who had neuroimaging-confirmed acute hemorrhagic stroke (AHS) and admitted in hospitals within one week after the sudden onset were enrolled in five major hospitals in Wenzhou regions of Zhejiang province, China, including the First Affiliated Hospital of Wenzhou Medical University, Ruian People's Hospital, Yueqing People's Hospital, Yongjia People's Hospital, and Pingyang People's Hospital. All of the participants provided written informed consent, and the study protocol was approved by the Clinical Research Ethics Committee of the five hospitals mentioned above.

2.2 Study participants

Clinical data were collected by the same professionally trained investigator using the electronic medical records at three different points: within 48 hours after admission, with 48 post discharge, and 3 months post discharge. The following data were collected including demographic variables (age, gender, BMI), stroke-related comorbidities (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, coronary heart disease), clinical assessments (NIHSS score and Barthel Index), and laboratory biochemical parameters (serum albumin, total lymphocytes and total cholesterol). The National Institutes of Health Stroke Scale (NIHSS) was used to evaluate the stroke severity on admission. The Barthel Index (BI) was used for the evaluation of activities of daily living (ADL). At the end of the 3 months after discharge, the data on the follow-up measures were collected by phone. A total of 349 patients with a medical diagnosis of AHS were consecutively enrolled from October to November in 2018. Of those, 21 patients were excluded because they missed a 3-month morbid assessment using the modified Rankin Scale (mRS).

2.3 CONUT score and NRS-2002

We used the CONUT score and the NRS-2002 for nutritional risk assessments. The CONUT score was calculated from the levels of three laboratory parameters including serum albumin, lymphocytes, and total cholesterol [14]. We set 2 as the cut-off value for CONUT score by a receiver operating characteristics (ROC) curves analysis (Figure S1) and categorized the patients into low-CONUT and high-CONUT groups according to the CONUT score: no or low risk of malnutrition (0-1) and high malnutrition risk (2-12). The NRS-2002 score of ≥ 3 points indicates the patient is at nutritional risk [22], considering that impaired nutritional status, the severity of the disease, and patients' age. Screening details on the CONUT and NRS-2002 scores were summarized in Table S1 and Table S2, respectively.

Body mass index (BMI) was calculated from the preoperative heights and weights of the study individuals, which were measured by our medical staff within a few hours after admission to hospital. The cutoff value of BMI < 18.5kg/m2 was defended as a malnutrition according to the World Health Organization standard.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 15 January 2021 doi:10.20944/preprints202101.0303.v1

2.4 Outcome measurements

The modified Rankin Scale (mRS) was applied to assess the degree of disability in stroke patients, and primary outcome was a poor functional prognosis with a mRS score of 3-6 at 3-month post discharge [23]. The secondary outcomes were an all-cause mortality at the 3-month post discharge, length of hospital stay (LOS), the ability at hospital discharge (evaluated by NIHSS score), ADL at hospital discharge (assessed by Barthel Index), hospitalization costs, nutritional support, and rates of complications during hospitalization.

2.5 Statistical Analysis

Data were expressed as percentages for categorical variables and median (interquartile range, IQR) or mean (standard deviation, SD) for continuous variables according to their normal distributions that were evaluated by using the Kolmogorov–Smirnov test. When comparing the difference in baseline valuables and follow-up outcomes between high-CONUT and low-CONUT groups, a t-test analysis was performed for the continuous normal-distribution data and the Mann-Whitney U test for the non-normal data, while the Chi-square test was used for categorical variables. To analyze the impact of malnutrition risk on primary poor outcomes at 3 months of follow-up, odds ratios (OR) with 95% confidential intervals (95% CI) were estimated by a univariate and multivariate-adjusted logistic regression model, respectively. The multivariate analyses were set to examine the association of CONUT or NRS-2002 scores with the primary outcomes (poor functional prognosis assessed by mRS). Age, gender, BMI, lifestyle factors, NIHSS scores, and marginally unbalanced variables at baseline (hypertension, hyperlipidemia and Batherl Index) that may have potential impacts on the prognostic endpoints were taken as independent covariates adjusted in the multivariate model. We established a statistical significance at the level of $p < 0.05$. All data were performed by the IBM SPSS Statistics (version 20.0). Receiver operating characteristic curves (ROC) with a calculation of the area under the curve (AUC) was made by Medcalc (version 19.5.3).

3. Results

Among 349 AHS patients，328 patients were successfully followed-up for 3 months after discharge. Of these, the mean age was 60.38 years and the proportions of men were 66.77%. Totally, 172 (52.44%) patients were at malnutrition risk assessed by using the CONUT score, 104 (31.71%) at malnutrition risk by the NRS-2002, and 16 (4.88%) at malnutrition status with BMI < 18.5 kg/m^2.

3.1 Baseline characteristics

The AHS participants' baseline demographic and clinical characteristics are shown in Table 1. The levels of total lymphocytes and total cholesterol were lower in the low-CONUT compared with the high-CONUT groups ($p < 0.001$ and $p = 0.012$, respectively). The high-CONUT patients tend to have lower proportions of hyperlipemia and higher hypertension than the low-CONUT patients, but the differences did not reach statistically significant ($p = 0.068$ and $p = 0.155$, respectively). No statistical differences were found between the two groups in demographic (age, gender, and BMI), lifestyle (smoking and drinking history) and other clinical characteristics (prevalent comorbidities and stroke-related scale assessments).

Table 1. Baseline demographic and clinical characteristics by CONUT score in the included AHS patients

Characteristics	Total (n=328)	CONUT scores		p-value [1]
		0-1(n=156)	2-12 (n=172)	
Demographic factors				
Age, mean±SD (year)	60.38±12.83	59.45±13.24	61.23±12.41	0.209
Male, n (%)	219(66.77)	105(67.31)	113(65.69)	0.666
BMI, mean±SD (kg/m2)	24.23±4.01	24.09±4.25	24.38±3.77	0.546
Lifestyle factors				
Smoking history, n (%)	103(31.40)	53(33.97)	50(29.07)	0.339
Drinking history, n (%)	113(34.45)	58(37.18)	55(31.98)	0.322
Clinical prognosis factors				
Atrial fibrillation, n (%)	20(6.10)	9(5.77)	11(6.40)	0.813

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 15 January 2021 doi:10.20944/preprints202101.0303.v1

Hypertension, n (%)	269(82.01)	123(78.85)	146(84.88)	0.155
Diabetes mellitus, n (%)	70(21.34)	35(22.44)	35(20.35)	0.645
Hyperlipidemia, n (%)	153(46.64)	81(51.92)	72(41.86)	0.068
Previous stroke, n (%)	34(10.37)	15(9.62)	19(11.05)	0.575
Barthel Index, median (IQR)	35(20-55)	35(20-55)	35(20-50)	0.227
NIHSS score, median (IQR)	4(1-9)	5(2-9)	4(1-9)	0.545
Laboratory parameters				
Albumin, mean±SD, g/dL	3.85±0.44	3.87±0.40	3.83±0.48	0.407
Total lymphocytes, mean±SD, 10^9/L	1.48±0.62	1.62±0.54	1.35±0.59	<0.001
Total cholesterol, mean±SD, mmol/L	5.11±1.31	5.32±1.18	4.93±1.40	0.012

Abbreviations: CONUT, Controlling Nutritional Status; AHS, acute hemorrhagic stroke; BMI, body mass index NIHSS, National Institute of Health stroke scale; IQR, interquantile range
[1] P value indicate a statistical significance between low-CONUT and high-CONUT score groups by using a t-test.

3.2 Primary and secondary outcomes

The comparisons of primary and secondary outcomes between the low-CONUT and high-CONUT groups is presented in Table 2. Totally, 104 (31.71%) patients had primary poor outcomes according to the mRS assessment, with a higher proportion of poor prognosis in the high-CONUT than that in the low-CONUT groups (38.37 vs. 24.36, p = 0.010). For individual secondary outcomes, patients at risk of malnutrition (high-CONUT scores) had more hospitalization costs (p = 0.021), NIHSS scores (p = 0.012), nutritional support (p = 0.007) during hospitalization, and infectious complications (p = 0.002) as well as a lower Barthel Index (p = 0.001) post discharge than those at no or low risk.

Table 2. Primary and secondary outcomes grouped by CONUT score in the AHS patients

Individual Outcome	CONUT scores		p-value [1]
	0-1 (n=156)	2-12 (n=172)	
Primary outcome measurements			
Follow-up mRS, median (IQR)	1 (0-2)	1.5 (1-4)	0.003
Poor outcome (MRS of 3-6), n (%)	38 (24.36)	66 (38.37)	0.010
Secondary outcome measurements			
Length of hospital stay, median (IQR), day	11 (8-15)	12 (9-16)	0.313
Hospitalization costs, median (IQR), 10^3 (CNY)	13 (10-21)	16 (10-29.75)	0.021
NIHSS scores, median (IQR)	2 (0-5)	3 (1-8)	0.012
Barthel post discharge, median (IQR)	55 (40-90)	45 (20-70)	0.001
Dysfunction after discharge（Bathel≤60）	90 (57.69)	110 (63.95)	0.070
Nutrition support, n (%)	15 (9.62)	35 (20.35)	0.007
Infectious complications, n (%)	33 (21.15)	63 (36.63)	0.002
All-cause Mortality, n (%)	7 (4.49)	12 (6.98)	0.335

Abbreviations: CONUT, Controlling Nutritional Status; AHS, acute hemorrhagic stroke; NIHSS, National Institute of Health stroke scale; IQR, interquantile range
[1] P value indicate a statistical significance between low-CONUT and high-CONUT score groups by using a t-test.

3.3 Poor outcome in relation to CONUT and NRS-2002 scores

Association of the CONUT and NR-S2002 scores with a 3-month poor prognosis in the AHS Patients was presented in Table 3. Patients with high-CONUT scores had a higher risk of the poor functional prognosis than those with low-CONUT scores (OR = 1.93; 95% CI: 1.20-3.12; p = 0.043), and this association remained to be statistically significant in the multivariate-adjusted model (adjusted OR = 2.32; 95% CI: 1.28-4.17; p = 0.005). Also, the high NRS-2002

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 15 January 2021 doi:10.20944/preprints202101.0303.v1

scores of 3-7 were associated with the poor outcome compared with the low NRS-2002 scores of 1-2, with a crude OR of 2.00 (95% CI:1.23-3.26; p = 0.005) and multivariate-adjusted OR of 1.93 (95% CI:1.02-3.62; p = 0.043).

Table 3. Association of CONUT and NRS200with a 3-month poor prognosis in the AHS Patients

Variables	Crude model			Adjusted model		
	OR[1]	95% CI	P-value	OR[1]	95% CI	P-value
CONUT (2-12 vs. 0-1)	1.93	1.20-3.12	0.007	2.32	1.28-4.17	0.005
NRS2002 (3-7 vs. 0-2)	2.00	1.23-3.26	0.005	1.93	1.02-3.62	0.043

Abbreviations: CONUT, Controlling Nutritional Status; NRS2002, Nutritional Risk Screening; AHS, acute hemorrhagic stroke; OR, odds ratio; CI, confidence interval.
[1] ORs with 95% CIs for the incident 3-month poor functional outcome were estimated by using a crude logistic model and a multivariate model with full adjustments for age, gender, BMI, lifestyle factors, hypertension, hyperlipidemia, NIHSS scores, and Batherl Index, respectively.

3.4 Subgroup analysis

Pre-specified subgroup analyses on the CONUT score in predicting the 3-month poor AHS outcomes were shown in Table S3. As compared to no malnutrition risk assessed by the low-CONUT score, malnutrition risk by high-CONUT score was independently associated with poor functional outcomes in the following strata of male (OR = 2.70; 95% CI: 1.28-5.68; p = 0.009), age ≤ 65 (OR = 2.71; 95% CI: 1.28-5.74; p = 0.009), hypertension (OR = 2.12; 95% CI: 1.11-4.04; p = 0.023), hyperlipidemia (OR = 3.45; 95% CI: 1.43-8.31; p = 0.006), Barthel Index ≤60 (OR = 2.14; 95% CI: 1.10-4.16; p = 0.024), and NIHSS <8 (OR = 2.98; 95% CI: 1.42-6.23; p = 0.004), respectively.

3.5 Receiver operating characteristics curve (ROC)

ROC comparisons between the CONUT and NRS-2002 scores in predicting the 3-month poor outcomes in the AHS patients were demonstrated in Figure S1 and Table 4. The estimated values of AUC were 0.58 (95% CI: 0.52–0.64, p = 0.016; sensitivity: 63.46%, specificity: 52.68%) for the CONUT and 0.60 (95% CI: 0.54–0.65, p< 0.001; sensitivity: 48.08%, specificity: 73.21%) for the NRS-2002, respectively. No significant difference in the estimated AUC was found between the two score systems (p = 0.603).

Table 4. ROC comparisons of CONUT with the NRS-2002 in predicting the 3-month prognosis outcome in AHS.

NSTs	mRS		
	AUC (95% CI)	P-value	Best cutoffs (Se, Sp)
CONUT scores	0.58 (0.52–0.64)	0.016	≥2 (63.46%, 52.68%)
NRS-2002	0.60 (0.54–0.65)	<0.001	≥3 (48.08%, 73.21%)

Abbreviations: AUC, area under the curve; ROC, receiver operator characteristic curve; CI, confidence interval; NSTs, Nutrition screening tools; mRS, The Modified Rankin Scale; CONUT, Controlling Nutritional Status; NRS, Nutritional Risk Screening; Se, sensitivity; Sp, specificity.

4. Discussion

The present study demonstrated that the patients with high-CONUT scores had a poor functional outcome evaluated by the MRS value of 3-6 compared to those with low-CONUT scores at 3 month of follow-up, and the CONUT, as a nutritional risk assessment tool, could be effective in predicting a 3-month functional prognosis in AHS. Such findings provide new evidence to support the prognostic value of CONUT in AHS and further develop a novel notion that the CONUT scores help identify the AHS patients who need additional nutritional managements, which may complement the gap in the stroke-related clinical practice.

One major finding of our study weas the CONUT appeared to be more sensitive than the NRS-2002 in identifying the AHS patients at malnutritional risk. Based on the accumulating evidence from the extensive clinical studies, stroke patients may have a high risk of malnutrition, which, in turn, are clearly related to a poor clinical prognosis [10, 24, 25]. To precisely predict the functional prognosis in clinical practice, there are currently many clinical guidelines that recommend the necessity for nutritional risk screening and nutritional management in stroke [14, 26, 27]. NRS-2002 score has been widely used to screen the nutritional risk in the critically ill hospitalized patients, with a high sensitivity and

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 15 January 2021 doi:10.20944/preprints202101.0303.v1

accuracy that have been repeatedly confirmed [13, 28, 29]. Unfortunately, the NRS-2002, in which the items need to be obtained by face-to-face inquiry, is not well applied in one third of stroke patients who have experienced aphasia [30]. Alternatively, as an emerging screening tool, CONUT has been widely used for the nutritional risk assessment in many hospitalized patients [31-33], including the AIS patients [12, 34, 35]. CONUT was calculated from laboratory indicators during hospitalization, which is quick, convenient and can be carried out without increasing the financial burden substantially. As showed in our study, there seemed to be a lower prevalence of patients at malnutrition risk assessed by the NRS-2002 (31.7%, 95%CI: 26.9%-36.9%) than that by the CONUT (52.4%, 95%CI: 47.0%-58.0%), suggesting that CONUT scores might have been more sensitive in nutritional risk assessment than NRS-2002.

Another major result from our study showed that patients with malnutrition risk determined using the CONUT score had higher rates of poor AHS outcomes than those without, and the malnutrition risk assessed by the CONUT was found to be positively associated with a poor prognosis. The CONUT has been widely used to predict prognosis in cancer and postoperative [33, 36, 37], and recent epidemiological studies have well documented the prognostic role of the CONUT score in AIS [34, 38]. For example, in a clinical analysis of the 1,518 AIS patients, malnutrition was independently associated with poor outcomes in patients with cardioembolic stroke (OR: 3.25, 95% CI: 1.02–10.4). This assentation was also seen in our recent study and a previous clinical investigation that proved that the CONUT score at admission could be a useful prognostic marker for a 3-month functional outcome in patients with AIS [20, 21]. Compared with the previous studies, our current study found the post-discharge patients with risk of malnutrition, according to CONUT score, were more likely to have higher NIHSS scores, rates of infectious complications, and hospitalization costs as well as lower Barthel Index than those without those. The AHS patients with nutritional risk also showed higher adverse functional prognosis at the 3 months of follow-up, as illustrated by mRS ≥ 3, and the risk of malnutrition based on CONUT was independently associated with 3-mongth prognosis. In addition, to compare the CONUT with the well-known NRS-2002 in predicting the AHS prognosis, ROC analyses found the NRS-2002 to be not superior to the CONUT as a comprehensive nutritional indicator, suggesting that both CONUT and NRS-2002 scores are likely to be equally effective in predicting the AHS prognosis. Give an operational merit with a simple application in clinical follow-up, the CONUT might be preferentially recommend for evaluating the malnutrition risk in AHS patients on admission.

In stratified analyses, the prognostic value of CONUT in AHS was more significant in several subgroups of male, age at less than 65 years, prevalent hypertension, Barthel Index ≤ 60, and NIHSS scores < 8. There are several possible reasons for explaining the current subgroup findings. Firstly, men lose more lean mass than women with the development of ageing4, which perhaps resulted in a higher risk of poor prognosis in male than in female patients. For example, in an observational epidemiological study of 3,286 elderly patients, the effects of malnutrition in men on health-related quality of life (HRQoL) were stronger than in women [39]. Another possibility was that there appeared to be some additional impacts on the estimated prediction with the CONUT scores, such as the damage degree of stroke. As defined by Barthel Index ≤ 60, AHS patients experienced a moderate to severe decline in ADL on admission that is confirmed to be associated with a poor prognosis. In contrast, in patients with a mild decline in ADL, patients with nutritional risk had a 37% higher risk of poor prognosis than those without, but this trend was not statistically significant. Similar predictive results were also more significant in the subgroup with the NIHSS scores < 8 and Barthel Index < 60, but the lack of statistical significance may be attributed to the small sample sizes of the two individual subgroups with NIHSS ≥ 8 or Barthel Index > 60, and thus nutrition screening by CONUT should be carried out in AHS regardless of the influence to ADL or the severity of the disease. Third, patients with hypertension tended to have nutrition risk or prevalent malnutrition [5], and malnutrition survivors are likely to develop excess hypertension in their later life [40]. Our subgroup analysis showed the CONUT score in predicting AHS outcome was more significant in patients with BMI ≥ 18.5, hypertension or dyslipidemia than in those without, suggesting that cardiometabolic risk factors would increase a possibility to magnify the prognostic role of the CONUT in predicting AHS outcomes.

Our study has several potential highlights. First, this is the first clinical prospective study that aimed to investigate whether the malnutrition risk determined by CONUT would have a prognostic value in AHS. Compared with previous studies that proved NRS-2002 score is a predictor in stroke, we advised the CONUT to be as a simple nutritional indicator for predicting AHS prognosis. Second, selection bias is likely to be minimized because the patients who were lack of ability to communicate with investigators were not excluded. Third, our current results showed that the malnutrition risk is a predictor of poor prognosis in AHS, which may contribute to an updated change in clinical nutrition practice.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 15 January 2021 doi:10.20944/preprints202101.0303.v1

There are some deficiencies that merit further considerations. The main limitation of the present study is that the number of sample patients is not large enough to reach a sufficient statistic power. Second, the 3-month duration of follow-up is relatively short, thus the current finding needs to be explained with more cautiousness and further verified in a long-term prospective study. Third, since a standardized procedure in nutrition risk assessment is currently lacking, it is difficult to compare the sensitivity and specificity of CONUT with NRS-2002 in predicting outcomes. Forth, due to the lacked details in nutritional information, including dietary intake, weight change during hospitalization, active intervention, and functional rehabilitation, the impacts upon the individual nutritional status could not be eliminated in the present study. Further prospective clinical studies are needed to determine whether nutritional intervention or therapy would better the prognostic outcome in stroke. Lastly, the possibility that the laboratory components of the CONUT score might be easily affected by concurrent disorders including infectious and inflammatory diseases other than nutritional status at mission could not be excluded, and thus it is necessary to conduct the nutritional risk assessment determined by using the CONUT scores at regular intervals during the period of the follow-up. In the following study, we will also continue to more accurately examine the prognostic value of the CONUT in the long-term stroke prognosis.

5. Conclusions

AHS patients with malnutrition risk had a poorer prognosis than those without at 3 months of follow-up, and the malnutrition status assessed using the CONUT score was independently associated with poor functional outcome in AHS. Given simplicity and convenience required in clinical practice, the CONUT scores should be advised to identify the AHS patients who need additional nutritional management.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Figure S1: Receiver operating characteristics curves analysis for the cut-off value of the CONUT scores, Figure S2: ROC curve analysis on comparing the CONUT with NRS in predicting a poor outcome classified by mRS; Table S1: Assessment of undernutrition degree by CONUT, Table S2: The detail scales in Nutritional Risk Screening (NRS-2002), Table S3: Subgroup analyses for the CONUT score in predicting the 3-month poor functional outcomes in AHS.

Author Contributions: Conceptualization, B.Y., B.-L.Z. and M.-M.Z.; methodology, B.Y. and B.-L.Z.; validation, B.Y., B.-L.Z. and M.-M.Z.; formal analysis, Y.-Z.W. and Z.-M.C.; investigation, Y.-Z.W., Z.-M.C., C.-W.L., Z.-P.L., H.-M.C., R.-Q.F. and S.-L.Y.; resources, X.-R.H., L.-Q.S., Q.-L.L. and X.-D.Z.; data curation, Y.-Z.W.; writing—original draft preparation, Y.-Z.W.; writing—review and editing, B.Y., B.-L.Z., M.-M.Z. and Z.-M.C.; supervision, B.Y. and B.-L.Z.; project administration, Y.-Z.W., X.-R.H., L.-Q.S., Q.-L.L. and X.-D.Z.; funding acquisition, B.-L.Z. and M.-M.Z. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the 2017 Chinese Nutrition Society (CNS) Nutrition Research Foundation – DSM Research Fund (grant number: 2017-008), and the Wenzhou Science and Technology Bureau Fund (grant number：Y20190561 & Y20190556).

Acknowledgments: We sincerely thank the patients with stroke who participated in the study and all of the medical staff who carefully finished the followed-up clinical measures to ensure that the study was conducted.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet. Neurology* **2019**, *18*, 459-480, doi:10.1016/s1474-4422(18)30499-x.
2. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet. Neurology* **2019**, *18*, 439-458, doi:10.1016/s1474-4422(19)30034-1.
3. Yousufuddin, M.; Moriarty, J.; Lackore, K.; Zhu, Y.; Peters, J.; Doyle, T.; Jensen, K.; Ahmmad, E.; Al Ward, R.; Al-Zu'bi, H., et al. Initial and subsequent 3-year cost after hospitalization for first acute ischemic stroke and intracerebral hemorrhage. *Journal of the Neurological Sciences* **2020**, *419*, 117181, doi:10.1016/j.jns.2020.117181.
4. Zhang, J.; Zhao, X.; Wang, A.; Zhou, Y.; Yang, B.; Wei, N.; Yu, D.; Lu, J.; Chen, S.; Wang, Y., et al. Emerging malnutrition during hospitalisation independently predicts poor 3-month outcomes after acute stroke: data from a Chinese cohort. *Asia Pacific Journal of Clinical Nutrition* **2015**, *24*, 379-386, doi:10.6133/apjcn.2015.24.3.13.
5. Hsieh, D.; Hung, J.; Chang, K.; Huang, Y.; Lee, T.; Chen, H. Malnutrition in Acute Stroke Patients Stratified by Stroke Severity-A Hospital Based Study. *Acta Neurologica Taiwanica* **2017**, 120-127.
6. Barret, M.; Malka, D.; Aparicio, T.; Dalban, C.; Locher, C.; Sabate, J.; Louafi, S.; Mansourbakht, T.; Bonnetain, F.; Attar, A., et al.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 15 January 2021 doi:10.20944/preprints202101.0303.v1

Nutritional status affects treatment tolerability and survival in metastatic colorectal cancer patients: results of an AGEO prospective multicenter study. *Oncology* **2011**, *81*, 395-402, doi:10.1159/000335478.

7. Reber, E.; Strahm, R.; Bally, L.; Schuetz, P.; Stanga, Z. Efficacy and Efficiency of Nutritional Support Teams. *Journal of Clinical edicine* **2019**, *8*, doi:10.3390/jcm8091281.
8. Marco, E.; Sánchez-Rodríguez, D.; Dávalos-Yerovi, V.; Duran, X.; Pascual, E.; Muniesa, J.; Rodríguez, D.; Aguilera-Zubizarreta, A.; Escalada, F.; Duarte, E. Malnutrition according to ESPEN consensus predicts hospitalizations and long-term mortality in rehabilitation patients with stable chronic obstructive pulmonary disease. *Clinical Nutrition (Edinburgh, Scotland)* **2019**, *38*, 2180-2186, doi:10.1016/j.clnu.2018.09.014.
9. Palma Milla, S.; Meneses, D.; Valero, M.; Calso, M.; García Vázquez, N.; Ruiz Garrido, M.; Martín-Vega, A.; Gómez-Candela, C. [Costs associated to disease-related malnutrition and treatment: a literature review]. *Nutricion Hospitalaria* **2018**, *35*, 442-460, doi:10.20960/nh.1204.
10. Roberts, A.; Penfold, S. Glycaemic management during the inpatient enteral feeding of people with stroke and diabetes. *Diabetic Medicine* **2018**, *35*, 1027-1036, doi:10.1111/dme.13678.
11. Burgos, R.; Bretón, I.; Cereda, E.; Desport, J.; Dziewas, R.; Genton, L.; Gomes, F.; Jésus, P.; Leischker, A.; Muscaritoli, M., et al. ESPEN guideline clinical nutrition in neurology. *Clinical Nutrition* **2018**, *37*, 354-396, doi:10.1016/j.clnu.2017.09.003.
12. Xiang, W.; Chen, X.; Ye, W.; Li, J.; Zhang, X.; Xie, D. Prognostic Nutritional Index for Predicting 3-Month Outcomes in Ischemic Stroke Patients Undergoing Thrombolysis. *Frontiers in Neurology* **2020**, *11*, 599, doi:10.3389/fneur.2020.00599.
13. Wang, J.; Luo, B.; Xie, Y.; Hu, H.; Feng, L.; Li, Z. Evaluation methods on the nutritional status of stroke patients. *European Review for Medical and Pharmacological Sciences* **2014**, *18*, 3902-3907.
14. Martineau, J.; Bauer, J.; Isenring, E.; Cohen, S. Malnutrition determined by the patient-generated subjective global assessment is associated with poor outcomes in acute stroke patients. *Clinical Nutrition* **2005**, *24*, 1073-1077, doi:10.1016/j.clnu.2005.08.010.
15. Suzuki, S.; Kanaji, S.; Yamamoto, M.; Oshikiri, T.; Nakamura, T.; Kakeji, Y. Controlling Nutritional Status (CONUT) Score Predicts Outcomes of Curative Resection for Gastric Cancer in the Elderly. *World Journal of Surgery* **2019**, *43*, 1076-1084, doi:10.1007/s00268-018-04889-6.
16. Takamori, S.; Toyokawa, G.; Taguchi, K.; Edagawa, M.; Shimamatsu, S.; Toyozawa, R.; Nosaki, K.; Seto, T.; Hirai, F.; Yamaguchi, M., et al. The Controlling Nutritional Status Score Is a Significant Independent Predictor of Poor Prognosis in Patients With Malignant Pleural Mesothelioma. *Clinical Lung Cancer* **2017**, *18*, e303-e313, doi:10.1016/j.cllc.2017.01.008.
17. Yang, C.; Wei, C.; Wang, S.; Han, S.; Shi, D.; Zhang, C.; Lin, X.; Dou, R.; Xiong, B. Combined Features Based on Preoperative Controlling Nutritional Status Score and Circulating Tumour Cell Status Predict Prognosis for Colorectal Cancer Patients Treated with Curative Resection. *International Journal of Biological Sciences* **2019**, *15*, 1325-1335, doi:10.7150/ijbs.33671.
18. Naito, H.; Nezu, T.; Hosomi, N.; Aoki, S.; Kinoshita, N.; Kuga, J.; Shimomura, R.; Araki, M.; Ueno, H.; Ochi, K., et al. Controlling nutritional status score for predicting 3-mo functional outcome in acute ischemic stroke. *Nutrition* **2018**, 10.1016/j.nut.2018.02.025, 1-6, doi:10.1016/j.nut.2018.02.025.
19. López Espuela, F.; Roncero-Martín, R.; Zamorano, J.; Rey-Sanchez, P.; Aliaga-Vera, I.; Portilla Cuenca, J.; Naranjo, I.; Morán-García, J.; Lavado-García, J. Controlling Nutritional Status (CONUT) Score as a Predictor of All-Cause Mortality at 3 Months in Stroke Patients. *Biological Research for Nursing* **2019**, *21*, 564-570, doi:10.1177/1099800419860253.
20. Cai, Z.; Wu, Y.; Chen, H.; Feng, R.; Liao, C.; Ye, S.; Liu, Z.; Zhang, M.; Zhu, B. Being at risk of malnutrition predicts poor outcomes at 3 months in acute ischemic stroke patients. *European Journal of Clinical Nutrition* **2020**, *74*, 796-805, doi:10.1038/s41430-020-0605-8.
21. Zhang, M.; Ye, S.; Huang, X.; Sun, L.; Liu, Z.; Liao, C.; Feng, R.; Chen, H.; Wu, Y.; Cai, Z., et al. Comparing the prognostic significance of nutritional screening tools and ESPEN-DCM on 3-month and 12-month outcomes in stroke patients. *Clinical Nutrition* **2020**, 10.1016/j.clnu.2020.11.001, doi:10.1016/j.clnu.2020.11.001.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 15 January 2021 doi:10.20944/preprints202101.0303.v1

22. Kondrup, J.; Rasmussen, H.; Hamberg, O.; Stanga, Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clinical Nutrition* **2003**, *22*, 321-336, doi:10.1016/s0261-5614(02)00214-5.
23. Kim, S.; Lee, H.; Kim, J.; Lee, K.; Kang, J.; Kim, B.; Han, M.; Choi, K.; Kim, J.; Shin, D., et al. Three-month modified Rankin Scale as a determinant of 5-year cumulative costs after ischemic stroke: An analysis of 11,136 patients in Korea. *Neurology* **2020**, *94*, e978-e991, doi:10.1212/wnl.0000000000009034.
24. Nip, W.; Perry, L.; McLaren, S.; Mackenzie, A. Dietary intake, nutritional status and rehabilitation outcomes of stroke patients in hospital. *Journal of Human Nutrition and Dietetics* **2011**, *24*, 460-469, doi:10.1111/j.1365-277X.2011.01173.x.
25. Ojo, O.; Brooke, J. The Use of Enteral Nutrition in the Management of Stroke. *Nutrients* **2016**, *8*, doi:10.3390/nu8120827.
26. Hankey, G. The Role of Nutrition in the Risk and Burden of Stroke: An Update of the Evidence. *Stroke* **2017**, *48*, 3168-3174, doi:10.1161/strokeaha.117.016993.
27. Serra, M. The Importance of Assessing Nutritional Status to Ensure Optimal Recovery during the Chronic Phase of Stroke. *Stroke Research and Treatment* **2018**, *2018*, 1297846, doi:10.1155/2018/1297846.
28. Poulia, K.; Klek, S.; Doundoulakis, I.; Bouras, E.; Karayiannis, D.; Baschali, A.; Passakiotou, M.; Chourdakis, M. The two most popular malnutrition screening tools in the light of the new ESPEN consensus definition of the diagnostic criteria for malnutrition. *Clinical Nutrition* **2017**, *36*, 1130-1135, doi:10.1016/j.clnu.2016.07.014.
29. Sanson, G.; Sadiraj, M.; Barbin, I.; Confezione, C.; De Matteis, D.; Boscutti, G.; Zaccari, M.; Zanetti, M. Prediction of early- and long-term mortality in adult patients acutely admitted to internal medicine: NRS-2002 and beyond. *Clinical Nutrition* **2020**, *39*, 1092-1100, doi:10.1016/j.clnu.2019.04.011.
30. Brady, M.; Kelly, H.; Godwin, J.; Enderby, P.; Campbell, P. Speech and language therapy for aphasia following stroke. *The Cochrane Database of Systematic Reviews* **2016**, 10.1002/14651858, doi:10.1002/14651858.CD000425.pub4.
31. Ahiko, Y.; Shida, D.; Horie, T.; Tanabe, T.; Takamizawa, Y.; Sakamoto, R.; Moritani, K.; Tsukamoto, S.; Kanemitsu, Y. Controlling nutritional status (CONUT) score as a preoperative risk assessment index for older patients with colorectal cancer. *BMC Cancer* **2019**, *19*, 946, doi:10.1186/s12885-019-6218-8.
32. Matsukawa, T.; Suto, K.; Kanaya, M.; Izumiyama, K.; Minauchi, K.; Yoshida, S.; Oda, H.; Miyagishima, T.; Mori, A.; Ota, S., et al. Validation and comparison of prognostic values of GNRI, PNI, and CONUT in newly diagnosed diffuse large B cell lymphoma. *Annals of Hematology* **2020**, *99*, 2859-2868, doi:10.1007/s00277-020-04262-5.
33. Sze, S.; Pellicori, P.; Zhang, J.; Weston, J.; Clark, A. The impact of malnutrition on short-term morbidity and mortality in ambulatory patients with heart failure. *The American Journal of Clinical Nutrition* **2020**, 10.1093/ajcn/nqaa311, doi:10.1093/ajcn/nqaa311.
34. Naito, H.; Hosomi, N.; Nezu, T.; Kuzume, D.; Aoki, S.; Morimoto, Y.; Yoshida, T.; Shiga, Y.; Kinoshita, N.; Ueno, H., et al. Prognostic role of the controlling nutritional status score in acute ischemic stroke among stroke subtypes. *Journal of the Neurological Sciences* **2020**, *416*, 116984, doi:10.1016/j.jns.2020.116984.
35. Shiga, Y.; Nezu, T.; Hosomi, N.; Aoki, S.; Nishi, H.; Naito, H.; Kinoshita, N.; Ueno, H.; Maruyama, H. Effect of tooth loss and nutritional status on outcomes after ischemic stroke. *Nutrition* **2020**, *71*, 110606, doi:10.1016/j.nut.2019.110606.
36. Xie, H.; Nong, C.; Yuan, G.; Huang, S.; Kuang, J.; Yan, L.; Ruan, G.; Tang, S.; Gan, J. The value of preoperative controlling nutritional status score in evaluating short-term and long-term outcomes of patients with colorectal cancer following surgical resection. *Journal of Cancer* **2020**, *11*, 7045-7056, doi:10.7150/jca.49383.
37. Kheirouri, S.; Alizadeh, M. Prognostic potential of the preoperative controlling nutritional Status (CONUT) score in predicting survival of patients with cancer: a systematic review. *Advances in Nutrition* **2020**, 10.1093/advances/nmaa102, doi:10.1093/advances/nmaa102.
38. Gon, Y.; Kabata, D.; Kawano, T.; Kanki, H.; Todo, K.; Sasaki, T.; Shintani, A.; Mochizuki, H. Hematological abnormalities and malnutrition mediate pathway between cancer and outcomes in ischemic stroke patients. *Journal of Stroke and Cerebrovascular*

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 15 January 2021 doi:10.20944/preprints202101.0303.v1

diseases **2020**, *29*, 104943, doi:10.1016/j.jstrokecerebrovasdis.2020.104943.

39. Kvamme, J.; Olsen, J.; Florholmen, J.; Jacobsen, B. Risk of malnutrition and health-related quality of life in community-living elderly men and women: the Tromsø study. *Quality of Life Research* **2011**, *20*, 575-582, doi:10.1007/s11136-010-9788-0.
40. Tennant, I.; Barnett, A.; Thompson, D.; Kips, J.; Boyne, M.; Chung, E.; Chung, A.; Osmond, C.; Hanson, M.; Gluckman, P., et al. Impaired cardiovascular structure and function in adult survivors of severe acute malnutrition. *Hypertension* **2014**, *64*, 664-671, doi:10.1161/hypertensionaha.114.03230.